Universitat Autònoma de Barcelona

Epidemiología y optimización del manejo clínico de la candidemia: Resultados de un estudio poblacional en España

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TESIS DOCTORAL

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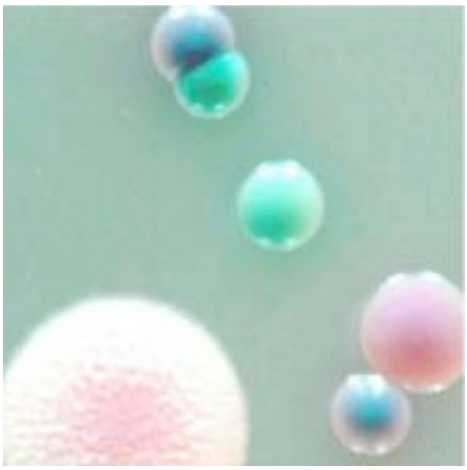

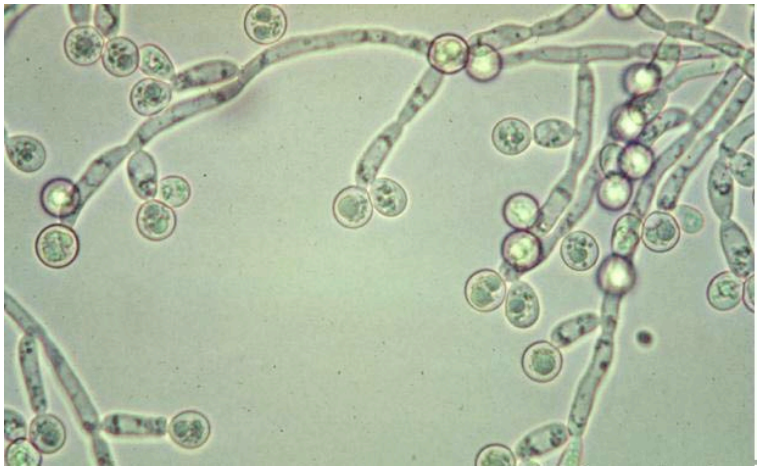

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Tesis presentada por

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para optar al grado de Doctora

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2016

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Que presenta la doctoranda **Mireia Puig Asensio**, ha sido realizada bajo su dirección, reúne las exigencias metodológicas y científicas necesarias y autoriza su presentación para que sea defendida delante del tribunal que corresponda.

Dr. Benito Almirante Gragera
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En Barcelona, 3 de mayo de 2016

A la meva família

"Cuando creíamos que teníamos todas las respuestas, de pronto, cambiaron todas las preguntas"

Mario Benedetti

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ABREVIATURAS

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ADN: Ácido Desoxirribonucleico

APACHE: Acute Physiology and Chronic Health Evaluation

CANDIPOP: Prospective Population Study on Candidemia in Spain

CLSI: Clinical Laboratory Standards Institute

CVC: Catéter Venoso Central

CMI: Concentración Mínima Inhibitoria

CNM: Centro Nacional de Micología

ESCMID: European Society of Microbiology and Infectious DIseases

EUA: Estados Unidos de América

EUCAST: European Committee on Antimicrobial Susceptibility Testing

IC: Intervalo de Confianza

IDSA: Infectious Diseases Society of America

ITS: Internal Transcribed Spacer

OR: Odds Ratio

PCR: Polymerase Chain Reaction (reacción en cadena de la polimerasa)

SDD: Sensibilidad Dependiente de la Dosis

UFC: Unidades Formadoras de Colonias

UCIs: Unidades de Cuidados Intensivos

1. INTRODUCCIÓN

1.1. Candidemia. Perspectiva global y magnitud del problema

La candidemia es una de las manifestaciones clínicas más frecuentes de la infección fúngica invasora, con una incidencia globalmente superior a la aspergilosis y una importante relevancia clínica, debido a que se asocia a una elevada morbi-mortalidad y a un incremento del coste económico sanitario (1-3).

La incidencia real de esta infección es difícil de precisar porque oscila notablemente entre los diferentes estudios epidemiológicos, variando especialmente entre zonas geográficas, centros hospitalarios y en el transcurso del tiempo (4). En conjunto, suele afectar a un colectivo de pacientes con unos factores de riesgo predisponentes bien determinados (inmunodepresión, presencia de CVC, nutrición parenteral, antibióticos de amplio espectro y antecedente de cirugía, especialmente abdominal). Por ello, es una infección muy frecuentemente de adquisición nosocomial o bien relacionada con los cuidados sanitarios (5).

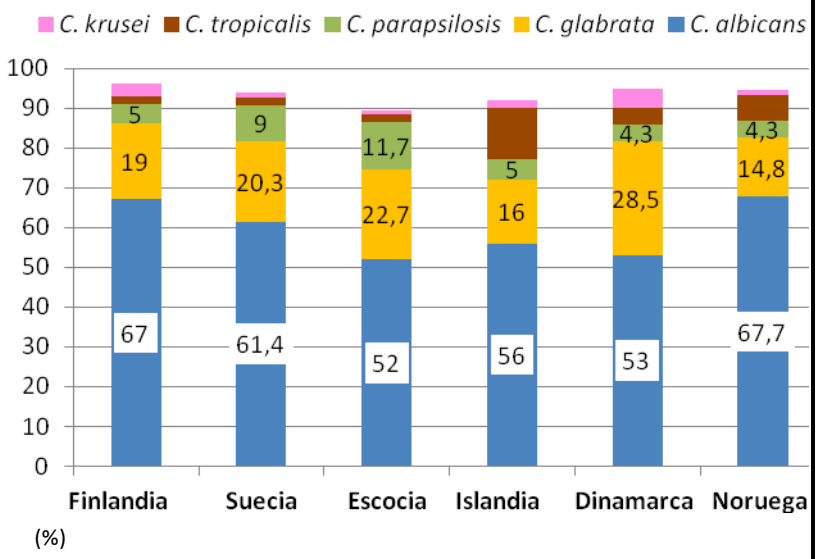
En el norte de Europa y Canadá, la incidencia estimada por estudios prospectivos de tipo poblacional se sitúa entre aproximadamente unos 3 a 10 casos por 100.000 habitantes/año. Estas cifras son muy inferiores a las descritas en algunas áreas metropolitanas de Estados Unidos (30,9 casos/100.000 habitantes/año en Baltimore en el año 2008 o 14,1 casos/100.000 habitantes/año en Atlanta durante el mismo período de tiempo) (Tabla 1) (1, 6-13). En cualquier caso, todos los estudios suelen coincidir en que la incidencia de candidemia alcanza cifras máximas en los extremos de edad y es especialmente relevante en los pacientes afectos de una enfermedad neoplásica, neonatos y en aquellos ingresados en las UCIs (4). Además, se trata de una infección en constante evolución, sujeta a constantes cambios epidemiológicos

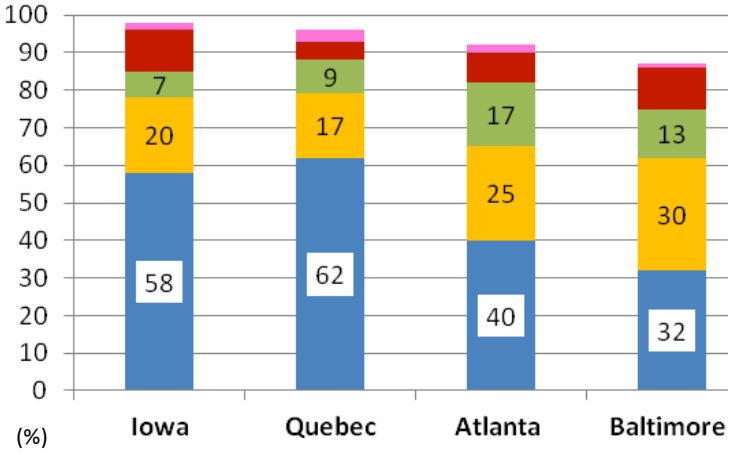
relacionados estrechamente con las prácticas sanitarias. Así por ejemplo, el progresivo envejecimiento de la población sometida a procedimientos invasivos podría explicar el aumento de la incidencia de candidemia detectado en el norte de Europa (6, 8, 13), el creciente protagonismo de los pacientes mayores de 60 años como población afectada (8, 13, 14), o bien, la importancia de los enfermos hospitalizados en plantas convencionales, médicas y quirúrgicas, como población susceptible de desarrollar una candidemia (15). Por todo ello, se podría decir que la población en riesgo de tener una candidemia es amplia, heterogénea y, además, podría estar extendiéndose a grupos hasta ahora considerados poco habituales.

Asimismo, otro de los aspectos más preocupante de la candidemia es su elevada mortalidad. A pesar de que en la última década se han producido mejoras en la atención sanitaria de los pacientes y se han introducido como opción terapéutica las equinocandinas, fármacos que poseen una potente actividad fungicida y escasos efectos secundarios, la mortalidad a los 30 días sigue siendo del 30-40% (6, 7, 16), o incluso superior en los pacientes más graves como los ingresados en las UCIs (17, 18). Así pues, la candidemia sigue constituyendo un problema de salud clínicamente relevante que precisa de estrategias preventivas y terapéuticas dirigidas a los grupos de más riesgo, para así mejorar el pronóstico de los pacientes con esta infección tan grave.

Tabla 1. Incidencia de candidemia y distribución de especies de *Candida* en estudios poblacionales recientes realizados en Europa y América del Norte (6-13, 19)

Región	Años	Incidencia[a]	Distribución y porcentaje de las principales especies de *Candida*
EUROPA			
Finlandia	2004-07	2,6-3,1	
Suecia	2005-06	4,2	
Escocia	2005-06	4,8	
Islandia	2000-11	4,4-7,6	
Dinamarca	2010-11	8,8-10,1[b]	
Noruega	2004-12	3,2-4,3	
AMÉRICA DEL NORTE			
Iowa (EUA)	1998-01	6	
Quebec (Canadá)	2003-05	3	
Atlanta (EUA)	2008-13	14,1-9,5[c]	
Baltimore (EUA)	2008-13	30,9- 14,4[c]	





[a] La incidencia poblacional se muestra por número de casos por 100.000 habitantes/año
[b] Esta incidencia está calculada incluyendo un porcentaje global de 1,6 a 1,8% de especies que no pertenecen al género *Candida*
[c] Indica descenso de la incidencia de candidemia entre los años 2008 y 2013

1.2. Aspectos microbiológicos con implicación clínico-terapéutica

Respecto a la etiología de la infección, cinco especies de *Candida* son responsables de más del 90% de los casos de candidemia (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis* y *C. krusei*) y, entre ellas, *C. albicans* es globalmente la especie más frecuentemente detectada (aproximadamente entre un 32 y un 68%) (Tabla 1). Sin embargo, esta información en sí misma es poco útil ya que la distribución de las especies de *Candida* depende de factores geográficos y climáticos, de la exposición previa del paciente a antifúngicos y de la epidemiología local de la cada unidad de hospitalización (2, 20). Desde el punto de vista práctico, el aspecto de mayor interés es conocer la distribución local de especies y disponer de la identificación de la especie de *Candida* lo antes posible. De hecho, la sensibilidad intrínseca de cada especie de *Candida* a los antifúngicos es predecible. Por ello, esta información puede ser utilizada como guía en la selección o en el cambio de un fármaco antifúngico empírico, incluso antes de saber la sensibilidad *in vitro* del patógeno detectado.

Por otra parte, cuando se comparan estudios que describen cifras de resistencia, ha de tenerse en consideración que en los últimos años se han producido cambios en los puntos de corte de sensibilidad de las especies de *Candida* (Tabla 2). Así pues, en una misma cohorte podemos encontrar cambios en el porcentaje de resistencias descritos según se hayan usado los criterios del CLSI previos al 2012 o los actualizados de acuerdo al EUCAST (21-23).

A modo de resumen, en el año 2007 el EUCAST estableció que los puntos de corte para *C. albicans*, *C. parapsilosis* y *C. tropicalis* a fluconazol tenían que ser ≤ 2 mg/L para cepas sensibles y > 4 mg/L para cepas resistentes (24). Estos puntos de corte no sólo

eran notablemente inferiores a los determinados por el CLSI (≤ 8 mg/L para cepas sensibles y ≥ 64 mg/L para cepas resistentes) (25), sino que además, por primera vez, se alertaba del hecho que fluconazol podía ser un tratamiento no óptimo para la candidemia producida por *C. glabrata*, tanto por sus valores de CMI intrínsecamente más elevados, como por su capacidad de desarrollar resistencias durante el tratamiento. Aún y cuando posteriormente, en el año 2012, se armonizaron los puntos de corte de EUCAST y CLSI para fluconazol en las principales especies de *Candida* [≤ 2 mg/L para cepas sensibles y > 4 mg/L para cepas resistentes, en caso de *C. albicans*, *C. parapsilosis* y *C. tropicalis* (26)], la categoría de cepa sensible a fluconazol prácticamente desapareció para *C. glabrata*. De esta manera, surgió la duda de si fluconazol podía ser una opción de tratamiento para *C. glabrata.* Esta cuestión es, aún en la actualidad, una incógnita que no tiene respuesta y que puede condicionar limitaciones en la práctica clínica. En primer lugar, fluconazol sigue siendo uno de los antifúngicos más usados como tratamiento empírico de la candidemia en pacientes hemodinámicamente estables, pero también como fármaco para la secuenciación a vía oral tras un tratamiento con equinocandinas o polienos (27-29). En segundo lugar, *C. glabrata* constituye la especie diferente de *C. albicans* más frecuentemente detectada en el norte de Europa, en EUA y en Canadá donde representa un 15-30% de todos los casos (6-13, 30, 31), cifra que podría estar incluso aumentando (8, 10, 31). Finalmente, se conoce que el uso prolongado de equinocandinas, la principal alternativa terapéutica a fluconazol, puede ir vinculado al desarrollo de cepas de *C. glabrata* resistentes a estos antifúngicos (32). Este hecho constituye por sí solo un problema terapéutico ya que dejaría como única opción de tratamiento a los polienos, fármacos

con un perfil de efectos secundarios más desfavorable. En definitiva, la eficacia clínica de fluconazol para *C. glabrata* es un tema de debate. Por este motivo se dedicará un apartado de la presente tesis doctoral para profundizar sobre el conocimiento de este problema.

Por último, otro aspecto microbiológico relevante es la menor sensibilidad *in vitro* a las equinocandinas que tiene *C. parapsilosis* en comparación al resto de especies (33). En estos casos, fluconazol parece ser el tratamiento recomendado debido al riesgo teórico de una mayor frecuencia de fracasos terapéuticos si se usan las equinocandinas (34). Estas consideraciones podrían ser clínicamente relevantes y, además, determinar la selección del tratamiento antifúngico en países con alta prevalencia de *C. parapsilosis,* como en Latinoamérica, en Australia y en el sur de Europa (5, 16, 35-38).

En resumen, cada especie de *Candida* tiene unas características microbiológicas propias que le confiere una mayor o menor sensibilidad intrínseca a cada uno de los antifúngicos, lo que puede ayudar tanto en las decisiones terapéuticas a nivel empírico, como en las encaminadas a definir el tratamiento etiológico más apropiado para cada paciente.

Tabla 2. Guía para interpretar la sensibilidad *in vitro* para fluconazol y anidulafungina de los aislados de *Candida* spp. según criterios de CLSI o EUCAST

	CRITERIOS ANTIGUOS de CMI (mg/L)			CRITERIOS VIGENTES de CMI (mg/L)				
	CLSI M27-S3 (2008) (25)			CLSI M27-S4 (2012) (26)			EUCAST (39)[a]	
Fluconazol	**S ≤**	**SDD**	**R ≥**	**S ≤**	**SDD**	**R ≥**	**S ≤**	**R >**
C. albicans	8	16-32	**64**	2	4	**8**	2	**4**
C. glabrata	**8**	16-32	64	-	≤ 32	64	**0,002**	32
C. parapsilosis	8	16-32	**64**	2	4	**8**	2	**4**
C. tropicalis	8	16-32	**64**	2	4	**8**	2	**4**
C. krusei [b]	-	-	-	-	-	-	-	-
Anidulafungina	**S**		**R**	**S**	**I**	**R**	**S**	**R**
C. albicans	2		2	0,25	0,5	1	0,03	0,03
C. glabrata	2		2	0,12	0,25	0,5	0,06	0,06
C. parapsilosis	2		2	2	4	8	0,002	4
C. tropicalis	2		2	0,25	0,5	1	0,06	0,06
C. krusei	2		2	0,25	0,5	1	0,06	0,06

CMI= Concentración mínima inhibitoria; S= sensible; I o SDD= intermedio o sensibilidad dependiente de la dosis; R= resistente

[a] En EUCAST la categoría de sensibilidad intermedia no está descrita en la tabla. Serían los valores comprendidos entre la categoría sensible y resistente

[b] Esta especie es considerada intrínsecamente resistente a fluconazol

1.3. Factores pronósticos de mortalidad. Aspectos clave del manejo de la candidemia

Los factores pronósticos asociados a la mortalidad en la candidemia han sido ampliamente estudiados. Sin embargo, las estrategias terapéuticas son las únicas variables que podrían modificarse para mejorar la supervivencia de estos pacientes. En este sentido, existe suficiente evidencia científica para recomendar el inicio precoz de un tratamiento antifúngico (40-42) y el control del foco de la infección (43), como pilares básicos del manejo de la candidemia. Otra cuestión más discutible sería establecer si el control del supuesto foco de infección conlleva siempre la retirada del

CVC o si el tratamiento de primera elección ha de ser siempre una equinocandina, tal y como recomienda actualmente la guía europea (44) y como ha sugerido el estudio de Andes *et al* (45). De hecho, no hay ningún ensayo clínico aleatorizado que demuestre una clara superioridad de un fármaco antifúngico respecto a otro (equinocandina, fluconazol y anfotericina B liposomal) (46-48). No obstante, ciertos análisis *post-hoc* sugieren una mayor eficacia de las equinocandinas en comparación con fluconazol en los pacientes más graves (49), incluso para el tratamiento de la candidiasis invasiva producida por especies altamente sensibles a los antifúngicos como *C. albicans* (50). En cualquier caso, el uso prolongado e indiscriminado de las equinocandinas y, en general de cualquier antifúngico, está estrechamente relacionado con la potencial aparición de resistencias. Así pues, el proceso final de selección del tratamiento antifúngico ante un episodio de candidemia dependerá no sólo de las características propias del paciente y de su gravedad clínica, sino también de la epidemiología y el patrón de resistencias locales y de los parámetros farmacocinéticos propios del fármaco.

1.4. Candidemia en España. Justificación del estudio.

Las consideraciones mencionadas en los apartados anteriores permiten deducir que la epidemiologia de cada zona geográfica es un conocimiento básico que influye directamente en el manejo médico de la candidemia. Sin embargo, obtener esta información de manera representativa permitiendo detectar auténticas diferencias geográficas, requiere de la realización de estudios poblacionales que recojan todos los episodios de candidemia de un área concreta (4, 51). En España, hasta el momento de

la presente tesis doctoral, los únicos estudios con este diseño habían sido realizados en el área de Barcelona (años 2002-2003) (5) y en la zona de Andalucía (años 2005-2006) (52). La metodología usada había sido similar a la desarrollada previamente en EUA por el Centers for Diseases Control and Prevention (53, 54). Posteriormente, la epidemiologia de la fungemia en España ha sido estudiada fundamentalmente en un estudio multicéntrico de 44 hospitales (estudio FUNGEMYCA) (55), que se centró principalmente en aspectos microbiológicos y que, además, podía incluir sesgos de selección al incorporar únicamente casos procedentes de hospitales terciarios. Es decir, en el momento en que se inició el presente trabajo, a mediados del año 2010, no existían conocimientos de la epidemiología ni de la resistencia a antifúngicos procedentes de un estudio poblacional a nivel nacional y, mucho menos, estimaciones de incidencia o bien información actualizada de las características clínicas y manejo terapéutico de la candidemia en la población española. Además, existía una preocupación creciente por el posible incremento de la resistencia adquirida a antifúngicos (a los azoles y a la posibilidad de aparición de resistencia a las equinocandinas), así como de un posible aumento de cepas intrínsecamente menos sensibles a fluconazol como *C. glabrata,* tal y como se estaba documentando en el norte de Europa, principalmente en Dinamarca (56).

Ante el escenario expuesto, con lagunas de conocimiento a nivel epidemiológico, microbiológico y clínico-terapéutico, en mayo del año 2010 se puso en marcha el primer estudio poblacional en España que proporcionaba información nacional representativa a partir de los datos obtenidos de cinco grandes áreas metropolitanas (Barcelona, Bilbao, Madrid, Sevilla y Valencia). El estudio fue denominado con el

acrónimo CANDIPOP y fue registrado en el ClinicalTrials.gov con el código NCT01236261 (Anexo 1).

Las publicaciones resultantes del análisis de los datos procedentes de la cohorte de pacientes del estudio CANDIPOP serán la base que constituye la presente tesis doctoral:

- El primer artículo, "**Epidemiology and predictive factors for early and late mortality in *Candida* bloodstream infections: a population-based surveillance in Spain"** proporciona una visión global del problema describiendo la incidencia, la epidemiología, el manejo terapéutico y el pronóstico de los pacientes con candidemia en nuestro entorno geográfico

- Los artículos segundo y tercero, "**Impact of therapeutic strategies on the prognosis of candidemia in the intensive care unit** " y "**Epidemiology and outcome of candidaemia in patients with oncological and haematological malignancies: results from a population-based surveillance in Spain**" se centran en dos subpoblaciones de alto riesgo de adquisición de candidemia, como son los enfermos adultos ingresados en las UCIs y los pacientes con una neoplasia oncohematológica de base. El objetivo de ambos trabajos es permitir optimizar las estrategias terapéuticas a grupos poblacionales con características propias diferenciales

- Por último, el cuarto artículo, **"Propensity score analysis of the role of initial antifungal therapy in the outcome of *Candida glabrata* bloodstream infections"** evalúa la eficacia de fluconazol como tratamiento inicial de la candidemia por *C. glabrata*. Su objetivo final es valorar la posibilidad de usar este antifúngico como tratamiento empírico de la candidemia, aún y cuando no se pueda descartar esta especie de *Candida*

2. HIPÓTESIS DE TRABAJO

Todos los artículos que constituyen la tesis doctoral siguen una misma línea de trabajo basada en las siguientes hipótesis:

- La distribución de especies de *Candida* y el patrón de resistencia a los antifúngicos de las cepas de candidemia detectadas en España podría diferir de la observada en otras zonas de Europa. Estas diferencias podrían ser relevantes para la elección de un tratamiento antifúngico adecuado y tener un impacto sobre el pronóstico de la infección
- Conocer los factores que se relacionan con la evolución de los enfermos afectados de una candidemia puede contribuir a mejorar su manejo terapéutico y reducir la elevada mortalidad relacionada con la infección
- Identificar características clínicas, epidemiológicas y de manejo clínico propias de ciertos grupos poblacionales o de ciertas etiologías de candidemia podría permitir elaborar recomendaciones terapéuticas específicas para estos pacientes

3. OBJETIVOS

El objetivo general de la presente tesis doctoral es aportar una información clínico-epidemiológica básica que permita optimizar el manejo terapéutico de la candidemia, adaptándose a la propia epidemiología de España y a las características de grupos poblacionales concretos o de etiologías específicas. Para ello, se hará un especial énfasis en la descripción y el análisis de los factores modificables relacionados con la mortalidad con la intención de intentar mejorar el pronóstico de los pacientes.

Objetivos específicos

- Proporcionar una visión actualizada de la incidencia de candidemia, su epidemiología y frecuencia de resistencia a los antifúngicos en España a partir de datos obtenidos en cinco grandes áreas metropolitanas: Barcelona, Bilbao, Madrid, Sevilla y Valencia
- Determinar la existencia de rasgos característicos de distribución de especies y patrón de sensibilidad a antifúngicos de la candidemia en subgrupos poblacionales concretos: pacientes ingresados en las UCIs y pacientes con neoplasia oncohematológica de base
- Analizar los factores pronósticos que influyen en la mortalidad y, específicamente, el impacto que tienen las principales estrategias terapéuticas recogidas en las guías clínicas (tratamiento antifúngico y retirada del CVC) en la mortalidad precoz y tardía de la infección
- Evaluar si el uso de fluconazol como tratamiento inicial de un episodio de candidemia por *C. glabrata* se asocia con un peor pronóstico (evaluado por criterios de mortalidad y fracaso terapéutico)

- Identificar puntos de mejora en la implementación de las estrategias terapéuticas en la práctica clínica habitual

4. MÉTODOS

4.1. Población, ámbito del estudio y diseño del estudio CANDIPOP

El estudio CANDIPOP se realizó en cinco de las principales áreas metropolitanas de España: Barcelona, Bilbao, Madrid, Sevilla y Valencia entre el 1 mayo del 2010 y el 30 de abril del 2011. Todos los episodios de candidemia detectados en cualquiera de los 29 hospitales participantes (Anexo 2) [área de referencia de 9.498.980 habitantes, aproximadamente un 20% de la población española según datos del censo nacional del año 2011 (57)] fueron registrados para el estudio. Se trataba de un estudio de naturaleza observacional, multicéntrico y prospectivo, diseñado con un enfoque poblacional. El principal objetivo era obtener una información representativa de las zonas geográficas incluidas y potencialmente orientativa de la situación en el resto de España. Así pues, los hospitales participantes constituían los centros relevantes de cada una de las 5 áreas metropolitanas y se consideró despreciable la probabilidad que ocurriera un episodio de candidemia en otros hospitales no incluidos.

4.2. Recogida de la información

Los episodios de candidemia eran detectados en los laboratorios de microbiología de los hospitales participantes y comunicados a un investigador clínico. Este investigador era el responsable de confirmar el caso de candidemia, solicitar el consentimiento informado al paciente y recoger la información demográfica, microbiológica y clínica necesaria en un cuaderno de datos previamente definido (Anexo 3). Todo el proceso era supervisado en cada una de las ciudades por uno o dos investigadores colaboradores (ej: la doctoranda en el área de Barcelona) para verificar la correcta recogida de los datos, asegurar la inclusión de todas las candidemias mediante la

realización de auditorías trimestrales y coordinar el envío de cepas detectadas al CNM en Majadahonda, Madrid para su posterior estudio microbiológico. Todos los pacientes eran seguidos hasta su fallecimiento (si este se producía antes de cumplir 30 días después del diagnóstico), o como mínimo hasta un total de 30 días después del hemocultivo inicial. Cuando el cuaderno de recogida de datos estaba completo, los investigadores colaboradoes de cada ciudad introducían los datos codificados en una aplicación informática creada específicamente para el estudio (página web de acceso: http://www.fundacionseimcgesida.org/estudios/candipop/index.asp).

4.3. Definiciones

El episodio de candidemia se definió como la detección de especies de *Candida* en cualquier hemocultivo extraído por venopunción en un paciente que presentara signos o síntomas de infección. La detección de la misma especie de *Candida* después de 30 días del hemocultivo inicial, o bien, una especie diferente de *Candida* en un mismo paciente durante el seguimiento fueron considerados como episodios distintos.

El diagnóstico de candidemia de catéter se estableció según los criterios de la IDSA (58). Estos criterios incluyen: 1) exudado purulento del punto de inserción del catéter con cultivo positivo para la misma especie de *Candida* obtenida en el hemocultivo; 2) cultivo semi-cuantitativo de la punta del catéter positivo (> 15 UFC); 3) hemocultivos cuantitativos de sangre extraída del catéter que mostraran una relación de 3:1 de UFC respecto a los hemocultivos de muestras obtenidas simultáneamente por venopunción periférica; 4) tiempo diferencial de crecimiento de *Candida* entre el hemocultivo de la extracción periférica y la del catéter con un valor igual o superior a 2 horas.

Considerar el tiempo diferencial como criterio diagnóstico en casos de candidemia puede ser controvertido. Pocos estudios han evaluado su utilidad en las infecciones fúngicas y, por lo tanto, no es un criterio universalmente aceptado (59). Sin embargo, se utiliza rutinariamente en la práctica clínica para diagnosticar las infecciones relacionadas con los catéteres cuando no es posible la retirada del dispositivo intravascular y, además, un estudio reciente ha analizado su aplicabilidad también en casos de candidemia mostrando una sensibilidad y especificidad global aceptables (85% y 82 %, respectivamente) (60).

Los focos secundarios de candidemia precisaron de la confirmación microbiológica del mismo aislado de *Candida* spp. en el presumible origen de la infección, en caso contrario fueron clasificados como candidemias de foco primario o desconocido.

La gravedad clínica del episodio se evaluó en todos los casos el día de la candidemia mediante la determinación de la puntuación de Pitt (61) (que valora los siguientes ítems: temperatura corporal, presión arterial, necesidad de ventilación mecánica, fallo cardíaco y nivel de consciencia) y la presencia de shock séptico o sepsis grave (62, 63). La puntuación del APACHE II se determinó sólo para los enfermos hospitalizados en las UCIs (64).

4.4. Estudios microbiológicos

De cada episodio de candidemia se estudió la cepa o cepas de *Candida* obtenidas en el primer hemocultivo. Las cepas detectadas en los centros participantes fueron guardadas a -70ºC y enviadas al CNM, para confirmar la identificación de especie y realizar las pruebas de sensibilidad antifúngica.

La identificación de especie se realizó mediante métodos moleculares con la secuenciación de las regiones ITS 1 y 2 del ADN ribosomal. Las regiones ITS 1 y 2 fueron directamente amplificadas por PCR desde una suspensión de levaduras y secuenciadas usando cebadores o "*primers*" universales (65, 66). En caso de discordancia entre el resultado microbiológico local y el del CNM, se usó la identificación de especie del CNM.

La sensibilidad antifúngica *in vitro* y la CMI de los aislados de *Candida* fue determinada mediante el método de microdilución propuesto por el European Committee on Antimicrobial Susceptibility Testing-Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST, documentos EDef 7.1 y EDef 7.2) (67, 68) en el CNM y, posteriormente, por CLSI M27-A3 (69) en el Hospital Universitario Gregorio Marañón, Madrid. Los antifúngicos evaluados fueron los siguientes: anfotericina B y flucitosina (Sigma Aldrich, Madrid, España); fluconazol, voriconazol y anidulafungina (Pfizer Pharmaceutical Group, NewYork, NY, EUA); itraconazol (Janssen Pharmaceutical Research and Development, Madrid, España); posaconazol y caspofungina (Merck & Co., Inc., Rahway, NJ, EUA) y micafungina (Astellas Pharma, Inc., Tokyo, Japón).

La interpretación de la sensibilidad a los antifúngicos se ha realizado según los puntos de corte establecidos por el EUCAST, usando las versiones actualizadas al momento de la publicación (versión 6.1 para los Trabajos 1, 2 y 3; versión 8.0 para el Trabajo 4) (39, 70). Para los objetivos de la presente tesis doctoral, las cepas se han clasificado en dos categorías: "sensibles" o "no sensibles" a fluconazol (incluyendo en esta última categoría las cepas con sensibilidad intermedia o bien resistentes). Brevemente, *C. albicans*, *C. tropicalis* y *C. parapsilosis* han sido consideradas como sensibles a

fluconazol si la CMI es ≤2 mg/L, C*. krusei* ha sido considerada intrínsecamente resistente y *C. glabrata* se ha clasificado como intermedia o bien resistente ya que no hay suficiente evidencia para considerar que la población salvaje de esta especie sea sensible a fluconazol. En el caso de *C. guilliemondii* no se han establecido puntos de corte específicos para fluconazol, pero debido a la escasa evidencia que este antifúngico sea una buena opción terapéutica para esta especie, se decidió considerarla de manera similar a *C. glabrata*. Respecto a las equinocandinas, debido a la variación interlaboratorio de la determinación de la CMI para caspofungina, EUCAST no ha establecido puntos de corte para este antifúngico. En estos casos, los aislados sensibles a anidulafungina y micafungina fueron considerados también como sensibles a caspofungina.

En definitiva, estos criterios de sensibilidad *in vitro,* junto con la dosificación del fármaco antifúngico administrado, han sido la base para catalogar como adecuado o inadecuado el tratamiento antifúngico de los episodios de candidemia (Tabla 3).

Tabla 3. Definiciones usadas para clasificar el tratamiento antifúngico en pacientes con candidemia

Tratamiento antifúngico
Tratamiento adecuado[a]
Fluconazol (ajustado según función renal)
≥400 mg/día (6 mg/kg/día) para las cepas sensibles
Equinocandinas[b]
Anidulafungina 200 mg de dosis de carga, seguido de 100 mg/día
Caspofungina 70 mg de dosis de carga, seguido de 50 mg/día
Micafungina 100 mg/día
Anfotericina B liposomal 3 mg/kg/día
Tratamiento inadecuado
Ausencia de tratamiento antifúngico
Dosis subóptimas de fluconazol
<400 mg/día (< 6 mg/kg/día) para cepas sensibles
Cualquier dosis de fluconazol para cepas no sensibles (sensibilidad intermedia o resistente), *C. glabrata* o *C. krusei*

[a] La dosificación considerada como adecuada en la población pediátrica se ha definido según la guía europea del ESCMID (71)
[b] En las especies de *Candida* sin puntos de corte establecidos por el EUCAST, se ha extrapolado la interpretación a partir de la sensibilidad de anidulafungina

4.5. Estimación de incidencias

Se calcularon las incidencias poblacionales, tanto a nivel global como estratificadas por grupos de edad y por zonas geográficas. Dichas incidencias fueron definidas como número de episodios por 100.000 habitantes, usando como denominador el número de personas residentes en las áreas metropolitanas según los datos del censo nacional del año 2011 (57). También se calcularon las incidencias hospitalarias de candidemia expresadas por 1.000 admisiones hospitalarias-año o bien 10.000 estancias hospitalarias-año, usando como denominador la suma de los datos suministrados por cada hospital durante el período de estudio.

4.6. Análisis estadístico

Las variables categóricas se expresaron como número y porcentaje y se compararon con el test de Chi-cuadrado o bien con el test exacto de Fisher, según fuera necesario. Las variables continuas se definieron como mediana y rango intercuartílico y se compararon con la prueba T de Student o con la prueba no paramétrica U de Mann-Whitney, según correspondiera.

Para identificar los factores asociados a la mortalidad se realizó un análisis multivariado mediante un modelo de regresión logística. Sólo se consideró un único episodio de candidemia por paciente (el primero). La hipótesis planteada fue que la mortalidad a largo plazo está altamente condicionada por las características basales del huésped (4, 72, 73), hecho que podría disminuir la estimación del beneficio de las estrategias terapéuticas cuando se evalúan tardíamente a los 30 días. Por este motivo, en todos los trabajos de la tesis, el impacto de las estrategias terapéuticas ha sido valorado de manera precoz (a los 7 días o excepcionalmente a los 14 días en caso de limitación por tamaño muestral). Sin embargo, a diferencia del estudio previo realizado también por nuestro grupo (5), se decidió no excluir de este análisis multivariado a los pacientes fallecidos durante las primeras 48 horas. Si bien es cierto que en este período difícilmente se puede disponer del resultado del hemocultivo positivo e implementar unas estrategias terapéuticas dirigidas, numerosos estudios han demostrado el beneficio de iniciar un tratamiento antifúngico en las primeras horas tras la obtención de la muestra para el hemocultivo (40-42). Por lo tanto, estos pacientes fueron incluidos en todos los análisis iniciales y se valoró *a posteriori* la posibilidad de realizar subanálisis complementarios con su exclusión.

El nivel de significación estadística se estableció con un valor de $p < 0,05$. El análisis estadístico se realizó con el programa SPSS, versión 15.0 (Chicago, IL, EUA), con el programa de software STATA, versión 13.0 (Stata Corp, College Station, TX, EUA), o bien, con el software de R comander, versión 3.0.3 (R Project Statistical Computing, http://www.r-project.org/), según el trabajo y tipo de análisis.

4.7 Aspectos éticos: confidencialidad de datos y consentimiento informado

La recogida de datos sobre los episodios de candidemia se realizó mediante unos cuadernos previamente definidos. La información se introdujo posteriormente en una base de datos informática mediante un sistema de codificación que garantizaba su confidencialidad. De esta manera sólo el investigador de cada hospital podía relacionar un episodio concreto con la identificación personal del paciente y su correspondiente historia clínica. El estudio fue aprobado por el comité ético de los centros participantes siendo necesario el consentimiento informado para que sus datos fueran introducidos en la base de datos y para que las cepas de *Candida* pudieran ser enviadas al CNM para su posterior estudio.

5. RESULTADOS

Este apartado muestra un resumen de los resultados más relevantes de cada uno de los trabajos de investigación que conforman la presente tesis doctoral. Puede encontrarse una copia de los artículos originales en el apartado 11 de esta tesis.

