UNIVERSITAT DE BARCELONA

Nuevos Desafíos En El Manejo De La Neutropenia Febril Y La Bacteriemia En Pacientes Inmunodeprimidos Con Malignidad

Mariana Chumbita

Nuevos Desafíos En El Manejo De La Neutropenia Febril Y La Bacteriemia En Pacientes Inmunodeprimidos Con Malignidad

Memoria presentada por Mariana Chumbita

Para optar al grado de Doctora en Medicina por la Universidad de Barcelona.

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DECLARAN QUE:

La memoria de tesis presentada por la Sra. Mariana Chumbita con **título "Nuevos Desafíos En El Manejo De La Neutropenia Febril Y La Bacteriemia En Pacientes Inmunodeprimidos Con Malignidad"**, ha sido realizada bajo nuestra dirección y que autorizamos su depósito para ser defendida y juzgada por un tribunal.

Barcelona, 29 de septiembre 2023

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Firmado el día 29 de septiembre de 2023.

Mariana Chumbita
Doctoranda

No necesito las luces ni los lujos de la ciudad

Canción “Los Querandíes”- Los Gardelitos

Cambia el rumbo el caminante

Aunque esto le cause daño

Y así como todo cambia

Que yo cambie no extraño

Canción “Todo Cambia”- Mecedes Sosa

Gracias a la vida que me ha dado tanto

Me ha dado la risa y me ha dado el llanto

Así yo distingo dicha de quebranto

Los dos materiales que forman mi canto

Canción “Gracias a la Vida”- Mecedes Sosa

Es larga la carretera

Cuando uno mira atrás

Vas cruzando las fronteras

Sin darte cuenta quizás

Canción “Para Mi Muerte”- Sui Generis

Agadecimientos.

Y finalmente llegó el momento que me tengo que sentar frente al ordenador a “agradecer”. Creo que son muchas las personas que han hecho que esta tesis sea una realidad en mi vida.

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2• ABREVIATURAS Y ACRÓNIMOS

BGN	Bacilos gramnegativos
BGN-MR	Bacilos gram negativos multiresistentes
BLEE	Beta-lactamasas de espectro extendido
BMR	Bacterias multirresistentes
CISNE	Clinical Index of Stable Febrile Neutropenia
CVC	Catéter venoso central
EEA	Espacio Económico Europeo
IDSA	Sociedad de Enfermedades Infecciosas de América
IRA	Insuficiencia Renal Aguda
MASCC	Multinational Association for Supportive Care in Cancer
MR	Multirresistencia
NF	Neutropenia febril
OMS	Organización Mundial de la Salud
SARM	*Staphylococcus aureus* resistente a la meticilina
SEOM	Sociedad Española de Oncología Médica
SIDA	Síndrome de inmunodeficiencia adquirida
TAEI	Tratamiento antibiótico empírico inapropiado
TAR	Terapia antirretroviral
TC	Tomografía Computada
TPH	Trasplante de progenitores hematopoyéticos
UCI	Unidades de cuidados intensivos
UE	Unión Europea
VIH	Virus de la inmunodeficiencia humana

VHB	Virus de la hepatitis B
VHV	Virus de la hepatitis C

3•ENUMERACIÓN DE LOS ARTÍCULOS DE LA TESIS

TESIS EN FORMATO DE COMPENDIO DE PUBLICACIONES

La tesis consta de 6 objetivos y 6 artículos.

3•1 ARTICULOS ORIGINALES

La presente tesis doctoral está constituida por los siguientes artículos publicados en revistas indexadas:

1. Documented Infection at febrile neutropenia onset in patients with hematological malignances in the Current Era of Microbiological Testing. **Chumbita M.,** Peyrony O., Teijón C., Monzó Gallo P., Aiello TF., Gallardo Pizarro A., Puerta-Alcalde P., Bodro M., Hernández Meneses M., Morata L., Del Rio A, Espasa M., Martínez C., Gaya A., Soriano A., Garcia-Vidal C.

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2. Resistance to empirical β-lactams recommended in febrile neutropenia guidelines in gram-negative bacilli bloodstream infections in Spain: a multicenter study. **Chumbita, M.,** Puerta-Alcalde, P., Yáñez, L., Cuesta, M. A., Chinea, A., Español Morales, I., Fernández Abellán, P., Gudiol, C., Guerreiro, M., González-Sierra, P., Rojas, R., Sánchez Pina, J. M., Sánchez Vadillo, I., Varela, R., Vázquez, L., Lopera, C., Monzó, P., Garcia-Vidal, C. *J Antimicrob Chemother.* 2022;77(7):2017-2023. doi:10.1093/jac/dkac135.

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3. High rate of inadequate antibiotics in patients with hematologic malignancies

and *Pseudomonas aeruginosa* bacteremia following international guideline recommendations. Chumbita, M., Puerta-Alcalde, P., Yáñez, L., Angeles Cuesta, M., Chinea, A., Español-Morales, I., Fernandez-Abellán, P., Gudiol, C., González-Sierra, P., Rojas, R., Sánchez-Pina, J. M., Vadillo, I. S., Sánchez, M., Varela, R., Vázquez, L., Guerreiro, M., Monzo, P., Lopera, C., Aiello, T. F., Peyrony, O., Garcia-Vidal, *C. Microbiol Spectr.* 2023;11(4): e0067423. doi:10.1128/spectrum.00674-23.

*Factor de impacto: 3.7, 2º cuartil.

4. Impact of empirical antibiotic regimens on mortality in neutropenic patients with bloodstream infection presenting with septic shock. Chumbita, M., Puerta-Alcalde, P., Gudiol, C., Garcia-Pouton, N., Laporte-Amargós, J., Ladino, A., Albasanz-Puig, A., Helguera, C., Bergas, A., Grafia, I., Sastre, E., Suárez-Lledó, M., Durà, X., Jordán, C., Marco, F., Condom, M., Castro, P., Martínez, J. A., Mensa, J., Soriano, A., Garcia-Vidal, C. *Antimicrob Agents Chemother.* 2022;66(2):e0174421. doi:10.1128/AAC.01744-21.

*Factor de impacto: 5.1, 1º cuartil.

5. Clinical Characteristics and outcome of bloodstream infections in HIV-infected patients with cancer and febrile neutropenia: A Case–Control Study. Puerta-Alcalde P, Ambrosioni J, Chumbita M, Hernández-Meneses M, Garcia-Pouton N, Cardozo C, Moreno-García E, Marco F, Mensa J, Rovira M, Esteve J, Martínez J.A, García F, Mallolas J, Soriano A, Miró J, Garcia-Vidal C. *Infectious diseases and therapy.*

2021; 10(2), 955–970. doi.org/10.1007/s40121-021-00445-3.

*Factor de impacto: 5.4, 2º cuartil.

6. Risk factors for mortality in hematopoietic stem cell transplantation recipients with bloodstream infection: points to be addressed by future guidelines. Puerta-Alcalde P, **Chumbita M,** Charry P, Castaño-Díez S, Celia Cardozo C, Moreno-García E, Marco F, Suárez-Lledó M, Garcia-Pouton N, Morata L., Fernández-Avilés F, Martínez-Roca A, Rodríguez G, Martínez J.A, Martínez C, Mensa J, Urbano A, Rovira M, Soriano A, Garcia-Vidal C. *Transplantation and Cellular Therapy.* 2021;27(6): 501.e1-501.e6. doi: 10.1016/j.jtct.2021.03.017.

*Factor de impacto: 3.2, 2º cuartil.

4• INTRODUCCIÓN

INTRODUCCIÓN

La neutropenia febril (NF) y la bacteriemia en pacientes con malignidades representan condiciones médicas críticas que están estrechamente vinculadas a una elevada morbimortalidad. Es de máxima importancia abordar estas complicaciones de manera rápida y efectiva. No obstante, en la actualidad, nos enfrentamos a desafíos significativos en el manejo de estas situaciones clínicas.

Las dificultades en la identificación etiológica de las infecciones, la epidemiología actual caracterizada por el aumento de microorganismos multirresistentes, que complica la elección óptima de antibióticos, y la falta de comprensión de los factores que tienen un mayor impacto en el pronóstico de los pacientes justifican plenamente el elevado interés en la investigación en esta área y la realización de esta tesis doctoral.

4•1 Pacientes con neoplasias: Quimioterapia, neutropenia febril y bacteriemia.

Desde la década de 1940, la quimioterapia se estableció como el pilar fundamental en el tratamiento del cáncer. Inicialmente, el uso de mostazas nitrogenadas y antagonistas del ácido fólico era frecuente, pero en breve hubo una potente y rápida revolución de los tratamientos quimioterápicos. A mediados de los años 60 se adoptaron combinaciones de quimioterápicos con diferentes mecanismos de acción, que condujeron a notables avances terapéuticos y lograron importantes mejoras en el pronóstico de los pacientes con neoplasias hematológicas y determinados tumores sólidos (1).

A pesar de su éxito, la quimioterapia tiene la desventaja de su alta toxicidad, ya que no distingue entre células normales y tumorales. No obstante, durante las últimas décadas, se han introducido nuevos agentes que ofrecen una mayor eficacia con un perfil de efectos secundarios más favorable. Estos avances han permitido una mejor personalización de los tratamientos, adaptándolos a las características específicas de cada tipo de cáncer y a las necesidades individuales de los pacientes.

Además, la investigación en el campo de la oncología ha llevado al descubrimiento de terapias dirigidas específicamente a las moléculas involucradas en el crecimiento y la propagación de las células cancerosas. Estas terapias han revolucionado el enfoque de tratamiento al proporcionar opciones más precisas y efectivas con menos toxicidad general para las células sanas.

La inmunoterapia también ha emergido como una estrategia prometedora en la lucha contra el cáncer. Al estimular el sistema inmunológico del paciente para que reconozca y ataque las

células cancerosas, la inmunoterapia ha demostrado ser eficaz en varios tipos de cáncer, brindando nuevas esperanzas a pacientes que anteriormente tenían opciones de tratamiento limitadas.

La combinación de estos avances en quimioterapia, terapias dirigidas e inmunoterapia ha mejorado significativamente las tasas de supervivencia y la calidad de vida de muchos pacientes con cáncer. Además, la investigación continúa avanzando, lo que sugiere un futuro prometedor en la búsqueda de tratamientos más efectivos y menos invasivos para esta enfermedad devastadora.

Desde el inicio de la quimioterapia, una de las complicaciones con mayor morbimortalidad para los pacientes fue la NF. Muy pronto, se evidenció la relación entre la leucopenia, la agranulocitosis, los agentes quimioterapéuticos y el aumento del riesgo de infecciones (2–4).

La incidencia de NF varía según el ciclo, dosis o tipo de terapia antineoplásica recibida, así como del tipo de tumor. En pacientes con neoplasias hematológicas la incidencia de NF puede llegar hasta un 80% de los casos, mientras que, en aquellos con tumores de órgano sólido, suele ser menos frecuente y oscila entre el 10% y el 50% (5). La NF se relaciona con una alta carga para los sistemas sanitarios, debido a su asociación con hospitalizaciones prolongadas y costosas, demoras en la administración de quimioterapias y, una elevada morbilidad y mortalidad.

Por ejemplo, un estudio del University Health System Consortium (UHC) en Estados Unidos analizando 55,276 hospitalizaciones de pacientes con cáncer diagnosticados con NF, observó

una estancia hospitalaria promedio de 11.5 días, con costos estimados de $1.06 mil millones durante seis años y tasas de mortalidad del 9.5%. Estas cifras fueron especialmente elevadas en pacientes con neoplasias hematológicas, destacando particularmente en aquellos con leucemia. Además, los pacientes con neoplasias hematológicas tuvieron una duración de la estancia significativamente mayor en comparación con los pacientes con tumores sólidos (19.7 días versus 8.7 días). Este estudio describe como la NF en las enfermedades hematológicas se asocia a hospitalizaciones más prolongadas, aumento de costes y mayor mortalidad (6).

Los pacientes con NF no constituyen un grupo homogéneo y el riesgo de presentar complicaciones graves depende de diversas variables como el tipo de enfermedad de base (tumor sólido versus hematológico), el origen de la infección, la presentación clínica inicial (si presenta inestabilidad hemodinámica o no) y otras comorbilidades, etc. Algunas poblaciones como los pacientes que viven con el virus de la inmunodeficiencia humana (VIH) que presentan NF en el tratamiento de una neoplasia están muy poco estudiadas.

Dada la relevancia de anticipar el riesgo de complicaciones severas en pacientes con NF, se han realizado múltiples investigaciones con el objetivo de estratificar dicho riesgo. Uno de los primeros fue el score de Talcott, introducido en 1988 (7). Este se basó en una revisión retrospectiva donde más de la mitad de los pacientes presentaban neoplasias hematológicas, estableciendo así cuatro grupos de riesgo. Según este modelo, se sugirió que aquellos pacientes neutropénicos con una neoplasia bajo control y sin patologías asociadas, que manifestaran fiebre fuera del entorno hospitalario, podrían presentar un riesgo de complicaciones menor al 5%. El score de MASCC (por sus siglas en inglés: Multinational

Association for Supportive Care in Cancer), aceptado por la Sociedad Europea de Oncología Médica y la Sociedad de Enfermedades Infecciosas de América (IDSA) desde el año 2002, es otra de las herramientas diseñadas para esta finalidad, validado ampliamente y probablemente el de mayor uso (8). Publicado en el año 2000, este score se enfoca en predecir un bajo riesgo de mortalidad y complicaciones graves en el momento de la NF. El score MASCC incluye variables tales como la gravedad de los síntomas atribuibles en su presentación inicial, las cifras tensionales, los antecedentes de enfermedad pulmonar crónica o infección fúngica, el estado de hidratación, la edad, y la condición del paciente, sea hospitalizado o ambulatorio, en el momento de aparición de la NF. Los resultados del conjunto de validación inicial encontraron que una puntuación MASCC de 21 o más identificó a los pacientes de bajo riesgo de complicaciones (6%) y baja mortalidad (1%) con un valor predictivo positivo del 91%, una especificidad del 68% y una sensibilidad del 71% (8). El score MASCC, pese a su amplio uso en la práctica clínica, presenta ciertas limitaciones en su capacidad para abordar integralmente el riesgo en pacientes con NF. La guía de la IDSA destaca que, aunque el score considera diversos factores, omite la duración y profundidad de la neutropenia, aspectos que son cruciales, especialmente cuando el recuento de neutrófilos es inferior a 100 y la neutropenia persiste por más de 7 días. Además, no incluye otros indicadores clínicos de alto riesgo, como la presencia de mucositis, síntomas abdominales, neurológicos y pulmonares, o la posibilidad de una infección asociada a un catéter (5). La ausencia de estos factores en el score podría explicar algunas de sus limitaciones al determinar el riesgo en pacientes con NF que presentan una infección. Algunos estudios han demostrado su limitada utilidad especialmente en la población con

neoplasias hematológicas. *Baskaran* (9) observó un 17% de graves complicaciones médicas en los pacientes clasificados como de bajo riesgo, mientras *Cherif* (10) informó de un 15% de graves complicaciones en este mismo grupo, notificando tasas de mortalidad de 7% y 2% respectivamente.

Por último, el grupo de trabajo de la Sociedad Española de Oncología Médica (SEOM) desarrolló el score CISNE (Clinical Index of Stable Febrile Neutropenia) (11) un índice diseñado para predecir complicaciones graves en pacientes con NF estable. A diferencia de los otros sistemas de puntuación, el CISNE ha demostrado tener una mayor precisión predictiva, con áreas bajo las curvas ROC de 0.868. El estudio FINITE (12) realizado por Carmona-Bayonas et al. en 2015, validó su eficacia, demostrando su capacidad para distinguir con precisión entre distintos niveles de riesgo de complicaciones, bacteriemia y mortalidad. A pesar de su eficacia, su aplicabilidad está limitada en ciertos contextos, principalmente en el caso de pacientes neoplasias hematológicas ya que se realizó en pacientes con tumores sólidos. La tabla 1 resume las variables incluidas por los diferentes sistemas de puntuación mencionados.

En conclusión, la utilización de estas herramientas como único medio para la estratificación del riesgo en pacientes con NF puede presentar limitaciones notables. La falta de valoración de algunas variables, así como definiciones subjetivas, como la "carga de la NF", puede generar ambigüedades en su aplicación destacando la necesidad de interpretarlos con cautela. Es relevante también considerar que muchos de estos scores se derivan de estudios con poblaciones heterogéneas, lo que puede no reflejar adecuadamente las características y riesgos de subgrupos específicos de pacientes; limitando así la aplicabilidad. En este marco,

scores como el MASCC deberían ser vistos como herramientas complementarias en el proceso de evaluación, y no como criterios absolutos.

Característica	TALCOTT	MASCC	CISNE
Población	Neoplasias Sólidas: 42%, Neoplasias Hematológicas: 58%	Neoplasias Sólidas: 41%, Neoplasias Hematológicas: 59%	Neoplasias Sólidas: 98%, Neoplasias Hematológicas: 2%
Variables Incluidas	Ubicación (internado/ambulatorio), comorbilidades, control del cáncer.	Gravedad, no hipotensión, no EPOC, tumor sólido, no infección fúngica, no deshidratación, edad <60 años, estado ambulatorio.	ECOG < 2 (2 puntos), Hiperglicemia inducida por estrés (2 puntos), EPOC (1 punto), Enfermedad cardiovascular crónica (1 punto), Mucositis grado >2 (1 punto), Monocitos < 200 Ul (1 punto).

Grupos de Riesgo	Grupo 1: Ingresados, Grupo 2: Ambulatorios con comorbilidad, Grupo 3: Ambulatorios sin comorbilidad, pero con cáncer sin control, Grupo 4: Ambulatorios con fiebre y neutropenia sin factores de riesgo adicionales.	Bajo riesgo (≥ 21 puntos), Alto riesgo (< 21 puntos).	Bajo riesgo (0 puntos), Intermedio (1-2 puntos), Alto riesgo (≥ 3 puntos).

Tabla 1. Tabla comparativa de los diferentes sistemas de puntuación de riesgo. (7,8,11).

Por todo lo comentado previamente, la NF es una situación clínica que requiere una aproximación inicial meticulosa, dada la urgencia de identificar el agente causal y administrar un tratamiento adecuado de forma precoz. Sin embargo, la ausencia de neutrófilos en estos pacientes puede atenuar la respuesta inflamatoria, haciendo que las manifestaciones clínicas de infecciones sean menos evidentes. Un estudio en pacientes con cáncer (13) estudió la relación entre el recuento de neutrófilos y ciertas características clínicas o analíticas. Según este estudio, los pacientes con neutropenia profunda presentaron menor frecuencia de esputo purulento en contexto de neumonía (8% vs 84% en no neutropénicos), menor piuria en infecciones urinarias (11% vs 93%), y menor tasa de fisuras en casos de infecciones anorrectales (23% vs 100%). Como consecuencia, el tratamiento empírico precoz es

fundamental en estos pacientes independientemente la ausencia de otros signos clínicos o síntomas de infección.

Debido a esta atenuación en la presentación clínica, es esencial llevar a cabo una anamnesis y examen físico exhaustivos. Las pruebas de laboratorio y microbiológicas, incluidos los hemocultivos y cultivos de lúmenes de catéter venoso central (CVC), son esenciales. Además, es necesario obtener cultivos de otros sitios sospechosos del origen de la fiebre (5). La utilidad de la radiografía de tórax puede ser más limitada. Un estudio retrospectivo en pacientes neutropénicos con neoplasias hematológicas mostró que el 80% de las radiografías resultaron normales, a pesar de presentar síntomas respiratorios (14). Por otro lado, la Tomografía Computada (TC) ha demostrado ser más sensible, identificando neumonías en el 60% de los pacientes con neutropenia y fiebre de origen desconocido con radiografía de tórax normal (15,16). Aún en pacientes estables se recomienda la realización de esta prueba tras tres días de persistencia de la fiebre.

Tras la identificación de un episodio de NF el inicio de un tratamiento empírico antibiótico debe ser certero y precoz. Históricamente, los pacientes con NF que desarrollaban infecciones bacterianas se enfrentaban a tasas de mortalidad especialmente elevadas, con tasas cercanas al 90% en los primeros estudios sobre bacteriemias por bacilos gramnegativos (BGN) (17). Afortunadamente, estas cifras disminuyeron significativamente gracias a la implementación de diferentes estrategias terapéuticas, destacando el tratamiento precoz con antibióticos.

Sin embargo, en los últimos años la administración de un tratamiento empírico adecuado es un reto para los médicos debido al aumento importante de las infecciones causadas por bacterias multirresistentes (BMR). La infección por BMR se ha asociado a altas probabilidades de un tratamiento inadecuado, factor directamente relacionado a un aumento de la mortalidad (18,19); especialmente en aquellos casos en que la infección es causada por BGN. Un estudio prospectivo sobre la epidemiología de la bacteriemia en pacientes hematológicos reveló que hasta el 24% de los pacientes recibieron tratamiento empírico inicial inapropiado. De manera más significativa, el 39% de las bacteriemias causadas por BGN multirresistentes (BGN-MR) tuvieron un tratamiento empírico inadecuado, en contraste con solo el 7% de las causadas por BGN no MR ($p < 0.001$) (20). Este tratamiento empírico inadecuado se relacionó con una mayor mortalidad.

Durante nuestro trabajo quisimos también focalizar nuestra investigación en aquellos pacientes con cáncer que presentaban bacteriemia, aún sin NF. Esta complicación se caracteriza por la presencia de microorganismos patógenos en la sangre, acompañándose de una elevada morbimortalidad.

La bacteriemia representa la complicación infecciosa microbiológicamente documentada más frecuente en los pacientes oncohematológicos, con tasas que varían del 11 al 38%, (21,22) siendo aún mayor en los pacientes receptores de trasplante de progenitores hematopoyéticos (TPH) (23).

Además de las consecuencias clínicas graves, las bacteriemias tienen un impacto significativo en la morbilidad y la mortalidad de los pacientes oncohematológicos con tasas variables,

pero con reportes alcanzando valores de hasta el 42% (24–26). En un estudio comparativo, se evidenció que las tasas de mortalidad aumentaron 4% en pacientes con neoplasias hematológicas sin bacteriemia a un 9% cuando presentaban bacteriemia. De manera similar, en los pacientes con tumores de órgano sólido, las tasas aumentaron del 3% al 13% (22). Sin embargo, es importante señalar que no se puede determinar hasta qué punto el propio cáncer, más que la bacteriemia en sí contribuyó a la mortalidad a corto plazo. En un análisis, tras una bacteriemia causada por cualquier patógeno, la mortalidad a 90 días fue del 35.8% en pacientes con cáncer, en contraste con el 23.5% en aquellos pacientes sin cáncer (27).

Otro aspecto relevante es el impacto económico de las bacteriemias en la atención médica hospitalaria. Estas infecciones no solo prolongan la duración del ingreso hospitalario, sino que también pueden requerir demoras o reducciones en las dosis de quimioterapia, lo que a su vez puede afectar negativamente la efectividad del tratamiento contra el cáncer. Esto agrega una capa adicional de preocupación, ya que no sólo se trata de la salud del paciente, sino también de la carga financiera que representa para los sistemas de atención médica (6,28).

En resumen, las bacteriemias representan una seria amenaza para la salud y el bienestar de los pacientes oncohematológicos. Su incidencia, asociación con NF, morbilidad y mortalidad significativas, así como su impacto en los costos de atención médica, hacen que la prevención, el diagnóstico temprano y el tratamiento efectivo de estas infecciones sean cuestiones críticas en la atención de estos pacientes.

Por todos los motivos expuestos previamente, nos ha parecido que la realización de esta tesis doctoral era de máxima importancia y relevancia clínica. Los resultados obtenidos en la realización de esta tesis tienen como objetivo principal aumentar las tasas de supervivencia y la calidad de vida en este grupo vulnerable de pacientes con neoplasias.

4•2 Epidemiología de la infección documentada en pacientes con hemopatías malignas y neutropenia febril en la era actual de pruebas microbiológicas.

Clásicamente, en un porcentaje significativo de episodios (45-50%) de NF no se logra determinar ni clínica ni microbiológicamente el origen de la fiebre (29). De hecho, un potencial microorganismo infeccioso se identificaba solamente en el 20-25% de los casos (figura 1).

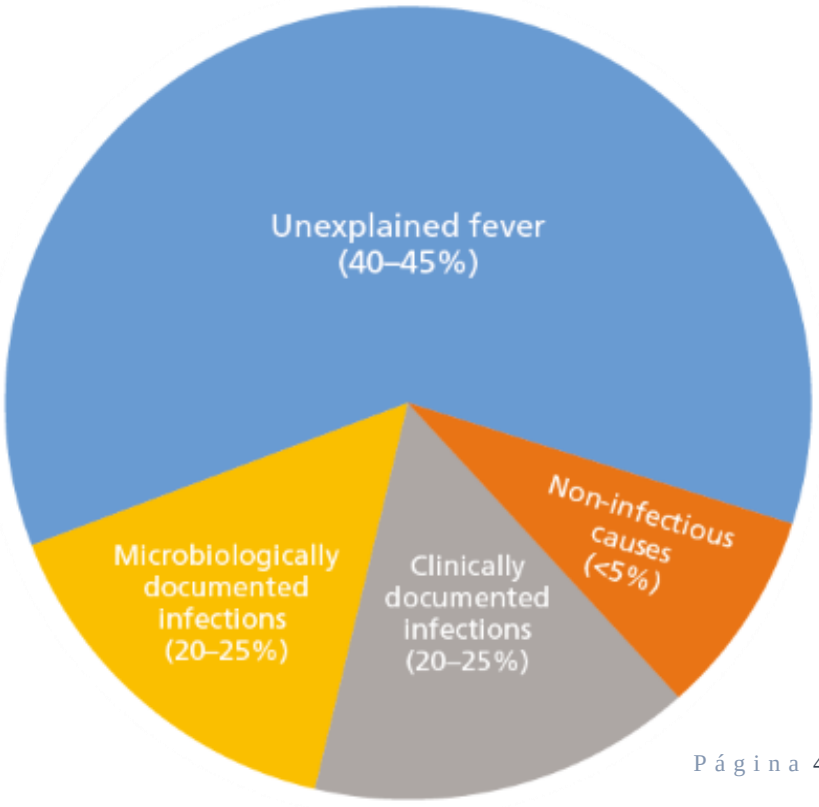

Figura 1. Representación gráfica de las causas de neutropenia febril. Reproducida de "Infections in patients with cancer", Lior Nesher, 2017, Management of cancer complications; página 2 (30).

La realidad es que la información sobre la variedad de infecciones documentadas en la actualidad durante los episodios de NF está pobremente descrita. La mayoría de los estudios publicados se centran en la descripción de pacientes con bacteriemia, pero en la práctica actual, se emplea un número creciente de pruebas microbiológicas para identificar diversas fuentes de infecciones bacterianas, virales y fúngicas. Adquirir una comprensión integral de la etiología subyacente de la fiebre es de suma importancia, ya que puede optimizar el uso del tratamiento con antibióticos. Al aparecer fiebre, comúnmente se administran antibióticos de amplio espectro para abordar posibles infecciones bacterianas. Sin embargo, es importante reconocer que la fiebre también puede surgir debido a causas virales, fúngicas o no infecciosas. Nuestra hipótesis es que un análisis integral que abarque todas las posibles causas de infección en esta población mostrará una amplia variedad de causas de fiebre que merecen un enfoque de tratamiento diferente y permitirán proceder a desescalar los antibióticos. Por lo tanto, el objetivo del primer artículo de la tesis fue describir las pruebas microbiológicas solicitadas en la actualidad para el diagnóstico etiológico de una infección en el momento de una NF y detallar las infecciones bacterianas, virales y fúngicas documentadas en la actualidad en una cohorte consecutiva de pacientes con malignidades hematológicas que presentan NF.

4•3 Problemática de la multirresistencia antibiótica en el tratamiento de los pacientes con cáncer.

La multirresistencia (MR) bacteriana se ha convertido en un desafío creciente a nivel mundial. La Organización Mundial de la Salud (OMS) ha identificado la resistencia a los antibióticos como una de las principales amenazas para la salud global. En respuesta a esta amenaza, en 2015, la OMS implementó el "Plan de Acción Mundial sobre la Resistencia a los Antimicrobianos" (31). Además, en 2019, la OMS destacó la Resistencia a los Antimicrobianos entre las diez principales amenazas para la salud global (32).

Esta situación también es preocupante en la Unión Europea (UE). Datos de EARS-Net en 2021, la red oficial europea de vigilancia de resistencia a antibióticos en patógenos invasivos de la UE y el Espacio Económico Europeo (EEA), mostraron un incremento significativo en la resistencia de *E. coli* y *K. pneumoniae* a la mayor parte de los antibióticos estudiados (33). En *E. coli,* es notable el incremento en la resistencia a cefalosporinas de 3ª generación, pasando del 1.6% en 2001 al 14% en 2021. Esta resistencia se debe principalmente a la producción de beta-lactamasas de espectro extendido (BLEE), que representó el 86,1% de las cepas resistentes a cefotaxima en 2021. En cuanto a *K. pneumoniae,* la resistencia a carbapenémicos ha aumentado desde un 2.8% en 2017 hasta 5.9% en 2021. En España, la presencia de bacterias productoras de BLEE en *E. coli* y *K. pneumoniae* ha ido en aumento desde 1988 (34).

A nivel mundial, las infecciones por bacterias resistentes causan la muerte de aproximadamente 700.000 personas anualmente. De estas, 33.000 ocurren en la UE. Un

estudio reciente sugiere que la resistencia antimicrobiana podría haber estado asociada a casi cinco millones de fallecimientos en 2019, siendo 1,27 millones de muertes atribuidas directamente a esta resistencia (35). En España, se estima que anualmente 3.000 fallecimientos son causados por esta problemática (36).

En este contexto, los pacientes con cáncer son especialmente susceptibles a la colonización y posterior infección por gérmenes MR debido a su continua exposición al entorno sanitario, los ingresos recurrentes y prolongados debido a tratamientos de quimioterapia, así como también por el uso frecuente de antibióticos de amplio espectro, lo que ocasiona pérdida de la flora intestinal natural (37,38). Desde finales del siglo XX, la literatura ha reflejado un aumento sostenido en las tasas de resistencia en esta población (38,39).

Por ejemplo, en un estudio analizando 589 episodios de bacteriemia en pacientes con leucemia aguda, el 18.7% de las bacteriemias estuvieron causadas por gérmenes MR, especialmente por BGN-MR (19). De forma similar, una investigación intercontinental reportó tasas de MR del 35.2% en 655 episodios de bacteriemia por BGN en pacientes receptores de TPH (40). Además, el 50.9% de los episodios estuvieron causados por BGN resistentes a los betalactámicos no-carbapenémicos (Piperacilina-tazobactam o Cefepime/Ceftazidima) y un 18.5% por BGN resistentes a los carbapenems. Otro estudio realizado en España entre 2006 y 2008 en pacientes oncohematológicos, el 12.6% de los episodios de bacteriemia por *E. coli* fueron causados por cepas productoras de BLEE y esto se asoció con una mayor admisión en unidades de cuidados intensivos (UCI) y una mayor mortalidad (41).

En este sentido, la aparición de enterobacterias resistentes a carbapenem en las últimas décadas representa uno de los desafíos más significativos para el sistema de salud. Esta característica está aumentando en todo el mundo, predominantemente entre *K. pneumoniae, E. coli, P. aeruginosa* y *A. baumannii* (42,43). Un estudio identificó 18 pacientes con neoplasias hematológicas que presentaron bacteriemia por enterobacterias resistentes a carbepenem (44). Además, en una encuesta retrospectiva realizada en 52 centros de trasplantes en Italia, la incidencia de infecciones por *K. pneumoniae* resistente a los carbapenémicos mostró un aumento de 6 veces entre el 2010 y el 2013, alcanzando tasas del 2.9% en el trasplante alogénico (45).

La prevalencia de *P. aeruginosa* multirresistente *(P. aeruginosa*-MR) también ha crecido en los últimos años, correlacionándose con mayores tasas de mortalidad. Por ejemplo, un estudio centrado en bacteriemia en pacientes con neoplasias hematológicas reveló que el 33% de las bacteriemias causadas por *P. aeruginosa* eran multirresistentes. En este contexto, solo la presencia de una enfermedad hematológica activa y la bacteriemia por *P. aeruginosa* se vincularon de manera independiente con un aumento significativo en la mortalidad. (46). Del mismo modo, un estudio en pacientes receptores de TPH mostró tasas de mortalidad atribuidas a *P. aeruginosa* de hasta el 39% (47). Por otro lado, una investigación prospectiva en Italia reportó tasas de mortalidad atribuidas a bacteriemia por *P. aeruginosa* del 31.6%. No obstante, esta mortalidad era claramente atribuible a las cepas MR (9.1% mortalidad en cepas no-MR vs 40.2% en cepas MR; P=0.006) (48). Asimismo, en un estudio previo de nuestro grupo, sobre bacteriemia en pacientes con leucemia aguda, haber tenido una

bacteriemia por una *P. aeruginosa* MR fue un factor de riesgo independiente de mortalidad (19).

El tratamiento empírico inadecuado se ha asociado a un aumento de la mortalidad en diversos estudios (18,20,49), siendo este más común en las infecciones causadas por bacterias resistentes (40). En el estudio de Satlin et al., (44) mencionado previamente, sobre 18 pacientes con bacteriemia por enterobacterias resistentes a carbapenem; el 85% recibió terapia empírica inadecuada, incluso siguiendo las directrices recomendadas. En este grupo, la mortalidad alcanzó el 56%, y fue especialmente elevada, del 69%, entre los 13 pacientes neutropénicos. De hecho, las tasas de mortalidad en infecciones causadas por la familia Enterobacteriaceae resistente a carbapenem pueden llegar hasta un 70% en poblaciones inmunocomprometidas (50), del mismo modo en otro estudio, la mortalidad por bacteriemia causada por *P. aeruginosa* se mantuvo en un 38.9%, y las infecciones causadas por cepas MR, que representaron más de un tercio de las cepas aisladas, se asociaron significativamente con un mayor riesgo de mortalidad (P = 0.005) y una menor adecuación de tratamiento apropiado (P = 0.001) (51).

Finalmente, la epidemiología bacteriana, así como también el patrón de resistencia no es homogéneo. Estas variaciones pueden ser atribuidas no solo a las condiciones clínicas subyacentes de los pacientes, sino también a factores individuales como la colonización personal, la historia previa de uso de antibióticos y las hospitalizaciones anteriores. Además, se observan diferencias significativas entre los diferentes centros hospitalarios y, en una escala más amplia, entre regiones o países.

Dada esta diversidad, es esencial mantener un conocimiento actualizado de la epidemiología local en cada institución donde se realicen las prácticas diarias. Es igualmente vital reconocer los factores de riesgo asociados a la colonización o infección por bacterias resistentes, y realizar una evaluación individualizada del riesgo en cada paciente para la elección del tratamiento más adecuado.

Uno de los desafíos más importantes en el manejo de los pacientes oncohematológicos es el abordaje del tratamiento en las infecciones causadas por bacterias MR, debido a su estrecha relación con la mejora del pronóstico del paciente, sobre todo en bacteriemias. Por este motivo la administración temprana de antibióticos de amplio espectro dirigidos principalmente a la cobertura empírica de BGN, y en particular a *P. aeruginosa* ha sido clave en todas las guías de tratamiento de NF. En este sentido, las guías de tratamiento tanto nacionales como internacionales han recomendado tradicionalmente la administración inmediata de un betalactámico con actividad antipseudomónica: cefalosporinas (cefepime o ceftazidima), piperacilina-tazobactam, o un carbapenem (meropenem o imipenem) (5), aunque su papel en el contexto de la actual epidemiología no está bien establecido.

En resumen, la creciente prevalencia de infecciones por bacterias MR en pacientes con NF es una preocupación importante para la atención médica. Aunque la epidemiología está cambiando, las guías de tratamiento empírico pueden no estar evolucionando al mismo ritmo.

Los desafíos en la toma de decisiones, la falta de evidencia clínica sólida y la necesidad de un enfoque individualizado pueden contribuir a la falta de cambios en las recomendaciones

de tratamiento. Sin embargo, es esencial que los médicos estén atentos a las tendencias locales de resistencia antimicrobiana y consideren cuidadosamente la elección de antibióticos para garantizar el mejor resultado posible para sus pacientes. En esta línea nuestros siguientes trabajos han intentado demostrar que es necesario un cambio en las guías de tratamiento empírico de los pacientes con NF que esté en consonancia con la actual epidemiología.

4•4 Resistencia a los β-lactámicos empíricos recomendados en las pautas para la neutropenia febril en bacteriemia por bacilos gramnegativos en España.

Como hemos comentado previamente, el cambio en la epidemiología de la bacteriemia en pacientes con NF es un fenómeno relevante y preocupante en el campo de la onco-hematología. Lo más preocupante es el aumento progresivo en las tasas de infección causada por BGN en este grupo de pacientes en los últimos años (39,52,53). En la década de los 70, los BGN constituían aproximadamente el 70% de las bacteriemias monomicrobianas. No obstante, hacia finales de los años 80 y 90, esta tendencia se invirtió, con un predominio de microorganismos grampositivos, especialmente estafilococos coagulasa-negativos y estreptococos. De hecho, la frecuencia de grampositivos como agentes causantes de bacteriemia, pasó del 29% en el período 1974-1976 al 65% entre 1988-1990(52). No obstante, la incidencia de bacteriemia por BGN volvió a aumentar a final de siglo y se ha mantenido en las últimas décadas con algunos estudios reportando una media de incremento del 51.3% en el período desde 2007-2013(17,39,53). Este cambio epidemiológico se ha visto agravado, en gran medida, por el aumento de la resistencia antimicrobiana en las bacterias gramnegativas a nivel mundial (18,38,52,54).

