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Revisión

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Síndrome de Austrian: Una rara manifestación de la enfermedad neumocócica invasiva. Presentación de un caso y revisión bibliográfica

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RESUMEN

El síndrome de Austrian es una patología producida por la infección diseminada de *Streptococcus pneumoniae* y caracterizada por la tríada de neumonía, endocarditis y meningitis Tiene una incidencia estimada de 0,9-7,8 casos por diez millones de habitantes y año y una mortalidad del 32%. El consumo de alcohol, como principal factor de riesgo, aparece solamente en cuatro de cada diez pacientes. Un 14% no presentan factores de riesgo. Dos de cada tres enfermos son varones y ocurre en la época media de la vida. Asienta sobre válvula nativa, lesionándose la aorta en la mitad de los afectados. Presentan regurgitación severa dos de cada tres pacientes. El tratamiento antimicrobiano apropiado y la cirugía temprana de la endocarditis disminuyen la mortalidad. Es posible que la epidemiología del síndrome de Austrian esté cambiando por la introducción de la vacuna antineumocócica conjugada 13-valente en el calendario infantil.

Palabras clave: Síndrome Austrian, *Streptococcus pneumoniae*, enfermedad neumocócica invasiva, vacunación.

Austrian syndrome: A rare manifestation of invasive pneumococcal disease. A case report and bibliographic review

ABSTRACT

The Austrian syndrome is a pathology caused by disseminated *Streptococcus pneumoniae* infection and characterized for the triad of pneumonia, endocarditis and meningitis. It has an estimated incidence of 0.9-7.8 cases per ten millions people each year, and a mortality of 32%. Alcohol abuse, as the main risk factor, appears only in four out of ten patients. Moreover, 14% of patientes do not have any risk factor. Two out of three patients are males and it occurs in the middle aged of life. It is more frequently on native valve, aortic valve is injured in the half of the cases. Severe regurgitation occurs in two per three patients. Appropriate antimicrobial treatment and early endocarditis surgery decrease mortality. It is possible that Austrian syndrome epidemiology is changing by the introduction of 13-valent pneumococcal conjugated vaccine in the children´s calendar.

Keywords: Austrian syndrome, *Streptococcus pneumoniae*, invasive pneumoccocal disease, vaccination

INTRODUCCIÓN

Streptococcus pneumoniae es un coco grampositivo, negativo para la catalasa, que prolifera en parejas o en cadenas cortas. A excepción de las cepas que producen conjuntivitis, este germen presenta una cápsula de polisacáridos que es la responsable de la respuesta inmune y permite clasificarlo en más de 90 serotipos [1].

Es un colonizador habitual de la rinofaringe en niños y adultos. La infección se produce cuando es transportado de manera directa a zonas anatómicas contiguas, como el oído medio, los senos paranasales, la tráquea, los bronquios o los pulmones. El resto de infecciones suelen ser por vía hematógena, y son agrupadas bajo el término de enfermedad neumocócica invasiva (ENI). La ENI se define como un episodio infeccioso, en el cual se aísla *S. pneumoniae* en fluidos normalmente estériles, como por ejemplo sangre o líquido cefalorraquídeo (LCR) [2]. También se puede emplear como método diagnóstico la detección del ácido desoxirribonucleico (ADN) o del antígeno bacteriano [3]. Sin embargo, hay que tener precaución al interpretar los resultados moleculares, ya que la presencia de ADN no implica necesariamente que exis-

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tan organismos viables. Se ha aislado ADN de *S. pneumoniae*, siete años después de padecer una endocarditis y no existir evidencia de infección [4].

La ENI puede ocasionar casi un centenar de procesos clínicos [5]. La forma de presentación más frecuente es la neumonía bacteriémica. Otros procesos habituales son: endocarditis [6], pericarditis [7], meningitis [8], artritis séptica [9], osteomielitis [10], peritonitis [11], salpingitis [12], abscesos cerebrales, empiemas subdurales [13], celulitis [14], empiema pleural [15], endometritis [16] o bacteriemia primaria [17]. Excepcionalmente se presenta como síndrome de Austrian (SA) [18]. La ENI origina una gran mortalidad [19] y en la misma intervienen factores relacionados con el huésped (edad y complicaciones), con los serotipos neumocócicos, y con las medidas terapéuticas empleadas [20].

La asociación de neumonía, meningitis y endocarditis fue descrita por primera vez en 1862 por Herchl tras realizar la autopsia a 5 pacientes. Osler, en 1881 describió también este síndrome y fue conocido como triada de Osler. Un año después, Netter volvió a poner de manifiesto dicha relación clínica, señalando una clara predisposición por la válvula aórtica [21]. En la actualidad se conoce como SA en honor a Robert Austrian, que en 1957 comunicó 8 casos, de los cuales 6 fallecieron, principalmente por rotura de la válvula aórtica [18].

Se ha realizado una revisión bibliográfica con los encabezamientos *"austrian syndrome"*, *"invasive pneumococcal disease"* *"streptococcus pneumoniae endocarditis"*, *"pneumococcal endocarditis"*, *"pneumococcus endocarditis"* *"streptococcus pneumoniae meningitis"*, *"pneumococcal meningitis"*, y *"pneumococcus meningitis"*. Las características clínico epidemiológicas de los 74 pacientes seleccionados con SA [6, 18, 21-83] se resumen en la tabla 1. Se incluye también el caso que exponemos a continuación.

CASO CLÍNICO

Presentamos un caso de un SA complicado con ictus y sordera neurosensorial. Se trata de un paciente de 44 años de edad, sin antecedentes médicos de interés, excepto diabetes mellitus no insulinodependiente, que acudió a urgencias hospitalarias por un cuadro confusional, fiebre elevada y signos meníngeos. En los días previos tuvo síntomas catarrales y tos productiva. En la radiografía de tórax se visualizó una neumonía (figura 1). Los hallazgos de la tomografía computarizada (TC) basal sin contraste fueron anodinos, sin anomalías significativas.

A la llegada a la UCI, se inició tratamiento con ceftriaxona, ampicilina, vancomicina y aciclovir de manera empírica por sospecha de meningitis. El LCR de la punción lumbar era de aspecto turbio sin crecimiento bacteriano. El hemocultivo solicitado en urgencias aisló *S. pneumoniae*.

La presencia de una auscultación cardiaca anómala determinó la realización de una ecocardiografía transtorácica (ETT), sin apreciarse alteraciones significativas, pero tras un aumento de la disnea, un ecocardiograma transesofágico (ETE) reveló una endocarditis sobre válvula aórtica nativa con insuficiencia severa de dicha válvula, además de un shunt izquierda-derecha en el tabique interauricular. Se realizó un recambio valvular aórtico urgente con implantación de una prótesis mecánica. También se cerró la comunicación interauricular tipo ostium secundum y de foramen ovale permeable. Dieciocho días después de la intervención se detectó un derrame pericárdico severo, que precisó drenaje subxifoideo.

Durante su estancia en planta apareció una sordera súbita del oído izquierdo. La exploración demostró una hipoacusia neurosensorial, que se achacó a una complicación neurológica de la meningitis. Al alta hospitalaria, fue remitido al Servicio de Rehabilitación Cardiaca.

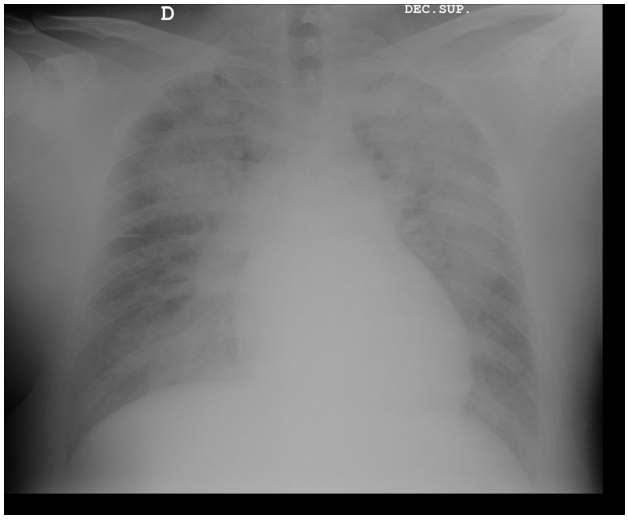

Figura 1 Radiografía de tórax: Afectación consolidativa bilateral de predominio apical.

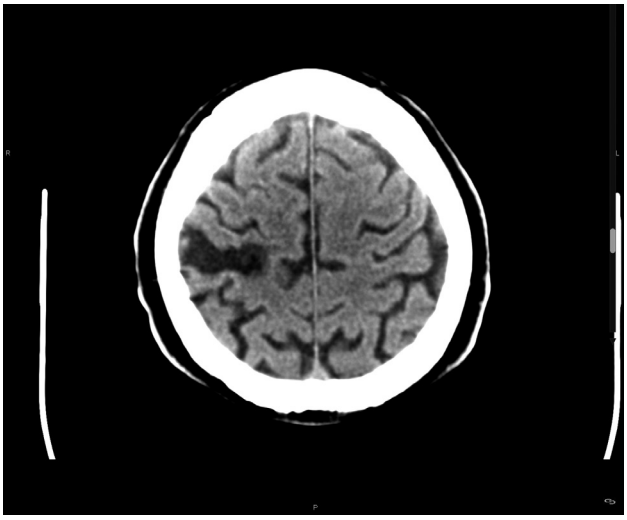

Figura 2 Tomografía computarizada craneal: Infarto cortical crónico.

Tabla 1 **Características de 74 casos con Síndrome de Austrian**

Referencia (Año)	Sexo/Edad	Antecedentes personales	Clínica	Serotipos	Válvula	Regurgitación Valvular	Cirugía	Tratamiento	Complicaciones	Resultado
18 (1957)	V/46	Sífilis	Alteración nivel conciencia. Fiebre. Rigidez de nuca	14	Aórtica	-	No	Sulfadiazina + Penicilina	IC	F
18 (1957)	V/65	-	Meningitis	12	Aórtica	-	No	-	Bacteriemia	F
65 (1961)	V/47	TBC	Tos. Fiebre. Rigidez de nuca	-	Aórtica	Severa	No	Penicilina + Sulfadiazina + Hidrocortisona	Parálisis VII par. Sordera izquierda. EAP. IC	F
26 (1991)	V/54	VIH+. TBC. Insuficiencia renal crónica	Fiebre elevada. Obnubilado. Tos. Disnea. Dolor torácico	-	Aórtica	-	No	Penicilina G sódica	Esofagitis	V
62 (1998)	V/53	Alcohol	IC	22F	Aórtica	-	-	-	No	V
62 (1998)	V/55	No	IC	12F	Aórtica	-	-	-	No	V
62 (1998)	M/49	Alcohol	IC	20	Aórtica	-	-	-	Fallo multiorgánico	F
22 (1998)	V/48	Alcohol. Cirrosis hepática. Fumador. Estenosis mitral	Síndrome febril. Síntomas catarrales. Clínica neurológica. Rigidez de nuca	-	Mitral	Leve	Si	Vancomicina	No	V
35 (1999)	V/48	Alcohol	Déficit visión. Rigidez de nuca. Fiebre. Cefalea. Alteración nivel de conciencia	-	Aórtica	Severa	Si	Ceftriaxona + Vancomicina + Ampicilina + Amikacina	Coroiditis	V
55 (1999)	V/53	Alcohol	Fiebre. Cefalea. Alteración nivel conciencia. Signos meníngeos	-	Mitral	Moderada	Si	Cefotaxima + Vancomicina + Dexametasona	Insuficiencia renal	V
29 (2002)	V/50	Alcohol. DM tipo II	Fiebre. Cefalea. Rigidez de nuca. Confusión	-	Aórtica	Severa	Si	Cefotaxima + Rifampicina	Sinusitis etmoidal. Absceso cerebral	V
41 (2003)	V/51	HTA. Arteriopatía periférica	Fiebre. Alteración nivel conciencia. Signos meníngeos	-	Aórtica	Severa	Si	Amoxicilina + Aminoglucósidos	Fallo multiorgánico	V
41 (2003)	M/70	No	Alteración nivel conciencia. Signos meníngeos. NAC	-	Mitral	Moderada	No	Vancomicina + Rifampicina + Dexametasona	Choque séptico	V
36 (2004)	M/43	-	Disnea de esfuerzo	-	Mitral y Aórtica	Severa	Si	-	Absceso aórtico y perforación aurícula izquierda	V
40 (2004)	V/23	Alcohol	Fiebre. Cefalea	-	Mitral y Aórtica	Severa	No	Penicilina + Aminoglucósidos + Cloranfenicol + Corticoides	Choque circulatorio. Embolo séptico cerebral	F
59 (2004)	M/7	No	Meningitis	6	Aórtica	Severa	Si	Ceftriaxona+ Vancomicina	Absceso paravalvular	V
21 (2004)	M/51	VIH+	Artritis séptica. Rigidez de nuca. Fiebre. Alteración nivel de conciencia	-	Tricúspide	Moderada	No	Vancomicina	IC	F
6 (2005)	V/56	Hepatitis C. ADVP	Esplenomegalia	8	Aórtica	-	Si	Cefotaxima + Vancomicina + Gentamicina + Clindamicina Meropenem + Piperacilina	Ictus. Fallo cardiaco	F

Tabla 1 **Características de 74 casos con Síndrome de Austrian. (cont.)**

Referencia (Año)	Sexo/Edad	Antecedentes personales	Clínica	Serotipos	Válvula	Regurgitación Valvular	Cirugía	Tratamiento	Complicaciones	Resultado
6 (2006)	V/55	Fumador. Alcohol	-	8	Tricúspide	-	No	Cefotaxima + Vancomicina + Gentamicina + Clindamicina	Ictus. Infección articular	F
49 (2006)	V/45	Alcohol	Fiebre. Alteración nivel de conciencia. Signos meníngeos. Cefalea	-	Aórtica	Severa	Si	Cefotaxima	IC	V
49 (2006)	M/61	No	Fiebre. Tos. Dolor hemitórax derecho. Alteración nivel de conciencia	-	Mitral	Moderada	No	Cefotaxima	Choque séptico. Absceso cerebral	F
44 (2006)	V/43	No	Tos. Alteración nivel conciencia. Fiebre. Rigidez de nuca	-	Aórtica	Severa	Si	-	Rotura aneurisma seno valsalva	V
23 (2006)	V/55	Alcohol	Fiebre. Rigidez nuca. Alteración nivel de conciencia. Disnea	-	Aórtica	Severa	Si	Ceftriaxona	EAP. IC	V
30 (2007)	M/44	Fumadora. TEP. Hepatitis C. ADVP	Alteración nivel de conciencia. Dolor torácico. Tos. Rigidez de nuca. Hipotensión	-	Aórtica	Severa	Si	Penicilina + Dexametasona	Ictus	V
52 (2007)	M/39	Linfoma Hodking. Esplenectomía	Fiebre. Tos. Cefalea. Vómitos. Confusión. Signos meníngeos	23 B	Aórtica	Severa	Si	Penicilina	Fístula auricular aórtica. Derrame pleural	V
38 (2008)	V/55	Alcohol. Enfermedad vascular periférica	Fiebre. Hipoxemia severa. Alteración nivel conciencia. Signos meníngeos	-	Aórtica	Severa	Si	Ceftriaxona + Penicilina	Absceso perivalvular. CIA. Fallo multiorgánico	V
6 (2008)	V/51	Anesplenia. Linfoma células B	Esplenomegalia	9V	Aórtica protésica	-	No	Vancomicina + Cefotaxima + Ceftriaxona	Absceso raíz aórtica Fallo cardiaco	V
45 (2008)	M/49	Alcohol	Fiebre. Disnea	-	Mitral	Leve	No	Ceftriaxona + Vancomicina + Gentamicina	Pericarditis	V
28 (2009)	M/69	-	Fiebre. Tos productiva. Cefalea. Alteración nivel conciencia	-	Aórtica	Severa	No	Penicilina + Claritromicina	Fallo cardíaco. Parada cardiorespiratoria. FA	V
57 (2009)	M/54	Esplenectomía. DM tipo II. Cirrosis hepática	Fiebre. Vómitos. Somnolencia	-	Mitral	Severa	No	Penicilina+ Ceftriaxona + Dexametasona + Amikacina + Levofloxacino	Colecistitis. IC	V
43 (2009)	V/38	VIH +. ADVP	NAC. Meningitis	-	Mitral y Aórtica	Severa	No	-	Ictus. IC	F
61 (2010)	V/13	Asma. Infección A (H1N1)	Fiebre. Hipotensión. Rigidez de nuca. Tos. Debilidad e hipertonía	-	Mitral	Moderada	Si	Ceftriaxona + Vancomicina + Dexametasona	Ictus	V
54 (2010)	V/64	-	Fiebre. Mialgias y artralgias. Tos productiva. Confusión. Rigidez de nuca	-	Mitral y Aórtica	Leve y leve	No	Ceftriaxona + Vancomicina + Meropenem	IC. Hemiparesia izquierda	V
74 (2010)	V/56	Drogas	Inconsciente. Fiebre, tos. Signos meníngeos	-	Aórtica	Moderada	No	Penicilina	No	V

Tabla 1 **Características de 74 casos con Síndrome de Austrian. (cont.)**

Referencia (Año)	Sexo/Edad	Antecedentes personales	Clínica	Serotipos	Válvula	Regurgitación Valvular	Cirugía	Tratamiento	Complicaciones	Resultado
25 (2010)	V/62	Alcohol	Fiebre. Clínica neurológica atípica. Tos productiva	-	Mitral y Aórtica	Severa	Si	Penicilina + Gentamicina	IAM	F
72 (2011)	V/44	Alcohol. HTA	Alteración conciencia. Insuficiencia respiratoria. Sepsis	-	Mitral	Severa	Si	Penicilina. Hidrocortisona	Insuficiencia renal. IAM	F
50 (2011)	M/26	-	Fiebre. Alteración del nivel de conciencia. Síntomas respiratorios y cardíacos	-	-	-	No	Ceftriaxona+ Vancomicina +Ampicilina + Meropenem	No	V
48 (2011)	V/59	No	Meningitis	-	Aórtica	Severa	Si	Cefalosporina 3ª generación	Ictus	V
31 (2011)	M/49	Alcohol	Fiebre. Alteración nivel conciencia. Tos. Diarrea. Rigidez de nuca	-	Aórtica	Severa	Si	Ceftriaxona + Ampicilina + Dexametasona	Choque séptico	V
47 (2011)	M/68	-	Fiebre. Confusión	6A	Mitral	Severa	No	Ceftriaxona + Dexametasona	Guillain-Barré. Absceso epidural	V
60 (2012)	V/84	HTA. Asma. Cáncer próstata	Fiebre. Confusión	-	Mitral	-	No	Levofloxacino + Ceftriaxona + Vancomicina	Insuficiencia respiratoria hipoxémica	F
53 (2012)	V/52	Alcohol. Esplenectomía	Fiebre. Alteración nivel conciencia	-	Mitral y Aórtica	Leve y moderada	Si	Piperacilina-Tazobactam + Levofloxacino + Vancomicina + Ceftriaxona	Infarto renal. FA paroxística	F
67 (2012)	V/37	Alcohol	Confusión	-	Aórtica	Severa	Si	Penicilina. Dexametasona	IC	V
46 (2012)	V/41	Fumador	Fiebre. Dolor torácico	-	Mitral y Aórtica	Severa	Si	-	Absceso miocardio. IC. Choque cardiogénico. Ictus	F
56 (2012)	V/55	Alcohol. Drogas	Alteración nivel de conciencia. Disnea. Vómitos. NAC	-	Mitral y Tricúspide	Moderada	No	Vancomicina + Ceftriaxona + Dexametasona	No	V
37 (2013)	M/61	Esplenectomía. Trasplante hígado	Fiebre. Alteración nivel conciencia. Rigidez de nuca	-	Mitral	Leve	No	Amoxicilina-clavulánico	Múltiples abscesos. Espondilodiscitis L4-5. Hemorragias retina	V
33 (2013)	V/61	HTA. DM. Válvula aórtica bicúspide	Fiebre. Tos. Hipoxemia. Alteración del nivel de conciencia	-	Aórtica	Severa	Si	Ceftriaxona + Vancomicina +Azitromicina + Meropenem	Derrame pericárdico	V
66 (2013)	V/72	Tricoleucemia. Esplenectomía	Dolor torácico dorsal. Fiebre. Confusión. Rigidez nuca	-	Mitral y Aórtica	Leve	No	Ceftriaxona	Shock séptico. Fallo multiorgánico	F
68 (2015)	M/71	EPOC	Dolor abdominal, anorexia, vómitos. Fiebre. Cefalea. Alteración conciencia. Rigidez nuca	-	Mitral	Severa	Si	Clindamicina. Corticoides. Manitol	Espondilodiscitis L2-3	V
77 (2015)	M/73	No	Disminución conciencia. Fiebre. Rinorrea purulenta. Rigidez nuca	-	Mitral y Aórtica	Severa	Si	Ceftriaxona. Dexametasona	Infarto cerebeloso y frontal. IC	F
77 (2015)	V/63	Alcohol. Fumador	Rinorrea, tos y expectoración mucopurulenta. Sensación febril. Rigidez de nuca	-	Mitral	Moderada	Si	Ceftriaxona + Ampicilina	No	V

Tabla 1 **Características de 74 casos con Síndrome de Austrian. (cont.)**

Referencia (Año)	Sexo/Edad	Antecedentes personales	Clínica	Serotipos	Válvula	Regurgitación Valvular	Cirugía	Tratamiento	Complicaciones	Resultado
83 (2015)	V/90	Leucemia linfática crónica	Fiebre. Alteración conciencia	-	Aórtica	Moderada	No	Ceftriaxona. Esteroides	No	F
27 (2015)	V/61	HTA	Dolor lumbar y cervical. Dificultad marcha. Fiebre. Cefalea. Estupor. Rigidez de nuca	18C	Mitral	Severa	Si	Ceftriaxona + Cefepima + Linezolid + Meropenem + Vancomicina + Dexametasona	Ictus	V
76 (2015)	V/63	VIH. Drogas. TEP. TBC pulmonar	Alteración conciencia. Tos. Fiebre	-	Tricuspide	Severa	No	Ceftriaxona + Sulfametoxazol/trimetoprim + Vancomicina	No	V
42 (2015)	M/30	Cocaína	Debilidad generalizada	-	Mitral y Aórtica	Severa	Si	Ceftriaxona+ Vancomicina	Choque. Ictus	V
	Sexo	Antecedentes personales	Clínica	Serotipos	Válvula	Regurgitación Valvular	Cirugía	Tratamiento	Complicaciones	Resultado
63 (2015)	M/40	-	Cefalea. Vómitos. Rigidez nuca. Alteración nivel de conciencia	-	Aórtica	Severa	Si	Ceftriaxona + Rifampicina + Linezolid	EAP. IC	V
64 (2015)	V/35	VIH +. Alcohol	Fiebre. Hipoxemia. Confusión	-	Aórtica	Severa	No	Ceftriaxona + Dexametasona	Absceso aórtico. Bacteriemia	F
79 (2016)	M/61	Alcohol	Inconsciente	-	Mitral	Severa	No	Ceftriaxona + Ampicilina + Vancomicina	Parada cardiorespiratoria. Fallo multiorgánico	F
39 (2016)	V/52	Fumador. Alcohol	Coma febril, alteración conducta, convulsiones, rigidez de nuca, miosis bilateral	-	Aórtica	Severa	Si	Cefotaxima + Gentamicina	IC	V
80 (2016)	M/57	Alcohol	Alteración conciencia. Fiebre	-	Mitral	-	No	Ceftriaxona + Vancomicina + Ampicilina	Ictus embólico	V
51 (2016)	V/56	Alcohol. ADVP	Encefalopatía aguda. Fiebre	-	Mitral y Tricúspide	Severa	Si	-	IC. Ictus	F
34 (2016)	M/73	HTA	Alteración nivel conciencia. Rigidez de nuca. Alucinaciones. Síndrome gripal	(+)	Mitral	-	No	Cloxacilina + Gentamicina	Fallo multiorgánico	F
58 (2017)	V/65	Hepatitis C. ADVP. Enfermedad coronaria	Tos. Mareo. Disnea	-	Mitral	-	No	Ceftriaxona+ Azitromicina + Vancomicina + Cefepima	Sepsis	V
82 (2017)	M/51	Hipertiroidismo. HTA	Alteración conciencia. Fiebre	-	Mitral	-	Si	Antibiótico amplio espectro	No	V
32 (2017)	V/48	DM	Fiebre. Tos productiva. Desorientación	-	Mitral	Moderada	No	Ceftriaxona + Moxifloxacino	Insuficiencia respiratoria	V
75 (2017)	V/49	No	Síndrome febril. Tos y expectoración, disnea. Crisis convulsiva, alteración conciencia. Rigidez nuca	-	Aórtica	Severa	Si	Penicilina. Dexametasona	No	V
24 (2017)	M/75	-	Neumonía. Alteración nivel conciencia	-	Mitral	Leve	Si	Vancomicina	Ictus. Absceso perianular	V
81 (2017)	V/54	No	Tos seca. Cefalea. Artralgias. Disnea	-	Aórtica	Severa	No	Ceftriaxona	Hemiparesia derecha. Convulsiones. Fallo multiorgánico	F

Tabla 1 **Características de 74 casos con Síndrome de Austrian. (cont.)**

Referencia (Año)	Sexo/Edad	Antecedentes personales	Clínica	Serotipos	Válvula	Regurgitación Valvular	Cirugía	Tratamiento	Complicaciones	Resultado
70 (2018)	V/60	Válvula Aórtica bicúspide	Tos. Alteración conciencia	-	Aórtica	-	Si	Ceftriaxona + Ampicilina. Dexametasona. Penicilina	Ictus embólico. Hidrocefalia. Absceso raíz aórtica. Pericarditis	V
71 (2018)	M/51	Esplenectomizada. PTI. HTA	Fiebre. Cefalea. Vómitos. Alteración conciencia. Rigidez nuca	-	Aórtica	Severa	No	Vancomicina + Meropenem. Dexametasona. Manitol	Fallo multiorgánico. CID	F
69 (2018)	M/48	VIH. Fumadora. Lesión escamosa cervix	Fiebre. Mal estado general. Rigidez nuca	-	Pulmonar	-	No	Linezolid + Ampicilina + Cefotaxima + Gentamicina. Dexametasona	Esplenomegalia. Embolismo pulmonar séptico	V
73 (2018)	V/52	Alcohol	Fiebre. Alteración conciencia	-	Aórtica	Severa	Si	Penicilina. Dexametasona	No	V
78 (2018)	V/51	Fumador. Drogas	Mal estado general. Alteración conciencia. Tos. Signos meníngeos. Febril	-	Aórtica	Severa	Si	Vancomicina + Gentamicina + Piperacilina/tazobactam. Corticoides	No	V
Presente caso (2017)	V/44	DM	Fiebre. Tos productiva. Confusión. Signos meníngeos	-	Aórtica	Severa	Si	Ceftriaxona + Ampicilina + Vancomicina + Aciclovir	Ictus. Sordera neurosensorial	V

V: Varón; M: Mujer; F: Fallecido; V: Vivo; ADVP: Adicto a drogas vía parenteral; CIA: Comunicación interauricular; CID: Coagulación intravascular diseminada; DM: Diabetes mellitus; EAP: Edema agudo de pulmón; FA: Fibrilación auricular; HTA: Hipertensión arterial; IAM: Infarto agudo de miocardio; IC: Insuficiencia cardíaca; NAC: Neumonía adquirida en la comunidad; PTI: Púrpura trombocitopénica idiopática; TBC: Tuberculosis; TEP: Tromboembolismo pulmonar; VIH: Virus inmunodeficiencia humana; (+): *Staphylococcus aureus*.