TRABAJO 1:

Epidemiology and predictive factors for early and late mortality in *Candida* bloodstream infections: a population-based surveillance in Spain.

Puig-Asensio M, Padilla B, Garnacho-Montero J, Zaragoza O, Aguado JM, Montejo M, Muñoz P, Ruiz-Camps I, Cuenca-Estrella M, Almirante B on behalf of the CANDIPOP project and GEIH-GEMICOMED (SEIMC) and REIPI.

Clinical Microbiology and Infection. 2014;20(4): O245-54.

Entre mayo de 2010 y abril de 2011 se detectaron 773 episodios de candidemia en 5 áreas metropolitanas de España, lo que proporcionaba una incidencia poblacional estimada de 8,1 episodios/100.000 habitantes/año, y unas incidencias hospitalarias de 0,89 episodios/1.000 admisiones y 1,36 episodios/10.000 estancias hospitalarias. Las incidencias poblacionales más elevadas se observaron en los extremos de edad: en los niños de edad inferior a 1 año (96,4 episodios/100.000 habitantes/año) y en los adultos con edades comprendidas entre los 71 y 80 años (26,5 episodios/100.000 habitantes/año).

De los 773 episodios detectados, 21 no pudieron ser incluidos en el análisis epidemiológico ni de factores de riesgo asociado a la mortalidad porque los pacientes no dieron su consentimiento informado para participar en el estudio. Así pues,

finalmente se analizaron 752 episodios de candidemia en 729 pacientes (23 pacientes presentaron más de un episodio) y 766 cepas de *Candida* (14 episodios con 2 especies diferentes de *Candida* en el hemocultivo inicial).

La distribución de especies fue la siguiente: *C. albicans* (348, 45,4%), *C. parapsilosis* (191, 24,9 %), *C. glabrata* (103, 13,4%), *C. tropicalis* (59, 7,7%), *C. krusei* (15, 2%) y otras especies de *Candida* (50, 6,5%). La sensibilidad a fluconazol fue del 79% (excluyendo las cepas de sensibilidad intermedia o resistente). Sin embargo, *C. albicans* y *C. parapsilosis* raramente fueron clasificadas como no sensibles a fluconazol, con una CMI ≥ 4 mg/L (1% y 5%, respectivamente). Asimismo, la presencia de resistencia a las equinocandinas fue casi anecdótica [4 cepas: 1 *C. albicans* (0,3%), 1 *C. glabrata* (1%) y 2 C. *tropicalis* (3,4%)] y una única cepa de *C. kefyr* (0,1%) fue resistente a la anfotericina B liposomal.

En los episodios en que se pudo demostrar el origen de la infección, la candidemia relacionada con el catéter fue el foco más frecuente (258 de 752 episodios, 34,3%). La candidemia secundaria a otros focos fue poco frecuente: urológico (40, 5,3%) y abdominal (25, 3,3%). Globalmente, los azoles fueron los fármacos más frecuentemente usados como tratamiento antifúngico de inicio (46,1%), seguido de las equinocandinas (27,1%). El tratamiento antifúngico adecuado se empezó en las primeras 48 horas en el 57,1% de los episodios. Por otra parte, el CVC fue retirado precozmente (≤48 horas) en el 47,8% de los pacientes con dicho factor de riesgo. Se realizaron hemocultivos de control en el 67,5% de los episodios-pacientes que sobrevivieron más de 2 días.

La mortalidad acumulada tras presentar un primer episodio de candidemia fue del 12,8% a los 7 días y del 30,6% a los 30 días. El análisis multivariado de los factores asociados a la mortalidad en la población adulta e infantil (edad superior a 1 año), demostró que la implementación precoz (≤ 48h tras la extracción del hemocultivo positivo inicial) de las estrategias terapéuticas recomendadas en las guías clínicas, es decir, un tratamiento antifúngico adecuado (OR 0,51, IC95% 0,27-0,95) y la retirada del CVC (OR 0,43, IC95% 0,21-0,87) estaban asociados con una menor mortalidad a los 7 días. Sin embargo, la mortalidad tardía (8-30 días) estaba asociada con factores propios del paciente (edad creciente e inmunosupresión), signos indirectos de disfunción orgánica (intubación orotraqueal o terapia renal sustitutiva), una presentación clínica grave de la infección (sepsis grave o shock séptico) y un foco primario de la candidemia.

En resumen, la candidemia continúa siendo una infección grave asociada con una mortalidad considerable. Sin embargo, nuestros resultados confirman que el mal pronóstico de la infección está altamente condicionado por la fragilidad clínica basal de los pacientes. Debemos centrar los esfuerzos en actuar sobre los factores modificables, especialmente mejorando la adherencia a las guías clínicas: instaurar un tratamiento antifúngico adecuado de manera precoz y valorar retirar el CVC como posible foco de la candidemia.

TRABAJO 2:

Impact of therapeutic strategies on the prognosis of candidemia in the intensive care unit

Puig-Asensio M, Pemán J, Zaragoza R, Garnacho-Montero J, Martín-Mazuelos E, Cuenca-Estrella M, Almirante B, on the behalf of CANDIPOP Project, GEIH-GEMICOMED (SEIMC) and REIPI.

Critical Care Medicine. 2014; 42 (6): 1423 - 1432.

Este subanálisis del estudio poblacional CANDIPOP está formado por una cohorte de 168 episodios de candidemia detectados en pacientes adultos (≥ de 18 años de edad) que estaban hospitalizados en las UCIs.

Las especies de *Candida* que se detectaron con más frecuencia fueron: *C. albicans* (90, 52%), *C. parapsilosis* (41, 23,7%), *C. glabrata* (22, 12,7%) y *C. tropicalis* (10, 5,8%). Un 79,2% de las cepas (137 de 173) fueron sensibles a fluconazol, mientras que la resistencia a equinocandinas fue infrecuente [1/90 (1,1%) de *C. albicans* y 1/22 (4,5%) de *C. glabrata*].

Se pudo establecer el origen de la candidemia en 75 de los 168 episodios (44,6 %), siendo la infección relacionada con el CVC (58 episodios, 34,5%) el foco más frecuente.

La mayoría de los de los episodios de candidemia (159, 94,6%) fueron tratados con antifúngicos (equinocandinas en el 50%, seguido en frecuencia por fluconazol en el 35,7%). Sin embargo, de los 162 episodios observados en pacientes portadores de un CVC como factor de riesgo de adquisición de la candidemia, únicamente en 77 (47,5%) se realizó una retirada precoz (primeras 48 horas) del dispositivo intravascular. Esta

cifra aún fue inferior en los episodios de pacientes que necesitaron técnicas de depuración extrarenal, o bien, los que presentaron sepsis grave o shock séptico en el debut de la candidemia (30,8% vs 52,8%, p=0,016 y 37,5% vs 62,1%, p=0,002, respectivamente).

La mortalidad acumulada a los 7 y 30 días fue del 16,5% y 47%, respectivamente. En el análisis multivariado, después de ajustar el modelo por el índice de gravedad APACHE II, la implementación de una estrategia combinada precoz (≤48horas) de tratamiento antifúngico adecuado y retirada del CVC se asoció con una menor mortalidad a los 7 días (OR 0,27, IC95% 0,08-0,91). Los factores asociados con una mortalidad tardía (8-30 días) dependieron de condiciones propias del huésped y de su estado basal: la edad (OR 1,04, IC95% 1,01-1,07), intubación orotraqueal (OR 7,24, IC95% 2,24-23,40), terapia renal sustitutiva (OR 6,12, IC95% 2,24-16,73) y un foco primario de la candidemia (OR 2,51, IC95% 1,06-5,95).

Así pues, estos resultados confirman un alto porcentaje de especies diferentes a *C. albicans* (48%) en las UCIs de España. Sin embargo, esta epidemiología se caracteriza por un claro predominio de *C. parapsilosis,* que constituye la segunda especie causante de candidemia. A pesar de que la mortalidad asociada a la candidemia adquirida en las UCIs es elevada, las comorbilidades basales de los pacientes juegan un papel importante en su pronóstico. La estrategia combinada de inicio precoz de un tratamiento antifúngico adecuado junto con la retirada del CVC pueden contribuir a disminuir la mortalidad precoz en este tipo de población.

Comentarios relacionados con el trabajo 2

Como aspectos complementarios de esta memoria, se añaden en el apartado Anexo 4 una Editorial y una Carta al Editor que se publicaron conjuntamente con el presente trabajo y que profundizan en su contenido:

- En la Editorial titulada "**Management of candidemia: getting better, but not there yet**" Leroy *et al* revisan algunos de los resultados clave de nuestro estudio. Asimismo, realizan una reflexión sobre ciertas limitaciones en la interpretación de los mismos así como de la problemática actual y potenciales puntos de mejora del manejo clínico de la candidemia en las UCIs.

- En la Carta al Editor titulada "**What is the impact of catheter removal on the outcome of non-catheter-related candidemia?"** se cuestiona el beneficio de la retirada del CVC en todos los casos de candidemia. En la respuesta **"The authors reply"** se muestra la dificultad en analizar esta estrategia terapéutica en los estudios observacionales y se razona la aplicabilidad de los resultados del trabajo original en la práctica clínica diaria.

TRABAJO 3:

Epidemiology and outcome of candidaemia in patients with oncological and haematological malignancies: Results from a population-based surveillance in Spain

Puig-Asensio M, Ruiz-Camps I, Fernández-Ruiz M, Aguado JM, Muñoz P, Valerio M, Delgado-Iribarren A, Merino P, Bereciartua E, Fortún J, Cuenca-Estrella M, Almirante B; on the behalf of CANDIPOP Project, GEIH-GEMICOMED (SEIMC), and REIPI.

Clinical Microbiology and Infection. 2015 May;21(5):491.e1-491.e10

De los 729 pacientes que sufrieron un episodio de candidemia en el estudio CANDIPOP, 238 (32,6%) ocurrieron en pacientes adultos (≥ 16 años) con una neoplasia: 195 (82%) con un tumor de órgano sólido y 43 (18%) con neoplasia hematológica.

En comparación con los pacientes con un tumor de órgano sólido, los pacientes con neoplasias hematológicas habían recibido con más frecuencia quimioterapia (53,5% vs 17,4%, p<0,001) o corticosteroides (41,9% vs 21%, p<0,001) y estaban neutropénicos en el momento de la candidemia (44,2% vs 1,5%, p<0,001). Globalmente, la candidemia de brecha (después de 3 o más días de recibir un fármaco antifúngico) sucedió en un 14,8% de los pacientes con neoplasia. La presencia de una infección diseminada se detectó en 18 (7,6%) de los pacientes (14% en neoplasia hematológica vs. 6,2% en pacientes con un tumor de órgano sólido, p=0,106).

Las especies de *Candida* más frecuentemente detectadas fueron las diferentes a *C. albicans,* tanto en el grupo de pacientes con un tumor de órgano sólido como en los hematológicos (55,6 % vs 71%, respectivamente, p=0,056). Así pues, después de *C. albicans*, *C. tropicalis* fue la segunda especie predominante (22,2%) en los pacientes

hematológicos, mientras *C. parapsilosis* (20,7%) y *C. glabrata* (19,2%) lo fueron en los pacientes con un tumor de órgano sólido. En total, un 27,6% de las cepas detectadas se clasificaron como no sensibles a fluconazol (resistentes o con sensibilidad intermedia), dos cepas con la mutación del gen FKS (1 *C. tropicalis* y 1 *C. glabrata*) fueron resistentes a las equinocandinas y 1 cepa de *C. kefyr* fue resistente a la anfotericina B liposomal.

Respecto a las estrategias terapéuticas, el uso de fluconazol como tratamiento antifúngico de primera elección y la retirada del CVC de manera precoz (≤ 48 horas) fue más frecuente en los pacientes con un tumor de órgano sólido en comparación con los hematológicos (60% vs 27,9%, p< 0,001 y 51% vs 29,7%, p=0,020, respectivamente). La mortalidad acumulada a los 7 y 30 días tras el hemocultivo inicial fue del 12,2% y 31,5 %, respectivamente, y no difirió entre ambos grupos de pacientes con neoplasia. El análisis multivariado del impacto de las estrategias terapéuticas en la mortalidad se realizó en la cohorte de pacientes con CVC. Después del ajuste del modelo por potenciales factores de confusión, se evidenció que el inicio precoz de un tratamiento antifúngico adecuado junto con la retirada del CVC se asoció a una disminución de la mortalidad tanto a los 7 días (OR 0,05, IC95% 0,01-0,42) como a los 30 días (OR 0,27, IC95% 0,16-0,46). Dicha asociación permaneció estable (OR 0,34, IC95% 0,20-0,59) al repetir el modelo multivariado excluyendo los fallecidos en las primeras 48 horas, es decir, al excluir los pacientes en los que podría no haberse implementado ningún tratamiento dirigido por desconocimiento del resultado de los hemocultivos, disminuyendo así un sesgo a favor de las estrategias terapéuticas.

En conclusión, los pacientes con neoplasia, en especial los pacientes con una neoplasia hematológica, tienen un claro predominio de especies diferentes a *C. albicans* como especies causantes de candidemia. En la cohorte, un 27,6% de las cepas fueron no sensibles a fluconazol y un 14,8% de los pacientes tuvieron fungemia de brecha, lo que indica la necesidad de estudios epidemiológicos periódicos para actualizar el patrón de resistencias y así poder adecuar el tratamiento antifúngico empírico. En el paciente con neoplasia no neutropénico las recomendaciones terapéuticas tendrían que ser similares a las de la población general, ya que la retirada del CVC junto con el tratamiento antifúngico precoz están asociadas con una menor mortalidad.

TRABAJO 4:

Propensity score analysis of the role of initial antifungal therapy in the outcome of *Candida glabrata* bloodstream infections

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Antimicrobial Agents and Chemotherapy. 2016 (en prensa).

Del total de 752 episodios de candidemia detectados en el estudio poblacional CANDIPOP, 94 correspondieron a un primer episodio de infección monomicrobiana por *C. glabrata* en pacientes adultos (≥ 16 años). De esta cohorte, se seleccionaron para el análisis los 69 pacientes que recibieron un tratamiento antifúngico inicial con fluconazol (n=34), o bien, con una equinocandina y/o anfotericina B liposomal (n= 35), durante un mínimo de 2 días consecutivos.

En el grupo de fluconazol, la mayoría de pacientes recibieron una dosis subóptima del fármaco (< 800 mg/día) según las recomendaciones actuales de tratamiento de la candidemia por *C. glabrata* [200 mg/día en 1 caso (2,9%) y 400 mg/día en 28 (82,4%)].

En comparación con los pacientes del grupo de fluconazol, los pacientes incluidos en el grupo de equinocandina/anfotericina B liposomal tuvieron unas características que sugerían una mayor gravedad de la presentación clínica de la candidemia o del estado basal: inmunosupresión (25,7% vs 5,9%, p=0,024), ingreso en la UCI (37,1% vs 17,6%, p=0,070), presencia de CVC (82,9% vs 64,7%, p=0,086). No hubo diferencias respecto a la demora en el inicio del tratamiento antifúngico (mediana 2 días en ambos grupos) o

respecto al porcentaje de pacientes en los que se controló el foco de origen de la candidemia tras haber iniciado el tratamiento antifúngico (77,1 vs 82,4%, p=0,591). Sin embargo, los pacientes en el grupo de fluconazol tuvieron con más frecuencia (55,9% vs 28,6%) y de manera más precoz (mediana de 3 vs 7 días) un cambio de tratamiento antifúngico a otro régimen.

En conjunto, la mortalidad a los 14 días y el fracaso terapéutico al tratamiento antifúngico (variable compuesta de mortalidad a los 14 días y/o candidemia persistente tras 48 horas de haber iniciado el antifúngico) fueron del 13% (9/69) y 34,8% (24/69), respectivamente. En el análisis multivariado, después de ajustar los grupos de tratamiento por las características basales de los pacientes mediante el método del *propensity-score*, el uso de fluconazol no se relacionó con un peor pronóstico de los pacientes: OR ajustada de mortalidad a 14 días de 1,16 (IC95% 0,22-6,17) y OR ajustada de fracaso terapéutico de 0,83 (IC95% 0,27-2,61).

En conclusión, el uso de fluconazol como tratamiento inicial de una candidemia por *C. glabrata* no se asocia con una peor evolución clínica de los pacientes. Estos resultados podrían respaldar la utilidad clínica del fluconazol como opción de tratamiento empírico en los pacientes estables sin exposición previa a los azoles. Sin embargo, en caso de no poder descartar una candidemia por *C. glabrata*, ha de tenerse la precaución de optimizar las dosis de fluconazol a 800 mg/día.

6. DISCUSIÓN

Una vez expuestos los resultados de los trabajos, procederemos a hacer una discusión conjunta siguiendo el orden de los objetivos de la tesis.

6.1. Proporcionar una visión actualizada de la incidencia de candidemia, su epidemiología y frecuencia de resistencia a los antifúngicos en España a partir de datos obtenidos en cinco grandes áreas metropolitanas: Barcelona, Bilbao, Madrid, Sevilla y Valencia

6.1.1. Incidencia

El estudio poblacional sobre candidemia en España (estudio CANDIPOP) es el primer trabajo que proporciona una estimación de la incidencia de esta infección en España, con un resultado entre el año 2010-2011 de 8,1 casos/100.000 habitantes/año y una alta variabilidad entre las áreas metropolitanas incluidas (desde 5,9 casos/100.000 habitantes/año en Sevilla hasta 11,5 casos/100.000 habitantes/año en Valencia) (74).

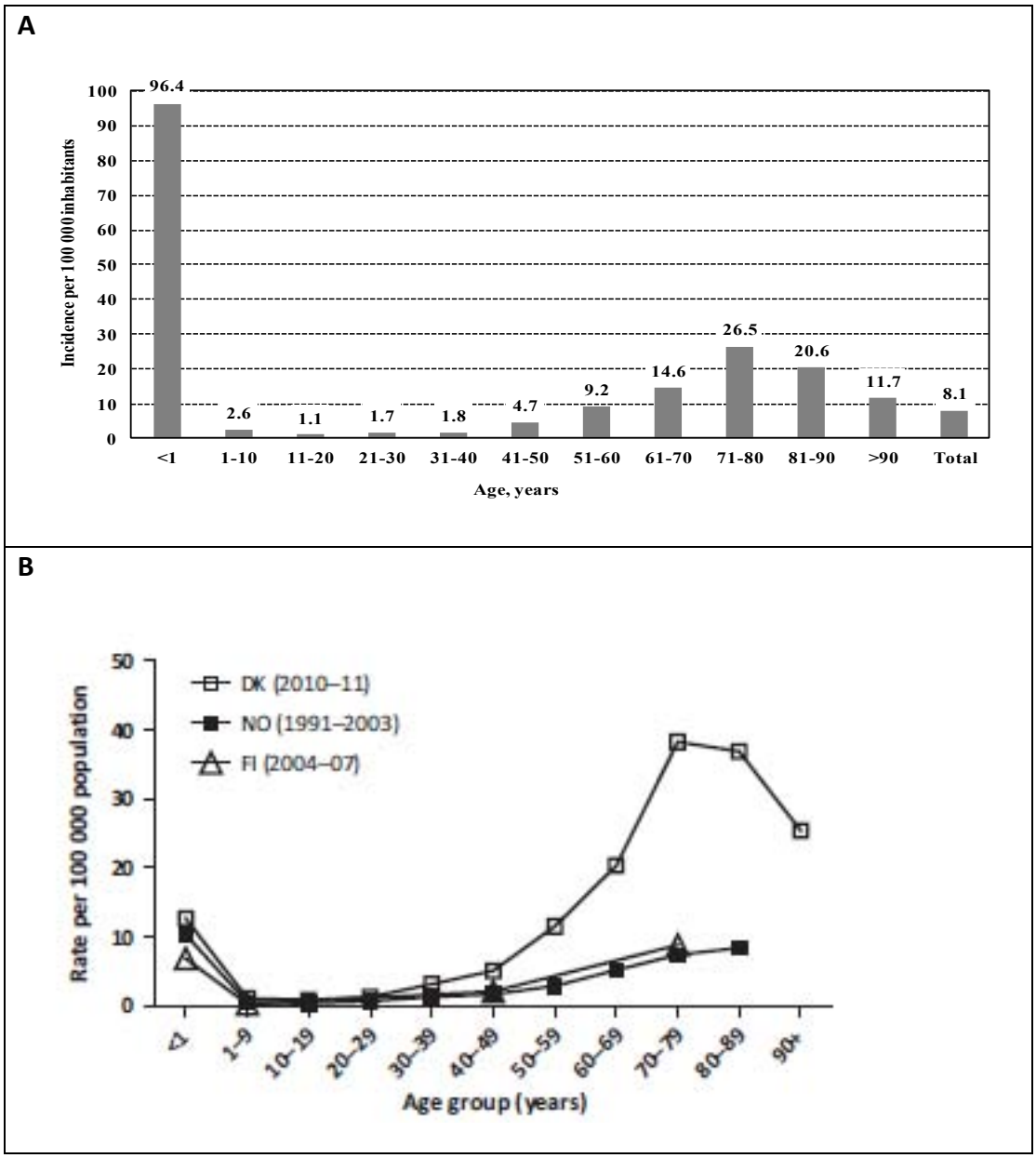
Si se comparan estas cifras con estudios poblacionales contemporáneos realizados en otros países, la incidencia en nuestro medio es similar a la descrita en Dinamarca (8,8 a 10,1/100.000 habitantes/año en los años 2010 y 2011, respectivamente) (8), pero contrasta con la baja incidencia descrita en otros países del norte de Europa (media aproximada de 3-5,7/100.000 habitantes/año) (6, 7, 11-13) o las altas tasas detectadas en EUA (13,3 casos/100.000 habitantes/año en Atlanta y 26,2 casos/100.000 habitantes/año en Baltimore en los años 2008-2010) (14). En conjunto, es posible que todas estas oscilaciones de incidencia estén influidas por aspectos demográficos de la población y por el número de sujetos en riesgo de desarrollar una candidemia. De

hecho, este es el argumento que se ha usado para explicar el aumento progresivo de la incidencia de la candidemia en ciertos estudios longitudinales (1, 8). Sin embargo, también es factible que otros factores como las medidas de control de la infección nosocomial y la prevención de la infección relacionada con los CVCs (9), la frecuencia de extracción de hemocultivos (7), o bien, la sensibilidad del sistema de cultivo utilizado (13, 75) jueguen un papel en las variaciones temporales y regionales de las estimaciones de incidencia.

Otro aspecto importante para discutir es cómo se distribuye la incidencia de la candidemia en la población. La mayoría de estudios coinciden en mostrar una tasa de incidencia más elevada de los pacientes situados en los extremos de edad. Sin embargo, uno de los hallazgos más relevantes del estudio CANDIPOP fue encontrar un pico excepcionalmente elevado en la población de edad inferior a 1 año (96,4 casos/100.000 habitantes/año), cifra marcadamente superior a la observada en otros estudios de Europa (6,9 a 20,7 casos/100.000 habitantes/año) (6-8, 13), en el estudio previo de Barcelona (38,8 casos/100.000 habitantes/año) (5) e incluso en EUA (16,6 casos/100.000 habitantes/año a 46,2 casos/habitantes/año) (9, 14). De hecho, este resultado difiere de la tendencia actual a considerar la población mayor de 60 años como el grupo más frecuentemente afecto de una candidemia (8, 13) y contrasta con el descenso de la contribución infantil en la tasa global de incidencia de candidemia observado en EUA (14) (Figura 1). Es posible que la incidencia en nuestra población infantil esté ligeramente sobrevalorada porque todas las zonas geográficas incluían hospitales pediátricos de referencia. Sin embargo, la alta prevalencia de *C. parapsilosis* en este grupo también podría sugerir la existencia de brotes nosocomiales y la

necesidad de mejorar los programas de control de la infección nosocomial en las UCIs neonatales (76, 77).

Figura 1. Distribución de la incidencia poblacional de candidemia por grupos de edad en el estudio CANDIPOP (A) y comparado con estudios de otros países del norte de Europa (B)



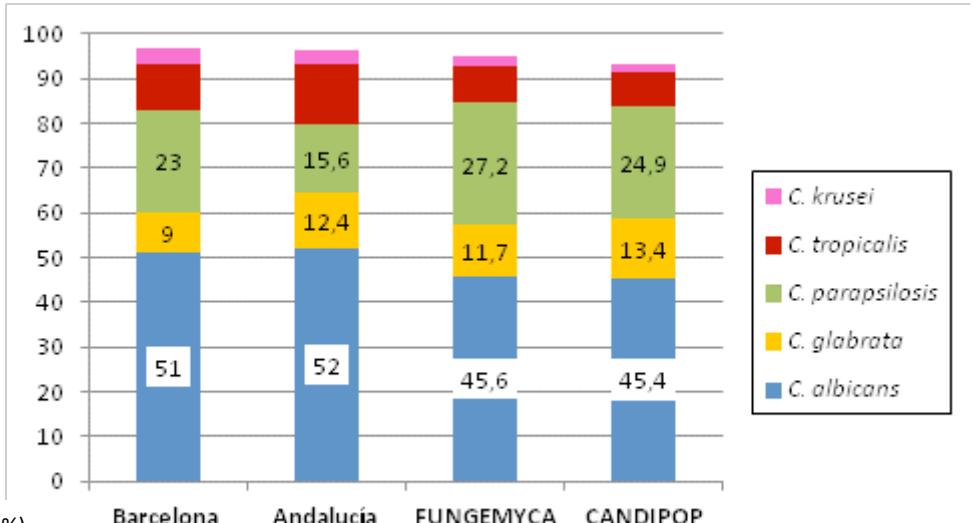
DK: Dinamarca; NO: Noruega; FI: Finlandia. Reproducido de Arendrup, M.C. (8)

6.1.2. Epidemiología y distribución por especies de *Candida*

Respecto a la distribución por especies de *Candida,* la epidemiología descrita en el estudio CANDIPOP no muestra grandes diferencias respecto a la observada en otros estudios españoles realizados durante la última década (5, 52, 55). Nuestros resultados demuestran que actualmente menos de la mitad de los episodios son causados por *C. albicans* y que, además, *C. parapsilosis* se consolida como la segunda especie más frecuentemente detectada en España (5, 55) (Figura 2). Esta epidemiología, concordante con la observada en Latinoamérica, en Australia y en el sur de Europa (16, 35-38) podría ser un rasgo diferencial respecto al norte de Europa, EUA y Canadá, donde *C. parapsilosis* juega un papel menos importante y es sustituida por *C. glabrata* que pasa a ser la especie diferente a *C. albicans* predominante (6-13, 30, 31). Sin embargo, no se puede descartar que exista, también en nuestro medio, una tendencia hacia un aumento del porcentaje de *C. glabrata*. Según resultados del estudio CANDIPOP, *C. glabrata* causa actualmente un 13,4% de los episodios, mientras que a inicios de la década de los años 2000 representaba aproximadamente un 9% de los aislados (5, 78). Aunque es difícil extraer conclusiones definitivas de estudios que abarcan diseños y áreas geográficas tan dispares, esta información puede ser clínicamente relevante. Tal y como ya se ha comentado, *C. glabrata* presenta una sensibilidad intrínsecamente disminuida a los azoles mientras que *C. parapsilosis* presenta una sensibilidad disminuida a las equinocandinas. Por lo tanto, el constante cambio en la distribución etiológica de las especies de *Candida* causantes de candidemia hace necesario realizar de manera periódica estudios de vigilancia epidemiológica. El conocimiento actualizado de la epidemiología local, tanto a nivel

poblacional, como en cada institución sanitaria o en cada zona geográfica, ofrece una ayuda considerable en el momento de aplicar las guías de práctica clínica y contribuye a elegir el tratamiento antifúngico empírico en los pacientes con candidemia.

Figura 2. Distribución de las cinco principales especies de *Candida* y el porcentaje global de cepas no sensibles a fluconazol según diferentes estudios españoles (5, 52, 55, 74)



Nº cepas estudiadas	n=351	n=216	n=1348	n=766
Diseño del estudio (nº hospitales participantes)	poblacional 1 zona geográfica (14)	poblacional 1 zona geográfica (16)	hospitales terciarios de España (44)	poblacional 5 áreas metropolitanas (29)
Criterios para interpretar la sensibilidad a los antifúngicos	**CLSI (criterios antiguos)**			**EUCAST**
% cepas no sensibles a fluconazol (resistentes)	6,8 % (1,7 %)	11 % (3,8 %)	7,7 % (2,9 %)	**21 %** (7 %)

6.1.3. Frecuencia de resistencia a los antifúngicos

Además de la distribución de especies previamente mencionada, conocer el patrón de resistencia a los antifúngicos es también indispensable para optimizar las estrategias terapéuticas. Los resultados del CANDIPOP muestran que la proporción de cepas sensibles a fluconazol es notablemente inferior a la determinada en estudios españoles realizados previamente. En el estudio poblacional de Barcelona en el año 2002-2003 (5) y en el FUNGEMYCA (55) más del 90% de las cepas de *Candida* fueron clasificadas como sensibles a fuconazol, cifra que habría disminuido a menos del 80% según los datos actuales. Aunque este hecho podría causar una cierta preocupación sobre el incremento de resistencia adquirida a este antifúngico, los resultados han de ser valorados con precaución. En primer lugar, el proyecto CANDIPOP es el primer estudio español que utiliza los nuevos puntos de corte de sensibilidad propuestos por el EUCAST (70) que, tal y como se ha comentado anteriormente, son considerablemente inferiores a los criterios de CLSI antiguos usados en estudios previos (25). Además, el porcentaje global de cepas estrictamente resistentes a fluconazol (CMI > 4 mg/L para *C. albicans*, C. *parapsilosis* y C. *tropicalis* o CMI > 32 mg/L para C. *glabrata*) fue aproximadamente del 7% (79). Este hecho sugiere que la disminución de la sensibilidad está altamente condicionada por un incremento de las cepas con sensibilidad intermedia y, muy posiblemente, por la consideración actual de *C. glabrata* como especie no sensible a fluconazol. En segundo lugar, en el presente estudio se detectó un porcentaje de resistencia a fluconazol inesperadamente elevado para *C. tropicalis* (22%), resultado que además contrasta con los estudios de sensibilidad repetidos *a posteriori* por la metodología CLSI (1,7%) (79). Una posible explicación para estas

discrepancias podría ser el fuerte efecto *trailing* (crecimiento residual) que tienen *in vitro* las cepas de *C. tropicalis* y que dificulta la determinación de los valores de la CMI, especialmente por la metodología EUCAST.

Por todo ello, se podría concluir que si bien la proporción en España de cepas no sensibles a fluconazol ha aumentado respecto a publicaciones previas, la resistencia propiamente dicha es baja (7%) e infrecuente para las especies más habituales en nuestro medio (*C. albicans* y C*. parapsilosis*). Además, también la resistencia actual a las equinocandinas es anecdótica. No obstante, este podría ser un problema emergente en los casos de exposición prolongada a estos antifúngicos y, particularmente, para las infecciones causadas por *C. glabrata* (80). De hecho, algunos centros terciarios de Estados Unidos ya han documentado que un 12%-18% de sus cepas de *C. glabrata* son resistentes a equinocandinas o tienen la mutación en el gen *FKS* que las predispone al fallo terapéutico (32, 81). Por este motivo, las recientemente publicadas guías americanas de la IDSA recomiendan, aunque con poca evidencia científica, comprobar la sensibilidad a las equinocandinas en los pacientes que han recibido tratamiento previo con estos antifúngicos (28). Aún así, ha de tenerse en consideración que en Europa la tasa global de resistencia de *C. glabrata* a las equinocandinas es aún baja (inferior al 4%) (80), muy posiblemente condicionado por diferencias en el uso de los antifúngicos en comparación con EUA. Por ello, es importante optimizar el uso y la duración del tratamiento o la profilaxis de estos fármacos. Con esta estrategia es posible que se pueda limitar el teórico incremento de resistencia a las equinocandinas y reservarlas para los casos en que realmente sea necesario.

En resumen, el estudio CANDIPOP es el primer estudio que ofrece una perspectiva actualizada de la incidencia, epidemiología y patrón de resistencias a los antifúngicos de la candidemia en España, permitiendo asentar las bases para optimizar y adaptar las estrategias terapéuticas a nuestro propio entorno geográfico. Es cierto que los resultados no son extrapolables fuera de las áreas de estudio y que, además, pueden existir variaciones entre territorios, hospitales y a lo largo del tiempo. Sin embargo, en conjunto, es posible que el predominio de *C. parapsilosis* añadido a una baja tasa global de resistencias a fluconazol pueda determinar que este antifúngico sea aún de utilidad en un gran número de casos de candidemia.

6.2. Determinar la existencia de rasgos característicos de distribución de especies y patrón de sensibilidad a antifúngicos de la candidemia en subgrupos poblacionales concretos: pacientes ingresados en las UCIs y pacientes con neoplasia oncohematológica de base

Los pacientes ingresados en las UCIs y los enfermos con una neoplasia son dos grupos especialmente vulnerables para desarrollar una candidemia, debido a que suelen tener varios de los factores de riesgo para adquirir la infección. De hecho, nuestros resultados confirman que aún actualmente un tercio de las candidemias se producen en pacientes de la UCI y que un porcentaje similar de pacientes tienen una neoplasia de base, especialmente un tumor de órgano sólido. Sin embargo, hasta la presente tesis doctoral, no existían estudios previos españoles que hubieran estudiado de manera exhaustiva la distribución de especies de *Candida* y el patrón de resistencias a

los antifúngicos en estas dos poblaciones concretas de pacientes. Así pues, existía un déficit de conocimiento local para poder adecuar el tratamiento antifúngico empírico según nuestra propia epidemiología.

6.2.1 Pacientes ingresados en las UCIs

En el análisis de la cohorte de pacientes adultos ingresados en las UCIs, la distribución de especies de *Candida* fue similar a la descrita en la totalidad de la población del proyecto CANDIPOP. A pesar de que casi la mitad de los casos fueron producidos por especies diferentes a *C. albicans*, entre ellas fue *C. parapsilosis* la especie más frecuentemente detectada (23,7%). Este hallazgo puede estar relacionado con diversas causas. En primer lugar, *C.parapsilosis* se relaciona frecuentemente con factores de riesgo específicos como la nutrición parenteral y los dispositivos intravasculares, muy habituales en los pacientes de las UCIs. Además, el incremento de las equinocandinas como tratamientos antifúngicos de primera elección (20, 82), o bien, la posible existencia de brotes nosocomiales (83) también podrían haber contribuido al predominio de esta especie. En cualquier caso, estudios previos ya han demostrado que la epidemiología en los pacientes de las UCIs no suele diferir significativamente de la de pacientes hospitalizados en plantas convencionales (55, 84). Es decir, que la distribución de especies de *Candida* de las UCIs acostumbra a ser paralela a la epidemiología local de la zona, tal y como también sugieren nuestros resultados. Por todo ello, aunque existe una preocupación el aumento de especies diferentes a *C. albicans* (85), la frecuencia de *C. parapsilosis* en las UCIs españolas debería ser

considerado como un elemento de relativo buen pronóstico debido a su menor virulencia y a la eficacia demostrada de las pautas de tratamiento habituales (76, 86).

Respecto al patrón de resistencia a antifúngicos, tal y como era de esperar por la distribución de especies descrita y por el hecho de que la profilaxis universal en los pacientes de las UCIs no está indicada (28, 44), la sensibilidad a fluconazol fue de nuevo similar a la cohorte global del CANDIPOP (79%). Los motivos de este porcentaje relativamente bajo de sensibilidad ya han sido expuestos anteriormente en esta tesis. Sin embargo, este patrón de sensibilidad adquiere una especial relevancia en las UCIs, donde un error en la selección del tratamiento inicial se podría relacionar con una peor evolución clínica debido a la extrema fragilidad de estos pacientes. En este sentido, se ha sugerido que la infradosificación de fluconazol en las cepas menos sensibles se podría asociar a un peor pronóstico (87). Por el contrario, las equinocandinas no precisan ajuste de dosis por insuficiencia renal, poseen escasas interacciones farmacológicas y además podrían ser más eficaces que fluconazol en este subgrupo de pacientes especialmente graves y vulnerables (49). Por todo ello, no es de extrañar que en el 50% de nuestros episodios de las UCIs el tratamiento inicial fuera una equinocandina, cifra que podría incluso ir en aumento según alguna serie reciente (88). Sin embargo, también ha de tenerse en consideración que el tratamiento empírico con equinocandinas en un contexto epidemiológico como el de nuestro entorno, con una alta prevalencia de *C. parapsilosis,* podría ser cuestionable. Afortunadamente, y a pesar de la menor sensibilidad *in vitro* de esta especie, existe cierta evidencia que el uso empírico de equinocandinas no tiene un impacto negativo en el pronóstico de los pacientes con una infección por *C. parapsilosis* (89). Así pues, aunque el tratamiento

óptimo de una candidemia por *C. parapsilosis* sea posiblemente el uso de fluconazol, la decisión de seleccionar inicialmente una equinocandina en los casos de inestabilidad hemodinámica no tendría que suponer un problema en la práctica clínica diaria.