Uno de los datos más alarmantes es que, a pesar de este cambio en la epidemiología y el aumento de la resistencia, muchas de las pautas de tratamiento para pacientes con NF han mantenido recomendaciones de enfoque antibiótico empírico prácticamente invariables durante más de dos décadas. Los antibióticos comúnmente recomendados para el

tratamiento empírico de la NF incluyen ceftazidima, cefepime, piperacilina/tazobactam, meropenem y amikacina (5,55–57).

En este contexto, el segundo artículo de nuestra tesis tiene como objetivo abordar este desfase entre la epidemiología cambiante de las infecciones en pacientes con NF y las recomendaciones terapéuticas estándar. Para lograrlo, se plantea describir la epidemiología actual de las bacteriemias causadas por BGN en una cohorte multicéntrica de pacientes hematológicos neutropénicos en España. Los aspectos clave que se investigan y se describen en tu estudio incluyen:

1) **Resistencia a los β-lactámicos:** Uno de los puntos centrales de la investigación es analizar la resistencia de las bacterias gramnegativas a los antibióticos β-lactámicos que se utilizan como tratamiento empírico en las pautas de NF. Evaluar la resistencia antimicrobiana nos parece fundamental para comprender cuán efectivas son estas terapias en la práctica clínica actual y ayudar a realizar una fotografía que permita una óptima recomendación de nuevas pautas antibióticas.

2) **Impacto del tratamiento empírico:** También se busca determinar el impacto del tratamiento antibiótico empírico inapropiado (TAEI) en la mortalidad de los pacientes con NF. Esto es esencial para evaluar si las pautas de tratamiento actuales están logrando resultados satisfactorios o si es necesario considerar ajustes terapéuticos para mejorar los desenlaces clínicos.

3) **Cohorte multicéntrica:** Nos parece imprescindible la inclusión de una cohorte multicéntrica para agregar robustez a los hallazgos, ya que permite recopilar datos

de múltiples centros de atención médica y, por lo tanto, obtener una imagen más completa de la situación epidemiológica y de resistencia antimicrobiana en España.

En última instancia, con nuestra investigación buscamos proporcionar evidencia sólida y actualizada sobre la epidemiología y la resistencia antimicrobiana en pacientes con NF, con un enfoque específico en las bacteriemias por BGN. Los resultados del estudio pueden tener implicaciones significativas en la formulación de recomendaciones terapéuticas más adecuadas y adaptadas a la realidad clínica actual, con el objetivo de mejorar la atención y los resultados de los pacientes hematológicos neutropénicos en España. Además, este tipo de investigación es esencial para abordar el desafío global de la resistencia antimicrobiana y garantizar un uso más prudente y eficaz de los antibióticos en la práctica clínica.

4•5 Alta tasa de uso inadecuado de antibióticos en pacientes con malignidades hematológicas y bacteriemia por *Pseudomonas aeruginosa* siguiendo las recomendaciones de las pautas internacionales.

En el escenario descrito hasta el momento una de las infecciones más importantes dentro de los BGN por su frecuencia y gravedad en estos pacientes son las bacteriemias causadas por *Pseudomonas aeruginosa*. (23,48). Por esta razón, lograr una cobertura óptima de este patógeno ha sido uno de los desafíos más importantes en las pautas de tratamiento de la NF (5,56) y por ello los antibióticos clásicamente recomendados en las guías de tratamiento de NF han sido cefepime, piperacilina-tazobactam y meropenem (5,57).

Sin embargo, la adecuada cobertura empírica de este patógeno en la actualidad se ha vuelto especialmente problemática debido al aumento progresivo de aislamientos de *P. aeruginosa* MR y extremadamente resistentes (XR) en todo el mundo (19,40). A pesar de este marcado cambio epidemiológico, como ya hemos comentado previamente, las pautas de tratamiento antibiótico más actualizadas para pacientes con malignidades hematológicas y neutropenia continúan recomendando un tratamiento empírico con los antiguos β-lactámicos (cefepime, piperacilina-tazobactam y meropenem) (5,56,57).

En el tercer artículo de nuestra tesis buscamos describir la actual epidemiología y las tasas de resistencia a los antibióticos β-lactámicos recomendados en las pautas internacionales para *P. aeruginosa* aislada en bacteriemias de pacientes con malignidades hematológicas. Además, pretendemos describir cuántos pacientes recibieron un tratamiento empírico inadecuado y su impacto en la mortalidad.

4•6 Impacto del tratamiento antibiótico empírico en la mortalidad en pacientes neutropénicos con bacteriemia que presentan shock séptico

El shock séptico representa la forma clínica más grave de la infección sistémica en el paciente neutropénico. Sin embargo, existe escasa información sobre la incidencia, las características y el pronóstico de los pacientes neutropénicos que presentan esta complicación (58–60). Esta información, no obstante, es ahora más relevante que nunca. Como hemos explicado previamente, las tasas de BGN en pacientes onco-hematológicos están aumentando de manera progresiva (18,54), lo que podría afectar a un mayor porcentaje de pacientes que presentan shock séptico (61) y a una mayor dificultad en acertar en tratamiento empírico adecuado según la multiresistencia. Es importante recordar que diferentes estudios en población neutropénica han demostrado que el TAEI se asocia con un aumento de la mortalidad (18,20,62).

Las pautas internacionales han recomendado ampliar el espectro antimicrobiano para abarcar microorganismos gramnegativos y grampositivos resistentes a los medicamentos en pacientes neutropénicos con shock séptico. Sin embargo, no se han incorporado nuevos antibióticos a estas recomendaciones. Los antibióticos recomendados consideran la adición de aminoglucósidos, quinolonas, vancomicina y/o tratamiento contra levaduras a los β-lactámicos anti-pseudomónicos clásicos (cefepime, ceftazidima, piperacilina-tazobactam o meropenem) (5).

En el siguiente artículo de nuestra tesis quisimos describir la frecuencia, las características clínicas y la etiología de las bacteriemias en pacientes neutropénicos febriles con shock

séptico y analizar los factores de riesgo de mortalidad. También evaluamos el impacto de diferentes pautas de tratamiento antibiótico empírico en la mortalidad.

4•7 Características clínicas y resultado de las bacteriemias en pacientes que viven con el VIH y presentan cáncer con neutropenia febril

Los pacientes con infección por el VIH que no reciben terapia antirretroviral (TAR) desarrollan el síndrome de inmunodeficiencia adquirida (SIDA) y, en muchos casos, tumores definitorios de SIDA (63). Con la introducción de la TAR combinada, sin embargo, la infección por VIH se ha convertido en una enfermedad crónica, y el número de personas viviendo con VIH continúa aumentando (64). Esto, a su vez, se ha asociado con un mayor riesgo de tumores no definitorios de SIDA (65). La incidencia e incluso la mortalidad por estos tumores no definitorios de SIDA parecen ser más altas en pacientes con VIH que en la población general. Los pacientes con VIH que desarrollan cáncer, especialmente aquellos con un nivel de CD4 más bajo, tienen inmunosupresión intrínseca, que se suma a la neutropenia y la toxicidad asociada con la quimioterapia (66). Además, algunos pacientes reciben regímenes de TAR con interacciones relevantes entre medicamentos que pueden complicar la administración de la quimioterapia y dar lugar a complicaciones adicionales.

La información sobre las características de las bacteriemias en pacientes con VIH y cáncer que desarrollan NF después de la quimioterapia es escasa, y no existen recomendaciones específicas para estos pacientes al inicio de la NF. En el quinto artículo de nuestra tesis comparamos las características clínicas y los resultados de las bacteriemias en pacientes con cáncer NF con y sin infección por VIH, y analizamos los factores pronósticos asociados a una mayor mortalidad.

4•8 Factores de riesgo de mortalidad en receptores de trasplante de células hematopoyéticas con bacteriemia: aspectos a abordar en futuras recomendaciones de pautas antibióticas empíricas.

La bacteriemia es una causa importante de morbilidad y mortalidad después de un TPH. Aunque la epidemiología de la bacteriemia en pacientes hematológicos ha experimentado cambios recientes, con una disminución de los cocos grampositivos, un aumento de los BGN y un aumento significativo de los BGN-MR, pocos estudios han evaluado lo que pasa concretamente en la subpoblación receptora de un trasplante hematopoyético (23,54,67). Esto es de suma importancia, ya que las recomendaciones de las pautas internacionales para los regímenes de antibióticos empíricos no han cambiado en los últimos años (5,56) y no especifican diferencias entre la diversa población de pacientes hematológicos con neoplasia. Un conocimiento integral de los factores asociados con un aumento de la mortalidad en receptores de TH con bacteriemia es fundamental para optimizar el manejo de los pacientes y mejorar el pronóstico. En el último trabajo de nuestra tesis definimos los factores de riesgo de mortalidad en receptores de TPH con bacteriemia en los últimos 10 años de nuestra experiencia clínica. En especial queremos describir la etiología de la bacteriemia y la adecuación de las actuales pautas de terapia antibiótica empírica.

4•9 Justificación de la tesis

La NF en los pacientes oncohematológicos representa uno de los desafíos clínicos más significativos en la medicina. Del mismo modo, poblaciones específicas como los pacientes con infección por VIH y neoplasias asociadas o aquellos receptores de trasplante de médula ósea, son más propensos a sufrir episodios de infecciones; condicionado por la inmunosupresión que presentan. Sin embargo, a pesar de los avances en el diagnóstico y tratamiento, persisten importantes brechas en nuestro conocimiento que requieren una investigación más exhaustiva.

Uno de los principales desafíos en el manejo de la NF está en la identificación etiológica de la infección. Actualmente existen muchas técnicas diagnósticas de microbiología, pero como utilizarlas y el rendimiento que nos ofrece cada prueba no están claros. Optimizar los recursos diagnósticos es importante para disminuir el uso innecesario de pruebas microbiológicas, y en consecuencia racionalizar el volumen de trabajo y el gasto. El reconocimiento preciso de sus causas, así como la comprensión de la incidencia real de infección, es esencial para un manejo clínico adecuado Es importante, por tanto, conocer con mayor precisión la proporción de episodios que son de origen bacteriano para optimizar el uso de antibióticos, minimizando el riesgo de resistencia y otros efectos adversos asociados a su uso indiscriminado.

El panorama epidemiológico de la NF ha experimentado cambios significativos en los últimos años, con un aumento notable en la frecuencia de BGN y, en particular, en las tasas de MR. Esta evolución plantea serias preocupaciones sobre la aplicabilidad de las guías actuales de

manejo de la NF. A pesar de seguir rigurosamente estas guías, se observan altas tasas de tratamiento antibiótico empírico inadecuado, lo que podría estar directamente relacionado con un aumento en la mortalidad, especialmente en pacientes con NF complicada con bacteriemia. Otro aspecto crítico es el cambio epidemiológico y las tasas de resistencia actuales. Las infecciones por BGN y, en particular, por *P.aeruginosa*, son especialmente preocupantes debido a las altas tasas de mortalidad que ocasionan. La comprensión actualizada de estas tasas y su evolución es esencial para adaptar y mejorar las estrategias terapéuticas.

Los pacientes con shock séptico son de extrema gravedad y hay poca información que detalle el impacto de los diferentes tratamientos empíricos en aquellos pacientes con neutropenia. Nuestro trabajo se justifica al describir la elección habitual del tratamiento empírico antibiótico en esta población, detallar el porcentaje de pacientes que reciben un tratamiento empírico inadecuado y analizar el impacto de este tratamiento inadecuado en el pronóstico.

Es esencial conocer los factores de riesgo vinculados a la mortalidad y al desarrollo de multirresistencia en pacientes inmunodeprimidos, especialmente en aquellos con infección por VIH. Esta infección, por sí misma, provoca inmunodepresión, y en algunos casos, estos pacientes pueden desarrollar neoplasias que requieran quimioterapia, elevando así el riesgo de bacteriemia. Asimismo, los pacientes receptores de trasplante son más propensos a adquirir infecciones por gérmenes multirresistentes por lo que es necesario identificar los factores de mal pronóstico.

En resumen, esta tesis busca abordar y llenar estas brechas críticas en nuestro entendimiento, con el objetivo de mejorar el pronóstico y tratamiento de los pacientes afectados.

5• HIPÓTESIS

1• En la era actual de la microbiología se realiza un gran número de pruebas a los pacientes con neutropenia febril y un bajo porcentaje son positivas.

2• La identificación de una etiología infecciosa en la era actual de diagnóstico de microbiología es mayor que las descritas hasta el momento.

3• Ha habido un cambio mundial en la epidemiología de las infecciones con un aumento en las infecciones por bacilos gran negativos y una creciente resistencia a los antibióticos recomendados empíricamente por las guías.

4• Las tasa de resistencia antimicrobiana de *P. aeruginosa* ha disminuido la eficacia de los antibióticos β-lactámicos tradicionalmente recomendados (cefepime, piperacilina-tazobactam y meropenem) en pacientes con malignidades hematológicas y neutropenia.

5• Las guías de manejo de la neutropenia febril están obsoletas en el actual contexto epidemiológico. Esto podría estar relacionado con altas tasas de tratamiento antimicrobiano empírico inapropiado a pesar de seguir las recomendaciones de las guías. El tratamiento antimicrobiano empírico inapropiado se puede relacionar con un aumento de la mortalidad en aquellos pacientes con neutropenia febril y bacteriemia.

6• Los pacientes con neutropenia febril y shock séptico tienen unas tasas de mortalidad elevadísimas. El tratamiento con un β-lactámico adecuado, así como la combinación ATB puede ser beneficiosa.

7• Los pacientes con infección por el VIH que desarrollan cáncer y experimentan neutropenia febril con bacteriemia presentan características clínicas y etiológicas distintas en

comparación con pacientes con cáncer sin infección por el virus de la inmunodeficiencia humana.

8• La epidemiología de la bacteriemia en receptores de trasplante hematopoyético difiere de la población general de pacientes hematológicos, con posibles variaciones en la etiología y resistencia bacteriana.

6• OBJETIVOS

Objetivo principal

El objetivo principal del proyecto es conocer las principales causas de neutropenia febril en los pacientes oncohematológicos, así como analizar las características de las bacteriemias en poblaciones específicas, con el objetivo de optimizar los tratamientos antibióticos empíricos y el pronóstico de estos pacientes.

5•1 Objetivos secundarios

5•1•1 Describir el uso de las diferentes técnicas microbiológicas contemporáneas y su impacto en el diagnóstico etiológico de infecciones en pacientes con malignidades hematológicas que presentan neutropenia febril.

5•1•2 Describir la epidemiología de la bacteriemia por bacilos gran negativos de pacientes hematológicos en España, así como evaluar las tasas de tratamiento antibacteriano empírico inapropiado y el seguimiento de las recomendaciones de las guías.

5•1•3 Describir las características de la bacteriemia por *P. aeruginosa* en pacientes hematológicos de España, así como las tasas de infección por *P. aeruginosa* multirresistente.

5•1•4 Conocer las características clínicas y describir la epidemiologia de los pacientes con bacteriemia y neutropenia febril que se presentan con shock séptico.

5•1•5 Comparar las características de las bacteriemias en pacientes con neutropenia febril con o sin infección por el virus de la inmunodeficiencia humana.

5•1•6 Evaluar los factores de riesgo de multirresitencia y mortalidad en la bacteriemia de los pacientes receptores de trasplante de progenitores hematopoyéticos.

7• MATERIAL, MÉTODOS Y RESULTADOS

El material, los métodos y los resultados obtenidos en esta tesis se presentan como un compendio de artículos de investigación:

7•1 Documented Infection at febrile neutropenia onset in patients with hematological malignances in the Current Era of Microbiological Testing.

Chumbita M., Peyrony O., Teijón C., Monzó Gallo P., Aiello TF., Gallardo Pizarro A., Puerta-Alcalde P., Bodro M., Hernández Meneses M., Morata L., Del Rio A., Espasa M., Martínez C., Gaya A., Soriano A., Garcia-Vidal C.

Submitted.

Resumen:

Introducción: La identificación de la etiología de la infección en la NF es esencial para el cuidado del paciente. Este estudio explora el enfoque microbiológico contemporáneo y su impacto en el diagnóstico de infecciones en pacientes con malignidades hematológicas con NF.

Métodos: Se realizó un análisis retrospectivo en el Hospital Clínic de Barcelona para detallar las estrategias de pruebas microbiológicas utilizadas para diagnosticar infecciones al inicio de la NF en pacientes con malignidades hematológicas entre enero de 2020 y marzo de 2022.

Resultados: De los 331 pacientes incluidos en el estudio, se observaron un total de 462 episodios de NF. Se logró documentación microbiológica en 200 (43,3%) de estos episodios. Un análisis exhaustivo de 4.047 muestras reveló una tasa de positividad del 7,2%. Esta tasa aumentó significativamente después del segundo episodio de NF, con un 9,3% de positividad, en comparación con el 6,4% durante el primer episodio (p=0,001). Las pruebas más solicitadas fueron los hemocultivos (37,5%) y las muestras de sangre sin cultivo (22,3%).

Estas pruebas mostraron las tasas de positividad más alta (9,6%) y más baja (3,3%), respectivamente. Las infecciones bacterianas fueron las más prevalentes (32,3%), con una distribución casi equitativa entre infecciones Gram-positivas y Gram-negativas. Las infecciones virales, en particular aquellas causadas por virus respiratorios, representaron el 14,3%, mientras que las infecciones fúngicas (2,6%) y parasitarias (1,3%) fueron menos comunes. La tasa de mortalidad a 60 días fue del 9,1%, y los pacientes con infecciones documentadas presentaron un riesgo mayor (15%).

Conclusión: En el panorama actual de diagnóstico antimicrobiano, nuestros hallazgos revelan una tasa elevada de infecciones documentadas microbiológicamente en el inicio de la NF. Aunque las infecciones bacterianas son comunes, nuestros datos resaltan la importancia de las infecciones virales como causa de fiebre. Aprender el manejo óptimo de los pacientes en este escenario representa un desafío para la desescalada antimicrobiana. Además, nuestros datos enfatizan la necesidad urgente de una gestión diagnóstica rentable.

Current Microbiological Testing Approaches and Documented Infections at Febrile Neutropenia Onset in Patients with Hematological Malignancies

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Key words: febrile neutropenia; epidemiology, bacteremia, hematologic patients

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Abstract:

Background: Identifying infection etiology in febrile neutropenia (FN) is vital for patient care. This study explores contemporary microbiological approach and their impact on diagnosing infections in hematological malignancy patients with FN.

Methods: A retrospective analysis was conducted at Hospital Clinic of Barcelona to detail the microbiological testing strategies used to diagnose infections at FN onset in patients with hematologic malignancies between January 2020 and March 2022.

Results: Among the 331 patients included in the study, a total of 462 episodes of FN were observed. Microbiological documentation was achieved in 200 (43.3%) of these episodes. A comprehensive analysis of 4,047 samples revealed a 7.2% positivity rate, which significantly increased after the second FN episode (9.3% positivity), compared to 6.4% during the first episode (p=0.001). The most commonly requested tests were blood cultures (37.5%) and non-culture blood samples (22.3%). These tests exhibited the highest (9.6%) and lowest (3.3%) positivity rates, respectively. Bacterial infections were the most prevalent (32.3%), with a near-even distribution between Gram-positive and Gram-negative infections. Viral infections (14.3%), particularly those caused by respiratory viruses, were also frequent, while fungal (2.6%) and parasitic (1.3%) infections were less common. The 60-day mortality rate was 9.1%, and patients with documented infections were at a higher risk (15%).

Conclusions: In the modern landscape of antimicrobial diagnostics, our findings revealed an elevated rate of microbiologically documented infections at FN onset. Bacterial

infections are common, but our data underscores the significance of viral infections as a cause of fever. Learning the optimal management of patients in this scenario poses a challenge for antimicrobial de-escalation. Furthermore, our data emphasizes the urgent need for cost-effective diagnostic stewardship.

INTRODUCTION

Febrile neutropenia (FN) is a critical medical condition that occurs in a substantial proportion of patients diagnosed with hematologic malignancies. It is associated with significant mortality rates that range from 10-30% (1–3).

At fever onset, ruling out an infectious etiology is of paramount importance. Recent decades have seen a revolution in diagnostic microbiology techniques, with significant optimization of infection diagnoses, especially those that are viral and fungal. However, there remains a poor understanding of how these techniques are employed and what results are obtained in the etiological diagnosis of FN infections.

Most published studies detailing infection etiology in FN primarily focus on describing patients with bacteremia (4,5), but in current practice, an increasing number of microbiological tests are used to identify various sources of bacterial, viral, and fungal infections. It is important to acquiring such an understanding especially within the context of crucial decisions regarding broad-spectrum empirical antibiotic treatments.

Therefore, our objective was to describe the current microbiological testing approaches and their impact on diagnosing documented current bacterial, viral and fungal infections in a consecutive cohort of patients with hematologic malignances and FN.

METHODS

Setting, study population, and design.

This descriptive, retrospective study was conducted at Hospital Clinic of Barcelona, a 700-bed university center that provides medical, surgical and intensive care to an urban population of 500,000 adults (>18 years). All episodes of FN in adult patients with hematologic malignancies hospitalized between January 2020 and March 2022, were included. High-quality data on demographic characteristics, clinical signs, laboratory tests, microbiological results, treatments and outcomes were collected directly from electronic medical records, as described elsewhere (6).

This study was approved by the Ethics Committee Board of Hospital Clinic of Barcelona (HCB/2022/0958). Informed consent was waived due to the retrospective nature of the study.

Definitions and microbiological methods.

Febrile neutropenia episodes

Each episode of FN was defined according to guidelines (1,7), i.e., an absolute neutrophil count ≤500 cells/mm and axillar temperature measurement >38°C. After five consecutive days with temperature measurements below 37°, a FN episode was considered as having ended.

Clinical samples from blood, urine, respiratory tract, or other sources were collected following a decision made from the attending physician at FN onset. Clinical investigators reviewed the relevance of positive microbiological results according to the following definitions.

A single positive culture was considered as significant if the microbe was clinically relevant or isolated in blood cultures. Of note, for bloodstream infections (BSI) due to coagulase-negative *staphylococci* (CoNS) whereby no catheter tip culture was available, at least two sets of positive blood cultures from different venipuncture sites were required to be considered as significant. Gram-negative bacilli (GNB) and gram-positive cocci (GP) were classified as multidrug-resistant (MDR) per prior consolidated definitions (8).

Overall mortality was defined as death from any cause within the first 30 and 60 days after the onset of the first FN episode.

Microbiological procedures

All clinical samples were processed using standard techniques for conventional culture in the microbiology department. Blood cultures were subjected to the Bactec FX system (Becton-Dickinson Microbiology Systems) with a 5-day incubation period; isolates were identified through standard techniques. Antimicrobial susceptibility testing was carried out using either the Phoenix system (Becton Dickinson, Franklin Lakes, NJ) microdilution systems or Etest (AB Biodisk, Solna, Sweden/bioMérieux, Mercy l'Etoile, France). For defining susceptibility or resistance to antimicrobial agents, we used version 9.0 of the EUCAST clinical critical point tables (9).

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In this study, we define 'non-cultured blood' as plasma or serum samples, distinguishing them from blood cultures. A list of each test can be found in Table 1 of the supplementary appendix (S1).

We routinely use multiplex real-time PCR panels to identify microorganisms in various types of clinical samples. These samples include respiratory tract specimens, such us bronchoalveolar lavage (BAL) and nasopharyngeal swabs; cerebrospinal fluid (CSF); and stool samples. A comprehensive list of microorganisms identified in each test can be found in Table 2 of the supplementary appendix (S2).

Additionally, all BAL samples are subjected to multiple diagnostic methods to identify specific pathogens. These methods include conventional culture techniques, staining and PCR for detecting *Pneumocystis jirovecii*, molecular assays for cytomegalovirus (CMV). and the use of lateral flow assays (LFA) in combination with commercial Enzyme-Linked Immunosorbent Assay (ELISA) staining to detect *Aspergillus*-specific antibodies.

Galactomannan (GM) antigen detection is conducted in both serum and BAL samples using a commercial enzyme immunoassay. The cut-off values are set at ≥ 0.5 for serum and ≥ 1.0 for BAL (10). Additionally, 1-3-β-D-glucan levels are determined in serum samples using the Wako commercial kit (Wako Pure Chemical Industries, Ltd, Tokyo, Japan), with a cut-off value of 11 pg/mL considered as positive.

All stool samples undergo testing for the presence of *Clostridioides difficile (C. difficile)* toxin in addition to conventional culture techniques.

Lastly, viral detection is determined by real-time PCR techniques assessing the viral load in various types of body fluids, including plasma, CSF, BAL samples, urine, and tissue samples (11).

Statistical analysis

Categorical variables were described as counts and percentages, whereas continuous variables were expressed as either means and standard deviations (SD) or medians and interquartile ranges (IQRs). The Chi-squared Pearson test and the Mann-Whitney U test or the t-student test were used to compare the distribution of categorical and continuous variables, respectively. Kaplan-Meier curves were constructed for survival analyses. The threshold for statistical significance was defined as a two-tailed $p<0.05$. All analyses were performed using SPSS software (version 25.0; SPSS, Inc., Chicago, IL).

Results

Patients characteristics

Table 1 summarizes the baseline characteristics of the included 331 patients with hematologic malignancies. These patients had 462 episodes of FN across the 419 hospital admissions. Overall, 241/331 (72.8%) patients had 1 FN episode; 60/331 (18.1%) had 2 episodes; 30/331 (9.1%) had 3 or more. Consequently, we reported 331 initial episodes of FN; 90 second episode of FN; and 41 third or more episodes of FN.

Microbiological testing requested and rates of test positivity.

A total of 4047 samples were requested in the 462 FN episodes; 292 (7.2%) were positive. Figure 1 shows the samples requested, as well as the positivity rates by ordered sample type. The most requested test was blood culture at 1516 (37.5%), followed by non-culture blood samples at 903 (22.3%). The frequency of positive microbiological samples documenting infections increased after the second episode: during the first episode, there were 185 (6.4%) positive results of the 2893 samples, compared to 107 (9.3%) of the 1154 samples acquired from the second episode onwards (p=0.001).

Microbiological documentation was achieved in 200/462 (43.3%) episodes, accounting for 233 positive results. These positive results correspond to 169 episodes with a single microorganism and 31 (6.7%) polymicrobial episodes (29 with 2 microorganisms, and 2 with 3 microorganisms). The 233 isolates were distributed as follows: bacterial infections in 149/462 episodes (32.3%); viral in 66/462 (14.3%); fungal in 12/462 (2.6%), and parasitic in 6/462 (1.3%). Figure 1 in the supplementary appendix details the distribution of bacterial, viral, fungal, and parasitic infections by first, second, and third or subsequent FN episode. Overall, the proportion of episodes with microbiological documentation increased from 39.6% (131/331) in the first episode to 52.7% (69/131) in the second and further episodes (p=0.010). In the first episode, 29.6% (98/331) had bacterial isolation vs 38.9% (51/131) in subsequent episodes (p=0.053) and 23% (76/331) with BSI to 30.5% (40/131) in second episode onwards(p=0.091). Viral and fungal infections were documented in 12.4% (41/331) and 2% (7/331) in the first episode and in 19% (25/ 131; p=0.064) and 3.8% (5/ 131; p=0.3) in the subsequent, respectively.

Figure 2 details the most common microorganisms isolated by first, second or more FN episode.

Bacterial etiology

Of the overall 292 positive samples, 197 (67%) documented bacterial infections in 149/462 (32%) episodes, mainly in blood cultures (114 episodes, 25% of total episodes), urine (23 episodes, 5%), stools (14 episodes, 3%), others (8 episodes, 2%), and the respiratory tract (4 episodes, 0.8%).

BSI was the most common bacterial infection, and it was caused by GP in 67/114 (59%) episodes and by GNB in 57/114 (50%). Twenty-three (4.9%) episodes were polymicrobial BSI. The most frequent bacterial isolated in BSI were CoNS in 37/149 (25%) episodes, *Escherichia coli* in 24/149 *(*16%) episodes, *Streptococcus* group in 13/149 (8.8%) episodes (*S. mitis* (5), *S. agalactiae* (2), *S. salivarius* (1), *S. parasanguis* (1), *S. gallolyticus* (1), *S. constellatus* (1), *S. anginosus* (1), *S.* grupo viridans (1)); *Enterococcus faecium* in 12/149 (8%), episodes, *Klebsiella pneumoniae* in 12/149 (8%) episodes, and *Pseudomonas aeruginosa* in 11/149 (7.5%) episodes. Remarkably, the incidence of *P. aeruginosa* BSI increase after the second FN episode: 2.1% (7/331) during the first episode of FN 2,2% (2/90) on the second, and 4.9% (2/41) on the third and subsequent (p=0.546).

Figure 3 details all the positive documented infections per requested sample.

Viral etiology

Viral infections were the second most documented cause of infection, with 75 positive tests in 66/462 (14.3%) episodes. Viruses were identified by naso-pharyngeal and respiratory tract samples (43; 57.3%), non-culture blood (25; 33.4%), urine (4; 5.3%), CSF (2; 2.7%), and stools (1; 1.3%).

Respiratory viruses were the most frequent, with 43 (57.3%) present in 38/462 (8.2%) episodes. Among respiratory viruses, SARS-CoV-2 was the most common in 20/43 (46.5%) episodes, followed by other coronaviruses (5/43; 11.6%), rhinovirus (5/43; 11.6%), human metapneumovirus (4/43; 9.3%), human parainfluenza virus (3/43; 7%), respiratory syncytial virus (2/43; 4.7%), influenza (2/43; 4.7%), and human adenovirus (2/43; 4.7%).

Viruses documented in non-cultured blood samples, specifically in plasma, were human herpes virus 6 (9/462; 2% episodes), cytomegalovirus (8/462; 1.7% episodes), herpes simplex virus type 1, (7/462; 1.5% episodes), and Epstein-Barr virus (1/462; 0.2% episodes). Finally, BK polyomavirus was isolated in urine (4/462; 0.8% episodes), JC polyomavirus (1/462; 0.2% episodes) and herpes simplex virus type 1 (1/462; 0.2% episodes) in CSF, and norovirus (1/462; 0.2% episodes) in stools.

Fungal etiology

A total of 14 fungal infections were documented in 12/462 (2.6%) episodes. The most frequent fungal infection was invasive aspergillosis in 9 (64%), detected in 8/462(1.7%) episodes. Diagnosis was done by GM antigen (5 cases positive in serum and 2 in BAL); by

LFA (1 episode) and by conventional culture of *Aspergillus fumigatus* (1 episode). It was followed by fungemia 2/462 (0.4%), caused by *C. glabrata* and *C. albicans.* Finally, there were positive cultures of candida in urine samples, all cases in patients with nephrostomy tube or double-J stent (3/462, 0.7% episodes).

Parasitic etiology

Parasites were isolated in 6/462 (1.3%) episodes. All were *Blastocystis* spp. isolated from stools samples in patients with diarrhea. All received specific treatment. In 4 episodes, the parasite was the only isolated during the NF episode. Other microbiological documentation was done in two cases.

Outcomes

Figure 4 represents the median duration of fever among different microbiological documented infections.

The 60 days mortality of the entire cohort was 9.1%, 15% for those patients with documented infection and 6.9% for those without a documented infection. Figure 5 displays Kaplan-Meier survival curves at 30 days according to the presence or not of documented infection (p=0.044), and documented bacterial, viral and fungi infection, respectively. The presence of viral infection was associated with the highest mortality.

Discussion

This study offers a comprehensive description of the microbiological tests employed and the subsequent documentation of infections during FN episodes in the current era. In contrast to previous studies that reported a relatively lower incidence of microbiologically documented infections at an average rate of 14-25% (12–15), our study reveals a higher incidence of microbiologically documented infections (43.3%), which increased to over 50% during second or subsequent episodes.

The significant expansion of microbiological diagnostic tools, particularly for non-bacterial infections, and the comprehensive investigation of etiology beyond bacteremia, elucidate the reasons behind our high rate of microbiological documentation. Bacterial cultures, especially blood cultures, are the most frequently ordered tests and yield the highest rate of positive results. The epidemiology described in our study aligns with other studies focusing on bacterial or fungal infections (4,16). Importantly, our results reveal an increased incidence of documented bacterial infections, particularly those caused by gram-negative bacteria, in the second or subsequent FN episodes. Notably, starting from the third FN episode onwards, 33% of these gram-negative bacterial infections are attributed to *P. aeruginosa*. This finding suggests that, from the second FN episode onward, the optimization of antipseudomonal therapy should be tailored according to the local epidemiology of each healthcare centre.

Our study reflects the revolution in viral infection diagnostics and demonstrates that a significant percentage of FN cases are attributed to virus, specially respiratory virus. As expected, in the context of the pandemic, SARS-CoV-2 infection has been the most

prevalent. It is noteworthy, however, that other viruses for which we lack extensive management knowledge and effective treatments (such as metapneumovirus, parainfluenza, or rhinovirus) have also been frequently detected. Future research should assess the optimal management strategies for neutropenic patients with respiratory viral infections, including considering the broad-spectrum antimicrobials stewardship in the absence of documented bacterial coinfection.

The advancement in etiological documentation of infection in FN should, however, not overshadow the equally important fact that currently, most microbiological tests requested, even in these patients with a high infection rate, yield negative results. Notably, only 7.2% of these samples yielded positive results. Among the various tests, blood cultures, which are the most frequently requested samples, exhibited the highest diagnostic yield with a positivity rate of 9.2%. However, other techniques such as additional non-cultures blood, the most expensive one, or urinary samples have had minimal impact on the etiological diagnosis of FN. The expanding diagnostic potential offered by microbiology services is constrained by a significant increase in laboratory work and diagnostic costs (17). In the forthcoming years, one of the most important challenges for clinicians and microbiologists will be to assess the cost-effectiveness of each diagnostic technique and establish optimal diagnostic stewardship strategies to streamline and economize diagnosis (17,18). Identifying patients with a higher likelihood of yielding positive results for each test requested and reducing the number of tests resulting in negative outcomes seems imperative. Perhaps clustering techniques or artificial

intelligence, which can potentially be beneficial in tailoring the management of hematological patients with hematologic malignancies, can be employed for this purpose.

Our study highlights once again that infection is a significant cause of mortality in patients with FN. This fact reinforces the idea that early diagnosis and optimal treatment are mandatory. Remarkably, our data reveals that the median duration of fever is significantly longer (3 days) when no bacterial infection is documented. This is important, suggesting that persistent fever after two days of antimicrobial treatment is less likely to indicate a bacterial infection. It emphasizes the value of exploring other etiologies and/or early discontinuation of empirical antimicrobial therapy.

The strengths of our study lie in the substantial number of FN episodes investigated, with a detailed description of all microbiological tests performed and the positive results obtained. It illustrates the broad spectrum of documented infections in patients with FN. Nevertheless, several limitations need to be acknowledged. The authors analyze real-world patient data; however, were the attending physicians who ordered all diagnostic techniques. This fact may have led to the potential underdiagnosis of certain infections. Data was collected directly from electronic medical records, which may have inherent limitations. While the findings from our single-center study can offer valuable insights and guide strategies such as stewardship efforts, it is essential to consider that different hospitals or geographic regions may exhibit varying epidemiology of documented infections in FN. Lastly, due to the design of our study, we were unable to assess non-infectious causes of fever within our cohort.

In conclusion, our study offers an updated and comprehensive insight into the contemporary diagnostic approach for infectious etiologies during FN episodes. In this new era of broad-spectrum antimicrobial diagnostics, we report the highest rates of microbiologically documented infections in the literature. Bacterial and viral infections were the most prevalent. The elevated rate of documented viral infections underscores the importance of advancing our understanding of the management and treatment of these infections in patients with FN, including antimicrobial stewardship decision making. The low positivity rates observed in certain tests employed emphasize the necessity of establishing a cost-effective diagnostic stewardship for these patients.

Table 1. Clinical and demographic characteristics of patients with febrile neutropenia.

Variable	N= 331(%)
Demographics, N (%)	
Age, median (IQR) years	59 (76-91)
Male sex	192 (58)
Hematological disease, N (%)	
Acute leukemia	149 (45)
Lymphoma	99 (30)
Multiple myeloma	38 (11.5)
Myelodysplastic syndrome	26 (7.8)
Chronic leukemia	22 (6.6)
Hematopoietic stem cell transplant	131 (39.6)
Solid neoplasm	58 (17.5)
Comorbidities, N (%)	
High Blood Pressure	88 (26.6)
COPD	40 (12.1)
Diabetes mellitus	35 (10.5)

Chronic kidney disease	19 (5.7)
Chronic liver disease	19 (5.7)
Outcomes	
60-day mortality	30 (9.1)

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Figure 1. Positivity rates by ordered sample type.