Seis meses después, tuvo una clínica de pérdida de memoria. Se efectuó una TC con contraste donde se observó un infarto cortical crónico en la región posrolándica derecha (figura 2). En la actualidad el paciente tiene un cuadro de pérdida de memoria inmediata a los números y a las palabras, así como de la memoria de retención a corto plazo. Presenta síntomas típicos de lesión en el hemisferio no dominante, como agnosia topográfica, prosopagnosia, o déficit de concentración.

Afortunadamente el *Capitán de los Hombres de la Muerte*, como definió Osler en 1901 a la neumonía, no ha cumplido su objetivo con este paciente; pero la disnea, el deterioro cognitivo y la hipoacusia, todas ellas secuelas de este síndrome, han deteriorado su calidad de vida.

CARACTERÍSTICAS EPIDEMIOLÓGICAS

La tasa de incidencia de la ENI varía según la zona geográfica analizada o la población estudiada [2]. En el año 2016, la tasa de incidencia global en Europa era de 5,4 por 100.000 habitantes y de 4,9 en España [84]. La incidencia en la población adulta aumenta con la edad [84-86], y es más elevada en hombres que en mujeres [87].

No hay datos de la incidencia del SA en la población general. Existen cifras de incidencia en ciertas patologías, como la meningitis o endocarditis, pero sin discriminar el germen causante de las mismas. Así, en una serie de 1.025 episodios de meningitis bacterianas, el SA es la forma de presentación del 0,48% de todas las meningitis o del 21% de las meningitis asociadas a endocarditis [88].

La incidencia de la endocarditis neumocócica es pequeña y representa únicamente el 0,5 % de todas las endocarditis infecciosas ocurridas en España entre 2003 y 2014 [89]. Supone entre un 0,6-1,2% de las bacteriemias por neumococo, con una incidencia de 0,36-3 pacientes por millón de habitantes y año [90-92]. Debido a que el SA aparece en el 26% de las endocarditis por *S. pneumoniae* [6], se puede inferir que el SA afecta a 0,9-7,8 pacientes por diez millones de habitantes y año. Si sigue la tendencia actual, esta incidencia podría disminuir en los próximos años, favorecida por la vacunación frente al neumococo en el calendario infantil [85].

El SA suele presentarse en la edad media de la vida. La mediana es de 52,5 años, con una media de 52,76 años y un rango de edad de 7 y 90 años. La presentación en niños es poco común y aparece más frecuentemente en hombres (64,86%) que en mujeres (35,14%).

PRESENTACIÓN CLÍNICA

El SA es un proceso agudo caracterizado por la presencia de neumonía, endocarditis y meningitis causado por *S. pneumoniae*. Únicamente existe un caso con aislamiento de *Staphylococcus aureus*, sin factores de riesgo previos [34]. La

neumonía suele ser la puerta de entrada de este cuadro devastador [5, 22, 56, 57, 93]. La evolución clínica es muy agresiva [26], con un mal pronóstico y una alta mortalidad. Fallecen el 32,43% de los afectados, siendo la destrucción valvular de la endocarditis, el principal factor implicado [27].

Endocarditis. El neumococo tiene efectos cardiotóxicos directos. Se cree que son producidos por la inhibición en la contractibilidad de los miocitos cardiacos, por la formación de lesiones microscópicas no purulentas llenas de neumococos y por ciertos componentes de su virulencia, como la neumolisina o el peróxido de hidrógeno. La formación de una cicatriz cardíaca, después de una infección neumocócica severa puede explicar que las personas que han estado hospitalizadas por neumonía tienen un mayor riesgo de muerte súbita durante el año siguiente a la infección [94, 95].

La endocarditis del SA se establece principalmente al lado izquierdo del corazón, asentándose sobre válvulas nativas. Excepcionalmente aparece en válvula protésicas. La aorta es la más frecuentemente dañada (49,32% de los pacientes), seguida de la mitral (28,77%) y la afectación conjunta de ambas (13,7%). La lesión de la válvula pulmonar, tricúspide, o la mitral y tricúspide de manera conjunta ocurre en menos del 5% de los casos. El motivo por el que la infección arraiga principalmente en la válvula aórtica es desconocido. Su lesión, comparada con la del resto de las válvulas, ocasiona un mayor número de perforaciones y abscesos perivalvulares precoces desencadenantes de insuficiencia cardiaca [22]. También aparecen más casos de regurgitación grave [93].

Los pacientes con endocarditis por el SA presentan una regurgitación importante debido a su predisposición por la válvula aórtica. La regurgitación valvular es severa en el 70,18% de los pacientes, moderada en el 19,3% y leve en el 10,53% de los mismos. El gran tamaño de las vegetaciones predispone a la embolización sistémica [93], por lo que la cirugía se indica con mayor frecuencia en estos pacientes (57,58%). La presentación subaguda es inusual, siendo más habitual en los pacientes de mayor edad [5, 22].

Es difícil determinar si la infección cardiaca ocurre antes o después de la meningitis, ya que la sintomatología inicial de la endocarditis suele ser inespecífica [88]. El diagnóstico temprano puede retrasarse por la ausencia de los estigmas clásicos de la endocarditis o por la aparición tardía de soplos cardíacos patológicos [31, 32]. No se encuentra estigmas asociados en dos de cada tres pacientes [63]. En algunos casos, la endocarditis puede aparecer tarde, incluso después de la iniciación de la terapia antibiótica correcta y la recuperación aparente de la neumonía [55]. Normalmente se diagnostica cuando aparece la clínica de insuficiencia valvular [28, 29], por lo que hay que realizar una exploración cardíaca apropiada ante la presencia de meningitis neumocócica, para descartar endocarditis lo más precozmente posible [26, 30, 63]. También debe sospecharse afectación cardiaca ante toda neumonía que responde mal al tratamiento antibiótico o presenta complicaciones hemodinámicas [35]. Para el diagnóstico se utilizan los criterios de Duke modificados, basados en parámetros clínicos, microbiológicos y de imagen [96].

El ETT es la prueba de imagen de primera elección si existe sospecha de endocarditis. Su sensibilidad (95%) es superior al ETT, como ha ocurrido en nuestro paciente, debido a su mejor visualización y resolución espacial [91]. La ausencia de lesiones valvulares en los registros de ETT puede ser frecuente y suponer un porcentaje elevado [22], por lo que se recomienda realizar un ETE a todo paciente con sospecha clínica de endocarditis y ETT negativa o no diagnóstica [96, 97]. La TC cardiaca y la tomografía por emisión de positrones con 18F-fluorodesoxiglucosa se ha utilizado para el diagnóstico de imágenes dudosas en la válvula afectada y para mejorar la detección de fenómenos vasculares silentes (complicaciones embólicas o aneurismas infecciosos) [24, 25, 98, 99].

Meningitis. El neumococo es la causa más común de meningitis bacteriana en adultos en gran parte del mundo [8]. Sin embargo cuando se asocia a endocarditis, sólo se observa en el 1% de las mismas [88]. Se ha sugerido una predisposición genética a sufrir meningitis neumocócica [100, 101, 102].

La forma de presentación clínica en el SA suele ser indistinguible de la que ocurre por otras etiologías. La fiebre y la alteración en el nivel de conciencia son síntomas habituales. Como ocurría en nuestro paciente, algunas características clínicas clásicas como la cefalea pueden estar ausentes, dificultando el diagnóstico [13, 103]. Parece existir más frecuencia de convulsiones, signos focales en las etapas tempranas de la enfermedad y afectación del VIII par craneal [104].

Neumonía. *S. pneumoniae* es el germen más frecuentemente aislado en las neumonías con hemocultivo positivo [105]. Suele presentarse de manera abrupta, con fiebre, escalofríos, tos con expectoración purulenta y dolor torácico de características pleuríticas. En pacientes ancianos, estas cualidades pueden estar ausentes. El patrón radiológico típico consiste en una consolidación homogénea no segmentaria.

Existe una considerable superposición en la presentación clínica, que no permite distinguir a los pacientes bacteriémicos de los no lo son. No obstante, en la neumonía bacteriémica los pacientes afectados son más jóvenes, presentan una temperatura más elevada, mayor taquicardia, o un ingreso hospitalario más precoz [106].

DIAGNÓSTICO Y TRATAMIENTO

El diagnóstico del SA requiere un alto índice de sospecha. Los hemocultivos positivos siguen siendo la piedra angular para el diagnóstico, tanto para la identificación del germen como para probar la susceptibilidad a los antibióticos [96, 107]. Un hemocultivo negativo, que ocurre hasta en un 31% de todos los casos, puede originar confusión, y a menudo plantea considerables dilemas diagnósticos y terapéuticos. Suele aparecer como consecuencia de un tratamiento antibiótico previo [31, 32, 108].

El tratamiento médico del SA se basa en la supresión de *S. pneumoniae* con fármacos antimicrobianos, aunque en un porcentaje elevado de pacientes es preciso realizar cirugía de la endocarditis [6]. Antes de la introducción de la penicilina

era un proceso mortal [22, 23]. La alta tasa de resistencia a la penicilina existente en España [84] desaconseja su utilización de manera empírica. Al existir meningitis, se recomienda utilizar ceftriaxona o cefotaxima a altas dosis en combinación con vancomicina, hasta obtener el patrón de sensibilidad antibiótica [96, 109, 110]. Aunque no hay datos suficientes para recomendar moxifloxacino como parte del tratamiento de la meningitis neumocócica, este fármaco se ha utilizado a veces en pacientes con alergias graves a cefalosporinas o vancomicina [111]. Una buena terapia antibiótica de inicio temprano, adecuada y mantenida, mejora el pronóstico [30].

Una revisión Cochrane de 2015 encontró que los corticoides reducen la mortalidad en la meningitis por *S. pneumoniae* (RR 0,84, IC95%: 0,72-0,98), la sordera neurosensorial (RR 0,74, IC95%: 0,63-0,87) y las secuelas neurológicas (RR 0,83, IC95% 0,69-1,00). Es aconsejable su utilización en el SA [41, 103].

Muchos pacientes con SA precisan tratamiento quirúrgico debido a las complicaciones graves que presentan, aunque supone un riesgo importante durante la fase activa de la enfermedad. Las indicaciones de una cirugía precoz son insuficiencia cardiaca progresiva, infección incontrolada y la prevención de complicaciones embolicas [96, 112]. La cirugía valvular temprana, realizada dentro de las 48 horas posteriores al diagnóstico, disminuye la mortalidad prematura [51, 63, 93,113]. También reduce el riesgo de complicaciones, como el embolismo sistémico, el choque cardiogénico o el fallo multiorgánico, comparado con la terapia convencional [27, 29, 60, 114, 115]. A pesar de la evidencia de una mayor supervivencia de los pacientes con cirugía precoz, hay que equilibrar los beneficios de la operación con los riesgos que presenta el paciente [28, 112]. Los pacientes con SA que han sido intervenidos quirúrgicamente representan la mitad de los casos (57,58%).

Serotipos. Las manifestaciones más infrecuentes de ENI, como el SA, suelen estar producidas por serotipos no incluidos en la vacuna antineumocócica conjugada 13-valente (VNC13), y presentan mayor resistencia a los antimicrobianos [116]. En la revisión bibliográfica que hemos realizado, solamente se refleja el serotipo causante del SA en uno de cada seis pacientes. La mayoría de ellos están incluidos en la vacuna antineumocócica polisacárida 23-valente (VNP23), y algo menos de la mitad en la VNC13. Hay que recordar que los casos revisados, aparecen en un periodo de tiempo amplio.

COMPLICACIONES

Las complicaciones del SA son diversas. Pueden ocasionar lesiones neurológicas, pericarditis, aneurismas infecciosos, manifestaciones osteomusculares o insuficiencia renal aguda, entre otras (tabla 1). El caso que hemos expuesto presentó ictus y sordera neurosensorial.

Ictus. El ictus es una complicación frecuente. Aparece en el 25% de los pacientes con meningitis [117], y en el 15% de los pacientes con endocarditis [118]. El riesgo con ambas patologías se incrementa al 38% [88] Aparece más frecuentemente en infección por *S. aureus* y afectación de la válvula mitral. Por el contrario, es infrecuente cuando ocurre por *S. pneumoniae* y la válvula aórtica es la dañada. El tratamiento antibiótico apropiado de manera precoz, disminuye el riesgo de complicaciones neurológicas [119]. En nuestra revisión aparece en el 22,97% de los pacientes.

El origen del ictus en el síndrome de Austrian puede deberse a la meningitis, endocarditis o la neumonía, no estando implicados en el mismo los factores de riesgo cardiovasculares clásicos [120]. La vasculitis, el espasmo, o la trombosis intraarterial son factores implicados en el origen meníngeo del ictus [121], aunque la vasculitis ha sido cuestionada recientemente [122]. La endocarditis puede ocasionarlo por embolismo del sistema nervioso central [6] y la neumonía por hipercoagulabilidad, activación plaquetaria y deterioro de la función endotelial [123].

Sordera neurosensorial. Aunque la endocarditis puede producir hipoacusia neurosensorial por laberintitis infecciosa o hipoxia secundaria a un embolo en el laberinto [124], la causa más probable en el SA parece ser debida a la meningitis. La pérdida de audición es una de las complicaciones más comunes de la meningitis neumocócica, ocurriendo hasta en el 36% de los sobrevivientes. La recuperación de la audición ocurre en un 40-65% de los pacientes [8, 125, 126], recuperación que no se ha producido en el caso que presentamos. Se ha achacado a la ototoxicidad de *S. pneumoniae* [127]. La gravedad de la infección es el determinante clave de la pérdida de la audición a largo plazo [128]. También influyen la edad avanzada, el serotipo o el sexo femenino [126, 129].

FACTORES DE RIESGO. COMORBILIDADES

La aparición de la ENI está influenciada por factores sociodemográficos. Es más frecuente en pacientes con bajo nivel socioeconómico [130], escaso nivel de estudios [131] y varones [87]. La prevalencia de la ENI aumenta con la edad debido a la inmunosenescencia (descenso de función inmune con la edad), y a las altas tasas de comorbilidades y de enfermedades agudas [132]. También es más frecuente en paciente fumadores [131] y en los que consumen alcohol [133].

Los pacientes inmunocomprometidos, con asplenia funcional o anatómica, los trasplantados, los que tienen tumores o hemopatía maligna, los que se encuentran en tratamiento con medicamentos inmunosupresores, corticoides, o con fármacos inmunobiológicos, y los que tienen fístulas del LCR o implantes cocleares presentan un aumento del riesgo de padecer ENI. Ciertas comorbilidades como diabetes mellitus, enfermedad renal, hepática, respiratoria, cardiaca o autoinmune también se han involucrado en un aumento de riesgo de padecer ENI. Así mismo se han descrito otros procesos como las infecciones en senos paranasales y oído, la infección por el virus gripal A (H1N1), la desnutrición, el consumo de cocaína o las drogas endovenosas [21, 22, 24, 40, 42, 50, 53, 86, 92, 134, 135].

El mayor riesgo de padecer ENI ocurre en los pacientes inmunodeprimidos, aunque un estudio realizado en una cohorte amplia de pacientes ha demostrado que la presencia de dos

condiciones de riesgo casi igualaba ese riesgo, y la presencia de tres factores lo duplicaba. Así por ejemplo, en los mayores de 65 años, el riesgo relativo de padecer una ENI en pacientes inmunodeprimidos es de 4,4 (IC95%:3,9-5,0), en los que presentan dos factores de riesgo es de 3,6 (IC95%:3,1-4,1), y los que presentan tres factores de riesgo 7,6 (IC95%:6,4-8,9) [136].

El SA presenta algunas peculiaridades a lo anteriormente descrito. No aparece más frecuentemente en los mayores de edad, sino que ocurre, como hemos visto, en la edad media de la vida. El consumo de alcohol como factor de riesgo es descrito más frecuentemente que en la ENI. Se cree que su influencia es debida a las alteraciones que ocasiona en las respuestas inmunes innatas y adaptativas para la defensa contra infecciones neumocócicas [137, 138]. No obstante, la noción de que el SA es una enfermedad que ocurre en pacientes alcohólicos es cuestionable, ya que sólo aparece como factor de riesgo en el 37,88% de los casos.

La diabetes, como ocurre en el caso que presentamos, aparece como factor de riesgo en el 7,58% de los pacientes. Se cree que es debido a los efectos nocivos de la hiperglucemia en la función inmune [139]. Es conocido que la diabetes, aumenta el riesgo de padecer neumonía neumocócica y ENI, y que su impacto es mayor en individuos menores de 64 años, siendo más pronunciado por debajo de los 40 años [140].

Uno de cada diez pacientes no presentaba antecedentes de riesgo. La pregunta de por qué un paciente inmunocompetente y sano, sufre un SA, permanece sin respuesta.

INFLUENCIA DE LA VACUNACIÓN EN EL SINDROME DE AUSTRIAN

En la década de 1970, Robert Austrian defendió la fabricación y distribución de una vacuna polisacárida 14-valente, que evolucionó a la formulación actual 23-valente. Actualmente se utilizan dos vacunas en la prevención de la ENI, la VNP23.y la VNC13. La vacuna que contiene polisacáridos, es la que más serotipos incluye, pero no genera memoria inmunológica ni respuesta secundaria de anticuerpos. Provoca un fenómeno de tolerancia inmunitaria, no actúa sobre la colonización nasofaríngea, y es poco inmunógena en menores de 2 años. La vacuna conjugada incluye un número menor de serotipos, induce memoria inmunológica y desarrolla una respuesta inmunitaria más potente que la vacuna polisacárida. Es inmunógena desde los primeros meses de vida y crea inmunidad en las mucosas, disminuyendo el estado de portador nasofaríngeo [141, 142].

La introducción de la VNC13 en el calendario vacunal en la Comunidad de Madrid, ha originado una reducción importante en la incidencia de la ENI producida por serotipos incluidos en la vacuna en todos los grupos de edad [3], lo que apoya la existencia de protección de grupo [143]. En Canadá se ha observado también una marcada reducción de ENI por serotipos incluidos en la VNC13, aunque de forma más modesta en la edad media de la vida [86], que es donde ocurre más frecuentemente el SA. Si bien la reducción de la incidencia global ha sido del 43%, se está produciendo un incremento de los casos ocasionados por serotipos no incluidos en la VNC13, especialmente en mayores de 59 años [3]. En Inglaterra y Gales se ha observado la misma tendencia [143].

Es posible que la epidemiología de la ENI, y por tanto la del SA, esté cambiando. Se cree que la implantación progresiva en el calendario infantil de la VNC13 realizará un efecto rebaño o inmunidad colectiva de los adultos no vacunados frente a estos serotipos [19, 144-146]. No obstante, la aparición de ENI en pacientes adultos por serotipos no incluidos en la VNC13 cuestiona la capacidad de crear protección global [86,[147, 148] y requerirá un enfoque diferente en las estrategias de vacunación. Los serotipos no incluidos en la misma podrían desempeñar un papel importante en la ENI de adultos en un futuro cercano [149, 150]. Una nueva vacuna conjugada 15-valente, que contiene las cepas 22F y 33F se está experimentando actualmente en ensayos clínicos [151]. La vacunación en grupos de riesgo, es una necesidad.

La introducción de las vacuna VNC7 supuso un descenso de la resistencia antibiótica. [152, 153], aunque en España se apreció un aumento achacable a serotipos no incluidos en dicha vacuna [154]. La posterior introducción de la VNC13, que incluía algunos de los serotipos resistentes, ha supuesto una disminución de la resistencia antibiótica en nuestro país [155]. Una evolución similar ha ocurrido en Dinamarca [156]. El efecto beneficioso se produce, al menos, de dos formas: desacelerando la propagación de serotipos especialmente resistentes, como el 19A, y evitando la utilización de antimicrobianos al prevenir la enfermedad [157, 158].

Una de las limitaciones de esta revisión es que únicamente se han incluido casos referenciados, que además aportaban información clínico-epidemiológica. Los incluidos en series de endocarditis o meningitis neumocócicas, sin información adicional [6, 92, 93, 159], no han sido reflejados en esta revisión.

CONCLUSIONES

El síndrome de Austrian es una realidad infrecuente que no debe obviarse por su gravedad. El diagnóstico de sospecha precoz puede evitar un desenlace fatal. Ante cualquier paciente con neumonía o meningitis neumocócica, especialmente de mediana edad, se aconseja realizar una exploración cardíaca para descartar la presencia de una endocarditis, y reemplazar si procede, la válvula afectada lo más rápidamente posible. No podemos olvidar, parafraseando a Osler, que la medicina es un arte de probabilidades y una ciencia de incertidumbres.

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Original

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Typing and antimicrobial susceptibility of 134 *Neisseria gonorrhoeae* strains from Southern Spain

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ABSTRACT

Introduction. Last guidelines have recommended the introduction of dual antimicrobial therapy in order to avoid treatment failure. In the present report, the susceptibility to some antibiotics was evaluated, and the typing of *Neisseria gonorrhoeae* strains was performed.

Material and methods. Gonococcal isolates were tested for susceptibility according to the recommendations of both CLSI and EUCAST. A total of 134 isolates were typed by the NG-MAST technique.

Results. Seventy-two different *N. gonorrhoeae* types were found, and the most frequent types obtained were ST 1407, ST 14958, ST 7192, ST 13251 and ST 5405. If CLSI/EUCAST criteria were applied, a ST 9807 type was found nonsusceptible to ceftriaxone and cefixime (MIC 0.5 mg/L), and a ST 12800 type was found nonsusceptible only to cefixime (MIC 0.25 mg/L). When only EUCAST breakpoints were taken into account, three strains were also resistant to cefixime (MIC 0.25 mg/L) and three isolates were resistant to ceftriaxone (MIC 0.19, 0.16 and 0.25 mg/L, respectively). The majority of strains were resistant to ciprofloxacin (68.6%), and all *N. gonorrhoeae* strains were susceptible to spectinomycin; 9.7% of isolates were resistant to azithromycin.

Conclusions. Molecular typing may be a useful tool to predict antimicrobial resistance. High rates of resistance to penicillin, tetracycline and ciprofloxacin were found in this area. It is highly recommended to carry out antimicrobial susceptibility in all gonorrhoea cases and to identify treatment failures to verify emerging resistance.

Keywords: *Neisseria gonorrhoeae*; susceptibility testing; molecular typing; epidemiology; resistance

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Tipado y sensibilidad a antimicrobianos de 134 cepas de *Neisseria gonorrhoeae* en el sur de España

RESUMEN

Introducción. Las últimas guías recomiendan la introducción de tratamiento antimicrobiano doble para evitar fallos de tratamiento. En esta publicación, se evaluó la sensibilidad a algunos antibióticos, y se realizó el tipado de las cepas de *Neisseria gonorrhoeae*.

Material y métodos. La determinación de sensibilidad fue realizada según las recomendaciones tanto del CLSI como del (EUCAST). Un total de 134 cepas fueron tipadas mediante la técnica de NG-MAST.

Resultados. Se encontraron 72 tipos diferentes de *N. gonorrhoeae*, siendo los más frecuentes el ST 1407, 14958, 7192, 13251 y 5405. Aplicando los criterios del CLSI/EUCAST, un tipo ST 9807 fue no sensible a ceftriaxona y cefixima (CMI 0,5 mg/L), y un tipo ST 12800 fue no sensible solo a cefixima (CMI 0,25 mg/L). Al aplicar solamente los puntos de corte de EUCAST, tres cepas fueron también resistentes a cefixima (CMI 0,25 mg/L) y tres lo fueron también a ceftriaxona (CMI 0,19, 0,16 y 0,25 mg/L, respectivamente). La mayoría de cepas fueron resistentes a ciprofloxacino (68,6%), y todas las cepas de *N. gonorrhoeae* fueron sensibles a espectinomicina; el 9,7% de aislamientos fueron resistentes a azitromicina.

Conclusiones. El tipado molecular puede ser una herramienta útil para predecir resistencia a antimicrobianos. En esta área se encontraron altas tasas de resistencia a penicilina, tetraciclina y ciprofloxacino. Se recomienda encarecidamente realizar estudio de sensibilidad a antibióticos en todos los casos de gonorrea e identificar fallos de tratamiento para verificar la aparición de resistencias.

Palabras clave: *Neisseria gonorrhoeae*; estudio de sensibilidad; tipado molecular; epidemiología; resistencia

INTRODUCTION

Infections due to *Neisseria gonorrhoeae* (NG) are the second most commonly reported sexually transmitted infections (STIs) worldwide caused by bacteria [1]. The prevalence of this infection varies among populations but it continues to present a serious public health problem in many countries [2], although the vast majority of the gonorrhoea burden globally is in low and middle-income countries [2]. Thus, an appropriate diagnosis and an effective treatment of this infection are important factors contributing to public health control and to prevent serious complications.

Treatment is usually given empirically following recommendations in evidence-based treatment guidelines. Ceftriaxone or dual antimicrobial therapy of ceftriaxone plus azithromycin is currently the only options for empirical first-line therapy in most countries [3, 4]. However, the increase of resistance to recommended treatments for gonorrhoea may seriously affect to infection control [5].

Recently, some authors have described failure of dual antimicrobial therapy in treatment of gonorrhoea [6] and during the last years several NG isolates exhibited decreased susceptibility and resistance to the third generation cephalosporins have been reported [7, 8]. In 2015, 1.7% of isolates from European countries showed decreased susceptibility to cefixime, and there was a high prevalence of resistance to ciprofloxacin (49.4%) and azithromycin (7.1%) [9].

Due to these facts, antimicrobial surveillance programs are necessary to detect patterns of resistance at international, national, but also at regional level to ensure treatment efficacy against this infection. In this sense, molecular epidemiology surveillance can help to provide additional information on the emergence and dissemination of antimicrobial resistance. Molecular studies for epidemiological surveillance are necessary to detect association between genotype and antimicrobial resistance and to know how resistant strains emerge and disseminate [10].

The main objective of the present study was to analyze the antimicrobial susceptibility of *N. gonorrhoeae* strains isolated from genital specimens in patients belonging to a health area of Southern Spain, as well as to perform the typing of these samples in order to detect epidemiological clusters of infection and possible modifications of the susceptibility patterns.

MATERIALS AND METHODS

Collection of NG strains. All NG strains isolated from January 2012 to December 2016 were included in this study. The genital samples were obtained from patients with STIs belonging to the health area of the Hospital of Poniente (El Ejido, Almería, Spain) composed by primary health care and the reference hospital, and were sent to the microbiology laboratory for culture. A total of 134 isolates were included for both antimicrobial susceptibility study and molecular typing. All samples were obtained from genital sites (urethral or endocervical/vaginal exudates). No extragenital samples (rectal and pharyngeal specimens) were included in this study because these kind of samples were not send to our laboratory. All samples were cultured in VCA agar (BioMérieux, France). The identification of NG suspected strains was performed by Gram stain, oxidase and catalase production, and finally with both biochemical analysis by the API NH system (BioMérieux, France) and proteomic analysis by MALDI-TOF technology (Vitek MS, bioMérieux, France). The identification of all strains was confirmed at the National Centre of Microbiology (Instituto de Salud Carlos III, Madrid, Spain).

Antimicrobial susceptibility testing. Gonococcal isolates were tested for susceptibility according the recommendations of Clinical and Laboratory Standards Institute (CLSI) [11] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [12]. All strains were tested for susceptibility to penicillin, ceftriaxone, cefixime, tetracycline, ciprofloxacin, azithromycin and spectinomycin by agar dilution tests. All isolates were also tested for penicillinase production using the Cefinase test (bioMérieux, Marcy-l'Etoile, France). MIC interpretation was performed according to both CLSI and EUCAST, and then compared.