6.2.2. Pacientes con enfermedad neoplásica

Los pacientes con enfermedad neoplásica, en especial los afectos de procesos hematológicos, constituyen un grupo poblacional con características claramente diferenciales. Durante años, el uso de profilaxis antifúngica con azoles en pacientes hematológicos de alto riesgo ha condicionado una diminución de la incidencia de candidemia y de la mortalidad asociada (90, 91). Sin embargo, esta estrategia muy posiblemente ha influido en la etiología de la infección fúngica y en el porcentaje de resistencias a fluconazol (20, 34, 92). En este sentido, también nuestros resultados coinciden en mostrar que en los pacientes hematológicos es habitual que *C. albicans* sea una causa poco frecuente de candidemia (29,8%). Además, C. *tropicalis* constituye una de las especies diferentes de *C. albicans* más frecuentemente aislada (93), posiblemente debido a su mayor capacidad invasiva desde el tracto gastrointestinal (86, 94). Por el contrario, los pacientes con tumores de órgano sólido tienen una distribución de especies donde *C. albicans* es aún una especie común (44,4% de los episodios en comparación con un 45,4% en la cohorte global del CANDIPOP), mientras que *C. parapsilosis* y *C. glabrata* son las especies diferentes de *C. albicans* más frecuentes. Es decir, que su epidemiología se asemeja más a la de la población general no neoplásica, con la única diferencia de un ligero incremento en el porcentaje de *C. glabrata* (hasta un 19,2%). La relevancia de *C. glabrata* en pacientes con tumor de

órgano sólido ya había sido previamente descrita en otros estudios (95) y podría ser debida a la edad avanzada de estos pacientes (96), la mayor prevalencia de cirugía abdominal (97), la exposición previa a azoles (20) o bien otros factores no bien conocidos (98).

En relación al patrón de sensibilidad antifúngica, el porcentaje de cepas no sensibles a fluconazol en la población de pacientes hematológicos fue elevada (casi un 30%) y similar a la de la población con tumores de órgano sólido, aunque por motivos distintos. La exposición previa a antifúngicos debe de haber jugado un papel importante en el patrón de sensibilidad y resistencia adquirida a fluconazol en el paciente hematológico. Por el contrario, en el paciente con un tumor de órgano sólido es posible que la distribución de especies y la proporción de *C. glabrata* hayan condicionado más estos resultados. Sin embargo, la valoración de la adquisición de resistencias a fluconazol es compleja. En conjunto, múltiples factores se han visto involucrados y es difícil saber la contribución de cada uno de ellos a nuestros resultados: la dosis y la duración de la exposición previa a antifúngicos (99), el uso de ciertos antibióticos (100) o la exposición a ciertos quimioterápicos (101), entre otros. Asimismo, aunque en nuestra cohorte la resistencia a equinocandinas fue infrecuente, ha de tenerse cierta precaución en usar empíricamente este antifúngico en pacientes que han recibido previamente este fármaco de manera prolongada (bien como profilaxis o como tratamiento). La posible aparición de resistencias, como ya se ha comentado previamente, podría ser un problema en auge a medida que el uso de equinocandinas se generalice (102).

En conclusión, los pacientes hematológicos constituyen un grupo claramente diferencial respecto al resto de la población con candidemia. Su propia epidemiología posiblemente esté relacionada con la implementación de estrategias concretas de profilaxis antifúngica y la posibilidad de adquirir la candidemia por mecanismo de translocación intestinal. De hecho, la baja frecuencia de *C. albicans* y la baja sensibilidad a fluconazol condicionan que el tratamiento empírico aconsejable en estos pacientes sea frecuentemente una equinocandina o, como alternativa, incluso la anfotericina B liposomal (28, 90). En cambio, los pacientes con un tumor de órgano sólido podrían ser tratados de una manera similar a la población general no neutropénica, teniendo en consideración que la proporción esperada de *C. glabrata* puede ser de casi el 20%. En todo este grupo de pacientes, la gravedad basal de enfermo, las potenciales interacciones farmacológicas y el perfil de seguridad son factores adicionales a la epidemiología que adquieren una especial relevancia para decidir la selección del tratamiento antifúngico empírico.

6.3. Analizar los factores pronósticos que influyen en la mortalidad y, específicamente, el impacto que tienen las principales estrategias terapéuticas recogidas en las guías clínicas (tratamiento antifúngico y retirada del CVC) en la mortalidad precoz y tardía

En nuestro estudio, la mortalidad global a los 30 días de los pacientes con candidemia fue del 30,6% (74), incrementándose notablemente en los pacientes más graves, como los ingresados en las UCIs (47%) (103). Aunque estas cifras de mortalidad coinciden

con las descritas en la mayoría de estudios contemporáneos (6, 7, 16, 18, 104, 105), es un punto especialmente preocupante para la comunidad científica. Por este motivo se ha destinado un apartado específico de la presente tesis doctoral para valorar el impacto que tienen los factores potencialmente modificables sobre la mortalidad y profundizar en el conocimiento de las causas asociadas al mal pronóstico de la candidemia.

Según nuestros resultados, la implementación precoz (≤ 48 horas) de las principales estrategias terapéuticas recomendadas en las guías clínicas (tratamiento antifúngico y retirada del CVC) se asocian con una disminución de la mortalidad precoz (0-7 días) en todos los grupos poblacionales analizados (población general, pacientes ingresados en las UCIs y enfermos no neutropénicos con neoplasia oncohematológica). En contraposición, se ha podido comprobar que el mal pronóstico a largo plazo de la candidemia, y consecuentemente su elevada mortalidad en el período tardío, están relacionados en gran medida con la propia fragilidad del paciente y con la gravedad clínica en la presentación clínica de la infección.

La relación entre la precocidad de iniciar un tratamiento antifúngico y una mejor supervivencia ha sido demostrada en varios estudios (40, 41). Sin embargo, recomendar la retirada del CVC en todos los casos de candidemia puede ser motivo de controversia, ya que no existe información concluyente sobre este tema procedente de ensayos clínicos aleatorizados. La evidencia científica disponible procede de estudios observacionales, algunos de los cuales no han mostrado ningún beneficio con la retirada sistemática precoz del CVC (106, 107). Sin embargo, el CVC es una causa frecuente de adquisición exógena de candidemia y su retirada parece lógica en

ausencia de otros focos alternativos. De hecho, en aproximadamente un tercio de casos de la cohorte global del CANDIPOP (74) se demostró que el origen de la infección era el CVC, cifra que podría ser incluso superior si se considera la posibilidad de episodios que se habrían clasificado en el grupo de candidemias primarias por ausencia de confirmación microbiológica. Posiblemente por ello, en la serie CANDIPOP se ha podido comprobar el beneficio de la retirada del CVC como estrategia terapéutica. No obstante, en pacientes portadores de CVC de tipo permanente y con dificultad para su retirada precoz, esta estrategia ha de ser individualizada en función de su situación clínica en el momento del diagnóstico de la candidemia. En este sentido, se ha de tener en consideración que el beneficio clínico de retirar el CVC en pacientes con otros focos secundarios de candidemia podría ser dudoso (108).

Asimismo, nuestros resultados no pueden generalizarse a toda la población neutropénica, en la que el origen de la candidemia podría ser gastrointestinal. La representación de esta población en la cohorte estudiada, igual que en estudios previos (45, 107, 108), es escasa. Sin embargo, en general, podría concluirse que incluso en el paciente con patología hematológica, el CVC ha de estudiarse siempre como potencial foco de infección, o bien, como una causa de candidemia persistente. De hecho, en nuestra cohorte un 37,2% de los pacientes con neoplasia hematológica presentaron, según los criterios de la IDSA, una candidemia relacionada con el catéter (109). Este porcentaje es difícil de contrastar con otras series de pacientes hematológicos debido a la disparidad de criterios usados para el diagnóstico de candidemia de catéter (110, 111). Sin embargo, hay que recordar que el CVC es un potencial factor de riesgo de adquisición de candidemia también en esta población y,

sobre todo, en el caso que la candidemia esté causada por *C. parapsilosis* (112, 113). Actualmente la guía europea (44) aconseja usar fármacos con actividad frente a las biopelículas (equinocandinas o anfotericina B liposomal) cuando la retirada del CVC no es posible. Esta recomendación se basa en la capacidad que tienen *in vitro* las especies de *Candida* de formar biopelículas en los dispositivos intravasculares (114, 115) y en los resultados del estudio clínico de Nucci *et al* en el que no se pudo demostrar el beneficio de la retirada de CVC en pacientes tratados con estos antifúngicos (107). De todas maneras, esta última recomendación ha de interpretarse con cautela ya que el control del posible foco de infección es un elemento básico para conseguir el éxito terapéutico y mejorar la supervivencia, especialmente en los pacientes inestables con shock séptico (43, 116). Nuestros trabajos sugieren que precisamente una estrategia combinada, en las primeras 48horas, de un tratamiento antifúngico adecuado y la retirada del CVC sería la más eficaz para disminuir la mortalidad precoz relacionada con la infección, particularmente en los pacientes más vulnerables como los ingresados en las UCIs (OR 0,27, IC95% 0,08–0,91), o bien, en aquellos con alteraciones de la inmunidad como los afectos de neoplasias oncohematológicas no neutropénicos (OR 0,05, IC95% 0,01–0,42). Por todo ello, uno de los puntos más novedosos que aportan nuestros resultados es que muestran por primera vez una aproximación del beneficio de las estrategias terapéuticas en un período precoz de la enfermedad (primeros 7 días) y, además, en grupos poblacionales concretos con un alto riesgo de mortalidad.

Para finalizar con este apartado de la discusión se han de mencionar ciertas limitaciones en la interpretación de los resultados. En primer lugar, habría sido

interesante evaluar el impacto de la retirada del CVC en función del foco de origen de la candidemia, para así determinar qué subpoblaciones de pacientes pueden beneficiarse más de esta estrategia. Lamentablemente el escaso número de eventos finales (pacientes fallecidos) en la cohorte de los pacientes de las UCIs y oncohematológicos limitó el poder estadístico para realizar análisis estratificados por foco de origen de la candidemia. No obstante, la retirada del CVC se plantea frecuentemente en la práctica clínica antes de tener la confirmación microbiológica. Además los diferentes análisis multivariados se ajustaron por variables de confusión y otras que se relacionan directa o indirectamente con el foco de infección (ej. *C. parapsilosis*, foco primario o foco abdominal). Asimismo, el beneficio de la retirada del CVC permaneció estable, tanto en la cohorte global como en los pacientes oncohematológicos, después de excluir aquellos que fallecieron en las primeras 48 horas. Este análisis refuerza la recomendación de retirar el CVC al disminuir un potencial sesgo a favor de las estrategias terapéuticas. Por todo ello, consideramos que nuestros resultados son una buena aproximación al beneficio de la retirada del CVC en la práctica clínica rutinaria y son útiles en la toma de decisiones médicas.

En conclusión, la mortalidad tardía de la candidemia se relaciona estrechamente con la fragilidad y la gravedad basal de los pacientes afectados. Este hecho podría explicar que la mortalidad de esta infección se mantenga preocupantemente elevada y que su pronóstico sea peor en los pacientes más debilitados como los ingresados en las UCIs. La implementación precoz de un tratamiento antifúngico adecuado y la retirada del CVC deberían ser las bases para mejorar el pronóstico en un período precoz de la

infección (primeros 7 días). Por lo tanto, los esfuerzos se han de centrar en controlar los factores modificables de mortalidad y en mejorar la adherencia a las guías clínicas.

6.4. Evaluar si el uso de fluconazol como tratamiento inicial de un episodio de candidemia por *C. glabrata* se asocia con un peor pronóstico (mortalidad y fracaso terapéutico)

El hallazgo más importante de este subanálisis del estudio CANDIPOP es que el uso inicial del fluconazol no se asoció con un incremento de la mortalidad o del fracaso terapéutico en los casos de candidemia por *C. glabrata*. Este resultado tiene una implicación directa para la práctica clínica habitual. Actualmente el fluconazol es aún un fármaco muy usado en pacientes hemodinámicamente estables ingresados en plantas de hospitalización convencional, también en nuestro medio (27, 74). Sin embargo, la menor sensibilidad *in vitro* de *C. glabrata* a los azoles junto con el peor pronóstico de los pacientes en los que se demora el inicio de un tratamiento "adecuado", ha creado una cierta preocupación sobre la posibilidad de usar este antifúngico como opción de tratamiento empírico de la candidemia. De hecho, esta circunstancia podría haber favorecido, en parte, que la guía europea haya generalizado el uso de las equinocandinas como tratamiento empírico de cualquier episodio de candidemia (44). Según nuestros resultados, fluconazol podría continuar siendo una opción válida para aquellos pacientes menos graves, sin exposición previa a los azoles, incluso cuando no se puede descartar la presencia de *C. glabrata*.

No existe ningún estudio aleatorizado que haya evaluado específicamente la eficacia de fluconazol en la candidemia por *C. glabrata*. La única información de la que se dispone procede dos estudios que no han podido demostrar un impacto negativo del uso de fluconazol en la mortalidad de la candidemia por *C. glabrata* (45, 117). En el primero de ellos, el estudio observacional de Eschenauer *et al*, se observó que el tratamiento inicial con fluconazol durante un mínimo de 5 días, en comparación con una equinocandina, no era un factor predictor de mortalidad a los 28 días (117). Sin embargo, su diseño retrospectivo y la falta de ajuste del análisis según la precocidad de inicio de tratamiento constituían limitaciones metodológicas importantes para la interpretación de los resultados. Por otra parte, el análisis de varios ensayos clínicos aleatorizados realizado por Andes *et al* (45), basándose en el subgrupo de 104 episodios de candidemia ocasionados por *C. glabrata*, tampoco encontró ninguna influencia de la selección del tratamiento antifúngico inicial en la mortalidad a 30 días. Por tanto, las publicaciones previas coinciden con nuestros resultados en la incapacidad para demostrar una asociación entre el uso inicial de fluconazol y un incremento de la mortalidad de la candidemia causada por *C. glabrata*. Aún y así, los estudios anteriormente citados difieren del presente trabajo en mostrar un mayor éxito terapéutico (mejoría clínica y erradicación microbiológica) si se utilizan las equinocandinas. En este sentido, es posible que la menor frecuencia de extracción de hemocultivos en nuestro grupo de fluconazol pueda haber infraestimado la frecuencia de candidemia persistente y, por tanto, haber limitado la posibilidad de detectar auténticas diferencias en las tasas de erradicación microbiológica entre los grupos de tratamiento. Sin embargo, el impacto de la candidemia persistente en el pronóstico de

los pacientes es dudoso (118) y los hemocultivos de control suelen repetirse con más insistencia en los pacientes con mala evolución clínica.

Otro aspecto sin resolver es saber cuál es las dosis óptima del fluconazol para el tratamiento de las candidemias causadas por *C. glabrata*. Actualmente, se considera que han de usarse dosis plenas de 800 mg/día (12 mg/kg/día) para tratar esta especie de *Candida,* debido a sus CMI intrínsecamente más elevadas (28). Según este criterio, tanto en nuestro estudio como en el de Eschenauer *et al*, la mayoría de pacientes recibieron una dosis subóptima de fluconazol posiblemente porque la prescripción antifúngica se realizó antes de tener la confirmación de especie. Por ello, podría deducirse que fluconazol mantiene cierta actividad frente a *C. glabrata,* aún y cuando la dosificación no sea óptima. Habría sido interesante poder estudiar en profundidad el impacto de la dosis de fluconazol y la relación entre dosis/CMI en el pronóstico de nuestros pacientes, pero el tamaño muestral limitó realizar análisis más detallados. Sin embargo, parece prudente recomendar una dosis de 800 mg/día de fluconazol en el tratamiento empírico de la candidemia, especialmente cuando no pueda descartarse una infección por *C. glabrata*.

Finalmente, no se ha de olvidar que no sólo la sensibilidad *in vitro* de las especies de *Candida* juega un papel en la selección del tratamiento antifúngico. Las propias características farmacocinéticas del fármaco son aspectos de gran relevancia. Así pues, el fluconazol podría ser de elección en casos de infección urinaria, o bien, de afectación ocular, ya que las equinocandinas no alcanzan buenos niveles ni en la orina ni en el humor vítreo o acuoso (119, 120).

El presente trabajo tiene una serie de limitaciones que han de mencionase para poder valorar los resultados adecuadamente. La primera de ellas es el posible sesgo de indicación en la prescripción del tratamiento antifúngico. Al no ser un estudio aleatorizado, los pacientes en peores condiciones clínicas recibieron más frecuentemente un régimen de tratamiento basado en una equinocandina y/o anfotericina B liposomal. Por ello, se utilizó la metodología del *propensity score* y el análisis multivariado se ajustó por factores de confusión asociados con la elección de tratamiento, la respuesta clínica y la mortalidad. Por otra parte, parece improbable que en un futuro se realice un ensayo clínico aleatorizado para valorar la eficacia de fluconazol en el tratamiento de la candidemia por *C. glabrata*, por lo que hemos de basarnos en la evidencia proporcionada por estudios observacionales para su aplicación en la práctica clínica. En segundo lugar, los pacientes en el grupo de fluconazol sufrieron más frecuentemente y con más precocidad un cambio de tratamiento a otro régimen antifúngico. Aunque los motivos por los que se produjeron estas modificaciones no fueron recogidos, esta estrategia puede reflejar la influencia de las guías clínicas actuales que favorecen el uso de las equinocandinas en el tratamiento de la candidemia por *C. glabrata.* Este hecho no debería de implicar, necesariamente, un cambio de tratamiento por una mala evolución clínica. Por último, el tamaño muestral podría haber limitado el poder estadístico para determinar auténticas diferencias entre ambos grupos de tratamiento. Por lo tanto, nuestros resultados han de ser interpretados con precaución, especialmente en las decisiones terapéuticas que puedan afectar a los pacientes más graves.

Como conclusión, el tratamiento inicial con fluconazol no se asocia con un peor pronóstico (mortalidad y fracaso clínico) en los pacientes con una candidemia por *C. glabrata*. Estos resultados sugieren que en contextos epidemiológicos con una baja tasa de resistencias a fluconazol, este antifúngico aún podría ser una opción razonable como tratamiento empírico de la candidemia antes de la identificación de la especie de *Candida*. Se necesitan más estudios para acabar de comprender el papel del fluconazol en el tratamiento empírico y dirigido de la candidemia por *C. glabrata*.

6.5. Identificar puntos de mejora en la implementación de las estrategias terapéuticas en la práctica clínica habitual

Las estrategias terapéuticas y de seguimiento clínico recomendadas en las guías clínicas de candidemia se aplican de una manera irregular en la práctica clínica habitual. En conjunto, en el estudio CANDIPOP el tratamiento antifúngico adecuado se administró precozmente en el 57,1% de los episodios, el CVC se retiró en las primeras 48 horas en el 47,8% y la obtención de hemocultivos de control se realizó en un 67,5% de los pacientes que sobrevivieron más de 2 días. Por lo tanto, estas cifras representan un claro punto de mejora en el manejo clínico de los pacientes con candidemia y, al mismo tiempo, reflejan las dificultades que los profesionales médicos tienen en la práctica clínica rutinaria para seguir las recomendaciones de las guías clínicas.

Según nuestros resultados, en ausencia de terapia antifúngica en el momento del hemocultivo, el inicio de un tratamiento específico para el episodio de candidemia se demoró una mediana de 2 días en todos los grupos evaluados (cohorte global,

pacientes ingresados en las UCIs y enfermos oncohematológicos). Esto indica que la causa más habitual por la cual el paciente no suele recibir un tratamiento antifúngico adecuado de manera precoz es, posiblemente, la falta de sospecha clínica junto con el retraso en el diagnóstico microbiológico. Los síntomas de la candidemia son inespecíficos y podrían confundirse con cualquier otro proceso infeccioso bacteriano subyacente. Además, los hemocultivos requieren una mediana de 2-3 días de incubación hasta la positividad (17), lo cual demora aún más el inicio de tratamiento antifúngico dirigido y la retirada del CVC como posible foco de origen. En una situación crítica donde los accesos vasculares son imprescindibles, o en pacientes con accesos vasculares permanentes, puede ser complicado plantear la retirada del CVC sin una confirmación microbiológica de una candidemia. Por este motivo es posible que en nuestro estudio la retirada precoz del CVC fuera inferior en los pacientes adultos con sepsis grave o shock séptico (37,5%), o bien, en los pacientes de la UCI que requerían técnicas de depuración extrarenal (30,8%).

En el momento actual, la única herramienta de la que disponen los profesionales médicos para discernir aquellos pacientes que se beneficiarán de un tratamiento antifúngico empírico o anticipado, es el conocimiento de los factores de riesgo para desarrollar una candidemia. Además, en los pacientes de las UCIs se han establecido varios índices clínicos (ej. “Candida Score”, “índice Ostrosky-Zeichner”) que se utilizan para determinar la probabilidad de candidiasis invasiva. Sin embargo su sensibilidad oscila entre un 50-80% y su valor predictivo positivo es bajo (aproximadamente del 10-14%), conllevando así un riesgo no despreciable de sobretratamiento (121). En consecuencia, uno de los principales retos para el futuro sería intentar desarrollar

pruebas que nos permitan un diagnóstico precoz de la infección fúngica, con una buena sensibilidad y especificidad. Numerosos estudios han investigado el uso de marcadores biológicos como el β-D-glucano o la PCR de *Candida* con el fin de reducir el retraso en el diagnóstico, pero lo cierto es que ninguno de ellos se utiliza de manera rutinaria. El β-D-glucano es poco específico (puede detectarse en otras infecciones fúngicas como *Aspergillus* o *Pneumocystis jirovecii*) y tiene el riesgo de falsos positivos. Por el contrario, la PCR es una técnica no estandarizada, frecuentemente influida por las variaciones técnicas y metodológicas de cada laboratorio, lo que dificulta la generalización de resultados y su implementación de manera universal (34). En la actualidad, la única técnica en desarrollo que parece ofrecer resultados esperanzadores es el panel T2*Candida*. Esta técnica automatizada es posible que permita detectar e identificar la especie de *Candida* directamente de una muestra de sangre en 3-5 horas, algo hasta ahora impensable (122, 123). Sin embargo, su elevado coste económico dificulta la posibilidad de uso en la mayoría de centros.

Otro aspecto que hay que mejorar en el manejo de la candidemia es la realización de hemocultivos de control a las 48-72 horas de iniciar un tratamiento antifúngico activo. Este procedimiento permite comprobar la erradicación de la candidemia y detectar pacientes con alto riesgo de tener una diseminación a distancia de la infección. Es fácil interpretar que la correcta evolución clínica es suficiente para el manejo del paciente con candidemia, sin embargo la extracción de hemocultivos de control es un elemento fundamental que contribuye a optimizar la duración del tratamiento antifúngico y mejorar el pronóstico de los pacientes (124).

En conclusión, el tratamiento antifúngico precoz se asocia con un mejor pronóstico, pero existen series limitaciones para realizar un diagnóstico temprano de la infección que condicionan una demora en el inicio de la terapia antifúngica. Asimismo, nuestros resultados demuestran la dificultad pero también la necesidad de mejorar el cumplimiento de las estrategias terapéuticas recomendadas en las guías clínicas. Si pretendemos disminuir la mortalidad de la candidemia es necesario optimizar el manejo médico considerando todos y cada uno de los aspectos que influyen en el pronóstico: tratamiento antifúngico adecuado, retirada precoz del CVC y realización de hemocultivos de control en el seguimiento evolutivo.

7. APLICABILIDAD PRÁCTICA DE LA TESIS Y LÍNEAS DE FUTURO

Los datos presentados en esta tesis ponen de manifiesto que aún existen cuestiones por resolver en el manejo de la candidemia. Es evidente que la introducción de las equinocandinas a principios de la década de los años 2000 supuso una revolución terapéutica porque proporcionaban una opción de tratamiento efectiva, segura y con escasos efectos secundarios. De hecho, actualmente son el tratamiento empírico de elección recomendado en las guías de las principales sociedades científicas (28, 93). Sin embargo, a lo largo de la tesis se ha intentado mostrar que utilizar un fármaco fungicida no es la única solución al problema de la elevada mortalidad de la candidemia. En realidad, así lo demuestran los estudios que siguen mostrando cifras de mortalidad preocupantemente elevadas a pesar de un incremento en el uso de equinocandinas (88). Mejorar el pronóstico de los pacientes implica optimizar las estrategias terapéuticas de las que se dispone y, en especial, tener una visión integral del paciente afecto considerando aspectos propios del huésped, del foco de infección y de la eficacia del antifúngico según la especie de *Candida* y la epidemiología local. Por todo ello, en este último apartado de la discusión consideramos importante hacer una reflexión final sobre algunas preguntas difíciles de responder y que deberían ser focos de atención para futuros trabajos.

7.1. ¿Cuál es el papel de fluconazol en el momento actual?

Según la vigente guía europea el tratamiento empírico de la candidemia en un paciente adulto no neutropénico ha de ser siempre una equinocandina con una evidencia científica grado A-I, dejando en una posición muy limitada el posible uso de fluconazol (44). Es cierto que las equinocandinas ofrecen una serie ventajas clínicas

respecto a fluconazol: amplio espectro farmacológico, escasas interacciones farmacológicas, no precisan ajuste de dosis en caso insuficiencia renal y poseen una clara actividad frente a las biopelículas de *Candida*. Además tienen una potente actividad fungicida que conlleva una mayor rapidez en el tiempo de erradicación microbiológica (50). Sin embargo, es discutible que la recomendación de usar siempre una equinocandina se base en estas apreciaciones. El único estudio aleatorizado de no inferioridad que ha comparado anidulafungina con fluconazol sugiere que la anidulafungina tendría una tendencia a ofrecer una respuesta global (clínica y microbiológica) superior (47), pero de estos resultados no se puede inferir que ello se relacione con una mejor supervivencia en todos los casos de candidemia, ni que la respuesta sea igual para todas las especies de *Candida*. De hecho, es posible que el subgrupo de pacientes más graves sean los que más se beneficien de un tratamiento inicial con este fármaco (49) y que, en contraposición, los pacientes con una candidemia por *C. parapsilosis* no obtengan un beneficio clínico significativo de su uso.

Por otra parte, aunque existe el estudio de Andes *et al* (45) que apoya el uso generalizado de las equinocandinas como tratamiento de elección en todos los casos de candidemia, la validez de estos resultados es cuestionable debido a la presencia de críticas metodológicas importantes (125, 126). Por todos estos motivos, la guía americana ha sido más conservadora y aún contempla la posibilidad de utilizar empíricamente fluconazol en pacientes hemodinámicamente estables sin exposición previa a los azoles (28). Nuestro grupo coincide plenamente con esta afirmación, considerando que el fluconazol no debería ser excluido como opción inicial del tratamiento empírico de la candidemia, sino que su uso debería individualizarse según

el paciente, el contexto clínico, la posibilidad de realizar un control del foco de infección y la epidemiología local. Extender la indicación de tratamiento con equinocandinas a todos los pacientes con candidemia podría conllevar un riesgo potencial de aparición de resistencias (32, 81) y un aumento innecesario del coste sanitario. Es evidente que en países donde existe una elevada frecuencia de cepas menos sensibles a fluconazol, como *C. glabrata*, la posibilidad de tratamiento inicial con fluconazol podría ser tema de controversia. Sin embargo, tal y como se ha expuesto previamente en esta tesis, la epidemiología de nuestro entorno geográfico tiene la peculiaridad de incluir un alto porcentaje de *C. parapsilosis* y, en consecuencia, una alta prevalencia de cepas que suelen ser sensibles a fluconazol (*C. albicans* y *C. parapsilosis* constituyen el 70% de los episodios). Además, siempre es posible ayudarse de otras herramientas adicionales, como aplicar una escala pronóstica para estimar la probabilidad que el paciente tenga una candidemia por una cepa no sensible a fluconazol (127). Por todo ello, consideramos que actualmente fluconazol es aún una opción razonable como tratamiento empírico de la candidemia, en pacientes seleccionados y hemodinámicamente estables. Asimismo también parece una opción segura y eficaz en el proceso de secuenciación a vía oral, tras comprobar la sensibilidad *in vitro* de la especie de *Candida* (29). Sin mencionar, que hay situaciones clínicas como las infecciones del tracto urinario o bien cuando hay afectación ocular, donde fluconazol es preferible frente a una equinocandina (44).

7.2. ¿Es posible realizar un manejo conservador del CVC con la técnica del "*antifungal-lock*"?

Como ya se ha comentado, cuando el catéter es el posible foco de origen de la candidemia, lo indicado es retirarlo con la intención de mejorar la supervivencia de los pacientes. Sin embargo, en ciertas ocasiones la dificultad de accesos venosos, las alteraciones de la coagulación, la necesidad de hemodiálisis o la presencia de inestabilidad hemodinámica pueden retrasar o dificultar la retirada del dispositivo intravascular, especialmente si no es fácilmente extraíble. En estos casos excepcionales, la instilación local de un antifúngico o un agente antiséptico en el dispositivo intravascular, junto con el tratamiento sistémico, podría ser una estrategia interesante a considerar para conseguir la esterilización del catéter. Es cierto que existe poca evidencia científica de la eficacia de la técnica de "*antifungal-lock*". La experiencia se limita a la descripción de casos clínicos aislados especialmente en la población pediátrica y usando soluciones con anfotericina B liposomal (128). De hecho, varios estudios *in vitro* han demostrado que tanto las equinocandinas como la anfotericina B liposomal tienen una excelente actividad frente a las biopelículas (129-131). Por ello, estos son los antifúngicos de elección para esta modalidad de tratamiento cuando la retirada del CVC no es posible (44). Además, aunque la teórica menor sensibilidad de *C. parapsilosis* a las equinocandinas podría suponer un problema, este efecto no ha sido generalmente reproducido en los estudios de actividad sobre biopelículas por lo que el uso de una equinocandina no debería suponer una limitación en la práctica clínica habitual (128). Como alternativa, otra substancia con actividad frente a biopelículas que también se ha investigado para el

sellado de catéter es el etanol. Los resultados para este agente también son prometedores mostrando éxito en la mayoría de pacientes en los que se ha usado (132-134). Sin embargo, el uso de etanol puede ir asociado a efectos adversos transitorios (mareo, enrojecimiento facial y náuseas) (135) que se pueden evitar aspirando la solución de sellado del catéter antes de su uso (128). Además, las soluciones de etanol deben de usarse con precaución ya que pueden comprometer la integridad de determinados tipos de catéters intravasculares, como por ejemplo los de poliuretano (136).

Respecto a la duración del tratamiento y el intervalo de administración local del antifúngico, no existe un protocolo estandarizado. Lo habitual, en los casos descritos en la literatura, es mantener el sellado durante 14 días desde la negativización de los cultivos (128).

En resumen, el tratamiento conservador de la candidemia cuyo origen es el CVC sólo debe considerarse en situaciones excepcionales. Cuando el CVC no puede retirarse, el uso de un tratamiento antifúngico sistémico y uno local con la técnica de "*antifungal-lock*" podrían ser una estrategia de tratamiento alternativa. En estos casos, el fármaco de elección suele ser una equinocandina, o bien, anfotericina B liposomal, pero se necesitan más estudios para esclarecer la eficacia clínica de esta estrategia.

8. CONCLUSIONES

8.1. Proporcionar una visión actualizada de la incidencia de candidemia, su epidemiología y frecuencia de resistencia a los antifúngicos en España

- La incidencia estimada de candidemia en España fue de 8,1 episodios por 100.000 habitantes/año, 0,89 episodios por 1.000 admisiones y 1,36 episodios por 10.000 estancias hospitalarias
- Las tasas de incidencia más elevada se observaron en la población de edad inferior a 1 año (96,4 episodios/100.000 habitantes/año) y en los adultos con edades comprendidas entre los 71 y 80 años (26,5 episodios/100.000 habitantes/año)
- Un 54,6% de los episodios fueron causados por especies diferentes a *C. albicans,* siendo entre ellas *C. parapsilosis* la especie más frecuente
- Este patrón de distribución de especies de *Candida* constituye un rasgo epidemiológico diferencial respecto a otras zonas del norte de Europa, Estados Unidos y Canadá
- La sensibilidad global a fluconazol en los aislados de *Candida* fue del 79% y la resistencia a equinocandinas fue anecdóctica
- Únicamente se detectó un aislado de *C. kefyr* resistente a la anfotericina B liposomal que pertenecía a la cohorte de pacientes con neoplasia oncohematológica

8.2. Determinar la existencia de rasgos característicos de distribución de especies y patrón de sensibilidad a antifúngicos de la candidemia en subgrupos poblacionales concretos

- Los pacientes ingresados en las UCIs presentaron unos rasgos epidemiológicos y un patrón de resistencia a los antifúngicos similares a la población general
- Los pacientes con un tumor de órgano sólido presentaron una proporción de *C. glabrata* superior a la población general y la tasa de cepas no sensibles a fluconazol fue del 27,3%
- Los pacientes con una neoplasia hematológica presentaron una baja frecuencia de *C. albicans* y un predominio de *C. tropicalis* como segunda especie en frecuencia. La tasa de cepas no sensibles a fluconazol fue elevada (28,9%)
- En la población oncohematológica la resistencia a equinocandinas fue inhabitual (1 único aislado de *C. tropicalis* y otro de *C. glabrata*)

8.3. Analizar los factores pronósticos que influyen en la mortalidad y, específicamente, el impacto que tienen las principales estrategias terapéuticas recogidas en las guías clínicas (tratamiento antifúngico y retirada del CVC) en la mortalidad precoz y tardía de la infección

- La mortalidad acumulada en la serie global de pacientes con candidemia fue del 12,8% a los 7 días y del 30,6% a los 30 días

- La implementación precoz (en las primeras 48 horas) de un tratamiento antifúngico adecuado y la retirada del CVC se asociaron con una disminución de la mortalidad precoz de la candidemia (0-7 días) en todos los grupos poblacionales evaluados
- La mortalidad tardía (8-30 días) de los pacientes con candidemia se relaciona principalmente con la fragilidad y la gravedad de base de los pacientes afectados

8.4. Evaluar si el uso de fluconazol como tratamiento inicial de un episodio de candidemia por *C. glabrata* se asocia con un peor pronóstico (mortalidad y fracaso terapéutico)

- El uso de fluconazol como tratamiento inicial de un episodio de candidemia por *C. glabrata* no se asocia con un peor pronóstico de los pacientes

8.5. Identificar puntos de mejora en la implementación de las estrategias terapéuticas en la práctica clínica habitual

- La retirada precoz (en las primeras 48 horas) del CVC y la obtención de hemocultivos de control son dos aspectos de manejo clínico potencialmente mejorables
- En la serie global de pacientes con candidemia, el inicio de un fármaco antifúngico se demoró una mediana de 2 días. El desarrollo e implementación de nuevas herramientas de diagnóstico rápido podría mejorar la administración temprana de un fármaco antifúngico

9. OTROS TRABAJOS COLABORATIVOS EN LA MISMA LÍNEA DE INVESTIGACIÓN

9.1. Trabajos colaborativos publicados en revistas indexadas

- **Initial use of echinocandins does not negatively influence outcome in *Candida parapsilosis* bloodstream infection: a propensity score analysis**

  Fernández-Ruiz M, Aguado JM, Almirante B, Lora-Pablos D, Padilla B, Puig-Asensio M, Montejo M, García-Rodríguez J, Pemán J, Ruiz Pérez de Pipaón M, Cuenca-Estrella M; CANDIPOP Project; GEIH-GEMICOMED (SEIMC); REIPI.

  Clin Infect Dis. 2014 May;58(10):1413-21.

- **A simple prediction score for estimating the risk of candidaemia caused by fluconazole non-susceptible strains**

  Cuervo G, Puig-Asensio M, Garcia-Vidal C, Fernández-Ruiz M, Pemán J, Nucci M, Aguado JM, Salavert M, González-Romo F, Guinea J, Zaragoza O, Gudiol C, Carratalà J, Almirante B; CANDIPOP Project; Validation Cohort Project.

  Clin Microbiol Infect. 2015 Jul;21(7):684.e1-9.

- ***Candida tropicalis* bloodstream infection: Incidence, risk factors and outcome in a population-based surveillance**

  Fernández-Ruiz M, Puig-Asensio M, Guinea J, Almirante B, Padilla B, Almela M, Díaz-Martín A, Rodríguez-Baño J, Cuenca-Estrella M, Aguado JM; CANDIPOP Project; GEIH-GEMICOMED (SEIMC); REIPI.