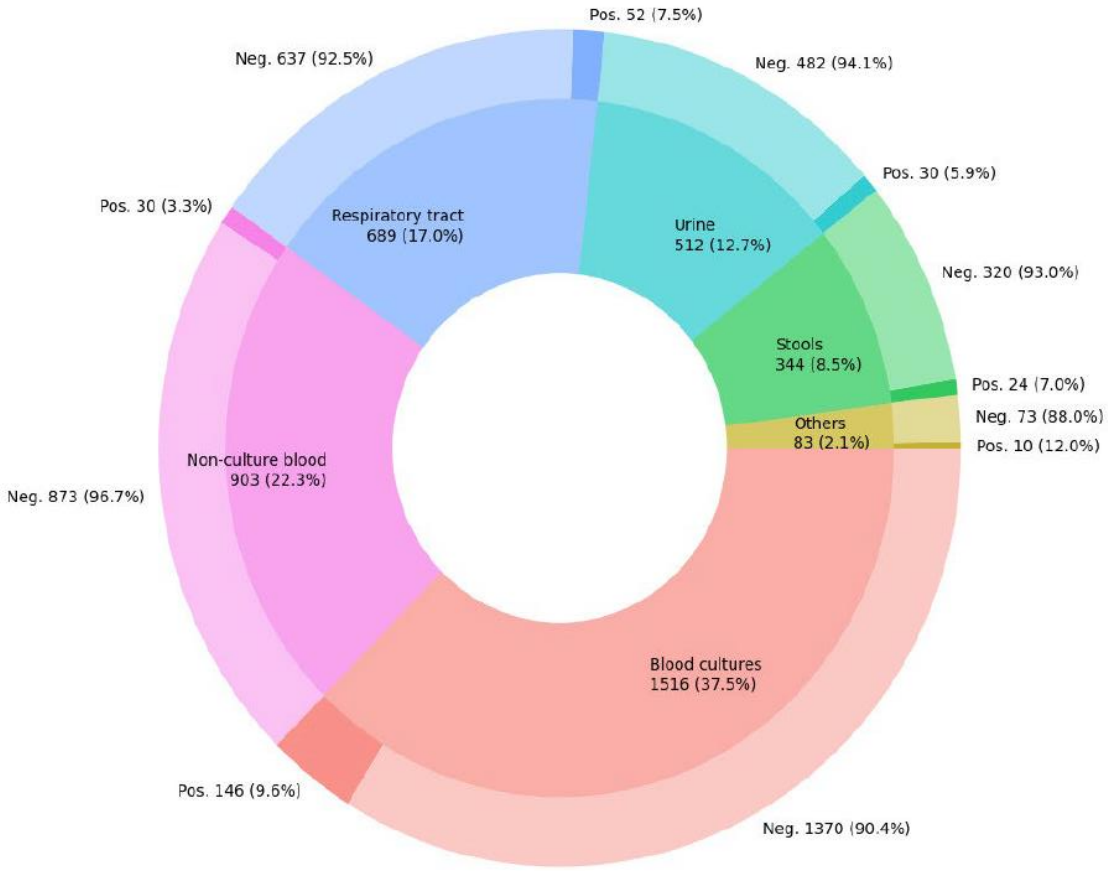
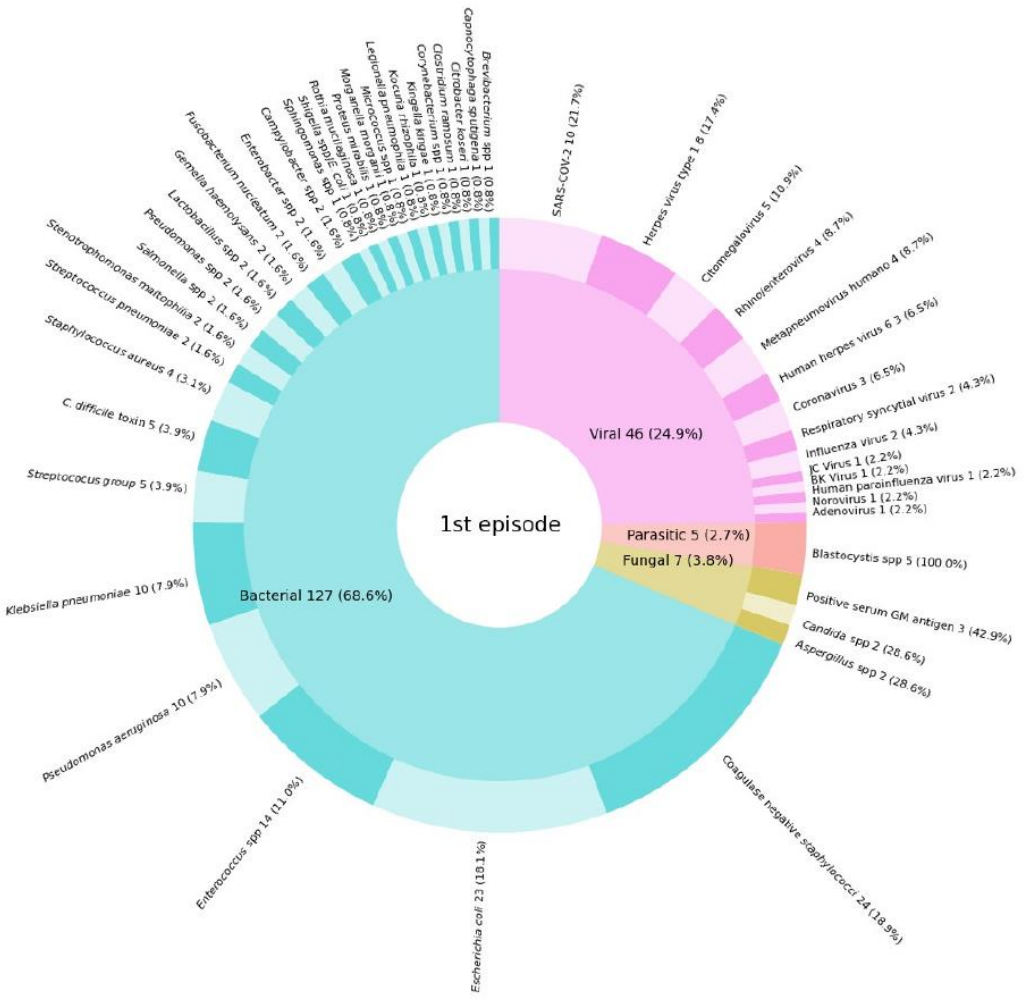
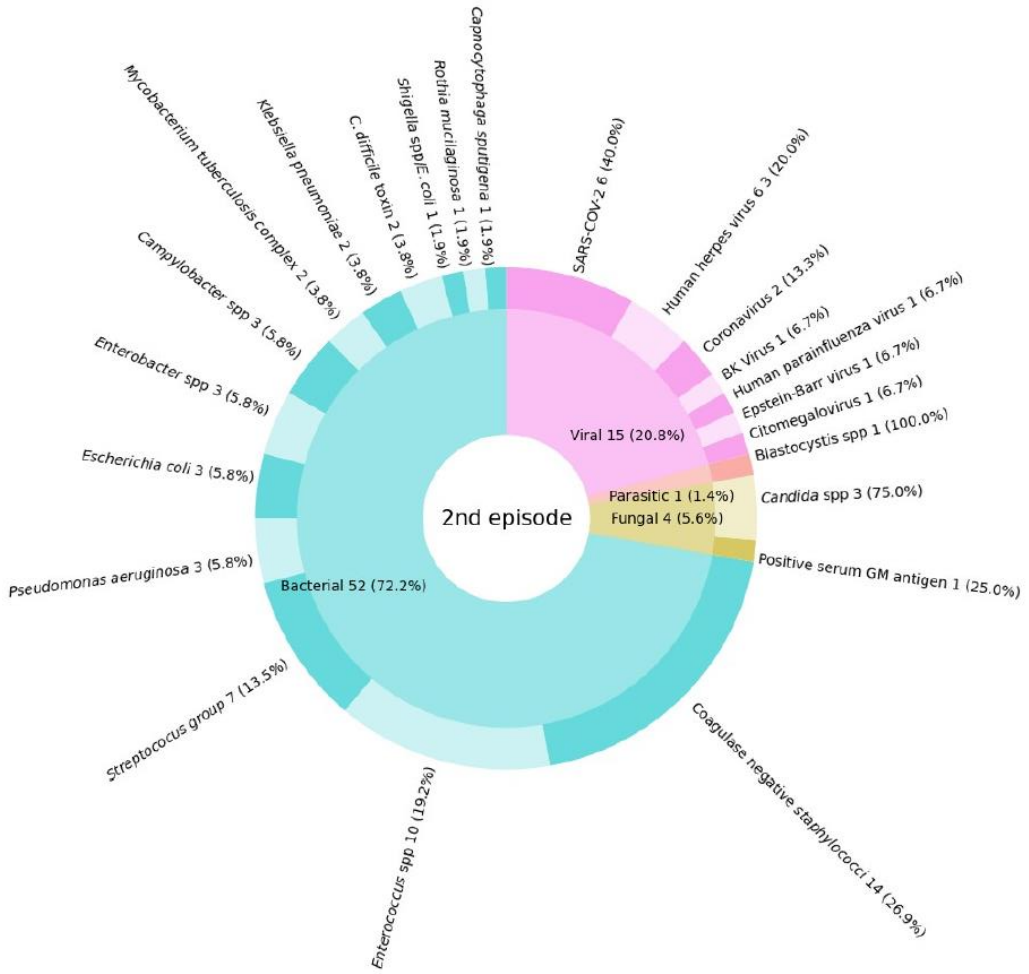


Figure 2: Prevalence of isolated microorganisms by febrile episode




2nd episode
Viral 15 (20.8%)
Parasitic 1 (1.4%)
Fungal 4 (5.6%)
Bacterial 52 (72.2%)
SARS-COV-2 6 (40.0%)
Human herpes virus 6 3 (20.0%)
Coronavirus 2 (13.3%)
BK Virus 1 (6.7%)
Human parainfluenza virus 1 (6.7%)
Epstein-Barr virus 1 (6.7%)
Citomegalovirus 1 (6.7%)
Blastocystis spp 1 (100.0%)
Candida spp 3 (75.0%)
Positive serum GM antigen 1 (25.0%)
Coagulase negative staphylococci 14 (26.9%)
Enterococcus spp 10 (19.2%)
Streptococcus group 7 (13.5%)
Pseudomonas aeruginosa 3 (5.8%)
Escherichia coli 3 (5.8%)
Enterobacter spp 3 (5.8%)
Campylobacter spp 3 (5.8%)
Mycobacterium tuberculosis complex 2 (3.8%)
Klebsiella pneumoniae 2 (3.8%)
C. difficile toxin 2 (3.8%)
Shigella spp/E. coli 1 (1.9%)
Rothia mucilaginosa 1 (1.9%)
Capnocytophaga sputigena 1 (1.9%)

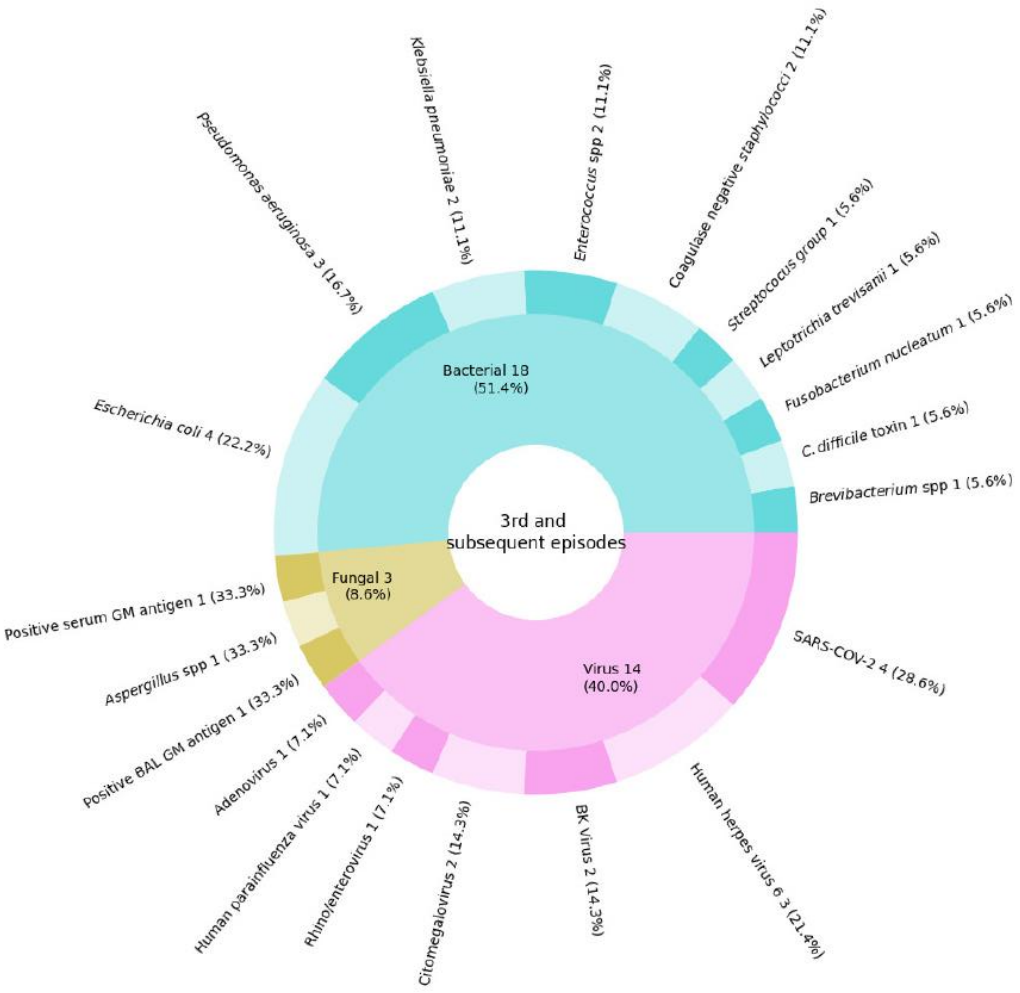

3rd and
subsequent episodes
Bacterial 18
(51.4%)
Fungal 3
(8.6%)
Virus 14
(40.0%)
Pseudomonas aeruginosa 3 (16.7%)
Klebsiella pneumoniae 2 (11.1%)
Enterococcus spp 2 (11.1%)
Coagulase negative staphylococci 2 (11.1%)
Streptococcus group 1 (5.6%)
Leptotrichia trevisanii 1 (5.6%)
Fusobacterium nucleatum 1 (5.6%)
C.difficile toxin 1 (5.6%)
Brevibacterium spp 1 (5.6%)
Escherichia coli 4 (22.2%)
Positive serum GM antigen 1 (33.3%)
Aspergillus spp 1 (33.3%)
Positive BAL GM antigen 1 (33.3%)
Adenovirus 1 (7.1%)
Human parainfluenza virus 1 (7.1%)
Rhinoenterovirus 1 (7.1%)
Citomegalovirus 2 (14.3%)
BK Virus 2 (14.3%)
Human herpes virus 6 3 (21.4%)
SARS-COV-2 4 (28.6%)

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Figure 3. Microbial isolation of documented infections by requested sample type.

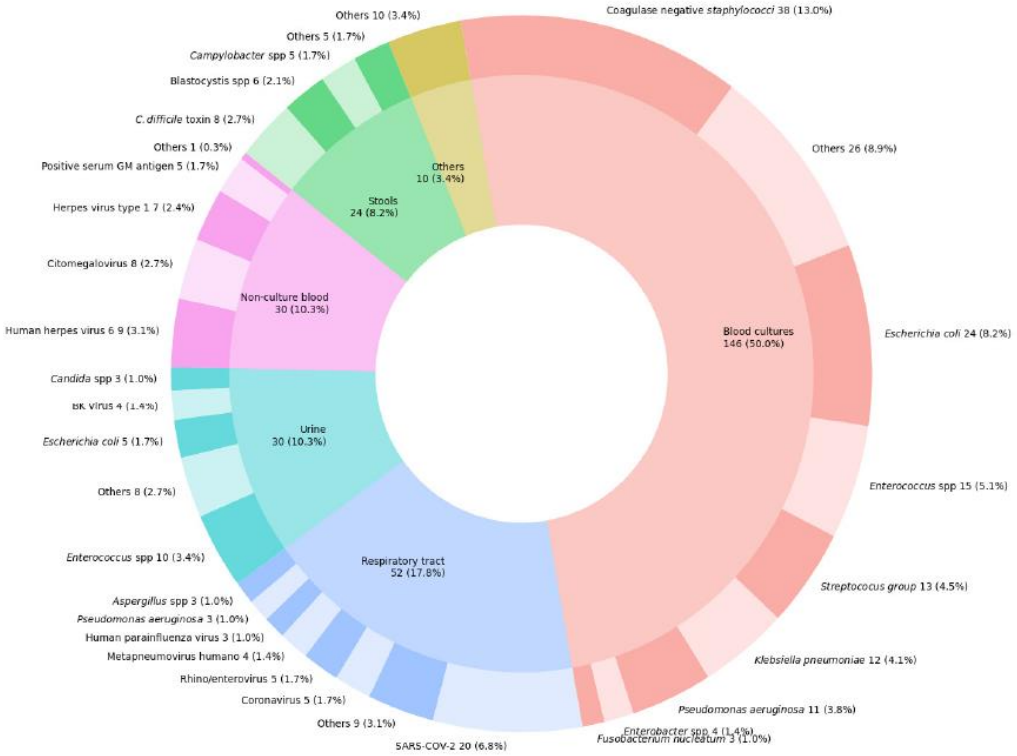
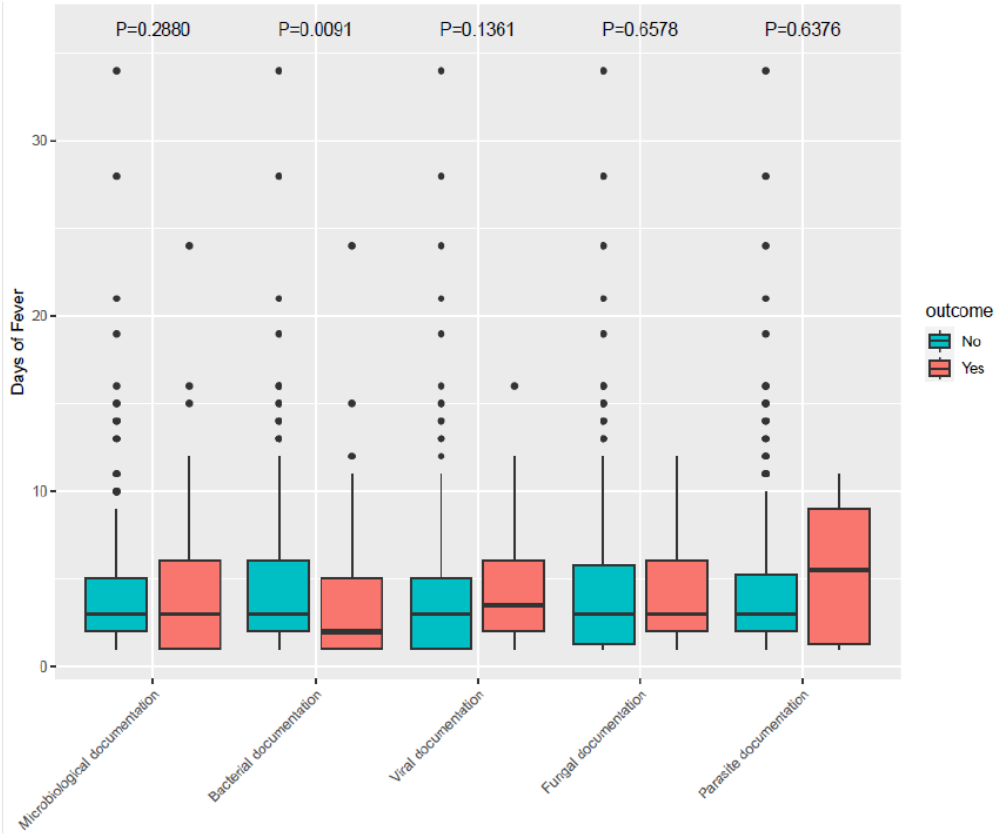


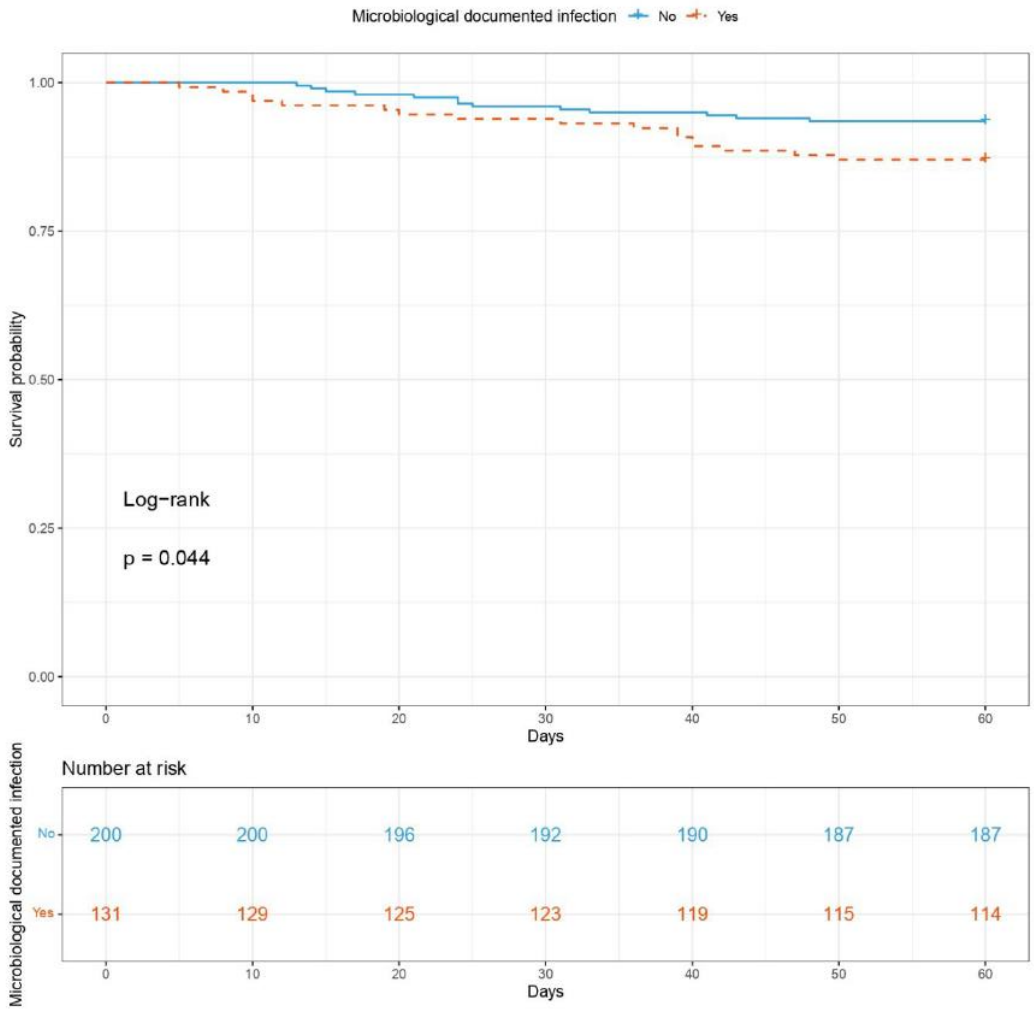
Fig 3. Among 197 bacterial isolations, 105 (53%) were Gram-positive while 90 (46%) were Gram-negative bacilli. Multidrug-resistant (MDR) organisms accounted for 31 (16%) of isolates. These MDR bacteria included 16 extended-spectrum beta-lactamases (ESBL) producers Enterobacterales, 6 dual ESBL and carbapenemase-producing Enterobacterales, 6 MDR non-fermenting Gram-negative bacilli, one carbapenemase-producing Enterobacterales, one methicillin-resistant *Staphylococcus aureus*, and one vancomycin-resistant *Enterococcus.*

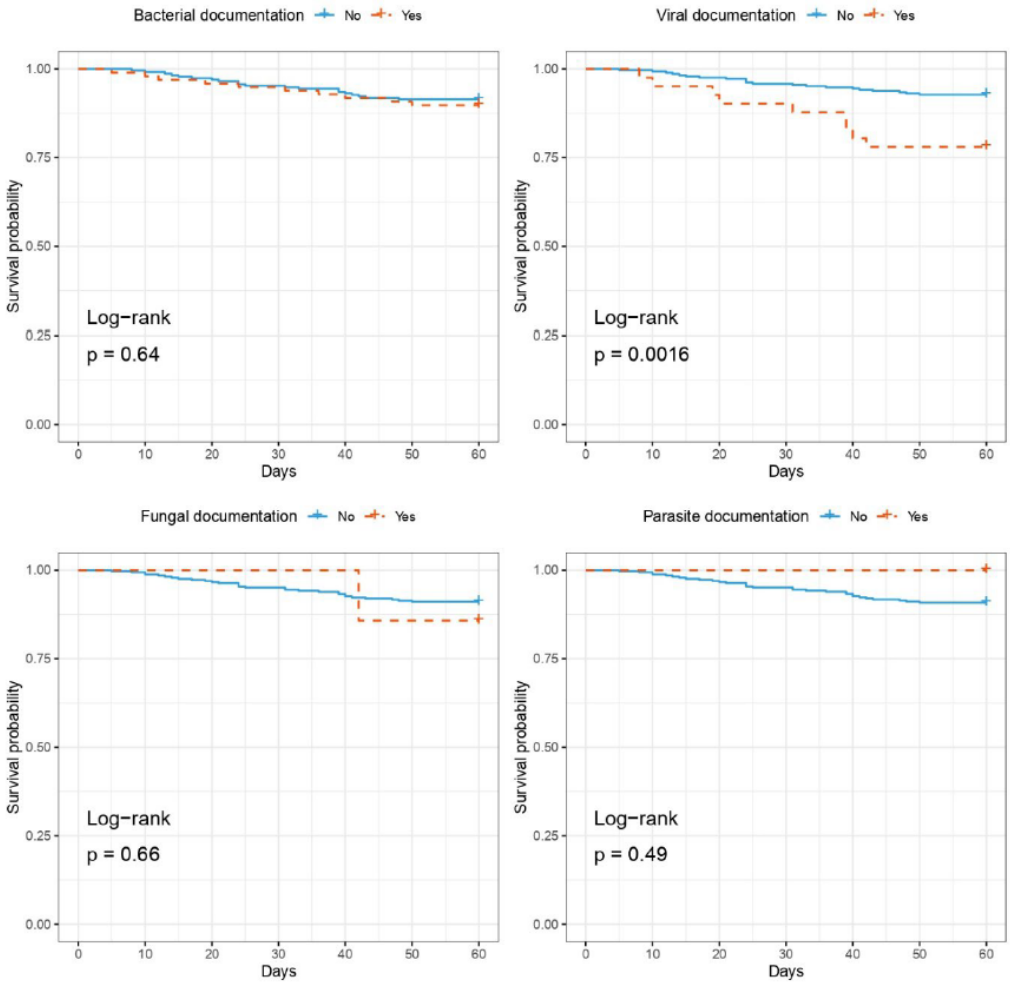
Figure 4. Median fever durations categorized by microbiological findings.



The figure illustrates median fever durations for infections, varying by type of microbiological documentation. (A) Microbiologically positive and negative documentation, with a median duration of 3 days, but different IQRs: 1-6 days with positive and 2-5 days with negative results. (B) Bacterial infection, positive cases having a median fever duration of 2 days (IQR 1-5) and negative cases, 3 days (IQR 2-6). (C) Viral infection, positive showing a median of 3.5 days (IQR 2-6) compared to the 3-day median for negative cases (IQR 1-5). (D) Fugal infection, both positive and negative, with a median fever duration of 3 days, but varying IQRs: 2-6 days with positive and 1-6 negative results. (E) Parasite infection, positive cases presented a median of 5.5 days (IQR 1-9.5), versus 3-day median for negative cases (IQR 2-5.75).

Figure 5. Kaplan-Meier Survival Plot: Mortality Differences in Microbiologically documented infection vs negative.




Bacterial documentation No Yes
Survival probability
1.00
0.75
0.50
0.25
0.00
Log−rank
p = 0.64
0 10 20 30 40 50 60
Days
Viral documentation No Yes
Survival probability
1.00
0.75
0.50
0.25
0.00
Log−rank
p = 0.0016
0 10 20 30 40 50 60
Days
Fungal documentation No Yes
Survival probability
1.00
0.75
0.50
0.25
0.00
Log−rank
p = 0.66
0 10 20 30 40 50 60
Days
Parasite documentation No Yes
Survival probability
1.00
0.75
0.50
0.25
0.00
Log−rank
p = 0.49
0 10 20 30 40 50 60
Days

27

Supplementary Appendix

Table 1 (S1): Microorganism Detection in Non-Cultured Blood Samples

Sample	Microorganism detected
Serum	*1-3-β-D-glucan* *Cryptococcal antigen* *Galactomannan antigen*
Plasma	*Cytomegalovirus* *Epstein-Barr virus* *Herpes simplex virus type 1* *Herpes simplex virus type 2* *Human herpes virus 6* *Parvovirus B19*

Table 2 (S2): Microorganisms detected in PCR multiplex assay.

Sample	Microorganism detected
Bronchoalveolar lavage fluid	*Adenovirus* *Chlamydia pneumoniae* *Coronavirus* *Enterovirus* *Human Bocavirus* *Human metapneumovirus* *Influenza A (H1N12009) virus* *Influenza A(H3N2) virus* *Influenza A virus* *Influenza B virus* *Influenza C virus* *Legionella pneumophila* *Mycoplasma pneumoniae* *Parainfluenza virus (1,2,3,4)* *Respiratory syncytial virus* *Rhinovirus*
Nasopharyngeal swab	*Adenovirus* *Coronavirus* *Enterovirus* *Human Bocavirus* *Human metapneumovirus*

	Influenza A (H1N12009) virus *Influenza A (H3N2) virus* *Influenza A virus* *Influenza B virus* *Influenza C virus* *Parainfluenza virus (1,2,3,4)* *Respiratory syncytial virus* *Rhinovirus*
Cerebrospinal fluid	*Cryptococcus neoformans/gattii* *Cytomegalovirus* *Enterovirus* *Escherichia coli K1* *Haemophilus influenzae* *Herpes simplex virus 1* *Herpes simplex virus 2* *Human herpes simplex virus 6* *Human parechovirus* *Listeria monocytogenes* *Neisseria meningitidis* *Streptococcus agalactiae* *Streptococcus pneumoniae* *Varicella zoster virus*
Stool	*Adenovirus group F* (serotypes 40,41) *Blastocystis* spp.

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	Campylobacter spp. *Cryptosporidium* spp. *Dientamoeba fragilis* *Entamoeba histolytica* *Giardia intestinalis / Giardia duodenalis* *Noroviruses* (genogroups G1, G2) *Rotavirus* group A *Salmonella* spp. *Shigella spp. / Enteroinvasive E. coli*

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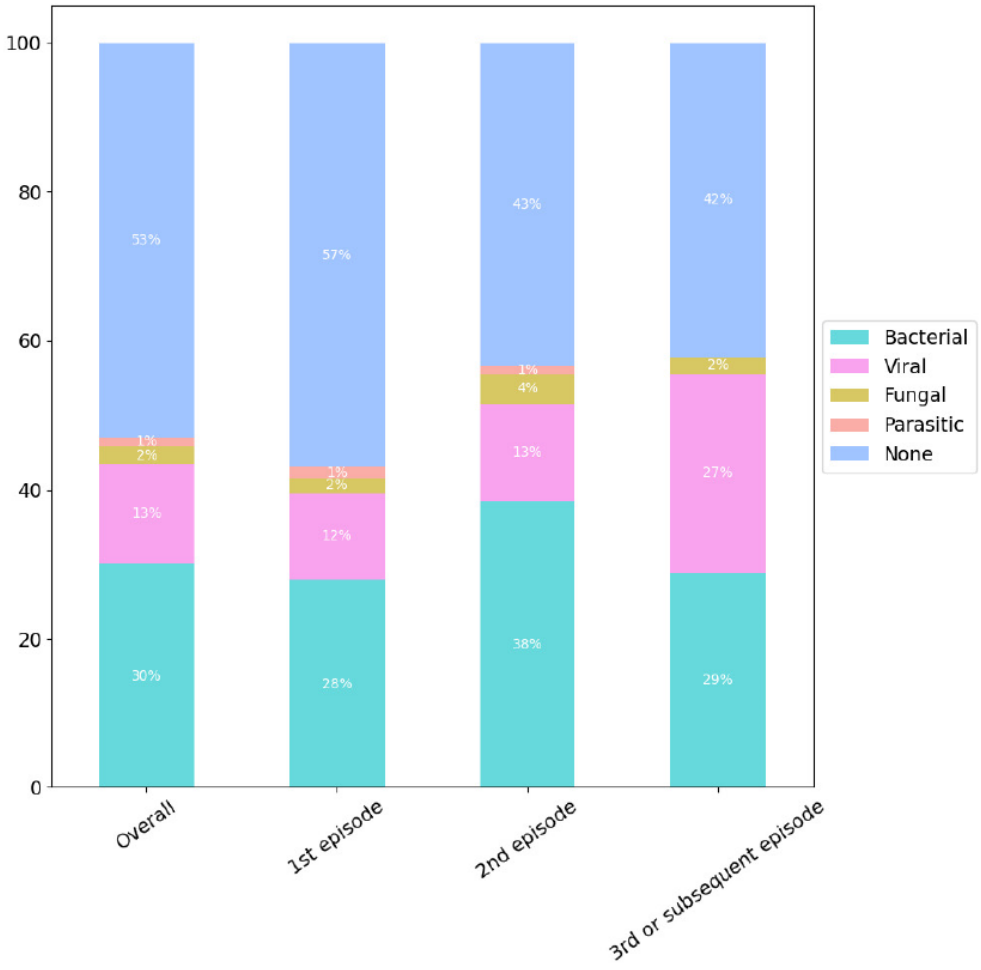
Figure 1: Rates of documented infections depending on the FN episode (first, second, third and subsequent).



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7•2 Resistance to empirical β-lactams recommended in febrile neutropenia guidelines in Gram-negative bacilli bloodstream infections in Spain: a multicentre study.

Chumbita, M., Puerta-Alcalde, P., Yáñez, L., Cuesta, M. A., Chinea, A., Español Morales, I., Fernández Abellán, P., Gudiol, C., Guerreiro, M., González-Sierra, P., Rojas, R., Sánchez Pina, J. M., Sánchez Vadillo, I., Varela, R., Vázquez, L., Lopera, C., Monzó, P., & Garcia-Vidal, C.

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Factor de impacto: 5.2, 1° cuartil.

Resumen:

Objetivos: Describir la resistencia actual a los β-lactámicos recomendados empíricamente en las guías en episodios de bacteriemia causados por BGN.

Métodos: Estudio de cohorte multicéntrico y retrospectivo de los últimos 50 episodios de bacteriemia en pacientes hematológicos en 14 hospitales universitarios en España. Se evaluaron las tasas de TAEI y su impacto en la mortalidad.

Resultados: De los 700 episodios de bacteriemia, 308 (44%) fueron causados por BGN, principalmente *Escherichia coli* (141; 20.1%), *Klebsiella* spp. (56; 8%) y *P. aeruginosa* (48; 6.9%). Entre los episodios de bacteriemia por BGN, 80 (26%) fueron causados por cepas MR. De aquellos causados por Enterobacterales, el 25,8% eran productores de BLEE y el 3,5% productores de carbapenemasas. Entre los episodios de bacteriemia por *P. aeruginosa*, el 18,8% fueron causados por cepas MR. En total, el 34,7% de los BGN aislados eran resistentes al menos a uno de los tres β-lactámicos recomendados en las guías para NF (cefepime,

piperacilina/tazobactam y meropenem). A pesar del alto cumplimiento con las recomendaciones de las guías (91.6%), el 16.6% de los episodios de bacteriemia causados por BGN recibieron TAEI, siendo más frecuente entre cepas BGN-MR (46,3% frente al 6,1%; P<0,001). La mortalidad a 30 días fue del 14,6%, alcanzando el 21,6% en pacientes que recibieron TAEI.

Conclusión: La resistencia actual a los β-lactámicos recomendados empíricamente en las guías para NF es alarmantemente alta y las tasas de TAEI son mayores de lo deseado. Existe una urgente necesidad de adaptar las guías a la epidemiología actual y de identificar mejor a los pacientes con un alto riesgo de desarrollar una infección por BGN-MR.

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Resistance to empirical β-lactams recommended in febrile neutropenia guidelines in Gram-negative bacilli bloodstream infections in Spain: a multicentre study

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Objectives: To describe current resistance to the β-lactams empirically recommended in the guidelines in bloodstream infection (BSI) episodes caused by Gram-negative bacilli (GNB).

Methods: Retrospective, multicentre cohort study of the last 50 BSI episodes in haematological patients across 14 university hospitals in Spain. Rates of inappropriate empirical antibiotic therapy (IEAT) and impact on mortality were evaluated.

Results: Of the 700 BSI episodes, 308 (44%) were caused by GNB, mainly *Escherichia coli* (141; 20.1%), *Klebsiella* spp. (56; 8%) and *Pseudomonas aeruginosa* (48; 6.9%). Among GNB BSI episodes, 80 (26%) were caused by MDR isolates. In those caused by Enterobacterales, 25.8% were ESBL producers and 3.5% were carbapenemase producers. Among *P. aeruginosa* BSI episodes, 18.8% were caused by MDR isolates. Overall, 34.7% of the isolated GNB were resistant to at least one of the three β-lactams recommended in febrile neutropenia guidelines (cefepime, piperacillin/tazobactam and meropenem). Despite extensive compliance with guideline recommendations (91.6%), 16.6% of BSI episodes caused by GNB received IEAT, which was more frequent among MDR GNB isolates (46.3% versus 6.1%; $P < 0.001$). Thirty day mortality was 14.6%, reaching 21.6% in patients receiving IEAT.

Conclusions: Current resistance to empirical β-lactams recommended in febrile neutropenia guidelines is exceedingly high and IEAT rates are greater than desired. There is an urgent need to adapt guidelines to current epidemiology and better identify patients with a high risk of developing MDR GNB infection.