Molecular typing. All NG strains (n= 134) were typed by the *N. gonorrhoae* multi-antigen sequence typing (NG-MAST) technique [13], which differentiates strains on the basis of sequence variation in fragments of two hypervariable genes, the subunit B of the transferring binding protein (*tbpB*) and the porin Por B (*porB*). The typing was performed at the National Centre of Microbiology (Instituto de Salud Carlos III, Madrid, Spain). Allele numbers and STs were assigned using NG-MAST databases (www.ng-mast.net). Moreover, all NG strains were also serotyped at this center by means of the Phadebact® Monoclonal GC Test (MKL Diagnostics AB, Sollentuna, Sweden).

RESULTS

One hundred and four samples were taken from men, and the remaining from women. Finally, 133 patients were included in this study. The age of patients included in this study range from 20 to 50 years old (median age= 32 years old). Sixty-nine (51.4%) samples were obtained from immigrant population and 65 (48.6%) from indigenous patients. The vast majority of strains were obtained from urethral samples (104/77.7%) whereas 30 (22.3%) strains were obtained from vaginal or endocervical fluid. From the 134 typed strains, 72 different STs were obtained and all NG strains included in this study belonged to the IB serotype. It can see the distribution of main types in table 1. The most frequent types found were STs 1407 (n=8), STs 14958 (n=8), STs 7192 (n=7), STs 13251 (n=7), STs 5405 (n=5), STs 2992 (n=4), STs 387 (n=4), STs 7232 (n=4), STs 5624 (n=4), and STs 5120 (n=4). An important finding is that a ST 9807 strain was nonsusceptible (according to CLSI and EUCAST criteria) to ceftriaxone and

Table 1 **Main types of *Neisseria gonorrhoeae* strains (NG-MAST) related to the susceptibility to some antimicrobials (according EUCAST).**

ST	Antimicrobial susceptibility			Allele	
	Ceftriaxone	Cefixime	Azithromycin	por B	tbpB
1407	S	S	S	908	110
1407	S	S	S	908	110
1407	R	S	S	908	110
1407	R	S	S	908	110
1407	S	R	R	908	110
1407	S	S	R	908	110
1407	S	S	S	908	110
1407	S	S	S	908	110
14958	S	S	S	8692	137
14958	S	S	S	8692	137
14958	S	S	S	8692	137
14958	S	S	S	8692	137
14958	S	S	S	8692	137
14958	S	S	S	8692	137
14958	S	S	S	8692	137
14958	S	S	S	8692	137
7192	S	S	S	90	138
7192	S	S	S	90	138
7192	S	S	S	90	138
7192	S	S	S	90	138
7192	S	S	S	90	138
7192	S	S	S	90	138
7192	S	S	S	90	138
13251	S	S	S	7696	137
13251	S	S	S	7696	137
13251	S	S	S	7696	137
13251	S	S	S	7696	137
13251	S	S	S	7696	137
13251	S	S	S	7696	137
13251	S	S	S	7696	137
5405	S	S	S	3279	1139
5405	S	S	S	3279	1139
5405	S	S	S	3279	1139
5405	S	S	S	3279	1139
5405	S	S	S	3279	1139
387	S	S	S	266	118
387	S	S	S	266	118
387	S	S	S	266	118
387	S	S	S	266	118
2992	S	S	S	1808	29
2992	S	R	R	1808	29
2992	S	S	S	1808	29
2992	S	S	S	1808	29
5120	S	S	S	3105	118
5120	S	S	S	3105	118
5120	S	S	S	3105	118
5120	S	S	S	3105	118
7232	S	S	S	1489	1388
7232	S	S	S	1489	1388
7232	S	S	S	1489	1388
7232	S	S	S	1489	1388
5624	S	S	S	90	953
5624	S	S	S	90	953
5624	S	S	S	90	953
5624	S	S	S	90	953
9807	R	R	S	5785	137
7072	S	R	S	4259	10

S: susceptible, R: resistant

Table 2 **Antimicrobial susceptibility comparison between CLSI and EUCAST recommendations.**

	CLSI					EUCAST			
	R	S	I	%NS		R	S	I	%NS
Penicillin	55	41	38	69.4	Penicillin	69	22	43	83.5
Ceftriaxone	1	133	0.7		Ceftriaxone	4	130	2.9	
Cefixime	2	132	1.4		Cefixime	5	129	3.7	
Tetracycline	74	35	25	73.8	Tetracycline	74	32	28	76.1
Ciprofloxacin	92	42	68.6		Ciprofloxacin	92	42	68.6	
Spectinomycin	134	0			Spectinomycin	134	0		
Azithromycin					Azithromycin	13	121	9.7	

R: resistant; S: susceptible; I: intermediate; NS: nonsusceptible; CLSI: Clinical and Laboratory Standards Institute; EUCAST: European Committee on Antimicrobial Susceptibility Testing

Table 3 **Susceptibility percentage to tested antibiotics comparing CLSI and EUCAST.**

Antibiotic	CLSI percentage	EUCAST percentage
Penicillin	30.6	16.5
Ceftriaxone	99.3	97.1
Cefixime	98.6	96.3
Tetracycline	26.2	23.9
Ciprofloxacin	31.4	31.4
Spectinomycin	100	100
Azythromycin		90.3

cefixime (MIC 0.5 mg/L for both antibiotics). Moreover, according to EUCAST criteria, four strains were also resistant to cefixime (ST 2992, ST 7072, ST 12800 and ST 1407; MIC 0.25 mg/L) and three more strains were resistant to ceftriaxone [ST 1407 (MIC 0.19 and 0.25 mg/L, respectively), and ST 225 (MIC 0.16 mg/L)]. All STs 1407 and 14958 included in this study were non-susceptible to ciprofloxacin.

Forty-seven isolates (35%) demonstrated penicillinase production. If only CLSI criteria are applied, only a gonoccocal strain (ST 9807) was nonsusceptible to ceftriaxone and cefixime, whereas according to EUCAST criteria five gonoccocal strains were resistant to cefixime and four were resistant to ceftriaxone. According to EUCAST criteria, only 22 (16.4%) gonoccocal strains were susceptible to penicillin, but if CLSI criteria are applied 41 (30.5%) isolates were susceptible to this antibiotic. The majority of isolates in this study were resistant to ciprofloxacin (92/68.6%). All NG strains were susceptible to spectinomycin. Regarding to azithromycin, 13 (9.7%) were resistant to this drug. MIC for 7 strains resistant to azithromycin was 1 mg/L, and the MIC for the remaining cases was 2 mg/L. Unfortunately, no data about previous treatment and co-infections could be obtained. The complete data corresponding to gonoccocal strains susceptibility and resistance are shown in table 2. Comparison data of antimicrobial susceptibility between CLSI and EUCAST are included in table 3.

From 134 samples, only 10 (7.4%) strains were susceptible to all antibiotics tested; 41 (30.5%) strains were resistant to more than three antibiotic (multirresistant), 28 (20.8%) were resistant to three antibiotics, 17 (12.6%) resistant to two antibiotics and finally 32 (23.8%) were resistant to only one antibiotic.

Regarding to isolates distribution in our health area, an epidemiological relationship could be observed. Three strains of ST1407 type, three strains of ST 5405 type, two strains of ST 2992 type and two strains of ST 5120 type are grouped and located in the same geographical area (health basic zone), so a presumptive relationship could be observed. Moreover, the strain ST 9807 (nonsusceptible to ceftriaxone and cefixime) was also located in the main epidemiological focus, considered as the geographical area in which the majority of strains were obtained.

A patient had two different isolates (ST 6715 and ST 4260) in two different cultures separated by 1 month. After a correct treatment, this patient had again the strain ST 6715 one year later in a new urethral sample.

From the 35 strains belonging to types ST 1407, ST 14958, ST 7192, ST 13251, and ST 5405, 25 of them were found in immigrant population and these strains appear to have had epidemiological relationship because they were located in the same health basic zone.

During the follow-up period, test of cure was not carried out in the majority of patients (86/64.1%), whereas test of cure was performed in the remaining patients at least 72 hours after completion of treatment. From these patients the culture was negative in 47, but in one patient, a new type of *N. gonorrhoeae* was found.

DISCUSSION

Gonorrhoea remains an important public health problem because of untreated infections may lead to severe sequelae. In 2012, the World Health Organization (WHO) estimated 78.3 million new global cases among adults worldwide, although the true incidence is probably underestimated [2]. Thus, effective

treatment of gonorrhoea is crucial to the disease control, but the progressive increase of resistance to recommended treatment regimens has compromised infection control efforts. Over the past decades, many countries already have high prevalence of gonococcal resistance to all antibiotics that have been used for treatment such as penicillins, sulphonamides, tetracyclines, quinolones and early generation macrolides and cephalosporins [3, 5, 14). The results of the present study also show a high percentage of isolates non-susceptible to these antibiotics such as penicillin [69.4% (CLSI); 83.5% (EUCAST)], tetracycline [73.8% (CLSI); 76.1% (EUCAST)], and ciprofloxacin (68.6%), so these antimicrobials cannot be used as empirical treatment.

When any laboratory results are available, the empirical first-line therapy guidelines recommend the use of extended spectrum cephalosporins (ceftriaxone or cefixime) [15] and, recently, European guidelines as well as most of therapeutic guidelines recommend the use of dual therapy with ceftriaxone plus azithromycin [16]. However, some gonococcal strains with low-level ceftriaxone and cefixime resistance have been described [3, 17]. Some of these reductions on susceptibility were accompanied with subsequent treatment failures [18]. In addition, multidrug-resistant (MDR) gonococcal strains have been detected [3, 5, 14], and highly ceftriaxone-resistant NG strains have been recently reported [7, 8, 19-21], and this fact shows that susceptibility to ceftriaxone is progressively decreasing.

In our study, the majority of strains were susceptible to extended spectrum cephalosporins, but according to EUCAST four isolates were resistant to ceftriaxone and five strains were resistant to cefixime. On the other hand, 13 (9.7%) strains were resistant to azithromycin. A recent study reported 32% of resistance to azithromycin from 384 NG isolates [22]. In view of these results, the best empirical treatment for gonoccocal infections in our health area should be the administration of dual therapy as it is recommended, although it is strongly recommended the susceptibility testing to antibiotics in order to detect resistance.

A similar study performed in Spain [23] with 100 NG strains shows three NG strains nonsusceptible to ceftriaxone and ten NG strains resistant to cefixime according to EUCAST criteria. The percentage of resistance to ceftriaxone was similar to the present study (4% vs 2.9%), although the percentage of resistance to cefixime was higher than in our study (11% vs. 3.7%). However, if CLSI criteria were applied, the percentages of resistance to ceftriaxone and cefixime were low and similar in both studies.

Regarding to the susceptibility to antimicrobials, there are some differences in the breakpoint criteria between CLSI and EUCAST. According to CLSI, susceptibility to ceftriaxone and cefixime is defined when MIC is ≤0.25 mg/L, whereas strains with MIC >0.25 mg/L are defined as nonsusceptible. According to EUCAST, however, susceptibility to these antibiotics is defined when MIC is ≤ 0.125 mg/L, and those with MIC >0.125 mg/L are classified as resistant. On the other hand, only EUCAST has defined resistance to azithromycin (MIC >0.5 mg/L). Due to these differences, a standardization of the breakpoints for the study of susceptibility to these antimicrobials according to clinical and microbiological criteria is necessary.

Regarding the empirical treatment applied to our patients with resistance to ceftriaxone and/or cefixime, all patients were correctly treated with ceftriaxone (250 mg, intramuscularly) and azithromycin 1 g orally. Test of cure was only performed in one of these patients, but no failure in the treatment was clinically demonstrated. Although it is not universally recommended to perform test of cure, some guidelines recommend it in order to ensure eradication of infection and identify emerging resistance [24]. Overall, test of cure was carried out in 48 (35.8%) patients in this study, so efforts should be taken to warn the physicians about the importance of the follow-up to the patients.

Seventy-two different types were isolated in this study, although both ST 1407 and ST 14958 were the most frequent. While considerable diversity was observed through the medical literature, ST 1407 was the most common type encountered in the recent report from Barcelona [23] as well as in some European countries [25, 26], being the wide dissemination of this type in Europe a recent phenomenon [27]. Due to some types have been associated with specific resistance phenotypes, it is highly recommended to perform molecular typing of the isolates in order to detect this association. Thus, ST 1407 is the clone that has been associated with resistance to ceftriaxone and cefixime [28, 29] and with treatment failures with extended spectrum cephalosporins [28]. Our data also support the evidence that all ST 1407 isolates in Europe are ciprofloxacin resistant, strongly associated with decreased susceptibility to cefixime [30]. All our STs 1407 strains were resistant to ciprofloxacin, as well as all isolates published recently by Chisholm et al coming from different countries of the European Union [30]. This fact enhances the usefulness of molecular typing techniques as a method to predict antimicrobial resistance. Moreover, the results of the present study demonstrate that other types such as ST 9807, ST 7072, ST 225, ST 12800 and ST 2992 showed decreased susceptibility to ceftriaxone and cefixime. To our knowledge, these strains that showed decreased susceptibility to cephalosporins have not been frequently reported and, until now, they have not been linked with resistance to cephalosporins.

The Centers for Disease Control and Prevention [31] recommends nucleic acid amplification tests to detect gonorrhoea in all laboratories, but it does recommend culture as well to monitor the antimicrobial susceptibility. Moreover, the introduction of correct empirical treatment based on antimicrobial susceptibility data at regional level as well as the adequate follow-up of patients in order to ensure the definitive eradication of the infection, are the other cornerstones of infection control.

Due to the increasing number of NG multirresistant strains, the introduction of antimicrobial surveillance programs should be mandatory, not only at national or international

level but also at regional level. The presence of quality regional surveillance data about antimicrobial resistance to *N. gonorrhoeae* is a good approach to estimate the global burden of resistance to this microorganism. The subsequent communication of data to physicians working in this health area is crucial to improve the control of gonoccocal infections and to know the appropriate empirical treatment at each moment.

Finally, main limitation of this study was the absence of data about extragenital samples (rectal or pharyngeal samples), as well as data about sexual orientation, sexual practice and HIV status of the patients included here. An additional limitation was the absence of data about previous treatment and co-infections of the patients with resistance to azithromycin.

The results of this study show that ST 1407, ST 14958, ST 7192, and ST 13251 are the main types found in our health area. Some NG types such as ST 1407, ST 225, ST 9807, ST 7072, ST 2992 and ST 12800 were associated with decreased susceptibility to third generation cephalosporins. Due to some types are associated to decreased susceptibility to these antibiotics, molecular typing may be a useful tool to predict antimicrobial resistance in absence of antimicrobial testing. Resistance to penicillin, tetracycline, and ciprofloxacin were high in this study, but resistance to azithromycin was lower than in other studies. Due to the low rates of resistance to cefixime and ceftriaxone in this population, these antimicrobials may be still used as empirical treatment of gonorrhoea in our patients.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Original

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Application of pharmacokinetic/pharmacodynamic analysis to evaluate the adequacy of antimicrobial therapy for pediatric acute otitis media in Spain before and after the introduction of the PCV7 vaccine

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ABSTRACT

Objectives. To evaluate, by applying pharmacokinetic/pharmacodynamic (PK/PD) analysis, if the change in antibiotic susceptibility after the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in Spain had any influence on the usefulness of the antimicrobials more frequently used as empirical treatment of pediatric acute otitis media (AOM).

Material and methods. PK parameters and susceptibility of *Streptococcus pneumoniae* and *Haemophilus influenzae* were obtained from bibliography. Monte Carlo simulation was used to estimate the cumulative fraction of response (CFR), understood as the expected probability of therapy success. For amoxicillin and amoxicillin/clavulanate, the target was free antibiotic concentration remaining above the minimum inhibitory concentration (MIC) for ≥50% of the dosing interval ($fT_{>MIC}$≥50%), whereas for cefuroxime axetil and cefotaxime, the target was $fT_{>MIC}$≥60%. CFR values ≥90% were considered successful.

Results. When all serotypes of *S. pneumoniae* are considered, amoxicillin and cefotaxime turned out to reach a high probability of success, and difference before and after vaccination was scarce. For *H. influenzae*, CFR values were higher with amoxicillin/clavulanate than with amoxicillin. For both microorganisms, cefuroxime axetil resulted in low probability of success in the two periods of study.

Conclusions. We have shown that the introduction of the PCV7 vaccination did not lead to changes in the probability of success of the current empiric treatments of the AOM. Integrated PK/PD analysis has demonstrated to be a useful tool to identify changes in antimicrobial activity after the implantation of a vaccination program, providing complementary information to the simple assessment of MIC values.

Keywords: acute otitis media, pharmacokinetics/pharmacodynamics analysis, 7-valent pneumococcal conjugate vaccine

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Aplicación del análisis farmacocinético/farmacodinámico en la evaluación de la adecuación de la terapia antimicrobiana de la otitis media aguda en niños en España antes y después de la implantación de la vacuna antineumocócica heptavalente

RESUMEN

Objetivo. Evaluar mediante análisis farmacocinético/farmadocinámico (PK/PD) si el cambio en la sensibilidad antimicrobiana tras la introducción en España de la vacuna antineumocócica heptavalente (VNC7) ha implicado cambios en la adecuación del tratamiento antibiótico de la otitis media aguda (OMA) en niños.

Materiales y métodos. Los parámetros PK y datos de sensibilidad de *Streptococcus pneumoniae* y *Haemophilus influenzae* fueron obtenidos de la bibliografía. Mediante simulación de Montecarlo, calculamos la probabilidad de éxito del tratamiento antibiótico, expresada como fracción de respuesta acumulada (CFR). Para amoxicilina y amoxicilina/ácido clavulánico, el objetivo farmacodinámico considerado fue el tiempo durante el cual las concentraciones libres en sangre permanecen por encima de la concentración mínima inhibitoria (CMI), expresado como porcentaje del intervalo de dosificación ($fT_{>CMI}$≥50%). Para cefuroxima axetilo y cefotaxima, el objetivo fue $fT_{>CMI}$≥60%. Valores de CFR≥90% se consideraron indicativos de éxito.

Resultados. Si se tienen en cuenta todos los serotipos de *S. pneumoniae*, amoxicilina y cefotaxima proporcionaron una

alta probabilidad de éxito, sin apenas diferencia entre ambos periodos. En el caso de *H. influenzae*, los valores de CFR fueron más altos con amoxicilina/ácido clavulánico que con amoxicilina. Para ambos microorganismos, las probabilidades de éxito de cefuroxima axetilo fueron bajas en ambos periodos de estudio.

Conclusiones. La introducción de la vacuna PCV7 no ha implicado cambios en la probabilidad de éxito del tratamiento antibiótico empírico de la OMA. Hemos demostrado la utilidad del análisis PK/PD para detectar cambios en la adecuación del tratamiento antibiótico tras la implantación de una vacuna, proporcionando información complementaria al seguimiento de los valores de CMI.

Palabras clave: otitis media aguda, análisis farmacocinético/farmacodinámico, vacuna antineumocócica heptavalente

INTRODUCTION

Acute otitis media (AOM) is one of the most frequent illnesses in children and the most commonly cited indication for antimicrobial treatment [1]. Since it is treated mainly empirically, the antimicrobial agents must target the most frequently isolated pathogens. *Streptococcus pneumoniae* has been the predominant pathogen related to AOM. The 7-valent pneumococcal conjugate vaccine (PCV7) has decreased AOM in children <2 years, as demonstrated by a ≥28% reduction in recurrent AOM [2,3] and a ≥43% reduction in AOM outpatient visits or prescriptions [4]. Since the introduction of the PCV7 for the prevention of invasive pneumococcal disease, many studies have shown a decrease in AOM cases in vaccinated as well as in non-vaccinated children due to herd protection [5]. In Spain, the PCV7 was introduced for child immunization in June 2001, and, as expected, it has induced a continuous decline in the prevalence of PCV7 serotypes. A recent study carried out in the north of Spain over a 12-year period [6] revealed that the most frequent serotypes of pneumococci causing AOM under the influence of the PCV7 were 19A (27.8%) and 3 (11.2%), serotypes not included in the vaccine, and 19F (9%). Specifically, the proportion of serotype 19A increased from 17.9% to 37.9%, and that of serotype 3 increased to 5.1% to 15.0%. However, the rate of serotypes included in the PCV7 sharply decreased from 62.4% in 1999-2001 to 2.2% in the 2008-2010. In another study carried out in Spain, a similar decrease in the proportion of PVC7 serotypes was shown: from 70.7% in 1999-2000 to 10.6% in 2009 [7]. On the other hand, in Spain the introduction of PCV7 has been associated to an increase in the proportion of AOM caused by *Haemophilus influenzae* [6]. In fact, the association of *H. influenzae* and *S. pneumoniae* in AOM has been largely demonstrated [8], especially in complex AOM [2,9,10], and several authors have suggested the possibility of an increased rate of *H. influenzae* AOM after the introduction of the PCV7 [11].

Pharmacokinetic/pharmacodynamic (PK/PD) analysis integrates information about the required concentration of antibiotic that reaches the infection site and produces the desirable effect, and information about the susceptibility of the pathogen against the antibiotic, expressed as minimum inhibitory concentration (MIC). PK/PD analysis with Monte Carlo simulation allows the researcher or clinician to select the optimal antibiotic and dosing regimen for each infectious process and patient in order to enhance the effect of the antibiotic, minimizing the side effect incidence and the emergence of resistance [12]. It can also be applied in drug development to scale from animal studies, establish the optimal dosing regimens in clinical trials or describe the kinetic and dynamic relation for new drugs, as required by regulatory agencies. Moreover, PK/PD analysis has also been proved to be useful to assess changing antimicrobial activity against clinical isolates, as complementary to the simply assessment of MIC values [13].

The goal of the current study was to elucidate, by means of PK/PD analysis, if the change in antibiotic susceptibility after the implementation of the PCV7 in Spain had any influence on the adequacy of the antimicrobials more frequently used as empirical treatment of pediatric AOM: amoxicillin, amoxicillin/clavulanate, cefuroxime axetil, and when oral antibiotics are not indicated, cefotaxime.

MATERIALS AND METHODS

The methodology included the following steps: (i) dosing regimen selection and acquisition of pharmacokinetic data; (ii) microbiological data acquisition; and (iii) Monte Carlo simulation of the antibiotics studied in children. Monte Carlo simulation allowed us to estimate the probability of target attainment (PTA), defined as the probability that at least a specific value of a PK/PD index is achieved at a certain MIC, and to calculate the cumulative fraction of response (CFR), defined as the expected population PTA for a specific drug dose and a specific population of microorganisms [14].

Dosing regimen selection and acquisition of pharmacokinetic data. Oral amoxicillin alone and associated with clavulanate, oral cefuroxime axetil, and intravenous cefotaxime were chosen based on their use for the treatment of AOM in children in Spain. The following drug regimens were evaluated: 1) amoxicillin and amoxicillin/clavulanate: 20 mg/kg, 40 mg/kg, 45 mg/kg and 50 mg/kg every 12h (q12h) and 13 mg/kg, 27 mg/kg, 30 mg/kg and 33 mg/kg every 8h (q8h); the dose of amoxicillin/clavulanate is expressed as amoxicillin and is administered as an oral suspension of 100/12.5 mg, 2) cefuroxime axetil: 10 mg/kg and 15 mg/kg q12h, and 3) cefotaxime: 33 mg/kg, 50 mg/kg and 66 mg/kg q8h, as a 0.5 h infusion. Pharmacokinetic parameters were obtained from published pharmacokinetic studies in pediatric populations [15-20]. All parameters were expressed as means and standard deviation (table 1). In the case of cefuroxime axetil and cefotaxime, published pharmacokinetic parameters were available only as mean values, without variability. In order to carry out the PK/PD analysis we assumed a variability (expressed as variation coefficient) of 20% for the volume of distribution (V) and elimination rate constant (K), and 25% for absorption rate con-

Table 1 **Pharmacokinetic parameters for each antimicrobial agent from published studies carried out in children (mean±standard deviation).**

	Amoxicillin	Cefuroxime axetil	Cefotaxime
V/F (L/Kg)	1.44 ± 0.37	0.72 ± 0.14	0.295 ± 0.059
K (h-1)	0.276 ± 0.137	0.5 ± 0.1	0.75 ± 0.15
Ka (h-1)	1.77 ± 0.99	0.43 ± 0.11	-
fu	0.8	0.6	0.6
Reference	[14,15]	[16]	[17-19]

V/F: volume of distribution/drug bioavailability, K: elimination constant rate, KA: absorption constant rate, fu: unbound fraction

stant (Ka). Unbound fraction was included as a fix value [21].

Acquisition of microbiological data. Susceptibility data of clinical isolates to each antibiotic before and after the implementation of the PCV7 were obtained from recently published studies (tables 2 and 3). Pre- (2000-2001) and post- (2010-2011) vaccination bacterial population MIC distribution of *S. pneumoniae* isolates for each antibiotic was provided by Fenoll et al. [7] (table 2). The proportion of the non-vaccine serotypes varied from 44.5% (85/191) in the pre-PCV7 period to 92.1% (128/139) in the post-PCV7 period. The most frequent serotypes in the post-vaccination period were 19A (47.5%, 66/139) and 3 (10.8%, 15/139). Pre-vaccination data of *H. influenzae* (1998-1999) were provided by the Medical Department of GlaxoSmithKline [22], and post-vaccination data of *H. influenzae* (2011) were obtained from a study performed by García-Cobos et al. [23] (table 3). The proportion of β-lactamase-producing *H. influenzae* strains varied from 20.6% in the pre-PCV7 period to 12.5% in the post-PCV7 period, and β-lactamase-nonproducing amoxicillin-resistant (BLNAR) strains varied from 25.3% to 22.9%.

The susceptibility (expressed as minimum inhibitory concentration, MIC) to amoxicillin, amoxicillin/clavulanate, cefuroxime axetil and cefotaxime was studied considering the Clinical and Laboratory Standards Institute (CLSI) breakpoints [24]. *H. influenzae* strains were classified as amoxicillin susceptible (MIC ≤ 1 mg/L), or resistant (MIC > 1 mg/L). BLNAR was determined according to the CLSI breakpoints.

Estimation of probability of target attainment (PTA). A 10,000 subject Monte Carlo simulation was conducted for each antibiotic agent using Oracle® Crystal Ball Fusion Edition v.11.1.1.1.00 (Oracle USA Inc., Redwood City, CA). As β-lactam antibiotics show time-dependent antimicrobial activity, the PK/PD parameter related to its activity is the percentage of time that free drug concentration remains over de MIC ($fT_{>MIC}$). The target was the unbound antibiotic concentration remaining above the MIC for ≥50% of the dosing interval for penicillins ($fT_{>MIC}$ ≥50%) and ≥ 60% for cephalosporins ($fT_{>MIC}$ ≥60%) [16, 25]. The fraction of time (expressed as percentage of the dosing interval) that the drug concentration remains above the MIC ($fT_{>MIC}$) was calculated for over an MIC range of serial twofold dilutions from 0.015 mg/L to 64 mg/L. We assumed a one-compartment pharmacokinetic model and, according statistical criteria, a log-normal distribution for the pharmacokinetic parameters was used.

For cefotaxime (intravenous infusion), the following equation was used to calculate $fT_{>MIC}$ [25]:

$$fT_{>MIC}\ (\%) = \left[\left(t_2 + t_{inf}\right) - t_1\right] x\ 100/\tau \quad \text{(Eq. 1)}$$

where t_{inf} (h) is the infusion time, t_1 (h) corresponds to the time at which the drug concentration reaches de MIC during the infusion phase, t_2 (h) corresponds to the post-infusion time at which the serum concentration equals the MIC and τ is the dosing interval. Assuming that cefotaxime shows linear pharmacokinetics, t_1 and t_2 were calculated as follows:

$$\left(MIC - fC_{min,ss}\right)/\left(fC_{max,ss} - fC_{min,ss}\right) \quad \text{(Eq. 2)}$$

$$t_2 = Ln\left(\frac{fC_{max,ss}}{MIC}\right) x\ V/CL_t \quad \text{(Eq. 3)}$$

where $fC_{min,ss}$ and $fC_{max,ss}$ are the minimum and maximum unbound serum concentrations (mg/L) at steady state, respectively.