  J Infect. 2015 Sep;71(3):385-94.

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11. COPIA DE LOS TRABAJOS QUE FORMAN PARTE DE LA TESIS DOCTORAL

Epidemiology and predictive factors for early and late mortality in *Candida* bloodstream infections: a population-based surveillance in Spain

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Abstract

A prospective, multicentre, population-based surveillance programme for *Candida* bloodstream infections was implemented in five metropolitan areas of Spain to determine its incidence and the prevalence of antifungal resistance, and to identify predictors of death. Between May 2010 and April 2011, *Candida* isolates were centralized to a reference laboratory for species identification by DNA sequencing and for susceptibility testing by EUCAST reference procedure. Prognostic factors associated with early (0–7 days) and late (8–30 days) death were analysed using logistic regression modelling. We detected 773 episodes: annual incidence of 8.1 cases/100 000 inhabitants, 0.89/1000 admissions and 1.36/10 000 patient-days. Highest incidence was found in infants younger than 1 year (96.4/100 000 inhabitants). *Candida albicans* was the predominant species (45.4%), followed by *Candida parapsilosis* (24.9%), *Candida glabrata* (13.4%) and *Candida tropicalis* (7.7%). Overall, 79% of *Candida* isolates were susceptible to fluconazole. Cumulative mortality at 7 and 30 days after the first episode of candidaemia was 12.8% and 30.6%, respectively. Multivariate analysis showed that therapeutic measures within the first 48 h may improve early mortality: antifungal treatment (OR 0.51, 95% CI 0.27–0.95) and central venous catheter removal (OR 0.43, 95% CI 0.21–0.87). Predictors of late death included host factors (e.g. patients' comorbid status and signs of organ dysfunction), primary source (OR 1.63, 95% CI 1.03–2.61), and severe sepsis or septic shock (OR 1.77, 95% CI 1.05–3.00). In Spain, the proportion of *Candida* isolates non-susceptible to fluconazole is higher than in previous reports. Early mortality may be improved with strict adherence to guidelines.

Keywords: Antifungal resistance, *Candida* bloodstream infections, early mortality, epidemiology, prognostic factors, surveillance
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Introduction

European surveillance studies show that the incidence of *Candida* bloodstream infections (BSI) ranges from nearly 3 to 8.6 per 100 000 population per year [1–6].

Despite the introduction of new antifungal agents, this infection remains a severe disease associated with significant mortality [7]. Hence, changes in clinical practices have already occurred, with prophylactic and empirical antifungal therapies in high-risk patients. However, these strategies may be linked to a shift towards non-*albicans* species and the emergence of isolates with decreased fluconazole susceptibility [8].

The epidemiology of candidaemia has been extensively studied in the USA [9–12] and northern and central Europe. In Spain, however, data are limited to surveys conducted in specific areas [6,13] or tertiary centres [14]. Furthermore, we are lacking information about the reasons for the poor current outcome of candidaemia. Studies that have reported determinants of mortality are based on retrospective data or have focused on the impact of therapeutic measures from a restricted viewpoint [15–20].

We conducted a population-based surveillance for *Candida* BSI in Spain to determine its incidence and the distribution and susceptibility pattern of *Candida* species, and to examine prognostic risk factors for mortality.

Materials and Methods

Setting, patients and study design

The CANDIPOP study is a prospective, population-based surveillance programme on *Candida* BSI, conducted from May 2010 to April 2011 in 29 hospitals located in five of the largest municipal areas of Spain: Barcelona, Bilbao, Madrid, Seville and Valencia (population 9 498 980, or 20% of the Spanish population). Patients were identified by local laboratories and reported to study coordinators, who collected data using a standardized case report form. Demographic characteristics, underlying conditions, predisposing risk factors within the preceding month, and 30-day follow-up outcome were recorded in a dedicated database created for the study. Given the observational nature of this research, patients were managed according to routine clinical care.

Audits were carried out to ensure that all cases were reported. The study was approved by the local institutional review boards, and written consent was obtained from patients.

Definitions

Definitions have been described in a previous publication [6]. In brief, an incident case was the first positive *Candida* spp. blood culture. Candidaemias occurring >30 days after the incident episode or isolation of a different *Candida* species after the initial case were considered new episodes. Outpatient-acquired cases were candidaemias detected ≤2 days after hospitalization. The Charlson index was used to represent comorbidity in adults [21]. Sepsis, severe sepsis or septic shock were recorded on the day of candidaemia [22]. Proven catheter-related candidaemia has been described elsewhere [23]. Timing to central venous catheter (CVC) removal and to antifungal administration was the interval between incident blood culture and implementation of these measures. Adequate antifungal treatment was the use of the correct dose of antifungal agent for a susceptible *Candida* isolate (see Supplementary material, Table S1). Patients receiving >3 days of systemic antifungal drug before the first positive blood culture were considered to have breakthrough candidaemias.

Incidence

Population and age-specific incidence rates were expressed as number of cases per 100 000 population, using the 2011 Spanish national census data. Overall incidence of hospitals was calculated using as denominators the summed number of admissions and patient-days of each hospital during the study period.

Microbiological studies

Candida isolates were forwarded to a reference laboratory, the Spanish National Centre for Microbiology in Madrid, for species confirmation and antifungal susceptibility testing. Species identification was performed by sequencing the internal transcribed spacer (ITS) regions from ribosomal DNA. ITS1 and ITS2 regions were directly amplified by PCR from yeast suspensions and sequenced using universal primers [24,25]. Susceptibility to antifungal drugs and interpretation of resistance rates were investigated according to the protocols [26,27] and clinical breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [http://www.eucast.org/clinical_breakpoints/]. Of note, *Candida glabrata* and *Candida guilliermondii* are considered intermediate or resistant to fluconazole, as there is insufficient evidence on whether the wild-type population of these pathogens can be considered fluconazole-susceptible.

Data analysis

Quantitative variables are reported as median and interquartile range (IQR) and qualitative variables as number (%). Categorical data were analysed using the chi-squared or Fisher exact test. Significance was set at a p-value of <0.05. Prognostic factors associated with early (0–7 days) and late (8–30 days) death were assessed using logistic regression analysis. To preserve the assumption of independence of observations, only the first episode of candidaemia recorded for an individual patient was included in this analysis. Neonates and infants younger than 1 year were excluded from the

predictor analysis because epidemiology and risk factors for candidaemia might differ from those described in adults and older children. Episodes caused simultaneously by different *Candida* species were also excluded. Variables with p <0.1 in the univariate analysis and considered clinically relevant were entered in a multivariate model. The best model was selected according to Mallows' Cp statistic. Model adequacy was assessed by the Hosmer–Lemeshow goodness-of-fit test and the area under the receiver operating characteristic curve. For early mortality, it was decided a priori that antifungal treatment and CVC removal would remain in the final multivariate analysis given the belief that these factors might be associated with outcome. Potential confounders of therapy were maintained in the multivariate model. No interactions between variables were found. Statistical analyses were performed with Microsoft SPSS-PC+, version 15.0 (SPSS, Chicago, IL, USA).

Results

Incidence rates

We identified 773 episodes of *Candida* BSI, yielding an annual incidence of 8.1 cases/100 000 inhabitants, 0.89/1000 admissions and 1.36/10 000 patient-days. Differences in incidence rates between geographical areas are shown in the Supplementary material (Table S2). Highest age-specific incidence was observed in infants younger than 1 year (96.4/100 000 inhabitants), and a later peak occurred in persons aged 71–80 years (26.5/100 000 inhabitants) (Fig. 1).

Study population

Twenty-one patients declined to participate. Hence, this report is based on 752 episodes of candidaemia detected in 729 patients. Baseline characteristics of the study population are outlined in Table 1. Ninety (12%) cases were outpatient-acquired, and the remaining occurred among hospitalized patients, including 264 (35.1%) admitted to the intensive care unit. Median length of hospitalization before *Candida* BSI was 22 days (IQR 13–39), and 356 (47.3%) cases had recent healthcare exposure (i.e hospitalization within the previous 3 months).

Clinical data

Sepsis was the clinical presentation of candidaemia in 512 (68.1%) cases. Regarding haematogenous dissemination, ocular candidiasis was reported in 20 cases (2.7%), endocarditis in 14 (1.9%), and metastatic renal infection in three (0.4%). Central nervous system involvement occurred in seven cases (0.9%), all but one in infants. Excluding the 45 patients who survived ≤48 h, follow-up blood samples were obtained in 477 (67.5%) cases at a median of 3 days (IQR 4–8). Of these, 144 (30.1%) cases had persistent candidaemia.

Species distribution and antifungal susceptibility testing

In 159 cases, incident blood culture was polymicrobial: a bacterial strain was identified in 145 (19.3%) and two different *Candida* species were simultaneously isolated in 14 (1.9%). Hence, 766 *Candida* strains were obtained from 752 episodes. *Candida albicans* was the predominant species (348, 45.4%), followed by *Candida parapsilosis* (191, 24.9%), *C. glabrata* (103, 13.4%), *Candida tropicalis* (59, 7.7%), *Candida krusei* (15, 2%), and other rarer species (50, 6.5%). Differences in distribution of *Candida* spp. between metropolitan areas are outlined in the Supplementary material (Figure S1).

Compared with other *Candida* species, *C. parapsilosis* was more likely to occur in children younger than 1 year (18.9% versus 9.9%, p 0.001) and in catheter-related candidaemia (48.1% versus 29.3%, p <0.001). *Candida glabrata* cases were more frequent in persons older than 65 years (62.9% versus 43.4%, p <0.001) and where there was an abdominal source of infection (8.2% versus 2.7%, p 0.011). *Candida albicans* was more often related to previous colonization by the same

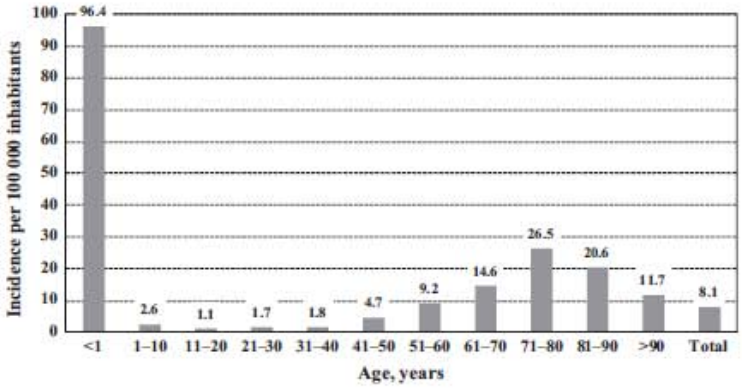

FIG. 1. Annual incidence of candidaemia by age in Spain from 2010 to 2011.

TABLE 1. Baseline characteristics of study population and clinical data of candidaemia episodes according to *Candida* species, Spain (2010–2011)

Characteristic	All cases (*N* = 752)	*Candida* species[a]				
		C. albicans (*n* = 337)	*C. parapsilosis* (*n* = 185)	*C. glabrata* (*n* = 97)	*C. tropicalis* (*n* = 57)	*C. krusei* (*n* = 14)
Demographics						
Median age, years	63 (43–75)	65 (45–75)	54 (6–69.5)	71 (56.5–78.5)	68 (54.5–78.5)	54.5 (47.5–66.8)
Age <1 year	92 (12.2)	43 (12.8)	35 (18.9)	1 (1)	4 (7)	–
Male sex	442 (58.8)	185 (54.9)	122 (65.9)	57 (58.8)	30 (52.6)	10 (71.4)
Outpatient	90 (12)	31 (9.2)	24 (13)	21 (21.6)	4 (7.1)	1 (7.1)
Days in hospital until *Candida* BSI[b]	22 (13–39)	20 (12–34)	28 (17–55)	23 (12.3–36.8)	20 (11–36.5)	24 (13–42.5)
Comorbidities						
Diabetes mellitus	161 (21.4)	76 (22.6)	29 (15.7)	29 (29.9)	16 (28.1)	2 (14.3)
Malignancy (≤1 year)	257/749 (34.3)	101/334 (33.2)	54 (29.2)	42 (43.3)	25 (43.9)	7 (50)
Previous renal failure	194 (25.8)	106 (31.5)	32 (17.3)	26 (26.8)	14 (24.6)	3 (21.4)
Transplant recipient	48 (6.4)	11 (3.3)	15 (8.1)	10 (10.3)	5 (8.8)	3 (21.4)
Liver cirrhosis	32 (4.3)	13 (3.9)	4 (2.2)	5 (5.2)	2 (3.5)	2 (14.3)
HIV infection	16 (2.1)	6 (1.8)	1 (0.5)	3 (3.1)	1 (1.8)	–
Risk factors for candidaemia						
Central venous catheter	581/750 (77.5)	258 (76.6)	156/183 (85.2)	66 (68)	38 (66.7)	13 (92.9)
Total parenteral nutrition	365 (48.5)	176 (52.2)	95 (51.4)	41 (42.3)	20 (35.1)	8 (57.1)
Immunosuppressive therapy[c]	168 (22.3)	68 (20.2)	40 (21.6)	18 (18.6)	14 (24.6)	6 (42.9)
Neutropenia (<500 cell/mm^3)	35 (4.7)	10 (3)	6 (3.2)	3 (3.1)	5 (8.8)	2 (14.3)
Intubation	188/751 (25)	98/336 (29.1)	51 (27.6)	16 (16.5)	7 (12.3)	4 (28.6)
Prior surgery (3 months)	382 (50.8)	181 (53.7)	98 (53)	47 (48.5)	27 (47.4)	5 (35.7)
Abdominal surgery	211 (28.1)	95 (28.2)	54 (29.2)	34 (35.1)	15 (26.3)	4 (28.6)
Prior antibiotic therapy[c]	699/748 (93.5)	324/334 (97)	165/184 (89.7)	87 (89.7)	54 (94.7)	11 (78.6)
Prior fungal therapy[c]	160/751 (21.3)	46 (13.6)	57 (30.8)	23/96 (24)	12 (21.1)	8 (57.1)
Azole exposure	117/750 (15.6)	37 (11)	34 (18.4)	20/96 (20.8)	7/56 (12.5)	7 (50)
Echinocandin exposure	45/751 (6)	9 (2.7)	23 (12.4)	5/96 (5.2)	4 (7)	2 (14.3)
Prior *Candida* colonization	284/750 (37.9)	157/336 (46.7)	50 (27)	42 (43.3)	18 (31.6)	4/13 (30.8)
Source of infection						
Primary	423 (56.3)	202 (59.9)	89 (48.1)	54 (55.7)	33 (57.9)	8 (57.1)
Catheter-related	258 (34.3)	101 (30)	89 (48.1)	24 (24.7)	16 (28.1)	5 (35.7)
Urological	40 (5.3)	22 (6.5)	2 (1.1)	9 (9.3)	5 (8.8)	–
Abdominal	25 (3.3)	9 (2.7)	5 (2.7)	8 (8.2)	3 (5.3)	–
Others	6 (0.8)	3 (0.9)	–	2 (2.1)	–	1 (7.1)
Severity of infection						
Bacteria in incident culture	145 (19.3)	63 (18.7)	38 (20.5)	20 (20.6)	10 (17.5)	5 (35.7)
Septic shock or severe sepsis	240 (31.9)	120 (35.6)	46 (24.9)	30 (30.9)	21 (36.8)	7 (50.7)
Therapeutic measures (≤48 h)						
Adequate antifungal therapy[d]	428/749 (57.1)	203/337 (60.2)	121/184 (65.8)	23/96 (24)[e]	36/56 (64.3)	8/14 (57.1)
CVC removal[f]	275/575 (47.8)	127/253 (50.2)	70/156 (44.9)	38/66 (57.6)	15/38 (39.5)	7/13 (53.8)

Values are reported as no./total no (%) or median (interquartile range) unless otherwise indicated.
BSI, bloodstream infection; CVC, central venous catheter; HIV, human immunodeficiency virus.
[a]Cases in which two *Candida* species were isolated on incident blood culture are not included.
[b]Only includes nosocomial candidaemias, cases with positive blood culture after 2 days of hospitalization.
[c]Within the preceding month. Immunosuppressive therapy includes corticoids, chemotherapy and other immunosuppressive drugs.
[d]Appropriateness of antifungal treatment in the first 48 h was not available for three cases.
[e]We considered that azole use in the first 48 h was unsuitable for treating *C. glabrata* infections in 21 episodes. Among them, one patient died within 7 days.
[f]Data regarding CVC removal in the first 48 h were missing in six of 581 cases.

Candida spp. (46.7% versus 30.3, p <0.001), and *C. tropicalis* to haematological malignancies (17.5% versus 6.3%, p 0.005). Regarding the impact of antifungal exposure within the previous month, *C. parapsilosis* was more frequent in cases with previous use of echinocandins (12.4% versus 4%, p <0.001) and *C. krusei* with previous azole exposure (50% versus 15%, p 0.003).

Table 2 shows antifungal susceptibility results. For fluconazole, 79% (604/766) of *Candida* isolates were susceptible. The resistance rate of *C. tropicalis* was 22% (13/59). However, fluconazole non-susceptible isolates (MIC ≥4 mg/L) were uncommon in both *C. albicans* and *C. parapsilosis* (1% and 5%, respectively). A single case of *Candida kefyr* was resistant to amphotericin B (0.1%). Rates of resistance to echinocandins were 0.3% (1/348) for *C. albicans*, 1% (1/103) *C. glabrata*, 3.4% (2/59) *C. tropicalis*, and no resistance was found among *C. krusei*.

Therapeutic measures

Of 749 cases in 726 patients with available data, 137 (18.3%) were receiving antifungal drugs at blood culture collection; 101 of these episodes were considered breakthrough candidaemias that occurred while receiving azoles (62, 61.4%), echinocandins (26, 25.7%) or amphotericin B (13, 12.9%). Overall, 673 (89.5%) episodes received targeted antifungal therapy for candidaemia. Excluding the 137 cases receiving antifungal drugs at candidaemia onset, treatment was started at a median time of 2 days (IQR 1–3) after the incident blood culture. A detailed description of therapies is provided in the Supplementary material (Table S3).

Outcome and predictors of mortality

Nine patients were lost to follow-up before day 30 (three before day 7). Overall, cumulative mortality at 7 and 30 days

TABLE 2. *In vitro* **susceptibilities of *Candida* bloodstream isolates to different antifungals[a]**

Species	Value	MIC (mg/L) Amphotericin B	Flucytosine	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Caspofungin	Micafungin	Anidulafungin
C. albicans	GM	0.051	0.16	0.21	0.016	0.016	0.015	0.31	0.03	0.03
	MIC_{90}	0.12	0.5	0.25	0.015	0.015	0.015	0.5	0.03	0.03
	Range	0.03–0.25	0.12–32	0.12–>64	0.015–>8	0.015–>8	0.015–8	0.12–2	0.03–1	0.03–0.25
C. parapsilosis	GM	0.14	0.49	0.48	0.018	0.017	0.016	1.36	0.84	0.93
	MIC_{90}	0.25	0.25	1	0.03	0.03	0.015	2	2	2
	Range	0.03–1	0.12–0.5	0.12–64	0.015–0.25	0.015–0.5	0.015–0.12	0.5–4	0.25–4	0.12–4
C. glabrata	GM	0.106	0.133	3.074	0.127	0.12	0.124	0.44	0.031	0.031
	MIC_{90}	0.25	0.12	16	1	0.5	0.5	1	0.03	0.03
	Range	0.03–0.5	0.12–>64	0.5–>64	0.015–>8	0.015–8	0.015–8	0.25–1	0.03–1	0.03–0.5
C. tropicalis	GM	0.079	0.154	1.83	0.057	0.13	0.047	0.41	0.034	0.034
	MIC_{90}	0.12	0.12	>64	8	>8	8	0.5	0.03	0.03
	Range	0.03–0.5	0.12–32	0.12–>64	0.015–>8	0.015–>8	0.015–>8	0.12–2	0.03–2	0.03–1
C. krusei	GM	0.236	3.48	33.5	0.066	0.3	0.048	0.87	0.08	0.034
	MIC_{90}	0.5	4	64	0.25	0.5	0.12	1	0.12	0.03
	Range	0.12–0.5	2–4	16–64	0.015–0.25	0.015–1	0.015–0.12	0.5–2	0.06–0.12	0.03–0.06
C. guilliermondii	GM	0.067	0.127	3.22	0.22	0.12	0.075	0.9	0.33	0.5
	MIC_{90}	0.12	0.25	16	1	0.25	0.25	2	0.5	1
	Range	0.03–0.12	0.12–0.25	0.12–32	0.06–2	0.06–0.25	0.015–0.25	0.5–2	0.25–0.5	0.25–1
C. lusitaniae	GM	0.06	0.287	0.45	0.02	0.023	0.018	0.92	0.05	0.036
	MIC_{90}	0.25	>64	32	0.12	0.5	0.06	1	0.06	0.12
	Range	0.03–0.25	0.12–>64	0.12–64	0.015–0.25	0.015–0.5	0.015–0.06	0.5–1	0.03–0.06	0.03–0.12

GM, geometric mean; MIC, minimum inhibitory concentration.
[a]The table describes susceptibility of species with higher prevalence ($n \geq 10$) in the CANDIPOP study.

after the first episode of candidaemia was 12.8% (93/726) and 30.6% (220/720), respectively.

On univariate analysis, numerous factors were associated with early mortality in patients older than 1 year (Table 3). When adjusted by primary source of candidaemia and severity of infection (severe sepsis or septic shock) in the multivariate regression analysis, appropriate antifungal treatment within the first 48 h was the only factor independently associated with lower mortality. To explore whether antifungal therapy was affected by CVC removal, a secondary analysis was performed in patients with CVCs. On multivariate analysis, adequate antifungal treatment (OR 0.51, 95% CI 0.27–0.95) and having the CVC removed (OR 0.43, 95% CI 0.21–0.87) within the first 48 h remained associated with decreased early mortality.

Independent risk factors for late mortality were related to host characteristics (age, immunosuppression), clinical presentation of candidaemia (septic shock or severe sepsis and primary infection), and signs of organ dysfunction (intubation and previous renal replacement therapy) (Table 4). To further assess the influence of CVC removal on late mortality, separate logistic regression analyses were performed. The possible benefit of CVC removal on univariate analysis disappeared after including host factors and clinical data in the multivariate analysis (OR 0.72, 95% CI 0.43–1.22). Similar results were obtained in patients with catheter-related candidaemia: none of the treatment-related factors were significantly associated with late mortality.

Because no paediatric severity of illness score was measured during the study and comorbidities may have an effect on outcome, similar multivariate models for early and late mortality were explored in the subgroup of adults (≥18 years). After entering the Charlson index as an independent variable, the benefit of therapeutic measures on early mortality remained stable. Conversely, the Charlson index was added as a prognostic factor for late mortality (OR 1.13, 95% CI 1.00–1.28) (data not shown).

Discussion

Candidaemia remains a life-threatening infection, especially in patients with severe underlying conditions. As our results show, overall incidence of *Candida* BSI in Spain is 8.1/100 000 population. Although we lack comparative studies, our incidence rate is similar to those of most population-based studies conducted in the USA between 1992 and 2001 [9–12] (6–8/100 000 population/year) and is comparable to a recent national surveillance performed in Denmark [4] (8.6/100 000 population). However, it differs from most northern and central European countries [2,3,5], which have described a much lower disease burden (nearly 3–5.7/100 000 population) and contrasts with the high rates in a contemporary US survey conducted in Atlanta and Baltimore (13.3 and 26.2 cases/100 000 population, respectively) [12]. In general, these geographic variations probably reflect demographic differences or variations in patient management.

In accordance with previous surveillance reports, the highest incidence rates are at the extremes of age. Of note, however, we found an unexpectedly high peak in children younger than 1 year (96.4 cases/100 000 population) in comparison with other European surveys [2–5] (range, 9.4–20.7/100 000 population).This result diverges from the

TABLE 3. Univariate and multivariate logistic regression analyses of prognostic factors for early mortality (0–7 days) in 629[a] patients

Variable	Alive (n = 547)	Died (n = 82)	Univariate analysis		Multivariate analysis[b]	
			OR (95% CI)	p value	OR (95% CI)	p value
Host factors						
Age, years	65.6 (51.3–76.0)	72.2 (55.4–80.2)	1.02 (1.01–1.04)	0.001	1.02 (1.01–1.04)	0.011
Male sex	317 (58)	57 (69.5)	1.65 (1.00–2.73)	0.048		
Charlson index[c]	2 (1–3)	3 (2–5)	1.23 (1.10–1.37)	<0.001		
Malignancy (≤1 year)	214/546 (39.2)	28/80 (35)	0.84 (0.52–1.36)	0.472		
Transplant recipient	42 (7.7)	3 (3.7)	0.46 (0.14–1.51)	0.199		
HIV infection	13 (2.4)	1 (1.2)	0.51 (0.07–3.93)	0.516		
Immunosuppressive therapy	137 (25)	16 (19.5)	0.73 (0.41–1.30)	0.278		
Neutropenia (<500 cell/mm^3)	29 (5.3)	5 (6.1)	1.16 (0.44–3.01)	0.766		
Abdominal surgery	166 (30.3)	20 (24.4)	0.74 (0.43–1.27)	0.272		
Previous RRT	40 (7.3)	5 (6.1)	0.82 (0.32–2.15)	0.691		
Intubation	111 (20.3)	21 (25.6)	1.35 (0.79–2.32)	0.272		
Clinical data						
Primary source	278 (50.8)	64 (78)	3.44 (1.99–5.96)	<0.001	3.43 (1.90–6.19)	<0.001
Catheter-related	208 (38)	11 (13.4)	0.25 (0.13–0.49)	<0.001		
Antifungal agent at time of blood culture collection	91/545 (16.7)	16 (19.5)	1.21 (0.67–2.18)	0.528		
Severe sepsis or septic shock	143 (26.1)	53 (64.6)	5.16(3.16–8.44)	<0.001	6.56 (3.85–11.17)	<0.001
Bacteria in incident culture	101 (18.5)	15 (18.3)	0.99 (0.54–1.80)	0.970		
Candida species						
C. albicans	249 (45.5)	38 (46.3)	1.03 (0.65–1.65)	0.889		
C. parapsilosis	132 (24.1)	12 (14.6)	0.54 (0.28–1.03)	0.060		
C. glabrata	77 (14.1)	15 (18.3)	1.37 (0.74–2.51)	0.315		
C. tropicalis	43 (7.9)	8 (9.8)	1.27 (0.57–2.80)	0.559		
C. krusei	10 (1.8)	4 (4.9)	2.75 (0.84–8.99)	0.093	3.10 (0.83–11.60)	0.092
Therapeutic measures (≤48 h)						
Adequate antifungal treatment	306/544 (56.3)	25 (30.5)	0.34 (0.21–0.56)	<0.001	0.35 (0.20–0.61)	<0.001
CVC removal[d]	206/416 (49.5)	13/55 (23.6)	0.32 (0.17–0.61)	0.001		

Values are reported as no./total no (%) or median (interquartile range).
CI, confidence interval; CVC, central venous catheter; HIV, human immunodeficiency virus; OR, odds ratio; RRT, renal replacement therapy.
[a]Only the first episode of candidaemia was included for patients with multiple episodes. Neonates and infants younger than 1 year, cases of candidaemia caused simultaneously by different species of *Candida*, and two adult patients who were lost to follow up in this period were excluded from the analysis.
[b]The best multivariate analysis model according to Mallows' Cp statistic included the following variables: age, primary source, severe sepsis or septic shock, *Candida krusei* and adequate antifungal treatment (Hosmer–Lemeshow p 0.90; area under the curve = 0.81).
[c]Recorded in adults (n = 600).
[d]Subset of patients with available information regarding CVC removal (n = 471 out of 474). Multivariate analysis in patients with CVC was as follows: increasing age (OR 1.03, 95% CI 1.00–1.05, p 0.017), primary source (OR 2.25, 95% CI 1.17–4.33, p 0.015), severe sepsis or septic shock (OR 4.50, 95% CI 2.40–8.44, p <0.001), *C. krusei* (OR 4.16, 95% CI 1.07–16.12, p 0.039), adequate antifungal treatment (OR 0.51, 95% CI 0.27–0.95, p 0.033), and CVC removal within 48 h (OR 0.43, 95% CI 0.21–0.87, p 0.019) (Hosmer–Lemeshow p 0.11; area under the curve = 0.79).

epidemiological trend towards the increasing relevance of the elderly population as the most important age-specific group affected by candidaemia [2,4,12]. We believe the high incidence rate in our infants is influenced by at least two factors. First, all the study regions included referral paediatric and neonatal units for community hospitals from other areas, which could have contributed to an overestimate of the incidence rates. Second, there was a high percentage of *C. parapsilosis* in children younger than 1 year in comparison with adults. Although the relevance of *C. parapsilosis* in neonatal candidaemia is well-recognized [28,29] and an endemic situation cannot be ruled out [30] these results may reflect the presence of nosocomial outbreaks and the need to improve infection control practices. Therefore, further molecular studies of *C. parapsilosis* strains are required, and particular consideration should be given to fluconazole prophylactic therapy in low-birthweight neonates, according to guidelines [31,32].

Over the last decade, there have been no substantial changes in *Candida* species distribution in Spain. The only exception is a possible increase in the percentage of *C. glabrata*, particularly in the elderly. In the present study, *C. glabrata* was the third most common species (13.4%), whereas in reports from the early 2000s its proportion was <9% [6,33]. Although these studies involved different surveillance regions and are not entirely comparable, the same trends have been reported in the USA [10,11], Denmark and Finland [2,4]. It is suggested that the rise in *C. glabrata* may be due to widespread azole use. However, this association remains unclear, and other host factors and medical practices may have contributed [34,35].

Our findings confirm that fluconazole susceptibility has decreased in Spain. Earlier studies in Barcelona [6,36] showed that >90% of *Candida* isolates were fluconazole-susceptible, whereas the present report documents fluconazole susceptibility at <80%. Although this decrease is mainly due to rises in *C. glabrata* infection, we also found significant fluconazole resistance in *C. tropicalis* strains (22%), never before reported in Spain. Resistance to echinocandins was very low, except for *C. parapsilosis*, which exhibited higher MICs than those of other *Candida* species. The clinical relevance of these findings warrants analysis in further studies because the correlation between MIC and clinical response to echinocandins remains uncertain.

TABLE 4. Univariate and multivariate logistic regression analyses of prognostic factors for late mortality (8–30 days) in 542[a] patients

Variable	Alive (n = 431)	Died (n = 111)	Univariate analysis		Multivariate analysis[b]	
			OR (95% CI)	p value	OR (95% CI)	p value
Host factors						
Age, years	64.7 (50.4–75.6)	68.7 (59.2–78.9)	1.02 (1.00–1.03)	0.001	1.03 (1.02–1.05)	<0.001
Male sex	256 (59.4)	57 (51.4)	0.72 (0.48–1.10)	0.127		
Charlson index[c]	2 (1–3)	3 (2–4)	1.18 (1.06–1.31)	0.002		
Malignancy (≤1 year)	168/430 (39.1)	44 (39.6)	1.02 (0.67–1.57)	0.913		
Transplant recipient	31 (7.2)	11 (9.9)	1.42 (0.69–2.92)	0.342		
HIV infection	9 (2.1)	4 (3.6)	1.75 (0.53–5.80)	0.358		
Immunosuppressive therapy[d]	100 (23.2)	36 (32.4)	1.59 (1.00–2.51)	0.047	2.50 (1.48–4.21)	0.001
Abdominal surgery	141 (32.7)	24 (21.6)	0.57 (0.35–0.93)	0.025		
Neutropenia (<500 cell/mm^3)	20 (4.6)	9 (8.1)	1.81 (0.80–4.10)	0.153		
Previous RRT	22 (5.1)	18 (16.2)	3.60 (1.86–6.98)	<0.001	2.87 (1.34–6.15)	0.007
Intubation	65 (15.1)	46 (41.4)	3.99 (2.51–6.32)	<0.001	4.24 (2.42–7.42)	<0.001
Clinical data						
Primary source	208 (48.3)	68 (61.3)	1.70 (1.11–2.60)	0.015	1.63 (1.03–2.61)	0.039
Catheter-related	172 (39.9)	34 (30.6)	0.67 (0.43–1.04)	0.074		
Severe sepsis or septic shock	95 (22)	48 (43.2)	2.70 (1.74–4.18)	<0.001	1.77 (1.05–3.00)	0.034
Antifungal agent at time of blood culture collection	70/429 (16.3)	21 (18.9)	1.20 (0.70–2.05)	0.514		
Bacteria in incident culture	75 (17.4)	25 (22.5)	1.38 (0.83–2.30)	0.216		
Persistent candidaemia[e]	86/308 (27.9)	26/74 (35.1)	1.40 (0.82–2.40)	0.222		
Candida species						
C. albicans	186 (43.2)	60 (54.1)	1.55 (1.02–2.36)	0.041		
C. parapsilosis	110 (25.5)	21 (18.9)	0.68 (0.40–1.15)	0.149		
C. glabrata	64 (14.8)	13 (11.7)	0.76 (0.40–1.44)	0.400		
C. tropicalis	35 (8.1)	7 (6.3)	0.76 (0.33–1.76)	0.525		
C. krusei	7 (1.6)	3 (2.7)	1.68 (0.43–6.61)	0.456		
Therapeutic measures (≤48 h)						
Adequate antifungal treatment	245/429 (57.1)	60/110 (54.5)	0.90 (0.59–1.37)	0.628		
CVC removal[f]	167/321 (52)	38/93 (40.9)	0.64 (0.40–1.02)	0.059		

Values are reported as no./total no (%) or median (interquartile range).
CI, confidence interval; CVC, central venous catheter; HIV, human immunodeficiency virus; OR, odds ratio; RRT, renal replacement therapy.
[a]Only the first episode of candidaemia was included for patients with multiple episodes. Neonates and infants younger than 1 year, cases of candidaemia caused simultaneously by different species of *Candida*, deaths that occurred at days 0–7, and five adult patients who were lost to follow up in this period were excluded from the analysis.
[b]The best multivariate analysis model according to Mallows' Cp statistic included the following variables: age, immunosuppressive therapy, previous RRT, intubation, primary source and severe sepsis or septic shock (Hosmer–Lemeshow p 0.75; area under the curve = 0.76).
[c]Recorded in adults (n = 513).
[d]Includes corticoids, chemotherapy and other immunosuppressive drugs within the preceding month.
[e]Persistent candidaemia was defined as persistently positive blood cultures for ≥3 days after the incident blood sample. Analysis performed in the subset of patients with follow-up blood cultures (n = 382).
[f]Subset of patients with available information regarding CVC removal (n = 414 out of 417). Multivariate analysis in patients with CVC was as follows: age (OR 1.04, 95% CI 1.02–1.05, p <0.001), previous RRT (OR 2.84, 95% CI 1.28–6.31, p 0.011), intubation (OR 3.57, 95% CI 1.98–6.45, p <0.001), primary source (OR 1.90, 95% CI 1.13–3.18, p 0.015), severe sepsis or septic shock (OR 1.42, 95% CI 0.79–2.57, p 0.243), and CVC removal (OR 0.72, 95% CI 0.43–1.22, p 0.222) (Hosmer–Lemeshow p 0.32; area under curve = 0.77).

Overall 30-day mortality in our study was high (30.6%), but similar to recent data [2,5]. Multivariate analysis suggested the benefit of prompt therapeutic measures for decreasing early mortality, in keeping with previous reports. Furthermore, and for the first time, it was clearly seen that host factors and severity of infection were the main variables influencing mortality in the later period. These results support current guidelines, which consider appropriate antifungal therapy and catheter removal as the cornerstones of treatment for candidaemia. Nonetheless, prompt CVC removal as a prognostic factor of mortality remains controversial. Current data are provided by observational studies [18,19], and some reports have failed to demonstrate the benefit of CVC removal on outcome [16,20]. We believe CVC management should be carefully evaluated in each patient and removal performed whenever possible, especially if the catheter is the suspected source of infection [19].

In light of the low percentage of adequate antifungal treatment for *C. glabrata* found in this study, we considered that azoles at any dose were inappropriate for non-susceptible isolates [http://www.eucast.org/clinical_breakpoints/]. This interpretation could be controversial and might have biased the benefit of antifungal therapy towards the reduction of its effect. However, even with this definition, antifungal treatment was associated with better early survival. Further studies are needed to elucidate whether fluconazole is a good option for *C. glabrata* in terms of clinical and microbiological responses.