Introduction

Bloodstream infection (BSI) is the most common infectious complication in patients with febrile neutropenia, being associated with both high morbidity and mortality.[1–3] In the last few years, BSI epidemiology in this population has been changing, with a progressive increase in Gram-negative bacilli (GNB) infection rates and the worldwide emergence of MDR GNB.[4–6] However, most guidelines for febrile neutropenic patients have constantly recommended the same empirical antibiotic approach for the past 25 years (ceftazidime, cefepime, piperacillin/tazobactam, meropenem and amikacin).[7–10]

Inappropriate empirical antibiotic treatment (IEAT) has been associated with increased mortality in neutropenic patients,

specifically in those with GNB infections.[5,11] As a result, empirical antibiotic coverage has become more challenging than ever. That stated, acquiring comprehensive knowledge of the current BSI epidemiology will be essential in updating national and international guidelines, in order to decrease the rates of IEAT, thus improving survival outcomes in patients with febrile neutropenia.

We aimed to describe the current epidemiology and antimicrobial resistance of GNB BSI in a large multicentre cohort of neutropenic haematological patients in Spain. We focused especially on resistance to the β-lactams empirically recommended in febrile neutropenia guidelines (cefepime, piperacillin/tazobactam and meropenem). We also describe the impact of IEAT on mortality.

Materials and methods

Setting, study population and design

This is a retrospective analysis of an observational, multicentre cohort study conducted across 14 Spanish university hospitals. In October 2019, each centre provided the last 50 episodes of monomicrobial BSI in adult haematological patients (aged >18 years). Patients were included only once. All fungaemia episodes were excluded. The following data were recorded: age and sex, baseline disease, causative agents, source of BSI, susceptibility profile, prior and concomitant antibiotic treatments, and 30 day mortality. Each episode underwent an evaluation for empirical treatment appropriateness and impact on mortality.

This study was approved by the Ethics Committee Board of Hospital Clinic of Barcelona (HCB/2021/0157).

Definitions

Patients with febrile neutropenia were defined as those who had a single temperature measurement of >38.3°C or measurements of >38.0°C over a 1 h course, and an absolute neutrophil count of ≤500 cells/mm^3.[8]

Prior antibiotic therapy was defined as the use of any antibiotic within the last 30 days. Breakthrough BSI was recorded when the patient was receiving systemic antibiotics, including quinolone prophylaxis, at the time of BSI. Empirical antibiotic therapy was defined as that administered at febrile neutropenia onset. Combination therapy was defined as the empirical administration of more than one antibiotic. IEAT was reported when empirical therapy did not include at least one *in vitro* active antibiotic against the isolated microorganism. The following GNB were classified as MDR: (1) ESBL-producing Enterobacterales; (2) carbapenemase-producing Enterobacterales; (3) non-fermenting GNB resistant to at least three classes of antibiotics: carbapenems, ureidopenicillins, cephalosporins (ceftazidime and cefepime), monobactams, aminoglycosides and fluoroquinolones. XDR GNB were those non-susceptible to ≥1 agent in all but ≤2 categories.[12] Mortality was defined as death by any cause within the first 30 days of BSI onset.

Microbiological methods

Blood samples were processed using the BACTEC 9240 system or BACTEC FX system (Becton Dickinson Microbiology Systems), with a 5 day incubation period. Isolates were identified by standard techniques. Antimicrobial susceptibility testing was performed with either an automated microdilution system (MicroScan WalkAway, Beckman Coulter, West Sacramento, CA, USA; Phoenix system, Becton, Dickinson and Company, Franklin Lakes, NJ, USA; or VITEK, bioMérieux, France), a semi-automated method (Sensititre®, Thermo Fisher Scientific) or gradient strips (Etest; AB BIODISK, Solna, Sweden/bioMérieux, Marcy-l'Étoile, France). ESBLs were suspected by MIC results and confirmed by double-disc synergy testing using discs containing cefotaxime, ceftazidime and cefepime that were applied to plates next to a disc with clavulanic acid.[13] Carbapenemase-producing Enterobacterales were phenotypically detected by the modified carbapenem inactivation method (mCIM),[14] in combination with the NG-Test® CARBA 5 lateral flow immunoassay (NG Biotech, France) to detect the five most prevalent carbapenemases (KPC, OXA-48-like, VIM, IMP and NDM).[15] Current EUCAST breakpoints for each year were used to define susceptibility or resistance to these antimicrobial agents; intermediate susceptibility was considered as resistance.

Statistical analysis

Categorical variables were described as counts and percentages, whereas continuous variables were expressed as means and standard deviations or medians and IQRs. The chi-squared Pearson test and either the Mann–Whitney *U*-test or Student's *t*-test were used to compare the categorical and continuous variable distributions, respectively. All analyses were performed with SPSS software (version 25.0; SPSS, Inc., Chicago, IL, USA).

Results

Epidemiology of BSI in haematological patients with febrile neutropenia

Overall, 700 haematological patients with febrile neutropenia and BSI were included. Table 1 details the microorganisms responsible for all BSI episodes. Of these, 382 (54.6%) were caused by Gram-positive cocci (GPC), 308 (44%) by GNB and 10 (1.4%) by Gram-positive bacilli (GPB). CoNS (224; 32%) and *Enterococcus* spp. (85; 12.1%) were the most common GPC. Among GNB, the most frequently isolated microorganism was *Escherichia coli* (141; 20.1%), followed by *Klebsiella* spp. (56; 8%) and *Pseudomonas aeruginosa* (48; 6.9%).

Patient characteristics and resistance profiles among episodes caused by GNB

Table 2 summarizes patients' demographic and clinical characteristics for the 308 episodes caused by GNB. The most frequent baseline disease was acute leukaemia (55.2%) and 47.4% of patients had received HSCT, of which 62.3% were allogenic. More than half of the patients (58.1%) had received antibiotic therapy within the month prior to BSI. The most common source of BSI was endogenous (50%), followed by catheter-related BSI (14.3%).

Among GNB BSI episodes, 80 (26%) were caused by MDR isolates. The following MDR GNB were isolated: 30 (9.7%) ESBL-producing (ESBL-)*E. coli*; two (0.6%) ESBL- and carbapenemase-producing *E. coli*; 12 (3.9%) ESBL-*Klebsiella* spp.; 6 (1.9%) ESBL- and carbapenemase-producing *Klebsiella* spp.; 9 (2.9%) MDR-*P. aeruginosa*; 9 (2.9%) ESBL-*Enterobacter* spp.; 9 (2.9%) *Stenotrophomonas maltophilia*; 2 (0.6%) ESBL-*Citrobacter freundii*; and one (0.3%) MDR *Pseudomonas mosselii*.

Among Enterobacterales, 59 of 229 (25.8%) were ESBL producers, accounting for 22.7% and 32.1% among *E. coli* and *Klebsiella* spp., respectively. Carbapenemase-producing isolates represented 3.5% of all Enterobacterales and 13.6% among ESBL producers. Of *P. aeruginosa* isolates, 9 of 48 (18.8%) isolates were MDR, of which most were XDR as well (7 of 9). Patients receiving prior antibiotic therapy and those presenting breakthrough BSI had higher rates of infection due to MDR GNB

Table 1. Aetiological microorganisms among all BSI episodes in haematological patients with febrile neutropenia

Causative agent	*n* (%) *N* = 700
GNB	308 (44)
E. coli	141 (20.1)
ESBL producer	30 (4.3)
Carbapenemase and ESBL producer	2 (0.3)
Klebsiella spp.	56 (8)
ESBL producer	12 (1.7)
Carbapenemase and ESBL producer	6 (0.9)
P. aeruginosa	48 (6.9)
MDR	9 (1.3)
XDR	7 (1)
Pseudomonas spp. (not *aeruginosa*)	5 (0.7)
MDR	1 (0.1)
Enterobacter spp.	17 (2.4)
ESBL producer	9 (1.3)
S. maltophilia	9 (1.3)
Leptotrichia spp.	5 (0.7)
Citrobacter spp.	5 (0.7)
ESBL producer	2 (0.3)
Other GNB[a]	22 (3.1)
MDR GNB	80 (11.4)
GPC	382 (54.6)
CoNS	224 (32)
Enterococcus spp.	85 (12.1)
Enterococcus faecalis	19 (2.7)
Enterococcus faecium	66 (9.4)
Viridans group streptococci	37 (5.3)
Streptococcus pneumoniae	8 (1.1)
Staphylococcus aureus	18 (2.6)
Other GPC[b]	10 (1.4)
GPB	10 (1.4)
Clostridium spp.	4 (0.6)
Other GPB[c]	6 (0.8)

[a]*Serratia marcescens* (4), *Bacteroides* spp. (3), *Capnocytophaga sputigena* (2), *Salmonella* Enteritidis (2), *Proteus mirabilis* (2), *Raoultella* spp. (2), *Acinetobacter* spp. (2), *Burkholderia cepacia* (2), *Campylobacter* spp. (1), *Fusobacterium* spp. (1), *Aeromonas veronii* (1).
[b]*Streptococcus pyogenes* (1), *Streptococcus agalactiae* (1), *Anaerococcus* spp. (1), *Granulicatella* spp. (2), *Micrococcus* spp. (2), *Rothia* spp. (1), *Leuconostoc* spp. (2).
[c]*Lysinibacillus* spp., *Listeria monocytogenes*, *Corynebacterium* spp., *Actinomyces* spp., *Bacillus cereus and Brevibacterium* spp.

Table 2. Demographics and clinical characteristics of 308 BSI episodes caused by GNB

Characteristic	Episodes, *n* (%) *N* = 308
Demographics	
Male sex	165 (53.6)
Age (years), median (IQR)	59 (49–67)
Haematological disease	
Acute leukaemia	170 (55.2)
Non-Hodgkin's lymphoma	59 (19.2)
Multiple myeloma	30 (9.7)
Myelodysplastic syndrome	18 (5.8)
Hodgkin's lymphoma	14 (4.5)
Others[a]	14 (4.5)
HSCT	146 (47.4)
Allogenic	91 (29.5)
Autologous	55 (17.9)
Antibiotic exposure	
Prior antibiotic therapy (within the last 30 days)	179 (58.1)
Current antibiotic use (at the time of BSI)	123 (39.9)
Quinolone prophylaxis	90 (29.2)
Source of BSI	
Endogenous/unknown	154 (50)
Catheter-related infection	44 (14.3)
Abdominal	41 (13.3)
Urinary tract	34 (11)
Pneumonia	15 (4.9)
Perianal infection	10 (3.2)
Others	8 (2.6)
30 day mortality	45 (14.6)

[a]Four chronic myeloid leukaemia, three chronic lymphocytic leukaemia, three myelofibrosis, two amyloidosis, one bone marrow aplasia and one polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormalities (POEMS) syndrome.

(34.1% versus 15.9%; $P < 0.001$; and 35% versus 21.2%; $P = 0.008$, respectively).

Patterns of resistance to empirical antibiotics recommended in febrile neutropenia guidelines

Table 3 shows resistance to different antibiotics recommended at febrile neutropenia onset. Overall, 34.7% of the isolated GNB were resistant to at least one of the three β-lactams recommended in the guidelines. The lowest resistance rate corresponded to meropenem (9.4%). However, 20.8% of *P. aeruginosa* isolates and 10.7% of *Klebsiella* spp. were meropenem resistant. BSI was caused by isolates resistant to piperacillin/tazobactam in 26.6% of episodes and to cefepime in 30.2%. Figure 1 shows antimicrobial resistance and MDR rates in the various participating hospitals. Important differences were found among centres.

Appropriateness of empirical antibiotic therapy and mortality in GNB BSI

The most frequent antibiotic used was meropenem (49.7%), followed by piperacillin/tazobactam (31.2%) and cefepime (10.7%). In 34.7% of episodes, patients underwent combination therapy, mainly with amikacin (17.2%) and colistin (9.4%). Even though guideline recommendations were followed in 91.6% of cases, a total of 51 (16.6%) episodes caused by GNB received IEAT. IEAT rates were 24.2% in patients receiving empirical treatment with cefepime, 21.1% in those receiving piperacillin/tazobactam and

7.8% in those receiving meropenem. Table 4 details the aetiological agents receiving IEAT. IEAT was more frequent in BSI episodes caused by MDR GNB isolates (46.3% versus 6.1%; $P<0.001$). Specifically, IEAT was more common among the following: ESBL-*E. coli* (28.1% in ESBL producers versus 2.8% in non-ESBL producers; $P<0.001$); ESBL-*Klebsiella* spp. (55.6% versus 7.9%; $P<0.001$); carbapenem-resistant *E. coli* (100% versus 7.2%; $P=0.007$); and carbapenem-resistant *Klebsiella* spp. (83.3% versus 16%; $P<0.001$). There was also a trend for higher IEAT in MDR-*P. aeruginosa* compared with non-MDR *P. aeruginosa* (33.3% versus 7.7%; $P=0.071$).

Overall, 30 day mortality was 14.6%. Mortality reached 16.3% in episodes caused by MDR GNB and 21.6% in patients receiving IEAT. Table 5 shows the mortality rates according to the appropriateness of empirical therapy for the most common causative agents.

Table 3. Resistance profiles among BSIs caused by GNB in haematological patients with febrile neutropenia

Antibiotic(s) that GNB were resistant to:	Episodes, *n* (%) *N* = 308
Quinolones	134 (43.5)
Cefepime	93 (30.2)
Piperacillin/tazobactam	82 (26.6)
Amikacin	49 (15.9)
Carbapenems	29 (9.4)
At least one of the β-lactam antibiotics recommended in the guidelines[a]	107 (34.7)

[a]Cefepime, piperacillin/tazobactam and/or meropenem.

Discussion

This study confirms that BSI caused by GNB—and more concerningly, MDR GNB—in haematological patients with febrile neutropenia is a common problem. Current recommendations by

Table 4. Causative agents receiving IEAT among GNB

Microorganism	IEAT, *n* (%) *N* = 51
Klebsiella spp.	13 (25.5)
ESBL producer	10 (19.6)
Carbapenemase producer	5 (9.8)
E. coli	12 (23.5)
ESBL producer	9 (17.6)
Carbapenemase producer	2 (3.9)
S. maltophilia	9 (17.6)
P. aeruginosa	6 (11.8)
MDR	3 (5.9)
Pseudomonas spp. (not *aeruginosa*)	4 (7.8)
MDR	1 (2)
Enterobacter spp.	4 (7.8)
ESBL producer	4 (7.8)
Citrobacter spp.	2 (3.9)
ESBL producer	1 (2)
Campylobacter spp.	1 (2)

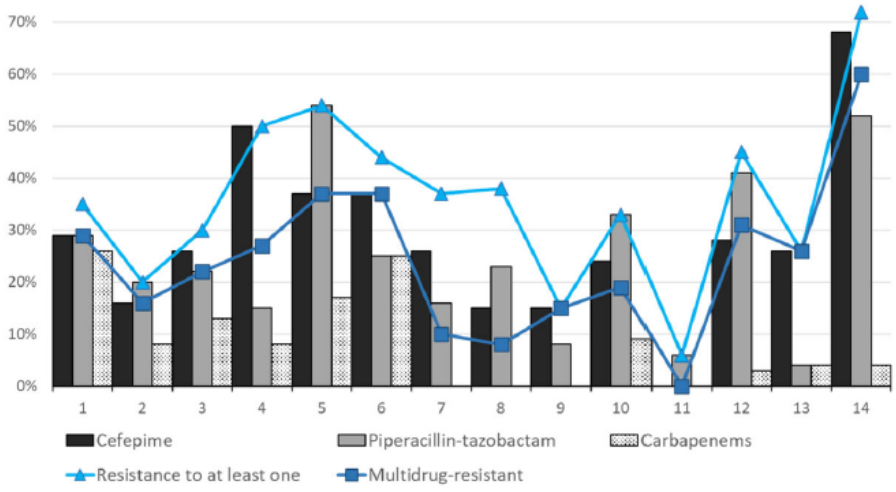

Figure 1. Antimicrobial resistance and MDR isolates across the different hospitals. The *y*-axis shows the rates of resistance and MDR. The *x*-axis shows the different participating hospitals. All participating hospitals performed allogenic HSCT except for those listed as hospitals 4 and 13. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 5. Mortality for the most common causative agents of BSI per appropriateness of empirical antibiotic treatment

Causative agent	Number of patients	Number of deaths (%)	Deaths in IEAT/Number of patients receiving IEAT (%)	Deaths in AEAT/Number of patients receiving AEAT (%)	*P* value
GNB	307	45 (14.7)	11/51 (21.6)	34/256 (13.3)	0.12
E. coli	140	12 (8.6)	0/12 (0)	12/128 (9.4)	0.599
ESBL producer	32	2 (6.3)	0/9 (0)	2/23 (8.7)	1.000
Klebsiella spp.	56	14 (25)	6/13 (46.2)	8/43 (18.6)	0.044
ESBL producer	18	5 (27.8)	4/10 (40)	1/8 (12.5)	0.314
Carbapenemase producer	6	3 (50)	3/5 (60)	0/1 (0)	1.000
P. aeruginosa	48	11 (22.9)	2/6 (33.3)	9/42 (21.4)	0.609
MDR *P. aeruginosa*	9	2 (22.2)	1/3 (33.3)	1/6 (16.7)	1.000
Enterobacter spp.	17	2 (11.8)	1/4 (25)	1/13 (7.7)	0.426
S. maltophilia	9	1 (11.1)	1/9 (11.1)	—	—
MDR GNB	80	13 (16.3)	8/37 (21.6)	5/43 (11.6)	0.227

AEAT, appropriate empirical antibiotic treatment.

national and international febrile neutropenia guidelines propose the use of empirical β-lactams,[8–10] which are not valid for more than a third of the isolated GNB. In what may be closely related, the reported frequency of IEAT is unacceptably high, especially in patients receiving empirical treatment with cefepime and/or those with MDR GNB infections.

IEAT has frequently been associated with increased mortality in previous studies conducted in neutropenic patients with BSI.[11,16] Our findings reiterate the urgent need to perform a personalized approach to reduce IEAT and possibly raise survival outcomes.

In this complex scenario, a few strategies may be considered. A classic and controversial approach has been the routine addition of an aminoglycoside to empirical regimens.[17] β-Lactams and aminoglycosides are known to be synergistic,[18] and current resistance to aminoglycosides is low, as shown in this study. A recent, international propensity-score matched study in haematological patients with febrile neutropenia and GNB BSI receiving appropriate empirical antibiotic treatment showed that combination therapy was associated with a significant decrease in mortality without a significant increase in acute kidney failure rates.[19] However, a large meta-analysis focusing on empirical treatment in neutropenic patients showed no benefits in terms of mortality, although most patients included in the study did not present a BSI, and the study was conducted a long time ago, when the rates of antimicrobial resistance were far lower than in the current era.[20] Additionally, associated toxicity raises great concerns, and some studies reported an exceedingly high mortality in neutropenic patients receiving aminoglycoside monotherapy when the β-lactam antibiotic was not active.[21,22]

A second strategy would be based on warranting the administration of an active β-lactam. In this sense, using newly available β-lactam/β-lactamase inhibitor combinations such as ceftazidime/avibactam or ceftolozane/tazobactam (and some others that will shortly be available) could prove to be an option, given their excellent coverage for most current MDR isolates. Some studies have shown the efficacy of these new antibiotics in treating infections caused by MDR isolates.[23–25] Indeed, a few studies including haematological patients[26–29] described a relationship between the use of such new β-lactam drugs and optimal outcomes. However, concerns exist regarding the use of these new drugs relating to increased costs and further selection of resistance.[30] Daily reassessment and antibiotic de-escalation within 24–48 h should, therefore, be endorsed whenever possible, following previously documented strategies.[31,32]

Recognition of the subset of patients who will develop MDR GNB infections at the time that physicians choose empirical antibiotics remains a major challenge. Some studies have identified risk factors for MDR GNB in haematological patients with BSI.[5,33–35] It is unknown, though, whether this scenario accurately reflects the precise moment when a patient develops febrile neutropenia. Moreover, these studies used small sets of manual entry data, with frequently limited local variables, which makes extrapolation to other areas perhaps difficult. Nonetheless, a study using a large number of high-quality data directly collected from electronic health records at the time of febrile neutropenia diagnosis has been recently published.[36] With an accuracy rate of nearly 80%, the use of machine learning techniques was able to predict which patients would present MDR GNB infection. There is potential with such an approach; however, challenges arise regarding the generalization of these supporting tools' utility, tool validation across different hospitals, and real-life applications of such tools. Lastly, novel rapid diagnostic methods are available, shortening the time required to identify MDR isolates.[37,38] As such strategies are limited due to increased costs, identifying those patients at high risk of MDR infection could help guide the personalized use of these promising methods.

The strength of this study is that it describes a current, prospective and multicentre cohort from different regions of Spain and includes a large number of patients. However, there are some limitations that must be acknowledged. First, the prospectively collected clinical data were limited, not allowing us to evaluate risk factors for MDR infection or mortality. Second, although adherence to international neutropenia guidelines was high, decisions regarding empirical antibiotics varied across the different centres. Third, EUCAST definitions and clinical breakpoints have

recently changed. According to current definitions, some intermediate isolates in this study would be classified as 'susceptible with increased exposure', instead of resistant.[39] Finally, local epidemiology of some centres can be conditioned by endemicity of some MDR strains. However, we truly believe that this fact reflects the real-life complexity found in this setting.

In conclusion, we showed that current resistance to empirical β-lactams recommended in neutropenia guidelines is exceedingly high. In what may be closely related, IEAT was found to be more frequent than desired. Adapting international guidelines to current epidemiology and identifying patients with a high risk of MDR GNB infection is urgently needed.

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7•3 High Rate of Inappropriate Antibiotics in Patients with Hematologic Malignancies and *Pseudomonas aeruginosa* Bacteremia following International Guideline Recommendations.

Chumbita, M., Puerta-Alcalde, P., Yáñez, L., Angeles Cuesta, M., Chinea, A., Español-Morales, I., Fernandez-Abellán, P., Gudiol, C., González-Sierra, P., Rojas, R., Sánchez-Pina, J. M., Vadillo, I. S., Sánchez, M., Varela, R., Vázquez, L., Guerreiro, M., Monzo, P., Lopera, C., Aiello, T. F., Peyrony, O., Garcia-Vidal, C.

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Microbiology spectrum**.**

Factor de impacto: 3.7, 2º cuartil.

Resumen:

Introducción: El tratamiento óptimo de *P. aeruginosa* en pacientes con NF es un desafío debido al incremento progresivo de la resistencia a los antibióticos a nivel mundial. Nuestro objetivo principal fue detallar las tasas actuales de resistencia a los antibióticos recomendados por las guías internacionales en la bacteriemia por *P. aeruginosa* de pacientes con neoplasias hematológicas. De manera secundaria, buscamos describir cuántos pacientes recibieron un TAEI y su impacto en la mortalidad.

Métodos: Se realizó un estudio de cohorte retrospectivo y multicéntrico de los últimos 20 episodios de bacteriemia causados por *P. aeruginos*a en pacientes con neoplasias hematológicas en 14 hospitales universitarios de España.

Resultados: De los 280 pacientes con neoplasias hematológicas y bacteriemia por *P. aeruginosa*, 101 (36%) presentaron cepas resistentes a al menos uno de los antibióticos β-lactámicos recomendados en las guías internacionales: cefepima, piperacilina-tazobactam y

meropenem. Además, el 21.1% y el 11.4% de las cepas cumplieron criterios para *P. aeruginosa* MR y extremadamente resistente, respectivamente. A pesar de seguir en su mayoría las guías internacionales, 47 pacientes (16.8%) recibieron TAEI y 66 (23.6%) recibieron un tratamiento empírico inadecuado con β-lactámicos. La mortalidad a los 30 días fue del 27.1%. En el análisis multivariante, el origen pulmonar de la infección (OR 2.22, 95% IC 1.14 a 4.34) y el TAEI (OR 2.67, 95% IC 1.37 a 5.23) se asociaron independientemente con un aumento de la mortalidad.

Conclusión: *P. aeruginosa* causante de bacteriemia en pacientes con neoplasias hematológicas frecuentemente es resistente a los antibióticos recomendados en las guías internacionales, lo que se asocia con TAEI frecuente y una mayor mortalidad. Se necesitan nuevas estrategias terapéuticas.

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RESEARCH ARTICLE

High Rate of Inappropriate Antibiotics in Patients with Hematologic Malignancies and *Pseudomonas aeruginosa* Bacteremia following International Guideline Recommendations

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ABSTRACT Optimal coverage of *Pseudomonas aeruginosa* is challenging in febrile neutropenic patients due to a progressive increase in antibiotic resistance worldwide. We aimed to detail current rates of resistance to antibiotics recommended by international guidelines for *P. aeruginosa* isolated from bloodstream infections (BSI) in patients with hematologic malignancies. Secondarily, we aimed to describe how many patients received inappropriate empirical antibiotic treatment (IEAT) and its impact on mortality. We conducted a retrospective, multicenter cohort study of the last 20 BSI episodes caused by *P. aeruginosa* in patients with hematologic malignancies from across 14 university hospitals in Spain. Of the 280 patients with hematologic malignancies and BSI caused by *P. aeruginosa*, 101 (36%) had strains resistant to at least one of the β-lactam antibiotics recommended in international guidelines, namely, cefepime, piperacillin-tazobactam, and meropenem. Additionally, 21.1% and 11.4% of the strains met criteria for MDR and XDR *P. aeruginosa*, respectively. Even if international guidelines were followed in most cases, 47 (16.8%) patients received IEAT and 66 (23.6%) received inappropriate β-lactam empirical antibiotic treatment. Thirty-day mortality was 27.1%. In the multivariate analysis, pulmonary source (OR 2.22, 95% CI 1.14 to 4.34) and IEAT (OR 2.67, 95% CI 1.37 to 5.23) were factors independently associated with increased mortality. We concluded that *P. aeruginosa*-causing BSI in patients with hematologic malignancies is commonly resistant to antibiotics recommended in international guidelines, which is associated with frequent IEAT and higher mortality. New therapeutic strategies are needed.

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IMPORTANCE Bloodstream infection (BSI) caused by *P. aeruginosa* is related with an elevated morbidity and mortality in neutropenic patients. For this reason, optimal antipseudomonal coverage has been the basis of all historical recommendations in the empirical treatment of febrile neutropenia. However, in recent years the emergence of multiple types of antibiotic resistances has posed a challenge in treating infections caused by this microorganism. In our study we postulated that *P. aeruginosa*-causing BSI in patients with hematologic malignancies is commonly resistant to antibiotics recommended in international guidelines. This observation is associated with frequent IEAT and increased mortality. Consequently, there is a need for a new therapeutic strategy.

KEYWORDS neutropenia, bacteremia, *P. aeruginosa*, mortality, empirical antibiotic treatment

Bloodstream infection (BSI) are the most frequent infectious complication in patients with hematologic malignancies, being related with high morbidity and mortality (1, 2). One of the most severe and difficult-to-treat bacteria causing BSI in this population is *Pseudomonas aeruginosa*. It is related to an elevated morbidity and mortality (3, 4). For this reason, optimal coverage of this pathogen has been one of the most formidable challenges in febrile neutropenic guidelines (5, 6).

Nowadays, proper empirical coverage of this pathogen has become even more problematic due to a progressive increase in multidrug-resistant (MDR) and extensively drug-resistant (XDR) *P. aeruginosa* isolates worldwide (7, 8). Despite this marked epidemiological change, the most up-to-date antibiotic guidelines for patients with hematologic malignancies and neutropenia continue recommending an empirical β-lactam treatment that includes cefepime, piperacillin-tazobactam, and meropenem (6, 9, 10). Our hypothesis is that most physicians still use these antibiotics as empirical treatment, given the observed high rates of inappropriate empirical antibiotic treatment (IEAT) and more elevated mortality.

We aimed to describe the current rates of resistance to β-lactam antibiotics recommended in international guidelines for *P. aeruginosa* isolated from BSI in patients with hematologic malignancies. Secondarily, we aimed to describe how many patients received IEAT and its impact on mortality.

RESULTS

Cohort and BSI characteristics. We analyzed 280 episodes of BSI caused by *P. aeruginosa* in patients with hematologic malignancies. Table 1 summarizes the demographic and clinical characteristics of the cohort. The most frequent hematologic malignancies were acute leukemia (36.8%) and non-Hodgkin lymphoma (26.4%). Furthermore, 114 (40.7%) patients had received a hematopoietic stem cell transplant, mostly allogeneic (69, 60.5%). A total of 170 (60.9%) patients were neutropenic at BSI onset. Most BSI were endogenous (86, 30.7%), followed by catheter-related and pulmonary source (55, 19.6% and 48, 17.1%, respectively).

Antimicrobial resistance profile and the appropriateness of empirical antibiotics. Of all isolated *P. aeruginosa*, 101 (36.1%) were resistant to at least one of the β-lactam antibiotics recommended in international guidelines, namely, cefepime, piperacillin-tazobactam, or meropenem (Table 2). The highest rate of resistance was to quinolones (82, 29.3%) and the lowest to amikacin (41, 14.6%). A total of 21.1% and 11.4% of the strains met criteria for MDR and XDR *P. aeruginosa*, respectively. Figure 1 shows the antimicrobial resistance distribution across the different participating centers.

The most frequently administered empirical antibiotic was meropenem (114, 40.7%), followed by piperacillin-tazobactam (103, 36.8%) and cefepime (45, 16.1%). An empirical antibiotic combination was administered in 68 (24.3%) patients, mainly with amikacin or colistin (17.1% and 5.7%, respectively).

Although international guidelines were followed in 262 (94%) of cases, 47 (16.8%) patients received IEAT, and 66 (23.6%) received inappropriate β-lactam empirical antibiotic treatment. Inappropriate β-lactam therapy was documented in 32% (36 of 114) of patients

TABLE 1 Demographic and clinical characteristics of the cohort

Characteristic	N = 280 (%)
Demographic	
Male sex	176 (63.1)
Median (IQR) age, yrs	60 (50–68)
Hematological disease	
Acute leukemia	103 (36.8)
Non-Hodgkin lymphoma	74 (26.4)
Multiple myeloma	39 (13.9)
Myelodysplastic syndrome	20 (7.1)
Hodgkin's lymphoma	13 (4.6)
Chronic lymphocytic leukemia	11 (3.9)
Bone-marrow aplasia	4 (1.4)
Others	16 (5.7)
Hematopoietic stem cell transplant	114 (40.7)
Allogenic	69 (24.6)
Neutropenia	170 (60.9)
Source of BSI	
Endogenous/unknown	86 (30.7)
Catheter-related	55 (19.6)
Pulmonary	48 (17.1)
Skin and soft-tissue infection	23 (8.2)
Abdominal	21 (7.5)
Urinary tract	19 (6.8)
Others	15 (5.3)

receiving meropenem, 20% (21/103) of those receiving piperacillin-tazobactam, and 16% (7 of 45) of those receiving cefepime. When the isolated *P. aeruginosa* was resistant to at least one of the antimicrobials recommended by the guidelines, IEAT increased significantly (43.6% versus 1.7%, $P < 0.001$). Likewise, IEAT was more common in those episodes caused by MDR-*P. aeruginosa* (42.4% versus 10%, $P < 0.001$) and XDR-*P. aeruginosa* (40.6% versus 13.7%, $P < 0.001$).

Outcomes. Overall, 30-day mortality was 76 (27.1%). Table 3 shows the univariate and multivariate analyses of risk factors for mortality. In the univariate analysis, mortality was higher in BSI episodes from a pulmonary source (42.8% versus 23.9%, $P = 0.009$) and episodes caused by either MDR-*P. aeruginosa* (42.4% versus 23.1%, $P = 0.003$) or an isolate that was resistant to at least one of the β-lactam antibiotics recommended by the guidelines (37.6% versus 21.2%, $P = 0.003$). Likewise, mortality was more elevated among those patients receiving IEAT (48.9% versus 22.7%, $P < 0.001$). Conversely, mortality was significantly lower when patients received a combination of two active antibiotics (12.8% versus 29.5%, $P = 0.030$).

TABLE 2 Resistance profiles among bloodstream infections caused by *Pseudomonas aeruginosa* in hematologic patients with febrile neutropenia[a]

Antibiotic	N = 280 (%)
Quinolones	82 (29.3)
Piperacillin-tazobactam	61 (21.8)
Cefepime	72 (25.7)
Meropenem	70 (25)
Amikacin	41 (14.6)
MDR-*P. aeruginosa*	59 (21.1)
XDR-*P. aeruginosa*	32 (11.4)
Resistance to at least 1 of the β-lactam antibiotics recommended in the international guidelines	101 (36.1)

[a]EUCAST MIC breakpoints R> (mg/L): Ciprofloxacin: >0.5; Piperacillin-tazobactam: >16; Cefepime: >8; Meropenem: >8; Amikacin: >16. Abbreviations: MDR, multidrug resistant; XDR, extensively drug resistant.

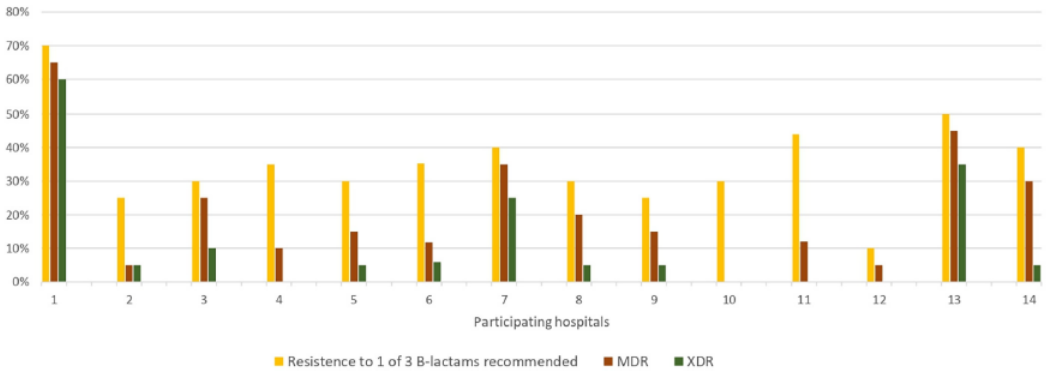

FIG 1 Rates of resistance to at least 1 of the β-lactam antibiotics recommended in the international guidelines, and rates of multi drug-resistant (MDR) and extensively drug-resistant (XDR) *P. aeruginosa* isolates, across the different hospitals.

In the multivariate analysis, pulmonary sources of BSI (OR 2.27, 95% CI 1.14 to 4.34) and IEAT (OR 2.67, 95% CI 1.37 to 5.23) were independently associated with increased mortality. The goodness of fit of the multivariate model was assessed using the Hosmer-Lemeshow test (0.819). The discriminatory power of the score, as evaluated by the area under the receiver operating characteristic curve, was 0.692 (95% CI 0.622 to 0.762). This figure demonstrated a good ability to predict 30-day mortality.

DISCUSSION

The current study describes the resistance to empirical antibiotic regimen in a multicenter cohort of patients with hematologic malignancies and *P. aeruginosa* bacteremia. The most important finding is that over a third of BSIs were caused by strains resistant to the anti-pseudomonal β-lactams recommended as empirical treatment in international guidelines. It is troubling to show that almost 20% of *P. aeruginosa* BSI episodes received IEAT and rose to almost 45% in those cases with resistance to at least one of the β-lactam

TABLE 3 Univariate and multivariate analysis for 30-day mortality among 280 episodes of bacteriemia due to *Pseudomonas aeruginosa*

Risk factor	Survivors N = 204 (%)	Deaths N = 76 (%)	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Male sex	123 (69.9)	53 (30.1)	1.98 (0.85–2.63)	0.159		
Over 70 yrs	41 (65.1)	22 (34.9)	1.62 (0.88–2.95)	0.115		
Acute Leukemia	76 (73.8)	27 (26.2)	0.92 (0.53–1.60)	0.790		
Allogeneic hematopoietic stem cell transplantation	49 (71)	20 (29)	1.13 (0.61–2.06)	0.692		
Neutropenia	121 (71.2)	49 (28.8)	1.23 (0.71–2.15)	0.458		
Pulmonary source	29 (58)	21 (42)	2.30 (1.21–4.36)	0.009	2.27 (1.14–4.34)	0.019
Unknown source	66 (75.9)	21 (24.1)	0.79 (0.44–1.42)	0.448		
Combination therapy with an aminoglycoside	37 (77)	11 (22.9)	0.76 (0.36–1.58)	0.469		
Combination therapy with colistin	10 (62.5)	6 (37.5)	1.66 (0.58–4.74)	0.337		
Active combination therapy[a]	34 (87.2)	5 (12.8)	0.35 (0.13–0.93)	0.030	0.40 (0.148–1.11)	0.080
Quinolone resistance	55 (67.1)	27 (32.9)	1.49 (0.85–2.62)	0.161		
Piperacillin-tazobactam resistance	39 (63.9)	22 (36.1)	1.72 (0.94–3.16)	0.076		
Cefepime resistance	47 (65.3)	25 (34.7	1.63 (0–91−2.92)	0.093		
Meropenem resistance	41 (58.6)	29 (41.4)	2.45 (1.37–4.36)	0.002	1.58 (0.80–4.49)	0.179
Amikacin resistance	23 (56.1)	18 (43.9)	2.44 (1.23–4.84)	0.009	1.38(0.62–3.09)	0.424
Resistance to at least 1 of the 3 antibiotics recommended by neutropenia guidelines[b]	63 (62.4)	38 (37.6)	2.23 (1.30–3.83)	0.003	0.85 (0.32–2.27)	0.751
Multidrug resistant *P. aeruginosa*	34 (57.6)	25 (42.4)	2.46 (1.34–4.48)	0.003	1.24 (0.45–3.42)	0.665
Inappropriate empirical antibiotic therapy	24 (51.1)	22 (48.9)	3.25 (1.70–6.22)	<0.001	2.67 (1.37–5.23)	0.004

[a]Beta-lactam and aminoglucoside or colistin combinations are active *in vitro*.
[b]Piperacillin-tazobactam, meropenem, or cefepime/ceftazidime.

antibiotics recommended by the guidelines and/or in MDR isolates. These results are in concordance with those previously published in similar populations in other countries (11, 12).