Total body clearance (CL), volume of distribution (V), and unbound fraction (f_u) were used to estimate $fC_{min,ss}$ and $fC_{max,ss}$ according to the following equations:

$$fC_{max,ss} = f_u \frac{D}{CL\ t_{inf}} \left(1 - e^{-\frac{CL}{V} t_{inf}}\right) \frac{1}{1 - e^{-\frac{CL}{V} \tau}} \quad \text{(Eq. 4)}$$

$$fC_{min,ss} = fC_{max,ss}\ e^{-\frac{CL}{V}(\tau - t_{inf})} \quad \text{(Eq. 5)}$$

For amoxicillin, amoxicillin/clavulanate and cefuroxime axetil, which are administered by oral route, the following equation was used:

$$C = \frac{F\ D\ K_a\ f_u}{V\ (K_a - K)} \left[\left(\frac{1 - e^{-n\ K\ \tau}}{1 - e^{-K\ \tau}}\right) e^{-K\ t} - \left(\frac{1 - e^{n\ K_a \tau}}{1 - e^{-K_a \tau}}\right) e^{-K_a\ t}\right] \quad \text{(Eq. 6)}$$

where F is the drug bioavailability, Ka is the absorption

Table 2 **Activity of the antibiotic studied against *S. pneumoniae* isolates from AOM in children on pre-vaccination period (May 2000-May 2001), and post-vaccination period (May 2010-May 2011). Pre-vaccination period: all isolates: 191, serotype 3: 18 isolates, serotype 19A: 18 isolates; post-vaccination period: all isolates: 139, serotype 3: 15 isolates, serotype 19A: 66 isolates.**

		% of strains inhibited at MIC (mg/L)												
All isolates		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
Amoxicillin	Pre-PCV7			40.8	3.7	4.7	9.9	12	18.3	3.7	6.3	0.5		
	Post-PCV7			41.0	2.9	4.3	10.1	10.1	7.9	18.7	5.0			
Cefuroxime axetil	Pre-PCV7	4.2	20.9	5.2	6.3	4.2	6.3	6.8	7.3	26.2	12.6			
	Post-PCV7	6.5	29.5		2.2	2.9	5	2.9	7.9	10.1	24.5	4.3	4.3	
Cefotaxime	Pre-PCV7	16.8	17.3	8.4	4.2	10.5	13.1	26.2	3.7					
	Post-PCV7	34.5	1.4	3.6	3.6	2.9	8.6	23.7	17.3	4.3				
		% of strains inhibited at MIC (mg/L)												
Serotype 19A		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
Amoxicillin	Pre-PCV7			66.7	5.6	5.6	16.7			5.6				
	Post-PCV7			7.6	1.5	4.5	16.7	12.1	12.1	37.9	7.6			
Cefuroxime axetil	Pre-PCV7		44.4	16.7	5.6			16.7		16.7				
	Post-PCV7	1.5	4.5		1.5	3			9.1	15.2	48.5	9.1	7.6	
Cefotaxime	Pre-PCV7	22.2	38.9	5.6	5.6	11.1	11.1	5.6						
	Post-PCV7	6.1			3	1.5	9.1	36.4	36.4	7.6				
		% of strains inhibited at MIC (mg/L)												
Serotype 3		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
Amoxicillin	Pre-PCV7			100										
	Post-PCV7			100										
Cefuroxime axetil	Pre-PCV7	27.7	55.5	11.1	5.5									
	Post-PCV7	26.7	73.3											
Cefotaxime	Pre-PCV7	77.0	22.0											
	Post-PCV7	100												

rate constant, K is the elimination rate constant, and n is the number of administered doses that ensures that the steady state is reached (10 doses was always selected).

Using Oracle® Crystal Ball, the values of time at which concentration equals the MIC values were calculated and used to estimate $fT_{>MIC}$ (%) as follows:

$$fT_{>MIC}(\%) = [t_2 - t_1]x\ 100/\tau \quad \text{(Eq. 7)}$$

where t_1 and t_2 corresponds to the time at which the drug concentration reaches the MIC in the ascendant and in the elimination phase of the plasma concentration-time curve, respectively.

The PTA (probability that $fT_{>MIC}$ (%) reaches the PK/PD target: 50% for amoxicillin, and 60% for cefuroxime axetil and cefotaxime), were estimated for every dosing regimen. The treatment was considered successful if the PTA was ≥90 % [26].

Estimation of cumulative fraction of response (CFR). The CFR, understood as the expected probability of success of a dosing regimen against bacteria in the absence of the specific value of MIC, was also calculated. It results from the total sum of the products of the PTA at a certain MIC times the frequency of isolates of microorganism exhibiting that MIC over the range of susceptibility, according to the following equation:

$$CFR(\%) = \sum_{i=1}^{n} PTA_i \cdot F_i \quad \text{(Eq. 8)}$$

where i indicates the MIC category, PTA_i is the PTA of each MIC category, and F_i is the fraction of microorganisms population in each MIC category. As for PTA, the dosing regimen was

Table 3 **Activity of the antibiotic studied against *H. influenzae* isolates from AOM in children in the pre-vaccination period (1998-1999, n=146 isolates), and in the post-vaccination period (2011, n=48 isolates).**

		% of strains inhibited at MIC (mg/L)												
Antimicrobial		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128
Amoxicillin	Pre-PCV7						54.1	18.5	6.8	1.4	19.2			
	Post-PCV7					62.5	18.7	6.3					4.2	8.3
Amoxicillin/clavulanate	Pre-PCV7		0.7	0.7	0.7	5.5	43.1	28.7	15.1	5.5				
	Post-PCV7				4.2	60.4	27.1	8.3						
Cefuroxime axetil	Pre-PCV7					7.5	11.0	47.3	22.6	10.3	1.4			
	Post-PCV7				2.1	25.0	47.9	25						
Cefotaxime	Pre-PCV7					99.2	0.3		0.3		0.3			
	Post-PCV7	81.3	18.8											

Table 4 **CFR values for *S. pneumoniae* pre- and post-PCV7.**

	All serotypes		Serotype 19A		Serotype 3	
Amoxicillin	Pre-PCV7	Post-PCV7	Pre-PCV7	Post-PCV7	Pre-PCV7	Post-PCV7
20 mg/kg q12h	85	80	**96**	63	**100**	**100**
40 mg/kg q12h	**93**	**90**	**98**	83	**100**	**100**
45 mg/kg q12h	**94**	**92**	**98**	86	**100**	**100**
50 mg/kg q12h	**94**	**93**	**99**	88	**100**	**100**
13 mg/kg q8h	88	83	**97**	69	**100**	**100**
27 mg/kg q8h	**95**	**94**	**96**	89	**100**	**100**
30 mg/kg q8h	**96**	**95**	**99**	**91**	**100**	**100**
33 mg/kg q8h	**96**	**96**	**99**	**93**	**100**	**100**
Cefuroxime axetil	Pre-PCV7	Post-PCV7	Pre-PCV7	Post-PCV7	Pre-PCV7	Post-PCV7
10 mg/kg q12h	49	47	73	11	**100**	**100**
15 mg/kg q12h	54	49	80	12	**100**	**100**
Cefotaxime	Pre-PCV7	Post-PCV7	Post-PCV7	Post-PCV7	Pre-PCV7	Post-PCV7
33 mg/kg q8h	**92**	83	**98**	70	**100**	**100**
50 mg/kg q8h	**95**	**90**	**99**	81	**100**	**100**
66 mg/kg q8h	**97**	**93**	**99**	86	**100**	**100**

Numbers in bold indicates CFR≥90%.

considered successful if the CFR value was equal to 90 % or higher [26].

RESULTS

Figure 1 features the PTA values of amoxicillin, cefuroxime axetil and cefotaxime for all the dosing regimens studied. As expected, for each target ($fT_{>MIC}$>50% for amoxicillin, and $fT_{>MIC}$>60% for cefuroxime axetil and cefotaxime), the highest PTA values were achieved with the highest doses. Regarding amoxicillin, if the infection is caused by microorganisms with an MIC≤1 mg/L, a high probability of therapy success (PTA≥90%) was achieved even with the lowest dose. For an MIC value of 2 mg/L, all dosing regimens except 20 mg/kg q12h and 13 mg/kg q8h provided PTA≥90%, and PTA was higher than 90% when the MIC is 4 mg/L only with the dose of 33 mg/kg q8h). Both cephalosporins, cefuroxime axetil and cefotaxime, cover infections caused by microorganisms with an MIC≤0.5 mg/L, but for a MIC value of 1 mg/L, only cefotaxime 66 mg/kg q8h ensured a probability of therapy success higher than 90%.

Table 5 **CFR values for *H. influenzae* in the pre- and post-PCV7.**

Amoxicillin	Pre-PCV7	Post-PCV7
20 mg/kg q12h	77	82
40 mg/kg q12h	86	86
45 mg/kg q12h	87	86
50 mg/kg q12h	88	86
13 mg/kg q8h	79	85
27 mg/kg q8h	89	87
30 mg/kg q8h	**90**	87
33 mg/kg q8h	**91**	87
Amoxicillin/clavulanate	Pre-PCV7	Post-PCV7
20 mg/kg q12h	89	**93**
40 mg/kg q12h	**96**	**98**
45 mg/kg q12h	**96**	**98**
50 mg/kg q12h	**97**	**98**
13 mg/kg q8h	**93**	**97**
27 mg/kg q8h	**98**	**99**
30 mg/kg q8h	**99**	**100**
33 mg/kg q8h	**99**	**100**
Cefuroxime axetil	Pre-PCV7	Post-PCV7
10 mg/kg q12h	38	46
15 mg/kg q12h	59	67
Cefotaxime	Pre-PCV7	Post-PCV7
33 mg/kg q8h	**97**	**100**
50 mg/kg q8h	**98**	**100**
66 mg/kg q8h	**99**	**100**

Numbers in bold indicates CFR≥90%.

The proportion of *S. pneumoniae* isolates amoxicillin-susceptible and cefotaxime-susceptible (MICs ≤ 2 mg/L and ≤ 1 mg/L, respectively) decreased 15% and 19% from pre-PCV7 to the post-PCV7 period, respectively. Table 4 shows CFR values of each antibiotic against *S. pneumoniae* taking into account the MIC distribution data in the pre- and post- vaccination periods (pre- and post-PCV7). When all serotypes of *S. pneumoniae* are considered, amoxicillin (except 20 mg/Kg q12h and 13 mg/Kg q8h) and cefotaxime turned out to reach a high probability of success (CFR≥90%), and difference before and after vaccination was scarce. However, for serotype 19A, CFR values decreased in the post-vaccination period, and the probability of success was ≥90% only with the highest doses of amoxicillin. As can be seen in table 4, serotype 3 is fully susceptible to all antimicrobial agents, and when this serotype is responsible for the infection, no difference in the probability of success of the antibiotic therapy between the pre- and post-vaccination period was detected.

Table 5 shows the CFR values obtained for *H. influenzae*. As expected, CFR values were higher with amoxicillin/clavulanate than with amoxicillin, and cefuroxime axetil resulted in a very low probability of success. In the two periods of study, cefotaxime led to a high probability of success (≥97%).

DISCUSSION

In the present work, we have studied the antimicrobial activity of the antibiotics used for the treatment of AOM in children against clinical isolates of *S. pneumoniae* and *H. influenzae* before and after the introduction of the PCV7 in Spain, by using integrated PK/PD analysis.

Since the availability of PCV7, there have been changes in the overall serotype distribution of *S. pneumoniae;* in particular, an increase in serotype 19A has been observed globally [27]. In Spain, the rate of non-PCV7 serotypes increased after the vaccine was introduced, including serotypes 19A and 3 [6].

The efficacy of an antimicrobial drug depends on the relationship between the MIC of the microorganism and the exposure of the microorganism to the agent in the patient. For β-lactams, the time for which free drug levels exceed the MIC, expressed as the percentage of the dosing interval ($fT_{>MIC}$), correlates best with bacterial eradication [28]. Accordingly, we have estimated the probability of treatment success as the probability of this index to reach the target value (50% for penicillins and 60% for cephalosporins), expressed as PTA. Current AOM management guidelines recommend high-dose amoxicillin (80-90 mg/kg/day) as the first-line drug of choice in children [29] and, according to our results, these dose levels would be effective against organisms with MICs up to 2 mg/L (figure 1). Taking into account the susceptibility patterns of *S. pneumoniae* (table 2), 89.5% (pre-PCV7) and 76.3% (post-PCV7) of all isolates have a MIC≤2 mg/L, although for the serotype 19A the rate of isolates with MIC≤2 mg/L has decreased from 94.4% to 54.5% after the implementation of the PCV7. In the case of *H. influenzae*, data are even more favorable, since most isolates present MIC≤2 mg/L for amoxicillin/clavulanate (table 3). Regarding cephalosporins, every dosing level is enough to treat infections due to microorganisms with MIC≤0.5 mg/L, but if MIC is 1 mg/L, only the highest dose of cefotaxime (66 mg/kg q8h) seems to be adequate.

Considering that AOM is typically treated empirically, the treatment of choice should target the most frequently isolated pathogens. As previously mentioned, in the post-vaccination period it was not only a serotype replacement, but also an increase of non-susceptibility rate of some serotypes not included in the vaccine against β-lactams, as serotype 19A [7]. Therefore we have calculated the probability of empirical treatment successful (CFR) in the pre- and post-vaccination period taking into account the MIC values. If we consider all serotypes of *S. pneumoniae*, only a slight decrease in the probability of success in the post-vaccination period was observed in comparison to the pre-vaccination period. Therefore, when the serotype is not identified, amoxicillin and cefotaxime may be good options for the treatment of AOM, although the prob-

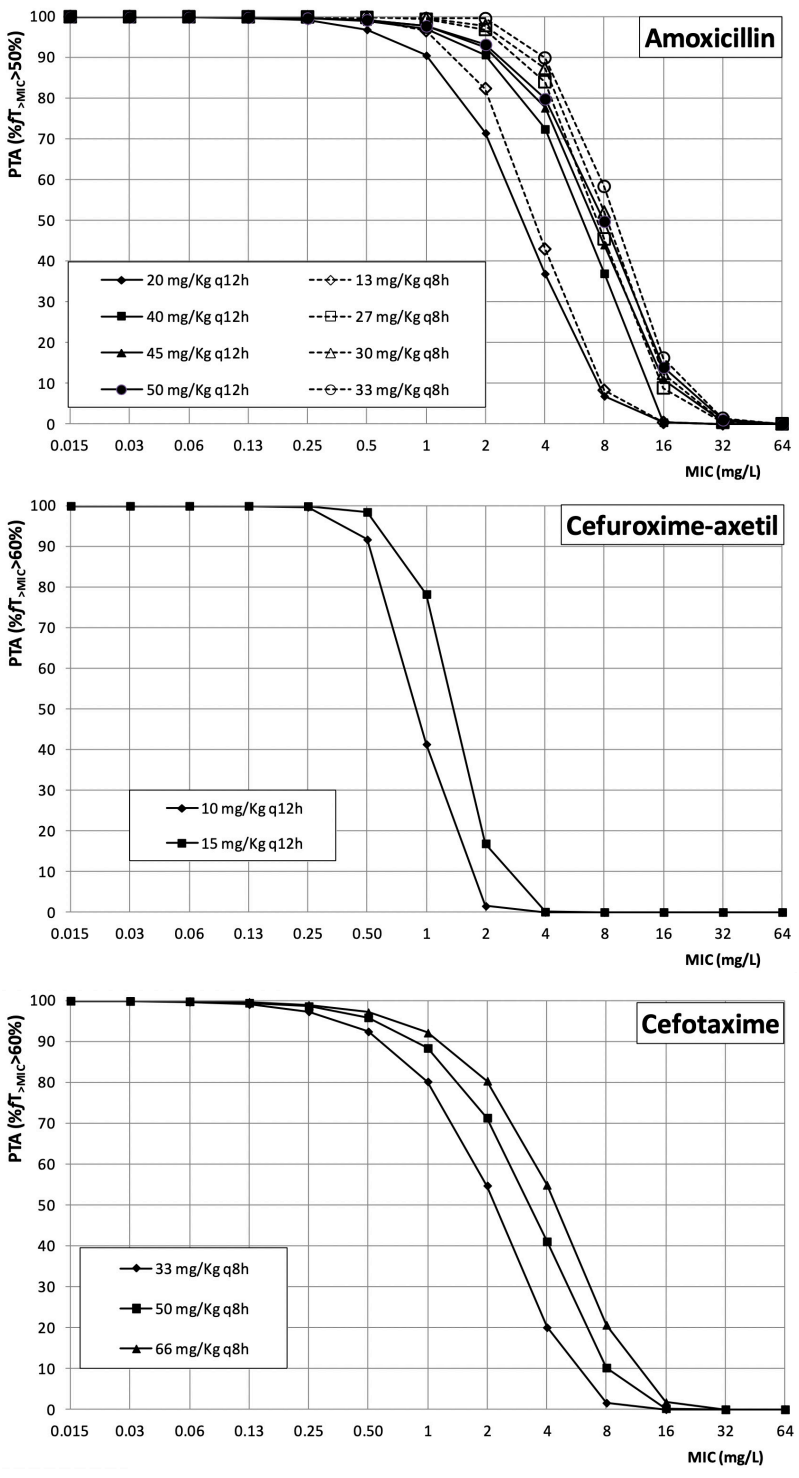

Figure 1 Probability of target attainment (PTA) of amoxicillin, cefuroxime-axetil, and cefotaxime in simulated pediatric patients. MIC: minimum inhibitory concentration.

ability of success slightly depends on the dose.

Although *H. influenzae* is not involved in the PCV7, mixed infections are common, and the association of this microorganism with *S. pneumoniae* has been widely demonstrated [9,10]. Moreover, an increase in the proportion of AOM cases caused by *H. influenzae* has been shown after the introduction of pneumococcal vaccines [2,3]. This is the reason why we have also studied the probability of treatment success before and after the introduction of the PCV7 when *H. influenzae* is responsible for the infection. According to the CFR values obtained and, as expected, the implantation of the vaccine hardly led to relevant changes in the activity of the antibiotics studied. In spite that in the post-PCV7 period, the rate of β-lactamase-producing *H. influenzae* strains was lower than before the introduction of the vaccine, and that the rate of BLNAR isolates hardly changed, only small differences in the CFR values of amoxicillin and amoxicillin/clavulanate were found between both periods. Amoxicillin/clavulanate provided slightly probabilities of treatment success than amoxicillin. Regarding cephalosporins, cefotaxime provided very high probability of therapy success both before and after the introduction of the PCV7. On the contrary, cefuroxime axetil resulted in a very low success probability in both periods.

National vaccination recommendations outside routine infant immunization programs differ among EU countries. Some countries have age-based vaccination programs, while others have risk-based programs, and some countries have regional variations with respect to recommendations [27]. Previous studies have shown that PK/PD analysis is a useful tool to identify differences in the antibiotic treatment success due to different susceptibility patterns [21]. Our study reveals that this methodology is also useful for the surveillance programs to evaluate the effect of a vaccine.

The change of serotype epidemiology due to the PCV7 has led to the development and introduction of higher-valent pneumococcal conjugate vaccines, including PCV13, which includes serotype 19A, to provide improved serotype coverage against pneumococcal diseases. In Spain, PCV13 has been available since June 2010 and vaccination is recommended for pediatric patients. However, before 2016 in most provinces of Spain, the vaccine was not financed by the public health insurance and it had to be paid by parents, leading to non-uni-

versal coverage. Although after the introduction of the PCV13, a reduction in the frequency of infections due to vaccine serotypes, mainly 19A and 1, was observed [30,31], the lack of available data does not allow to include the post-PCV13 period in the present study.

In conclusion, this study demonstrates the value of integrated PK/PD analysis to identify changes in antimicrobial activity after the implantation of a vaccination program, providing complementary information to the simply assessing of MIC values. We have shown that the introduction of the PCV7 vaccination did not lead to changes in the probability of success of the current empiric treatments of the AOM.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Efficacy of an information system addressed to nursing staff for diminishing contaminated blood cultures: a blind clinical trial

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ABSTRACT

Introduction. Evaluate the efficacy of an information system addressed to nursing staff to lower the blood culture contamination rate.

Methods. A blind clinical trial was conducted at Internal Medicine and Emergency Departments during 2011. After following a reeducation program in BC extraction, participants were randomly selected in a 1:1 ratio. Every participant of the experimental group was informed of each worker's individual performance; whereas the control group was only informed of the global results.

Results: A total of 977 blood extractions were performed in 12 months. Blood culture contamination rate was 7.5%. This rate was higher in the Emergency Department than in Internal Medicine (10% vs. 3.8%; *p*=0.001). Factors associated with the higher risk of contamination were, in the univariate analysis, the extraction through a recently implanted blood route and the time of professional experience, while those associated with a lower risk were the extraction in Internal Medicine and through a butterfly needle. On multivariate analysis, extraction through a recently placed access was an independent risk factor for an increased contamination rate (OR 2.29; 95%CI 1.18-4.44, *p*=0.014), while individual information about the blood culture results (OR 0.11; 95%CI 0.023-0.57; *p*=0.008), and more than 9 years of professional experience were associated with fewer contaminations (OR 0.30; 95%CI 0.12-0.77; *p*=0.012). In the intervention group the contamination rate diminished by a 26 %.

Conclusions: Drawing blood cultures through a recently taken peripheral venous access increased their risk of contamination. The intervention informing the nurse staff of the contamination rate is effective to decrease it.

Keywords: contamined blood culture, nursing staff, feedback information

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Eficacia de un sistema de información dirigido al personal de enfermería para disminuir la contaminación de los hemocultivos: un ensayo clínico ciego

RESUMEN

Objetivos. Evaluar la eficacia de un sistema de información dirigido al personal de enfermería, en la reducción de la tasa de contaminación de los hemocultivos.

Métodos. Durante el año 2011, se realizó un ensayo clínico en los servicios de Medicina Interna y de Urgencias. Después de seguir un programa de reeducación en la extracción de los hemocultivos, los participantes, fueron aleatorizados en una proporción de 1:1. En el grupo de intervención se informó del porcentaje de hemocultivos contaminados de cada profesional y en el grupo control se aportaba la información del porcentaje global de contaminaciones.

Resultados. Durante un periodo de 12 meses se realizaron 977 extracciones. La tasa de contaminación de los hemocultivos fue del 7,5%. Esta tasa fue mayor en Urgencias que en Medicina Interna (10% versus 3,8%, *p*=0,001). Los factores asociados con mayor riesgo de contaminación fueron, en el análisis univariable: la extracción a través de una vía sanguínea recientemente implantada y el tiempo de experiencia profesional; mientras que los que se asociaron con menor riesgo fueron la extracción en Medicina Interna (versus en Urgencias) y a través de una palomilla.

En el análisis multivariable, la extracción de los hemocultivos de una vía recientemente implantada se relacionó de forma independiente con un incremento de las contaminaciones (OR 2,29, IC 95% 1,18-4,44, *p*=0,014),

mientras que la información individual sobre los resultados de los hemocultivos (OR 0.11; IC 95% 0,023-0,57; *p*=0,008) y la experiencia profesional mayor de 9 años, lo hizo con menos contaminaciones (OR 0,30, IC 95% 0,12-0,77, *p*=0,012). En el grupo de intervención la tasa de contaminaciones se redujo en un 26%.

Conclusión. La extracción de hemocultivos a través de una vena periférica recientemente implantada aumentó el riesgo de contaminación de los mismos. La intervención informativa a los enfermeros de la tasa de contaminación de los hemocultivos, es eficaz para disminuirla.

Palabras Clave: hemocultivos contaminados, personal de enfermería, información de retroalimentación

INTRODUCTION

Blood culture (BC) is a critical tool for health care professionals as a means to detect dangerous pathogens in the bloodstream [1,2]. However, culture bottle's contamination by bacteria of the patient's skin, staff hands or contaminated fomites is a frequent event during handling. Contamination carries an important human and economic cost [3,4]. Many studies have been performed to identify the cause of contamination. Among the suspected factors are the site of venipuncture, the lack of asepsis at the skin and bottle cap, and the use of a single versus double needle for the bottle inoculation [1,5].

Some studies have highlighted the value of an educational intervention and the implementation of an adequate protocol for BC extraction [4-6]. Contamination has been associated with the lack of utilization of antiseptic fluid use independent of its type, of repeated palpation of the vein, the use of extraction from a non-peripheral vein location and the disinfection of the bottle port. Another study focused on an educational intervention when 3 contamination episodes were attributable to a single blood extractor, finding on multivariate analysis, that only the absence of the educational intervention was an independent variable associated with BC contamination [4].

Given the high contamination rate in our Internal Medicine (IM) and Emergency Departments (ED) (around 8%), we undertook this study to evaluate the efficacy of an educational intervention comparing contamination rates in a group that received feedback on each worker's individual performance vs a group given only information on the global results of the blood cultures contamination.

METHODS

We performed, during 2011, a blind clinical trial to compare contamination rates in a group given feedback on each worker's individual performance vs a group given only feedback on the global performance. It took place in the Internal Medicine and Emergency Departments at Hospital Severo Ochoa, a 450-bed secondary care academic medical center.

The study was approved by the local Ethics Committee and informed consent was obtained before participants were selected for participation in the study. Nurses were randomly selected and paired in the intervention group or in the control group in a 1:1 ratio. It was done by a computer program, stratified by hospital departments, and sampled in blocks of 5. Sealed envelopes provided the results of BC contamination. During the first two months of the study no information was supplied to the participants. Thereafter, the control group received every month by internal mail a report of the number of BCs included in the study till then and the ongoing global contamination percentage. The nurses of the intervention group received not only that information but their individual contamination rate as well. The isolation of a germ was considered as contamination depending on the growth of a particular organism and the patient's clinical condition. Although *Corynebacterium* sp., *Lactobacillus* sp., *Propionibacterium acnes* and *Staphylococcus* coagulase negative were accepted as possible contaminants, these organisms may be true pathogens under certain conditions (for example in the presence of intravascular foreign bodies such as catheters or prosthetic valves). The decision of BC contamination was established by an evaluating committee composed by a microbiologist, an internist and an infectious disease specialist who determined the clinical significance of each isolations. They reviewed also the medical records.

We selected consecutive cultures drawn by the nurses during the study period (paired BC taken from patients in the inpatient unit of IM and the ED). Only extractions by direct venipuncture or when extraction was performed immediately after insertion of the peripheral route were included. We excluded from the analysis: 1) cultures extracted from an old central or peripheral vein; 2) one or more than two extractions for a single patient. The reasons for their exclusion were the higher risk of contamination and to homogenize the sample.

The unit of randomization was the extracting nurse. Every demographic characteristic, employment detail and professional experience time of the nurses as well as every clinical factor of patients proven relevant to a difficult blood extraction was collected. In addition, independently of the assigned group, the nurse sent in each extraction to the laboratory a form in which data about the protocol were collected [hand disinfection, use of gloves, preparation of patient skin and bottle ports, products and methods for disinfection, use of butterfly at the blood drawing, (a butterfly shaped device to handle the needle), if it was a difficult extraction or help by another nurse and if cultures were drawn from a peripheral vein immediately after placement].