This study has some limitations. First, the epidemiology described is influenced by local medical practices, which limits the ability to generalize the results to other geographical areas. Second, it was difficult to control the analysis of prognostic risk factors of mortality for the variable severity of illness, since APACHE II score was only available in adult intensive care unit patients. Nevertheless, we used other markers related with concurrent illnesses (Charlson index) and we explored a wide range of clinical variables to adjust for confounding factors, which lends strength to the results. Third, the precise number of metastatic candidiasis cases could not

be determined because diagnostic procedures were performed at the physicians' discretion.

In conclusion, candidaemia is a severe infection that remains associated with high morbidity and mortality. Although our results confirm that the poor prognosis may be strongly associated with the fragile status of affected patients in whom the risk of death is inherently high, we should focus on the control of modifiable risk factors for mortality and improve adherence to guidelines. Prompt initiation of appropriate antifungal treatment and CVC removal could decrease early mortality in these patients.

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Authors Contributions

BP, JGM, IRC, BA and MCE conceived, designed and coordinated the study. BP, JGM, JMA, RZ, MM and BA were local study coordinators ensuring correct data collection. OZ and MCE were responsible for *Candida* species confirmation and antifungal susceptibility testing. MPA and BA were responsible for data analysis and interpretation, and prepared the final version of the article. JGM, JMA, RZ, MM, PM and IRC contributed to the original intellectual content, reviewing and adding a critique of the report. All authors read the manuscript and approved the final version.

Transparency Declaration

BP has received honoraria for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas and Novartis. JGM has received honoraria for talks on behalf of Gilead Sciences, Merck Sharp and Dohme and Astellas. JMA has received grant support from Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer, The Instituto de Salud Carlos III and The Mutua Madrileña Foundation. He has been an advisor/consultant to Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme and Pfizer. He has received honoraria for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer and Astellas Pharma. RZ has received honoraria for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer and Astellas and a grant support from Pfizer. MM has received grant support from Pfizer, Astellas Pharma, Novartis, Merck Sharp and Dohme and Gilead Sciences. PM has received honoraria for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas and Novartis. IRC has received honoraria for talks on behalf of Pfizer, Merck Sharp and Dohme, Gilead, Astellas and Novartis. MCE has received grant support from Astellas Pharma, bioMérieux, Gilead Sciences, Merck Sharp and Dohme, Pfizer, Schering Plough, Soria Melguizo SA, Ferrer International, the European Union, the ALBAN programme, the Spanish Agency for International Cooperation, the Spanish Ministry of Culture and Education, the Spanish Health Research Fund, the Instituto de Salud Carlos III, the Ramon Areces Foundation and the Mutua Madrileña Foundation. He has been an advisor/consultant to the Pan-American Health Organization, Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. He has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough. BA has received grant support from Gilead Sciences, Pfizer and the Instituto de Salud Carlos III, and he has received honoraria for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas and Novartis. MPA and OZ declare that they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Percentages of *Candida* species among the 766 isolates according to each metropolitan area of Spain.

Table S1. Definitions used to classify the appropriateness of antifungal treatment.

Table S2. Incidence of candidaemia and characteristics of participating centres.

Table S3. Initial therapeutic measures for *Candida* bloodstream episodes in paediatric and adult patients.

Appendix 1

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MATERIAL SUPLEMENTARIO

Table S1. Definitions used to classify the appropriateness of antifungal treatment

Antifungal treatment
Appropriate therapy[a]
Fluconazole (adjusted for renal function)
≥400 mg/day [6 mg/kg/day] for fluconazole-susceptible isolates
Echinocandins[b]
Anidulafungin 200 mg loading dose, then 100 mg/day
Caspofungin 70 mg loading dose, then 50 mg/day
Micafungin 100 mg/day
Amphotericin (lipid formulation) B 3 mg/kg/day
Inappropriate therapy
No antifungal treatment
Insufficient fluconazole dose
<400 mg/day for fluconazole-susceptible isolates
Fluconazole at any dose for non-susceptible *Candida* isolates or *C. glabrata* and *C.Krusei*

MIC,minimum inhibitory concentration.

[a]The use of the correct dose of antifungal agent for a susceptible *Candida* isolate. Resistance was determined according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) [http://www.eucast.org/clinical_breakpoints/]. Adequate dosing of antifungals shown in this table refers to adult patients. The appropriateness of dosing for paediatric patients is based on ESCMID guidelines [31].

[b]In *Candida* isolates without clinical breakpoints determined by EUCAST, we arbitrarily used the anidulafungin threshold.

Table S2. Incidence of candidaemia and characteristics of participating centres

Metropolitan areas	Barcelona	Bilbao	Madrid	Seville	Valencia	Overall
No. hospitals	6	3	11	5	4	29
No. beds						
>1000	1	1	4	1	1	8
600-1000	2	1	3	1	1	8
<600	3	1	4	3	2	13
Population	1 625 319	1 203 804	3 815 118	2 062 690	792 049	9 498 980
No. episodes	127	85	349	121	91	773
Incidence per[a]						
10^3 admissions	0.69	0.76	1.04	1.02	0.80	0.89
10^4 patient-days	1.15	1.47	1.44	1.48	1.18	1.36
10^5 inhabitants	7.8	7.1	9.1	5.9	11.5	8.1

[a]All 773 episodes identified during the study period were used to calculate incidence rates by 2011 Spanish national census

Table S3. Initial therapeutic measures for *Candida* bloodstream episodes in paediatric and adult patients

	Overall (N=752)	Episodes in paediatric patients (<18 years) (N=121)	Episodes in adults (≥18 years) (N=631)		
			Severe sepsis or septic shock (n=202)	Sepsis (n=429)	p value[a]
Initial antifungal treatment[b]					
Azole	346/750 (46.1)	23/119 (19.3)	73 (36.1)	250 (58.3)	<0.001
Echinocandin	203/750 (27.1)	8/119 (6.7)	77 (38.1)	118 (27.5)	0.007
Amphotericin B	105/750 (14)	77/119 (64.7)	13 (6.4)	15 (3.5)	0.09
Combination therapy	17/750 (2.3)	5/119 (4.2)	5 (2.5)	7 (1.6)	0.54
No targeted antifungal treatment[c]	79 (10.5)	6 (5)	34 (16.8)	39 (9.1)	0.005
Therapeutic measures (≤ 48h)					
Appropriate antifungal treatment[d]	428/749 (57.1)	98/119 (82.4)	115/202 (56.9)	215/428 (50.2)	0.12
CVC removal[e]	275/575 (47.8)	56/112 (50)	61/161 (37.9)	158/302 (52.3)	0.003
Combined treatment[f]	194/572 (33.9)	52/110 (47.3)	47/161 (29.2)	95/301 (31.6)	0.60

Values are reported as no./total no (%), unless otherwise indicated.

[a]Comparison between adults in the group with severe sepsis or septic shock and sepsis.

[b]Antifungal medication data were not available for two paediatric cases.

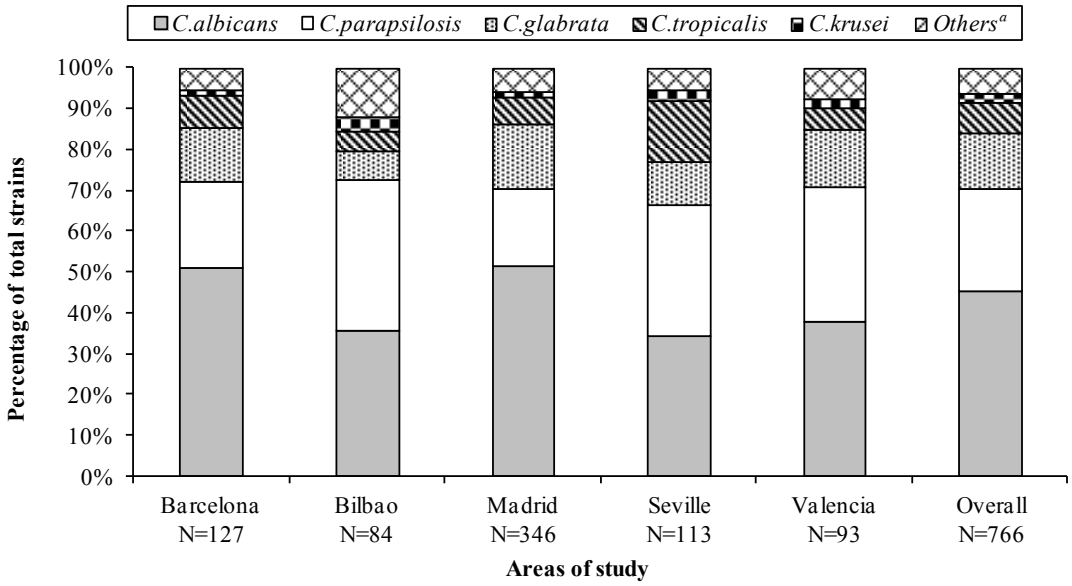
[c]This group includes 5 patients who died while receiving antifungal treatment for another reason, but before the current candidaemia episode had been diagnosed.

[d]Antifungal medication was missing for two paediatric cases. Time at which antifungal therapy was started was missing in one adult case in the sepsis group.

[e]The analysis of CVC removal included 575 cases out of 581 in which the time of withdrawal was available: 112 in the paediatric group, 161 in adults with severe sepsis or shock septic, and 302 in adults with sepsis at clinical presentation.

[f]Catheter(s) removed in addition to receiving appropriate antifungal treatment.

Figure S1. Percentages of *Candida* species among the 766 isolates according to each metropolitan area of Spain



[a]The "others" category includes: *C. guilliermondii* in 13 cases, *C. lusitaniae* in 10, *C. orthopsilosis* in 7, *C. dubliniensis* in 4, *C. lipolytica* in 4, *C. kefyr* in 4, *C. metapsilosis* in 2, *P. anomala* in 2, *C. intermedia* in 1, *C. nivariensis* in 1, *C. pulcherrima* in 1, and *P. fabianii* in 1.

Impact of Therapeutic Strategies on the Prognosis of Candidemia in the ICU*

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*See also p. 1554.

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Objectives: To determine the epidemiology of *Candida* bloodstream infections, variables influencing mortality, and antifungal resistance rates in ICUs in Spain.

Design: Prospective, observational, multicenter population-based study.

Setting: Medical and surgical ICUs in 29 hospitals distributed throughout five metropolitan areas of Spain.

Patients: Adult patients (≥ 18 yr) with an episode of *Candida* bloodstream infection during admission to any surveillance area ICU from May 2010 to April 2011.

Interventions: *Candida* isolates were sent to a reference laboratory for species identification by DNA sequencing and susceptibility testing using the methods and breakpoint criteria promulgated by the European Committee on Antimicrobial Susceptibility Testing. Prognostic factors associated with early (0–7 d) and late (8–30 d) mortality were analyzed using logistic regression modeling.

Measurements and Main Results: We detected 773 cases of candidemia, 752 of which were included in the overall cohort. Among these, 168 (22.3%) occurred in adult ICU patients. The rank order of *Candida* isolates was as follows: *Candida albicans* (52%), *Candida parapsilosis* (23.7%), *Candida glabrata* (12.7%),

Candida tropicalis (5.8%), *Candida krusei* (4%), and others (1.8%). Overall susceptibility to fluconazole was 79.2%. Cumulative mortality at 7 and 30 days after the first episode of candidemia was 16.5% and 47%, respectively. Multivariate analysis showed that early appropriate antifungal treatment and catheter removal (odds ratio, 0.27; 95% CI, 0.08–0.91), Acute Physiology and Chronic Health Evaluation II score (odds ratio, 1.11; 95% CI, 1.04–1.19), and abdominal source (odds ratio, 8.15; 95% CI, 1.75–37.93) were independently associated with early mortality. Determinants of late mortality were age (odds ratio, 1.04; 95% CI, 1.01–1.07), intubation (odds ratio, 7.24; 95% CI, 2.24–23.40), renal replacement therapy (odds ratio, 6.12; 95% CI, 2.24–16.73), and primary source (odds ratio, 2.51; 95% CI, 1.06–5.95).

Conclusions: Candidemia in ICU patients is caused by non-*albicans* species in 48% of cases, *C. parapsilosis* being the most common among these. Overall mortality remains high and mainly related with host factors. Prompt adequate antifungal treatment and catheter removal could be critical to decrease early mortality. (*Crit Care Med* 2014; 42:1423–1432)

Key Words: antifungal agents; candidiasis; epidemiology; intensive care units; mortality; treatment outcome

Candida bloodstream infections (BSIs) represent a severe healthcare-related complication in critically ill patients. The relevance of the disease in ICUs was recently underscored by the Extended Prevalence of Infection in Intensive Care (EPIC-II) study, which reported that 17% of ICU-acquired infections are caused by *Candida species* (1). Furthermore, the Hospitals in Europe Link for Infection Control through Surveillance (HELICS) project estimated that candidemia represented 6.3% of all ICU BSIs in 2004 and 2005 (2).

Despite the existence of effective antifungal drugs, recent studies continue to report high mortality rates, ranging from 40.2% to 56% (3–7). Attempts have been made to decrease the prevalence of candidemia with the use of antifungal prophylaxis or preemptive therapy in selected high-risk patients. However, these strategies could lead to an increased risk of fluconazole nonsusceptible isolates and contribute to the emergence of non-*albicans Candida* species (8, 9). In fact, the epidemiology of fungal infection can significantly differ between geographical regions owing to the influence of differing medical practice.

Numerous studies have focused on describing the current epidemiology and management of *Candida* BSI in the ICU setting (3, 5, 10–14). However, little effort has been dedicated to providing an in-depth understanding of the reasons for the poor prognosis of candidemia in ICU patients. In particular, few studies have assessed the risk factors for death in this population (6, 10, 15), and the benefit of modifiable therapeutic strategies has been mainly generalized from data provided by selected hospitals or studies that included patients who were not critically ill (16–18).

This study reports the candidemia episodes occurring in our ICU setting through analysis of the data from a population-based surveillance program conducted in five metropolitan areas of Spain.

The aims of the study were to describe the epidemiology of *Candida* BSI in Spanish ICUs, to determine the prevalence of antifungal drug resistance, and to identify predictors of death. In relation to this last objective, our hypothesis was that the potential effect of treatment-related variables had to be assessed in an early stage of the infection because of indications that the patient's outcome might be adversely affected by host factors (19).

MATERIALS AND METHODS

Design, Setting, and Study Population

The design of the Prospective Population Study on Candidemia in Spain study has been previously described (20). It was a prospective, population-based surveillance for *Candida* BSI conducted from May 2010 to April 2011 in five of the largest metropolitan areas of Spain: Barcelona, Bilbao, Madrid, Seville, and Valencia (population 9,498,980). Twenty-nine public and private hospitals participated, accounting for all ICUs that were representative of the Spanish healthcare system. We report here all cases of *Candida* BSI occurring in adults (≥ 18 yr) following admission to the medical or surgical ICU of any hospital in the surveillance area. Patients with a hospital stay less than or equal to 48 hours and candidemias that were already present at ICU admission were excluded.

Definitions

An incident case was the first positive *Candida* species blood culture in a surveillance area resident. Candidemias occurring more than 30 days after the incident episode or isolation of a different *Candida* species after the initial case were considered new episodes. Proven catheter-related candidemia was defined according to the following criteria: 1) evidence of catheter exit site exudate with the same *Candida* species that was isolated from the bloodstream; 2) semiquantitative catheter tip culture yielded greater than 15 colony-forming units (CFUs) of the same *Candida* species; or 3) simultaneously quantitative cultures of blood samples showed a ratio of 3:1 of CFU between blood samples obtained through a catheter and peripheral vein, or the differential time to positivity was greater than or equal to 2 hours (21). Secondary candidemias occurred after a potential origin of infection was identified based on the isolation of the same *Candida* species in blood culture and the presumed source of infection. In detail, abdominal origin required a positive culture from intra-abdominal space obtained during surgery or needle aspiration and the evidence of abdominal infection or abscess. Urinary source was identified by the isolation of *Candida* species from urine culture or tissue from affected site and the presence of urologic conditions (e.g., manipulation or obstruction of the urinary tract). Candidemia was classified as primary when there was no apparent infection at another site. Severity of illness was measured by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score on the day of candidemia (22) and the presence of severe sepsis or septic shock at presentation (23).

To assess the impact of therapeutic measures on outcome, antifungal therapy and central venous catheter (CVC) removal were evaluated in accordance with the following definitions: 1) early, adequate antifungal treatment was the administration of the recommended dose of an antifungal drug within 48 hours after blood culture collection for a susceptible *Candida* isolate, according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (24). Fluconazole at any dose was considered inappropriate for nonsusceptible *Candida* species, *Candida glabrata*, *Candida guilliermondii*, and *Candida krusei*. For species with no established EUCAST breakpoints to micafungin and caspofungin, we arbitrarily used the anidulafungin threshold to decide the adequacy of antifungal treatment; 2) early CVC removal was established when the catheter was removed within 48 hours after obtaining blood culture, and in patients with multiple CVCs, when at least the responsible CVC was removed within this timeframe (it was a retrospective judgment made once all necessary investigations had been performed); 3) early, appropriate combined treatment was defined as receiving adequate antifungal medication in addition to CVC removal within the first 48 hours. The outcome variables were early (≤ 7 d) and late (8–30 d) mortality.

Data Collection

Laboratory-based reporting of cases from the participating institutions went to regional study coordinators (i.e., specialists in infectious diseases or intensivists) who collected the data with the use of a standardized case report form. Demographic characteristics, predisposing risk factors within the preceding 30 days, clinical management, and 30-day follow-up period were recorded in a dedicated database created for the study. Information was then revised by one study collaborator (M.P.-A.) to verify data accuracy and completeness. Patient management was at the discretion of the attending physician. Laboratories were audited to ensure that all cases were reported. The institutional review board of each participating center approved the study protocol, and informed consent was obtained from patients.

Microbiological Methods

Candida isolates were centralized to the Mycology Reference Laboratory (MRL), National Center for Microbiology (Madrid, Spain), for species confirmation and antifungal susceptibility testing. Species identification was performed with molecular methodology by sequencing the internal transcribed spacer regions (ITS1 and ITS2) from ribosomal DNA. The identities of *Candida parapsilosis* sensu stricto, *Candida orthopsilosis*, and *Candida metapsilosis* isolates were confirmed as described by Tavanti et al (25, 26). Molecular reidentification of all *C. glabrata* sensu lato isolates into the species *C. glabrata* sensu stricto, *Candida nivariensis*, and *Candida bracarensis* was performed as described by Alcoba-Flórez et al (27). When MRL and submitted laboratory identifications differed, the MRL data were used. In vitro antifungal susceptibilities of isolates were evaluated according to the EUCAST-Antifungal Susceptibility Testing microdilution method (28, 29). *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 were used as quality control strains for antifungal drug susceptibility testing.

Statistical Analysis

Descriptive data were presented per disease episodes or per patients depending on whether it was a characteristic of the episode of candidemia or the patient, respectively. Quantitative variables are reported as median and interquartile range (IQR), and categorical variables as counts (%). The chi-square test or Fisher exact test was used to compare the distribution of categorical variables, and the Student *t* test or Mann-Whitney *U* test for quantitative variables. Significance was set at a p value of less than 0.05. Only the first episode of candidemia recorded for an individual patient was considered for mortality analysis. The Kaplan-Meier curve was performed to show the relationship between therapeutic strategies and 30-day survival. Follow-up period was divided into early (0–7 d) and late (8–30 d) mortality to evaluate variables related to death. This division was based on the belief that mortality is highly determined by patients' baseline characteristics and may confuse the effect of potential modifiable factors such as therapeutic measures when assessed at 30 days. A univariate logistic regression model was fitted for each variable to test its relationship with mortality outcomes. Variables clinically relevant and statistically significant ($p < 0.1$) on univariate analysis were considered to build the multivariate regression model. Clinical interventions were maintained in the final model as a fixed variable. Variables that did not improve likelihood ($p < 0.10$) were excluded. Potential confounders of treatment strategies (APACHE II score) were tested. Significant interactions between variables were ruled out. Statistical analyses were performed with Microsoft SPSS-PC+, version 15.0 (SPSS, Chicago, IL).

RESULTS

A total of 773 episodes of candidemia were detected in the CANDIPOP study. Of these, 21 case-patients were excluded because they declined to participate. Within the remaining cohort, 264 (35.1%) occurred in hospitalized patients (> 48 hr) who were admitted to the ICU. Among them, 85 pediatric patients (≤ 18 yr) and 11 candidemias that were already present at ICU admission were excluded. Hence, this report is based on 168 episodes of candidemia identified in 164 patients.

At the time of candidemia, 79 case-patients (47.0%) were admitted in medical-surgical ICUs, 50 (29.8%) in surgical ICUs, and 39 (23.2%) in medical ICUs. The median length of hospitalization before *Candida* BSI was 19 days (IQR, 12–34 d). Ninety-five cases (56.5%) were previously colonized with the same *Candida* species, and 27 of them had multifocal colonization. Baseline characteristics of the study population are outlined in **Table 1**.

Microbiological Findings

There were five episodes where two *Candida* species were simultaneously isolated in the incident blood culture and three episodes where two different species were obtained on separate days during the 30-day follow-up period (at 1, 5, and

TABLE 1. Characteristics of Patients Who Developed Candidemia and Description of All Episodes of *Candida* Bloodstream Infection Included in the Study

Variable	*n/N* (%)[a]
Patients admitted to ICU ($n = 164$)	
Males	108 (65.9)
Age in years, median (IQR)	63.0 (49.0–74.0)
Acute Physiology and Chronic Health Evaluation II score, median (IQR)	19 (14–25)
No. of days in hospital to candidemia onset, median (IQR)	19 (12–34)
Comorbidities	
Diabetes mellitus	40 (24.4)
Malignancy (active treatment within 1 yr)	33 (20.1)
Chronic obstructive pulmonary disease	17 (10.4)
Transplant recipient	14 (8.5)
Liver cirrhosis	6 (3.7)
HIV infection	4 (2.4)
Episodes of candidemia ($n = 168$)	
Risk factors for candidemia	
Previous antibiotic therapy (1 mo)	164 (97.6)
Central venous catheter	162/166[b] (97.6)
Intubation	120 (71.4)
Renal replacement therapy[c] (before or due to candidemia)	39 (23.2)
Previous surgery (3 mo)	111 (66.1)
Abdominal surgery	60/111 (54.1)
Parenteral nutrition	106 (63.1)
Previous *Candida* colonization	95 (56.5)
Previous hospitalization (3 mo)	67 (39.9)
Neutropenia at candidemia onset (< 1,000 cells/mm^3)	8 (4.8)
Previous corticosteroids (1 mo)[d]	65 (38.7)
Recent antifungal exposure (< 1 mo)	54 (32.1)
Azoles	36 (21.4)
Echinocandins	25 (14.9)
Source of candidemia	
Primary	93 (55.4)
Proven catheter-related	58 (34.5)
Abdominal	10 (6)
Urologic tract	2 (1.2)
Others	5 (3)
Clinical presentation of *Candida* bloodstream infection	
Septic shock or severe sepsis	98 (58.3)
Concomitant bacteremia	35 (20.8)
Initial antifungal therapy	
Echinocandin	84 (50)
Azole	60 (35.7)
Amphotericin B	12 (7.1)
Combination therapy[e]	3 (1.8)
No targeted antifungal treatment[f]	9 (5.4)

IQR = interquartile range.

[a]Values are reported as no./total no. (%) of patients or episodes unless otherwise indicated.

[b]Data regarding the presence of a central venous catheter was missing in two out of 168 cases.

[c]Hemodialysis or hemodiafiltration.

[d]More than 10 mg of systemic methylprednisolone per day (or equivalent) during ≥ 5 d.

[e]Combination therapy of an echinocandin plus azole was used in two cases and combination of amphotericin B plus azole was used in one case.

[f]One patient died while receiving voriconazole treatment due to isolation of *Aspergillus* species from bronchoalveolar lavage.

8 d, respectively). In addition, a bacterial pathogen was isolated in conjunction with *Candida* species in 35 cases (20.8%) (the most common: coagulase-negative staphylococci in 17, gram-negative rods in 6, and anaerobes in 5). Overall, 173 yeast strains were obtained from 168 episodes. *Candida albicans* was the leading agent (90; 52%), followed by *C. parapsilosis* (41; 23.7%), *C. glabrata* (22; 12.7%), *Candida tropicalis* (10; 5.8%), *C. krusei* (7; 4%), *C. guilliermondii* (1; 0.6%), *Candida kefyr* (1; 0.6%), and *C. orthopsilosis* (1; 0.6%). Species distribution varied substantially between areas. *C. albicans* was the causal species in 31.8–64.5% of cases and predominated in Barcelona (64.5%), Madrid (64.4%), and Seville (48.1%). In Bilbao and Valencia, however, *C. parapsilosis* was the most common isolate (45.5% and 35.3%, respectively).

The results of in vitro susceptibility testing are summarized in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/A858). Overall, 79.2% of *Candida* isolates (137 of 173) were susceptible to fluconazole. Specifically, all *C. albicans* showed fluconazole susceptibility, but 12.2% of *C. parapsilosis* (5 of 41) and 10% of *C. tropicalis* (1 of 10) were intermediate or resistant (minimum inhibitory concentration [MIC] ≥ 4 mg/L). Resistance to anidulafungin was uncommon: 1.1% for *C. albicans* (1 of 90), 4.5% for *C. glabrata* (1 of 22), and no resistance among *C. tropicalis* and

C. krusei. However, the MIC_{90} of echinocandins against *C. parapsilosis* (2 mg/L) was higher than those recorded for the most common *Candida* species. All isolates were susceptible to amphotericin B.

Clinical Data and Candidemia Management

Severe sepsis or septic shock was the clinical presentation of candidemia in 98 cases (58.3), and 21 (12.5) required renal replacement therapy (RRT) (hemodialysis or hemodiafiltration) due to infection. Evidence of metastatic candidiasis was found in 9 episodes (5.4%): eight cases of endophthalmitis (one in the course of echocardiography-documented endocarditis and two in the context of concomitant septic thrombophlebitis) and one case of metastatic renal infection in a patient receiving corticosteroids.

Fifty-two cases (31%) were receiving an antifungal agent at candidemia onset (fluconazole in 25, 14.9%; anidulafungin in 11, 6.5%; caspofungin in 8, 4.8%; micafungin in 3, 1.8%; voriconazole in 3, 1.8%; and amphotericin B in 2, 1.2%). In these cases, the median time during which the antifungal drug had been given before positive blood culture was 7 days (IQR, 3–13 d). Interestingly, these episodes were more likely to be caused by *Candida* strains intermediate or resistant to fluconazole than those not exposed to antifungal agents (17 of 52, 32.7% vs 19 of 116, 16.4%; $p = 0.017$). In the remaining cohort, treatment was started after the blood sample was drawn, at a median of 2 days (IQR, 1–3 d). Overall, 159 cases (94.6%) received specific antifungal treatment for candidemia. Antifungal agents administered are shown in Table 1. Echinocandins were the initial antifungal agent most frequently used as a single drug (84 cases, 50%). Nine cases never received targeted antifungal therapy, and eight of them died before blood culture results became available.

With respect to CVC management, the indwelling catheter was investigated for the source of infection in 74.1% of cases (120 of 162), and early CVC removal was performed in 47.5% (77 of 162). Cases needing RRT before or after candidemia and those with severe sepsis or septic shock were less likely to have prompt catheter removal (30.8% vs 52.8%, $p = 0.016$, and 37.5% vs 62.1%, $p = 0.002$, respectively).

Regarding other care processes, follow-up blood samples were obtained in 115 of the 154 patients (74.7%) who survived more than 48 hours. Blood cultures were persistently positive for more than 3 days in 27% (31 of 115).

Outcome and Predictors of Mortality

Cumulative mortality at 7 and 30 days after the first episode of candidemia was 16.5% (27 of 164) and 47% (77 of 164), respectively. Median time from blood sample collection to death was 10 days (IQR, 4.5–19.5 d). The 30-day mortality according to the initiation time of therapeutic measures is shown in **Figure 1**. The Kaplan-Meier survival curves in **Figure 2** show that cases receiving appropriate combined therapy ($n = 59$) within the first 48 hours had a greater likelihood of 30-day survival compared to cases with delayed treatment or no combined intervention therapy ($n = 99$) ($p = 0.024$ by log-rank test).

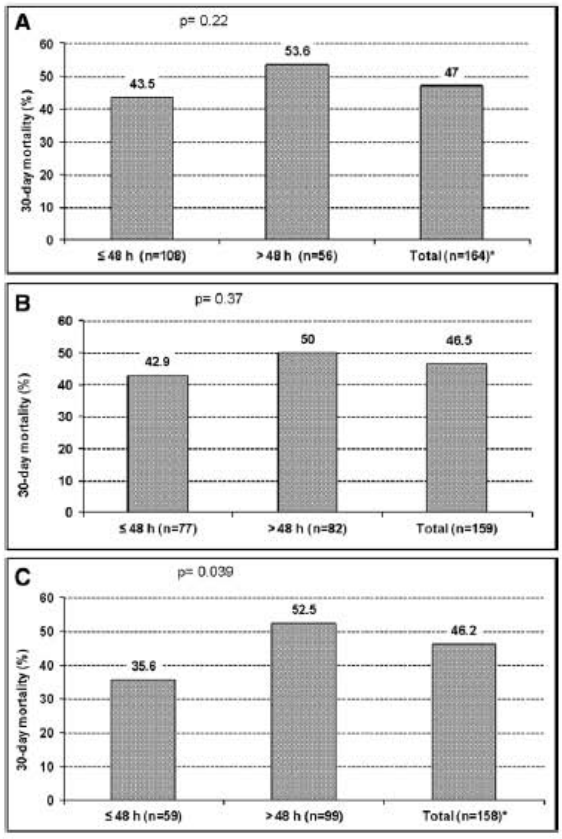

Figure 1. Overall 30-day mortality in relation to time of initiation of adequate antifungal therapy (**A**), time of central venous catheter removal (**B**), and time of initiation of appropriate combined treatment (**C**). *Data regarding time to starting antifungal treatment were missing in one patient.

To better understand the reason for the high mortality rates in ICU patients with *Candida* BSI and to elucidate the impact of therapeutic measures on death, we assessed predictors of mortality at two time points: early (≤ 7 d) and late (8–30 d) mortality. On multivariate analysis and controlling for APACHE II score, combined appropriate treatment (odds ratio [OR], 0.27; 95% CI, 0.08–0.91) and abdominal source (OR, 8.15; 95% CI, 1.75–37.93) were independently associated with early mortality (**Table 2**). Independent risk factors for late mortality were primary source (OR, 2.51; 95% CI, 1.06–5.95), host factors such as age (OR, 1.04; 95% CI, 1.01–1.07), and variables that categorized patients as more seriously ill (intubation and RRT) (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/A859).

DISCUSSION

This is the first population-based description of candidemia specifically dedicated to the critical care setting in Spain, and it is performed according to the methods used by Almirante et al (30) in the 2002–2003 Barcelona Candidemia Project. Our study indicates that the considerable mortality associated with

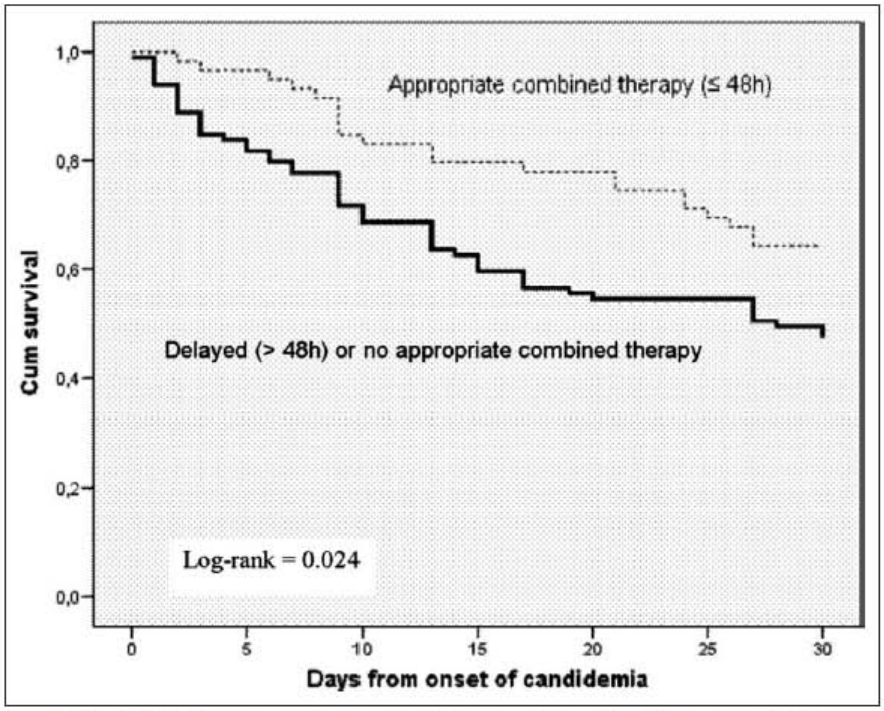

Figure 2. Kaplan-Meier 30-day survival curves according to appropriate combined therapy in the first 48 hr after candidemia diagnosis. Dashes indicate appropriate combined therapy receiving adequate antifungal medication in addition to central venous catheter removal within the first 48 hr.

Candida BSI is related with the severe comorbidities of affected patients and points out that updated epidemiological data are crucial for guiding empirical antifungal treatment.

During the last decade, there has been a shift toward an increasing prevalence of non-*albicans Candida* species, especially in critically ill patients (3, 10, 13). Our results confirm the importance of these microorganisms, which accounted for almost half the isolates in this setting. We observed that *C. parapsilosis* was the most frequent non-*albicans* species in our ICUs (23.7% of isolates), in keeping with the epidemiology described in a previous Spanish multicenter study (31) and Italian ICUs (3, 13). Nonetheless, it contrasts with data from France and the United States, where *C. glabrata* is the second cause of candidemia (8, 10, 11). The predominance of *C. parapsilosis* could be a positive factor, since this species has been associated with a better outcome (32). We believe that the high prevalence of *C. parapsilosis* in our study may be influenced by multiple factors. First, *C. parapsilosis* is commonly related to parenteral nutrition and catheter-related infection due to its capability to adhere to and form biofilms in foreign material. Both risk factors are particularly frequent in ICU patients. Second, although our distribution of *Candida* species better represents the regional epidemiology than series from single centers, further molecular studies would be needed to assess the possibility of institutional outbreaks (12). Lastly, current guidelines recommend empirical use of echinocandins in critically ill patients (33), a fact that may have contributed to increasing their use as first-line agent. Considering the increased frequency of *C. parapsilosis* after caspofungin exposure (34, 35), clinical practice changes could also justify our findings.

Another important finding is the relatively low percentage of *Candida* isolates that were susceptible to fluconazole (79.2%). This was related, in part, to lowering of the new EUCAST breakpoints and classification of *C. glabrata* as intermediate or resistant (24). The impact of decreased susceptibility to fluconazole on clinical outcomes remains uncertain. However, some reports have suggested a potentially increased risk of mortality if fluconazole is underdosed in less susceptible *Candida* isolates (36). This fact, together with the potential rise in fluconazole resistance, must be considered when deciding empirical treatment and supports the recommendation given in the latest European guidelines to use echinocandins as the first choice agent (37). However, for fluconazole-susceptible strains and for *C. parapsilosis*, the preferred treatment is fluconazole, since increasing use of echinocandins may also lead to emergence of resistant isolates (38, 39).

It is a cause of concern that candidemia remains associated with high mortality rates. Our study showed an overall 30-day mortality of 47%, similar to other contemporary reports (3–7). The multivariate model of early mortality highlighted the importance of the severity of illness (APACHE II score) and an abdominal source of infection to predict death, as well as the benefit of therapeutic strategies on outcome. However, the data analysis for late mortality clearly revealed the influence of host-related factors and the need for external support (e.g., intubation and RRT) as determinants of death. These results reinforce the idea that comorbid status at baseline may be strongly involved in the current high mortality rates of candidemia. In fact, previous reports have suggested that infection per se does not seem to be associated with an increase in either ICU- or hospital-attributable mortality (7, 19). To our knowledge, this is the first time that early and late mortality have been described separately in ICU patients with candidemia.