This observation is not surprising given the current epidemiology of multiresistance in *P. aeruginosa* strains worldwide. In our cohort, over 20% and 10% of the isolates met criteria for MDR and XDR, respectively. This, however, varied widely among centers. Previous studies conducted in immunocompromised hosts (4, 13–16) also reported rates of MDR isolates between 23% and 33%. Similar data have also been published in nonneutropenic patients from a large multicenter cohort from Spain; 26.2% of isolates were classified as MDR and 17.3% as XDR (17). More importantly, however, resistance to each of the different beta-lactam antibiotics recommended by international guidelines reached more than 20% (9, 10).

This information is extremely important, since IEAT has been clearly related to increased mortality in these patients (18–20). In line with previous evidence, IEAT was an independent risk factor for a more elevated mortality rate in the current cohort. The likelihood of death in those patients who received incorrect empirical antibiotics doubled.

Considering the high rates of IEAT and related increased mortality, new strategies are needed to improve patients' prognosis. Different studies have attempted to describe risk factors for MDR-*P. aeruginosa* BSI to reduce the probability of IEAT (11, 14, 21). However, mostly described risk factors are general and unspecific, and result in low applicability to real-life scenarios. In the coming years, though, via analysis of multiple variables in real-time, big data, and artificial intelligence algorithms may prove useful in predicting the specific risk of an MDR isolate (22, 23). These algorithms could guide the employment of new rapid diagnostic tests for multidrug resistance. The role that surveillance cultures can play in identifying patients at high risk of multidrug resistance remains to be investigated.

Another potential strategy to improve the prognosis of these patients may be antibiotic combination therapies. We have previously described that amikacin combination was an independent protective factor in patients with neutropenia, BSI, and septic shock (24). However, in this paper and other similar publications, combination therapy was only beneficial when both amikacin and the β-lactam were active (13, 19, 25). Conversely, when only amikacin was active, mortality was exceedingly high. These results suggest that the potential benefit of amikacin does not widen the antimicrobial spectrum; instead, it confers a synergistic effect alongside the β-lactam.

Given all of the aforementioned information, it is paramount to ensure the appropriateness of the initial β-lactam. In recent years, new anti-pseudomonal β-lactams have become available, namely, ceftolozane-tazobactam, ceftazidime-avibactam, and cefiderocol. Even in the current scenario of high MDR-*P. aeruginosa* prevalence, these antibiotics remain active against more than 90% of the isolated *Pseudomonas* (17). Additionally, a few studies have already shown that these new antibiotics could be even more effective in patients with hematologic malignancies (26–29). In a study conducted at the MD Anderson Cancer Center, empirical treatment with ceftolozane-tazobactam was associated with better clinical outcomes than standard of care (cefepime, meropenem, or piperacillin-tazobactam) in patients with hematologic malignancies and febrile neutropenia (26). However, in this same study, only 6 of the 100 enrolled patients had a microbiologically documented infection. In another study, Bergas et al. (28) retrospectively compared ceftolozane-tazobactam against other antibiotics in patients with hematologic malignancies and *P. aeruginosa* BSI, in which most episodes (91%) were due to MDR isolates. In this study, treatment with ceftolozane-tazobactam was significantly associated with both a lower need for mechanical ventilation and reduced mortality. This drug has also shown good efficacy in real-life patients with severe ESBL-producing Enterobacterales infections (30).

Considering these results, ceftolozane-tazobactam should be considered an initial empirical antibiotic therapy in patients with hematologic malignancies in those centers with a current resistance rate of more than 10% against one of the three classical anti-pseudomonal antibiotics in *P. aeruginosa* infections, as well as with a low incidence of

carbapenemase-producing Enterobacterales infections. In hospitals with a high incidence of carbapenemase-producing Enterobacterales infections in patients with hematologic malignancies, ceftazidima/avibactam appears to be a suitable option. Early antibiotic deescalation is possible and safe after clinicians rule out *P. aeruginosa* BSI within the first 24 to 48 h (31, 32).

The strength of this study includes a description of a current, prospective, and multicenter cohort from different regions of Spain and a large number of patients. However, there are some limitations that must be acknowledged. We performed a noninterventional study. Consequently, decisions regarding empirical antibiotics varied across the centers and respective local epidemiology is probably determined by the endemicity of some MDR pseudomonal strains. Also, the attending physician decided the management of intermediate antibiotic breakpoints. In addition, we included all university hospitals. It is likely that the IEAT rates are higher in centers which are not university hospitals. It is mandatory to be familiar with the ecology of each region and create personalized treatment protocols that respond to patients' needs.

In conclusion, we found that over a third of *P. aeruginosa* strains-causing BSI in patients with hematologic malignancies are resistant to the antibiotics recommended in international guidelines. In this scenario, IEAT was frequent and independently associated with increased mortality. Novel strategies to address this situation are needed.

MATERIALS AND METHODS

Setting, study population, and design. This is a retrospective study of a multicenter, observational, and prospective cohort, which was conducted across 14 tertiary hospitals in Spain. In October 2019, we collected the last 20 episodes of BSI caused by *P. aeruginosa* in adult (>18 years) patients with hematologic malignancies from each center. We recorded the following data: age and sex, baseline disease, source of BSI, antimicrobial susceptibility profile, empirical antibiotic treatments, and 30-day mortality.

This study was approved by the Ethics Committee Board of Hospital Clinic (HCB/2021/0157).

Definitions. Patients with febrile neutropenia were defined as those who had a single temperature measurement of >38.3°C or that of >38.0°C sustained over a 1-h period, and an absolute neutrophil count of ≤500 cells/mm^3 (5). The source of bacteremia was defined according to standard Centers for Disease Control (CDC) criteria (33).

Empirical antibiotic therapy was defined as that administered at BSI onset. Combination therapy was defined as administering more than one antibiotic empirically. IEAT was reported when the empirical antibiotic therapy did not include at least one *in vitro* active antibiotic. Additionally, *P. aeruginosa* was classified as MDR or XDR per prior consolidated definitions (34). Mortality was defined as death by any cause within the first 30 days of BSI onset.

Microbiological methods. Blood samples were processed using the Bactec 9240 system or Bactec FX system (Becton, Dickinson Microbiology Systems), with a 5-day incubation period. Isolates were identified by standard techniques. Antimicrobial susceptibility testing was performed using either a microdilution system (Microscan WalkAway Dade Behring, West Sacramento, CA or Phoenix system, Becton, Dickinson, Franklin Lakes, NJ) or the Etest (AB Biodisk, Solna, Sweden/bioMérieux, Mercy l'Etoile, France).

To define susceptibility or resistance to these antimicrobial agents, EUCAST version 9.0 of the EUCAST clinical breakpoint tables was used (35).

Statistical analysis. Categorical variables were described by counts and percentages, whereas continuous variables were expressed as means and standard deviations (SD) or medians and interquartile ranges (IQRs). The Chi-squared Pearson test and Student's t-test were used to compare categorical and continuous variables, respectively. A multivariate regression model (step-forward procedure) was used to identify independent risk factors for mortality. The multivariate analysis included all statistically significant variables in the univariate analysis. The goodness of fit of the multivariate model was assessed by the Hosmer-Lemeshow test and the area under the receiver operating characteristic curve. The threshold for statistical significance was defined as a two-tailed $P < 0.05$. All analyses were performed using SPSS software (version 25.0; SPSS, Inc., Chicago, IL).

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7•4 Impact of Empirical Antibiotic Regimens on Mortality in Neutropenic Patients with Bloodstream Infection Presenting with Septic Shock.

Chumbita, M., Puerta-Alcalde, P., Gudiol, C., Garcia-Pouton, N., Laporte-Amargós, J., Ladino, A., Albasanz-Puig, A., Helguera, C., Bergas, A., Grafia, I., Sastre, E., Suárez-Lledó, M., Durà, X., Jordán, C., Marco, F., Condom, M., Castro, P., Martínez, J. A., Mensa, J., Soriano, A., Garcia-Vidal, C.

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Resumen:

Objetivo: Analizar los factores de riesgo asociados con la mortalidad en pacientes con NF y bacteriemia que desarrollaron shock séptico y evaluar el impacto del tratamiento antibiótico empírico.

Métodos: Se realizó un estudio retrospectivo multicéntrico (2010-2019) en dos cohortes prospectivas, comparando episodios de bacteriemia en pacientes con o sin shock séptico. Se llevó a cabo un análisis multivariante para identificar factores de riesgo independientes para la mortalidad en episodios con shock séptico.

Resultados: De los 1,563 pacientes con bacteriemia, 257 (16%) presentaron shock séptico. Estos pacientes mostraron una mortalidad significativamente mayor que aquellos sin shock séptico (55% frente al 15%). Los BGN causaron el 81% de los episodios con shock séptico, los cocos gran positivos el 22%, y las especies de Candida el 5%. En el 17.5% de los episodios de

shock séptico se administró un TAEI. La combinación empírica de β-lactámicos con otros antibióticos activos se asoció con menor mortalidad. Cuando la amikacina fue el único antibiótico activo, la mortalidad alcanzó el 90%. La adición empírica de cobertura específica para grampositivos no tuvo impacto en la mortalidad. La mortalidad fue más alta cuando se administró TAEI (76% versus 51%). La edad superior a 70 años, el TAEI para Candida spp. o BGN, la lesión renal aguda y la amikacina como único antibiótico activo, fueron factores de riesgo independientes para mortalidad. Mientras que la combinación de un β-lactámico con amikacina mostró un efecto protector.

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CLINICAL THERAPEUTICS

Impact of Empirical Antibiotic Regimens on Mortality in Neutropenic Patients with Bloodstream Infection Presenting with Septic Shock

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ABSTRACT We analyzed risk factors for mortality in febrile neutropenic patients with bloodstream infections (BSI) presenting with septic shock and assessed the impact of empirical antibiotic regimens. A multicenter retrospective study (2010 to 2019) of two prospective cohorts compared BSI episodes in patients with or without septic shock. Multivariate analysis was performed to identify independent risk factors for mortality in episodes with septic shock. Of 1,563 patients with BSI, 257 (16%) presented with septic shock. Those patients with septic shock had higher mortality than those without septic shock (55% versus 15%, $P < 0.001$). Gram-negative bacilli caused 81% of episodes with septic shock, Gram-positive cocci caused 22%, and *Candida* species caused 5%. Inappropriate empirical antibiotic treatment (IEAT) was administered in 17.5% of septic shock episodes. Empirical β-lactam combined with other active antibiotics was associated with the lowest mortality observed. When amikacin was the only active antibiotic, mortality was 90%. Addition of empirical specific Gram-positive coverage had no impact on mortality. Mortality was higher when IEAT was administered (76% versus 51%, $P = 0.002$). Age of >70 years (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.2 to 4.7), IEAT for *Candida* spp. or Gram-negative bacilli (OR, 3.8; 95% CI, 1.3 to 11.1), acute kidney injury (OR, 2.6; 95% CI, 1.4 to 4.9), and amikacin as the only active antibiotic (OR, 15.2; 95% CI, 1.7 to 134.5) were independent risk factors for mortality, while the combination of β-lactam and amikacin was protective (OR, 0.32; 95% CI, 0.18 to 0.57). Septic shock in febrile neutropenic patients with BSI is associated with extremely high mortality, especially when IEAT is administered. Combination therapy including an active β-lactam and amikacin results in the best outcomes.

KEYWORDS bacteremia, empirical treatment, mortality, neutropenia, shock

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Bloodstream infections (BSI) are the most frequent infection in febrile neutropenic, onco-hematological patients, with incidence rates spanning from 10% to 38% (1–3). Septic shock is the most severe clinical presentation form of such infection. However, there is scarce information on incidence, characteristics, and outcomes of neutropenic patients who present with this complication (4–6). This information, nonetheless, is now more important than ever. Rates of Gram-negative bacilli (GNB) in onco-hematological patients are progressively increasing (7, 8), which could impact a greater percentage of patients presenting with septic shock (9). Additionally, empirical antibiotic therapy is challenging in the era of emerging multidrug-resistant (MDR) GNB. Indeed, inappropriate empirical antibiotic therapy (IEAT) has been associated with increased mortality in patients with febrile neutropenia and BSI (8, 10, 11).

For many years, international guidelines have recommended broadening the antimicrobial spectrum to cover drug-resistant Gram-negative and Gram-positive microorganisms in neutropenic patients with septic shock. This includes considering the addition of aminoglycosides, quinolones, vancomycin, and/or anti-*Candida* coverage to classic anti-pseudomonal β-lactams (cefepime, ceftazidime, piperacillin-tazobactam, or meropenem) (12). However, based on the current epidemiological context, we hypothesized that such antibiotic recommendations should be reassessed.

Therefore, we aimed to describe the frequency, clinical characteristics, and etiology of BSI in febrile neutropenic patients with septic shock and analyze risk factors for mortality. We also assessed the impact of different empirical antibiotic regimens on mortality.

RESULTS

Characteristics of and outcomes in patients with and without shock. Over the study period, 1,563 BSI episodes were identified in onco-hematological patients with febrile neutropenia. Of these, 257 (16%) presented with septic shock. Table 1 and also Table S2 in the supplemental material describe the main clinical and demographic characteristics in patients with and without shock. Overall, 30-day mortality was 22%, being higher in patients with septic shock (55% versus 15%, $P < 0.001$).

Table 2 displays the etiological microorganisms involved in episodes presenting with or without shock. Overall, GNB caused 56% of bacteremia episodes, with 13% of all episodes being caused by MDR-GNB. Gram-positive cocci (GPC) caused 42% of all BSI episodes, and *Candida* spp. caused 3%. Of all bacteremia episodes, 12% were polymicrobial. In patients with septic shock, specifically, 81% of the episodes were caused by GNB, 22% by GPC, and 5% by *Candida* spp.

Figure S1 details the most significant differences in baseline characteristics, epidemiology, and outcomes between patients with and without septic shock.

Antibiotic therapy and outcomes in patients with septic shock. Table S3 shows the comparison of antibiotic therapy in patients with and without septic shock. Among those episodes presenting with septic shock, 17.5% received IEAT, mainly in BSI caused by *Pseudomonas aeruginosa* and *Candida* spp. Table S4 summarizes the set of etiological agents of episodes with septic shock receiving IEAT. Acute kidney injury (AKI) presented in 71.5% of patients with septic shock.

Figure 1 shows additional values for specific Gram-positive coverage and amikacin, respectively, in patients with septic shock. Both Gram-positive coverage and amikacin were administered almost exclusively in combination with other antibiotics. Specific Gram-positive coverage (including vancomycin, teicoplanin, daptomycin, and linezolid) was used in 87 of 257 (34%) cases. In 27 of 87 (31%) cases, the isolated microorganism was susceptible to specific Gram-positive coverage, and Gram-positive coverage was the only active antibiotic in 16 of 87 (18%) cases. Amikacin was used in 137 (53%) episodes. In 126 (85%) of these 137 cases, the isolated microorganism was susceptible to this antibiotic, and in 10 (7%) of these 137 cases, amikacin was the only active antibiotic.

Risk factors for mortality in patients with septic shock. Overall, 141 (55%) patients with septic shock died within 30 days of BSI onset. In the univariate analysis, patients with BSI and septic shock who had chronic leukemia (91% versus 53%, $P = 0.014$), pulmonary source of BSI (69% versus 52%, $P = 0.032$), BSI caused by MDR

TABLE 1 Clinical and demographic characteristics of patients with BSI episodes presenting with and without septic shock[c]

Characteristic	All episodes (n = 1,563)	No septic shock (n = 1,306)	Septic shock (n = 257)	P value
Demographic data				
Age, median (IQR), yr	59 (48–67)	61 (51–69)	59 (47–66)	0.616
Male sex	918 (59)	768 (59)	150 (58)	0.896
Underlying disease				
Hematological malignancy	1,348 (86)	1,168 (89)	180 (70)	<0.001
Solid neoplasm[a]	238 (15)	157 (12)	81 (32)	<0.001
Hematopoietic stem cell transplant	400 (26)	355 (27)	45 (18)	0.001
Allogenic/autologous	249/151 (62/38)[b]	215/140 (61/39)[b]	34/11 (76/24)[b]	0.051
Any comorbidity	456 (29)	366 (28)	90 (35)	0.024
Corticosteroid therapy	588 (38)	461 (35)	127 (49)	<0.001
Nosocomial BSI (vs health care or community acquired)	999 (64)	883 (68)	116 (45)	<0.001
Source of BSI				
Endogenous/unknown	763 (49)	650 (50)	113 (44)	0.089
Catheter related	333 (21)	309 (24)	24 (9)	<0.001
Abdominal	102 (7)	72 (6)	30 (12)	<0.001
Pulmonary	97 (6)	49 (4)	48 (19)	<0.001
Urinary	83 (5)	62 (5)	21 (8)	0.025
Inappropriate empirical antibiotic therapy	471 (30)	426 (32.6)	45 (17.5)	<0.001
For Gram-positive cocci	290 (18.6)	277 (21.2)	13 (5.1)	<0.001
For Gram-negative bacilli	146 (9.3)	121 (9.3)	25 (9.7)	0.816
Outcome				
Mechanical ventilation requirement	100 (6.6)	29 (2.3)	71 (27.6)	<0.001
30-day mortality	342 (21.9)	201 (15.4)	141 (54.9)	<0.001

[a]There were 25 patients who had both a hematological malignancy and a solid neoplasm.
[b]Percentage among hematopoietic stem cell transplant recipients.
[c]Abbreviations: IQR, interquartile range; BSI, bloodstream infection. All values except age are shown as no. (%).

P. aeruginosa (85% versus 53%, $P = 0.042$), and episodes presenting with AKI (62% versus 38%, $P = 0.001$) and requiring mechanical ventilation (85% versus 44%, $P < 0.001$) experienced higher mortality. Conversely, an endogenous source was associated with lower mortality (48% versus 60%, $P = 0.043$).

Empirical β-lactam (53% versus 79%, $P = 0.032$) was associated with lower mortality in patients with septic shock compared to those who did not receive empirical β-lactam. Empirical combination therapy with a β-lactam plus amikacin was associated with lower mortality compared to those receiving β-lactam without amikacin (41% versus 70%, respectively; $P < 0.001$). Combination therapy including Gram-positive coverage (namely, vancomycin, teicoplanin, daptomycin, or linezolid) had no significant impact on mortality (48.8% in episodes receiving specific Gram-positive coverage versus 57.9% in those not receiving Gram-positive coverage, $P = 0.169$).

Mortality in episodes receiving IEAT was 76%, contrasting with the 51% reported in patients receiving appropriate empirical treatment ($P = 0.002$). Specifically, in those episodes caused by GNB presenting with shock, mortality was 83% in cases of IEAT and 51% in cases of appropriate empirical therapy ($P = 0.003$). When analyzing BSI episodes due to GPC, we did not observe any significant differences in mortality regarding appropriateness of empirical treatment (54% versus 52%, $P = 0.926$).

Table 3 shows mortality rates according to active empirical antibiotic coverage administered to patients with GNB BSI presenting with septic shock. In those cases, in which amikacin was the only active antibiotic administered (mainly because the isolated microorganism was resistant to the combined β-lactam), the mortality rate was 90%. Conversely, when only a β-lactam was active, mortality was 66%. The lowest mortality reported was when patients received an active combination of β-lactam and either amikacin (39%) or quinolone (33%). When selecting those episodes caused by microorganisms susceptible to both β-lactam and amikacin, mortality was 65.6% (40/61) in patients

TABLE 2 Etiological microorganisms in BSI episodes presenting with and without septic shock[a]

Microorganism	All episodes (n = 1,563)	No septic shock (n = 1,306)	Septic shock (n = 257)	P value
Gram-positive cocci	656 (42)	600 (46)	56 (22)	<0.001
Coagulase-negative staphylococci	291 (19)	280 (21)	11 (4)	<0.001
S. aureus	72 (5)	65 (5)	7 (3)	0.142
MRSA	12 (17)*	8 (12)*	4 (57)*	0.120
Enterococcus spp.	222 (14)	205 (16)	17 (7)	<0.001
E. faecalis	66 (30)*	56 (27)*	10 (59)*	0.772
E. faecium	148 (67)*	142 (69)*	6 (35)*	<0.001
E. faecium, vancomycin resistant	10 (5)*	10 (5)*	0	0.383
Streptococcus spp.	98 (6)	76 (6)	22 (9)	0.098
S. pneumoniae	17 (17)*	10 (13)*	7 (32)*	0.006
Gram-negative bacilli	881 (56)	674 (52)	207 (81)	<0.001
E. coli	376 (24)	284 (22)	92 (36)	<0.001
ESBL	80 (21)*	67 (24)*	13 (14)*	0.962
Carbapenemase	2 (1)*	2 (1)*	0	1.000
Klebsiella spp.	137 (9)	103 (8)	34 (13)	0.006
ESBL	32 (23)*	27 (26)*	5 (15)*	0.900
Carbapenemase	3 (2)*	3 (3)*	0	1.000
P. aeruginosa	234 (15)	162 (12)	72 (28)	<0.001
MDR	59 (25)*	46 (28)*	13 (18)*	0.238
XDR	38 (16)*	30 (19)*	8 (11)*	0.438
Enterobacter spp.	56 (4)	49 (4)	7 (3)	0.418
AmpC-hyperproducer strain	9 (16)*	8 (16)*	1 (14)*	1.000
S. maltophilia	35 (2)	33 (3)	2 (1)	0.104
MDR-GNB	210 (13)	171 (13)	39 (15)	0.371
Candidemia	50 (3)	37 (3)	13 (5)	0.064
C. albicans	11 (22)*	6 (16)*	5 (38)*	0.009
Non-*albicans* candidemia	39 (78)*	31 (84)*	8 (62)*	0.487
Polymicrobial	180 (12)	146 (11)	34 (13)	0.347

[a]Abbreviations: MRSA, methicillin-resistant *S. aureus*; ESBL, extended-spectrum β-lactamase; MDR, multidrug resistant; XDR, extensively drug resistant; GNB, Gram-negative bacilli. *, asterisk indicates percentage among its species.

receiving monotherapy with a β-lactam versus 39.6% (42/106) in those receiving combination therapy with amikacin.

Table 4 shows the univariate and multivariate analyses of risk factors for mortality in patients with shock. In the multivariate analysis, age of >70 years (odds ratio [OR], 2.4; 95% confidence interval [CI], 1.2 to 4.7), IEAT for GNB or *Candida* spp. (OR, 3.8; 95% CI, 1.3 to 11.1), episodes presenting with AKI (OR, 2.6; 95% CI, 1.4 to 4.9), and the reception of amikacin as the only active antibiotic (OR, 15.2; 95% CI, 1.7 to 134.5) were independent risk factors for increased mortality, while combination therapy with a β-lactam and amikacin was protective (OR, 0.3; 95% CI, 0.2 to 0.6). The Hosmer-Lemeshow test was 0.232, and the area under the receiver operating characteristic (ROC) curve was 0.74 (95% CI, 0.68 to 0.80), showing a moderate ability to predict mortality. The same variables, with minor changes in OR values, were independently associated with mortality when the propensity score for receiving IEAT in BSI caused by GNB or *Candida* spp. was incorporated into the model (ROC curve, 0.77; 95% CI, 0.70 to 0.83). The Durbin-Watson test was 2.161 and variance inflation factor was <2 for all variables, suggesting the lack of collinearity among variables used in the multivariable analysis.

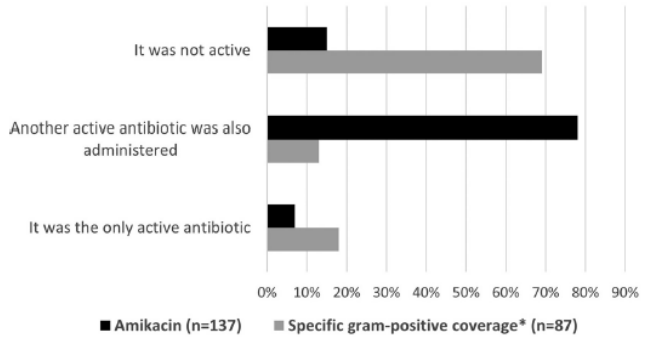

FIG 1 Additional value for empirical combination treatment with specific Gram-positive coverage and amikacin in patients with septic shock regarding antimicrobial susceptibility of the isolated microorganism. For specific Gram-positive coverage, (i) isolated microorganism was resistant to Gram-positive coverage in 69% of cases; (ii) isolated microorganism was susceptible to Gram-positive coverage, but another active antibiotic was also administered in 13% of cases; and (iii) Gram-positive coverage was the only active antibiotic in 18% of cases. For amikacin, (i) isolated microorganism was resistant to amikacin in 15% of cases; (ii) isolated microorganism was susceptible to amikacin, but another active antibiotic was also administered in 78% of cases; and (iii) amikacin was the only active antibiotic in 7% of cases. *, including glycopeptides (vancomycin and teicoplanin), daptomycin, and linezolid.

DISCUSSION

The current study showed that neutropenic patients with BSI frequently presented with septic shock (16%), especially those with solid neoplasms or who had received corticosteroids. The fact that oncologic patients with BSI present with septic shock more frequently than hematological patients has been previously reported (13–15) and may be related to the higher incidence of pulmonary, abdominal, and urinary source in this population. Another potential explanation is the higher presence of coagulase-negative staphylococcal BSI in hematological patients, which are less likely associated with septic shock.

Remarkably, BSI with septic shock is essentially caused by GNB, predominantly by *Escherichia coli*, *P. aeruginosa*, and *Klebsiella* spp. GNB and *E. coli*, especially, have been previously associated with the presence of septic shock in neutropenic patients (9, 16, 17). In fact, in the current study, these three pathogens together caused over three-quarters of all BSI episodes in patients with septic shock. Most importantly, and similar to a recent Korean study (16), almost 20% of GNB isolates producing septic shock were MDR. Conversely, GPC caused only 20% of BSI episodes with septic shock, and approximately one-third of those were polymicrobial episodes along with GNB. This was not unexpected, as most Gram-positive bacteria in this cohort were low-virulence pathogens like coagulase-negative staphylococci and *Enterococcus* spp. causing catheter-related episodes. Additionally, the overall prevalence of *Staphylococcus aureus* and *Streptococcus* spp. was relatively low.

TABLE 3 Mortality according to active empirical antibiotic coverage administered in Gram-negative bloodstream infection with septic shock[a]

Active antibiotic(s)	Survival, *n* (%)	Death, *n* (%)
Only 1 β-lactam was active ($n = 64$)	22 (34)	42 (66)
Only amikacin was active ($n = 10$)	1 (10)	9 (90)
Combined β-lactam and amikacin were both active ($n = 101$)	62 (61)	39 (39)
Combined β-lactam, quinolone, and amikacin were all active ($n = 4$)	2 (50)	2 (50)
Combined β-lactam and quinolone were both active ($n = 6$)	4 (67)	2 (33)
No active empirical antibiotic was administered ($n = 22$)	3 (14)	19 (86)

[a]*P* value for all data is <0.001.

TABLE 4 Risk factors for overall mortality, by univariate and multivariate analysis[a]

Risk factor	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Male sex	0.78 (0.48–1.30)	0.346		
Age ≥70 yr	2.23 (1.20–4.15)	**0.010**	2.36 (1.19–4.68)	**0.014**
Acute leukemia	0.65 (0.38–1.13)	0.125		
Non-Hodgkin lymphoma	0.94 (0.52–1.72)	0.847		
Multiple myeloma	0.90 (0.37–2.19)	0.811		
Chronic leukemia	8.78 (1.10–69.63)	**0.014**	5.02 (0.60–42.22)	0.138
Solid neoplasia	0.96 (0.57–1.64)	0.906		
Hematopoietic stem cell transplantation	1.29 (0.67–2.48)	0.446		
Any comorbidity	1.04 (0.62–1.75)	0.870		
Corticosteroid therapy	1.16 (0.71–1.89)	0.560		
Nosocomial acquisition	1.41 (0.86–2.31)	0.177		
Pulmonary source	2.06 (1.06–4.01)	**0.032**	1.35 (0.58–3.18)	0.486
Endogenous/unknown source	0.60 (0.37–0.98)	**0.043**	0.69 (0.39–1.23)	0.211
Catheter-related BSI	0.81 (0.35–1.87)	0.615		
Acute kidney injury	2.48 (1.41–4.37)	**0.001**	2.60 (1.39–4.90)	**0.003**
Empirical β-lactam	0.26 (0.73–0.94)	**0.037**	0.41 (0.08–2.16)	0.294
Empirical carbapenem	0.94 (0.58–1.55)	0.819		
Empirical β-lactam plus aminoglycoside	0.30 (0.18–0.50)	**<0.001**	0.32 (0.18–0.57)	**<0.001**
Empirical β-lactam plus specific Gram-positive coverage	0.69 (0.41–1.17)	0.169		
Amikacin as the only active antibiotic	7.84 (0.98–62.83)	**0.025**	15.24 (1.73–134.45)	**0.014**
β-Lactam as the only active antibiotic	1.81 (1.01–3.26)	**0.046**	1.66 (0.72–3.82)	0.236
Coagulase-negative staphylococci	0.34 (0.09–1.34)	0.193		
Staphylococcus aureus	2.10 (0.40–11.01)	0.462		
Enterococcus spp.	1.19 (0.44–3.23)	0.734		
Streptococcus spp.	1.08 (0.45–2.55)	0.867		
E. coli	0.97 (0.58–1.62)	0.901		
Klebsiella spp.	0.80 (0.39–1.64)	0.541		
Pseudomonas aeruginosa	1.32 (0.76–2.29)	0.329		
MDR *P. aeruginosa*	3.19 (0.87–11.71)	0.096		
MDR-GNB	1.57 (0.77–3.18)	0.208		
Candidemia	4.82 (1.05–22.22)	**0.042**	2.18 (0.34–13.94)	0.411
Polymicrobial	1.86 (0.86–3.99)	0.108		
Inappropriate empirical antibiotic therapy for GNB or *Candida* spp.	5.74 (2.14–15.38)	**<0.001**	3.81 (1.31–11.11)	**0.014**

[a]Abbreviations: ESBL, extended-spectrum β-lactamase; MDR, multidrug resistant; GNB, Gram-negative bacilli. Boldface indicates statistically significant values (*P* value < 0.05).

Mortality in neutropenic patients with BSI and septic shock was extremely high (55%). Most series of patients with septic shock and BSI including nonneutropenic patients report remarkably lower mortalities ranging from 35% to 45% (9, 18, 19). This highlights the pivotal role of granulocytes in controlling infection (20), emphasizing the importance of early and effective treatment to diminish this devastating mortality in neutropenic patients.

The Infectious Diseases Society of America (IDSA) febrile neutropenic guidelines recommend adding specific Gram-positive coverage in patients with hemodynamic instability (12), even though common empirical regimens offer pertinent coverage for most GPC, excluding methicillin-resistant staphylococci and *Enterococcus* spp. However, in our cohort, we did not find that empirical, specific Gram-positive coverage had a significant impact on mortality. Several studies have demonstrated toxicity due to vancomycin in neutropenic patients (21), and new drugs like daptomycin could be associated with increased costs. In view of these results, specific Gram-positive coverage is questionable in patients without proven infection, suspicion of catheter-related BSI, or methicillin-resistant *S. aureus* (MRSA) colonization.

In this study, combination therapy with a β-lactam plus amikacin was an independent factor for lower mortality in patients with septic shock compared to those not receiving amikacin combination. A prior meta-analysis failed to demonstrate any benefit of β-lactam–aminoglycoside combination in neutropenic patients with cancer (22). However, this is still a controversial issue. For example, Martinez et al. showed that aminoglycoside combination was able to reduce mortality, but only in those episodes

presenting with septic shock or neutropenia (23). It has been hypothesized that a potential benefit of combination therapy may be the broadening of the initial antimicrobial spectrum and a resulting decreased likelihood of IEAT (23). However, in this study, amikacin as the only active antibiotic (basically when the isolated microorganism is resistant to empirical β-lactam) was independently associated with increased mortality, suggesting that any potential benefit is mainly due to a synergistic effect (24, 25). Similar results were recently found in the AMINOLACTAM study, in which our hospitals participated (26), analyzing only BSI episodes receiving adequate empirical antibiotic therapy. In that study, focusing on hematologic neutropenic patients, empirical short-course aminoglycoside combined with a β-lactam significantly improved the 7-day case fatality rate, without significantly impairing renal function. However, as in the present study, mortality increased when the aminoglycoside was the only active antibiotic, suggesting again that the benefit of combination is mainly driven by an enhanced bactericidal effect.

AKI is commonly associated with increased mortality in patients with shock. In this sense, some may speculate that the protective role of amikacin in this cohort was due to less administration of the drug in those patients with AKI. However, in the multivariate analysis performed, both AKI and combination therapy with amikacin were independently associated with mortality.

Our study reinforces the relevance of β-lactam therapy adequacy to improve patient outcomes. Approximately 20% of patients with septic shock received IEAT, and this was mainly due to *P. aeruginosa* and *Candida* spp. Most importantly, mortality in episodes caused by GNB and *Candida* spp. presenting with septic shock and receiving IEAT was extremely high (83% and 90%, respectively). Considering that amikacin "monotherapy" is associated with increased mortality, warranting an active β-lactam is essential to improve the prognosis of this highly lethal entity. In this sense, new β-lactams such as ceftazidime-avibactam and ceftolozane-tazobactam should be considered empirical therapeutic options for patients with a higher risk of MDR-GNB, even in a potentially synergistic association with carbapenems (27). Following this broad and aggressive approach, early antibiotic deescalation is safe (28, 29) and must be a priority. Finally, identifying patients at risk of candidemia is critical when considering coverage for this relatively uncommon yet fatal complication (30).

The strengths of this study are the large number of patients included, prospective data collection, and thorough evaluation by an infectious disease expert. Additionally, a propensity score analysis was included to make the groups receiving appropriate versus inappropriate empirical antibiotic treatment comparable. Some limitations should, however, be acknowledged. (i) External validity of this study could be limited since it was performed in two centers from the same geographical area. Global epidemiology and prevalence of MDR pathogens may vary in other centers. (ii) Different definitions for septic shock have existed throughout the study period (31, 32). As we do not have the lactate values available for older episodes, some of them may not have met criteria for septic shock according to the current guidelines. (iii) Exact time to initiation of antibiotic, which impacts the outcome of these patients, was not available. (iv) The broad confidence interval ranges in some of the multivariate analysis variables suggest there may exist some sparse data bias. (v) Finally, as this is not a randomized clinical trial, there is no way to completely exclude confounding variables driving the observed associations.

Conclusion. Septic shock in febrile neutropenic patients with BSI is essentially caused by GNB and is associated with extremely high mortality, especially in patients receiving IEAT. Empirical Gram-positive coverage had no impact on mortality. Empirical combination of a β-lactam plus amikacin was associated with lower mortality compared to those patients who did not receive amikacin. However, when amikacin was the only active antibiotic (mainly because the isolated microorganism was resistant to the empirical β-lactam), mortality was 90%. Administering an active β-lactam in

combination with amikacin should be strongly considered in neutropenic patients with septic shock.

MATERIALS AND METHODS

Setting, study population, and design. This descriptive, retrospective study was conducted in two university hospitals in Barcelona, Spain: Hospital Clinic and Hospital de Bellvitge (700-bed centers). This study was approved by the Ethics Committee Board (Comité de Ética de la Investigación con medicamentos) of our institution (HCB/2020/0509). Informed consent was waived due to the retrospective nature of the study. A specific database prospectively collected all BSI episodes occurring in onco-hematological patients. For this study, we retrospectively analyzed all episodes of BSI in adult (>18 years) neutropenic patients, identified between 2010 and 2019. The following data had been gathered in specific prospectively collected databases in both centers: age and gender, comorbidities and baseline disease, source of BSI, causative agents and their antibiotic susceptibility profiles, empirical antibiotic treatments, septic shock at onset, mechanical ventilation requirement, and 30-day mortality. For this study, both databases underwent unification. Episodes presenting with septic shock were compared with those without septic shock.

Definitions. Patients with febrile neutropenia were defined as those who had either a single temperature measurement of >38.3°C or that of >38.0°C sustained over a 1-h period, and an absolute neutrophil count of ≤500 cells/mm^3. Per hospital protocols, patients with expected grade IV neutropenia over 10 days received prophylaxis with levofloxacin at Hospital Clinic but not at Hospital Bellvitge. Septic shock was defined as sepsis episodes requiring the use of vasopressors due to persistent hypotension despite fluid therapy (31), with a causal and temporal relationship with the BSI episode. Acute kidney injury (AKI) was defined as a rise in serum creatinine by >0.3 mg/dL within 2 days of BSI (33). Prior antibiotic therapy was defined as the usage of any antimicrobial agent for ≥3 days throughout the month before the BSI episode, including quinolone prophylaxis. In this paper, we refer to active antibiotic according to its susceptibility testing. In this sense, "β-lactam as the only active antibiotic" or "amikacin as the only active antibiotic" refers to the fact that although other antibiotics may have been administered, these were the only active antibiotics according to susceptibility testing.