Statistical analysis. Experimental and control groups were categorized depending on potential risk factors, including characteristics of each nurse or patient and data of extraction protocol. Descriptive statistics were conducted to characterize the overall study population. Patient-related, nurse-related and extraction-related contamination risk factors were analyzed with multivariate logistic regression (backward stepwise selection) being the dependent variable BC contamination after implementation of the intervention. Variables were tested in a bivariate analyses and considered for inclusion in the final multivariate

model when p was lower than 0.20. All analyses were performed using SPSS package version 20 for MAC (IBM SPSS Statistics).

RESULTS

Baseline nurse characteristics are shown in table 1. Both groups were similar with the exception of age (controls were 2.8 years younger). The Microbiology laboratory received 977 sets of blood cultures, 60.5 % from the ED. One hundred and twenty three were excluded because of rejection criteria mentioned (figure 1).

Sixty four (7.5 %) of the 854 BC included were contaminated (table 2). This rate was significantly higher in the ED than in IM (10% vs. 3.8%; p= 0.001). The percentage of true positive BCs was 6.2% and similar in both departments (7.1% in ED and 5.2% in Internal Medicine; p= 0.267). As 7.5% of BC were contaminated and 6.2% were true positive, the probability a microorganism growing which needed no-treatment was 55% (likelihood that the isolation in the blood culture corresponds to a contaminated blood culture).

We evaluated 600 extractions (second period) for the analysis of the main outcome, excluding the BC that took place in the first 2 months of the study because of the absence of any intervention (first period) (figure 1). The contamination rate was 26% lower in the experimental group (5.7% vs. 7.7%), not being statistically different (p= 0.33). There were no statistically significant differences in the prevalence during the first and the second period (7.3 vs 5.7%; p= 0.46) in the intervention or in the control group (7.3 vs 7.7%; p= 0.84). We noticed a clinically relevant drop in the contamination rate in the experimental group along the study, from 7.2% in the first six months to 3.6% in the last six months, close to the 3% recommended by the American Society of Microbiology.

Experimental and control groups categorized by the potential risk factors are shown in table 3. There were differences in gloves use, butterfly-needle and ethanol use, in the time waited (less than 30 seconds or not), in the preparation of bottle top and in the age of the nurse staff between the control group and the intervention group.

Factors associated significantly to a higher contamination risk on bivariate analysis were the extraction through a recently placed line (versus to direct venipuncture), and having less than 9 years of professional experience, whereas extraction in IM and through a butterfly needle were related to a lower contamination risk (table 4).

We found a lower contamination rate with chlorhexidine that when it was not used, not achieving statistical significance due to the disproportion of sample size, since it was only used in 26% of extractions.

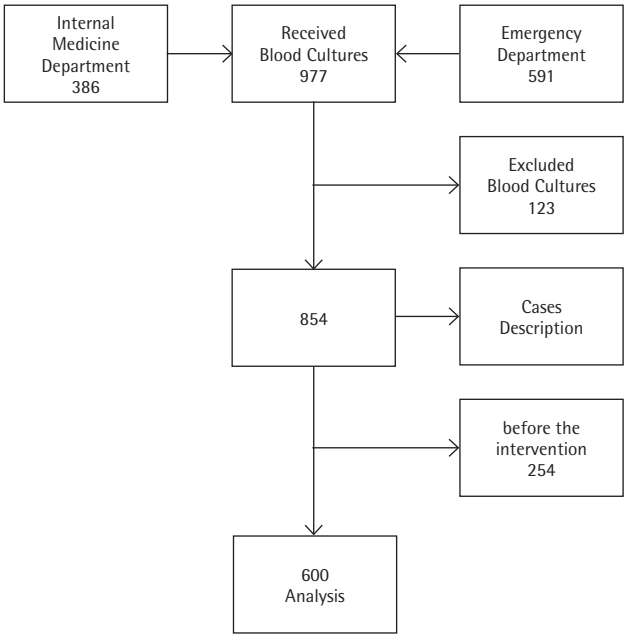

Figure 1 Flowchart of the blood cultures before and after of intervention

Table 1 Baseline nurse characteristics.

	Control (N=25)	Intervention (N=31)	P
Age (years)	34.3	31.5	0.050*
Years of professional experience (mean)	10.4	8.9	0.279
Years of professional experience in the same department (mean)	6.4	5.6	0.363
Males, n (%)	5 (20)	4 (12.9)	0.493
Temporary employment, n (%)	17 (40)	10 (54.8)	0.269
Department			
Internal Medicine, n (%)	11 (44)	19 (61.3)	0.197
Emergency Department, n (%)	14 (56)	12 (38.7)	

Table 2 Blood culture results.

	Number	Percentage
Negative blood cultures	737	86.3%
True positive blood cultures	53	6.2%
Contaminated blood cultures	64	7.5%

On multivariate analysis, the extraction through a recently placed line was an independent risk factor for an increased contamination rate, whereas individual information on the BC results and more than 9 years of professional experience were

Table 3 **Experimental and control groups categorized by the potential risk factors**

Variable	(n)	Intervention	Control	P
Difficult extraction	Yes (119)	56 (21.2)	63 (18.8)	0.453
	No (481)	208 (78.2)	273 (81.2)	
Hemodynamic instability	Yes (66)	31 (11.7)	35 (10.4)	0.606
	No (534)	233 (88.3)	301 (89.6)	
Recently inserted line vs direct venepuncture	Yes (158)	72 (27.3)	84 (25)	0.529
	No (442)	192 (72.7)	252 (75)	
Gloves use	Yes (583)	249 (94.3)	334 (99.4)	0.001*
	No (17)	15 (5.7)	2 (0.6)	
Ethanol use	Yes (400)	193 (73.1)	207(61.6)	0.003*
	No (200)	71(26.9)	129 (38.4)	
Chlorhexidine use	Yes (128)	50 (18.9)	78 (23.2)	0.205
	No (472)	214 (81.1)	258 (76.8)	
Povidone-iodine use	Yes (418)	179 (67.8)	239 (71.1)	0.379
	No (182)	85 (32.2)	97 (28.9)	
Cleansing in concentric circles	Yes (479)	214 (81.4)	265 (78.9)	0.448
	No (120)	49 (18.6)	71 (21.1)	
Waiting 30 seconds	Yes (464)	219 (83)	245 (72.9)	0.004*
	No (136)	45 (17)	91 (27.1)	
Preparation of bottle top	Yes (154)	50 (18.9)	104 (31)	0.001*
	No (446)	214 (81.1)	232 (69)	
Arterial extraction	Yes (37)	19 (7.2)	18 (5.4)	0.352
	No (563)	245 (92.8)	318 (94.6)	
Help by a colleague	Yes (332)	138 (52.3)	194 (57.7)	0.181
	No (268)	126 (47.7)	142 (42.3)	
Butterfly-needle use	Yes (303)	164 (62.1)	139 (41.1)	0.001*
	No (297)	100 (37.9)	197 (58.6)	
Department	Internal M (255)	146 (55.3)	109 (32.4)	0.001*
	Emergency D. (345)	118 (44.7)	227 (67.6)	
Professional experience time	<9 years (299)	130(49.2)	169 (50.3)	0.797
	>9 years (301)	134 (50.8)	167 (49.7)	
Professional experience time in the department	<4.5 years (137)	69 (26.1)	68 (20.2)	0.088
	>4.5 years (463)	195 (73.9)	268 (79.8)	
Age	<31 years (194)	99 (37.5)	95 (28.3)	0.016*
	>31 years (406)	165 (62.5)	241 (71.7)	

significantly associated with fewer contaminations. The individualized knowledge of the culture results was associated with a drop of contamination of 89% (table 5).

The use of butterfly needles for the extraction of blood cultures was the factor that was most related to the reduction of the risk of contamination in the univariate analysis. However, probably, because its use was not very widespread (62.1% in intervention group and 41.1% in control group), its association in multivariate analysis could not be demonstrated.

DISCUSSION

Several strategies have been tried to reduce BC contamination. The most effective measure to reduce it is the availabil-

Table 4 **Univariate analysis of contamination-related factors.**

Variable	(n)	N (%) Contaminated BC	OR (95%CI)	P
Difficult extraction	Yes (119)	10 (8.4)	1.33 (0.63-2.80)	0.448
	No (481)	31 (6.4)	1	
Hemodynamic instability	Yes (66)	7 (10.6)	1.75 (0.74-4.11)	0.197
	No (534)	34 (6.4)	1	
Recently inserted line	Yes (158)	18(11.4)	2.342 (1.23-4.47)	0.008*
	No(442)	23 (5.2)	1	
Gloves use	Yes (583)	41 (7.0)		0.621
	No (17)	0		
Ethanol use	Yes (400)	28 (7.0)	1.08 (0.55-2.14)	0.819
	No (200)	13 (6.5)	1	
Chlorhexidine use	Yes (128)	6 (4.7)	0.611(0.25-1.50)	0.278
	No (472)	35 (7.4)	1	
Povidone-iodine use	Yes (418)	29 (6.9)	1.06 (0.53-2.20)	0.878
	No (182)	12 (6.6)	1	
Cleansing in concentric circles	Yes (479)	35 (7.3)	1.50 (0.62-3.65)	0.371
	No (120)	6 (5.0)	1	
Waiting 30 seconds	Yes (464)	32 (6.9)	1.05 (0.49-2.25)	0.910
	No (136)	9 (6.6)	1	
Preparation of bottle top	Yes (154)	9 (5.8)	0.80 (0.37-1.72)	0.573
	No (446)	31 (7.2)	1	
Arterial extraction	Yes (37)	4 (10.8)	1.72 (0.58-5.13)	0.308
	No (563)	37 (6.6)	1	
Help by a colleague	Yes (332)	28 (8.4)	1.81 (0.92-3.56)	0.084
	No (268)	13 (4.9)	1	
Butterfly-needle use	Yes (303)	12 (4.0)	0.38 (0.19-0.76)	0.005*
	No (297)	29 (9.8)	1	
Department	Internal M (255)	11 (4.3)	0.47 (0.23-0.96)	0.035*
	Emergency D. (345)	30 (8.7)	1	
Professional experience time	<9 years (191)	19 (9.9)	1.94 (1.03-3.68)	0.039*
	>9 years (409)	22 (5.4)	1	
Professional experience time in the department	<4.5 years (210)	19 (9)	1.66 (0.88-3.12)	0.115
	>4.5 years (390)	22 (5.6)	1	
Age	<31 years (299)	21 (7)	1.06 (0.56-2.002)	0.854
	>31 years (301)	30 (6.6)	1	
Intervention group	Intervention (264)	15 (5.7)	0.72 (0.37-1.39)	0.322
	Control (336)	26 (7.7)	1	

BC: blood culture.

Table 5 Multivariate analysis of contamination-related factors

Variable	(n)	ORA (95%CI)	P
Use of recently inserted line	Yes (158)	2.29 (1.18-4.44)	0.014*
	No (442)	1	
Help by a colleague	Yes (332)	0.93 (0.41-2.12)	0.856
	No (268)		
Professional experience time	>9 years (409)	0.30 (0.12-0.77)	0.012*
	<9 years (191)	1	
Intervention group	Intervention (264)	0.11 (0.023-0.567)	0.008*
	Control (336)	1	

ity of an experienced phlebotomy team [7-9]. In small hospitals which lack these teams, like ours, an alternative method could be to register and give individualized and personalized information of the own contamination rate to the nurse staff, as shown by a pilot study by Robert [10], in which contamination was reduced by 50% with this measure. On the other hand, feedback to individuals of their personal rates is a well-known technique to improve workers' performance, and it has been successfully used in other situations, such as the reduction of surgical wound infection [11].

In this study, we have been able to show than individualized information can reduce contamination rate by 89%. A higher contamination rate in the less experienced nurses suggests than an experienced team is the best option. An alternative solution to reduce contamination rates could be the assignment of experienced nurses to the supervision of the extractions and the teaching of a correct technique.

Globally, our BC contamination rate was a 7.5%, higher than the interval reported in other studies (0.6-6.25%) [10].

An important finding is that our contamination rate increases significantly when BCs are drawn from a recently inserted line vs. direct venipuncture. This increased contamination rate had been described in an observational prospective study in a pediatric ED [12]. In this study, contamination rate dropped from 9.1% to 2.8% after changing BC drawing from a recently inserted line to direct venipuncture. Proper disinfection of the extraction site is considered nowadays the most important factor to reduce the contamination rate. Several studies show lower contamination when the skin is treated with chlorhexidine versus povidone-iodine [6, 13-15]. The effect of chlorhexidine is improved by the addition of ethanol [16]. In our study, we found a lower contamination rate with use of chlorhexidine although, not achieving statistical significance due to the disproportion of sample size.

Another important factor is the handling of blood during extraction. We have found factors, related to the contamination rate, which had not been mentioned in the previous literature. One is the use of butterfly needles, in which extracted blood is directly inoculated in culture bottles, avoiding secondary manipulation and reducing significantly the contamination rate in our study. The use of butterfly needles for the extraction of blood cultures was the factor that was most related to the reduction of the risk of contamination in univariate analysis. However, probably, because its use was not very widespread, its association in multivariate analysis could not be demonstrated.

The other factor is the intervention of more than one person in blood drawing, which increased contamination although non-significantly. The intervention of multiple people could be a confounder related to the severity of the condition affecting the patient, but in our study we did not find differences in contamination rate in relation to the clinical state of the patient thereby excluding that possibility. After multivariate analysis, performed to avoid biases owed to differences between departments such as the number of extractions, the antiseptic solutions used, the professional experience time and the clinical care, the only three factors which remained significant for the contamination risk were a personalized information of the own culture results, the extraction through a recently inserted line and having more than 9 years of professional experience.

The main strength of our research was that the information gathered from biomedical research could lead us to determine the causes of excessive contamination in the extraction of blood cultures. The limitation of the study was that we did not include all blood culture extractions performed, especially in the ED, due to difficulties owed to the overload of care. It was not possible to rule out the possible exchange of information between the control and the information group as they did not belong to different units.

We believe that personalized information to nurses drawing BC on their individual results should be implemented and that cultures through previously established lines should be interpreted with caution. The study suggests the usefulness of butterfly needles for the extraction of blood cultures.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Effectiveness and safety of daclatasvir/sofosbuvir with or without ribavirin in genotype 3 hepatitis C virus infected patients. Results in real clinical practice

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ABSCTRACT

Objectives. Direct-acting antivirals have shown high efficacy in all hepatitis C virus (HCV) genotypes, but genotype 3 (G3) treatments continue to be a challenge, mainly in cirrhotic patients. The aim of this study is to analyse effectiveness and safety of daclatasvir associated with sofosbuvir with or without ribavirin in G3-HCV infected patients in real clinical practice.

Patients and methods. An observational, prospective, cohort study over 2.5 years, in G3-HCV infected adult patients, in all fibrosis stages including patients with decompensated cirrhosis. Treatment was a combination of sofosbuvir 400 mg/day + daclatasvir 60 mg/day, with or without a weight-adjusted dosing of ribavirin for 12 or 24 weeks. The primary efficacy endpoint was sustained virologic response rates 12 weeks after therapy (SVR12). The primary safety endpoint was treatment withdrawal rates secondary to severe adverse events.

Results. A total of 111 patients were enrolled, 32.4% cirrhotics and 29.9% treatment-experienced. The global SVR12 rate was 94.6%, while the SVR12 rate in F3-4 fibrosis stage patients was 90.8% versus 100% in patients with F0-2 fibrosis (p=0.03). In cirrhotic patients, SVR12 was 100% versus 40% depending on whether ribavirin was added or not to daclatasvir/sofosbuvir (p=0.001). No other patient or treatment basal variables influenced the treatment effectiveness. No patient treatment withdrawal secondary to severe adverse events was observed.

Conclusions. Daclatasvir/sofosbuvir ± ribavirin is highly effective in G3-HCV infected patients. Advanced degrees of fibrosis significantly decrease the effectiveness of this treatment, which motivates the need for the addition of ribavirin in cirrhotic patients. The regimen was safe and well tolerated.

Keywords: hepatitis C; genotype 3; daclatastir; sofosbuvir; ribavirin.

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Efectividad y seguridad de daclatasvir/sofosbuvir con o sin ribavirina en pacientes infectados por el genotipo 3 del virus de la hepatitis C. Resultados en práctica clínica real

Objetivos. Los antivirales de acción directa han demostrado una alta eficacia en todos los genotipos del virus de la hepatitis C (VHC), pero los tratamientos para el genotipo 3 (G3) siguen siendo un desafío, principalmente en pacientes cirróticos. El objetivo de este estudio es analizar la efectividad y la seguridad del daclatasvir asociado con sofosbuvir con o sin ribavirina en pacientes infectados por G3-VHC en la práctica clínica real.

Pacientes y métodos. Estudio observacional, prospectivo, de cohorte de más de 2,5 años, en pacientes adultos infectados con G3-VHC, en todos los estadios de fibrosis, incluidos los pacientes con cirrosis descompensada. El tratamiento fue una combinación de sofosbuvir 400 mg / día + daclatasvir 60 mg / día, con o sin una dosis de ribavirina ajustada por peso durante 12 o 24 semanas. El criterio de valoración principal de eficacia fue la tasa de respuesta virológica sostenida 12 semanas después del tratamiento (RVS12). La variable principal de seguridad fue la tasa de suspensiones de tratamiento secundaria a eventos adversos graves.

Resultados. Se incluyeron 111 pacientes, 32.4% cirróticos y 29.9% con experiencia previa de tratamiento antiviral. La tasa global de RVS12 fue del 94,6%, mientras que la tasa de RVS12 en pacientes con estadio de fibrosis F3-4 fue del 90,8% frente al 100% en pacientes con fibrosis F0-2 (p = 0,03). En pacientes cirróticos, la RVS12 fue del 100% en comparación con el 40%, dependiendo de si se agregó o no ribavirina a daclatasvir / sofosbuvir (p = 0,001). Ninguna otra variable basal del paciente o del tratamiento influyó en la efectividad del tratamiento. No se observó ninguna suspensión del tratamiento secundario a eventos adversos graves.

Conclusiones. Daclatasvir / sofosbuvir ± ribavirina es altamente efectivo en pacientes infectados por G3-VHC. Los

grados avanzados de fibrosis disminuyen significativamente la efectividad de este tratamiento, lo que motiva la necesidad de la adición de ribavirina en pacientes cirróticos. El régimen fue seguro y bien tolerado.

Palabras clave: hepatitis C; genotipo 3; daclatastir; sofosbuvir; ribavirina

INTRODUCTION

World Health Organization (WHO) states that viral hepatitis is a major public health problem and that globally, in 2015, 71 million people were living with chronic hepatitis C virus (HCV) infection [1]. The distribution of HCV by viral genotype varies from one region to another, with genotype 3 (G3) being the second most prevalent worldwide after genotype 1, which implies around 30% of chronic hepatitis C (CHC) cases [2]. In addition, G3-HCV chronic infection is characterised by a faster progression to liver cirrhosis [3-6] and development of hepatocellular carcinoma (HCC) [7], as well as higher rates of hepatic steatosis development as the result of multiple mechanisms [8-11]. Another remarkable feature of G3-HCV is the lower rates of sustained virologic response (SVR) observed with direct-acting antivirals (DAAs), mostly in advanced liver fibrosis and/or non-responders to previous treatments, compared with other genotypes [12]. Therefore, the evaluation of the real-practice effectiveness of antiviral treatment against G3-HCV chronic infection in the era of DAAs is of special interest.

Treatment of CHC with DAAs in G3-HCV infected patients has rapidly evolved in accordance with the efficacy and safety results of clinical trials were known. Initially, the treatment of choice was based on the association of sofosbuvir (SOF) to ribavirin (RBV) [13] or peg-interferon (peg-IFN) and RBV, with discrete SVR rates; later, the combination of ledipasvir (LDV) and SOF, which achieved higher SVR12 rates. Nowadays, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) Guidance [14] recommends various therapeutic options based on the patient's previous treatments and the presence/absence of cirrhosis, among which is the association of daclatasvir (DCV) + SOF ± RBV [15], with a level of the evidence I that supports a strength of recommendation A; this recommendations are based on phase III pivotal clinical trials, where this association reached a SVR12 of 90% in naïve patients and 86% in treatment-experienced patients, and rates of SVR12 in non-cirrhotic patients of 96% versus 63% in patients with cirrhosis [16]. In addition, the analysis of viral response in patients with decompensated cirrhosis deserves special attention, due to the lower efficacy of antiviral treatment in this subgroup of HCV patients, especially in genotype 3 [16, 17], which translates into specific treatment recommendations in the main reference guides [14, 18]. However, in real clinical practice, few studies have evaluated the use of DCV/SOF ± RBV in G3-HCV infected patients, with a limited number of patients with advanced liver disease included. Therefore, more data about the use of this combination of DAAs will shed more light on clinical outcomes in real life.

Based on the above, the objective of this study is to analyse the effectiveness and safety of 12-24 weeks treatment regimens of DCV associated with SOF with or without RBV in a cohort of G3-HCV infected patients in real clinical practice.

PATIENTS AND METHODS

Study design and patient selection. We are looking at a unicentric, observational, prospective, cohort study of G3-HCV infected patients who started antiviral treatment with DCV/SOF±RBV between January 2015 and June 2017 and who had reached week 12 post-treatment before January 2018. Treatment decisions corresponded to the prescribing specialist (infectious diseases specialists or hepatologist), under usual clinical practice conditions valid during the study period. The therapeutic regimen was the one authorised by the European Medicine Agency (EMA) and consisted of a fixed combination of SOF 400 mg/day (Sovaldi®; Gilead Sciences International Ltd.) plus DCV 60 mg/day (Daklinza®; Bristol Myers Squibb Pharma EEIG), associated or not with the corresponding dose of RBV (Ribavirina Normon®; Normon Lab.), adjusted to body weight and patient characteristics. It was administered for 12 or 24 weeks, based on EMA recommendations. Inclusion criteria selected adult patients (≥18 years of age), with G3-HCV chronic infection, naïve or treatment-experienced to peg-INF + RBV or DAAs, in all fibrosis stages (F0-4) including patients with decompensated cirrhosis or portal hypertension, human immunodeficiency virus (HIV) co-infected patients or liver transplant patients.

Effectiveness and safety variables. Pharmacological treatment effectiveness and a safety evaluation were carried out through SiMON [19], a local intelligent computerised monitoring system designed specifically for CHC patients on antiviral treatment. This system recorded, through an automated and anonymous way from clinical history data, the necessary effectiveness events for the evaluation of antiviral treatment based on algorithms previously defined by physicians and pharmacists responsible for CHC patients. These systems also allowing for registering patient reported outcomes as the adverse events (AEs).

The HCV viral load was determined using the real-time PCR technique with the Cobas® AmpliPrep platform from Roche; the kit is HCV Quantitative Test, version 2.0. The limits of detection and quantification in plasma (there is no significant difference in the serum) were 11 IU/mL (10-13 IU/mL, 95%CI) for the lower limit of detection (LOD) with a 95% positive result rate and 15 UI/mL for LOD with positive results. Viral load determinations were made at the baseline, week 4, at the end of antiviral treatment (week 12 or 24) and 12 weeks after antiviral treatment was completed. Transient elastography was used for the staging of liver fibrosis (Fibroscan®), stratifying patients according stiffness results in fibrosis F0-1 (<7.6 kPa), F2 (7.6-9.5 kPa), F3 (9.6- 14.4 kPa) or F4=cirrhosis (>14.4 kPa in HCV mono-infected patients and> 14.0 kPa in HIV co-infected patients).

Adherence rates were made following continuous measurement of the medication acquisition (CMA) method [20], during the monthly visits to the Hospital Pharmacy Service where the study was conducted, from the beginning to the end of the treatment.

The primary efficacy endpoint was the percentage of patients with SVR12, defined as the ribonucleic acid (RNA) HCV un-detectability 12 weeks post-treatment. Secondary efficacy variables were based on the analysis of covariates such as the presence of cirrhosis, fibrosis stage, previous antiviral treatments, hepatic decompensation, RBV addition to the combination of DAAs, HIV co-infection and liver transplantation. Treatment failure was defined as a lack of SVR12 due to a virologic breakthrough (RNA-HCV detectability in a patient with previous RNA-HCV un-detectability on treatment), relapse (RNA-HCV detectability 12 weeks post-treatment in a patient with RNA-HCV detectability at the end-of-treatment), virologic failure (no RNA-HCV un-detectability on treatment) or missing RNA-HCV data 12 weeks post-treatment due to on-treatment withdrawal secondary to severe AEs o death. The primary safety endpoint was the percentage of treatment withdrawal secondary to severe AEs; secondary variables included the patient reported AEs stratified into mild, moderate or severe and emergent haematological abnormalities stratified according to CTCAE v4.0 [21].

Statistical analysis. The Intention-To-Treat (ITT) evaluable population included all patients who took at least one dose of the prescribed treatment. Both baseline variables (demographics, clinical, histological and laboratory values and frequencies) and primary or secondary effectiveness and safety end-points were collected and analysed by a modified ITT (mITT) analysis, including ITT evaluable population patients and excluding patients without quantification of RNA-HCV 12 weeks post-treatment for reasons other than treatment failure. Quantitative variables were expressed as mean ± standard deviation (SD) or as median and interquartile range if their distributions were normal or non-normal, respectively, and were analysed using the Student's t-test or the Mann-Whitney U-test according to data distribution. Qualitative variables were expressed as count and percentage, with confidence interval at 95% and were compared using a Chi-square test or Fisher's exact test. Primary end-points were expressed as a percentage and exact 95% binomial confidence interval. To determine any baseline factor influence on primary end-points, relative risk with a 95% confidence interval (Katz) for cohort studies was calculated using the Chi-square association test without Yates correction or Fisher's exact bilateral test according to the number of cases analysed. To detect differences between treatment subgroups and predictors of response, a univariate analysis was performed. Statistically significant results were considered when the p value was <0.05. Statistical analysis was carried out using the Epidat 3.1 program.

Ethical aspects. This study complies with the Declaration of Helsinki of Good Clinical Practices. It was classified as "Observational Post-Authorization Study with Human Medicines" by the Spanish Agency of Medicines and Health Products (LMF-NAA-2016-01), dependent on the Ministry of Health and it was authorized by the Clinical Research Ethics Committee (CREC) of the Regional Health Service (number 2016/161). Patients signed an informed consent approved by the CREC for participation in the study and all their data was anonymised.

RESULTS

Baseline patient demographics and characteristics. A total of 950 adult patients started antiviral treatment during the study period at our institution, of which 132 were G3-HCV infected patients. Of these, 14 patients started antiviral treatment with different regimens of DCV/SOF ± RBV and 7 patients who completed the therapeutic regimen did not attend their appointments for the determination of viral load 12 weeks post-treatment for reasons other than treatment failure. So, 111 patients constitute the study population for the mITT analysis. The average adherence to antiviral treatment was 99.3% (98.7% -99.9%, 95%CI). The patients were mostly men under 65 years of age, naïve to antiviral treatment, HCV mono-infected, with low HCV viral loads (<6_1 log UI/mL) and with advanced fibrosis (58.4% F3-4) although mostly non-cirrhotic (table 1). The majority of non-naïve patients had experienced recurrence to previous antiviral treatment based on Peg-Interferon + RBV and only one patient had received previous DAAs treatment. A small percentage of cirrhotic patients had suffered hepatic decompensation before the start of antiviral treatment. No patient had, at the beginning of treatment, a MELD score (Model of End-stage Liver Disease) higher than 10 points. Seven patients had a liver transplant. Also, 81.6% of cirrhotic patients had a treatment duration of 24 weeks compared to 6.7% of non-cirrhotic patients (p<0.0001). Meanwhile, 81.6% of cirrhotic patients associated RBV with DCV/SOF versus 13.3% of non-cirrhotic patients (p<0.0001).