Over the last years, the combination of prompt antifungal therapy and catheter withdrawal has been the cornerstone of treatment for *Candida* BSI (33, 37), and the benefits of this approach were corroborated in our study. At least three recent

TABLE 2. Univariate and Multivariate Logistic Regression Analyses of Factors Influencing Early Mortality in Patients With *Candida* Bloodstream Infections in the ICUs

Variable	Alive ($n = 137$)	Died ($n = 27$)	Univariate Analysis		Multivariate Analysis	
			OR (95% CI)	p	OR (95% CI)	p
Males	88 (64.2)	20 (74.1)	1.59 (0.63–4.03)	0.327		
Age, yr	62.7 (47.3–71.6)	69.6 (55.0–76.0)	1.03 (1.00–1.07)	0.039		
Acute Physiology and Chronic Health Evaluation II	18.0 (13.0–23.0)	23.0 (19.5–29.0)	1.10 (1.04–1.17)	0.001	1.11 (1.04–1.19)	0.002
Comorbidities and risk factors						
Diabetes mellitus	32 (23.4)	8 (29.6)	1.38 (0.55–3.45)	0.489		
Renal replacement therapy	30 (21.9)	8 (29.6)	1.50 (0.60–3.77)	0.386		
Malignancy (≤ 1 yr)	30 (21.9)	3 (11.1)	0.45 (0.13–1.59)	0.211		
Chronic obstructive pulmonary disease	10 (7.3)	7 (25.9)	4.45 (1.52–13.02)	0.007		
Transplant recipient	13 (9.5)	1 (3.7)	0.37 (0.05–2.93)	0.344		
Neutropenia (< 1,000 cell/mm^3)	6 (4.4)	2 (7.4)	1.75 (0.33–9.15)	0.509		
Liver cirrhosis	5 (3.6)	1 (3.7)	1.02 (0.11–9.05)	0.989		
Intubation	98 (71.5)	20 (74.1)	1.14 (0.45–2.90)	0.788		
Prior corticosteroids[a]	53 (38.7)	11 (40.7)	1.09 (0.47–2.53)	0.841		
Antifungal agent at incident blood culture	40 (29.2)	8 (29.6)	1.02 (0.41–2.52)	0.964		
Microbiology						
Candida albicans	75 (54.7)	15 (55.6)	1.03 (0.45–2.37)	0.938		
Candida parapsilosis	38 (27.7)	2 (7.4)	0.21 (0.05–0.92)	0.039	0.21 (0.04–1.04)	0.055
Candida glabrata	15 (10.9)	6 (22.2)	2.32 (0.81–6.67)	0.117		
Candida tropicalis	7 (5.1)	1 (3.7)	0.71 (0.08–6.05)	0.758		
Candida krusei	4 (2.9)	3 (11.1)	4.16 (0.87–19.76)	0.073		
Strains intermediate/ resistant to fluconazole	25 (18.2)	9 (33.3)	2.24 (0.90–5.57)	0.082		
Source of candidemia						
Primary	71 (51.8)	18 (66.7)	1.86 (0.78–4.43)	0.161		
Catheter-related	54 (39.4)	4 (14.8)	0.27 (0.09–0.82)	0.020		
Abdominal	5 (3.6)	5 (18.5)	6.00 (1.60–22.44)	0.008	8.15 (1.75–37.93)	0.008
Urologic	2 (1.5)	0 (–)	–	–		
Clinical severity						
Severe sepsis or septic shock	73 (53.3)	23 (85.2)	5.04 (1.66–15.35)	0.004		
Bacteria in incident culture	32 (23.4)	2 (7.4)	0.26 (0.06–1.17)	0.079		

(*Continued*)

TABLE 2. (*Continued*). Univariate and Multivariate Logistic Regression Analyses of Factors Influencing Early Mortality in Patients With *Candida* Bloodstream Infections in the ICUs

Variable	Alive ($n = 137$)	Died ($n = 27$)	Univariate Analysis		Multivariate Analysis	
			OR (95% CI)	p	OR (95% CI)	p
Therapeutic measures (≤ 48 hr)						
Central venous catheter removal[b]	69/133 (51.9)	8/26 (30.8)	0.41 (0.17–1.01)	0.054		
Adequate antifungal treatment[c]	92/136 (67.6)	15/27 (55.6)	0.60 (0.26–1.39)	0.230		
Appropriate combined treatment	55/132 (41.7)	4/26 (15.4)	0.26 (0.08–0.78)	0.017	0.27 (0.08–0.91)	0.035

OR = odds ratio.

[a]More than 10 mg of systemic methylprednisolone per day (or equivalent) during ≥ 5 d.

[b]Considering episodes with central venous catheter as a risk factor for candidemia ($n = 159$).

[c]Data concerning time when adequate antifungal treatment was initiated were missing for one patient.

All data are given as *n*/*N* (%) or median (interquartile range) unless otherwise indicated. Only the first episode of candidemia is included for patients with multiple episodes.

reports (15, 16, 40) have demonstrated a close relationship between the combination measures and survival, especially in patients with septic shock (40). Nevertheless, catheter withdrawal remains a controversial issue: there are no data from randomized controlled trials, and some reports have failed to confirm the association between early CVC removal and survival (41). The conflicting results may result, in part, from limitations in the study designs and inability to properly control the analysis for severity of illness. However, there are other relevant aspects to consider. Garnacho-Montero et al (16) pointed out that the benefit of CVC withdrawal might be disputable when the source of candidemia is not the catheter. In our study, there were very few secondary candidemias, and we were unable to investigate whether CVC removal provides no benefit in this specific origin of infection. Nucci et al (41) found no clinical benefit of CVC removal in adults treated with an echinocandin or with liposomal amphotericin B, which have in vitro activity against biofilms. Such results have led recently published European guidelines to recommend the use of these antifungals when catheter removal is not possible (37). Based on the expert guidelines and our findings, we believe that CVC withdrawal should be attempted in all ICU patients. There is, however, sufficient evidence in the literature to support the strategy of early administration of antifungal therapy in patients with invasive candidiasis (42–45). In fact, several score systems and serum biomarkers (e.g., *Candida* score, β-D-glucan) (46) have been evaluated to reduce delays in treatment. Nonetheless, the potential interest of preemptive therapy was not the objective of our study.

Some limitations of this study should be mentioned. First, although this multicenter study includes five of the largest cities in Spain and is probably representative of the overall spectrum of ICU patients in our country, our epidemiology cannot be extrapolated to all settings. Second, patients who died before candidemia was diagnosed could not be excluded from the analysis of early mortality because sample size limited the ability to perform an accurate statistical evaluation. Although this might have introduced a bias favoring the benefit of therapeutic measures, the multivariate model was adjusted for potential outcome confounders, a fact that lends strength to the results. Finally, the frequency of *Candida* species colonization was probably underestimated because screening surveillance cultures were not systematically performed.

CONCLUSIONS

The present study confirms the high prevalence of non-*albicans Candida* species in ICU patients (nearly half of all isolates in our setting) and the presence of *C. parapsilosis* as the second most common species in Spain. A total of 20.8% of isolates were nonsusceptible to fluconazole and this finding should be taken into account when deciding empirical treatment. Thirty-day mortality remained high (47%), but late mortality was mainly related with host factors indicating the importance of comorbidities on death. Early mortality may be decreased with strict adherence to guidelines.

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Epidemiology and outcome of candidaemia in patients with oncological and haematological malignancies: results from a population-based surveillance in Spain

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Abstract

A prospective, population-based surveillance on candidaemia was implemented in five metropolitan areas of Spain from May 2010 to April 2011. We aimed to describe the distribution and susceptibility pattern of *Candida* species, and to evaluate risk factors for mortality in patients with oncological (solid tumours) and haematological malignancies. Adults (≥16 years) with cancer were included in the present report. Impact of therapeutic strategies on 7- and 30-day mortality were analysed by logistic regression, adjusting for propensity score by inverse weighting probability of receiving early antifungal treatment and catheter removal. We included 238 (32.6%) patients (195 oncological, 43 haematological). Compared with oncological patients, haematological patients were more likely to have received chemotherapy (53.5% versus 17.4%, $p < 0.001$) or corticosteroids (41.9% versus 21%, $p < 0.001$), and have neutropenia (44.2% versus 1.5%, $p < 0.001$). Overall, 14.8% of patients developed breakthrough candidaemia. Non-*albicans Candida* species (71.1% versus 55.6%, p 0.056) and *Candida tropicalis* (22.2% versus 7.6%, p 0.011) were more frequent in haematological patients. Based on EUCAST breakpoints, 27.6% of *Candida* isolates were non-susceptible to fluconazole. Resistance to echinocandins was negligible. Mortality at 7 and 30 days was 12.2% and 31.5%, respectively, and did not differ significantly between the patient groups. Prompt antifungal therapy together with catheter removal (≤48 hours) was associated with lower mortality at 7 days (adjusted OR 0.05; 95% CI 0.01–0.42) and 30 days (adjusted OR 0.27; 95% CI 0.16–0.46). In conclusion, non-*albicans* species are emerging as the predominant isolates, particularly in haematological patients. Prompt, adequate antifungal treatment plus catheter removal may lead to a reduction in mortality.

Keywords: Antifungal agents, cancer, Candidiasis, drug resistance, epidemiology, fluconazole, haematological malignancies
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Introduction

Candidaemia is a severe fungal infection closely associated with cancer and the complications of its treatment. Estimates of the incidence of this infection vary substantially because surveillance programmes in this population are scarce and most reports are focused on haematological malignancies [1,2]. Despite improvements in the management of patients with this condition and the introduction of echinocandins, candidaemia 30-day mortality rates range from 35% to nearly 50% [2–5]. In addition, a shift towards an increasing prevalence of non-*albicans* species with potentially decreased fluconazole susceptibility has been reported [6,7]. Unfortunately, there is less related information in patients with solid tumours, but it appears that the species isolated in oncological patients are similar to those in the general population [4,8].

In this study, we present episodes of candidaemia occurring in cancer patients by analysing data from a prospective population-based surveillance in Spain (CANDIPOP study). We aim to describe *Candida* species distribution and antifungal drug resistance in patients with underlying malignancies, to update the prognosis of *Candida* bloodstream infections (BSI) in the oncological and haematological population, and particularly, to assess the impact of therapeutic strategies on mortality.

Material and methods

Study design, setting and patients

The CANDIPOP study was a prospective, population-based surveillance for *Candida* BSI conducted from May 2010 to April 2011 in 29 hospitals located in five metropolitan areas of Spain. The study methods were described previously [9]. Briefly, case reporting was laboratory-based. Each candidaemia episode was reported to regional study collaborators who collected the clinical data and recorded the 30-day follow-up outcome (i.e. survival or death). Patient management and antifungal prophylaxis policy was at the discretion of the attending physician. *Candida* isolates were sent to the Mycology Reference Laboratory at the National Centre for Microbiology in Madrid, Spain, for species confirmation and antifungal susceptibility testing. Species were identified by sequencing the internal transcribed spacer regions 1 and 2 from ribosomal DNA. Susceptibility to antifungal drugs was assessed according to the protocols [10,11] and clinical breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (Clinical breakpoints-fungi, Table v 6.1. Available at: http://www.eucast.org/clinical_breakpoints/, accessed 1 May 2013). The study protocol was approved by the ethics committees of the participating centres.

This report focuses on *Candida* BSI episodes in adult patients (≥16 years) with underlying solid organ tumours or haematological malignancies. Patients who had not received treatment for oncological/haematological disease within the previous 12 months were excluded. Only the first episode of candidaemia per patient was included. All patients provided written informed consent for participation.

Definitions

The definitions have been reported elsewhere [9,12]. In summary, proven catheter-related candidaemia was defined as follows: 1) evidence of catheter exit site exudate with the same *Candida* spp. that was isolated from the bloodstream; 2) semi-quantitative culture of the catheter tip yielded >15 CFU of the same *Candida* spp.; or 3) simultaneously quantitative cultures of blood samples showed a ratio of 3:1 of CFU between blood samples obtained through the catheter and a peripheral vein, or the differential time to positivity was ≥2 hours for non-*glabrata* *Candida* BSI [13,14]. Secondary foci required identification of the same *Candida* species at the affected site. Episodes with no defined secondary source or without proven catheter-related origin were classified as primary. Breakthrough candidaemia was established on detection of *Candida* BSI in patients who had been receiving antifungal drugs for >3 days. Neutropenia was described as granulocyte count <500 cell/mm^3 at time of first positive *Candida* species blood culture collection. Severity of illness was measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score for patients admitted to the Intensive Care Unit (ICU) and the Pitt bacteraemia score on the day of candidaemia [15,16]. Adequate antifungal treatment was defined as use of the correct dose of antifungal agent for a susceptible *Candida* isolate. Appropriate fluconazole dosing was 6 mg/kg/day (adjusted for renal function if necessary) except for non-susceptible *Candida* spp., *Candida glabrata*, *Candida guilliermondii* and *Candida krusei*, which was considered inappropriate (see Supporting information, Table S1). Early central venous catheter (CVC) removal was established when the line was removed within 48 hours of the incident BSI, and in patients with multiple CVCs, when at least the responsible CVC was removed within this timeframe.

Statistical analysis

Categorical data are expressed as the count and percentage, and numerical data as the median and interquartile range. Categorical variables were compared with the chi-squared or Fisher exact test, and continuous variables with the Mann–Whitney *U*-test. All statistical tests were two-tailed, and significance was set at $p < 0.05$.

Logistic regression analysis was applied to identify predictive factors of 7-day and 30-day mortality. As our aim was to

investigate the effect of the two therapies considered standard of care in candidaemia—use of adequate antifungal agents and catheter removal—only patients with a CVC in place at candidaemia onset were included in this analysis. The reason for choosing 7-day mortality as a primary endpoint for multivariate analysis was based on the hypothesis that it would adequately represent the impact of therapies in patients with an intrinsically high risk of death due to their comorbidities [7,17]. Variables with p values <0.2 in the univariate analysis and considered clinically relevant underwent multivariate analysis. Therapies were maintained in the final model as a fixed variable. To limit confounding by patient's pretreatment characteristics, the method of adjustment used was the inverse probability of receiving appropriate combined treatment (CVC removal and antifungal treatment) weighting, on the basis of estimated propensity scores. The propensity score, inverse probability of early implementation of therapeutic strategies, was calculated using multivariate logistic regression model and included the following variables: host factors and baseline comorbidities (Charlson index, age and neutropenia), severity of illness (APACHE-II score and Pitt score), clinical features of candidaemia onset (septic shock and breakthrough candidaemia) and factors that might have influenced prompt CVC removal (presence of long-term CVC, renal replacement therapy and parenteral nutrition). Statistical analyses were performed with STATA software package (version 13.1, Stata Corp, College Station, TX, USA).

Results

Over the study period, 773 episodes of *Candida* BSI were detected. Twenty-one patients were excluded because they did not agree to participate, leaving 752 episodes in 729 patients in the overall CANDIPOP study. Among them, 238 (32.6%) incident episodes of candidaemia in adults with cancer were analysed in the present report: 195 (82%) in patients with solid organ tumours (oncological patients) and 43 (18%) in patients with haematological malignancies.

Patient characteristics

The epidemiological and clinical characteristics of the patients are outlined in Table 1. Most cases involved patients with an active underlying cancer (i.e. newly diagnosed or relapsing/resistant malignancy). Compared with oncological patients, haematological patients were more likely to have received chemotherapy or corticosteroids, and have neutropenia or mucositis at candidaemia onset. Presence of a long-term CVC was also more frequent in the haematological population. Oncological patients were older and more likely to have received parenteral nutrition or undergone surgery within the previous 3 months than haematological patients.

Candida species and antifungal susceptibility testing

The distribution of *Candida* species is shown in Table 1. Overall, *Candida albicans* was the most common isolate (101 of 243, 41.6%), followed by *Candida parapsilosis* (47, 19.3%), *C. glabrata* (43, 17.7%), *Candida tropicalis* (25, 10.3%), *C. krusei* (7, 2.9%), *C. guilliermondii* (6, 2.5%) and others (14, 5.8%). Candidaemia was predominantly caused by non-*albicans* species in both haematological (32 of 45 strains, 71.1%) and oncological (110 of 198 strains, 55.6%) patients.

Sixty-seven of 243 (27.6%) *Candida* isolates were non-susceptible to fluconazole. Specifically, 57 (85.1%) of these strains were isolates belonging to species with reduced susceptibility to fluconazole (*C. glabrata*, *Candida nivariensis*, *C. guilliermondii* and *C. krusei*). Only 1% of *C. albicans* (1/101) and 4% of *C. parapsilosis* (2/47) were intermediate or resistant to fluconazole (MIC $\geq$ 4 mg/L) (see Supporting information, Table S2). Interestingly, the rate of fluconazole non-susceptible isolates was similar in haematological and oncological patients (13/45 (28.9%) versus 54/198 (27.3%), p 0.83). Resistance to one or more echinocandins was uncommon (one *C. tropicalis* and one *C. glabrata*), and was associated with FKS1 and FKS2 gene alterations, respectively [18]. A single *Candida kefyr* strain was resistant to amphotericin B.

Clinical data

Catheter-related candidaemia was the most frequent established source of infection in both oncological and haematological patients (36.4% and 37.2%, respectively). Haematogenous dissemination of *Candida* spp. was reported in 18 (7.6%) patients, two of whom had multiple metastatic infections: ocular candidiasis 11, skin lesions four, endocarditis three, and liver and lung involvement, one each. Cutaneous metastatic foci were only observed in neutropenic haematological patients.

Of 237 patients with available information, 35 (14.8%) had breakthrough candidaemia that occurred while they were receiving azoles (27, 11.4%) (mainly fluconazole in 20), echinocandins (6, 2.5%), or amphotericin B (2, 0.8%). These episodes were diagnosed after a median of 11 days (interquartile range 8–14) of antifungal exposure. Because of its potential relevance and differential features, breakthrough candidaemia is compared with non-breakthrough cases in Table 2.

Therapeutic measures

Therapeutic measures are detailed in Table 3. Overall, 217 (91.2%) patients received targeted antifungal treatment for candidaemia. Echinocandins in monotherapy were used more

TABLE I. Main demographic and clinical characteristics of 238 adult patients with candidaemia and cancer

Characteristics	Underlying cancer		p-value
	Haematological malignancy[a] (n = 43)	Solid organ tumour (n = 195)	
Demographics			
Median age, years	62.2 (50.9–70.8)	69.4 (60.2–76.7)	<0.001
Male sex	21 (48.8)	121 (62.1)	0.110
Outpatient[b]	–	23 (11.8)	0.018
Days in hospital until *Candida* BSI	18 (10–36)	22 (14–40)	0.137
Charlson index	2 (2–4)	3 (2–4)	0.194
In ICU at diagnosis	7 (16.3)	33 (16.9)	0.919
APACHE II score	22 (18–29)	19 (15–23)	0.175
Comorbidities			
Diabetes mellitus	5 (11.6)	47 (24.1)	0.073
Chronic obstructive pulmonary disease	4 (9.3)	29 (14.9)	0.339
Chronic renal failure	–	16 (8.2)	0.084
HIV infection	4 (9.3)	3 (1.5)	0.022
Liver cirrhosis	–	5 (2.6)	0.588
Underlying malignancy status			
Newly diagnosed cancer	18 (41.9)	102 (52.3)	0.215
Relapsing cancer	6 (14)	27 (13.8)	0.985
Progressive/resistant tumour or partial remission	11 (25.6)	47 (24.1)	0.838
Complete response or stable disease	8 (18.6)	14 (7.2)	0.035
Others[c]	–	5 (2.6)	0.588
Risk factors for candidaemia			
Prior antibiotic therapy[d]	42 (97.7)	186/194 (95.9)	1.000
Anti-anaerobic agents[d]	36 (83.7%)	164/194 (84.5)	0.894
CVC placement	37 (86)	156 (80)	0.359
Long-term CVC[e]	21 (48.8)	36 (18.5)	<0.001
Surgery (<3 months)	5 (11.6)	140 (71.8)	<0.001
Abdominal surgery	4 (9.3)	92 (47.2)	<0.001
TPN	16 (37.2)	109 (55.9)	0.026
Intubation at diagnosis	3 (7.0)	26 (13.3)	0.249
Prior RRT[f]	2 (4.7)	8 (4.1)	1.000
Prior *Candida* spp. colonization	10 (23.3)	68/194 (35.1)	0.136
Prior antifungal exposure	20 (46.5)	37/194 (19.1)	<0.001
Echinocandins	8 (18.6)	5/193 (2.6)	<0.001
Azoles	15 (34.9)	32/193 (16.6)	0.007
Previous corticosteroids[g]	18 (41.9)	41 (21)	0.004
Chemotherapy	23 (53.5)	34 (17.4)	<0.001
Neutropenia	19 (44.2)	3 (1.5)	<0.001
Mucositis at diagnosis	12/41 (29.3)	9/194 (4.6)	<0.001
Source of infection			
Primary	26 (60.5)	99 (50.8)	0.249
Catheter-related[h]	16 (37.2)	71 (36.4)	0.922
Abdominal source	1 (2.3)	10 (5.1)	0.694
Urological tract	–	13 (6.7)	0.133
Others	–	2 (1)	1.000
Clinical features			
Pitt bacteraemia score at onset	2 (1–4)	1 (0–3)	0.091
Septic shock at onset	4 (9.3)	24 (12.3)	0.580
Bacteria in incident blood culture	6 (14)	40 (20.5)	0.324
Disseminated infection	6 (14)	12 (6.2)	0.106
***Candida* species**[i]			
C. albicans	13/45 (28.9)	88/198 (44.4)	0.056
C. parapsilosis	6/45 (13.3)	41/198 (20.7)	0.258
C. tropicalis	10/45 (22.2)	15/198 (7.6)	0.011
C. glabrata	5/45 (11.1)	38/198 (19.2)	0.200
C. krusei	2/45 (4.4)	5/198 (2.5)	0.617
C. guilliermondii	2/45 (4.4)	4/198 (2)	0.308
Others[j]	7/45 (15.6)	7/198 (3.5)	0.006

Values are reported as no./total no. (%) or median (interquartile range) unless otherwise indicated. Previous use of antibiotics, antifungal exposure, corticosteroids and chemotherapy refers to within the previous month before the first positive blood culture.

Abbreviations: BSI, bloodstream infection; ICU, intensive care unit; HIV, human immunodeficiency virus; CVC, central venous catheter; TPN, total parenteral nutrition; RRT, renal replacement therapy.

[a]The haematological disease was leukaemia in 26, lymphoma in 16, and multiple myeloma in one patient. Among them, nine were haematological transplant recipients.

[b]Candidaemias detected ≤2 days after hospitalization.

[c]Palliative treatment in two, unknown tumour staging in three.

[d]Include β-lactam/β-lactamase inhibitor, carbapenems, metronidazole and clindamycin.

[e]Include skin-tunnelled catheters and totally implantable catheters.

[f]Peritoneal dialysis, haemodialysis or haemodiafiltration.

[g]>10 mg of systemic methylprednisolone per day (or equivalent) during ≥5 days.

[h]Catheter-related candidaemia was diagnosed according to the following definition criteria: positive semi-quantitative tip culture in 76 (87.4%) patients, differential time to positivity in 9 (10.3%) patients without *C. glabrata* bloodstream infection, and differential quantitative blood cultures showing a ratio 3 : 1 of CFU in 2 (2.3%) patients.

[i]*Candida* species distribution among 243 isolates. Include five episodes of mixed candidaemias caused by two *Candida* species (three in oncological patients and two in haematological patients).

[j]Others include *C. lusitaniae* (3), *C. hypolitica* (3), *C. kefyr* (2), *C. dubliniensis* (2), *C. metapsilosis* (1), *C. orthopsilosis* (1), *C. nivariensis* (1), and *Pichia anomala* (1).

often as first-line therapy in haematological patients (41.9% versus 26.2%, p 0.040), whereas oncological patients were more likely to receive azoles (60% versus 27.9%, p < 0.001). In non-breakthrough cases, treatment was started at a median time of 2 days (interquartile range 1–3) after the incident blood culture. Of particular note, 106 patients (44.5%) did not receive

TABLE 2. Characteristics and outcome of cancer patients with breakthrough and non-breakthrough candidaemia

Characteristics	Breakthrough (n = 35)	Non-breakthrough (n = 202)	p-value
Demographics			
Median age, years	64.1 (52.0–71.8)	68.8 (58.7–76.1)	0.014
Male sex	20 (57.1)	122 (60.4)	0.717
Days in hospital until *Candida* BSI[a]	29 (17.5–40.3)	20 (12.8–40)	0.057
Underlying cancer			
Solid tumour	19 (54.3)	175 (86.6)	<0.001
Leukaemia	15 (42.9)	11 (5.4)	<0.001
Lymphoma/myeloma	1 (2.9)	16 (7.9)	0.480
Haematological transplant recipient	5 (14.3)	4 (2)	0.004
Risk factors for candidaemia			
Prior antibiotic therapy	35 (100)	192/201 (95.5)	0.363
Anti-anaerobic agents[b]	33 (94.3)	166/201 (82.6)	0.079
CVC placement	33 (94.3)	159 (78.7)	0.030
Long-term CVC	13 (37.1)	44 (21.8)	0.050
TPN	21 (60)	103 (51)	0.324
Previous corticosteroids	9 (25.7)	49 (24.3)	0.853
Previous *Candida* spp. colonization	9 (25.7)	69/201 (34.3)	0.317
Digestive tract colonization	4 (11.4)	11/201 (5.5)	0.248
Chemotherapy	16 (45.7)	41 (20.3)	0.001
Neutropenia	13 (37.1)	9 (4.5)	<0.001
Mucositis at diagnosis	9/34 (26.5)	12/200 (6)	0.001
Source of infection			
Primary	17 (48.6)	108 (53.5)	0.592
Catheter-related	15 (42.9)	71 (35.1)	0.381
***Candida* species**			
C. albicans	9 (25.7)	88 (43.6)	0.047
C. parapsilosis	8 (22.9)	37 (18.3)	0.527
C. glabrata	8 (22.9)	32 (15.8)	0.306
C. tropicalis	2 (5.7)	22 (10.9)	0.545
C. krusei	3 (8.6)	3 (1.5)	0.043
Mixed fungaemia	–	5 (2.5)	1.000
Fluconazole non-susceptible isolate	14 (40)	52 (25.7)	0.082
Clinical features			
Septic shock at onset	4 (11.4)	24 (11.9)	1.000
Disseminated infection	5 (14.3)	13 (6.4)	0.156
7-day mortality	5 (14.3)	24 (11.9)	0.779
30-day mortality	12 (34.3)	63 (31.2)	0.716

Values are reported as no./total no. (%) or median (interquartile range) unless otherwise indicated.
Abbreviations: BSI, bloodstream infection; CVC, central venous catheter; TPN, total parenteral nutrition.
[a]Only includes nosocomial candidaemias, cases with positive blood culture after 2 days of hospitalization.
[b]Include β-lactam/β-lactamase inhibitor, carbapenems, metronidazole and clindamycin.

adequate antifungal treatment within the first 48 hours after blood sampling; 58 of them (54.7%) due to a delay in starting therapy.

Early catheter removal (≤48 h) was performed in 46.8% of episodes (89 of 190 patients with available data). Nevertheless, haematological patients were less likely to undergo catheter removal in a timely manner.

Follow-up blood cultures were obtained in 66.8% (151/226) of patients who survived >48 hours, and persistent candidaemia for >3 days after incident culture was documented in 32.5%

TABLE 3. Therapeutic measures and outcomes of patients by underlying malignancy

	Overall (n = 238)	Haematological malignancy (n = 43)	Solid tumour (n = 195)	p-value
Initial antifungal agent				
Azole	129 (54.2)	12 (27.9)	117 (60)	<0.001
Echinocandin	69 (29)	18 (41.9)	51 (26.2)	0.040
Amphotericin B	12 (5)	5 (11.6)	7 (3.6)	0.045
Combination	7 (2.9)	4 (9.3)	3 (1.5)	0.022
No targeted antifungal treatment	21 (8.8)	4 (9.3)	17 (8.7)	1.000
Therapeutic measures (≤48 h)				
CVC removal[a]	89/190 (46.8)	11/37 (29.7)	78/153 (51)	0.020
Adequate antifungal therapy	132/238 (55.5)	28/43 (65.1)	104/195 (53.3)	0.159
Clinical response and outcome				
Persistent candidaemia[b]	49/151 (32.5)	10/30 (33.3)	39/121 (32.2)	0.908
Drug-related toxicity	8 (3.4)	6 (14)	2 (1)	0.001
Median days of treatment[c]	20 (15–28)	23.5 (17.0–35.5)	19 (15.0–26.3)	0.048
Median time to death	11 (3–18)	11 (3–17.5)	10.5 (4–18)	0.910
7-day mortality	29 (12.2)	5 (11.6)	24 (12.3)	0.902
30-day mortality	75 (31.5)	13 (30.2)	62 (31.8)	0.842

Values are reported as no./total no. (%) or median (interquartile range) unless otherwise indicated.
Abbreviation: CVC, central venous catheter.
[a]Data concerning time of CVC removal were missing for three patients.
[b]Analysis performed in the subset of patients with follow-up blood cultures ≥3 days after incident blood culture (n = 151).
[c]Among 30-day survivors (n = 163).

(49/151), with similar percentages in the two patient groups. In the subset of patients with CVCs, persistent candidaemia was less frequent in those treated with adequate antifungals (≤48 h) and early CVC removal than in those in whom both therapeutic strategies were not implemented (25% (11/44) versus 44.3% (39/88), p 0.031).

Outcome and predictors of mortality

Cumulative mortality was 12.2% at day 7 and 31.5% at day 30, with no significant differences between oncological and haematological patients. Variables associated with 7-day mortality are described in Table 4. On multivariate analysis, and after including the propensity score adjustment, combined treatment (CVC removal plus antifungal therapy) within the first 48 hours was independently associated with 7-day mortality (adjusted OR 0.05; 95% CI 0.01–0.42). Inclusion of specific sources of the infection (primary candidaemia or catheter-related candidaemia) in the final multivariate model did not significantly change the impact of adequate combined treatment (data not shown). To further assess the impact of therapeutic strategies at a later time point, variables potentially associated with 30-day-mortality were analysed (see Supporting information, Table S3). On propensity score adjusted multivariate analysis, combined treatment still remained associated with lower 30-day mortality (adjusted OR 0.27; 95% CI 0.16–0.46), while primary source of candidaemia (adjusted OR 3.47; 95% CI 2.05–5.89) and *C. krusei* (adjusted OR 12.59; 95% CI 2.46–64.48) were added as prognostic factors. Finally, because inclusion of patients who died early in the course of candidaemia—before they could undergo CVC removal or receive antifungal treatment—might have introduced a bias favouring the association between therapeutic measures and lower odds of mortality, a separate multivariate analysis was performed to account for this possibility. After excluding patients who died within the first 48 hours of candidaemia onset (n = 9), the benefit of prompt antifungal therapy together with catheter removal on 30-day mortality remained stable (adjusted OR 0.34; 95% CI 0.20–0.59).

Discussion

The present report constitutes the largest population-based surveillance for candidaemia performed in cancer patients in

TABLE 4. Univariate and multivariate logistic regression analyses of prognostic factors for early mortality (0–7 days) in 193 cancer patients with CVC in place at candidaemia diagnosis

			Univariate analysis		Multivariate analysis[a]	
Variable	**Alive (n = 171)**	**Died (n = 22)**	**OR (95% CI)**	**p value**	**Adjusted OR (95% CI)**	**p value**
Host factors						
Age, years	66.7 (56.9–75.0)	64.3 (55.2–75.2)	1.00 (0.97–1.03)	0.931		
Charlson index	2 (2–4)	2 (2–6)	1.26 (1.03–1.54)	0.024	1.15 (0.89–1.48)	0.274
In ICU at diagnosis	34 (19.9)	4 (18.2)	0.90 (0.28–2.82)	0.850		
Solid tumour	138 (80.7)	18 (81.8)	1.08 (0.34–3.39)	0.900		
Haematological transplant recipient	8 (4.7)	0 (-)	–	–		
Newly diagnosed cancer	84 (49.1)	13 (59.1)	1.50 (0.61–3.68)	0.381		
HIV infection	4 (2.3)	1 (4.5)	1.99 (0.21–18.63)	0.547		
Neutropenia	18 (10.5)	3 (13.6)	1.34 (0.36–4.98)	0.660		
Previous surgery (<3 months)	105 (61.4)	14 (63.6)	1.10 (0.44–2.77)	0.839		
Chemotherapy (<1 month)	41 (24)	7 (31.8)	1.48 (0.56–3.88)	0.425		
Previous RRT	8 (4.7)	2 (9.1)	2.04 (0.40–10.27)	0.388		
Intubation	25 (14.6)	3 (13.6)	0.92 (0.25–3.35)	0.902		
Long term CVC	53 (31)	4 (18.4)	0.49 (0.16–1.53)	0.223		
Clinical data						
Primary source	79 (46.2)	15 (68.2)	2.50 (0.97–6.43)	0.058	3.64 (1.11–11.90)	0.033
Catheter-related	80 (46.8)	6 (27.3)	0.43 (0.16–1.14)	0.090		
Secondary source[b]	12 (7)	1 (4.5)	0.63 (0.08–5.10)	0.666		
Breakthrough candidaemia	29/170 (17.1)	4 (18.2)	1.08 (0.34–3.43)	0.895		
Septic shock	16 (9.4)	7 (31.8)	4.52 (1.61–12.72)	0.004	3.27 (0.75–14.16)	0.114
Bacteria in incident culture	30 (17.5)	5 (22.7)	1.38 (0.47–4.04)	0.554		
***Candida* species**						
C. albicans	71 (41.5)	8 (36.4)	0.80 (0.32–2.02)	0.644		
C. parapsilosis	40 (23.4)	4 (18.2)	0.73 (0.23–2.28)	0.585		
C. glabrata	32 (18.7)	2 (9.1)	0.43 (0.10–1.95)	0.277		
C. tropicalis	13 (7.6)	4 (18.2)	2.70 (0.80–9.17)	0.111		
C. krusei	4 (2.3)	1 (4.5)	1.99 (0.21–18.63)	0.547		
Fluconazole non-susceptible isolates	48 (28.1)	5 (22.7)	0.75 (0.26–2.16)	0.598		
Therapeutic measures (≤48 h)						
Adequate antifungal treatment	106 (62)	11 (50)	0.61 (0.25–1.50)	0.282		
CVC removal[c]	85/168 (50.6)	4 (18.2)	0.22 (0.07–0.67)	0.008		
Adequate combined treatment[d]	61/168 (36.3)	1 (4.5)	0.08 (0.01–0.64)	0.017	0.05 (0.01–0.42)	0.006

Values are reported as no./total no. (%) or median (interquartile range) unless otherwise indicated.
Abbreviations: BSI, bloodstream infection; CVC, central venous catheter; HIV, human immunodeficiency virus; ICU, intensive care unit; RRT, renal replacement therapy.
[a]Multivariate analysis is adjusted by using a propensity score inverse weighting probability of receiving adequate combined treatment.
[b]Secondary source refers to abdominal, urologic or other non-catheter-related origins of candidaemia.
[c]Data concerning time when CVC was removed were missing in three patients.
[d]Adequate antifungal treatment in addition to CVC removal.

Spain. Our results provide an updated overview of the current epidemiology and management of candidaemia in patients with underlying malignancies.

Although the shift to non-*albicans Candida* species is a cause of concern for clinicians, the predominance of these species in cancer patients has been the rule worldwide [2,3,6,8]. The lower percentage *C. albicans* in haematological patients may be partially explained by the widespread prophylactic use of azoles [6,7,19,20]. However, other factors such as geographical differences and institution-specific variables may contribute to the epidemiology. In this line, and in keeping with previous reports, we found that the most common non-*albicans* species in haematological patients was *C. tropicalis* [3,21]. In contrast, but in agreement with the epidemiology described in the overall population of Southern Europe and Latin America [5,22,23], *C. parapsilosis* and *C. glabrata* were the predominant non-*albicans* species in oncological malignancies.

Not surprisingly, a higher percentage of haematological than oncological patients had recent azole exposure. However, similar rates of non-susceptible strains (around 28%) were found in both populations. These findings may reflect the influence of other variables, apart from antifungal drug exposure, in selecting non-susceptible strains (e.g. suboptimal dosing or length of previous antifungal exposure [4,24] and different exposure to antibacterial compounds [25]). In addition, we observed that resistance rates to echinocandins in non-*parapsilosis* isolates were negligible. Unfortunately, there is no updated information in cancer patients to compare our results, but in general, surveillance programmes have described low resistance to echinocandins [26,27]. However, further studies are needed because the increasing use of these antifungals can lead to higher percentages of resistant isolates [28].

Regarding breakthrough candidaemia, our data confirm that multiple factors might be involved. First, breakthrough infection was more likely in patients with leukaemia, neutropenia, or disruption of mucosal barriers, such as mucositis. These findings suggest that translocation from the gastrointestinal tract may be a major factor in breakthrough candidaemia. Second, breakthrough cases were often caused by fluconazole non-susceptible isolates, especially *C. krusei*. This might reflect failure of azole prophylaxis or emergence of azole-resistant species from the gastrointestinal tract due to changes in the patient's colonization. However, it should be noted that breakthrough candidaemia also occurred in patients receiving echinocandins, and included susceptible isolates such as *C. parapsilosis*. This suggests that an exogenous source of infection such as CVCs also contributes to some breakthrough cases.