Definitions of comorbidities and site of infection have been previously provided (7, 34, 35). Catheter-related BSI was defined as the presence of one positive peripheral blood culture and a positive semiquantitative or quantitative catheter tip culture that grew the same microorganism found in the peripheral blood culture. In the absence of a positive catheter tip culture, patients were diagnosed with catheter-related BSI when local signs of phlebitis were present and there was an absence of other evident, infectious foci (36). Specifically, in the case of BSI due to coagulase-negative staphylococci without an available catheter tip culture, at least two sets of positive blood cultures drawn from different venipuncture localizations were required to make a diagnosis of BSI. The BSI was considered to be from an unknown or endogenous source when no other source was identified. Nosocomial infection was defined when clinical manifestations appeared 48 h after hospital admission. Healthcare-associated infection was defined when the subject met at least one of the following criteria: recent hospitalization (within the last 30 days), admission from a long-term-care facility, and being on either chronic hemodialysis or intravenous treatment in the previous month. The remaining patients were classified as having community-acquired BSI. IEAT was considered as such when empirical therapy did not include at least one *in vitro* active antibiotic against the isolated microorganism. GNB were classified as MDR per prior consolidated definitions (37). Mortality was defined as death by any cause within the first 30 days of BSI onset.

Microbiological methods. Blood samples were processed using either the Bactec 9240 system or Bactec FX system (Becton, Dickinson Microbiology Systems), with an incubation period of 5 days. Isolates were identified by standard techniques. Antimicrobial susceptibility testing was performed with a microdilution system (MicroScan WalkAway [Dade Behring, West Sacramento, CA] or Phoenix system [Becton, Dickinson, Franklin Lakes, NJ]) or the Etest (AB Biodisk, Solna, Sweden/bioMérieux, Marcy l'Etoile, France). Current CLSI or EUCAST breakpoints for each year were used to define susceptibility or resistance to these antimicrobial agents, and intermediate susceptibility was considered resistance. Blood culture systems and antimicrobial susceptibility methods were equivalents between the two hospitals.

Statistical analysis. Categorical variables were described by counts and percentages, whereas continuous variables were expressed as means and standard deviations (SDs) or medians and interquartile ranges (IQRs). Pearson's chi-squared test and either the Mann-Whitney U test or Student *t* test were used to compare the distributions of categorical and continuous variables, respectively. Factors associated with mortality were evaluated with univariate and multivariate analyses; the multivariate analysis included all significant variables ($P < 0.05$) from the univariate analysis. Given the lack of randomization that could cause differences in the likelihood of receiving IEAT, a propensity score for IEAT was estimated using a backward stepwise logistic regression model that included variables related to IEAT with *P* values of ≤0.05 in the univariate analysis. For the propensity score analysis, only those episodes caused by GNB or *Candida* spp. were considered, because mortality is much lower in episodes caused by coagulase-negative staphylococci. The following variables were included based on their presence (yes/no) during the BSI episode: nosocomial BSI; previous antibiotic therapy, empirical β-lactam plus aminoglycoside combination, BSI caused by *E. coli*, BSI caused by *Klebsiella* spp., BSI caused by MDR *P. aeruginosa*, and candidemia. Univariate and multivariate analyses for receiving IEAT are detailed in the supplemental material (Table S1). The goodness of fit of the propensity score was assessed with the Hosmer-Lemeshow test ($P = 0.844$). The discriminatory power of the model, as evaluated by the area under the receiver operating characteristic (ROC) curve, was 0.87 (95% CI, 0.81 to 0.94), showing a

strong ability to predict IEAT in episodes due to either GNB or *Candida* spp. Finally, a multivariate regression model (step-forward procedure) was used to identify independent risk factors for mortality in patients with BSI episodes presenting with shock. The propensity score for IEAT was used as a covariate in the multivariate analysis to adjust for potential confounding factors. The goodness of fit of the final multivariate model was assessed again with the Hosmer-Lemeshow test and the area under the ROC curve. The Durbin-Watson test and the variance inflation factor were used to evaluate for collinearity. The threshold for statistical significance was defined as a two-tailed P of <0.05. All analyses were performed with SPSS software (version 25.0; SPSS, Inc., Chicago, IL).

Data availability. The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.4 MB.

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7•5 Clinical Characteristics and Outcome of Bloodstream Infections in HIV-Infected Patients with Cancer and Febrile Neutropenia: A Case-Control Study.

Puerta-Alcalde, P., Ambrosioni, J., **Chumbita, M.,** Hernández-Meneses, M., Garcia-Pouton, N., Cardozo, C., Moreno-García, E., Marco, F., Mensa, J., Rovira, M., Esteve, J., Martínez, J. A., García, F., Mallolas, J., Soriano, A., Miró, J. M., & Garcia-Vidal, C.

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Infectious diseases and therapy.

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Resumen:

Objetivo: Nuestro objetivo fue comparar las características clínicas y los resultados de la bacteriemia en pacientes con cáncer que presentan NF, con y sin infección por VIH, y analizar los factores pronósticos para la mortalidad.

Métodos: Se recopilaron prospectivamente episodios de bacteriemia en pacientes neutropénicos febriles tras la quimioterapia (1997-2018). Se realizó un subanálisis de casos (infectados por VIH) y controles (no infectados por VIH) en una proporción de 1:2, emparejando a los pacientes por edad, género, enfermedad de base y microorganismo etiológico.

Resultados: De 1755 episodios de bacteriemia en pacientes con cáncer y neutropenia, 60 (3.4%) ocurrieron en aquellos con infección por VIH. Las características de los pacientes con VIH fueron: 51.7% hombres que tienen relaciones sexuales con hombres; 58.3% tenían

menos de 200 CD4; 51.7% tenían una carga viral de VIH-1 RNA detectable antes del episodio de bacteriemia; 70.0% cumplían criterios de enfermedad definitoria de SIDA; y 93.3% estaban bajo terapia antirretroviral, siendo el régimen basado en inhibidores de la proteasa el más común (53.0%). Los pacientes infectados por VIH eran más jóvenes, predominantemente masculinos y presentaban con más frecuencia enfermedad hepática crónica ($p<0.001$ en todos los casos). Las bacteriemia debido a *Enterococcus* spp. fué significativamente más frecuente en pacientes con VIH ($p = 0.017$), sin diferencias en otros patógenos. Los pacientes con cáncer infectados por VIH presentaron shock con más frecuencia ($p = 0.014$) y tuvieron una mayor mortalidad (31.7% vs. 18.1%, $p = 0.008$). En el análisis de casos y controles, los casos (infectados por VIH) presentaban enfermedad hepática crónica con más frecuencia ($p = 0.003$), mientras que la leucemia aguda ($p = 0.013$) y el trasplante de células madre hematopoyéticas ($p = 0.023$) eran más comunes entre los controles. Hubo una tendencia no significativa para que los casos tuvieran una mayor mortalidad ($p = 0.084$). Sin embargo, en el análisis multivariante, la infección por VIH no se asoció con la mortalidad ($p = 0.196$).

Conclusión: Los pacientes con cáncer infectados por VIH que desarrollan NF y bacteriemia tienen perfiles epidemiológicos y clínicos diferentes y experimentan una mayor mortalidad. Sin embargo, la infección por VIH por sí sola no se asoció con la mortalidad.

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ORIGINAL RESEARCH

Clinical Characteristics and Outcome of Bloodstream Infections in HIV-Infected Patients with Cancer and Febrile Neutropenia: A Case–Control Study

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ABSTRACT

Introduction: We aimed to compare the clinical characteristics and outcomes of bloodstream infections (BSI) in cancer patients presenting febrile neutropenia with and without HIV infection, and analyze the prognostic factors for mortality.

Methods: BSI episodes in febrile neutropenic patients following chemotherapy were prospectively collected (1997–2018). A case (HIV-infected)–control (non-HIV-infected) subanalysis was performed (1:2 ratio), matching patients by age, gender, baseline disease, and etiological microorganism.

Results: From 1755 BSI episodes in neutropenic cancer patients, 60 (3.4%) occurred in those with HIV. HIV characteristics: 51.7% were men who have sex with men; 58.3% had < 200 CD4; 51.7% had a detectable HIV-1 RNA viral load before the BSI episode; 70.0% met AIDS-defining criteria; and 93.3% were on antiretroviral therapy, with a protease inhibitor-based regimen being the most common (53.0%). HIV-infected patients were younger, more frequently male and more commonly presenting chronic liver disease ($p < 0.001$ for all). BSI due to *Enterococcus* spp. was significantly more frequent among patients with HIV ($p = 0.017$) with no differences in other pathogens. HIV-infected patients with cancer presented with shock more frequently ($p = 0.014$) and had higher mortality

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(31.7% vs. 18.1%, $p = 0.008$). In the case–control analysis, cases (HIV-infected) had chronic liver disease ($p = 0.003$) more frequently, whereas acute leukemia ($p = 0.013$) and hematopoietic stem-cell transplant ($p = 0.023$) were more common among controls. There was a non-significant trend for cases to have higher mortality ($p = 0.084$). However, in multivariate analysis, HIV infection was not associated with mortality ($p = 0.196$).

Conclusion: HIV-infected patients with cancer developing febrile neutropenia and BSI have different epidemiological and clinical profiles, and experience higher mortality. However, HIV infection by itself was not associated with mortality.

Keywords: Bacteremia; HIV; Multidrug resistance; Neutropenia

Key Summary Points

Why carry out this study?

Patients with HIV who develop cancer face intrinsic immunosuppression in addition to the neutropenia and toxicity associated with chemotherapy.

We aimed to compare the clinical characteristics and outcomes of BSI in febrile neutropenic cancer patients with and without HIV infection.

BSI characteristics in cancer patients with HIV may be different and HIV can be associated with increased mortality.

What was learned from the study?

HIV-infected patients with cancer, febrile neutropenia, and BSI have different clinical and etiological profiles from non-HIV-infected patients.

HIV cancer patients present with shock more frequently and have higher mortality.

However, in the case–control cohort, HIV was not an independent prognostic factor for mortality.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14319479.

INTRODUCTION

Bloodstream infections (BSI) are the most frequent infectious complications in patients with post-chemotherapy febrile neutropenia, associated with high morbidity and mortality [1, 2]. Antibiotic treatment is challenging due to the rise in multidrug-resistant organisms, and inappropriate empirical treatment is associated with an increase in mortality [3–6].

Patients with human immunodeficiency virus (HIV) infection not undergoing antiretroviral therapy (ART) develop AIDS and, in many cases, AIDS-defining tumors [7, 8]. With the introduction of combined ART, however, HIV infection has become a chronic disease, and the number of individuals living with HIV continues to increase [9–11]. This has in turn been associated with an increased risk of non-AIDS-defining tumors [12–14]. Incidence of, and even mortality from, these non-AIDS-defining tumors appear to be higher in patients with HIV than in the general population [15, 16].

Patients with HIV who develop cancer, especially those with a lower CD4 level, have intrinsic immunosuppression, which is added to the neutropenia and toxicity associated with chemotherapy [13–15]. Moreover, some patients receive ART regimens having relevant drug–drug interactions that may complicate chemotherapy administration and lead to additional complications. Information concerning characteristics of BSI in patients with HIV and cancer who develop febrile neutropenia following chemotherapy is absent, and no specific recommendations are available for these patients upon febrile neutropenia onset.

We aimed to compare the clinical characteristics and outcomes of BSI in febrile neutropenic cancer patients with and without HIV

infection, and to analyze prognostic factors for mortality.

METHODS

Setting and Data Collection

This study was performed at the Hospital Clinic in Barcelona (Spain), a 700-bed university center providing specialized and broad medical, surgical, and intensive care for an urban population of 500,000 people. The HIV Unit of the Hospital Clinic has currently close to 6000 HIV-positive patients on active follow-up.

Since 1997, data on vital signs, laboratory and microbiological tests, complementary imaging explorations and administered treatment have been computerized. Concurrently, our institution has conducted a blood culture surveillance program identifying and monitoring all patients with bacteremia, as well as a parallel program that follow all patients with HIV. The collected data have been entered into specific databases designed for these programs.

Study Population and Design

For this study, we identified all episodes of febrile neutropenia following chemotherapy occurring in patients with cancer and HIV from January 1997 to March 2018.

The following data were obtained from all patients: age, gender, comorbidities, treatment with antibiotics or steroids in the previous month, recent hospitalization (within the last month), current administration of antibiotic treatment, neutrophil count, CD4 lymphocyte count, HIV viral load, microbiological isolates and their susceptibility profile, empirical antibiotic treatment, definitive antibiotic therapy, and 30-day mortality. A case (HIV-infected)–control (non-HIV-infected) sub-analysis was performed with a ratio of 1:2, matching patients for age, gender, baseline disease, and etiological microorganism. Wherever feasible, the match with the closest year of BSI was chosen.

This study was performed in accordance with the Helsinki Declaration, and followed privacy laws regarding active anonymity. This study was approved by the Ethics Committee Board of our institution (Comité de Ética de la Investigación con medicamentos, Hospital Clínic de Barcelona) with the following approval verdict: HCB/2019/0764. Informed consent was waived due to the retrospective nature of the study.

Definitions

Patients with febrile neutropenia were defined as those who had a single oral temperature measurement of >38.3 °C or of >38.0 °C sustained over a 1-h period, and an absolute neutrophil count of <500 cells/mm^3 [17]. Prior antibiotic therapy was defined as the use of any antimicrobial agent for ≥ 3 days during the month prior to the occurrence of the bacteremia episode [18]. Since 1995, according to the protocols of our hospital, patients with expected neutropenia over 10 days received prophylaxis with fluoroquinolone [19]. Breakthrough bacteremia was defined as a BSI occurring despite the patient receiving antibiotic treatment that was active against the isolated pathogen. Chronic renal failure was defined as an abnormality of kidney structure or function, present for >3 months, with a decreased glomerular filtration rate (<60 ml/min/1.73 m^2). For HIV viral load and CD4 cell count, the most recent value available before the BSI was considered. Corticosteroid therapy was defined as the use of a dose ≥ 20 mg of daily prednisone or equivalent. Nosocomial infection was defined as that occurring 48 h after hospital admission. Healthcare-associated infection was defined when the subject met at least one of the following criteria: recent hospitalization (within the last 30 days), admission from long-term care facility, and chronic hemodialysis or intravenous treatment during the previous month. The remaining patients were classified as community-acquired [19]. BSI was considered to be from an unknown or endogenous source where no other source was identified. Catheter-related infections were defined as: (1) at least one positive blood culture and a positive semi-

quantitative catheter-tip culture with growth of the same microorganism, and (2) a positive paired central and peripheral blood culture that grew the same microorganism; i.e., the former blood culture was positive ≥ 2 h earlier, or the site of insertion of vascular access showed signs of infection [19, 20]. Overall mortality was defined as death by any cause within the first 30 days of BSI onset.

Microbiological Methods

Blood samples were processed using the BACTEC 9240 system or BACTEC FX system (Becton–Dickinson Microbiology Systems), with an incubation period of 5 days. Isolates were identified by standard techniques. Antimicrobial susceptibility testing was performed by using a microdilution system (Microscan WalkAway; Dade Behring, West Sacramento, CA, USA, or Phoenix system; Becton Dickinson, Franklin Lakes, NJ, USA) or the Etest (Biodisk: Solna, Sweden/bioMérieux, Mercy l'Etoile, France). Current Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for each year were used to define susceptibility or resistance to these antimicrobial agents, and intermediate susceptibility was considered as resistance [6]. Viral load limit of detection varied over time. A cut-off of < 50 copies/mL was considered as undetectable.

Statistical Analysis

Categorical variables were described by counts and percentages, whereas continuous variables were expressed as means and standard deviations (SD) or medians and interquartile ranges (IQRs). Pearson's chi-squared test and the Mann–Whitney *U* test or Student's *t* test were used to compare the distribution of categorical and continuous variables, respectively. Chi-squared for trend was used to compare the HIV characteristics over time. Factors associated with 30-day mortality in the case–control cohort were assessed using logistic regression models. All analyses were performed with SPSS software (v.18.0; SPSS, Chicago, IL, USA).

RESULTS

Between 1997 and 2018, a total of 1755 episodes of bacteremia were documented in patients with neutropenia following chemotherapy. Of these, 60 (3.4%) episodes were identified in patients with HIV infection (Fig. 1).

Characteristics of HIV-Infected Patients Regarding their Baseline Disease

Table 1 details the characteristics of patients with HIV in relation to baseline disease, and compares these characteristics in terms of patient mortality as a result of the bacteremia. The most prevalent risk behavior was that of men who have sex with men (46.7%), 58.3% had < 200 CD4, and 70% met AIDS-defining criteria. Overall, 38.3% had a positive HIV-1 RNA viral load prior to the bacteremia episode, with a mean viral load of 484,982 copies/mL (SD 934,076). Most patients (91.4%) were on ART at the time of the BSI; a protease inhibitor-based ART was the most common regimen (53.0%) and median time since initiation of treatment was 23 months (IQR 4–48). ART regimens including a nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) were more prevalent among those who survived ($p = 0.019$). Additionally, 14 (25.0%) patients had hepatitis C virus (HCV), 12 (21.4%) hepatitis B virus (HBV) and 6 (10.0%) both.

Table 2 displays the evolution of HIV characteristics over time. Throughout the study period, no changes were observed in risk behaviors, CD4 counts, and rates of patients receiving ART or meeting AIDS criteria. However, the percentage of patients with detectable viral load decreased over time ($p = 0.046$), and the percentage of patients receiving an integrase inhibitor increased ($p < 0.001$).

Comparison of Bacteremia Episodes in Cancer Patients with and Without HIV Infection

Table 3 compares bacteremia episodes according to the patient's HIV status. Patients with

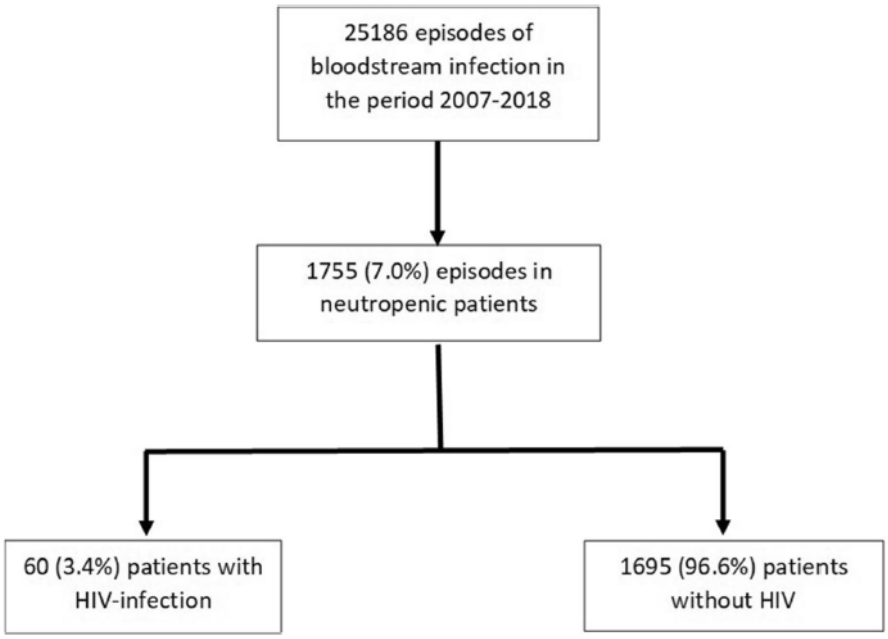

Fig. 1 Flowchart of bloodstream infection episodes

HIV were younger, more frequently male, and more commonly presented with chronic liver disease ($p < 0.001$ for all). Conversely, HIV-infected patients underwent significantly fewer hematopoietic stem cell transplantations (HSCT) ($p < 0.001$).

There was no difference in the source of bacteremia. BSI due to *Enterococcus* spp. was significantly more frequent among patients with HIV ($p = 0.017$), with no differences in other pathogens. Finally, HIV-infected patients presented with shock and required intensive care unit (ICU) admission more frequently ($p = 0.014$ and $p = 0.006$, respectively) and experienced higher mortality (31.7% vs. 18.1%, $p = 0.008$).

Supplementary Table 1 shows the changes over time in the main causative agents and their antimicrobial susceptibility.

Prognostic Factors in HIV-Infected Patients with Cancer

An analysis of risk factors for mortality was performed by selecting only those patients with HIV-infection and cancer. In the univariate study, diabetes mellitus ($p = 0.031$), abdominal source ($p = 0.028$), shock ($p = 0.026$), and *E. coli* BSI ($p = 0.023$) were associated with higher mortality. However, ART containing an NRTI ($p = 0.019$) and catheter-related bacteremia ($p < 0.001$) were associated with lower mortality. Patients with HIV infection and a detectable viral load showed a trend to higher mortality (43.5% vs. 24.3%, $p = 0.121$), while those receiving ART showed a trend to have lower mortality (28.3% vs. 60.0%, $p = 0.167$).

In multivariate analysis, factors independently associated with increased mortality in patients with HIV-infection and cancer were diabetes mellitus (OR 23.962, 95% CI 1.882–305.102) and shock (OR 9.918, 95% CI 2.093–46.998).

Table 1 Characteristics of patients with HIV regarding their baseline disease

	Episodes $n = 60$ (%)	Alive $n = 41$ (%)	Dead $n = 19$ (%)	p value
Risk behavior				
MSM	28 (46.7)	18 (43.9)	10 (52.6)	0.528
Heterosexual	18 (30.0)	13 (31.7)	5 (26.3)	0.672
IVDU	9 (15.0)	5 (12.2)	4 (21.1)	0.445
Unknown	5 (8.3)	5 (12.2)	0 (0)	0.168
Prior CD4 count				
< 100	21 (35.0)	14 (34.1)	7 (36.8)	0.839
101–200	14 (23.3)	8 (19.5)	6 (31.6)	0.304
201–350	8 (13.3)	7 (17.1)	1 (5.3)	0.416
> 350	10 (16.7)	7 (17.1)	3 (15.8)	1.000
NA	7 (11.7)	5 (19.2)	2 (16.7)	1.000
Detectable viral load				
Yes	23 (38.3)	13 (31.7)	10 (52.6)	0.121
No	31 (51.7)	23 (56.1)	8 (42.1)	0.313
NA	6 (10.0)	5 (12.2)	1 (5.3)	0.654
AIDS criteria	42 (70.0)	29 (72.5)	13 (68.4)	0.747
ART	53 (91.4)	38 (95.0)	15 (83.3)	0.167
ART family				
NRTI	46 (76.7)	35 (85.4)	11 (57.9)	**0.019**
NNRTI	14 (23.3)	7 (17.1)	7 (36.8)	0.092
PI	31 (51.7)	23 (56.1)	8 (42.1)	0.313
INSTI	16 (26.7)	11 (26.8)	5 (26.3)	0.967
Boosted	24 (40.0)	17 (41.5)	7 (36.8)	0.734

Significant p values in bold

MSM men who have sex with men, *IVDU* intravenous drug use, *NA* not available, *ART* antiretroviral treatment, *NRTI* nucleoside reverse transcriptase inhibitors, *NNRTI* non-nucleoside reverse transcriptase inhibitors, *PI* protease inhibitors, *INSTI* integrase inhibitors

Comparison of Cases and Controls

Table 4 shows the comparison between cases (HIV-infected) and controls (non-HIV-infected). Cases had chronic liver disease more frequently ($p = 0.003$), while controls more commonly had acute leukemia ($p = 0.013$) and HSCT ($p = 0.023$). There was a non-significant trend for cases to receive inappropriate empirical antibiotic treatment (IEAT) ($p = 0.206$), present with shock ($p = 0.105$), and have higher mortality ($p = 0.084$).

Table 2 Evolution of HIV characteristics over time

	1997–2003 $n = 16$ (%)	2004–2010 $n = 23$ (%)	2011–2018 $n = 21$ (%)	p value for trend
Risk behavior				
MSM	7 (43.8)	9 (39.1)	12 (57.1)	0.381
Heterosexual	4 (25.0)	10 (43.5)	4 (19.0)	0.592
IVDU	2 (12.5)	2 (8.7)	5 (23.8)	0.302
Unknown	3 (18.8)	2 (8.7)	0 (0)	**0.043**
Prior CD4 count				
< 100	6 (37.5)	4 (17.4)	11 (52.4)	0.264
101–200	3 (18.8)	8 (34.8)	3 (14.3)	0.651
201–350	2 (12.5)	5 (21.7)	1 (4.8)	0.421
> 350	3 (18.8)	4 (17.4)	3 (14.3)	0.714
NA	2 (20.0)	2 (16.7)	3 (18.8)	0.957
Detectable viral load				
Yes	9 (56.3)	9 (39.1)	5 (23.8)	**0.046**
No	5 (31.3)	13 (56.5)	13 (61.9)	0.076
NA	2 (12.5)	1 (4.3)	3 (14.3)	0.785
AIDS criteria	11 (68.8)	17 (73.9)	14 (66.7)	0.640
ART	13 (86.7)	20 (90.9)	20 (95.2)	0.368
ART family				
NRTI	13 (81.3)	13 (56.5)	20 (95.2)	0.220
NNRTI	2 (12.5)	8 (34.8)	4 (19.0)	0.747
PI	11 (68.8)	10 (43.5)	10 (47.6)	0.240
INSTI	0 (0)	3 (13.0)	13 (61.9)	< **0.001**
Boosted	4 (25)	10 (43.5)	10 (47.6)	0.181

Significant p values in bold

MSM men who have sex with men, *IVDU* intravenous drug use, *NA* not available, *ART* antiretroviral treatment, *NRTI* nucleoside reverse transcriptase inhibitors, *NNRTI* non-nucleoside reverse transcriptase inhibitors, *PI* protease inhibitors, *INSTI* integrase inhibitors

Prognostic Factors in the Case–Control Cohort

In the univariate analysis of the case–control cohort, diabetes mellitus ($p = 0.028$), myelodysplastic syndrome ($p = 0.020$), solid neoplasm ($p = 0.005$), pulmonary ($p < 0.001$), and abdominal source ($p = 0.030$), candidemia ($p = 0.001$), and shock ($p < 0.001$) were associated with increased mortality. Conversely, Hodgkin's lymphoma ($p = 0.030$) and catheter-related BSI ($p < 0.001$) were associated with decreased mortality.

Table 5 describes the prognostic factors in the case–control cohort. Factors independently associated with increased mortality were: myelodysplastic syndrome (OR 11.208, CI

Table 3 Comparison of bloodstream infection episodes in patients with and without HIV infection

	HIV $n = 60$ (%)	Non-HIV $n = 1695$ (%)	p value
Demographic characteristics and baseline disease			
Median age (IQR)	49 (38–59)	56 (43–66)	< **0.001**
Male sex	52 (86.7)	966 (57.0)	< **0.001**
Diabetes mellitus	5 (8.3)	134 (7.9)	0.904
COPD	1 (1.7)	68 (4.0)	0.729
Chronic liver disease	9 (15)	40 (2.4)	< **0.001**
Chronic renal failure	2 (3.3)	51 (3.0)	0.702
Solid neoplasia	6 (10.0)[a]	274 (16.2)	0.200
Hematologic malignancy	57 (95.0)	1489 (87.8)	0.093
Hematopoietic stem cell transplantation	1 (1.7)	449 (26.5)	< **0.001**
Episode characteristics			
Central venous catheter	46 (88.5)	1251 (89)	0.896
Corticosteroids	27 (45.8)	690 (42.5)	0.620
Bacteremia source			
Endogenous/unknown	27 (45.0)	914 (53.9)	0.173
Catheter-related	18 (30.0)	410 (24.2)	0.303
Pulmonary	6 (10.0)	112 (6.6)	0.302
Abdominal	3 (5.0)	46 (2.7)	0.233
Shock	17 (28.3)	275 (16.3)	**0.014**
ICU admission	10 (16.7)	121 (7.1)	**0.006**
Microbiological characteristics			
Gram-negative bacilli	32 (53.3)	865 (51.0)	0.726
E. coli	9 (15.0)	415 (24.5)	0.092
P. aeruginosa	10 (16.7)	212 (12.5)	0.341
Klebsiella spp.	3 (5.0)	102 (6.2)	1.000
Gram-positive cocci	24 (40.0)	784 (46.3)	0.340
CoNS	11 (18.3)	500 (29.5)	0.061
Enterococcus spp.	11 (18.3)	155 (9.1)	**0.017**
S. aureus	4 (6.7)	62 (3.7)	0.282
S. pneumoniae	1 (1.7)	14 (0.8)	0.408
Candidemia	5 (8.3)	67 (4.0)	0.093
Polymicrobial	7 (11.7)	151 (8.9)	0.463
Outcomes			

Table 3 continued

	HIV $n = 60$ (%)	Non-HIV $n = 1695$ (%)	p value
IEAT	19 (31.7)	405 (24.4)	0.198
30-day mortality	19 (31.7)	303 (18.1)	**0.008**

Significant p values in bold

IQR interquartile range, *COPD* chronic obstructive pulmonary disease, *BSI* bloodstream infection, *ICU* intensive care unit, *CoNS* coagulase-negative staphylococci, *IEAT* inappropriate empirical antibiotic treatment

[a] Including 3 patients with Kaposi's sarcoma and hematological malignancy

1.775–70.774), solid neoplasm (OR 5.283, CI 1.139–24.513), pulmonary source (OR 11.515, CI 2.504–52.961), abdominal source (OR 72.323, CI 2.752–1900.833), shock (OR 6.477, CI 2.254–18.613), and candidemia (OR 15.297, CI 4.298–54.453). Hodgkin's lymphoma as a baseline disease was protective (OR 0.077, CI 0.006–0.971). The goodness-of-fit of the multivariate model was evaluated using the Hosmer–Lemeshow test (0.439), and the discriminatory power of the score, evaluated by the area under the receiver operating characteristics curve, was 0.826 (95% CI 0.756–0.897), demonstrating a strong ability to predict mortality at 30 days. HIV was not an independent factor associated with mortality (OR 1.957, 95% CI 0.708–5.410, $p = 0.196$).

DISCUSSION

The current study describes the characteristics of BSI episodes in HIV-infected patients with cancer and febrile neutropenia following chemotherapy compared to patients without HIV infection, and evaluates the risk factors for mortality in this population. The most important findings were: (1) HIV-infected patients with cancer, febrile neutropenia, and BSI are younger, more commonly present chronic liver disease and enterococcal BSI, and undergo HSCT less frequently; (2) HIV-infected patients present with shock more frequently and have a higher mortality; (3) in patients with HIV and cancer, diabetes mellitus and shock are independent risk factors for mortality; (4) in the case–control cohort, independent risk factors for mortality were myelodysplastic syndrome, solid neoplasm, pulmonary source, abdominal source, shock and candidemia, while Hodgkin's lymphoma was protective; and (5) HIV infection by itself was not an independent risk factor associated with mortality.

Patients with HIV and cancer had different demographic and epidemiological characteristics that those patients without HIV. For example, patients with HIV received HSCT less frequently. This could be because most patients with HIV had lymphomas, whereby HSCT is indicated only in cases of relapse after first-line treatment. It is also possible that social problems or drug addiction contraindicated transplant or a discriminatory effect due to HIV status existed.

In this study, most patients with HIV and cancer were men who have sex with men with low prevalence of intravenous drug use. Although the present study evaluates a long period of time (21 years), this is in line with most current series in Western countries [21]. Most patients were on ART; however, 38.3% of patients had a detectable viral load prior to febrile neutropenia and only 16.7% had a CD4 count > 350. Furthermore, 70.0% met AIDS-defining criteria. A likely explanation for the high rates of detectable viral load and low CD4 counts despite high rates of ART could be that many patients were either late presenters who recently initiated ART and/or had begun treatment at the time of cancer diagnosis. Indeed, mean detectable viral loads were high and time since initiation of ART was mainly brief. Another possible explanation could be low adherence to ART, which is in turn related to a higher likelihood of developing cancer [8]. Unfortunately, we do not have data on

Table 4 Comparison of cases and controls matched by the main variables

	HIV $n = 60$ (%)	Non-HIV $n = 120$ (%)	p value
Demographic characteristics and baseline disease			
Median age (IQR)	49 (38–59)	52 (39–62)	0.432
Male sex	52 (86.7)	97 (80.8)	0.329
Diabetes mellitus	5 (8.3)	7 (5.8)	0.526
COPD	1 (1.7)	4 (3.3)	0.666
Chronic liver disease	9 (15.0)	3 (2.5)	**0.003**
Chronic renal failure	2 (3.3)	6 (5.0)	0.721
Solid neoplasia	6 (10.0)[a]	7 (6.1)	0.769
Hematologic malignancy	57 (95.0)	113 (94.2)	0.309
Type of hematologic malignancy			
Acute leukemia	2 (3.3)	19 (16)	**0.013**
MDS	3 (5.0)	5 (4.2)	1.000
Multiple myeloma	2 (3.3)	6 (5.0)	0.720
NHL	41 (68.3)	68 (57.1)	0.148
HL	9 (15)	13 (10.9)	0.433
Hematopoietic stem cell transplantation	1 (1.7)	15 (12.5)	**0.023**
Episode characteristics			
Corticosteroids	27 (45.8)	60 (50.0)	0.524
Bacteremia source			
Endogenous/unknown	27 (45.0)	62 (51.7)	0.399
Catheter-related	18 (30.0)	33 (27.5)	0.726
Pulmonary	6 (10.0)	8 (6.7)	0.431
Abdominal	3 (5.0)	3 (2.5)	0.402
Skin/soft tissues	3 (5.0)	6 (5.0)	1.000
Urinary	1 (1.7)	6 (5.0)	0.427
Mucositis	2 (3.3)	2 (1.7)	0.602
Neutropenia < 100	40 (66.7)	79 (69.9)	0.661
Shock	17 (28.3)	21 (17.8)	0.105
ICU admission	10 (16.7)	8 (6.7)	**0.035**
Microbiological characteristics			
Gram-negative bacilli	32 (53.3)	68 (56.7)	0.671
E. coli	9 (15.0)	22 (18.3)	0.577
P. aeruginosa	10 (16.7)	17 (14.2)	0.658

Table 4 continued

	HIV $n = 60$ (%)	Non-HIV $n = 120$ (%)	p value
Klebsiella spp.	3 (5.0)	10 (8.3)	0.548
Pseudomonas spp. (not *aeruginosa*)	3 (5.0)	5 (4.2)	1.000
Enterobacter spp.	1 (1.7)	6 (5.0)	0.427
Fusobacterium spp.	1 (1.7)	3 (2.5)	1.000
S. maltophilia	1 (1.7)	3 (2.5)	1.000
Proteus spp.	1 (1.7)	1 (0.8)	1.000
Serratia spp.	1 (1.7)	1 (0.8)	1.000
Bacteroides spp.	1 (1.7)	1 (0.8)	1.000
Other GNB[b]	1 (1.7)	2 (1.7)	1.000
Gram-positive cocci	24 (40.0)	52 (43.3)	0.670
CoNS	11 (18.3)	24 (20.0)	0.790
Enterococcus spp.	11 (18.3)	14 (11.7)	0.223
S. aureus	4 (6.7)	8 (6.7)	1.000
Streptococcus spp.	2 (3.3)	6 (5.0)	0.721
Other Gram-positive cocci[c]	0 (0)	2 (1.7)	0.553
Candidemia	5 (8.3)	11 (9.2)	0.853
Polymicrobial	7 (11.7)	12 (10.0)	0.732
Outcomes			
IEAT	19 (31.7)	27 (22.9)	0.206
30-day mortality	19 (31.7)	24 (20.0)	0.084

Significant p values in bold

IQR interquartile range, *COPD* chronic obstructive pulmonary disease, *MDS* myelodysplastic syndrome, *NHL* Non-Hodgkin's lymphoma, *HL* Hodgkin's lymphoma, *BSI* bloodstream infection, *ICU* intensive care unit, *CoNS* coagulase-negative staphylococci, *IEAT* inappropriate empirical antibiotic treatment

[a] Including 3 patients with Kaposi's sarcoma and hematological malignancy

[b] Including 1 *Acinetobacter* spp., 1 *Citrobacter* spp., and 1 *Clostridium* spp.

[c] Including 1 *Leuconostoc* spp., and 1 *Gemella haemolysans*

adherence of such patients prior to febrile neutropenia. Finally, the percentage of patients with a detectable viral load decreased over time, probably following the overall, gradually improved management of patients with HIV.

Protease inhibitor-based ART was the most commonly used regimen. Protease inhibitors are potent inhibitors of the cytochrome P450 3A4, and frequently cause problematic drug-drug interactions with several chemotherapeutic and immunosuppressive agents [22]. This can lead to increased toxicity and a potential delay in chemotherapy treatments. In this setting, non-boosted integrase inhibitors are increasingly being used due to a more favorable drug–drug interaction profile and better tolerability [23, 24], as observed in our cohort. Although this may have impact on the

Table 5 Prognostic factors in the case–control cohort

Risk factor	Odds ratio (95% confidence interval)	*p* value
Hodgkin's lymphoma	0.077 (0.006–0.971)	0.047
Myelodysplastic syndrome	11.208 (1.775–70.774)	0.010
Solid neoplasia	5.283 (1.139–24.513)	0.034
Pulmonary source	11.515 (2.504–52.961)	0.002
Abdominal source	72.323 (2.752–1900.833)	0.010
Shock	6.477 (2.254–18.613)	0.001
Candidemia	15.297 (4.298–54.453)	< 0.001
HIV-infection	1.957 (0.708–5.410)	0.196

Adjusted for: chronic liver disease, diabetes mellitus, chronic renal failure, HIV, corticosteroid use, catheter-related source, inappropriate empirical antibiotic treatment, coagulase-negative staphylococci bacteremia, *S. pneumoniae* bacteremia, intensive care unit requirement

outcomes of patients with HIV receiving chemotherapy, we found no differences regarding ART regimen, particularly in the setting of febrile neutropenic BSI.