Effectiveness outcomes. All patients achieved virologic response at the end of treatment, but 6 of them relapsed after 12 weeks of follow-up, so the SVR12 was 94.6% (89.9%-99.3%, 95%CI). One hundred per cent of patients with low fibrosis (F0-2) reached SVR12 (92.3%-100%, 95%CI) compared to 90.8% (83.0% - 98.6%, 95%CI) of patients with advanced fibrosis F3-4 (p=0.03) and the differences in effectiveness between F3 or F4 patients versus F0-2 patients were very similar (p=0.10 or p=0.16, respectively). No statistically significant differences were observed in SVR12 among cirrhotic patients with or without previous hepatic decompensation (84.6% vs 95.7%, p=0.6). SVR12 in naïve and pretreated patients was 96.2% and 90.3% respectively (p=0.35). One of the 4 patients with Child-Pugh-Turcotte (CPT) B grade did not reach SVR12 compared to 2 of the 32 CPT A grade patients. All patients treated after liver transplantation reached SVR12, including the patient with previous treatment based on DAAs; also, all HIV co-infected patients reached SVR12. SVR12 rates according to basal fibrosis stage are shown in figure 1. One hundred per cent (91.4%-100%, 95%CI) of patients treated with DCV/SOF with

Table 1 **Baseline patient demographics and characteristics.**

Characteristic	HCV-G3 infected patients (n=111)
Males, % (n)	78.4% (87)
Age, mean (years ± SD)	50.21±6.98
Age ≥ 65 years, % (n)	1,80% (2)
HIV co-infection, % (n)	24.3% (27)
Fibrosis stage, % (n)	
F0-1	9.0% (10)
F2	32.4% (36)
F3	26.2% (29)
F4	32.4% (36)
Elastography kPa, median (rank)	9.95 (4.0–72.1)
Previous clinical decompensation, % (n)	11,7% (13)
CTP classification, % (n)	
A	88.9% (32)
B	11.1% (4)
Hepatocellular carcinoma, % (n)	5.4% (6)
Liver transplant, % (n)	6.3% (7)
HCV viral load, log UI/mL (median)	6.13
≥ 6_1 UI/mL, % (n)	16.2% (18)
Platelets 10^9/mL (mean ± SD)	155.5±61.5
Albumin mg/dL (mean ± SD)	4.19±0.37
Bilirubin mg/dL (mean ± SD)	0.77±0.70
Estimated Glomerular Filtration Rate ≥ 60 ml/min, % (n)	92.8% (103)
Previous antiviral treatment, % (n)	
Naïve	72.1% (80)
Treatment-experienced	27.9% (31)
Response to previous antiviral treatment, % (n)	
Recurrent	54.8% (17)
Null responder	19.4 % (6)
Intolerant to treatment	12.9 % (4)
Unknown	12.9 %(4)
Treatment duration, % (n)	
12 weeks	67.6% (75)
24 weeks	32.4% (36)
RBV addition, % (n)	36.9% (41)

SD: standard deviation. kPa: kilopascals. HIV: human immunodeficiency virus. CPT: Child-Pugh-Turcotte. HCV: hepatitis C virus. RVB: ribavirin.

RBV reached SVR12, compared to 91.9% (85.0%-98.8%, 95% CI) of the patients who did not receive RBV (p=0.083). In the cirrhotic patients subgroup, SVR12 was 100% or 40.0% depending on the addition or not of RBV (p=0.001). Other potential baseline patient or treatment factors that could influence treatment effectiveness have not been identified, so no significant differences has been seen in SVR12 according to the patient's gender, HIV co-infection, previous liver transplantation, basal HCV viral load, platelets or albumin levels, previous antiviral treatment experience or treatment duration (table 2).

Safety outcomes. During follow-up, the rate of any degree of AEs secondary to DCV/SOF±RBV was 57.7% (48.0%-67.3%, 95%CI), although none of the patients required treatment withdrawal. Meanwhile, 4.5% of patients (1.5%-10.2%, 95%CI) developed serious AEs: three patients manifested severe headaches (which responded to the use of non-steroidal analgesics), one patient reported itching in lower limbs with bleeding (associated with grade II thrombocytopenia) and one patient presented constipation which required a visit to the Hospital Emergency Department and the use of a rectal enema. Beyond this, 9.9% (3.9%-15.9%, 95%CI) of patients developed moderate AEs: 5 with fatigue/asthenia, 3 with headache, 2 with anxiety and 5 with various symptoms (drowsiness, myalgia, insomnia, irritability and diarrhoea). Mild AEs were reported by 43.2% of patients (33.6%-52.9%, 95%CI), presenting a median of 1 event per patient, that usually disappeared after the first or second week of antiviral treatment. Table 3 shows the main safety data. Two patients required hospital admission, one secondary to hydropic decompensation and another due to respiratory infection. Both were cirrhotic patients, stage Child-Pugh-Turcotte (CTP) B and finally reached SRV12. During the antiviral treatment, no patient included in this study died.

Neither gender, HIV co-infection, liver transplantation, presence of liver cirrhosis, experience with previous antiviral treatments or treatment duration statistically had influenced on AEs development (p> 0.24). However, RBV addition to DCV/SOF had a significant negative impact on treatment safety, both at the level of general or serious AEs, and, specifically, on the development of fatigue/asthenia or pruritus, although no patient required treatment withdrawal secondary to RBV addition. Also, 16.2% (8.9%-23.5%, 95%CI) of patients developed different degree cytopenias with respect to their baseline pretreatment situation: 2 patients experienced severe haematological alterations (one grade III neutropenia; other one thrombocytopenia grade III) and 11 patients minor alterations grade I-II (7 leukopenia, 6 thrombocytopenia, 3 anemia and 2 neutropenia). Cytopenia development is linked to liver cirrhosis with a relative risk of 4.2 (1.7-10.2, 95% CI, p = 0.0016) and to RBV addition to DCV/SOD, with a relative risk of 5.8 (2.1- 16.9, 95% CI, p = 0.0002). Also, 12 patients developed hyperbilirubinemia (8 grade I and 4 grade II).

DISCUSSION

Based on the results of our real clinical practice study, DCV/SOF ± RBV shows a high antiviral effectiveness in G3-HCV in-

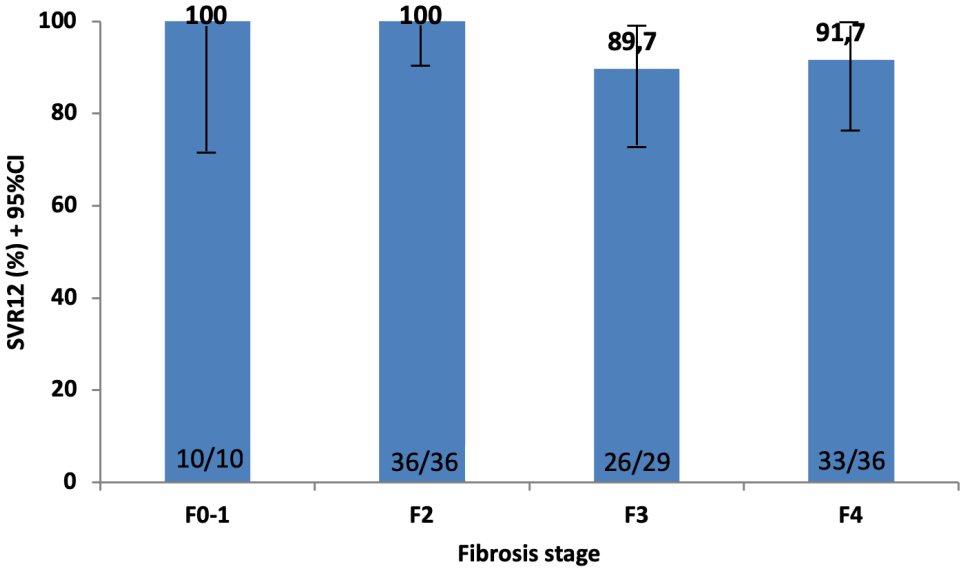

Figure 1 | **Sustained Virologic Response 12 (95%CI) according to basal fibrosis stage.**

Table 2 | **Evaluation of basal factors associated with SVR12.**

Basal factor	Relative risk ratio (CI 95%)	p
Gender: male vs female	1.07 (1.01 - 1.14)	0.19
HIV co-infection: yes vs no	1.08 (1.01 - 1.14)	0.15
Liver transplantation: yes vs no	1.06 (1.01 - 1.11)	0.99
HCV basal viral load ≥ 6_1 UI/mL: yes vs no	0.93 (0.78 - 1.10)	0.24
Platelets 10^9/mL: <100 vs ≥100	0.94 (0.80 - 1.10)	0.31
Albumin (mg/dL): <3.5 vs ≥3.5	0.88 (0.61 - 1.26)	0.32
Treatment-experienced patient: yes vs no	0.94 (0.83 - 1.06)	0.21
Treatment duration: 12 weeks vs 24 weeks	1.05 (0.94 - 1.18)	0.34

SVR12: sustained virologic response 12. HIV: human immunodeficiency virus. HCV: hepatitis C virus.

fected patients, with an overall SVR12 rate of 94.6%. This data is slightly higher than those observed in the pivotal phase III clinical trial ALLY-3 [16], where the SVR12 overall rate was 89% with a study population very similar to our study (25% of cirrhotic patients and 34% of previous non-responders to antiviral treatment). These differences in SVR12 are due to the high antiviral effectiveness shown in cirrhotic patients in our study compared with ALLY-3 (92% vs 66%), because we have implemented therapeutic strategies like 24 weeks treatment duration or RBV addition in cirrhotic patients (p<0.0001), as the pivotal phase III clinical trial authors postulate to increase the effectiveness of DCV/SOF. Also, as ALLY-3 clinical trial, our study revealed higher rates of SVR12 in naïve compared to experienced patients, although this difference is not statistically significant.

We have observed a significantly lower effectiveness of DCV/SOF ± RBV in patients with advanced fibrosis F3-4 compared to patients with low fibrosis F0-2 (p = 0.03). This is consistent with the results of the ALLY-3+ clinical trial [22], where SVR12 was 90% in a population of 50 patients with advanced fibrosis or compensated cirrhosis and also with the results observed in cirrhotic patients in the DCV European Compassionate Use Program (SVR12: 88-89%) [23], or in the DCV French Compassionate Use Program (SVR12: 85-90%) [24]. Studies in real clinical practice, such as the one published by Alonso et al [25] documented SVR12 rates of 94% in G3-HCV cirrhotic patients (both in CTP A and CTB B/C) and authors suggest that this high effectiveness in patients with advanced liver disease with regarding previous studies may be due to the fact that all cirrhotic patients were treated over 24 weeks with an RBV addition to the antiviral regimen. In fact, when analysing the influence of RBV on SVR12 in our study, it is observed that 100% of patients who have been added RBV to DCV/SOF reached SVR12 compared to 91.4% in those without RBV, and this superior effectiveness is a clinical and statistically significant difference when analysed in patients F4 (SVR12: 100% vs 40%, p = 0.001), confirming the importance of adding RBV to DCV/SOF in cirrhotic G3-HCV infected patients. This strategies are still necessary with the most recent DAAs, such as elbasvir/grazoprevir, sofosbuvir/velpatasvir (SOF/VEL), glecaprevir/pribentasvir (GLE/PRI), that require an RBV addition and/or antiviral treatment prolongation when the G3-HCV infected patient is cirrhotic and/or is not naïve to antiviral treatment. Apart from the RBV addition, no other baseline factor dependent on the patient or treatment (except for advanced fibrosis) has been identified as significant on treatment effectiveness in this study.

Regarding the analysis in other patient subgroups (although with a limited sample), it is noteworthy that all liver transplant patients have achieved SVR12, in accordance with the high effectiveness of DCV/ SOF ± RBV observed in patients with advanced cirrhosis or post-liver transplantation recurrence, in which SVR12 rates of 83% and 91% have been reported respectively [26]. Likewise, treatment has been effective in all HIV co-infected patients, reproducing the results of other studies in these patients [27-29]. Patients with decompensated cirrhosis included in this study obtain an SVR12 around 85%, which, while not statistically inferior to the response obtained

Table 3 Percentage of patients with drug-related adverse events

Event (%)	GLOBAL (n=111)	DCV/SOF (n=70)	DCV/SOF+RBV (n=41)	p
Treatment withdrawal due to drug-related AE	0.0%	0.0%	0.0%	0.999
Any drug-related AE	57.7%	45.7%	75.6%	0.004
Any drug-related serious AE	7.2%	1.4%	17.1%	0.007
Hospitalization during treatment	1.8%	0.0%	4.9%	0.260
Death	0.0%	0.0%	0.0%	0.999
Any grade AE with global incidence > 2.5%:				
Fatigue/asthenia	36.0%	25.7%	53.7%	0.006
Headache	21.6%	18.6%	26.8%	0.435
Insomnia	9.0%	5.7%	14.6%	0.215
Gastrointestinal upset	7.2%	5.7%	9.8%	0.678
Nausea	5.4%	5.7%	4.9%	0.805
Anxiety	4.5%	4.3%	4.9%	0.742
Diarrhoea	4.5%	4.3%	4.9%	0.742
Myalgia	3.6%	1.4%	7.3%	0.281
Irritability	3.6%	1.4%	7.3%	0.281
Constipation	3.6%	2.9%	4.9%	0.981
Pruritus	3.6%	0.0%	9.8%	0.033
Emergent haematological abnormalities				
Leukopenia	6.3%	0.0%	17.1%	0.0007
Thrombocytopenia	5.4%	2.9%	14.6%	0.0498
Anaemia	2.7%	0.0%	7.3%	0.0481
Neutropenia	2.7%	2.9%	7.3%	0.3565
All	17.1%	5.8%	46.3%	<0.001

DCV: daclatasvir. SOF: sofosbuvir. RBV: ribavirin. AE: adverse event.

in patients with compensated cirrhosis (around 96%), could be considered clinically relevant in the current context of elevated effectiveness of antiviral treatment. Some previous studies have analysed the efficacy and safety of DAAs in HCV patients with decompensated cirrhosis. Curry MP et al [30] conducted an open phase 3 clinical trial (ASTRAL 4) that evaluated SOF associated with velpatasvir with or without RBV for 12 weeks or without RBV for 24 weeks in HCV patients genotype 1 to 6 with decompensated cirrhosis; RVS12 in the small group of 39 HCV genotype 3 patients was 50% if RBV had not been associated with DAAs and 85% in those who did associate it; these results are very similar to those of our study and reinforce the importance of the RBV addition to the antiviral regimen in patients with decompensated cirrhosis. Also, Foster GR et al [31] evaluated the response to a 12-week treatment with SOF+DAC or SOF/LPV associated or not with RBV (according to non-protocolized medical criteria) in 192 HCV genotype 3 patients with decompensated cirrhosis; SVR12 in regimens based on LDP was around 40% or 60% (depending on the absence or presence of RBV) and in regimens with DAC of 61% or 73% respectively; this low effectiveness observed in this study, much lower than that achieved in our experience, reinforces the hypothesis of the importance of the addition of RBV to DAAs and treatment durations of 24 weeks in HCV genotype 3 patients with decompensated cirrhosis, as the authors conclude in their work.

It is also important to assess the results of our study in the context of the current reference therapeutic guidelines. European Association for the Study of the Liver (EASL) considers therapeutic options the association of SOF/VEL 12 weeks or GLE/PRI 8-12 weeks (according to previous therapeutic experience) for patients HCV genotype 3 without cirrhosis, GLE/PRI 12-16 weeks (according to previous therapeutic experience) or SOF/VEL/voxilaprevir (SOF/VEL/VOX) for 12 weeks for patients with compensated cirrhosis, and SOF/VEL + RBV 12 weeks or SOF/VEL 24 weeks (if intolerance or contraindication to RBV)

in patients with decompensated cirrhosis [18]; these recommendations can be considered in line with the results obtained in our study, since the observed SVR12 with SOF + DAC in patients F3 or F4 is improved with the therapeutic options proposed, although in decompensated cirrhosis (with due caution due to the limited population analysed) they are similar to the results observed with SOF/VEL. On the other hand, AASLD/IDSA Guidance still recommends SOF + DAC + RBV for 12 weeks in patients with decompensated cirrhosis, in line with the results of our study, in addition to SOF/VEL + RBV [14]. In both cases, the scientific societies consolidate the importance of the addition of RBV and/or prolongation of the antiviral treatment in patients with decompensated cirrhosis, also in agreement with the data of our study.

In relation to safety, it is noteworthy that no patient required antiviral treatment withdrawal secondary to severe AEs, even among patients who were hospitalised, so we consider DCV/SOF ± RBV safe in G3-HCV infected patients treated in real clinical practice. Rates of patients affected by any grade of AEs or serious AEs are very similar to those observed in clinical trials or observational studies, as well as in the recent review carried out by Cornberg et al [32]. Also, we must highlight the incidence of fatigue/asthenia, headache, insomnia and gastrointestinal upset. Our study has also detected the development of cytopenias, which is usually mild or moderate during antiviral treatment, associated with advanced liver disease. On the other hand, both in the case of general AEs and in the development of cytopenias, the RBV addition to DCV/SOF has a significant negative effect on treatment safety, as has been reflected by Ferreira et al in a meta-analysis about interferon-free treatments safety in CHC [33].

In summary, although our study has the inherent limitations of its design and the impossibility of performing a multivariate analysis on predictors of response due to the high effectiveness of the treatment, it has the strength to present results in a large population of patients in real clinical practice, and may conclude that DCV/SOF ± RBV is highly effective and safe for G3-HCV infected patients, with a lower effectiveness in patients with advanced fibrosis F3-4, as well as that RBV addition is determinant on the effectiveness of this antiviral treatment in cirrhotic patients, which also influences their safety.

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CONFLICT OF INTEREST

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Original

Monitoring the antimicrobial susceptibility of Gram-negative organisms involved in intraabdominal and urinary tract infections recovered during the SMART study (Spain, 2016 and 2017)

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ABSTRACT

Introduction. Continuous antimicrobial resistance surveillance is recommended by Public Health authorities. We updated data from the SMART (Study for Monitoring Antimicrobial Resistance Trends) surveillance study in Spain.

Material and methods. The antimicrobial susceptibility data and extended-spectrum beta-lactamase (ESBL) production in isolates recovered from intra-abdominal (IAI) (n=1,429) and urinary tract (UTI) (n=937) infections during the 2016-2017 SMART study in 10 Spanish hospitals were analysed.

Results. *Escherichia coli* was the most frequently microorganism isolated (48.3% and 53.7%) followed by *Klebsiella* spp. (11.5% and 21.9%) in IAIs and UTIs, respectively. Figures for *Pseudomonas aeruginosa* were 9.0% and 6.1%, being more frequently recovered from patients with nosocomial infections. Overall, 9.9% (IAI) and 14.0% (UTI) of *E. coli*, *Klebsiella* spp. and *Proteus mirabilis* isolates were ESBL-producers, being *Klebsiella pneumoniae* (34.5%) from UTI of nosocomial origin the most frequent. ESBL-producers were higher in patients >60 years in both IAIs and UTIs. As in previous years, amikacin (96.3%-100% susceptibility), ertapenem (84.2%-100%) and imipenem (70.3%-100%) were the most active antimicrobials tested among Enterobacterales species. The activity of amoxicillin-clavulanic, piperacillin-tazobactam, and ciprofloxacin susceptibility was lower, particularly among ESBL-producers. Ertapenem susceptibility (88.9%-100%) was retained in ESBL-*E. coli* isolates that were resistant to these antimicrobials but decreased (28.6%-100%) in similar isolates of *K. pneumoniae*.

Conclusions. Continuous antimicrobial resistance surveillance from the SMART study reveals overall maintenance of ESBL-producers in Spain, although with higher presence in isolates from UTIs than from IAIs. Moreover, ertapenem activity was high in *E. coli* irrespective of ESBL production but decreased in *K. pneumoniae*, particularly among ESBL-producers.

Key words: antimicrobial resistance surveillance, intra-abdominal infection, urinary tract infection, extended-spectrum-beta-lactamases, carbapenems

Seguimiento de la sensibilidad antimicrobiana de microorganismos gramnegativos procedentes de infecciones intraabdominales y urinarias del estudio SMART (España, 2016 y 2017)

RESUMEN

Introducción. Las autoridades de Salud Pública re-

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comiendan la vigilancia continua de la resistencia a los antimicrobianos. Se actualizan los datos del estudio SMART (*Study for Monitoring Antimicrobial Resistance Trends*) en España.

Material y métodos. Se analizaron los datos de sensibilidad antimicrobiana y la producción de betalactamasas de espectro extendido (BLEE) en aislamientos obtenidos en el estudio SMART de infecciones intraabdominales (IIA) (n=1.429) y del tracto urinario (ITU) (n=937) durante 2016-2017 en 10 hospitales españoles.

Resultados. *Escherichia coli* fue el microorganismo más frecuente (54,5% y 57,5%, respectivamente), seguido de *Klebsiella* spp. (18,4% y 25,4%) en IIA y en ITU. En *Pseudomonas aeruginosa* estas cifras fueron 9% y 6%, siendo más frecuente en la infección nosocomial. El 9,9% (IIA) y el 14% (ITU) del total de los aislados de *E. coli*, *Klebsiella* spp. y *Proteus mirabilis* producían BLEE, obteniéndose la tasa más alta en *Klebsiella pneumoniae* (34.5%) en ITU nosocomial. El mayor porcentaje de aislados con BLEE se observó en pacientes >60 años, tanto en IIA como en ITU. Como en años anteriores, amikacina (sensibilidad 96,3%-100%), ertapenem (84,2%-100%) e imipenem (70,3%-100%) fueron los antimicrobianos más activos en Enterobacterales. La sensibilidad a amoxicilina-ácido clavulánico, piperacilina-tazobactam y ciprofloxacino fue menor, en particular en los productores de BLEE. La sensibilidad a ertapenem (88,9%-100%) se mantuvo en *E. coli* con BLEE resistente a estos antimicrobianos, pero disminuyó (28,6%-100%) en aislados similares de *K. pneumoniae*.

Conclusiones. La vigilancia continua de la resistencia a los antimicrobianos en el estudio SMART revela el mantenimiento de la frecuencia de aislados productores de BLEE en España, pero con mayor presencia en las ITUs que en las IIAs. Además, la sensibilidad a ertapenem fue alta en *E. coli* con independencia de la producción de BLEE, pero disminuyó en *K. pneumoniae*, sobre todo en los productores de BLEE.

Palabras clave: vigilancia epidemiológica de la resistencia, infección intraabdominal, infección urinaria, betalactamasas de espectro extendido, carbapenems

INTRODUCTION

The increase in antimicrobial resistance is a worldwide reality that threatens the prevention and effective treatment of an increasing number of infections, challenging clinical microbiologists and infectious disease specialists [1]. Two of the most common infections are urinary tract (UTI) and intra-abdominal (IAI) infections caused mainly by Enterobacterales, in particular *Escherichia coli* and *Klebsiella* species [2,3]. In the 1980s, extended spectrum beta-lactamase (ESBL)-producing Enterobacterales were considered one of the leading causes of nosocomial infections and later also of those acquired in the community [4]. These enzymes have the ability to hydrolyze beta-lactam antibiotics, including penicillins, cephalosporins and the monobactam aztreonam but not carbapenems [5]. As a consequence, carbapenems were considered the antimicrobials of choice for the treatment of infections caused by ESBL producers, however the prevalence of carbapenemases, enzymes that inactivate them, continue to increase worldwide [6]. In addition, the production of ESBL combined with mutations affecting permeability can also contribute to the carbapenems resistance. This situation warns the need for surveillance of susceptibility to antimicrobials, especially to carbapenems. Global surveillance programs such as SMART (Study for Monitoring Antimicrobial Resistance Trends) that evaluates antimicrobial susceptibility to beta-lactam antibiotics, including carbapenems, and also aminoglycosides and quinolones, against a large number of Gram-negative bacilli species collected from IAI and UTI fulfills this function.

In this study, we analysed the antimicrobial susceptibility data from isolates recovered in 2016 and 2017 in Spain from abdominal samples in patients with diagnosis of IAI and urinary samples from patients with UTI included in the SMART database. The ESBL production of these isolates is also presented.

MATERIAL AND METHODS

Microorganisms and participating sites. All isolates studied were obtained from abdominal samples from patients with diagnosis of IAI and from urinary samples from patients with UTI. Details on sampling and criteria for the inclusion of microorganisms were previously described [7]. During the 2 years of the study (2016 and 2017) a total of 10 Spanish hospitals participated (H. Universitario Gregorio Marañón, Madrid, H. Clínico San Carlos, Madrid, H. Universitario Virgen Macarena, Sevilla, H. Universitario Virgen del Rocío, Sevilla, H. Universitario Marqués de Valdecilla, Santander, H. Universitario Son Espases, Palma de Mallorca, H. Clínico Universitario Lozano Blesa, Zaragoza, H. Universitario Bellvitge, Hospitalet de Llobregat, Barcelona, H. Universitario y Politécnico La Fe, Valencia, and H. Universitario Ramón y Cajal, Madrid).

A total of 1,429 intra-abdominal isolates were collected; the most frequent were recovered from peritoneal fluid (41%), intra-abdominal abscesses (31%) and gall bladder (18%), and to a lesser extent and in decreasing order, from the liver, appendix, pancreas, colon, rectum, and other sources. Most of the isolates were obtained during surgery procedures and others from paracentesis and percutaneous aspiration of intra-abdominal abscesses. Regarding UTI, a total of 937 isolates were obtained, being virtually all urine samples (98%). Isolates from other locations (i.e. blood, abdominal drainages, superficial wounds or perirectal abscesses) were excluded.

The identification of the isolates was performed at each hospital and sent to a central laboratory (International Health Management Associates, SA. Schaumburg, IL, US) to confirm the identification and to establish the susceptibility to different antimicrobials of choice for the treatment of IAIs or UTIs. All results were included in a centralized database. In addition to the source of the sample, patient's age was considered. Following the standard criteria of the *Centers for Disease Control and Prevention* (CDC) the organisms were also rated as isolates obtained within 48 h after hospitalization

(community-acquired infection) and isolates obtained after 48 h of hospital stay (nosocomial infection) [8].

Antimicrobial susceptibility and ESBL production. Antimicrobial susceptibility testing results were obtained at a central laboratory (International Health Management Associates) using the standard ISO broth microdilution method [9]. MIC results were interpreted each year according to the most recent EUCAST guidelines (http://www.eucast.org/clinical_breakpoints/). Dried MicroScan (Beckman, West Sacramento, CA, US) microdilution panels were used. The antimicrobials analyzed in this study were: piperacillin-tazobactam, cefotaxime, ceftazidime, cefepime, imipenem, ertapenem, amikacin and ciprofloxacin. In addition, susceptibility to amoxicillinclavulanate was measured with a MIC gradient test (Etest®, bioMérieux, Lyon, France). The quality controls strains used were *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, *Klebsiella pneumoniae* ATCC 700603 (positive ESBL control) and *P. aeruginosa* ATCC 27853. *E. coli*, *Klebsiella* spp. and *Proteus mirabilis* isolates were classified as ESBL following CLSI criteria [10].

Statistical analysis. The frequency comparison (incidence between hospital and community isolates) was performed using the chi-squared test (χ^2) taking $P<0.05$ as statistically significant.