All-cause 30-day mortality in the present cohort remained high (30.9%) and did not differ between oncological and haematological patients. However, mortality in these populations often results from conditions apparently unrelated to candidaemia, such as the baseline underlying disease [8]. In our multivariate analysis of risk factors for 7-day and 30-day mortality, catheter removal together with adequate antifungal treatment within the first 48 hours after candidaemia onset were protective factors. Although these results are consistent with American and European guidelines [29,30], some aspects should be highlighted. First, our findings cannot be generalized to the entire neutropenic population, because only 6.3% of patients analysed had neutropenia. As a rule, this subgroup of patients has been poorly represented in previous studies that have assessed the influence of CVC removal on the prognosis of candidaemia [31]. Hence, future evaluations are needed to facilitate a rational approach of CVC management in this specific population. Second, prompt CVC removal is not always feasible because of certain cancer-related factors and because it may not be possible to insert a new line. Hence, there is no clear consensus on how to handle long-term CVCs in cancer patients. Unfortunately our study was not designed to elucidate this particular issue. Third, catheter removal is especially desirable in cases of *C. parapsilosis* because this species is associated with intravascular device infection [32,33]. This point is of special interest, because contemporary reports have detected a rise in *C. parapsilosis* BSI [3,8]. This finding may be influenced by local epidemiology, but it might also be related to the increasing use of echinocandins [34] combined with higher percentages of CVC-related candidaemia in haematological patients [2]. In the present study, the percentage of proven CVC-related candidaemia was similar in both oncological and haematological patients (37.2% versus 36.4%, respectively), and it increased when only the subset of breakthrough candidaemias was considered (42.9%). Taken as a whole, these data suggest that all catheters should be investigated as a potential focus of infection regardless of the underlying malignancy, and that a targeted CVC removal strategy should be carefully evaluated on an individual basis.

This study has some limitations. First, although the overall CANDIPOP study was a population-based surveillance, we lack general data on the number of patients with underlying malignancies who were at risk for candidaemia during the study period, precluding the calculation of candidaemia incidence rates in cancer patients. Second, management policies for cancer patients may not have been homogeneous, which limits the ability to generalize our results to other areas. Third, because a significant number of our patients received different antifungal agents for the treatment of their candidaemia episode, no further analysis was performed on the impact of each antifungal drug class on outcome. Finally, the precise number of disseminated candidiasis remains undefined because

of the observational nature of the study and lack of systematic diagnostic procedures.

In conclusion, 27.6% of *Candida* isolates in Spain were non-susceptible to fluconazole, indicating that updated local epidemiological studies are needed to guide empirical antifungal therapy. Catheter removal within 48 hours after candidaemia and adequate antifungal treatment may lead to a reduction in mortality.

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Authors' contributions

IRC, MCE and BA conceived, designed and coordinated the study. MFR, JMA, PM, MV, ADI, PM, EB and JF were local study coordinators ensuring correct clinical data and microbiological collection. MCE was responsible for *Candida* species confirmation and antifungal susceptibility testing. MPA, IRC and BA were responsible for data analysis and interpretation, and prepared the final version of the article. MFR, JMA, PM, MV, MCE and PM contributed to the original intellectual content, reviewing and adding a critique of the report. All authors read the manuscript and approved the final version.

Transparency declaration

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MPA, MV, ADI and EB declare that they have no conflicts of interest.

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Appendix A. Supporting information

Supporting information related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2014.12.027.

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Propensity Score Analysis of the Role of Initial Antifungal Therapy in the Outcome of *Candida glabrata* Bloodstream Infections

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Candida glabrata **isolates have reduced *in vitro* susceptibility to azoles, which raises concerns about the clinical effectiveness of fluconazole for treating bloodstream infection (BSI) by this *Candida* species. We aimed to evaluate whether the choice of initial antifungal treatment (fluconazole versus echinocandins or liposomal amphotericin B [L-AmB]-based regimens) has an impact on the outcome of *C. glabrata* BSI. We analyzed data from a prospective, multicenter, population-based surveillance program on candidemia conducted in 5 metropolitan areas of Spain (May 2010 to April 2011). Adult patients with an episode of *C. glabrata* BSI were included. The main outcomes were 14-day mortality and treatment failure (14-day mortality and/or persistent *C. glabrata* BSI for ≥48 h despite antifungal initiation). The impact of using fluconazole as initial antifungal treatment on the patients' prognosis was assessed by logistic regression analysis with the addition of a propensity score approach. A total of 94 patients with *C. glabrata* BSI were identified. Of these, 34 had received fluconazole and 35 had received an echinocandin/L-AmB-based regimen. Patients in the echinocandin/L-AmB group had poorer baseline clinical status than did those in the fluconazole group. Patients in the fluconazole group were more frequently (55.9% versus 28.6%) and much earlier (median time, 3 versus 7 days) switched to another antifungal regimen. Overall, 14-day mortality was 13% (9/69) and treatment failure 34.8% (24/69), with no significant differences between the groups. On multivariate analysis, after adjusting for baseline characteristics by propensity score, fluconazole use was not associated with an unfavorable evolution (adjusted odds ratio [OR] for 14-day mortality, 1.16, with 95% confidence interval [CI] of 0.22 to 6.17; adjusted OR for treatment failure, 0.83, with 95% CI of 0.27 to 2.61). In conclusion, initial fluconazole treatment was not associated with a poorer outcome than that obtained with echinocandins/L-AmB regimens in patients with *C. glabrata* BSI. (This study has been registered at ClinicalTrials.gov under registration no. NCT01236261.)**

AQ: B *Candida glabrata* has emerged as one of the most common non-*albicans Candida* species causing invasive candidiasis. The incidence of this infection is increasing, particularly in the United States, Canada, and Northern Europe, where *C. glabrata* accounts for 13% to 29% of all episodes of *Candida* bloodstream infection (BSI) (1–8).

The choice of optimal antifungal therapy for treating these patients and, particularly, whether fluconazole use is appropriate remain uncertain. According to current microbiological criteria, *C. glabrata* wild-type strains are considered intermediate or susceptible, dose dependent, to fluconazole, which means that prescribing fluconazole without confirmation of isolate susceptibility would not be recommended. Based on this evidence, the latest European and American guidelines have relegated the use of fluconazole to a step-down strategy for managing *C. glabrata* infection, favoring echinocandins as first-line empirical therapy (9, 10). Nonetheless, evidence from observational studies suggests that the maximum fluconazole dose (800 mg/day, or an amount equivalent to 12 mg/kg of body weight/day adjusted for renal failure) may achieve clinical success in infections caused by *C. glabrata* isolates with MIC values of ≤32 mg/liter (11).

Clinical efficacy analyses related to the choice of initial antifungal drug have been rarely performed in recent series of patients with *C. glabrata* infection (12). Thus, the aim of this study was to analyze the impact of initial antifungal treatment on the outcome of *C. glabrata* BSI and to determine whether initial use of fluconazole is associated with a poorer outcome than that obtained with echinocandin/liposomal amphotericin B (L-AmB)-based regimens.

MATERIALS AND METHODS

Study design, setting, and patients. The CANDIPOP study (ClinicalTrials.gov number NCT01236261) is a prospective, multicenter, population-based candidemia surveillance program (29 hospitals from 5 metro-

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politan areas) conducted in Spain between May 2010 and April 2011. Complete details on the study design and its main results have been published elsewhere (13). Briefly, blood cultures positive for *Candida* spp. were identified by the microbiology laboratories of the participating hospitals and reported to regional study coordinators, who obtained clinical data from the patients' medical records using a standardized case report form. Pertinent demographic, clinical, treatment, and 30-day follow-up data were compiled.

The choice of antifungal drug used and the timing of follow-up blood cultures to confirm candidemia clearance were left to the discretion of the attending physicians. Written informed consent was obtained from all patients, according to the requisites of the local institutional review boards.

The present report includes adult patients (≥16 years of age) diagnosed with *C. glabrata* BSI. Episodes in which two different *Candida* species were simultaneously identified were excluded. Only the first episode of *C. glabrata* BSI per patient was included in the analysis. This analysis was reported in accordance with the STROBE recommendations (14).

Microbiology. Isolates were forwarded to the Spanish National Microbiology Centre (Instituto de Salud Carlos III, Majadahonda, Madrid, Spain), where *Candida* species were definitively identified by sequencing the internal transcribed spacer 1 (ITS1) and ITS2 regions from ribosomal DNA (rDNA). Antifungal susceptibility testing was carried out according to the EUCAST (E.Def7.1 and E.Def7.2) (15, 16) and CLSI M27-A3 (17) broth microdilution methods. The second procedure was performed at Hospital General Universitario Gregorio Marañón (Madrid, Spain). Both these methods were used because previous microbiological data from the CANDIPOP study showed that the CLSI method offers higher MIC values for fluconazole in our *C. glabrata* strains than the EUCAST method (18). MICs of azoles and echinocandins were obtained after 24 h of incubation at 35°C and were defined as the antifungal drug concentration producing 50% growth inhibition relative to that of drug-free control growth. MICs by the CLSI method were additionally read at 48 h to avoid misclassification of borderline-resistant isolates because of a MIC shift (19). The CLSI (20) and EUCAST species-specific clinical breakpoints, published in the EUCAST website (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/AFST/Clinical_breakpoints/Antifungal_breakpoints_v_8.0_November_2015.pdf), were applied to categorize isolate susceptibilities. The presence of *FKS1* or *FKS2* gene mutations was investigated in isolates showing phenotypic resistance to one or more echinocandins. The hotspot 1 and 2 regions were amplified as previously described (18).

Outcomes and definitions. We aimed to evaluate potential differences in therapy response between patients initially treated with fluconazole (fluconazole group) and those treated with an echinocandin and/or L-AmB (echinocandin/L-AmB group). The primary study outcome was 14-day all-cause mortality, starting from the time of the first positive blood culture. The secondary outcome was treatment failure, defined as the composite variable of 14-day all-cause mortality and/or persistent *C. glabrata* BSI for ≥48 h despite antifungal initiation. To be included in the evaluation of these outcomes, patients had to receive at least 2 consecutive days of therapy with either fluconazole or an echinocandin and/or L-AmB as initial antifungal therapy after blood culture collection (except for patients who died within the first 48 h, who had to receive at least 1 complete day of therapy for inclusion). As an approach to study the pharmacokinetic/pharmacodynamic (PK/PD) parameters that best correlated with fluconazole efficacy, we also investigated potential correlations between the patient's prognosis and the fluconazole daily dose/MIC ratio as a surrogate marker of the area under the concentration-time curve/MIC ratio (11).

Episodes occurring after 2 days of hospitalization were considered hospital acquired. Breakthrough candidemia was defined as development of *C. glabrata* BSI in patients who had been receiving antifungal drugs for >3 days. The criteria for proven catheter-related candidemia have been described elsewhere (21). Secondary foci required isolation of the same *Candida* species in the presumed source of infection. Adequate source control included removal of all central venous catheters (CVC) within the first 24 h after initiation of antifungal treatment or drainage of intra-abdominal abscesses if a collection was present. Episodes occurring in patients without an intravascular device or potentially drainable source were considered as having adequate source control. On the day of blood sample extraction, the Pitt bacteremia score (22) and the acute physiology and chronic health evaluation II (APACHE II) score for intensive care unit (ICU) patients (23) were recorded to estimate disease severity. In detail, the Pitt bacteremia score was calculated based on oral temperature (35.1 to 36.0°C or 39.0 to 39.9°C, 1 point; ≤35 or ≥40°C, 2 points), blood pressure (hypotension, 2 points), mental status (disorientation, 1 point; stupor, 2 points; coma, 4 points), respiratory status (mechanical ventilation, 2 points), and cardiac status (cardiac arrest, 4 points).

Statistical analysis. Quantitative variables are reported as the medians (interquartile range [IQR]) and qualitative variables as absolute numbers and relative frequencies. The chi-square test or Fisher's exact test was used for comparisons of categorical variables, and the Student *t* test was used for continuous variables. The Mann-Whitney *U* test was applied in variables with a nonnormal distribution.

Determinants of 14-day mortality and treatment failure were analyzed by logistic regression analysis. Given the limited sample size and imbalances between the baseline characteristics of the treatment groups, a propensity score-based approach was used to minimize the risk of confounding by indication. The probability of receiving fluconazole or an echinocandin/L-AmB was estimated using a penalized logistic regression model that included variables with *P* values of <0.2 in the univariate analysis. Specifically, the full model was developed by using a penalized maximum likelihood estimation to directly correct for overfitting (i.e., a small data set with a large number of candidate predictors in relation to the number of events). It was further simplified by decreasing the number of predictors based on recommendations in the related literature (24, 25). Ultimately, 4 variables were included in the final model (age, ICU admission, immunosuppressive therapy, and prior surgery). The propensity score model obtained showed an area under the receiving operating characteristic (ROC) curve of 0.795, thus suggesting good predictive ability. The propensity score was then entered as a covariate into the multivariate models analyzing the primary and secondary outcome measures to adjust for the effects of confounding factors (26, 27). In addition, the center effect was controlled by performing a sensitivity analysis on outcome variables (14-day mortality and treatment failure) by using multilevel models according to the participating center. Because the APACHE II score was not available for all patients, a composite variable reflecting disease severity was created to adjust for this potential host confounder of mortality. Patients were classified as having *high severity of illness* when they met any of the following criteria: APACHE II score of ≥15, Pitt score of ≥3, or severe renal failure, defined as dependence on renal replacement therapy at candidemia onset. Statistical analyses were performed with Microsoft SPSS-PC+, version 15.0 (SPSS, Chicago, IL, USA), and R software package, version 3.0.3 (R Project for Statistical Computing, http://www.r-project.org/).

RESULTS

In total, 773 episodes of *Candida* BSI were identified during the 1-year study period. Twenty-one case-patients declined to participate, resulting in 752 evaluable episodes. Of these, 103 (13.4%) were caused by *C. glabrata*, yielding an annual incidence of 1.08 episodes per 100,000 inhabitants, 0.56 episodes per 1,000 admissions, and 0.93 episodes per 10,000 patient-days.

Patient characteristics of the entire cohort. Among the 103 episodes of *C. glabrata* BSI, 94 different patients-episodes met the inclusion criteria and were ultimately analyzed (Fig. 1). The median age of the patients was 71.8 (IQR, 59.1 to 79.2) years, and 24 patients (25.5%) were hospitalized in the ICU at the time of BSI onset. The most common comorbidities and predisposing risk

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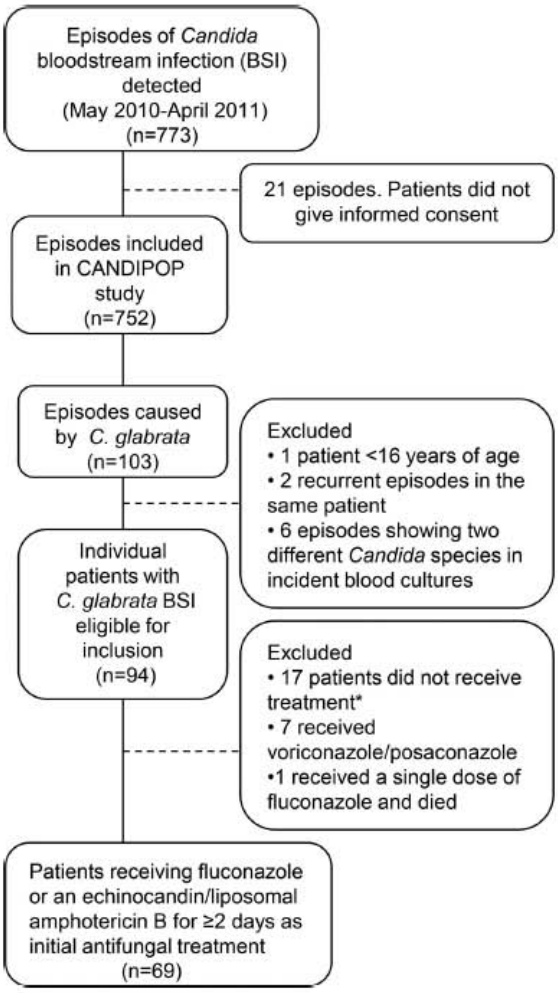

FIG 1 Flow chart of patients included in the study.

factors for candidemia were the presence of malignancy in 41 (43.6%), CVC placement in 63 (67%), and prior gastrointestinal surgery in 34 (36.2%) patients.

Treatment groups. Seventy-seven (81.9%) patients received antifungal therapy for the episode, and 69 were eligible for the clinical outcome evaluation: 34 (49.3%) in the fluconazole group and 35 (50.7%) in the echinocandin and/or L-AmB group (Fig. 1).

In the fluconazole group, 1 patient (2.9%) received 200 mg/day, 28 patients (82.4%) received 400 mg/day, and 5 patients (14.7%) received 800 mg/day (or equivalent doses after adjusting by renal function). In the echinocandin/L-AmB group, 30 patients (85.7%) received echinocandins, 4 (11.4%) L-AmB, and 1 (2.9%) a combination of caspofungin and L-AmB. All antifungal agents were dosed according to universally accepted dosing regimens (9, 10).

Demographic and clinical characteristics of the patients by treatment group are shown in Table 1. Compared to fluconazole-treated patients, patients in the echinocandin/L-AmB group were more likely to be receiving immunosuppressive therapy (25.7% versus 5.9%, $P = 0.024$), be admitted to the ICU at diagnosis (37.1% versus 17.6%, $P = 0.070$), or have a CVC in place (82.9% versus 64.7%, $P = 0.086$). There were no significant differences in the source of candidemia, the median time to receive antifungal therapy, or the rate of adequate source control. However, a higher percentage of patients in the echinocandin/L-AmB had follow-up blood cultures after starting antifungal treatment (91.4% [32/35] versus 58.8% [20/34], $P = 0.002$). T1

Duration of initial antifungal regimen. Median duration of the initial antifungal regimen was shorter in the fluconazole group than in the echinocandin/L-AmB group (5 days [IQR, 3 to 14] versus 13 days [IQR, 7 to 22], $P = 0.001$). Nineteen patients (55.9%) in the fluconazole group were switched to other antifungal regimens after a median of 3 days (range, 2 to 20): 17 to echinocandins, 1 to L-AmB, and 1 to voriconazole. Ten patients (28.6%) in the echinocandin/L-AmB group were transitioned to fluconazole (8 patients) or voriconazole (2 patients) after a median of 7 days (range, 3 to 39). None of the aforementioned antifungal changes were due to drug-related adverse events.

Antifungal susceptibility testing. Antifungal susceptibility results for all 94 isolates are shown in Table 2. In the subset of 69 episodes evaluable for clinical outcome, fluconazole resistance was found in 5.8% of isolates according to the EUCAST method and in 11.6% by the CLSI procedure after 24 h of incubation. Regarding the CLSI technique, identical resistance rates were found when MICs were additionally determined at 48 h. The EUCAST and 24-h CLSI methods agreed on identification of a single isolate resistant to all echinocandins in the overall cohort. It should be noted, however, that EUCAST has not yet established clinical breakpoints for caspofungin; hence, isolates that were susceptible to anidulafungin as well as micafungin were considered susceptible to caspofungin. The single echinocandin-resistant strain was harboring a deletion of the F659 amino acid in the *FKS2* gene (18). All isolates were susceptible to L-AmB, and none of the fluconazole-resistant isolates were also resistant to any echinocandin. AQ:C/

Outcomes and fluconazole pharmacodynamics. Overall, 14-day mortality was 13% (9/69) and treatment failure 34.8% (24/69), with no significant differences between the groups (Table 1). None of the patients had evidence of hematogenous dissemination of *C. glabrata* (e.g., endophthalmitis, endocarditis) within 30 days after the first positive blood culture.

To explore whether patients who had an early switch from fluconazole to another antifungal regimen may have benefitted from this change, the 11 patients who received a short duration of initial fluconazole treatment (≤3 days) were compared with those who were switched later or those who did not change the initial fluconazole therapy ($n = 23$). In this analysis, no differences in 14-day mortality (9.1% [1/11] versus 13% [3/23], $P = 1$) or treatment failure (27.3% [3/11] versus 34.8% [8/23], $P = 1$) were found between the two cohorts.

Because of the low 14-day mortality (4 of 34, 11.8%) and treatment failure (11 of 34, 32.4%) rates in the fluconazole group, we did not perform correlation analyses between fluconazole MIC values or fluconazole pharmacodynamic parameters (fluconazole dose/MIC ratio) and outcomes. However, 29 of the 34 patients (85.3%) had a daily fluconazole dose/24-h CLSI MIC ratio of ≥25,

TABLE 1 Comparison between patients who received fluconazole or an echinocandin and/or liposomal amphotericin B as initial treatment for *C. glabrata* bloodstream infection[a]

Variable	Initial antifungal therapy		*P* value
	Fluconazole ($n = 34$)	Echinocandin and/or L-amphotericin B ($n = 35$)	
Demographics			
Age (yr)	75.4 (57.8–82.3)	65.6 (55.2–73.2)	0.118
Male sex	20 (58.8)	22 (62.9)	0.731
Hospital-acquired candidemia	27 (79.4)	29 (82.9)	0.714
Time (days) in hospital to candidemia onset	18 (11–35)	25 (14.5–38.5)	0.409
In ICU at diagnosis	6 (17.6)	13 (37.1)	0.070
APACHE II score	21.5 (14.8–25)	19 (14–25)	0.970
Comorbidities			
Charlson index score	2 (1–4)	2 (1–3)	0.407
Hematologic malignancy	0 (0)	4 (11.4)	0.114
Diabetes mellitus	9 (26.5)	11 (31.4)	0.650
Chronic renal failure	4 (11.8)	5 (14.3)	1.000
Renal replacement therapy	2 (5.9)	3 (8.6)	1.000
HIV infection	0 (0)	2 (5.7)	0.493
Liver cirrhosis	1 (2.9)	1 (2.9)	1.000
Predisposing risk factor			
Central venous catheter	22 (64.7)	29 (82.9)	0.086
Previous surgery (3 mo)	22 (64.7)	17 (48.6)	0.176
Gastrointestinal surgery	18 (52.9)	12 (34.3)	0.118
Total parenteral nutrition	14 (41.2)	19 (54.3)	0.276
Immunosuppressive treatment	2 (5.9)	9 (25.7)	0.024
Prior antibiotic therapy (1 mo)	31 (91.2)	34 (97.1)	0.356
Prior azole exposure (1 mo)	6 (17.6)	6/34 (17.6)	1.000
Breakthrough candidemia	3 (8.8)	7/34 (20.6)	0.171
Clinical data at candidemia onset			
Septic shock	5 (14.7)	7 (20)	0.562
Intubation	5 (14.7)	9 (25.7)	0.256
Neutropenia (<500 cells/mm^3)	0 (0)	1 (2.9)	1.000
Pitt score	1 (0–4)	1 (0–4)	0.902
Bacteria in incident blood culture	5 (14.7)	6 (17.1)	0.782
Source of infection			
Primary	18 (52.9)	16 (45.7)	0.548
Catheter related	10 (29.4)	8 (22.9)	0.535
Abdominal	2 (5.9)	5 (14.3)	0.428
Urologic	4 (11.8)	4 (11.4)	1.000
Others	0 (0)	2 (5.7)	0.493
Therapeutic strategies			
Time (days) to receiving antifungal therapy[b]	2 (0–3)	2 (1–3)	0.391
CVC removal (≤48h)[c]	13/22 (59.1)	17/29 (58.6)	0.973
Adequate source control	28 (82.4)	27 (77.1)	0.591
Outcomes			
14-day all-cause mortality	4 (11.8)	5 (14.3)	1.000
Persistent candidemia[d]	7/20 (35)	10/32 (31.3)	0.779
Treatment failure at 14 days	11 (32.4)	13 (37.1)	0.676

[a] Unless noted otherwise, values represent the absolute no. (%) of patients in the category; continuous variables are expressed as the median (interquartile range). IQR, interquartile range; ICU, intensive care unit; CVC, central venous catheter.
[b] Data missing for 1 patient.
[c] Considering patients with central venous catheter as a risk factor for candidemia ($n = 51$).
[d] Follow-up blood cultures were obtained after start of antifungal treatment in 52 of 69 patients (74.5%) at a median of 3.5 days (IQR, 2 to 7), with no significant differences between the groups.

TABLE 2 Antifungal susceptibility testing of 94 *C. glabrata* isolates by CLSI and EUCAST broth microdilution methods after 24 h of incubation[a]

Antifungal agent	EUCAST method results				CLSI method results			
	GM	MIC_{90} (mg/liter)	MIC range (mg/liter)	Resistance rate, *n*/*N* (%)	GM	MIC_{90} (mg/liter)	MIC range (mg/liter)	Resistance rate, *n*/*N* (%)
Anidulafungin	0.031	0.03	0.03–0.5	1 (1.1)	0.032	0.06	0.007–1	1 (1.1)
Caspofungin	0.44	1	0.25–1	NA	0.15	0.25	0.007 to >2	1 (1.1)
Micafungin	0.031	0.03	0.03–1	1 (1.1)	0.016	0.03	0.007–2	1 (1.1)
Fluconazole	3.19	16	0. 5 to >64	6 (6.4)	10.26	64	1 to >64	10 (10.6)
Voriconazole	0.13	0.5	0.015–8	NA	0.12	0.5	0.003 to >2	NA

[a] Abbreviations: GM, geometric mean; MIC_{90}, 90% MIC; NA, not applicable; *n*/*N*, ratio of resistant isolates to total isolates.

which is a reported predictor of treatment success (11). Of note, 2 patients with fluconazole-resistant isolates survived despite receiving inadequate initial treatment (400 mg of fluconazole/day or a dose/MIC ratio of 3.125 assuming an average weight of 70 kg). These patients had prompt source control, were not admitted to the ICU, and were not categorized as having high severity of illness at presentation.

Predictors of mortality and clinical failure. On univariate analysis, several host- and infection-related factors were associated with 14-day mortality and treatment failure (Table 3). We were unable to construct a single multivariate model including all potential confounders of treatment outcome (e.g., disease severity, infection source, and source control). That analysis would have overfitted the model with an excessive number of variables compared to the number of events (9 deaths and 24 treatment failures). As an alternative, we created a number of different multivariate models in which only one covariate was added at a time to fluconazole use and the propensity score. After adjusting the model for baseline characteristics with the propensity score, use of fluconazole or an echinocandin/L-AmB as initial antifungal therapy was not significantly related to the risk of death or response to treatment (adjusted OR for 14-day mortality, 1.16, with 95% CI of 0.22 to 6.17; adjusted OR for treatment failure, 0.83, with 95% CI of 0.27 to 2.61). Further multilevel adjustment for participating center did not meaningfully modify these results (Fig. 2).

In addition, because current guidelines consider voriconazole as an alternative agent for treating candidemia and all triazole classes have decreased activity against *C. glabrata*, we repeated the same analyses comparing patients who received any triazole as initial antifungal therapy (fluconazole [34 patients], voriconazole [6 patients], or posaconazole [1 patient]) with those who received an echinocandin-based/L-AmB regimen (35 patients). Again, no association was found between the initial antifungal treatment and either outcome measure (adjusted OR for 14-day mortality, 1.04, with 95% CI of 0.21 to 6.15; adjusted OR for treatment failure, 0.98, with 95% CI of 0.36 to 2.71).

DISCUSSION

In this observational study, the choice of initial antifungal agent (fluconazole versus echinocandin/L-AmB-based regimens) had no apparent impact on the risk of 14-day mortality or treatment failure in patients with *C. glabrata* BSI. Although patients initially receiving echinocandin/L-AmB were in poorer baseline condition than those receiving fluconazole, there were no significant differences in the outcomes of the two groups after adjusting by the propensity score and disease severity. These findings are clinically relevant. Fluconazole is still the most commonly prescribed antifungal in hemodynamically stable patients who are not hospitalized in ICUs (13, 28), and published data on its effectiveness for *C. glabrata* BSI treatment are scarce and a matter of debate. The results found here do not support initial use of fluconazole for all cases of candidemia and in all settings, but rather, they suggest that fluconazole may be a valid option as initial treatment for less severely ill patients who have not been exposed to azoles, even when *C. glabrata* cannot be ruled out. This clinical approach may decrease overuse of echinocandins as first-line agents, thereby reducing hospital expenditure and limiting the emerging risk of echinocandin-resistant strains (29).

To date, only one randomized clinical trial has compared fluconazole at a standard dose of 400 mg/day and anidulafungin for invasive candidiasis (30). The treatment response in the echinocandin arm was not inferior to that of fluconazole. However, this study was not designed to assess treatment differences between subgroups of *Candida* species, and only 38 patients with *C. glabrata* were evaluated for overall treatment response; hence, definitive conclusions could not be drawn for this species. Two more-recent studies that focused on *C. glabrata* BSI demonstrated that echinocandin therapy was associated with greater treatment success but not with increased survival (12, 31). The first of these, a retrospective observational study by Eschenauer et al. found no differences in 28-day mortality between patients with *C. glabrata* BSI initially treated with fluconazole for ≥5 days and patients receiving echinocandins (12). Nonetheless, fluconazole tended to be less effective in the ICU population, thus supporting preferred use of echinocandins in more severely ill patients. Similarly, a patient level quantitative review of randomized clinical trials found no influence of antifungal therapy on 30-day mortality when the subgroup of 104 episodes of *C. glabrata* was analyzed (31). Notwithstanding this, both investigations differ from our results in showing that echinocandins were predictors of treatment success. It is possible that the lower frequency of blood sampling in our fluconazole group may have influenced the evaluation of treatment response and limited the capacity to detect real differences in microbiological eradication between treatment groups. However, our data lend support to previous studies that have also failed to demonstrate an association between antifungal choice and mortality in *C. glabrata* BSI.

Another matter under discussion is the optimal fluconazole dosing for *C. glabrata* infection. Given the decreased susceptibility of *C. glabrata* to fluconazole, current guidelines recommend the maximum dose of 800 mg/day (or 12 mg/kg/day) for treating these infections (10). However, 65% of patients in Eschenauer's study and most of our patients received an inadequate fluconazole dose according to this criterion, mainly because antifungal treat-

TABLE 3 Univariate logistic regression analyses of prognostic factors for 14-day all-cause mortality and treatment failure in patients with *C. glabrata* bloodstream infection receiving fluconazole or echinocandin/liposomal-amphotericin B-based regimens as initial treatment[a]

Variable	Mortality (primary outcome)				Treatment failure (secondary outcome)			
	Alive ($n = 60$)	Died ($n = 9$)	OR (95% CI)	*P* value	Success ($n = 45$)	Failure ($n = 24$)	OR (95% CI)	*P* value
Age (yr)	68.8 (51.4–77.2)	78.0 (64.9–83.5)	1.05 (0.99–1.12)	0.088	70.6 (51.9–78.7)	69.9 (63.0–77.9)	1.01 (0.98–1.03)	0.749
Male sex	36 (60)	6 (66. 7)	1.33 (0.30–5.85)	0.703	26 (57.8)	16 (66.7)	1.46 (0.52–4.11)	0.472
Comorbidities and risk factors								
Charlson index score	2 (1–4)	2 (1–3)	0.77 (0.49–1.20)	0.247	2 (1–4)	2 (1–3)	0.83 (0.62–1.10)	0.190
Malignancy (≤1 yr)	30 (50)	0 (0)			22 (48.9)	8 (33.3)	0.52 (0.19–1.47)	0.217
Immunosuppressive treatment	11 (18.3)	0 (0)			10 (22.2)	1 (4.2)	0.15 (0.02–1.27)	0.082
Neutropenia (<500 cells/mm^3)	1 (1.7)	0 (0)			1 (2.2)	0 (0)		
Gastrointestinal surgery	26 (43.3)	4 (44.4)	1.05 (0.26–4.29)	0.950	18 (40)	12 (50)	1.5 (0.55–4.07)	0.426
Prior RRT	2 (3.3)	3 (33.3)	14.5 (2.01–104.68)	0.008	1 (2.2)	3 (12.5)	8.8 (0.92–83.84)	0.059
Intubation	9 (15)	5 (55.6)	7.08 (1.59–31.54)	0.010	5 (11.1)	9 (37.5)	4.80 (1.38–16.65)	0.013
Antifungal agent at blood culture collection	10/59 (16.9)	4 (55.6)	6.13 (1.39–26.91)	0.016	7/44 (15.9)	8 (33.3)	2.64 (0.82–8.53)	0.104
Source of infection								
Primary	28 (46.7)	6 (66.7)	2.29 (0.52–10.00)	0.272	22 (48.9)	12 (50)	1.05 (0.39–2.82)	0.930
Catheter related	18 (30)	0 (0)			13 (28.9)	5 (20.8)	0.65 (0.20–2.10)	0.470
Abdominal	4 (6.7)	3 (33.3)	7.00 (1.26–38.99)	0.026	2 (4.4)	5 (20.8)	5.66 (1.01–31.80)	0.049
Urologic	8 (13.3)				7 (15.6)	1 (4.2)	0.24 (0.03–2.04)	0.190
Others	2 (3.3)				1 (2.2)	1 (4.2)	1.91 (0.11–32.01)	0.652
Clinical data at candidemia onset								
High severity of illness	20 (33.3)	8 (88.9)	16.0 (1.87–136.95)	0.011	16 (35.6)	12 (50)	1.81 (0.66–4.96)	0.247
Septic shock	8 (13.3)	4 (44.4)	5.20 (1.15–23.56)	0.032	7 (15.6)	5 (20.8)	1.43 (0.40–5.10)	0.583
Therapeutic strategies								
Fluconazole	30 (50)	4 (44.4)	0.80 (0.20–3.27)	0.756	23 (51.1)	11 (45.8)	0.81 (0.30–2.19)	0.676
Echinocandins-L-AmB	30 (50)	5 (55.6)	1.25 (0.31–5.11)	0.756	22 (48.9)	13 (54.2)	1.24 (0.46–3.34)	0.676
CVC removed within 24 h after[b] starting antifungal treatment	31/44 (70.5)	2/7 (28.6)	0.168 (0.03–0.98)	0.047	24/32 (75)	9/19 (47.4)	0.30 (0.09–1.00)	0.050
Adequate source control	49 (81.7)	6 (66.7)	0.45 (0.10–2.08)	0.306	39 (86.7)	16 (66.7)	0.31 (0.09–1.03)	0.056
Time (days) to receiving antifungal therapy	2 (1–3)	0 (0–3)	0.75 (0.46–1.22)	0.248	2 (1–3)	1 (0–3)	0.81 (0.59–1.12)	0.197

[a] Unless noted otherwise, values represent the absolute no. (%) of patients in the category; continuous variables are expressed as the median (interquartile range). Abbreviations: IQR, interquartile range; RRT, renal replacement therapy; CVC, central venous catheter.

[b] Considering patients with CVC as a risk factor for candidemia ($n = 51$).