In this study, patients with HIV and cancer experienced higher mortality than those without HIV. Several factors may explain this finding. In the overall cohort, patients with HIV more commonly presented some features associated with higher mortality in univariate analysis (besides HIV itself), e.g., chronic liver disease, enterococcal infection, IEAT, and shock. In the case–control cohort, despite matching for age, sex, baseline disease, and etiological microorganism, there was still a trend for patients with HIV to have higher mortality, and present with higher chronic liver disease and higher ICU requirement. It remains unclear why patients with HIV who develop BSI in the context of febrile neutropenia present with higher enterococcal infection, shock, and ICU requirement. As previously mentioned, the drug–drug interaction problem could have had an influence on prognosis. Co-infection rates with HCV and/or HBV in the HIV population was high, and this variable could have also impacted mortality, although this variable was not available in patients without HIV. It could also be possible that patients with HIV were a more vulnerable population after previous opportunistic infections or as a result of a more fragile baseline status. In fact, enterococcal infection has classically been associated with fragile patients, and reports of an increased prevalence in the HIV population already exist, although precise drivers are unknown [25, 26]. Lastly, defects in innate immunity and neutrophil function have been described in patients with HIV, comprising lower bactericidal ability, malfunctioning degranulation, and poor phagocytosis and chemotaxis [27]. This could have played a deleterious role in these patients; however, knowledge about such pathways in neutropenic patients with HIV is scarce.

Low CD4 cell count has been previously associated with prolonged febrile neutropenia and increased mortality due to infection following chemotherapy [28]. However, in this study, we describe the characteristics of patients who already present a BSI in the context of febrile neutropenia following chemotherapy, which is when many also have profound lymphopenia. In this setting, however, prior CD4 count was not found to be an independent predictor of mortality.

The strengths of this study are the large number of febrile neutropenic cancer patients with BSI included; the prospective collection of the data; the comprehensive clinical and microbiological data gathered; and the matched case–control comparison. Additionally, to our best knowledge, this is the first study to evaluate

the characteristics and outcomes of patients with HIV and cancer who develop BSI and febrile neutropenia.

There are, nonetheless, some limitations that should be acknowledged. The number of patients with HIV was relatively low, especially when considering the extended length of the study period. Continuous variations occur in the characteristics and treatments of patients with HIV, and larger, up-to-date studies are needed. Secondly, this study was conducted in a single center, and microbiological epidemiology varies significantly in different geographical contexts. Lastly, cases and controls were matched by several characteristics (including etiology) in an attempt to assess the true impact of HIV; however, this precluded any evaluation of potentially different etiological microorganisms in otherwise similar patients.

CONCLUSIONS

In conclusion, in comparison to controls, overall HIV-infected patients with cancer who develop febrile neutropenia and a BSI have different epidemiological and clinical profiles, and experience higher mortality. However, in the case–control study, HIV infection by itself was not associated with mortality.

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Compliance with Ethics Guidelines. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments, and followed privacy laws regarding active anonymity. This study was approved by the Ethics Committee Board of our institution (Comité de Ética de la Investigación con medicamentos, Hospital Clínic de Barcelona) with the following approval verdict: HCB/2019/0764. Informed consent was waived due to the retrospective nature of the study.

Data Availability. The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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7•6 Risk Factors for Mortality in Hematopoietic Stem Cell Transplantation Recipients with Bloodstream Infection: Points To Be Addressed by Future Guidelines.

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Resumen:

Introducción: En años recientes, se han descrito cambios epidemiológicos significativos en los receptores de trasplante de células madre hematopoyéticas y bacteriemia. Se ha observado un incremento en BGN y BGN-MR. Estos cambios han sido asociados con un preocupante aumento en la mortalidad.

Nuestro objetivo fue definir los factores de riesgo para la mortalidad de pacientes con trasplante de células madre hematopoyéticas y bacteriemia.

Métodos: Se recolectaron prospectivamente todos los episodios de bacteriemia en pacientes con trasplante de células madre hematopoyéticas entre 2008 y 2017. Se realizaron análisis multivariados para determinar los factores de riesgo.

Resultados: Se documentaron un total de 402 episodios de bacteriemia en 293 pacientes sometidos a trasplante de células madre hematopoyéticas (75.4% alogénicos, 32.3% autólogos, 19.3% segundo trasplante de células madre hematopoyéticas). El tiempo medio desde el trasplante de células madre hematopoyéticas hasta la bacteriemia fue de 62 días. Los cocos gram-positivos representaron el 56.7% de los episodios y los BGN, el 42%. Los microorganismos más comunes fueron estafilococos coagulasa-negativos (30.6%) y *P. aeruginosa* (15.9%). Los BGN-MR causaron el 11.9% de todos los episodios. Las características clínicas, origen de la bacteriemia, etiología y resultados variaron según el tiempo transcurrido desde el trasplante de células madre hematopoyéticas. Globalmente, el 26.6% de los episodios fueron tratados con terapia antibiótica empírica inapropiada, con mayor frecuencia en episodios de BSI causados por *P. aeruginosa, P. aeruginosa* MR y BGN-MR. La mortalidad a 30 días fue del 19.2%. Los factores de riesgo independientes para la mortalidad fueron BSI ocurriendo 30 días después del trasplante de células madre hematopoyéticas, shock, bacteriemia causada *por P. aeruginosa* MR, y terapia antibiótica empírica inapropiada para BGN o *Candida* spp.

Conclusión: Los receptores de trasplante de células madre hematopoyéticas que experimentan bacteriemia tienen alta mortalidad relacionada con factores del huésped, factores del procedimiento, microorganismo causante y terapia antibiótica empírica. Es esencial desarrollar estrategias para identificar receptores de trasplante de células madre hematopoyéticas con riesgo de *P. aeruginosa* MR y reducir la terapia antibiótica empírica inapropiada para disminuir la mortalidad.

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Risk Factors for Mortality in Hematopoietic Stem Cell Transplantation Recipients with Bloodstream Infection: Points To Be Addressed by Future Guidelines

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A B S T R A C T

In recent years, important epidemiologic changes have been described in hematopoietic stem cell transplantation (HSCT) recipients with bloodstream infection (BSI), with increases in gram-negative bacilli and multidrug resistant (MDR) gram-negative bacilli. These changes have been linked to a worrisome increase in mortality. We aimed to define the risk factors for mortality of HSCT patients experiencing BSI. All episodes of BSI in patients with HSCT between 2008 and 2017 were prospectively collected. Multivariate analyses were performed. A total of 402 BSI episodes were documented in 293 patients who had undergone HSCT (75.4% allogenic, 32.3% autologous, 19.3% second HSCT). The median time from HSCT to BSI was 62 days (interquartile range, 9 to 182 days). Gram-positive cocci accounted for 56.7% of the episodes; gram-negative bacilli, for 42%. The most common microorganisms were coagulase-negative staphylococci (30.6%) and *Pseudomonas aeruginosa* (15.9%). MDR gram-negative bacilli caused 11.9% of all episodes. Clinical characteristics, source of BSI, etiology, and outcomes changed depending on time since HSCT. Globally, 26.6% of episodes were treated with inappropriate empiric antibiotic therapy, more frequently in BSI episodes caused by *P. aeruginosa*, MDR *P. aeruginosa*, and MDR gram-negative bacilli. The 30-day mortality was 19.2%. Independent risk factors for mortality were BSI occurring ≥30 days after HSCT (odds ratio [OR], 11.21; 95% confidence interval [CI], 4.63 to 27.19), shock (OR, 7.10; 95% CI, 2.98 to 16.94), BSI caused by MDR *P. aeruginosa* (OR, 4.45; 95% CI, 1.12 to 17.72), and inappropriate empiric antibiotic therapy for gram-negative bacilli or *Candida* spp. (OR, 3.73; 95% CI, 1.27 to 10.89). HSCT recipients experiencing BSI have high mortality related to host and procedure factors, causative microorganism, and empiric antibiotic therapy. Strategies to identify HSCT recipients at risk of MDR *P. aeruginosa* and reducing inappropriate empiric antibiotic therapy are paramount to reduce mortality.

INTRODUCTION

Bloodstream infection (BSI) is a major cause of morbidity and mortality after hematopoietic stem cell transplantation (HSCT) [1-3]. The epidemiology of BSI in hematologic patients has been changing recently, with a decrease in gram-positive cocci, an increase in gram-negative bacilli, and a significant rise in multidrug-resistant (MDR) gram-negative bacilli [4-7].

In this new epidemiologic era, very few studies have evaluated the impact of an increasing MDR isolation and empiric antibiotic adequacy as risk factors for mortality in HSCT recipients with BSI [6,8]. This is very important, as international guideline recommendations for empiric antibiotic regimens have not changed in recent years [9,10]. Comprehensive

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knowledge of the factors associated with increased mortality in HSCT recipients with BSI is mandatory to optimize patient management and improve prognosis.

Here we aimed to define the risk factors for mortality in HSCT recipients with BSI in the last 10 years of our experience, with particular emphasis on BSI etiology and appropriateness of empiric antibiotic therapy.

METHODS

Setting and Data Collection

This study was performed at Hospital Clinic of the University of Barcelona, a 700-bed university center that provides broad and specialized medical, surgical, and intensive care attention for an urban population of 500,000 people. During the 10-year study period, a total of 1013 HSCTs were performed at the center, of which 503 were allogenic and 510 were autologous. Throughout this same period, our institution oversaw a blood culture surveillance program, identifying all patients with bacteremia. The program sought to collect epidemiologic, clinical, laboratory, and microbiological data, as well as information on prior and current treatment and outcomes. After thorough evaluation, a senior infectious disease specialist determined the source of infection and introduced the data gathered into a specific database.

Study Population and Design

We analyzed all consecutive episodes of BSI occurring in patients who had undergone HSCT between 2008 and 2017 at any time after transplantation. Data were prospectively collected and retrospectively analyzed. For this specific study, more specific data regarding transplantation variables were reviewed retrospectively. The study was approved by the Ethics Committee Board of our institution (HCB/2018/0010). These episodes have been previously reported as part of a 25-year epidemiologic description of BSI episodes in our HSCT cohort [7]. The present study focused on the risk factors for mortality in the last 10 years of that cohort.

Definitions

Neutropenia was defined as an absolute neutrophil count of <500 cells/mm^3. Definitions for comorbidities, site of infection, catheter-related infections, prior antibiotic therapy, inappropriate empiric antibiotic therapy, and overall and transplantation-related mortality have been reported previously [7]. In accordance with hospital protocols, all patients received prophylaxis with a fluoroquinolone and an azole following transplantation. Antibiotic therapy at the onset of BSI was defined as any antibiotic already being administered to a patient (including prophylaxis) when blood cultures were drawn. Previous infection was defined as any infection (bacterial, viral, fungal, or parasitic) occurring in the 30 days prior to BSI. Gram-negative bacilli were classified as MDR or extensively drug-resistant according to previously published definitions [11]. In those patients who underwent a second HSCT, BSI always occurred after the second HSCT.

Microbiological Methods

Blood samples were handled using either the BACTEC 9240 system or BACTEC FX system (BD Diagnostic Systems, Wokingham, UK), with an incubation period of 5 days. Isolates were recognized with standard techniques. Antimicrobial susceptibility testing was performed with either a microdilution system (Microscan WalkAway; Dade Behring, West Sacramento, CA or the Phoenix system; BD, Franklin Lakes, NJ) or the Etest (AB Biodisk, Solna, Sweden/bioMérieux, Marcy l'Etoile, France). Clinical and Laboratory Standards Institute or European Committee on Antimicrobial Susceptibility Testing breakpoints for each respective year were used to define susceptibility or resistance to these antimicrobial agents; intermediate susceptibility was considered resistance. Extended-spectrum beta-lactamases (ESBLs) were detected by MIC results, as well as by a double-disk synergy test using disks containing cefotaxime, ceftazidime, and cefepime that are applied to plates next to a disk with clavulanic acid.

Statistical Analysis

Categorical variables were recorded as count and percentage, and continuous variables were recorded as mean and SD or median and interquartile range (IQR). The Pearson chi-squared test and either the Mann-Whitney *U* test or the Student *t* test were used to compare the distributions of categorical and continuous variables, respectively. Three different multivariate regression models (step-forward procedure) were used to identify the independent risk factors for mortality, independent risk factors for MDR *Pseudomonas aeruginosa* BSI, and independent risk factors for receiving inappropriate empiric antibiotic therapy. The analysis of the risk factors for mortality was based on the total number of subjects with 1 or more BSIs (instead of total episodes of BSI). The goodness of fit of the multivariate models was assessed with the Hosmer-Lemeshow test and area under the receiver operating characteristic curve. The threshold for statistical significance was defined as a 2-tailed *P* value <.05. All analyses were performed using SPSS version 25.0 (IBM, Armonk, NY).

Table 1
HSCT Status, Immunosuppression, and Clinical Characteristics at BSI Onset (N = 402 Episodes)

Characteristic	Value
HSCT status	
Post-transplantation status, n (%)	
Complete response	193 (48)
Relapse	74 (18.4)
Graft failure	27 (6.7)
Not evaluable	108 (26.9)
Prior month conditions, n (%)	
Chemotherapy	231 (57.5)
GVHD	174 (43.3)
Corticosteroid therapy	243 (60.4)
Tacrolimus	98 (24.4)
Second- or third-line therapy for GVHD	57 (14.2)
Any immunosuppression*	324 (80.6)
Site of acquisition, n (%)	
Nosocomial	265 (65.9)
Healthcare	137 (34.1)
Clinical conditions	
Neutropenia, n (%)	217 (54)
Profound neutropenia (<100), n (%)	193 (48)
Days of neutropenia, median (IQR)†	14 (9-21)
Prolonged neutropenia (>7 d), n (%)	173 (43)
Previous antibiotic therapy (last month), n (%)	250 (62.2)
Quinolone prophylaxis, n (%)	132 (32.8)
Antibiotic therapy at the time BSI developed, n (%)‡	221 (55)
Previous infection, n (%)	261 (64.9)
Type of previous infection, n (%)	
Bacterial	180 (44.8)
Viral	81 (20.1)
Fungal	16 (4)
Parasitic	5 (1.2)
Source of bacteremia	
Endogenous/unknown	187 (46.5)
Catheter-related	134 (33.3)
Pulmonary	39 (9.7)
Urinary tract	14 (3.5)
Skin and soft tissue infection	10 (2.5)
Abdominal	7 (1.7)
Other§	8 (2.0)
Missing data	3 (0.7)
Clinical presentation and empiric treatment, n (%)	
Shock	48 (11.9)
Inappropriate empiric antibiotic therapy	107 (26.6)
Outcomes, n (%)	
ICU requirement	108 (26.9)
30-day mortality	77 (19.2)
Related mortality	43 (10.7)

GVHD indicates graft-versus-host disease; ICU, intensive care unit.

* Considering those patients receiving chemotherapy, prednisone, tacrolimus, or second- or third-line therapy for GVHD.

† Considering only those patients who were neutropenic.

‡ Including those receiving quinolone prophylaxis.

§ Including 3 meningitis, 3 mucositis and 2 endocarditis.

Table 2
Most Frequent BSI-Causing Microorganisms (N = 402)

Microorganism	n (%)
Gram-negative bacilli	169 (42)
E. coli	54 (13.4)
ESBL*	17 (31.5)
P. aeruginosa	64 (15.9)
MDR*	31 (48.4)
Carbapenem-resistant*	36 (56.3)
XDR*	30 (46.9)
K. pneumoniae	22 (5.5)
ESBL*	0 (0)
S. maltophilia	8 (2)
Gram-positive cocci	228 (56.7)
CoNS	123 (30.6)
Enterococcus spp	62 (15.4)
*E. faecalis**	33 (53.2)
*E. faecium**	30 (48.4)
S. aureus	13 (3.2)
MRSA*	4 (30.8)
Streptococcus spp	32 (8)
*S. pneumoniae**	18 (56.3)
Candida spp	16 (4)
*C. albicans**	1 (6.3)
C. non-*albicans**	15 (93.7)
Polymicrobial	33 (8.2)
MDR-GNB	48 (11.9)
Any MDR	51 (12.7)

XDR indicates extensively drug-resistant; CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *S. aureus*; GNB, gram-negative bacilli.
Overall, there were 435 microorganisms because there were 33 polymicrobial episodes. Apart from the gram-negative bacilli and gram-positive cocci listed in the table, there were 2 gram-negative cocci (1 *Moraxella atlantae* and 1 *Neisseria flava*), 7 gram-positive bacilli (2 *Listeria monocytogenes*, 3 *Bacillus* spp, and 2 *Rothia* spp), and 3 gram-variables (*Leptotrichia* spp). In addition, there were 9 episodes with 2 different gram-positive cocci isolated and 1 episode with 2 different gram-negative bacilli.

* Percentage among their species.

RESULTS

Patient Characteristics

Throughout the study period, 402 BSI episodes occurred in 293 patients who had undergone HSCT. Supplementary Table S1 describes the main cohort characteristics, including comorbidities, baseline disease, and transplantation characteristics. Table 1 shows HSCT status, immunosuppression, and clinical characteristics at BSI onset.

BSI Epidemiology and Treatment

The median time from HSCT to BSI was 62 days (IQR, 9 to 182 days). Table 2 details the most frequent causative microorganisms. Gram-positive cocci accounted for 56.7% of episodes; gram-negative bacilli, for 42%. There were also 33 (8.2%) polymicrobial episodes and 16 (4%) candidemias (15 non-*albicans*). Among gram-positive cocci, the most common microorganisms were coagulase-negative staphylococci (30.6%) and *Enterococcus* spp (15.4%). The most frequent gram-negative bacilli was *P. aeruginosa* (15.9%), followed by *Escherichia coli* (13.4%) and *Klebsiella pneumoniae* (5.5%). Overall, there were 48 (11.9%) episodes caused by MDR gram-negative bacilli: 31 MDR *P. aeruginosa* (accounting for 48.4% of all pseudomonal BSIs) and 17 ESBL *E. coli* (31.5% of all *E. coli* BSIs).

Figures 1 and 2 present clinical characteristics, source of BSI, etiology, and outcomes with respect to time after HSCT. Three different periods were set: <30 days, 30 to 100 days, and >100 days after HSCT. Rates of neutropenia at BSI decreased with time since transplantation, whereas rates of graft-versus-host disease and prior infection increased. Regarding the source of BSI, endogenous source decreased with time, while pulmonary and other sources increased. Regarding etiology, rates of gram-negative bacilli increased with time since transplantation owing to a decrease in coagulase-negative staphylococci and increases in *K. pneumoniae* and *P. aeruginosa*. Candidemia was also augmented. Finally, all inappropriate treatment, need for intensive care unit admission, shock, and mortality were higher in BSIs occurring later after transplantation.

Characteristics of Episodes Receiving Inappropriate Empiric Antibiotic Therapy

Overall, 26.6% of BSI episodes received inappropriate empiric antibiotic therapy. Baseline disease, HSCT, and BSI characteristics did not differ in appropriateness of empiric treatment, except in cases of neutropenic patients, who received inappropriate empiric antibiotic therapy less frequently ($P = .047$). Regarding etiology, inappropriate empiric antibiotic therapy was less frequent in episodes caused by *Streptococcus pneumoniae* ($P = .005$) and *E. coli* ($P < .001$). Conversely, BSI episodes caused by *P. aeruginosa* (45.3% versus 23.1%; $P < .001$), MDR *P. aeruginosa* (61.3% versus 23.7%; $P < .001$), and MDR gram-negative bacilli (45.8% versus 24%; $P = .001$) received inappropriate empiric antibiotic therapy more frequently. Supplementary Table S2 shows univariate and multivariate analysis for receiving inappropriate empiric antibiotic therapy.

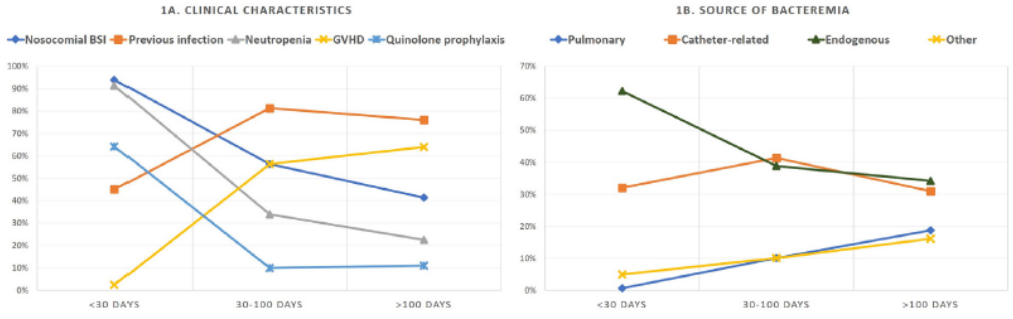

Figure 1. Changes in clinical characteristics (A) and source of BSI (B) depending on the time since transplantation.

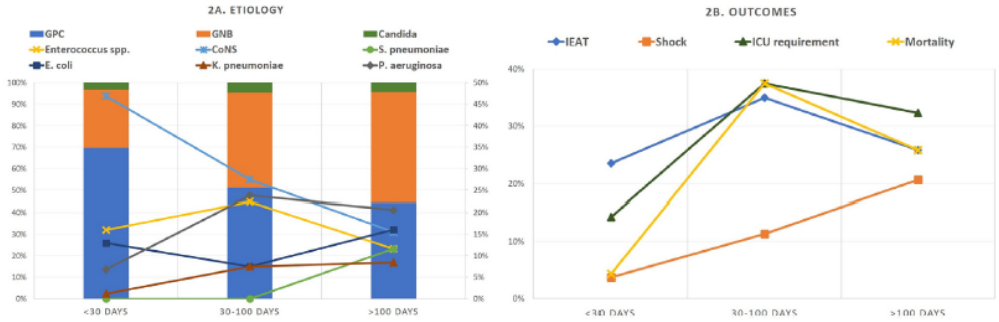

Figure 2. Changes in etiology (A) and outcomes of BSI (B) depending on the time since transplantation. Regarding etiology (A), left axis is referred to rates of gram-negative bacilli, gram-positive cocci, and *Candida*, and the right axis is referred to the rates of specific microorganisms.

Clinical Course, Outcomes, and Risk Factors for Mortality

Overall, 11.9% of all episodes presented with shock, and 30-day mortality was 19.2% when considering the different episodes of BSI and 19.1% when considering the 293 patients with BSI episodes. Table 3 presents the results of univariate and multivariate analyses of risk factors for mortality. In the multivariate analysis, independent risk factors for mortality were BSI occurring ≥30 days after HSCT (odds ratio [OR], 11.21; 95% confidence interval [CI], 4.63 to 27.19), shock (OR, 7.10; 95% CI, 2.98 to 16.94), BSI caused by MDR *P. aeruginosa* (OR, 4.45; 95% CI, 1.12 to 17.72), and BSI caused by gram-negative bacilli or *Candida* spp. receiving inappropriate empiric antibiotic therapy (OR, 3.73; 95% CI, 1.27 to 10.89). The goodness of fit of the multivariate model was assessed with the Hosmer-Lemeshow test (0.855). The discriminatory power of the score, as evaluated by the area under the receiver operating characteristic curve, was 0.865 (95% CI, 0.819 to 0.911), demonstrating a very strong ability to predict overall mortality in patients with HSCT and BSI.

Risk Factors for BSI Caused by MDR P. aeruginosa

Because MDR *P. aeruginosa* was identified as an independent risk factor for mortality, risk factors for experiencing a BSI caused by MDR *P. aeruginosa* were specifically analyzed. Supplementary Table S3 shows the results of univariate and multivariate analyses for risk factors for BSI caused by MDR *P. aeruginosa.* In the multivariate analysis, independent risk factors for BSI caused by MDR *P. aeruginosa* were total body irradiation (TBI) (OR, 4.26; 95% CI, 1.50 to 12.07), cord blood transplantation (OR, 4.42; 95% CI, 1.07 to 18.31), prior immunosuppression (OR, 0.17; 95% CI, 0.05 to 0.54), nosocomial BSI (OR, 12.37; 95% CI, 3.31 to 46.18), quinolone prophylaxis (OR, 0.22; 95% CI, 0.07 to 0.75), pulmonary source of BSI (OR, 16.34; 95% CI, 4.98 to 53.62), and prior use of ceftazidime or piperacillin/tazobactam (OR, 7.40; 95% CI, 2.64 to 20.75). The goodness of fit of the multivariate model was assessed with the Hosmer-Lemeshow test (0.378). The discriminatory power of the score, as evaluated by the area under the receiver operating characteristic curve, was 0.886 (95% CI, 0.826 to 0.947), demonstrating a very strong ability to predict MDR *P. aeruginosa* in patients with HSCT and BSI.

DISCUSSION

In this study, we evaluated the characteristics and risk factors for mortality in 402 BSI episodes in HSCT recipients over a 10-year period. Overall, mortality of HSCT recipients experiencing a BSI is high. Risk factors for mortality are mainly related to host and procedure factors (time since BSI), severity of infection (shock), causative microorganism (MDR *P. aeruginosa*), and selection of empiric antibiotic therapy (inappropriate empiric antibiotic therapy for gram-negative bacilli or *Candida* spp.).

BSI occurring ≥30 days since HSCT was an independent risk factor for mortality. Some previous studies have also reported higher mortality in BSI occurring after engraftment [6,12]. As in those studies, episodes occurring close to transplantation were most commonly found to be endogenous BSI or catheter-related episodes caused mainly by coagulase-negative staphylococci; conversely, in later episodes, a pulmonary source was more frequent, as was *P. aeruginosa* BSI with septic shock. It is also likely that in the near-post-transplantation setting, patients are more closely monitored and more aggressively and promptly treated. Nonetheless, most patients still received immunosuppression in the month prior to BSI, and more than one-half of them had some prior infection. Finally, like in previous studies, patients with septic shock had higher mortality [6,13]. Further studies are needed to evaluate characteristics and optimal empiric treatments of hematologic patients presenting with septic shock in the current epidemiologic era.

P. aeruginosa is a frequent and worrisome cause of infection in HSCT recipients [8,12,14,15]. Most importantly, almost one-half of pseudomonal isolates in our cohort were MDR, and MDR *P. aeruginosa* represented two-thirds of all MDR isolates in the cohort. In addition, mortality in these MDR isolates was almost 50%. Most of these patients (61%) received inappropriate empiric antibiotic therapy, similar to other recent series [8,15]. The impact of inappropriate empiric antibiotic therapy on mortality in patients with MDR *P. aeruginosa*, other gram-negative bacilli BSI, or candidemia is enormous [3,14,16,17], yet despite the current epidemiologic context of increasing MDR *P. aeruginosa* and the appearance of new active antipseudomonal antibiotics, current febrile neutropenic guideline recommendations and HSCT protocols have not changed much in recent years [9,10]. Identifying patients at risk of MDR *P. aeruginosa* is essential to consider the empiric use of combination therapies and/or ceftolozane-tazobactam or ceftazidime-avibactam, if necessary. As in other previous studies [14,15], nosocomial BSI, pulmonary source, and prior exposure to antipseudomonal antibiotics were associated with an increased risk of MDR *P. aeruginosa*. Finally, despite the low occurrence of candidemia, this was associated with high mortality. Within the context of wide azole prophylaxis, almost all species were non-*albicans*. Identifying episodes of febrile

Table 3
Univariate and Multivariate Analysis of Risk Factors for Mortality

Factor	Survivors (N = 237)	Deaths (N = 56)	Univariate OR (95% CI)	*P* Value	Multivariate OR (95% CI)	*P* Value
Demographics						
Male sex	139 (58.6)	33 (58.9)	0.99 (0.55-1.79)	.970	-	-
Age >65 yr	22 (9.3)	6 (10.7)	1.17 (0.45-3.04)	.743	-	-
Hematologic disease						
Acute leukemia	84 (35.4)	17 (30.4)	0.79 (0.42-1.49)	.471	-	-
Hodgkin lymphoma	21 (8.9)	3 (5.4)	0.58 (0.17-2.03)	.588	-	-
Myelodysplastic syndrome	23 (9.7)	2 (3.6)	0.35 (0.08-1-51)	.186	-	-
Plasmatic cell disease	38 (16.0)	8 (14.3)	0.87 (0.38-1.99)	.746	-	-
HSCT						
Autologous	73 (30.8)	10 (17.9)	0.49 (0.23-1.02)	.053		
Allogenic	164 (69.2)	46 (82.1)	2.05 (0.98-4.23)	.053	-	-
Second HSCT	40 (16.9)	9 (16.1)	0.94 (0.43-2.08)	.884	-	-
≥30 d after HSCT	101 (42.6)	50 (89.3)	11.21 (4.63-27.19)	**<.001**	12.83 (4.44-37.10)	**<0.001**
Prior month conditions						
Neutropenia	146 (61.6)	24 (42.9)	0.50 (0.30-0.84)	**.011**	1.92 (0.85-4.34)	0.119
GVHD	79 (33.3)	32 (57.1)	2.67 (1.47-4.83)	**.001**	1.12 (0.44-2.85)	0.807
Corticosteroid therapy	129 (54.4)	40 (71.4)	2.09 (1.11-3.94)	**.021**	2.04 (0.95-4.39)	0.068
Tacrolimus	56 (23.6)	11 (19.6)	0.79 (0.38-1.63)	.523	-	-
Second- or third-line therapy for GVHD	27 (11.4)	8 (14.3)	1.30 (0.55-3.03)	.548	-	-
Any immunosuppression	188 (79.3)	41 (73.2)	0.71 (0.36-1.39)	.320	-	-
Previous infection	132 (55.7)	44 (78.6)	2.92 (1.46-5.80)	**.002**	1.15 (0.63-3.51)	0.368
Site of acquisition						
Nosocomial	158 (66.7)	35 (62.5)	0.83 (0.46-1.53)	.554	-	-
Healthcare	79 (33.3)	21 (37.5)	1.20 (0.66-2.20)	.554	-	-
Clinical conditions						
Antibiotic therapy when BSI developed	151 (63.7)	24 (42.9)	0.43 (0.24-0.77)	**.004**	2.33 (0.99-5.50)	0.053
Source of BSI						
Endogenous/unknown	119 (50.2)	19 (33.9)	0.51 (0.28-0.94)	**.028**	0.81 (0.35-1.87)	0.615
Catheter-related	80 (33.8)	15 (26.8)	0.72 (0.38-1.38)	.316	-	-
Pulmonary	16 (6.8)	14 (25.0)	4.60 (2.09-10.14)	**<.001**	1.87 (0.66-5.34)	0.241
Urinary	5 (2.1)	4 (7.1)	3.57 (0.93-13.75)	.071	-	-
Microorganisms						
Gram-negative bacteria	73 (30.8)	37 (66.1)	4.38 (2.368-8.12)	**<.001**	-	-
E. coli	28 (11.8)	9 (16.1)	1.43 (0.63-3.23)	.388	-	-
ESBL	5 (2.1)	3 (5.4)	2.63 (0.61-11.33)	.181	-	-
P. aeruginosa	19 (8.0)	19 (33.9)	5.89 (2.85-12.17)	**<.001**	-	-
MDR	7 (3.0)	10 (17.9)	7.14 (2.59-19.74)	**<.001**	4.45 (1.12-17.72)	**0.034**
Carbapenem-resistant	9 (3.8)	12 (21.4)	6.91 (2.75-17.38)	**<.001**	-	-
Gram-positive bacteria	157 (66.2)	23 (41.1)	0.36 (0.20-0.65)	**.001**	-	-
Coagulase-negative staphylococci	86 (36.3)	5 (8.9)	0.17 (0.07-0.45)	**<.001**	0.45 (0.15-1.39)	0.167
Enterococcus spp	40 (16.9)	12 (21.4)	1.34 (0.65-2.77)	.423	-	-
E. faecalis	21 (8.9)	5 (8.9)	1.01 (0.36-2.80)	.987	-	-
E. faecium	20 (8.4)	7 (12.5)	1.55 (0.62-3.87)	.345	-	-
S. aureus	9 (3.8)	3 (5.4)	1.43 (0.38-5.48)	.706	-	-
Candida spp.	6 (2.5)	3 (5.4)	2.66 (0.94-7.56)	.270	-	-
Polymicrobial	11 (4.6)	7 (12.5)	5.67 (1.25-5.70)	**.028**	2.61 (0.74-9.21)	.135
MDR GNB	12 (5.1)	13 (23.2)	5.67 (2.42-13.26)	**<.001**	-	-
Outcomes						
Shock	18 (7.6)	22 (39.3)	7.87 (3.83-16.18)	**<.001**	7.10 (2.98-16.94)	**<.001**
ICU requirement	44 (18.6)	33 (58.9)	6.29 (3.37-11.76)	**<.001**	-	-
Inappropriate empiric antibiotic therapy	50 (21.1)	19 (33.9)	1.92 (1.02-3.63)	**.042**	-	-
Inappropriate empiric antibiotic therapy for GNB or *Candida* spp)	14 (5.9)	13 (23.2)	4.82 (2.12-10.96)	**<.001**	3.73 (1.27-10.89)	**.016**

Significant *P* values ($P < .05$) are in bold type.
*Significant ($P < .05$) variables in univariate analysis were included in multivariate analysis, except for those that were collinear.

neutropenia with a high risk of candidemia is essential to consider the empiric use of echinocandins [18].

The strengths of this study are the prospective and thorough collection of most data by a senior specialist collecting and evaluation of all clinical and microbiological data, as well as the exhaustive description of HSCT characteristics. Moreover, the series is a large cohort with a high number of BSIs. Nonetheless, some limitations should be acknowledged. The study was conducted at a single center performing quinolone prophylaxis, and different microbiology and drug resistance patterns have been described in other areas.

In conclusion, the HSCT recipients in this study experiencing BSI faced high mortality related to host and procedure factors, the causative microorganism, empiric therapy, and clinical presentation. MDR isolates, especially MDR *P. aeruginosa*, were frequent. Inappropriate empiric antibiotic therapy for gram-negative bacilli and *Candida* spp. was independently associated with mortality. Strategies that help identify HSCT recipients at risk of MDR *P. aeruginosa* and reducing inappropriate empiric antibiotic therapy are paramount to reduce mortality.

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Conflict of interest statement: P.P-A. has received honoraria for talks on behalf of Gilead Science and Pfizer. C.G-V. has received honoraria for talks on behalf of Gilead Science, Merck Sharp and Dohme, Pfizer, Jannsen, Novartis and Lilly, as well as grant support from Gilead Science and Merck Sharp and Dohme. A.S. has received honoraria for talks on behalf of Merck Sharp and Dohme, Pfizer, Novartis, and Angellini, as well as grant support from Pfizer. J.M. has received honoraria for talks on behalf of Merck Sharp and Dohme, Pfizer, Novartis, and Angellini.

DATA AVAILABILITY

All data and databases will be completely available upon acceptance or request.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2021.03.017.

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8• DISCUSIÓN

La presente tesis doctoral está centrada en varios aspectos complementarios respecto a los desafíos actuales en el manejo de la NF y la bacteriemia en pacientes inmunodeprimidos con malignidad. En resumen, se han intentado abordar los siguientes aspectos: **i)** Características actuales de las infecciones documentadas en pacientes hematológicos con neutropenia febril, teniendo en cuenta los avances en las técnicas microbiológicas que nos permiten un diagnóstico optimizado; **ii)** Grado de resistencia a los antibióticos recomendados por las guías internacionales de NF en pacientes hematológicos con bacteriemia; **iii)** Impacto del tratamiento empírico inapropiado en pacientes neutropénicos con bacteriemia que se presentan con shock séptico; y por último, **iv)** Características particulares de dos poblaciones específicas como los pacientes infectados por VIH con NF y los pacientes receptores de TPH.

Conocer las potenciales causas de la NF e intentar obtener un diagnóstico microbiológico es fundamental para optimizar el tratamiento empírico y dirigido de estos pacientes. Además, las pruebas microbiológicas han mejorado su rendimiento en los últimos años y esto podría redundar en un diagnóstico más preciso. En este sentido, en nuestro primer estudio se ofrece una descripción exhaustiva de las pruebas microbiológicas empleadas y la posterior documentación de infecciones durante episodios de NF en la era actual. A diferencia de estudios previos que informaban de una incidencia relativamente menor de infecciones documentadas microbiológicamente, con una tasa media del 14-25% (29,68–70), nuestro estudio reveló una mayor incidencia de infecciones documentadas microbiológicamente (43.3%), que aumentó a más del 50% durante los segundos episodios o posteriores de NF.

La importante expansión de las herramientas de diagnóstico microbiológico, particularmente para las infecciones no bacterianas, y la investigación exhaustiva de la etiología más allá de

la bacteriemia, dilucidan las razones de nuestra elevada tasa de documentación microbiológica. Es destacable que los cultivos bacterianos, especialmente los hemocultivos, son las pruebas que se solicitaron con mayor frecuencia y también las que aportaron la mayor tasa de resultados positivos. La epidemiología descrita en nuestro estudio coincide con la de otros estudios centrados en infecciones bacterianas o fúngicas (71,72). Es importante destacar que nuestros resultados revelan una mayor incidencia de infecciones bacterianas documentadas a partir del segundo episodio de NF o posteriores, en particular con infecciones causadas por bacterias gramnegativas. Específicamente a partir del tercer episodio de NF, el 33% de las infecciones bacterianas por BGN se atribuyeron a *P. aeruginosa.* Este hallazgo sugiere que, a partir del segundo episodio de NF, la optimización del tratamiento antipseudomónico debería adaptarse en función de la epidemiología local de cada centro sanitario. Además, nuestro estudio refleja la revolución en el diagnóstico de las infecciones víricas y demuestra que un porcentaje significativo de los casos de NF se atribuyen a virus respiratorios. Como era de esperar, en el contexto de la pandemia mundial, la infección por SARS-CoV-2 fue la infección viral más prevalente. Sin embargo, cabe destacar que también se detectaron con frecuencia otros virus para los que carecemos de un claro conocimiento respecto al manejo óptimo, así como de tratamientos eficaces (como metapneumovirus, parainfluenza o rinovirus). Las investigaciones futuras deberán evaluar las estrategias de manejo óptimas para los pacientes neutropénicos con infecciones víricas respiratorias, incluida la posibilidad de suspender los antimicrobianos de amplio espectro en ausencia de coinfección bacteriana documentada.