RESULTS

During 2016 and 2017, a total of 1,429 isolates from IAI and 937 isolates from UTI recovered in the 10 Spanish hospitals were included (tables 1 and 2). In IAI, the Enterobacterales (1,265) constituted 85.5% of the total isolates. This figure was 876 isolates (93.4%) in UTI. Overall, *E. coli* was the most frequently isolated microorganism (48.3% and 53.7%), followed by *Klebsiella* spp. (11.5% and 21.8%) in IAIs and UTIs, respectively. Figures for *Pseudomonas aeruginosa* were 9.0% and 6.1%, being more frequently recovered in patients with nosocomial infections. When the origin of the isolates was considered (tables 1 and 2), 43.2% of IAI isolates were considered to be acquired in the community compared to 56.8% that had their origin in the nosocomial setting. In UTI, there was also a lower number of isolates from community (47.8%) than from nosocomial origin (52.2%). In 1.5% of IAI isolates, their origin was not specified in the data collection sheets.

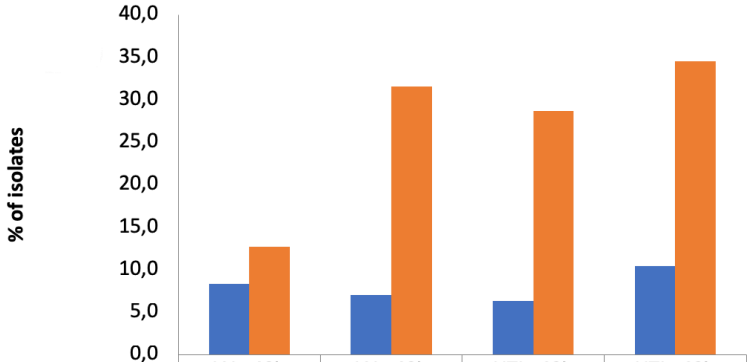
Table 1 **Distribution of the most common Gram-negative organisms collected in intra-abdominal infections in Spain in the SMART Study (2016-2017).**

		Community associated		Nosocomial associated	
Organisms	No. isolates	No.	%	No.	%
Escherichia coli	690	337	54.6	353	43.4
Klebsiella pneumoniae	165	54	8.7	111	13.6
Klebsiella oxytoca	69	39	6.3	30	3.6
Proteus mirabilis	46	17	2.7	29	3.5
Enterobacter cloacae	75	30	4.8	45	5.5
Citrobacter freundii	31	19	3.0	12	1.4
Morganella morganii	27	6	0.9	21	2.5
Serratia marcescens	25	9	1.4	16	1.9
Other Enterobacterales	137	44	7.1	93	11.4
Pseudomonas aeruginosa	129	54	8.7	75	9.2
Other Gram-negative bacilli	35	8	1.2	27	3.3
TOTAL	1,429	617	43.2	812	56.8

Table 2 **Distribution of the most common Gram-negative organisms collected in urinary tract infections in Spain in the SMART Study (2016-2017).**

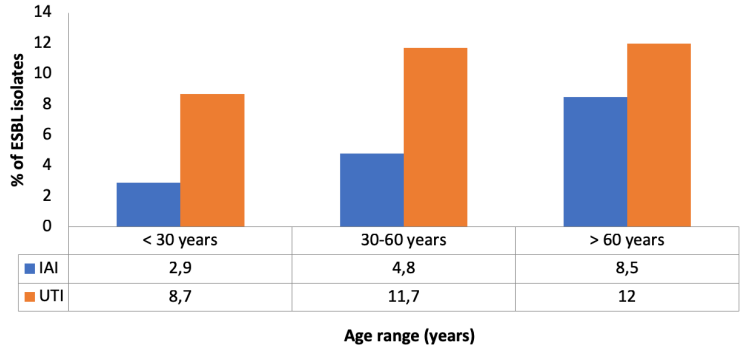
		Community associataed		Nosocomial associated	
Organisms	No. isolates	No.	%	No.	%
Escherichia coli	504	284	63.3	220	44.9
Klebsiella pneumoniae	205	66	14.7	139	28.4
Klebsiella oxytoca	18	9	2.0	9	1.8
Proteus mirabilis	61	31	6.9	30	6.1
Enterobacter cloacae	16	5	1.1	11	2.2
Citrobacter freundii	11	6	1.3	5	1.0
Morganella morganii	21	8	1.7	13	2.6
Serratia marcescens	7	3	0.6	4	0.8
Other Enterobacterales	33	13	2.9	20	4.0
Pseudomonas aeruginosa	57	22	4.9	35	7.1
Other Gram-negative bacilli	4	1	0.2	3	0.6
TOTAL	937	448	47.8	489	52.2

Tables 1 and 2 also show the distribution of the most frequent microorganisms according with their origin. The percentage of *E. coli* of isolates in IAI (table 1) acquired in the community (54.6%) was higher than in those of nosocomial origin (43.4%) (P<0.01). On the contrary, the percentage in *P. aeruginosa* was higher in infections acquired in the hospital (9.2% vs. 8.7%) but without statistical significance (P=0.751). The same situation occurs, even to a greater extent, in the UTIs



	IAI <48h	IAI >48h	UTI <48h	UTI >48h
E. coli	8,3	7,0	6,3	10,4
K. pneumoniae	12,7	31,5	28,7	34,5

Figure 1 Percentage of *Escherichia coli* and *Klebsiella pneumoniae* isolates with extended spectrum β-lactamases by origin of acquisition of infection in the SMART study in Spain comparing intra-abdominal (IAI) and urinary tract infections (UTI) infections.



	< 30 years	30-60 years	> 60 years
IAI	2,9	4,8	8,5
UTI	8,7	11,7	12

Figure 2 Frequency of Enterobacterales (*Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca* and *Proteus mirabilis*) with extended spectrum β-lactamases according to age of the patients in the SMART study in Spain comparing intra-abdominal (IAI) and urinary tract infections (UTI) infections.

(Table 2). In *E. coli*, the corresponding numbers are 63.3% in the community and 44.9% in nosocomial infection (p<0.01). In *P. aeruginosa* these percentages were 4.9 and 7.1, respectively (P=0.150).

Overall, the Enterobacterales with AmpC-type inducible chromosomal β-lactamases, such as *Enterobacter cloacae, Morganella morganii* and *Serratia marcescens*, were mainly recovered in infections of hospital origin, both in IAI and in UTI (tables 1 and 2).

The presence of ESBL in Enterobacterales such as *E. coli, Klebsiella* spp. and *Proteus mirabilis* was specifically studied in IAI and in UTI. In IAI a total of 96 (9.9%) were ESBL producers. The highest frequency was found in *K. pneumoniae* (25.4%), followed by *E. coli* (7.6%) and *K. oxytoca* (1.4%). In *P. mirabilis* none was found. In UTI the same pattern was followed with higher percentages: *K. pneumoniae* had a higher percentage of ESBL (32.6%) followed by *E. coli* (8.1%), *K. oxytoca* (5.5%) and *P. mirabilis* (1.6%). In all microorganisms with ESBL, the frequency of these enzymes was higher in nosocomially acquired than in community infections (figure 1), with the exception of *E. coli* and *P. mirabilis* in IAI. Likewise, an increase of the ESBL isolates was observed in parallel with the increase of the age of the patients, reaching a frequency higher than 8% in those over 60 years in both types of infection (figure 2).

The susceptibility profile for the antibiotics studied of the most common microorganisms is detailed in table 3. In IAI, the most active antibiotics in Enterobacterales were amikacin (susceptibility rates range: 96.3%-100%), ertapenem (84.2%-100%) and imipenem (70.3%-100%). Ciprofloxacin demonstrated less activity with a percentage of resistance in *E. coli* greater than 25% and close to 40% in *K. pneumoniae*. Regarding the associations of penicillins with beta-lactamase inhibitors, piperacillin-tazobactam susceptibility ranged from 66.6% to 100% and amoxicillin-clavulanic acid from 58.3% to 81.5% (table 3). In *P. aeruginosa*, amikacin, imipenem and ceftazidime, were the most active compounds (96.9%, 76.7% and 72.8% susceptible, respectively).

In UTI the most active antibiotics against Enterobacterales were the same as in IAI, with similar figures for amikacin (97%-100% susceptibility) and higher ones for ertapenem (94.7%-100%) and imipenem (90.4%-100%). Regarding ciprofloxacin, the loss of activity against isolates from urine is noteworthy: only 63% of *E. coli*, 57% of *K. pneumoniae* and 54.1% of *P. mirabilis* were susceptible to this fluoroquinolone.

On the other hand, considering the most frequent microorganisms recovered from IAI (n=1,429), 43.2% were of community origin compared to 56.8% of hospital origin. Of those responsible for the UTIs (n=937), 47.8% were community acquired and 52.2% were of hospital origin. Tables 4 and 5 comparatively analyze the activity of the different antibiotics against community and hospital isolates. Systematically, in the isolates with higher numbers (*E. coli* and *K. pneumoniae*), the activity of all antimicrobials was higher in those originated in the community. However, in the remaining species, there were some exceptions. In those from IAI (table 4), the opposite occurs in *C. freundii* with piperacillin-tazobactam and the third-generation cephalosporins and in *M. morganii* with ciprofloxacin. In UTI (table 5), exceptions occurred with amoxicillin-clavulanate and *K. pneumoniae*, with the third-generation cephalosporins and *P. mirabilis*, *C.*

Table 3 **Activity of different antimicrobial used in intra-abdominal (IAI) and urinary tract infections (UTI) against the most common microorganisms collected in Spain in the SMART study (2016-2017).**

	Percentage of susceptible isolates[a]																	
Organism	A/C[a]		P/T		CTX		CAZ		FEP		IPM		ETP		AK		CIP	
Type of infection	IAI	UTI	IAI	UTI	IAI	UTI	IAI	UTI	IAI	UTI	IAI	UTI	IAI	UTI	IAI	UTI	IAI	UTI
Escherichia coli	81.5	77.7	90.0	90.9	90.5	90.1	89.8	89.1	92.0	90.9	99.7	99.8	99.4	99.4	97.9	99.0	72.4	63.0
Klebsiella pneumoniae	58.3	94.1	66.6	69.7	72.7	64.3	67.8	64.8	72.7	65.3	95.1	97.0	84.2	86.8	98.7	97.0	62.4	57.0
Klebsiella oxytoca	76.3	100.0	85.5	84.2	97.1	94.7	97.1	94.7	100.0	94.7	100.0	100.0	100.0	94.7	100.0	100.0	97.1	89.4
Proteus mirabilis	74.1	100.0	100.0	100.0	100,0	96.7	100.0	93.4	100.0	100.0	91.3	100.0	100.0	100.0	100.0	100.0	60.8	54.1
Enterobacter cloacae	_[b]	_[b]	78.6	58.8	73.3	52.9	72.0	58.8	84.0	82.3	96.0	94.1	85.3	94.1	97.3	100.0	90.6	70.5
Citrobacter freundii	_[b]	_[b]	70.9	90.9	70.9	72.7	54.8	63.6	87.1	90.9	93.5	90.9	96.7	90.9	100.0	100.0	93.5	81.8
Morganella morganii	_[b]	_[b]	100,0	95.2	51.8	71.4	74.0	66.6	96.3	95.2	70.3	90.4	100.0	100.0	96.3	100.0	70.3	66.6
Serratia marcescens	_[b]	_[b]	88,0	100,0	72.0	100.0	96.0	100.0	92.0	100.0	92.0	100.0	92.0	100.0	100.0	100.0	96.0	85.7
Other Enterobacterales	36.3	60.0	79.8	74.1	82.4	84.8	72.8	78.7	98.2	93.9	99.1	100.0	96.4	100.0	98.2	100.0	91.2	87.8
Pseudomonas aeruginosa	_[b]	_[b]	66.6	81.8	_[b]	_[b]	72.8	77.5	72.0	74.1	76.7	81.0	_[b]	_[b]	96.9	91.3	70.5	67.2

[a]**EUCAST criteria except A/C in which CLSI criteria were considered. A/C: amoxicillin-clavulanic acid, P/T: piperacillin/tazobactam; CTX: cefotaxime; CAZ: ceftazidime; FEP: cefepime; IPM: imipenem; ETP: ertapenem; AK: amikacin; CIP: ciprofloxacin**

[b]**This antimicrobial is not considered adequate against the microorganism tested.**

freundii and *M. morganii*, with ciprofloxacin in *P. mirabilis* and *M. morganii* and with imipenem in *S. marcescens*. Moreover, in *P. aeruginosa* recovered from IAI, all the antibiotics tested were more active when this pathogen was originated in the community, but in the UTI this premise was not observed with piperacillin-tazobactam, ceftazidime and cefepime.

When ESBL producers were considered and compared with non-ESBL producers in IAI (figure 3), the activity of imipenem (99.6% non-ESBL, 100% ESBL) and ertapenem (99.3% non-ESBL, 100% ESBL) remained about at the same level in *E. coli* whereas amikacin was slightly affected (98.9% non ESBL, 86.7% ESBL). On the contrary, the associations of penicillins with the beta-lactamase inhibitors, as well as third generation cephalosporins and ciprofloxacin importantly decreased their activity. In *K. pneumoniae*, amikacin susceptibility (100% non-ESBL, 95.2% ESBL) was little affected compared with that of imipenem (97.5% non-ESBL, 88.1% ESBL) and especially with ertapenem (97.5% non ESBL, 45.2% ESBL) and decreases drastically in the rest of antibiotics as described in *E. coli*. In UTI, *E. coli* isolates showed similar results than those described for IAI. In *K. pneumoniae*, the activity of ertapenem was affected (96.3% non ESBL, 67.1% ESBL), although to a lesser extent than in the IAI isolates.

Finally, when analyzing the activity of carbapenems both in ESBL and in non-ESBL producing *E. coli* and *K. pneumoniae* that were resistant to amoxicillin-clavulate, piperacillin-tazobactam or ciprofloxacin from IAI and UTI (table 6), it was observed that in *E. coli* both the activity of imipenem (data not shown) and that of ertapenem was scarcely modified with susceptibility values higher than 88%. However, in *K. pneumoniae*, ertapenem activity was retained to a lesser extent. In IAI, 28.6% of ESBL producers that were also resistant to amoxicillin-clavulanate were susceptible to ertapenem and in UTI 38.9% of ESBL producers that were resistant to piperacillin-tazobactam were susceptible to ertapenem.

DISCUSSION

Antimicrobial resistance is a global increased problem and poses challenges for the effective treatment of many types of infections, including IAI and UTI. This situation, mainly due to its wide dispersion, is especially alarming in relation to microorganisms that produce ESBL. As a consequence, carbapenems are generally considered the treatment of choice for these infections [11,12], although a decrease in the susceptibility to these compounds have been observed due to the production of carbapenemases or alterations in the porins combined with the production of ESBL or AmpC cephalosporinases [13,14]. Epidemiological surveillance studies analyze trends in resistance but also allow data to progressively adapt treatment guidelines over time, providing valuable information for the selection of initial antibiotic treatment, often empirical. The SMART study (Study for Antimicrobial Resistance Trends), initiated in 2002, is a worldwide program designed to longitudinally monitor the involvement of aerobic and facultative Gram-negative bacilli in IAI, both from community and nosocomial acquisition, as well as their patterns of resistance [15-18]. As of 2009, microorganisms isolated from UTI were also included. The program has been developed in Spain uninterruptedly since 2002 and has had the participation of a significant number of Microbiology Departments of Spanish University Hospitals. Previous

Table 4 **Susceptibility of community-associated (CA) and hospital-associated (HA) microorganisms collected of IAI in Spain in the SMART study (2016-2017).**

Organism	Percentage of susceptible isolates[a]																	
	A/C[a]		P/T		CTX		CAZ		FEP		IPM		ETP		AK		CIP	
Type of infection	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA
Escherichia coli	88.7	75.9	93.4	86.6	91.3	89.8	91.0	88.6	91.6	92.3	100,0	99.3	99.4	99.4	98.5	97.4	75.3	69.9
Klebsiella pneumoniae	83.8	48.7	85.4	57.6	87.2	65.7	85.4	59.4	87.2	65.7	100.0	92.7	96.3	78.3	100.0	98.2	74.5	55.8
Klebsiella oxytoca	84.2	68.4	92.3	76.6	97.4	96.6	97.4	96.6	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	97.4	96.6
Proteus mirabilis	62.5	78.2	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	94.1	89.6	100.0	100.0	100.0	100.0	64.7	58.6
Enterobacter cloacae	_[b]	_[b]	93.3	68.8	83.3	66.6	80.0	66.6	90.0	80.0	100.0	93.3	93.3	80.0	100.0	95.5	96.6	86.6
Citrobacter freundii	_[b]	_[b]	68.4	75.0	68.4	75.0	57.8	50.0	89.4	83.3	94.7	91.6	100.0	91.6	100.0	100.0	94.7	91.6
Morganella morganii	_[b]	_[b]	100.0	100.0	66.6	47.6	66.6	76.1	100.0	95.2	83.3	66.6	100.0	100.0	100.0	95.2	50.0	76.1
Serratia marcescens	_[b]	_[b]	88.8	87.5	66.6	75.0	100.0	93.7	100.0	87.5	100.0	87.5	100.0	87.5	100.0	100.0	100.0	93.7
Pseudomonas aeruginosa	_[b]	_[b]	79.6	57.3	_[b]	_[b]	85.1	64.0	88.8	60.0	88.8	68.0	_[b]	_[b]	98.1	96.0	79.6	64.0

[a]EUCAST criteria except A/C in which CLSI criteria were considered. A/C: amoxicillin-clavulanic acid, P/T: piperacillin/tazobactam; CTX: cefotaxime; CAZ: ceftazidime; FEP: cefepime; IPM: imipenem; ETP: ertapenem; AK: amikacin; CIP: ciprofloxacin

[b]This antimicrobial is not considered adequate against the microorganism tested.

Table 5 **Susceptibility of community-associated (CA) and hospital-associated (HA) microorganisms collected of UTI in Spain in the SMART study (2016-2017).**

Organism	Percentage of susceptible isolates[a]																	
	A/C[a]		P/T		CTX		CAZ		FEP		IPM		ETP		AK		CIP	
Type of infection	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA
Escherichia coli	77.6	78.2	91.5	90.0	92.6	86.8	91.5	85.9	92.6	88.6	100.0	99.5	99.6	99.0	99.3	98.6	64.0	61.3
Klebsiella pneumoniae	90.0	100.0	71.2	69.0	66.6	63.3	69.7	62.5	69.7	63.3	100.0	95.6	92.4	84.1	98.4	96.4	59.0	56.1
Klebsiella oxytoca	100.0	0.0	88.8	77.7	100.0	88.8	100.0	88.8	100.0	88.8	100.0	100.0	100.0	88.8	100.0	100.0	100.0	77.7
Proteus mirabilis	100.0	100.0	100.0	100.0	93.5	100.0	90.3	96.6	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	51.6	56.6
Enterobacter cloacae	_[b]	_[b]	100.0	36.3	80.0	36.3	100.0	36.3	100.0	72.7	100.0	90.9	100.0	90.9	100.0	100.0	100.0	54.5
Citrobacter freundii	_[b]	_[b]	100.0	80.0	66.6	80.0	50.0	80.0	100.0	80.0	100.0	80.0	100.0	80.0	100.0	100.0	83.3	80.0
Morganella morganii	_[b]	_[b]	100.0	92.3	50.0	84.6	37.5	84.6	100.0	92.3	87.5	92.3	100.0	100.0	100.0	100.0	62.5	69.2
Serratia marcescens	_[b]	_[b]	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	66.6	100.0	100.0	100.0	100.0	100.0	100.0	75.0
Pseudomonas aeruginosa	_[b]	_[b]	72.7	77.1	_[b]	_[b]	77.2	80.0	72.7	77.1	81.8	80.0	_[b]	_[b]	95.4	88.5	68.1	68.5

[a]EUCAST criteria except A/C in which CLSI criteria were considered. A/C: amoxicillin-clavulanic acid, P/T: piperacillin/tazobactam; CTX: cefotaxime; CAZ: ceftazidime; FEP: cefepime; IPM: imipenem; ETP: ertapenem; AK: amikacin; CIP: ciprofloxacin

[b]This antimicrobial is not considered adequate against the microorganism tested.

articles represent the general picture of antimicrobial susceptibility in our country; the last one (7) updates up to 2015 the evolution of ESBL producing isolates in IAIs in Spain. In the present study, the following two years (2016 and 2017) were analyzed but also including information from UTI pathogens. In general, the results are in line with those obtained in the 2011-2015 period and with others from different regions of the world [13,19-21].

We confirm the relevance of *E. coli* in IAI and UTI and in both cases it is isolated in greater proportion in community-acquired infections than in nosocomial infections, in line with other recent publications [20-22]. *K. pneumoniae* is the second microorganism in order of frequency in both types of infections and unlike the previous period (2011-2015) a greater proportion of isolates was found in nosocomial compared to community infections, both in IAI and in UTI.

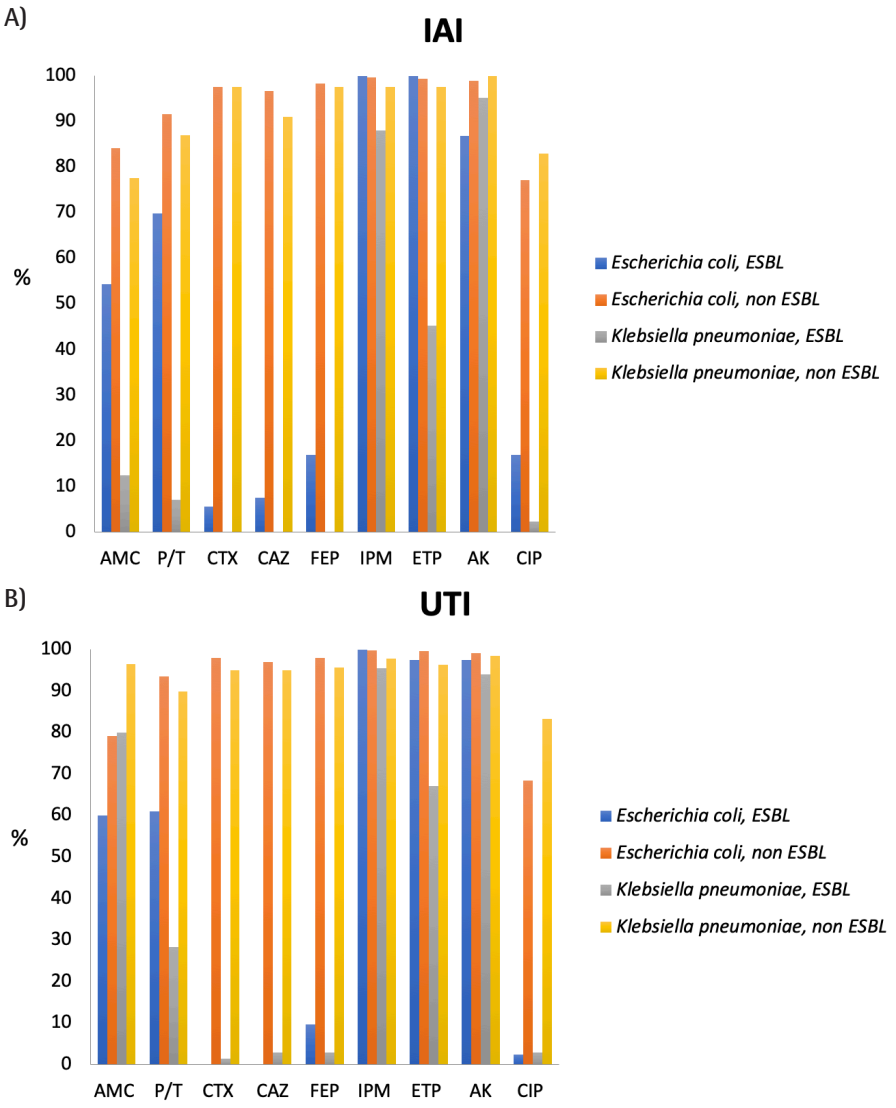


Figure 3 | **Percentage of susceptibility of different antimicrobials used in intra-abdominal (A) and urinary tract infections (B) against ESBL producing and non-ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* in the SMART study in Spain (2016-2017).**

A/C: amoxicillin-clavulanic acid, P/T: piperacillin/tazobactam; CTX: cefotaxime; CAZ: ceftazidime; FEP: cefepime; IPM: imipenem; ETP: ertapenem; AK: amikacin; CIP: ciprofloxacin

Given its epidemiological importance, knowledge of the antimicrobial susceptibility of *E. coli* is crucial regarding empirical therapy, as well as for attempts to control the spread of ESBL and, more recently, of carbapenemases. As in other studies [3,13,19,21], imipenem, ertapenem and amikacin were the most active antimicrobials tested against *E. coli* in both IAIs (>97%), and UTIs (>99%) (21) and there is no evidence of loss of activity in 2016 and 2017 compared to 2011-2015 [7]. On the contrary, in *K. pneumoniae* a decrease in the activity of ertapenem in IAI is verified by comparing the two time periods (95.5% in 2011-2015 *versus* 84.2% in 2016-2017) [7]. In UTI, the percentage of susceptibility is 86.8%, slightly lower to that published in studies from other countries [3,21].

In a recent publication, small decreases, although statistically significant, of ertapenem susceptibility in Enterobacterales isolated from IAI and UTI were observed in most regions of the world. Nevertheless, the susceptibility remains above 90% in all regions, except in Asia [22]. In community infections, the activity was >92% in all regions against Enterobacterales [22] despite the existence of communications that alert of the increase in resistance [6]. Another recent study, unrelated to SMART,

Table 6 **Activity of ertapenem in ESBL producing *Escherichia coli* and *Klebsiella pneumoniae* isolates resistant to amoxicillin-clavulanate, piperacillin-tazobactam and ciprofloxacin in intra-abdominal (IAI) and urinary tract infections (UTI) of the SMART study (2016-2017) in Spain.**

Microorganisms	ESBL	Antimicrobial	IAI				UTI			
			No. (% of resistant isolates)	Ertapenem			No. (% of resistant isolates)	Ertapenem		
				Susceptible No. (%)	Intermediate No. (%)	Resistant No. (%)		Susceptible No. (%)	Intermediate No. (%)	Resistant No. (%)
Escherichia coli	Negative		65 (15.8)	64 (98.4)		1 (1.6)	26 (20.8)	26 (100)		
		A/C								
	Positive		16 (45.7)	16 (100)			4 (40)	4 (100)		
	Negative		46 (7.2)	43 (93.4)	1 (2.2)	2 (4.4)	18 (3.8)	17 (94.4)	1 (5.6)	
		P/T								
	Positive		10 (18.8)	10 (100)			9 (21.9)	8 (88.9)	1 (11.1)	
	Negative		126 (19.7)	123 (97.7)		3 (2.3)	137 (29.4)	136 (99.3)	1 (0.7)	
		CIP								
	Positive		42 (79.2)	42 (100)			39 (95.1)	38 (97.4)	1 (2.6)	
Klebsiella pneumoniae	Negative		17 (22)	14 (82.4)		3 (17.6)	1 (3.4)	1 (100)		
		A/C								
	Positive		28 (87.5)	8 (28.6)		20 (71.4)	1 (20)	1 (100)		
	Negative		14 (33.3)	11 (78.6)		3 (21.4)	11 (7.9)	6 (54.5)		5 (45.5)
		P/T								
	Positive		38 (30.6)	16 (42.1)		22 (57.9)	36 (53.7)	14 (38.9)	2 (5.5)	20 (55.6)
	Negative		15 (35.7)	13 (86.7)		2 (13.3)	16 (11.5)	12 (75)		4 (25)
		CIP								
	Positive		40 (32.2)	17 (42.5)	1 (2.5)	22 (55)	61 (91)	40 (65.6)	2 (3.3)	19 (31.1)

A/C: amoxicillin-clavulanate; P/T: piperacillin/tazobactam; CIP: ciprofloxacin

reported a percentage of susceptibility to ertapenem in the Enterobacterales group of 94.5% (98.7% in *E. coli* and 87.4% in *K. pneumoniae*) [23]. In the study of Lob et al. [22], susceptibility to ertapenem significantly decreased in *K. pneumoniae* between 2012 and 2016 in Africa (6%), Europe (8%) and US/Canada (2.5%). Despite this fact, in 2016 the susceptibility of *K. pneumoniae* to ertapenem remains above 90% in the US/Canada and in the South Pacific area, being greater than 80% in the rest of the world.