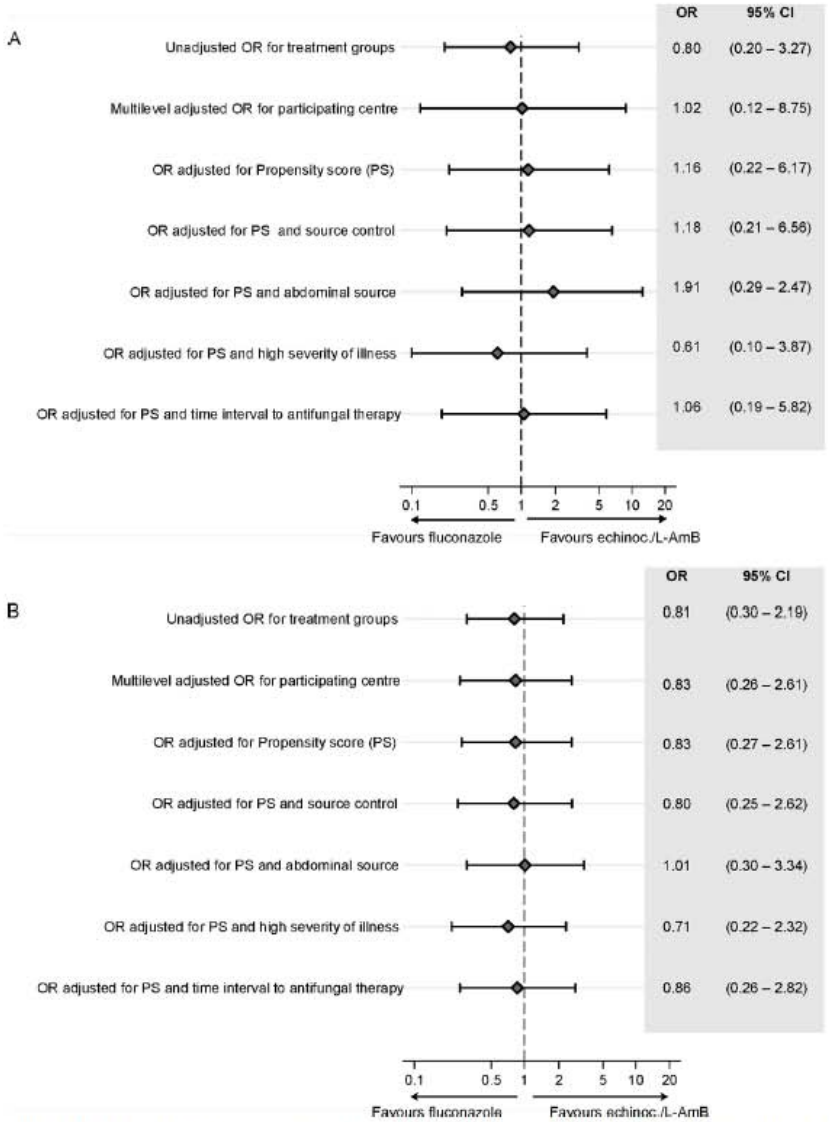

FIG 2 Adjusted odds ratios for 14-day mortality (A) and treatment failure (B) according to initial antifungal therapy (fluconazole or echinocandin/liposomal amphotericin B).

ment was prescribed before the *Candida* species had been identified. Nevertheless, we stress that initial use of fluconazole was not associated with a poorer prognosis, even in these circumstances. These findings suggest that suboptimal fluconazole doses may still exert a certain activity against *C. glabrata* strains. Current recommendations for high-dose fluconazole in *C. glabrata* infection are based on studies that have analyzed treatment success or cure rates rather than mortality as the endpoint (11). However, previous pharmacokinetic/pharmacodynamic analyses have demonstrated a clear relationship between fluconazole dose, MIC values, and response to antifungal treatment (32). Thus, we believe that when fluconazole is used as initial treatment for candidemia and *C. glabrata* infection cannot be ruled out, a prudent approach would be administration of the maximum dose of 800 mg/day. With this clinical strategy, more than 85% of susceptible dose-dependent *C. glabrata* isolates would be covered in settings with low rates of resistance to fluconazole, such as Spain, some areas of the United States, Northern Europe, and South America (8, 18, 33, 34).

To further complicate the evaluation of the response to antifungal treatment, other factors apart from microbiological aspects seem to come into play and should be considered. Two patients in the fluconazole group in our study survived, even though the *C. glabrata*

strains isolated were resistant to fluconazole. This means that despite the relevance of MIC values and susceptibility testing to estimate drug activity, they are only a part of the picture. Source control, underlying host immune status, and baseline disease severity also have an impact on treatment success or failure and should be included in the decision of the initial antifungal therapy to be used. Additionally, drug distribution to the site of the infection is also a relevant factor. In particular, fluconazole is preferred over echinocandins in cases of *C. glabrata* urinary tract infection because it can reach urine concentrations that exceed the MIC for susceptible dose-dependent strains, whereas echinocandins do not (35).

This study has some limitations. First, because of its observational nature, the choice of initial antifungal drug was not randomized and patients with a poorer baseline status were more frequently given an echinocandin/L-AmB regimen than fluconazole. However, a propensity score analysis was performed and the multivariate model was adjusted by factors and confounders known to be associated with therapy choice, treatment response, and mortality. Second, the reasons why the initial antifungal drug was changed are unknown. It is true that patients in the fluconazole group were more frequently and much earlier switched to another antifungal regimen, but this strategy does not necessarily reflect patients' unfavorable evolution. It might also highlight the influence of current guidelines favoring the use of echinocandins for infections caused by *C. glabrata*. Third, follow-up blood cultures were not performed for all patients. This could have led to an underestimation of the true incidence of persistent candidemia and introduced bias in the analysis of treatment failure. However, paired blood cultures are typically repeated in patients who are not responding to treatment and those with signs of an unfavorable clinical course. Furthermore, the clinical relevance of persistent candidemia on a patient's final outcome has not been well established (36). Finally, the sample size was too small to enable a single multivariate analysis including all confounding factors, thus limiting the statistical power of the study. Therefore, our results should be interpreted with caution, especially when dealing with severely ill patients.

In conclusion, this multicenter study based on of patients with *C. glabrata* BSI found that initial treatment with fluconazole was associated with 14-day all-cause mortality and treatment failure similar to those associated with echinocandin/L-AmB-based regimens. These results suggest that in settings with low rates of fluconazole-resistant *C. glabrata* strains, this agent may be still a reasonable option for treating stable patients with candidemia before the *Candida* species is identified. Further clinical studies are needed to better understand the role of fluconazole as an optional treatment for *C. glabrata* BSI.

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12. ANEXOS

ANEXO 1. Hoja de registro del estudio CANDIPOP

ClinicalTrials.gov
Protocol Registration System

Protocol Registration Receipt
11/05/2010

Prospective Population Study on Candidemia in Spain (CANDIPOP)

This study has been completed.

Verified by Fundacion SEIMC-GESIDA, November 2010

Sponsor:	Fundacion SEIMC-GESIDA
Collaborators:	Astellas Pharma Inc Gilead Sciences Merck Pfizer
Information provided by:	Fundacion SEIMC-GESIDA
ClinicalTrials.gov Identifier:	NCT01236261

Purpose

The aim of this study is to describe the epidemiology of fungal blood infections in Spain (with emphasis on the incidence, fungal species distribution and antifungal susceptibility). The study is to be performes in five big cities which represent different geograpic areas: Barcelona, Bilbao, Madrid and Valencia.

Condition	Intervention
Fungemia	Non intervention

Study Type: Observational
Study Design: Case-Only, Prospective
Official Title: Prospective Population Study on Candidemia in Spain (Estudio Poblacional Prospectivo Sobre Candidemia en España)

Further study details as provided by Fundacion SEIMC-GESIDA:

Biospecimen Retention: Samples Without DNA

ANEXO 2. Miembros y centros participantes del estudio CANDIPOP

Belén Padilla, Patricia Muñoz y Jesús Guinea (Hospital General Universitario Gregorio Marañón, Madrid); José Ramón Paño, Julio García y Carlos García (Hospital Universitario La Paz, Madrid); Jesús Fortún, Pilar Martín y Elia Gómez (Hospital Universitario Ramón y Cajal, Madrid); Pablo Ryan y Carolina Campelo (Hospital Infanta Leonor, Madrid); Ignacio de los Santos y Buenaventura Buendía (Hospital Universitario La Princesa, Madrid); Beatriz Perez y Mercedes Alonso (Hospital Universitario del Niño Jesús, Madrid); Francisca Sanz y José María Aguado (Hospital Universitario "12 de Octubre", Madrid); Paloma Merino y Fernando González (Hospital Clínico San Carlos, Madrid); Miguel Gorgolas e Ignacio Gadea (Fundación Jiménez Díaz, Madrid); Juan Emilio Losa y Alberto Delgado-Iribarren (Hospital de Alcorcón, Madrid); Antonio Ramos, Yolanda Romero e Isabel Sánchez (Hospital Universitario Puerta de Hierro-Majadahonda, Madrid); Oscar Zaragoza y Manuel Cuenca-Estrella (Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Madrid); Jesús Rodriguez-Baño y Ana Isabel Suarez (Hospital Universitario Virgen Macarena, Sevilla); Ana Loza, Ana Isabel Aller y Estrella Martín-Mazuelos (Hospital Universitario Virgen de Valme, Sevilla); Maite Ruiz y José Garnacho-Montero (Hospital Universitario Virgen del Rocío, Sevilla); Carlos Ortiz (Hospital Sagrado Corazón, Sevilla); Mónica Chávez y Fernando L. Maroto (Hospital San Juan de Dios de Aljarafe, Sevilla); Miguel Salavert y Javier Pemán (Hospital Universitari La Fe, Valencia); José Blanquer y David Navarro (Hospital Clínico Universitario de Valencia); Juan José Camarena y Rafael Zaragoza (Hospital Universitario Dr. Peset, Valencia); Vicente Abril y Concepción Gimeno (Consorcio

Hospital General Universitario de Valencia); Silvia Hernáez y Guillermo Ezpeleta (Hospital de Basurto, Bilbao); Elena Bereciartua, José L. Hernández y Miguel Montejo (Hospital Universitario de Cruces, Bilbao); Rosa Ana Rivas y Rafael Ayarza (Hospital de Galdakano, Bilbao); Ana Mª Planes, Isabel Ruiz-Camps y Benito Almirante (Hospital Universitari Vall d´Hebron, Barcelona); José Mensa y Manel Almela (Hospital Clínic-IDIBAPS, Barcelona); Mercè Gurgui y Ferran Sánchez-Reus (Hospital Universitari de Sant Pau i Santa Creu, Barcelona); Joaquin Martinez-Montauti y Montserrat Sierra (Hospital de Barcelona, Barcelona); Juan Pablo Horcajada, Luisa Sorli y Julià Gómez (Hospital del Mar, Barcelona); Amadeu Gené y Mireia Urrea (Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona).

Miembros colaboradores del estudio CANDIPOP: Maricela Valerio, Mario Fernández-Ruiz (Madrid), Ana Díaz-Martín (Sevilla), Francesc Puchades (Valencia), Alessandra Mularoni (Bilbao) y Mireia Puig-Asensio (Barcelona).

ANEXO 3. Cuaderno de recogida de datos del estudio CANDIPOP

CRD Estudio CANDIPOP Versión 4_28 junio de 2010

DATOS VISITA

Código Episodio: __ __ __ / __ __ __

Información

Fecha del episodio de fungemia (dd/mm/aaaa): ____/____/ _____

¿Se ha recogido algún episodio anterior en este estudio?: Sí ___ No___
Se considerará un nuevo episodio si cumple estos criterios: (1) aislamiento de una levadura de diferente especie a la que se aisló previamente, o (2) la misma especie aislada pero 1 mes después del episodio actual.

Código del episodio anterior __ __ __ / __ __ __

Sexo: Masculino __ Femenino __

Fecha de nacimiento (dd/mm/aaaa) ___/___/ ____

¿Donde se encontraba el paciente cuando se obtuvo el hemocultivo +?

Urgencias: ____ Hospitalizado ___ (Fecha hospitalización): ____/____/_____

Sala de hospitalización cuando se obtuvo el hemocultivo + para levadura:

□ Medicina: (Indique la especialidad):

□Medicina Interna □Digestivo □Cardiología □Neumología □Nefrología □Reumatología □Neurología □Oncología □Hematología □Otra:.....

□Cirugía: (Indique la especialidad):

□General □Urología □Vascular □Neurocirugía □Cardiaca □ Torácica □Traumatología □Otra:.....

□Otros (Indique la especialidad):

□Quemados □Pediatría □Obstetricia/Ginecología □Unidad trasplante □Hospital de Día □Hospitalización domiciliaria □Otro:.....

□Unidad de Cuidados Intensivos (Indique el tipo de UCI):

□Coronaria □UCI Mixta Adultos □UCI Médica Adultos □REA postQ □UCP □UCI Neonatal □UCI Pediatría

APACHE II:..... (para pacientes adultos ingresados en UCI en el día de la fungemia)

Procedía el paciente de otro hospital/institución, al ingresar en el centro donde ocurrió la fungemia?: Sí__ No__ Desconocido__

Si es sí, indicar tipo de centro:

□Hospital □Centro cuidados crónicos □Otros:.....

DATOS VISITA BASAL

Código Episodio: __ __ __ / __ __ __

¿Estuvo ingresado en un hospital (mas de 24 horas) durante los 3 meses anteriores al hemocultivo + para levadura?

Sí__ No__ Desconocido__

Factores predisponentes y enfermedad de base (presentes en los 3 meses previos a

¿Existían factores predisponentes?: Sí__ No__

Si es que sí, seleccione entre las siguientes (puede ser más de una):

Tumor sólido/hematológico:

Sí__ No__ Desconocido __ □ Leucemia □ Linfoma □ Órgano sólido

Situación clínica en el momento de la fungemia:

□Debut □Remisión completa □R. parcial □Tumor resistente □ Recidiva □Otro……

Fecha del último tratamiento para la enfermedad de base: ___ /___ /____

□QT 1ª línea □ QT 2ª línea □AutoTMO □AloTMO □Radioterapia □Mantenimiento

□Cirugía en el mes previo (como tratamiento del tumor) □Otra especificar):….. .....

Otra condición hematológica (aplasia, hemoglobinopatía, etc):

Sí__ No__ Desconocido ___

Receptor de trasplante: Sí____ No_____ Desconocido _____

Si sí, marcar el órgano(s) trasplantado(s): □ Riñón □ Corazón □ Pulmón □ Hígado □ Páncreas □ Intestino delgado □ Médula ósea □ *Stem cells* □ Otro:……

Neutropenia (cuando la fungemia): Sí__ No___ Desconocido ___

Si sí, recuento de neutrófilos: 0: <100 1: <500 2: <1000

Mucositis: Sí__ No__ Desconocido __

Diarrea: Sí__ No__ Desconocido __

VIH+: Sí__ No__ Desconocido __

Si sí: ¿cumple criterios de SIDA (estadio C y/o 3)?: Sí__ No__ Desconocido __

Recuento CD4+ más reciente:_____, y fecha: ___ /___ /___

DATOS VISITA BASAL

Código Episodio: __ __ __ / __ __ __

Factores predisponentes y enfermedad de base (presentes en los 3 meses previos a la fungemia)

Enfermedad cardiovascular: Sí__ No__ Desconocido ___

Si sí, especificar diagnóstico: □ Cardiopatía isquémica □ Insuficiencia cardiaca □ Otras (especificar):……

Enfermedad pulmonar: Sí__ No__ Desconocido __

Si sí, especificar diagnóstico: □ Asma □ EPOC □ Otras (especificar):……

Enfermedad hepática: Sí__ No__ Desconocido ___

Si sí, especificar diagnóstico: □ Cirrosis □ Hepatitis crónica □ Hepatitis aguda □ Otras (especificar):……

Insuficiencia renal: Sí__ No__ Desconocido ___

Si sí, especificar diagnóstico:

□.Insuficiencia renal aguda □.Insuficiencia renal crónica

¿Sigue el paciente diálisis?:

□ No □ Hemodiálisis □ Diálisis peritoneal □ Hemodiafiltración

Si hemodiálisis, a través de:

□ FAV □ CVC yugular □ CVC femoral □ CVC subclavia

Diabetes mellitus: Sí__ No__ Desconocido ___

Si sí, especificar tratamiento: □ Insulina □ Antidiabéticos orales □ Dieta exclusivamente □ Desconocido

Enfermedad neurológica: Sí__ No__ Desconocido ___

Si sí, especificar diagnóstico:

□ ACV □ Demencia □ Epilepsia □ Otros (especificar):……..

Enfermedad autoinmune: Sí__ No__ Desconocido ___

Si sí, especificar diagnóstico:

□.Artritis reumatoide □ LES □ Esclerodermia □ Otros especificar):……..

¿Se trata con inmunosupresores? Sí__ No__ Desconocido ___

DATOS VISITA

Código Episodio: _ _ _ _ / _ _ _ _

Factores predisponentes y enfermedad de base (presentes en los 3 meses previos a la fungemia)

Enfermedad inflamatoria intestinal: Sí__ No__ Desconocido __

¿Se trata con inmunosupresores? Sí__ No__ Desconocido __

Cirugía (en los 3 meses previos) Sí__ No__ Desconocido __

Si sí, tipo de cirugía:

□ Abdominal □ Cardio-torácica □ Urológica □ Ginecológica

□ Otras (especificar):.....

Quemado (quemadura de tercer grado en los 3 meses previos):

Sí__ No__ Desconocido __

Neonatos o pacientes menores de 3 meses:

Parto: □ Vaginal □ Cesárea

Prematuro: Sí__ No__ Peso al nacer (grs):..... Edad gestacional (semanas):.....

SI EL PACIENTE PRESENTABA OTRO FACTOR PREDISPONENTE NO SEÑALADO PREVIAMENTE, ESPECIFICAR AQUÍ:

DATOS VISITA

Código Episodio: __ __ __ / __ __ __

Tratamiento médico previo (en el mes previo a este episodio)

Tratamiento antifúngico sistémico: Sí__ No__ Desconocido __

Si sí, especifique el fármaco y la dosis recibida:

Tratamiento antifúngico (escribir el/los fármacos)	**Dosis mg/kg o mg/m²**	**Dosis total recibida en mg/día**	Fecha inicio (dd/mm/aaaa)	Fecha fin (dd/mm/aaaa)

Tratamiento antibacteriano durante el mes previo: Sí__ No__ Desconocido __

Si sí, especificar fármacos:.....
.....
.....

Corticoides el mes previo (> 10mg/día de metilprednisolona durante ≥ 5 días):

Sí__ No__ Desconocido __

Tratamiento inmunosupresor: Sí__ No__ Desconocido __

□ Corticoides □ Ciclosporina □ Azatioprina □ Metotrexate □ Ciclofosfamida □ Quimioterapia

□ Otros (FK-506, ATG, OKT3, biológicos,...): Especificar:.....

DATOS MOMENTO DE LA Código Episodio: __ __ __ / __ __ __

Signos clínicos y biológicos

Manifestaciones clínicas en el día de la fungemia (Definiciones en el manual para el investigador):

□ Sepsis □ Sepsis grave □ Shock séptico

Score de Pitt: _____

Origen de la fungemia:

□ Primaria

□ Secundaria: Catéter___ Abdominal___ Urológico___ Otros (especificar):.....

Indique si estaba intubado o con ventilación invasiva en el momento del hemocultivo + para levadura:

Sí__ No__ Desconocido __ Si sí, fecha intubación: ___ /___ /____

¿Requirió diálisis como consecuencia de la fungemia?

Sí__ No__ Desconocido __

¿Ingresó el paciente en UCI como consecuencia de la fungemia?

Sí__ No__ Desconocido __ Si sí, fecha de ingreso: ___ /__ /____

¿Estaba el paciente recibiendo nutrición parenteral? :

Sí__ No__ Desconocido __ Si sí, fecha de inicio: ___ /__ /____

Otros órganos afectados por la fungemia:

Sí__ No__ Desconocido __ Si sí, especificar los órganos implicados:

Órgano afectado	Fecha	Código de documentación: Diagnosticoclínico/Histología/Radiología/Microbiología
Riñón		
Hígado		
Bazo		
Piel		
Ojos		
Corazón		
Otro (especificar):		

DATOS MOMENTO DE LA

Código Episodio: __ __ __ / __ __ __

Diagnóstico y tratamiento del episodio

Especie de levadura aislada:

□ *C. albicans* □ *C. parapsilosis* □ *C. krusei* □ *C. tropicalis* □ *C. lusitaniae*
□ *C. glabrata* □ Otra:.....

Si se aísla más de una especie en el mismo episodio se codificarán igual que el número de caso incluyendo al final a, b, c… (en caso de que haya más de dos especies):

Especie N° __ __ __ / __ __ __ / __ Especie: .....
Especie N° __ __ __/ __ __ __ / __ Especie: .....

¿Se realizó antifungigrama? Sí____ No_____ Sí si, apuntar los resultados:

	Especie Nº __ __ __ /__ __ __ / __		Especie Nº __ __ __ /__ __ __ / __	
	Método empleado	Valor CMI	Método empleado	Valor CMI
Anfotericina B				
5-Flucitosina				
Fluconazol				
Itraconazol				
Voriconazol				
Posaconazol				
Caspofungina				
Anidulafungina				
Micafungina				

¿Tuvo el paciente más hemocultivos positivos con aislamiento de hongos durante este episodio? (se considera este supuesto si aparece a las 72 horas o más): Sí__ No__

Si la respuesta es sí, ¿la sensibilidad de la especie aislada fue igual a la previa?: Sí__ No__

Sí la respuesta a la anterior pregunta es NO, indicar el nombre de la especie y el antifúngico en el/los que existe un cambio de CMI:

Especie:..... Código: ___/___/_ (fecha:__/__/____) Antifúngicos/os:.....

Especie:.....Código: ___/___/_ (fecha:__/__/____)
Antifúngicos/os:.....

DATOS MOMENTO DE LA

Código Episodio: __ __ __ / __ __ __

Diagnóstico y tratamiento del episodio

Se aislaron otros microorganismos en el hemocultivo + para levadura?

Sí__ No__ Si sí indique, que especie bacteriana:

□ *S. aureus* □ *Staphylococcus* coagulasa negativo □ Otros Gram + aerobios
□ E.*coli* □*P.aeruginosa* □ Otros BGN aerobios □ Anaerobios □ Otros:…….....

Antes o durante el aislamiento en el hemocultivo + para levadura, se aisló alguna levadura en otra localización diferente a la sangre?:

Sí__ No__ Desconocido __

Si sí, indique la especie…….. y la localización /localizaciones de dónde fue aislada:

□ Oral □ Orina □ Tracto respiratorio superior □ Tracto respiratorio inferior □ Tracto intestinal □ Vagina □ Piel □ Otra:……

Datos relacionados con catéteres

¿Era el paciente portador de catéter en el momento de la fungemia?

Sí__ No__ Si sí, indique el o los catéteres insertados

Tipo de catéter	**Fecha de inserción**
□ Venoso periférico	
□ Venoso central yugular	
□ Venoso central subclavia	
□ Venoso central femoral	
□ Venoso central de inserción periférica (tipo Drum)	
□ Venoso central tunelizado	
□ Venoso central implantable con reservorio	
□ Arterial	
□ Catéter para diálisis peritoneal	
□ Otro (especificar):……	

DATOS MOMENTO DE LA

Código Episodio: __ __ __ / __ __ __

¿Se utilizaba alguno de los catéteres para nutrición parenteral?

Sí__ No__ Desconocido __ Si sí, especificar cuál de ellos: ....

¿Se realizaron hemocultivos cuantitativos de lisis-centrifugación?:

☐ Sí, positivos ☐ Sí, negativos ☐ No ☐ Desconocido

¿Se realizaron hemocultivos diferenciales de tiempo?

☐ Sí, positivos (indicar al tiempo:...........................horas) ☐ Sí, negativos ☐ No ☐ Desconocido

¿Se retiró el catéter como parte del tratamiento de la fungemia?:

Sí__ No__ Desconocido __

Si retirada, indique que catéter, fecha de la retirada y datos del cultivo:

Tipo de catéter	**Fecha retirada** (DD/MM/AAAA)	**¿Se realizó cultivo?**	**Resultado del cultivo**	**Si cultivo positivo:**
		☐ Sí ☐ No	☐ Positivo ☐ Negativo	☐ Igual especie ☐ Otra especie y/o bacteria ☐ Desconocido
		☐ Sí ☐ No	☐ Positivo ☐ Negativo	☐ Igual especie ☐ Otra especie y/o bacteria ☐ Desconocido
		☐ Sí ☐ No	☐ Positivo ☐ Negativo	☐ Igual especie ☐ Otra especie y/o bacteria ☐ Desconocido
		☐ Sí ☐ No	☐ Positivo ☐ Negativo	☐ Igual especie ☐ Otra especie y/o bacteria ☐ Desconocido
		☐ Sí ☐ No	☐ Positivo ☐ Negativo	☐ Igual especie ☐ Otra especie y/o bacteria ☐ Desconocido
		☐ Sí ☐ No	☐ Positivo ☐ Negativo	☐ Igual especie ☐ Otra especie y/o bacteria ☐ Desconocido

Si se hizo cultivo de la punta de catéter ¿qué método se empleó?:

☐ Semicuantitativo ☐ Cualitativo

DATOS DE LA VISITA

Código Episodio: __ __ __ / __ __ __

Tratamiento antifúngico del episodio

¿Recibió tratamiento antifúngico para este episodio de fungemia?:

Sí____ No_____ Si sí, indique el fármaco que recibió (todos los que haya recibido y las diferentes dosificaciones del mismo fármaco):

Tratamiento antifúngico (Especificar el/los antifúngicos)	**Dosis mg/kg o mg/m²**	**Dosis total recibida en mg/día**	Fecha inicio	Fecha fin

Indique si el paciente tuvo evidencia de toxicidad como resultado de la administración de cualquiera de estos antifúngicos: Sí____ No_____

Si sí, marque cual fue el antifúngico responsable, el tipo de toxicidad: renal, hematológica, hepática, neurológica, otra (especificar)

Antifúngico	**Toxicidad**	**¿Se retiró el fármaco?**	**Evolución de la toxicidad**
		□ Sí □ No	□ Resolución □ Mejoría □ NO resolución □ Desconocido
		□ Sí □ No	□ Resolución □ Mejoría □ NO resolución □ Desconocido
		□ Sí □ No	□ Resolución □ Mejoría □ NO resolución □ Desconocido
		□ Sí □ No	□ Resolución □ Mejoría □ NO resolución □ Desconocido

¿Se realizaron hemocultivos de control durante el seguimiento?

Sí____ No_____ Si sí, indicar fecha/s y resultado:

Fecha:__/__/___ Resultado: □Negativos □(+) con igual levadura □(+) con distinto microorg

Fecha:__/__/___ Resultado: □Negativos □(+) con igual levadura □(+) con distinto microorg

DATOS DE LA VISITA

Código Episodio: __ __ __ / __ __ __

Evolución y cierre del episodio

Fecha última visita: ___ / ___ / ____

Causa Fin de episodio:

□ Muerte □ Alta médica □ Sigue hospitalizado, aunque asintomático

□ Se abre un nuevo episodio por aislarse otra levadura diferente en hemocultivo

□ Otras (especificar): .....

Sí muerte, ¿cuál fue la causa de la muerte?:

□ Complicación relacionada con la fungemia

□ Otra no relacionada (especificar): .....

□ Causa desconocido

Fecha de fallecimiento: ___/___/____

Si fallecimiento, ¿se realizó autopsia?: □ Sí □ No □ Desconocido

¿Se encontró afectación orgánica por *Candida* sp. en la autopsia?:

□ Sí □ No □ Desconocido

Si sí, indique en que órganos:
□Riñón □Corazón □Pulmón □Hígado □Páncreas □Intestino delgado
□Medula ósea □Otro

COMENTARIOS DE INTERES QUE SE QUIERAN RESALTAR:

(Rellenar una solo vez por hospital al final del estudio)

DATOS GENERALES DEL HOSPITAL:

Hospital (nombre y código): .....

Población de referencia: ..... habitantes

Tipo de hospital: □Público □Privado □Otros.....

□Tercer nivel □Comarcal □Otros.....

Camas de hospitalización: .....

Camas de Cuidados críticos: .....

S° Neonatología: □Sí □No

UCI Neonatal: □Sí □No

¿Se realizan trasplantes en tu hospital?: □Sí □No

Tipo de trasplante:.....

Ingresos en el periodo de estudio (mayo de 2010 a abril de 2011 inclusive): .....

Estancias en el periodo de estudio (mayo de 2010 a abril de 2011 inclusive):

.....

N° de episodios de fungemia en el periodo de estudio: .....

N° de pacientes con fungemia en el periodo de estudio:.....

N° de pacientes incluidos en el estudio:.....

N° de pacientes NO incluidos en el estudio: .....

Motivos de pacientes NO incluidos en el estudio

N° Fallecimiento precoz: .....

N° Falta de datos: .....

N° No firma el consentimiento informado: .....

ANEXO 4

- **Editorial relacionada con el trabajo 2**

Management of Candidemia: Getting Better, But Not There Yet*

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*See also p. 1423.

Key Words: antifungal agents; candidiasis; epidemiology; treatment outcome

Dr. Leroy served as board member for MSD and lectured for MSD, Astellas, and Novartis. Dr. Alfandari lectured for Gilead, MSD, Novartis, and Pfizer.

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Candidemia and invasive candidiasis remain a challenging problem. Their prevalence is growing worldwide (1). The epidemiology is changing with a shift toward an increased prevalence of non-*albicans Candida* and the emergence of fluconazole and even multidrug-resistant *Candida* species (2). Despite pharmaceutical progresses and the discovery of new antifungal drugs (echinocandins, new triazoles, and new formulations of polyenes), mortality associated with candidemia and invasive candidiasis remains high, always ranging from 20% to 50% or more. Finally, as underlined by Puig-Asensio et al (3) in this issue of *Critical Care Medicine*, only few studies have studied predictors of death in ICU patients suffering from candidemia.

Recent American and European guidelines provide recommendations for optimal management of candidemia and

invasive candidiasis (4, 5). First, the delay between the onset of candidemia and the initiation of antifungal therapy must be as short as possible. Second, antifungal therapy must be effective against the causative *Candida* species. Although the choice of antifungal drug should take into account several variables, the experts favor echinocandins as first-line treatment before definite *Candida* species identification. Finally, the removal of central venous catheters is recommended. In the absence of randomized studies on this topic, this later point is often debated. Nevertheless, a recent individual patient-level quantitative review of seven randomized trials for treatment of invasive candidiasis demonstrated that removal of a central venous catheter was associated with decreased mortality (odds ratio = 0.50; 95% CI, 0.35–0.72; $p = 0.0001$) (6).

In this issue of *Critical Care Medicine*, Puig-Asensio et al (3) report data about the epidemiology of candidemia in Spanish ICUs, the prevalence of antifungal drug resistance, and the predictors of outcome. The authors separated outcome variables in early (≤ 7 d) and late (8–30 d) mortality. Interestingly, reported results give us the opportunity to compare guidelines recommendations with "real-life" practices and modestly to assess the truthfulness of some debated propositions.

From May 2010 to April 2011, the Prospective Population Study on Candidemia in Spain (CANDIPOP) study collected 773 candidemias occurring in 29 hospitals in five major areas of Spain. Among them, 264 cases occurred in patients admitted in medical or surgical ICUs since at least 48 hours. After exclusion of cases occurring in pediatric patients, 168 episodes in 164 patients were studied. Thus, candidemias occurring in adult ICU patients represent in this series only one fifth of candidemias. *Candida albicans* was the most frequent (52%) of 173 studied strains, but this percentage varied between areas, ranging 31.8–64.5%. Resistance to echinocandins was uncommon but 20.8% of *Candida* isolates were not susceptible to fluconazole. These data support guidelines recommendations favoring echinocandins as first-line treatment of candidemia. In the CANDIPOP study, 50% of ICU patients received echinocandin as initial antifungal treatment and 47.5% had their central venous catheters removed within 48 hours after obtaining blood culture. While these percentages might appear low, it is generally admitted that implementing guidelines and changing behavior in a critical care setting are complex, and thus, approximately 50% guideline compliance only a few years after publication can be considered as a good result.

To evaluate the prognostic impact of antifungal treatment and central venous catheter removal, Puig-Asensio et al (3) created a composite factor named "early appropriate combined treatment" and defined as administration of adequate antifungal treatment and central venous catheter removal, both within the first 48 hours following blood culture collection. In multivariate analysis, early appropriate combined treatment was an independent factor improving early survival. However, while associated with a greater likelihood of late, 30-day survival, this was not significant in multivariate analysis. These results confirm the severity of candidemia in ICU patients and support current treatment guidelines. Nevertheless, some negative points must be underlined. First, only 37.3% of patients received an early appropriate combined treatment. Second, and it is a weakness of this study, the authors did not detail the reasons for early treatment inappropriateness and particularly about inadequacy of antifungal therapy. Inadequacy could be due to a nonrecommended dose, nonsusceptibility of the *Candida* isolate, or administration beyond the first 48 hours. The median time between blood collection and start of treatment was 2 days (interquartile range, 1–3 d), but the number of treatments begun beyond 48 hours is unknown. Current recommendations emphasize that the optimal time point to start empiric antifungal treatment remains undetermined. Puig-Asensio et al (3) state that assessment of interest of preemptive therapy was not an objective of their study. This lack of data about delayed treatment is regrettable because improvement of clinical practices without precise knowledge of faulty practices will be difficult.

The second part of the prognostic analysis performed by Puig-Asensio et al (3) focused on the 47%, 30-day mortality, and identified four independent predictors of mortality—primary source, age, mechanical ventilation, and renal replacement therapy—during candidemia. For Puig-Asensio et al (3), such results were in accordance with the previous report suggesting that high mortality of candidemia mainly depends on underlying comorbid status and that ICU-acquired candidemia per se were not associated with any attributable ICU or hospital ICU mortality (7). However, the possible relationship between need for supportive techniques such as mechanical ventilation and/or renal replacement therapy and inappropriateness of early combined treatment was not clearly studied by Puig-Asensio et al (3), and this might be a bias masking attributable mortality.

In conclusion, this study demonstrates growing compliance to recent guidelines and underlines the urgent need for better tools to identify the best moment to initiate antifungal treatment.

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♦ **Carta al Editor relacionada con el trabajo 2 y su correspondiente respuesta**

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What Is the Impact of Catheter Removal on the Outcome of Non–Catheter-Related Candidemia?

To the Editor:

We read with great interest the article by Puig-Asensio et al (1) that investigated the impact of therapeutic strategies on the outcome of candidemia in the ICU. They concluded that combined early appropriate antifungal treatment and catheter removal would be independently associated with 7-day mortality (odds ratio, 0.27; 95% CI, 0.08–0.91) (1). Although the positive impact of early removal of catheter on the outcome of patients with catheter-related candidemia is reasonable (2, 3), the impact of early removal of catheter on the prognosis of patients with non–catheter-related candidemia may not be evident. Thus, we wonder whether the effect of early removal of catheter on the prognosis of candidemia in this study would be different between patients with catheter-related candidemia and non–catheter-related candidemia. In this study (1), only 58 of 168 candidemia episodes (34.5%) were identified as catheter-related bloodstream infections, and most of candidemia episodes (65.5%) were defined as non–catheter-related candidemia. It is possible that the true effect of removal of catheter in this study may be diluted by the large group with non–catheter-related candidemia. Therefore, we would like to suggest that the study about the association between catheter removal and the prognosis of candidemia should be evaluated according to the different sources of candidemia, such as catheter-related candidemia and non–catheter-related candidemia.

The authors have disclosed that they do not have any potential conflicts of interest.

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The authors reply:

We appreciate the interest Hsu and Chao (1) have shown regarding our observational, population-based study on candidemia (2). Vascular catheters have been identified as risk factors for candidemia, and it is likely to assume that removal of this potential focus of infection is necessary to achieve antifungal treatment success. Recent guideline statements from both the Infectious Diseases Society of America (3) and the European Society for Clinical Microbiology and Infectious Diseases (4) strongly recommend to attempt central venous catheter (CVC) removal in all patients with candidemia in order to improve their outcome. However, the quality of the published evidence is grade II and grade III, indicating that there are no data from randomized controlled trials. In addition, some observational studies supporting CVC withdrawal have serious limitations in study design such as an inappropriate adjustment of the analysis for severity of illness, whereas others have failed to confirm the benefit of early CVC withdrawal in patients with candidemia. Hence, the real impact of CVC removal is still under debate, and it is not clear which patients would benefit the most from this clinical practice. In our study, we found that early implementation (≤48 hr) of therapeutic strategies—use of adequate antifungal treatment and CVC withdrawal—was associated with decreased 7-day mortality (odds ratio, 0.27; 95% CI, 0.08–0.91). Nevertheless, as Hsu and Chao (1) mention in their letter, the effect of CVC withdrawal could be different depending on the source of the infection. Intuitively, a higher benefit should be expected in patients with catheter-related candidemia, reinforcing the idea that CVC management should be carefully evaluated in each patient. Garnacho-Montero et al (5) have already pointed out that CVC removal could be not useful in secondary non–catheter-related candidemias in which the venous catheter is not the origin of infection. Unfortunately, one limitation of the present study is that we could not perform a separate multivariate analysis of mortality by the source of infection because of the limited sample size. Nevertheless, we believe that we looked for the best statistical approach to assess the real effect of CVC removal. First, in our ICU patients, the majority of episodes had intravascular catheters as a potential source of infection. We found that 34.5% of candidemias (58 of 168) were proven catheter-related and 55.4% (93 of 168) were primary. It should be noted that primary candidemias could refer to possible or not proven catheter-related candidemias. Hence, the real percentage of catheter-related candidemias might have been underestimated, and the results of our study could be closer to the real effect of CVC removal than

expected. Second, multivariate analysis of 7-day mortality was adjusted not only for host confounders (Acute Physiology and Chronic Health Evaluation II score) but also by other factors that were related to the source of infection such as *Candida parapsilosis*, often related to parenteral nutrition and catheter-related infection, and abdominal secondary origin of infection.

Thus, although it might have been interesting to analyze the effect of CVC removal according to different sources of candidemia, we believe that our results could be a good initial approach to clinical practice where prompt CVC removal is usually performed before the origin of infection is confirmed.

The authors have disclosed that they do not have any potential conflicts of interest.

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