El avance en la documentación etiológica de la infección en la NF no debe, sin embargo, eclipsar el hecho, igualmente importante, de que actualmente la mayoría de las pruebas microbiológicas solicitadas arrojan resultados negativos. Cabe destacar que incluso en esta población con una tasa de infección tan elevada, sólo el 7.2% de las muestras dieron algún resultado positivo. Entre las distintas pruebas, los hemocultivos, que son las muestras solicitadas con mayor frecuencia, presentaron el mayor rendimiento diagnóstico, con una tasa de positividad del 9.2%. Sin embargo, otras técnicas como los cultivos bacterianos diferentes de los hemocultivos, o las muestras urinarias, tuvieron un impacto mínimo en el diagnóstico etiológico de la NF. Además, el creciente potencial diagnóstico que ofrecen los Servicios de Microbiología se ve limitado por el aumento significativo en los costes del diagnóstico (73). En los próximos años, uno de los retos más importantes para clínicos y microbiólogos será evaluar la rentabilidad de cada técnica diagnóstica, así como establecer estrategias óptimas para racionalizar y economizar el diagnóstico (73,74). En este sentido, parece imperativo identificar a los pacientes con mayor probabilidad de obtener resultados positivos en cada prueba solicitada y reducir el número de pruebas que dan lugar a resultados negativos, quizás a través de técnicas de agrupación o el uso de inteligencia artificial.

Otro hallazgo importante derivado de nuestro estudio fue que la duración media de la fiebre fue significativamente mayor (3 días) cuando no se documentó una infección bacteriana. Esto es importante, ya que sugiere que la fiebre persistente tras dos días de tratamiento antimicrobiano tiene menos probabilidades de indicar una infección bacteriana y enfatiza el

valor de explorar otras etiologías y/o la interrupción temprana de la terapia antimicrobiana empírica.

Posteriormente, el segundo y tercer trabajo de esta tesis doctoral están dirigidos a describir el grado de resistencia a los antibióticos recomendados por las guías internacionales de NF en pacientes hematológicos con bacteriemia. En estos estudios multicéntricos, pudimos demostrar que la bacteriemia causada por BGN y lo que es más preocupante, por BGN-MR y por *P. aeruginosa* MR, es un problema frecuente en pacientes hematológicos con NF. Las recomendaciones actuales de las guías nacionales e internacionales de NF proponen el uso de β-lactámicos empíricos (5,56,57) que no son apropiados para más de un tercio de los BGN que se aíslan en los hemocultivos. Específicamente en *P. aeruginosa* más de un tercio de los casos estuvieron causados por cepas que eran resistentes al menos a uno de los β-lactámicos recomendados por las guías. Asimismo, en la cohorte multicéntrica analizada como parte de esta tesis doctoral, más del 20% y el 10% de los aislados de *P. aeruginosa* cumplían criterios de MR y extremadamente resistentes, respectivamente. No obstante, esto varió ampliamente entre centros. Estudios previos realizados en huéspedes inmunocomprometidos (46,48,75,76) también informaron de tasas de *P. aeruginosa* MR entre el 23% y el 33%. También se han publicado datos similares en pacientes no neutropénicos de una gran cohorte multicéntrica de España, donde el 26.2% de las cepas aisladas se clasificaron como MR y el 17.3% como extremadamente resistentes (77). Asimismo, hay que destacar que la resistencia a cada uno de los diferentes antibióticos β-lactámicos recomendados por las guías internacionales superó asimismo el 20% de casos (5,57).

De una forma estrechamente relacionada, la frecuencia reportada de tratamiento TAEI en pacientes hematológicos con bacteriemia es inaceptablemente alta, especialmente en aquellos pacientes que reciben tratamiento empírico con cefepime y/o aquellos con infecciones causadas por BGN-MR o *P. aeruginosa* MR. De hecho, es muy preocupante mostrar que casi el 20% de los episodios de bacteriemias por *P. aeruginosa* recibieron un TAEI, y este porcentaje se elevó hasta casi el 45% en aquellos casos con resistencia a al menos uno de los antibióticos β-lactámicos recomendados por las guías y/o en aquellas cepas MR. Estos resultados coinciden con los publicados previamente en poblaciones similares de otros países (78,79).

Esta información es extremadamente importante, dado que el TAEI se ha asociado con un incremento en la mortalidad en estudios previos realizados en pacientes neutropénicos con bacteriemia (20,67). En consonancia con la evidencia previa, en la cohorte de pacientes con bacteriemia por *P. aeruginosa*, el TAEI supuso un factor de riesgo independiente de mortalidad. Concretamente, los pacientes que recibieron antibióticos empíricos incorrectos presentaron el doble de probabilidad de morir. Estos hallazgos reiteran la necesidad urgente de realizar un abordaje personalizado para reducir el TAEI y posiblemente mejorar los resultados de supervivencia de forma secundaria. En este complejo escenario, pueden considerarse algunas estrategias. Un enfoque clásico y controvertido ha sido la adición rutinaria de un aminoglucósido a los regímenes antibióticos empíricos (80). Se sabe que los β-lactámicos y los aminoglucósidos son sinérgicos (81), y estudios recientes demuestran que la resistencia actual a los aminoglucósidos es baja. Un estudio internacional reciente, emparejado por puntuaciones de propensión, evaluó pacientes hematológicos con NF y

bacteriemia por BGN que recibían un tratamiento antibiótico empírico adecuado. En este estudio, el tratamiento combinado con un aminoglucósido se asociaba a una disminución significativa de la mortalidad sin un aumento significativo de las tasas de insuficiencia renal aguda (IRA) (82). Sin embargo, un gran metaanálisis centrado en el tratamiento empírico en pacientes neutropénicos no mostró beneficios en términos de mortalidad con la adición de un aminoglucósido. No obstante, la mayoría de los pacientes incluidos en dicho análisis no presentaban bacteriemia, y el metaanálisis incluía en su mayoría estudios realizados hace varios años, cuando las tasas de resistencia a los antimicrobianos eran mucho más bajas que en la era actual (83). También es importante destacar que la toxicidad asociada a los aminoglucósidos suscita una gran preocupación, y que algunos estudios han reportado una mortalidad excesivamente alta en pacientes neutropénicos que recibían monoterapia con aminoglucósidos cuando el antibiótico β-lactámico no era activo (84,85). Estos resultados reforzarían el concepto de que el beneficio potencial de la amikacina no reside en ampliar el espectro antimicrobiano, sino en el efecto sinérgico que se consigue junto a los β-lactámicos.

Una segunda estrategia para reducir el TAEI, sería identificar aquellos pacientes con riesgo de padecer bacteriemia por BGN-MR y así ampliar el espectro antibiótico y reducir el riesgo de TAEI. No obstante, el reconocimiento del subconjunto de pacientes que desarrollarán infecciones por BGN-MR en el momento en que los médicos han de elegir el tratamiento antibiótico empírico sigue siendo un gran desafío. Algunos estudios han identificado factores de riesgo de BGN-MR en pacientes hematológicos con bacteriemia (18,19,40,86) y también se han desarrollado estudios específicos sobre el riesgo de presentar una infección causada por *P. aeruginosa* MR (79,87,88). Sin embargo, estos estudios, sobre pacientes con

infecciones ya documentadas, no reflejan con exactitud el momento preciso en que un paciente desarrolla NF, que es cuando se ha de decidir el tratamiento antibiótico empírico. Además, todos estos estudios han utilizado pequeños conjuntos de datos adquiridos de forma manual, con variables locales frecuentemente limitadas que hacen que la extrapolación a otras áreas sea probablemente difícil. Adicionalmente, la mayoría de los factores de riesgo que han sido descritos son generales e inespecíficos, por lo que son poco aplicables a escenarios reales. Recientemente se ha publicado un estudio que utilizó un gran número de datos de alta calidad recogidos directamente de las historias clínicas electrónicas en el momento del diagnóstico de la NF (89). En este estudio, el uso de big data y técnicas de aprendizaje automático fueron capaz de predecir qué pacientes presentarían infección por BGN-MR con una tasa de precisión cercana al 80%. Pese al gran potencial de este enfoque, existen desafíos con respecto a la generalización de la utilidad de estas herramientas, la validación de la herramienta en diferentes hospitales, y las aplicaciones de dichas herramientas en la vida real. Por último, existen nuevos métodos de diagnóstico rápido que permiten acortar el tiempo necesario para identificar los aislados MR (90,91). No obstante, dado que estas técnicas están limitadas por su alto coste, la identificación de los pacientes con alto riesgo de infección por gérmenes MR podría ayudar a orientar el uso personalizado de estos prometedores métodos. Queda por investigar el papel que pueden desempeñar los cultivos de vigilancia en la identificación de pacientes con alto riesgo de MR.

Una última estrategia para reducir el TAEI se basaría en garantizar la administración de un β-lactámico activo. En este sentido, el uso de nuevos β-lactámicos recientemente disponibles como el cefiderocol, o de nuevas combinaciones de β-lactámico + inhibidor de β-lactamasa

como ceftazidima-avibactam (CAZ-AVI) o ceftolozano/tazobactam (así como otros disponibles próximamente), podría resultar una opción, dada su excelente cobertura frente a la mayoría de los aislados MR actuales. De hecho, estudios recientes han demostrado la eficacia de estos nuevos antibióticos en el tratamiento de infecciones causadas por gérmenes MR (92–94), y como estos antibióticos conservan la actividad frente a más del 90% de las cepas de *P. aeruginosa* MR (77). Asimismo, algunos estudios incluyendo pacientes hematológicos (95–98) han demostrado que el uso de estos nuevos β-lactámicos se asocia a desenlaces óptimos en pacientes con infecciones causadas por enterobacterias MR y también por *P. aeruginosa* MR (99–102). En un estudio realizado en el MD Anderson Cancer Center de Houston (EEUU), el tratamiento empírico con ceftolozano/tazobactam se asoció a mejores resultados clínicos que el tratamiento estándar (cefepime, meropenem o piperacilina/tazobactam) en pacientes con neoplasias hematológicas y NF (100). Sin embargo, en este mismo estudio, sólo 6 de los 100 pacientes incluidos presentaron una infección microbiológicamente documentada. En otro estudio, Bergas y colaboradores (99) compararon retrospectivamente ceftolozano/tazobactam frente a otros antibióticos en pacientes con neoplasias hematológicas y bacteriemia por *P. aeruginosa.* En dicho estudio, la mayoría de los episodios (91%) fueron causados por cepas MR, y el tratamiento con ceftolozano/tazobactam se asoció significativamente tanto con una menor necesidad de ventilación mecánica invasiva, así como con una reducción de la mortalidad. Este fármaco también ha demostrado una buena eficacia en pacientes reales con infecciones graves por Enterobacterales productores de BLEE (103). Teniendo en cuenta estos resultados, habría de considerarse el uso de ceftolozano/tazobactam como antibioterapia empírica en pacientes

con neoplasias hematológicas en aquellos centros con una tasa actual de resistencia de *P. aeruginosa* superior al 10% frente a uno de los tres β-lactámicos antipseudomónicos clásicos, así como con una incidencia baja de infecciones por Enterobacterales productores de carbapenemasas. En los hospitales con una incidencia elevada de infecciones por Enterobacterales productores de carbapenemasas, ceftazidima/avibactam podría ser una opción adecuada en pacientes con neoplasias hematológicas. Sin embargo, existen preocupaciones con el uso de estos nuevos fármacos en cuanto al aumento asociado de los costos y la potencial selección de resistencias (94). Por este motivo, se debe promover la reevaluación diaria y la desescalada precoz de antibióticos dentro de las 24-48 horas, siguiendo estrategias previamente documentadas (104,105).

En los primeros estudios que conforman esta tesis, hemos evaluado las características microbiológicas de los episodios de NF, así como las tasas de resistencia a los antibióticos recomendados en las guías internacionales y su impacto en una elevada frecuencia de TAEI. A continuación, en nuestro cuarto trabajo quisimos analizar el impacto de este TAEI en pacientes neutropénicos con bacteriemia que además presentaban un shock séptico. Para ellos llevamos a cabo un estudio también multicéntrico, en el que observamos que los pacientes neutropénicos con bacteriemia presentaban shock séptico de forma frecuente (16%), especialmente aquellos pacientes con neoplasias sólidas o que habían recibido corticosteroides. Este hecho ha sido reportado previamente (106–108) y puede estar relacionado con la mayor incidencia de bacteriemia de foco pulmonar en esta población.

De forma notable, la bacteriemia en pacientes con shock séptico estuvo causada esencialmente por BGN, predominantemente por *E. coli*, *P. aeruginosa* y *Klebsiella* spp. De

hecho, en nuestro estudio, estos tres patógenos juntos causaron más de tres cuartas partes de todos los episodios de bacteriemia en pacientes con shock séptico. Los BGN, y particularmente *E. coli*, se han asociado previamente con la presencia de shock séptico en pacientes neutropénicos (62,109,110). De forma relevante, y similar a un estudio coreano reciente (110), casi el 20% de los aislamientos de BGN que produjeron shock séptico fueron cepas MR. Por el contrario, los Cocos grampositivos causaron solo el 20% de los episodios de bacteriemia con shock séptico y aproximadamente un tercio de ellos fueron episodios polimicrobianos causados de forma conjunta con un BGN. No obstante, esto no fue inesperado ya que la mayoría de las bacterias grampositivas de esta cohorte eran patógenos poco virulentos como los estafilococos coagulasa-negativos y *Enterococcus* spp. causando episodios de bacteriemia relacionada con el catéter. Además, la prevalencia global de *S. aureus* y *Streptococcus* spp. fue relativamente baja.

La mortalidad en pacientes neutropénicos con bacteriemia y shock séptico fue extremadamente alta (55%). La mayoría de las series de pacientes con shock séptico y bacteriemia, basadas en pacientes no neutropénicos, informan de mortalidades notablemente inferiores que oscilan entre el 35% y el 45% (61,111,112). Esto pone de manifiesto el papel fundamental de los granulocitos en el control de la infección (2), enfatizando la importancia de un tratamiento precoz y eficaz para disminuir esta devastadora mortalidad en pacientes neutropénicos.

Las directrices sobre NF de la IDSA recomiendan añadir cobertura específica frente a grampositivos en pacientes con inestabilidad hemodinámica (5), a pesar de que los regímenes empíricos comunes ofrecen una cobertura pertinente para la mayoría de los

Cocos grampositivos, excluidos los estafilococos resistentes a la meticilina y *Enterococcus* spp. Sin embargo, en nuestra cohorte, no encontramos que la cobertura empírica específica frente a grampositivos tuviera un impacto significativo en la mortalidad. Varios estudios han demostrado la toxicidad debida a la vancomicina en pacientes neutropénicos (113), y los nuevos fármacos como la daptomicina podrían asociarse a un franco aumento de los costes. En vista de estos resultados, la cobertura específica de grampositivos es cuestionable en pacientes sin infección probada, sospecha de bacteriemia relacionada con el catéter o colonización por *Staphylococcus aureus* resistente a la meticilina (SARM).

En nuestro estudio, el tratamiento combinado con un β-lactámico más amikacina fue un factor independiente de menor mortalidad en pacientes con shock séptico, en comparación con aquellos pacientes que no recibieron la combinación de amikacina. Como se ha comentado previamente, un metaanálisis publicado hace unos años no logró demostrar ningún beneficio de la combinación de un β-lactámico y aminoglucósido en pacientes neutropénicos con cáncer (114). No obstante, este sigue siendo un tema controvertido. Por ejemplo, Martínez y colaboradores demostraron que la combinación con aminoglucósidos era capaz de reducir la mortalidad en pacientes con bacteriemia, pero solo en aquellos episodios que presentaban shock séptico o neutropenia (115). Como también se ha comentado previamente, se ha hipotetizado que un beneficio potencial del tratamiento combinado se derivaría de la ampliación del espectro antimicrobiano inicial y la consiguiente disminución de la probabilidad de realizar un TAEI (115). Sin embargo, en nuestro estudio, la amikacina como único antibiótico activo (básicamente cuando el microorganismo aislado era resistente a los β-lactámicos empíricos) se asoció de forma independiente con un aumento

de la mortalidad. Este hecho sugiere que el potencial beneficio de la combinación antibiótica se debe básicamente a un efecto sinérgico junto al β-lactámico (116).

La IRA se ha asociado frecuentemente a un aumento de la mortalidad en pacientes con shock. En este sentido, se podría especular que el papel protector de la amikacina en esta cohorte fuera secundario a una menor administración del fármaco en aquellos pacientes con IRA. Sin embargo, en el análisis multivariante realizado, tanto la IRA como el tratamiento combinado con amikacina se asociaron de forma independiente con la mortalidad.

Nuestro estudio refuerza la importancia de la adecuación del tratamiento β-lactámico para mejorar los desenlaces de los pacientes. Aproximadamente el 20% de los pacientes con shock séptico recibieron un TAEI, y esto se debió principalmente a *P. aeruginosa* y *Candida* spp. De forma transcendente, la mortalidad en los episodios causados por BGN y *Candida* spp. que se presentaron con shock séptico y recibieron TAEI fue extremadamente alta (83% y 90%, respectivamente). Teniendo en cuenta que la "monoterapia" con amikacina se asociaba independientemente a un aumento de la mortalidad, garantizar un β-lactámico activo es esencial para mejorar el pronóstico de esta entidad altamente letal. En este sentido, los nuevos β-lactámicos como ceftazidima-avibactam y ceftolozano-tazobactam deben ser considerados como opciones terapéuticas empíricas para pacientes con un riesgo elevado de BGN-MR, incluso en forma de una asociación potencialmente sinérgica con carbapenems (117). Tras este abordaje inicial extenso y agresivo, la desescalada antibiótica precoz se puede realizar de forma segura (104,105) y debe ser prioritaria. Por último, identificar aquellos pacientes con riesgo de candidemia es fundamental a la hora de considerar la

cobertura de esta complicación relativamente infrecuente pero asociada a una elevadísima mortalidad (118).

Como conceptos finales, en el quinto y sexto estudio de esta tesis doctoral, quisimos analizar las características diferenciales de los episodios de bacteriemias en dos poblaciones específicas: los pacientes infectados por VIH con NF, y los pacientes receptores de un TPH.

En el estudio centrado en los pacientes infectados por VIH con cáncer y NF, estos se compararon con pacientes sin infección por el VIH, y se evaluaron los factores de riesgo de mortalidad en esta población. Los hallazgos más importantes de dicho estudio fueron: i) los pacientes infectados por el VIH con cáncer, NF y bacteriemia eran más jóvenes, presentaban con más frecuencia hepatopatía crónica y bacteriemia por *Enterococcus* spp., y se sometían con menor frecuencia a un TPH; ii) los pacientes infectados por el VIH presentaron con más frecuencia shock séptico y tenían una mayor mortalidad; iii) en los pacientes con VIH y cáncer, la diabetes mellitus y el shock séptico fueron factores de riesgo independientes de mortalidad; iv) en la cohorte de casos y controles, los factores de riesgo independientes de mortalidad fueron el síndrome mielodisplásico, la neoplasia sólida, el foco pulmonar, el foco abdominal, el shock y la candidemia, mientras que el linfoma de Hodgkin fue protector; v) la infección por VIH por sí misma no fue un factor de riesgo independiente asociado a la mortalidad.

Los pacientes con VIH y cáncer tenían características demográficas y epidemiológicas diferentes a las de los pacientes sin VIH. Por ejemplo, los pacientes con VIH recibieron TPH con menos frecuencia. Esto podría deberse a que la mayoría de los pacientes con VIH tenían

linfomas, en los cuales el TPH sólo está indicado en casos de recaída tras un tratamiento de primera línea. También cabría la posibilidad de los problemas sociales o la drogadicción contraindicaran el trasplante o que existiera un efecto discriminatorio debido al estado seropositivo de VIH.

En nuestro estudio, la mayoría de los pacientes con VIH y cáncer eran hombres que mantenían relaciones sexuales con hombres, con una baja prevalencia de consumo de drogas intravenosas. Aunque en dicho estudio evaluábamos un largo período de tiempo (21 años), este perfil de pacientes coincide con la mayoría de las series actuales de pacientes infectados con VIH en los países occidentales (119). La mayoría de los pacientes recibían TAR; sin embargo, el 38.3% de los pacientes tenían una carga viral detectable antes de la NF y sólo el 16.7% tenían un recuento de CD4 >350. Además, el 70% cumplía criterios definitorios de SIDA. Una potencial explicación de las elevadas tasas de carga viral detectable y los bajos recuentos de CD4 a pesar de las elevadas tasas de TAR podría ser que en muchos casos se tratara de pacientes con presentación tardía que habían iniciado recientemente el TAR y/o que hubieran comenzado el tratamiento en el momento del diagnóstico del cáncer. En esta línea, las cargas virales medias fueron elevadas y el tiempo transcurrido desde el inicio del TAR fue mayormente corto. Otra posible explicación podría ser la baja adherencia al TAR, que a su vez está relacionada con una mayor probabilidad de desarrollar cáncer (120). Lamentablemente, no disponemos de datos sobre la adherencia de los pacientes incluidos antes de la NF. Por último, el porcentaje de pacientes con una carga viral detectable disminuyó con el tiempo, probablemente como consecuencia de la mejora gradual del tratamiento general de los pacientes con VIH. La TAR basada en inhibidores de la proteasa

fue la más utilizada. Los inhibidores de la proteasa son potentes inhibidores del citocromo P450 3A4 y suelen provocar interacciones farmacológicas problemáticas con varios agentes quimioterapéuticos e inmunosupresores (121). Esto puede provocar un aumento de la toxicidad y un retraso potencial de los tratamientos quimioterapéuticos. En este contexto, los inhibidores de la integrasa no potenciados se utilizan cada vez más debido a su perfil de interacciones farmacológicas más favorable y a su mejor tolerabilidad (122), como se observó en nuestra cohorte. Aunque esto puede repercutir en los desenlaces de los pacientes con VIH que reciben quimioterapia, en nuestro estudio no encontramos diferencias en cuanto a la pauta de tratamiento antirretroviral al presentar bacteriemia en el contexto de la NF.

En este estudio, los pacientes con VIH y cáncer experimentaron una mayor mortalidad que los que no tenían VIH. Varios factores pueden explicar este hallazgo. En la cohorte global, los pacientes con VIH presentaban con mayor frecuencia algunas características asociadas a una mayor mortalidad en el análisis univariante (además del propio VIH) como, por ejemplo, hepatopatía crónica, infección enterocócica, TAEI y shock. En la cohorte de casos y controles, a pesar del emparejamiento por edad, sexo, enfermedad de base y agente etiológico, seguía existiendo una tendencia a que los pacientes con VIH tuvieran mayor mortalidad y presentaran hepatopatía crónica con mayor frecuencia, así como una mayor necesidad de ingreso en UCI. La razón por la cual los pacientes con VIH que desarrollan bacteriemia en el contexto de la NF presentan mayores tasas de infección enterocócica, shock y necesidad de UCI, es incierta. Como se ha mencionado previamente, el problema de la interacción medicamentosa podría haber influido en el pronóstico. Las tasas de coinfección con el virus

de la hepatitis tipo C (VHC) y/o el virus de la hepatitis tipo B (VHB) en la población VIH fueron elevadas, y esta variable podría asimismo haber influido en la mortalidad, aunque esta variable no estuvo disponible en los pacientes sin VIH. También sería posible que los pacientes con VIH fueran una población más vulnerable tras infecciones oportunistas previas o como resultado de un estado basal más frágil. De hecho, la infección enterocócica se ha asociado clásicamente a pacientes frágiles, y ya existen informes de una mayor prevalencia de la misma en la población con VIH, aunque se desconocen los desencadenantes específicos (123,124). Por último, se han descrito defectos en la inmunidad innata y en la función de los neutrófilos en pacientes con VIH, que comportan una menor capacidad bactericida, así como un mal funcionamiento de la degranulación y una fagocitosis y quimiotaxis deficientes (125)(126). Esto podría haber desempeñado un papel deletéreo en estos pacientes. No obstante, el conocimiento sobre estas vías en pacientes neutropénicos con VIH es muy escaso.

El recuento bajo de linfocitos CD4 se ha asociado con anterioridad a una NF prolongada y a un aumento de la mortalidad por infección tras el tratamiento quimioterápico [28]. Sin embargo, en nuestro estudio se describieron las características de los pacientes que presentaban un episodio de bacteriemia en el contexto de una NF post quimioterapia, que es cuando muchos presentan también una linfopenia profunda. Sin embargo, en este escenario específico, no se observó que el recuento previo de CD4 fuera un factor independiente predictor de mortalidad.

Respecto a la evaluación de las peculiaridades de los pacientes receptores de TPH con bacteriemia, llevamos a cabo un estudio unicéntrico donde se evaluaron las características y

los factores de riesgo de mortalidad en 402 episodios de bacteriemia en receptores de TPH durante un periodo de 10 años. De forma global, la mortalidad de los receptores de TPH que sufrían un episodio de bacteriemia fue elevada. Los factores de riesgo de mortalidad estuvieron relacionados principalmente con factores del huésped y del procedimiento (tiempo transcurrido desde la bacteriemia), gravedad de la infección (shock), microorganismo causante (*P. aeruginosa* MDR) y selección del tratamiento antibiótico empírico (TAEI para BGN o *Candida* spp.).

El hecho de que el episodio de bacteriemia ocurriera ≥30 días después del TPH fue un factor de riesgo independiente de mortalidad. Algunos estudios previos también han reportado una mayor mortalidad en los episodios de bacteriemia que tenían lugar después del implante del TPH (67,127). Al igual que en esos estudios, se observó que los episodios de bacteriemia que ocurrían cerca del trasplante eran con mayor frecuencia bacteriemias endógenas o bacteriemias de catéter causadas principalmente por estafilococos coagulasa negativos. Por el contrario, en los episodios más tardíos, el foco pulmonar de la bacteriemia era más frecuente, como también lo era bacteriemia por *P. aeruginosa* con shock séptico. También es plausible, que en el contexto del postrasplante reciente, los pacientes estén sometidos a un seguimiento más estrecho y reciban un tratamiento más agresivo y precoz. A pesar de esto, en el mes previo a la bacteriemia, la mayoría de los pacientes seguían recibiendo inmunosupresión, y más de la mitad de ellos había presentado alguna infección previa. Por último, al igual que en estudios previos, los pacientes con shock séptico presentaron una mayor mortalidad (67,128). En este sentido, el estudio realizado en el seno de esta tesis sobre pacientes neutropénicos con shock séptico puede ser de gran utilidad y sugeriría que

la terapia combinada con un aminoglucósido podría mejorar el pronóstico, y especialmente que es fundamental la optimización del tratamiento β-lactámico, intentando asegurar la adecuación del tratamiento antibiótico empírico. Sin embargo, en el estudio centrado en pacientes receptores de TPH, casi la mitad de los pacientes eran no neutropénicos en el momento de la bacteriemia. En este sentido, se necesitan más estudios para evaluar los tratamientos empíricos óptimos de los pacientes hematológicos no neutropénicos que presentan un shock séptico en la era epidemiológica actual.

P. aeruginosa es una causa frecuente y preocupante de infección en pacientes receptores de TPH (19,40,127,129). De forma trascendente, casi la mitad de las cepas de *P. aeruginosa* aisladas en nuestra cohorte eran MR, y a su vez, la *P. aeruginosa* MR representaba dos tercios de todos los aislados MR de la cohorte. Adicionalmente, la mortalidad en las bacteriemias causadas por estas cepas MR fue de casi el 50%. La mayoría de estos pacientes (61%) recibieron un TAEI, similar al de otras series recientes. Estos datos son similares, a los observados en el estudio multicéntrico descrito previamente como parte de esta tesis doctoral. El impacto del TAEI en la mortalidad de los pacientes con bacteriemia causada por *P. aeruginosa* MR, otras bacteriemias por BGN, o candidemias, es enorme (19,20,130,131). Sin embargo, como se ha comentado previamente, a pesar del contexto epidemiológico actual de aumento de *P. aeruginosa* MR y de la aparición de nuevos antibióticos con elevada actividad antipseudomónica, las recomendaciones actuales de las guías de NF, así como los protocolos en pacientes receptores de TPH, apenas se han modificado en los últimos años (5,56). En este sentido, la identificación de pacientes con riesgo de *P. aeruginosa* MR es esencial para considerar el uso empírico de terapias combinadas y/o ceftolozano-tazobactam

o ceftazidima-avibactam. Al igual que en otros estudios previos (19,129), la bacteriemia de origen nosocomial, el foco pulmonar y la exposición previa a antibióticos con actividad antipseudomónica se asociaron a un mayor riesgo de bacteriemia causada por *P. aeruginosa* MR. Por último, a pesar de la baja incidencia de candidemia, ésta se asoció a una elevada mortalidad. En el contexto de una amplia profilaxis con azoles, casi todas las especies aisladas fueron no-albicans. La identificación de episodios de NF con alto riesgo de candidemia es esencial para considerar el uso empírico de equinocandinas.

Limitaciones y fortalezas de los estudios incluidos en la presente tesis doctoral:

Los estudios incluidos en la presente tesis doctoral tienen diversas fortalezas, pero también algunas limitaciones. Respecto al estudio de las características actuales de las infecciones documentadas en pacientes hematológicos con NF, el principal punto fuerte consistió en el importante número de episodios de NF evaluados, con una descripción detallada de todas las pruebas microbiológicas realizadas y los resultados positivos obtenidos. Creemos que dicho estudio ilustra de forma clara, actualizada y completa, el amplio espectro de infecciones documentadas en pacientes con NF. Respecto a los estudios que evaluaban las tasas de resistencia a los antibióticos recomendados por las guías internacionales de NF en pacientes hematológicos con bacteriemia, la principal fortaleza residió en el hecho de que los dos estudios incluidos fueron realizados en cohortes contemporáneas, prospectivas y multicéntricas de diferentes regiones de España, que incluyeron un gran número de pacientes. En relación con el estudio que evaluaba a los pacientes neutropénicos con bacteriemia y shock séptico, los principales puntos fuertes residieron asimismo en el gran número de pacientes incluidos, la recogida prospectiva de datos y la evaluación exhaustiva de todos los casos de bacteriemia por parte de un experto en enfermedades infecciosas. Además, se incluyó un análisis de emparejamiento por puntuación de propensión para hacer comparables los grupos que recibieron un tratamiento antibiótico empírico adecuado frente a los que no lo recibieron. Por último, los estudios evaluando las características particulares de dos poblaciones específicas como los pacientes VIH con NF, y los receptores de TPH, también tuvieron algunas fortalezas. El primero de ellos, ha sido el primer estudio en evaluar las características y los desenlaces de los pacientes VIH y cáncer que desarrollan bacteriemia

en el contexto de la NF. Además, este estudio incluyó un gran número de bacteriemias en pacientes con cáncer, con datos recogidos prospectivamente, y con la realización de una comparación emparejada de casos y controles. Respecto a la cohorte de pacientes receptores de TPH, se trata asimismo de una serie con un gran número de bacteriemias recogidas prospectivamente, y con un alto nivel de detalle de las variables clínicas y microbiológicas, así como de las características relacionadas con el TPH.

No obstante, existen varias limitaciones que han de ser reconocidas. Por una parte, tres de los estudios incluidos en la presente tesis son estudios unicéntricos. En este sentido, la generalización de los datos derivados de estos estudios es compleja dada la gran variabilidad de la epidemiología y la resistencia antibiótica entre diferentes áreas geográfica e incluso entre centros de la misma área. Además, es importante remarcar que nuestro centro realiza profilaxis antibiótica con quinolonas en pacientes hematológicos con neutropenias prolongadas, y eso podría condicionar parcialmente nuestra epidemiología. En cambio, los estudios que incluían un mayor número de centros, pese a ser más generalizables, estaban limitados por el número relativamente escaso de variables recogidas, que no nos permitió ahondar en la detección de factores de riesgo o mortalidad. Asimismo, aunque el cumplimiento de las guías internacionales de neutropenia fue elevado en dichos estudios, las decisiones relativas a los antibióticos empíricos variaron entre los distintos centros, y además la epidemiología local de algunos de estos centros podría estar condicionada por la endemicidad de algunas cepas MR. También es importante remarcar, que todos los hospitales incluidos en dichos estudios eran centros terciarios. Es plausible que las tasas de gérmenes MR sean algo menores en centros no universitarios, pero también condicionado

por el hecho de una menor presencia de pacientes de alta complejidad, en comparación a los incluidos en nuestros estudios. Además de esto, existen algunas limitaciones más específicas de los diversos estudios de forma individual. Respecto al estudio de las características de las infecciones documentadas en pacientes hematológicos con NF, fueron los médicos tratantes los que decidieron acerca de que pruebas diagnósticas se solicitaban. Esto podría haber derivado en un cierto infradiagnóstico de algunas entidades. Además, los datos se obtuvieron directamente de la historia clínica electrónica, lo cual tiene algunas limitaciones inherentes. Por último, dado el diseño del estudio, no se pudieron evaluar causas no infecciosas de fiebre. Respecto a los estudios centrados en la evaluación de las resistencias a los antibióticos recomendados por las guías internacionales, además de las limitaciones ya comentadas, una potencial limitación se derivaría del hecho de que las definiciones de resistencia y los puntos de corte definidos por el EUCAST han cambiado recientemente. Según las definiciones actuales, algunos aislados intermedios de este estudio se clasificarían como susceptibles con un aumento de la exposición, en lugar de resistentes. Respecto al estudio sobre el shock en pacientes neutropénicos, es importante destacar que la validez externa de este estudio podría ser limitada, ya que se realizó en dos centros de la misma zona geográfica. Además, durante el período incluido en el estudio han existido diferentes definiciones de shock séptico (132,133). Dado que en nuestro estudio no disponíamos de los valores de lactato de los episodios más antiguos, es posible que algunos de estos episodios no cumplieran los criterios de shock séptico según las directrices actuales. Por último, los amplios intervalos de confianza en algunas de las variables del análisis multivariante sugieren que puede existir cierto sesgo por escasez de datos. Respecto al

estudio de los pacientes con VIH y NF, el mayor limitante fue que el número total de pacientes con VIH fue relativamente bajo, especialmente si se tiene en cuenta que el período de estudio incluido era muy prolongado. Las variaciones en las características y los tratamientos de los pacientes con VIH son continuas, y, por tanto, se necesitan estudios más amplios y actualizados. Además, los casos y los controles se emparejaron según varias características (incluida la etiología) en un intento de evaluar el verdadero impacto del VIH. Sin embargo, esto impidió cualquier evaluación de diferencias etiológicas en pacientes que fueran por lo demás similares.

9• CONCLUSIONES

1. Aproximadamente la mitad de los pacientes neutropénicos tuvieron una infección microbiológicamente documentada, principalmente causadas por bacterias y virus. Esto supone un claro aumento respecto a estudios previos, probablemente reflejando la mejoría en las técnicas de diagnóstico microbiológico. Sin embargo, la alta tasa de negatividad en algunas pruebas subraya la necesidad de establecer protocolos para su uso coste-efectivo.

2. La alta frecuencia de infecciones virales documentadas subraya la necesidad de mejorar el manejo y el tratamiento de estas infecciones en los pacientes con neutropenia febril.

3. La resistencia actual de los bacilos gramnegativos a los β-lactámicos empíricos recomendados en las guías internacionales para la neutropenia febril es muy elevada. En las bacteriemias causadas por *Pseudomonas aeruginosa,* más de un tercio de las cepas son resistentes a los antibióticos recomendados en las guías.

4. El tratamiento antibiótico empírico inapropiado en pacientes hematológicos con bacteriemia es frecuente, especialmente en episodios causados por microorganismos multirresistentes. En los episodios causados por *P. aeruginosa,* el tratamiento empírico inapropiado se asoció de forma independiente con un aumento de la mortalidad.

5. Es imperativo adaptar las guías internacionales de neutropenia febril a la epidemiología actual y desarrollar estrategias para identificar a los pacientes con alto riesgo de infección por bacilos gramnegativos multirresistentes.

6. En pacientes neutropénicos que presentan bacteriemia, el shock séptico conlleva una tasa de mortalidad extremadamente alta, especialmente cuando el tratamiento antibiótico empírico es inadecuado.

7. La combinación empírica de un β-lactámico activo junto con amikacina reduce significativamente la mortalidad en pacientes neutropénicos con bacteriemia y shock. Sin

embargo, cuando la amikacina es el único antibiótico activo la tasa de mortalidad aumenta significativamente, llegando a niveles extremos. Además, el tratamiento empírico específico para grampositivos resistentes no aporta beneficios significativos.

8. Los pacientes infectados por VIH con cáncer que presentan neutropenia febril y bacteriemia muestran un perfil epidemiológico y clínico distintos respecto a los pacientes no VIH, así como mayor mortalidad. Sin embargo, la infección por VIH en sí no se asocia con una mayor mortalidad.

9. Los receptores de un trasplante de progenitores hematopoyéticos que presentan bacteriemia tienen una elevada mortalidad relacionada con factores del huésped, el tipo de microorganismo implicado, y la presentación clínica. El tratamiento antibiótico empírico inapropiado para bacilos gramnegativos y *Candida* spp. se asocia de forma independiente con un aumento de la mortalidad.

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