In recent years, there is a continuous increase in the rates of Enterobacterales with ESBL around the world, especially in Asia [24]. In a recent review of the global epidemiology, the prevalence of CTX-M ESBLs increased over time in all geographic regions, especially in community isolates [25]. In our study, in IAI the percentage of ESBL in *E. coli* is overall 7.6% (8.3% in community and 7% in nosocomial infection), keeping the total figures in line with the period 2011-2015 [7]. It is noteworthy that the rate is somewhat higher in community-acquired infections, a fact not communicated in most of the published surveillance studies [13,21], although the reports on the spread of ESBL in the community are worrisome [26,27]. In *K. pneumoniae*, the ESBL rate increased with respect to previous years, from 18.6% in 2015 to 25.4% in 2016-2017, especially at the expense of infections of nosocomial origin (12.7% community and 31.5% nosocomial). In UTI, the figures in ESBL producing *E. coli* are slightly higher (overall 8.1%; 6.3% community and 10.4% nosocomial) and much higher in *K. pneumoniae* (overall 32.6%; 28.7% community and 34.5% nosocomial). Our rates of ESBL in *K. pneumoniae* are difficult to compare with those published in other regions where there are large variations, although it can be summarized that they are lower than those of most countries in Asia, especially China and Thailand [3], and higher than those of the US/Canada [28]. Our study also shows that the highest percentage of ESBL isolates occurs in IAI of hospital origin and in patients of advanced ages. Both circumstances have already been indicated as risk factors for the acquisition of infections due to ESBL producers [29]. In this line, in a recent study in UTI in the US when data are stratified by sex, age and time of hospital stay, there is a higher percentage of ESBL isolations in men, patients ≥65 years and in nosocomial infections [28].

In IAI, the activity of imipenem, ertapenem and amikacin in ESBL-producing *E. coli* isolates remains practically at the

same level in relation to those that do not produce ESBLs. This fact is also confirmed in other publications [13,21,22]. However, one of these articles [13] found some evidence of increased resistance among isolates from the community, in addition to the known decreasing trends in susceptibility to quinolones and third-generation cephalosporins. In ESBL-producing *K. pneumoniae,* the activity of imipenem decreased by almost 10% and that of ertapenem by more than 50%. This decrease is not reflected so strongly in any other study and follows the trend already mentioned in the study of the years 2010-2016 in Spain [7]. Ertapenem susceptibility figures below 90% (83.6% in Africa and 85.5% in Europe) have already been published, although data came from a joined analysis including *E. coli, K. pneumoniae, K. oxytoca* and *P. mirabilis* ESBL producers from IAI and UTI and not from an individualized analysis [22].

In UTI, the behavior of imipenem, ertapenem and amikacin in *E coli.* and *K. pneumoniae* is similar to that commented for IAI. However, the activity of ertapenem decreased to a lesser extent (somewhat less than 30%) in *K. pneumoniae* being higher than in other publications [3,21]. Regarding the origin of the isolates, *E. coli* slightly decreased their susceptibility to the most active compounds (imipenem, ertapenem and amikacin) when having a hospital origin both in IAI and in UTI, in line with what it is reflected in other studies [3,19,21]. In *K. pneumoniae*, in IAI, the susceptibility decreased to a greater extent, data not sufficiently confirmed in other studies to date [3,19,21].

As in the 2011-2015 study the co-resistance analysis, which is relevant to designing antimicrobial treatment protocols [30], showed that both imipenem (data not shown) and ertapenem have a good activity against ESBL-producing *E. coli* recovered from IAI and UTI that were also resistant to amoxicillin-clavulanic acid, piperacillin-tazobactam or fluoroquinolones. Nevertheless, the same did not occur in the case of ESBL-producing *K. pneumoniae*, although ertapenem retained its activity in 28.6%, 42.1% and 42.5% of amoxicillin-clavulanic acid, piperacillin-tazobactam or ciprofloxacin resistant isolates, respectively. These figures were more favorable in UTI, particularly for ciprofloxacin resistant isolates (65.6% of ertapenem susceptibility). The reason for the increased loss of susceptibility to ertapenem in *K. pneumoniae* was analyzed in a recent study and concluded that it was not only due to production of carbapenemases but to permeability defects [31]. The genes encoding the OmpK35 and OmpK36 porins of the outer membrane were studied and most of the isolates (83.0%) had one or both genes affected. In isolates with higher ertapenem MICs (>4 mg/L), 60.5% of the total isolates, a mutation was found in both porin genes.

Despite the above observations, carbapenems are still considered as empirical therapy of choice in infections suspected to be caused by ESBL producers or AmpC hyperproducers both in IAI and UTI [12,32,33]. Regardless of the spread of ESBL worldwide, a very recent study showed that ertapenem was active against more than 90% of Enterobacterales isolates recovered from IAI and UTI with the ESBL phenotype in Latin America, Middle East, South Pacific, US and Canada. Our study also shows that ertapenem continue to exhibit good activity, despite the emergence of carbapenemases in Spain [34,35], when compared to broad spectrum cephalosporins and associations of penicillins with beta-lactamase inhibitors. This activity is higher in isolates from community origin and may be a viable option to reduce the length of hospitalization of stable patients together with its easy once-a-day dosing, safety and tolerability [36,37]. Continuous surveillance efforts should be performed at local and global levels, since knowledge of the patterns and resistance trends are essential for making decisions about empirical treatment and support infection control efforts.

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CONFLICTS OF INTEREST

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Original

Comparación de distintas estrategias para la predicción de muerte a corto plazo en el paciente anciano infectado

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RESUMEN

Objetivo. Evaluar la capacidad del lactato o el índice de Charlson para mejorar la capacidad del SIRS y el qSOFA para identificar el riesgo de muerte a corto plazo de los pacientes ancianos, sin deterioro funcional grave, atendidos por sospecha de infección en urgencias.

Metodología. Estudio de cohorte observacional prospectivo que incluyó a todos los pacientes de 75 años o más, sin deterioro funcional, atendidos por una infección aguda en 69 servicios de urgencias españoles durante 2 días en cada periodo estacional. Se recogieron datos demográficos, clínicos y analíticos. La variable de resultado principal fue la mortalidad por cualquier causa a los 30 días de la visita índice.

Resultados. Se incluyeron 739 pacientes con una edad media de 84,9 (DE 6,0) años y 375 (50,7%) fueron mujeres. Noventa y un (12,3%) pacientes fallecieron dentro de los 30 días posteriores a la visita a urgencias. El ABC para el SIRS ≥ 2 y el qSOFA ≥ 2 fue de 0,637 (IC 95% 0,587-0,688; p<0,001) y 0,698 (IC 95% 0,635-0,761; p<0,001), respectivamente. La comparación entre esta curvas muestra una mejor capacidad de clasificación por parte del qSOFA ≥ 2 (p=0,041). Ambas escalas incrementan su capacidad de clasificación al añadir el lactato, siendo el ABC para SIRS más lactato de 0,705 (IC95% 0,652-0,758; p<0,001) y para qSOFA más lactato de 0,755 (IC95% 0,696-0,814; p<0,001), existiendo una tendencia estadística a un mejor rendimiento pronóstico de la segunda estrategia (p=0,0727). No ocurre lo mismo con el índice de Charlson, que no tiene efectos de mejora en la clasificación realizada con el SIRS (p=0,2269) ni con qSOFA (p=0,2573).

Conclusiones. La inclusión de la valoración del lactato a las escalas SIRS y qSOFA mejoran su capacidad para identificar pacientes ancianos atendidos por infección en riesgo de muerte a corto plazo. La valoración del índice de Charlson no tiene efecto.

Palabras claves: sepsis; paciente anciano infectado; pronóstico; urgencias; mortalidad; SIRS; qSOFA

Comparison of different strategies for short-term death prediction in the infected older patient

ABSTRACT

Objective. The aim of this study was to determine the utility of a post hoc lactate added to SIRS and qSOFA score to predict 30-day mortality in older non-severely dependent patients attended for infection in the Emergency Department (ED).

Methods. We performed an analytical, observational, prospective cohort study including patients of 75 years of age or older, without severe functional dependence, attended for an infectious disease in 69 Spanish ED for 2-day three seasonal periods. Demographic, clinical and analytical data were collected. The primary outcome was 30-day mortality after the index event.

Results. We included 739 patients with a mean age of 84.9 (SD 6.0) years; 375 (50.7%) were women. Ninety-one (12.3%) died within 30 days. The AUC was 0.637 (IC 95% 0.587-0.688; p<0.001) for SIRS ≥ 2 and 0.698 (IC 95% 0.635-0.761; p<0,001) for qSOFA ≥ 2. Comparing receiver operating characteristic (ROC) there was a better accuracy of qSOFA vs

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SIRS (p=0.041). Both scales improve the prognosis accuracy with lactate inclusion. The AUC was 0.705 (IC95% 0.652-0.758; p<0.001) for SIRS plus lactate and 0.755 (IC95% 0.696-0.814; p<0.001) for qSOFA plus lactate, showing a trend to statistical significance for the second strategy (p=0.0727). Charlson index not added prognosis accuracy to SIRS (p=0.2269) or qSOFA (p=0.2573).

Conclusions. Lactate added to SIRS and qSOFA score improve the accuracy of SIRS and qSOFA to predict short-term mortality in older non-severely dependent patients attended for infection. There is not effect in adding Charlson index.

Keywords: sepsis; infected older patient; prognosis; emergency; mortality; SIRS; qSOFA

INTRODUCCIÓN

Las enfermedades infecciosas constituyen un grave problema de salud, asociándose con una elevada morbi-mortalidad [1]. Los pacientes diagnosticados de infección en los servicios de urgencias hospitalarios (SUH) en España han aumentado en la última década, constituyendo actualmente el 14,3% de las asistencias [2]. Además, 1 de cada 3 pacientes atendidos por infección en el SUH tiene 75 años ó más [3].

El SUH representa un eslabón clave en la atención del paciente infectado, ya que es donde se realiza la sospecha clínica y comienza el tratamiento específico. Una de las decisiones iniciales más trascedentes es la estratificación pronóstica de los pacientes, que puede determinar las medidas terapéuticas y diagnósticas a poner en marcha y, sobre todo, la rapidez con la que se hacen, así como indicar la necesidad de ingreso o no de los pacientes [4]. Estas decisiones iniciales pueden condicionar la evolución clínica del paciente [5].

Los ancianos constituyen un segmento poblacional de enorme complejidad de cara al diagnóstico y a la estratificación pronóstica. La inmunosenescencia, los cambios fisiológicos propios de la edad, el deterioro funcional, el acúmulo de comorbilidad, la polifarmacia o la frecuente exposición al sistema sanitario hacen que con frecuencia presenten sintomatología atípica, escasa respuesta inflamatoria que limita los hallazgos analíticos e incluso una limitada alteración en sus constantes vitales [6,7]. Constituyen, por tanto, un grupo donde el riesgo de malos resultados puede infra-estimarse durante la evaluación inicial en urgencias, y en consecuencia el manejo inadecuado podría ser más habitual [8].

A raíz de la publicación de las definiciones de Sepsis-3 [9] se ha instaurado en la literatura científica una importante discusión acerca de la efectividad de la escala qSOFA (*Quick Sequential Sepsis-related Organ Failure Assessment*) para identificar pacientes con sepsis. En los últimos años, se han venido publicando múltiples estudios que evalúan la precisión del qSOFA o el síndrome de respuesta inflamatoria sistémica (SIRS) en la evaluación inicial del paciente con sospecha de infección [10,11], observándose resultados discrepantes que podrían estar relacionados con la heterogeneidad de las poblaciones estudiadas. En general, los resultados muestran una inferior sensibilidad del qSOFA respecto al SIRS, que podría condicionar una menor capacidad para la detección en los SUH de pacientes potencialmente graves.

El lactato es un biomarcador barato y de rápida y sencilla determinación a pie de cama del paciente, que se ha asociado en múltiples estudios a un mayor riesgo de resultados adversos para los pacientes [12,13]. Por este motivo, es el biomarcador más utilizado en los SUH de cara a la estratificación pronóstica de los pacientes a su llegada. Sin embargo, durante el desarrollo de los estudios de cara a establecer las definiciones de Sepsis-3, el lactato sérico no cumplió con los umbrales estadísticos para su inclusión en la construcción del modelo de qSOFA, hecho que podría justificarse por la gran cantidad de pacientes con valores ausentes de lactato [9].

Por último, mencionar que el índice Charlson, como medida cuantitativa de la comorbilidad acumulada por el paciente, ha mostrado ser una variable independiente que aumenta significativamente la mortalidad de los pacientes durante el ingreso hospitalario cuando éste es mayor de 2 [14].

En base a lo expuesto previamente, el objetivo de nuestro estudio fue evaluar, en población con sospecha de infección de 75 años o más y sin dependencia funcional grave, la capacidad del qSOFA y el SIRS para identificar pacientes con riesgo de muerte a corto plazo, así como determinar si la inclusión del valor inicial del lactato o del índice de Charslon a estas escalas pueden mejorar su capacidad para estratificar el riesgo de los pacientes.

METODOLOGÍA

Diseño. Se realizó un estudio de cohorte observacional prospectivo que incluyó a todos los pacientes de 75 años o más atendidos por una infección aguda en 69 SUH españoles durante 2 días en 3 períodos estacionales (1 y 22 de octubre de 2015, 12 y 19 de enero de 2016 y 13 y 27 Abril de 2016). El Comité de Ética del centro de referencia aprobó el estudio. Todos los pacientes o tutores legales dieron su consentimiento informado para participar en el estudio. Los SUH que participaron en el estudio están incluidos en la red de centros del Grupo de Enfermedades Infecciosas de la Sociedad Española de Medicina de Emergencia (INFURG-SEMES) (adendum).

Selección de pacientes. Se incluyeron pacientes mayores de 75 años que no tenían dependencia funcional grave (índice de Barthel > 40), se les diagnosticó clínicamente una infección aguda en los SUH participantes y aceptaron participar en el estudio.

Definición de las variables. Se recogieron datos demográficos (edad y sexo), comorbilidades (índice de Charlson), estado funcional basal (índice de Barthel), datos clínicos y analíticos a la llegada del paciente al SUH (estado del mental según la escala de coma de Glasgow, frecuencia cardíaca y respiratoria, temperatura, presión arterial, saturación de oxígeno, nivel de lactato y recuento de leucocitos) y el modelo de infección (urinaria, respiratoria, intraabdominal, de piel y tejidos blandos u otras infecciones).

Se consideró comorbilidad grave cuando el paciente presentaba un índice de Charlson de 3 o más. Se estableció como

variable dependiente la mortalidad por cualquier causa durante los primeros 30 días tras la visita índice al SUH.

Se consideró SIRS si se presentaron dos o más de los siguientes parámetros: temperatura corporal >38ºC o <36ºC, frecuencia cardíaca >90 latidos por minuto, hiperventilación documentada por una frecuencia respiratoria >20 respiraciones por minuto o PaCO2 <32 mmHg y un recuento de leucocitos >12.000 células/µl o <4.000/µl. Para la consideración del qSOFA se tuvieron en cuenta la presencia de una presión arterial sistólica ≤100 mmHg, una frecuencia respiratoria ≥22 y una alteración de estado mental definido como una puntuación de <15 en la escala de coma de Glasgow.

Las variables se registraron en un formulario electrónico creado ad hoc para el presente estudio. Los diferentes criterios y parámetros fueron definidos previamente por el grupo en base a las pautas clínicas actuales y posteriormente todos los investigadores fueron informados por el investigador principal de cada centro. El seguimiento fue realizado por el investigador principal de cada centro consultando la historia clínica electrónica o por teléfono para determinar la muerte dentro de los primeros 30 días después de haber sido atendido en el SUH.

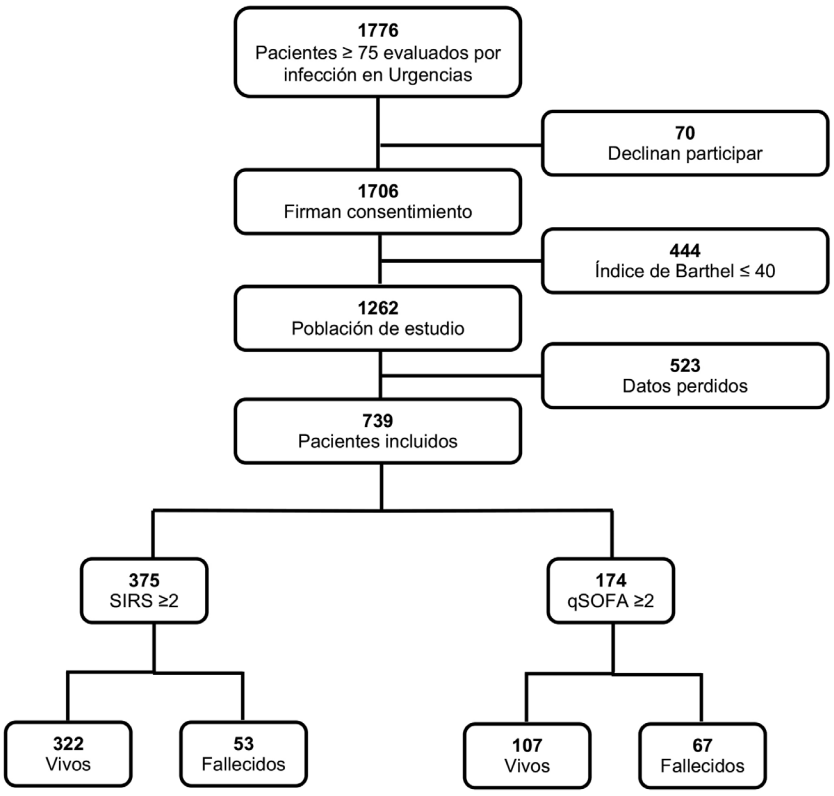


Figura 1 | **Flujograma de los pacientes incluidos en el estudio**

Análisis estadístico. Las variables cuantitativas se expresan como media y desviación estándar (DE) y las variables cualitativas se expresan como frecuencias absolutas y relativas. Las variables cualitativas se analizaron usando la prueba exacta de Chi-cuadrado o Fisher, si más del 25% de las frecuencias esperadas eran menores de 5, y la prueba de la t de Student se utilizó para las variables cuantitativas.

Se calculó el áreas bajo la curva (ABC) para las puntuaciones de sepsis y qSOFA, así como la asociación de éstas con el lactato y con el índice de Charlson. Se calcularon la sensibilidad, especificidad y la razón de verosimilitud positiva y negativa y los intervalos de confianza del 95% (IC 95%).

El ABC y el rendimiento de las diferentes escalas predictivas se compararon por una prueba no paramétrica. Consideramos un error α menor que 0,05. Los análisis estadísticos se realizaron utilizando el paquete estadístico SPSS 18.0® (SPSS Inc., Chicago, Illinois, EE. UU.) Y STATA 12.0 (StataCorp LP, CollegeStation, Texas, EE. UU.).

RESULTADOS

Se incluyeron 739 de los 1.776 pacientes infectados evaluados en el SU. Setenta pacientes no aceptaron participar en el estudio, 444 pacientes tenían dependencia funcional grave y 523 pacientes no se disponían de todos los datos necesarios para el cálculo del qSOFA y el SIRS, o no se había solicitado lactato durante la primera atención en el SUH (figura 1).

La edad media de los pacientes fue de 84,9 (DE 6,0) años y 375 (50,7%) fueron mujeres. La tabla 1 muestra las características de los pacientes incluidos en el estudio. En el momento de la primera evaluación en el SUH, 375 (50,7%) tenían ≥ 2 criterios SIRS y 174 (23,5%) una puntuación qSOFA ≥ 2. Noventa y un (12,3%) pacientes fallecieron dentro de los 30 días posteriores a la visita al SUH. La tabla 2 muestra el análisis univariante que relaciona mortalidad a 30 días con las escalas pronósticas utilizadas y el nivel de lactato.

La tabla 3 muestra el rendimiento pronóstico para predecir la mortalidad a 30 días de los criterios de SIRS, qSOFA y las distintas estrategias establecidas combinando estas escalas con el nivel de lactato y la comorbilidad, evaluada mediante el índice de Charlson. La sensibilidad para el SIRS ≥ 2 fue de 73,63 (IC 95% 64,02-83,23) y su especificidad 52,47 (IC 95% 48,55-56,39), mientras que para el qSOFA ≥ 2 la sensibilidad resultó de 58,24 (IC 95% 47,56-68,92) y su especificidad 81,33 (IC 95% 78,25-84,40). El ABC para el SIRS ≥ 2 y el qSOFA ≥ 2 fue de 0,637 (IC 95% 0,587-0,688; p<0,001) y 0,698 (IC 95% 0,635-0,761; p<0,001), respectivamente. La comparación entre esta curvas muestra una mejor capacidad de clasificación por parte del qSOFA ≥ 2 (p=0,041).

Tabla 1 **Características de los pacientes incluidos en el estudio.**

	Total (N=739)
Datos demográficos	
Edad (años) [media (DE)]	84,9 (6,0)
Sexo mujer [N(%)]	375 (50,7)
Comorbilidad	
Hipertensión arterial [N(%)]	542 (73,3)
Diabetes mellitus [N(%)]	171 (23,1)
Cardiopatía isquémica [N(%)]	135 (18,3)
Insuficiencia renal crónica [N(%)]	126 (17,1)
Enfermedad cerebrovascular [N(%)]	118 (16,0)
Enfermedad vascular periférica [N(%)]	68 (9,2)
Enfermedad pulmonar obstructiva crónica [N(%)]	197 (26,7)
Insuficiencia cardiaca crónica [N(%)]	123 (16,6)
Demencia [N(%)]	201 (27,2)
Hepatopatía [N(%)]	25 (3,4)
Ulcera gastrointestinal [N(%)]	31 (4,2)
Cáncer [N(%)]	73 (9,9)
Tumor metastásico [N(%)]	22 (3,0)
Enfermedad del tejido conectivo [N(%)]	18 (2,4)
Leucemia [N(%)]	10 (1,4)
Linfoma [N(%)]	11 (1,5)
Comorbilidad grave (Índice de Charlson ≥ 3) [N(%)]	319 (43,2)
Factores de riesgo para infección por microorganismos resistentes	
Catéter urinario [N(%)]	46 (6,2)
Vía central [N(%)]	5 (0,7)
Instrumentalización [N(%)]	50 (6,8)
Procedente de residencia [N(%)]	147 (19,9)
Tratamiento corticoideo crónico [N(%)]	50 (6,8)
Tratamiento inmunosupresor [N(%)]	26 (3,5)
Hospitalización en el mes previo [N(%)]	169 (22,9)
Antibioterapia en el mes previo [N(%)]	204 (27,6)
Variables hemodinámicas	
Nivel de consciencia (escala de Glasgow) [media (DE)]	14.1 (1,7)
Presión sistólica (mmHg) [media (DE)]	131,3 (28,9)
Frecuencia respiratoria (rpm) [media (DE)]	21,5 (8,0)
Frecuencia cardiaca (lpm) [media (DE)]	90,1 (21,2)
Temperatura (ºC) [media (DE)]	36.9 (1,0)
Tipo de infección	
Infección del tracto urinario	156 (21,1)
Infección del tracto respiratorio	445 (60,2)
Infección intraabdominal	85 (11,5)
Infección de piel y partes blandas	49 (6,6)
Otros	4 (0,6)

***DE: desviación estándar; lpm: latidos por minuto; rpm: respiraciones por minuto.**

Tabla 2 **Análisis univariante. Mortalidad a 30 días en función de las escalas pronósticas y valor de lactato.**

	Total [n (%)]	Mortalidad [n (%)]	Valor de la p
SIRS ≥ 2	375 (50,7)	67 (17,9)	<0,001
qSOFA ≥ 2	174 (23,5)	53 (30,5)	<0,001
Índice Charlson ≥ 3	319 (43,2)	46 (14,4)	0,129
Lactato ≥ 2 mmol/L	283 (38,3)	63 (22,3)	<0,001
Lactato ≥ 3 mmol/L	139 (18,8)	51 (36,7)	<0,001
Lactato ≥ 4 mmol/L	81 (11)	32 (39,5)	<0,001

SIRS: síndrome de respuesta inflamatoria sistémica; qSOFA: quick Sequential Sepsis-related Organ Failure Assessment

Ambas escalas incrementan su rendimiento pronóstico al añadir el lactato, indistintamente del punto de corte de éste, al producirse un aumento significativo del ABC y del índice de discriminación (tabla 3). No ocurre lo mismo con el índice de Charlson, que no tiene efectos de mejora en la clasificación realizada con el SIRS (p=0,2269) ni con qSOFA (p=0,2573).

El ABC para el para el SIRS ≥ 2 + lactato ≥ 2 mmol/L fue de 0,721 (IC 95% 0,666-0,775; p<0,001); para el SIRS ≥ 2 + lactato ≥ 3 mmol/L de 0,760 (IC 95% 0,705-0,815; p<0,001); y para el SIRS ≥ 2 + lactato ≥ 4 mmol/L de 0,720 (IC 95% 0,663-0,778; p<0,001). Las diferencias estadísticas al comparar las ABC fueron: SIRS ≥ 2 vs SIRS ≥ 2 + lactato ≥ 2 mmol/L, p=0,0002; SIRS ≥ 2 vs SIRS ≥ 2 + lactato ≥ 3 mmol/L, p<0,001; y SIRS ≥ 2 vs SIRS ≥ 2 + lactato ≥ 4 mmol/L, p<0,001.

El punto de corte ≥ 3 para el lactato es, en el caso del SIRS, el que mayor ABC y mayor índice de discriminación presenta. Las diferencias estadísticas al comparar las ABC obtenidas para el SIRS con los diferentes puntos de corte de lactato fueron: SIRS ≥ 2 + lactato ≥ 3 mmol/L vs SIRS ≥ 2 + lactato ≥ 2 mmol/L, p=0,0163; SIRS ≥ 2 + lactato ≥ 3 mmol/L vs SIRS ≥ 2 + lactato ≥ 4 mmol/L, p=0,0156.

El ABC para el qSOFA ≥ 2 + lactato ≥ 2 mmol/L fue de 0,749 (IC 95% 0,691-0,807; p<0,001); para el qSOFA ≥ 2 + lactato ≥ 3 mmol/L de 0,768 (IC 95% 0,708-0,827; p<0,001); y para el qSOFA ≥ 2 + lactato ≥ 4 mmol/L de 0,743 (IC 95% 0,683-0,803; p<0,001). Las diferencias estadísticas al comparar las ABC fueron: qSOFA ≥ 2 vs qSOFA ≥ 2 + lactato ≥ 2 mmol/L, p=0,0007; qSOFA ≥ 2 vs qSOFA ≥ 2 + lactato ≥ 3 mmol/L, p=0,0007; y qSOFA ≥ 2 vs qSOFA ≥ 2 + lactato ≥ 4 mmol/L, p=0,0005.

El punto de corte ≥ 3 para el lactato es, en el caso del qSOFA, el que presenta un mayor índice de discriminación y una mayor ABC, pero sin diferencias estadísticamente significativas frente a otros puntos de corte. Las diferencias estadísticas al comparar las ABC obtenidas para el qSOFA con los diferentes puntos de corte de lactato fueron: qSOFA ≥ 2 + lactato ≥ 3 mmol/L vs qSOFA ≥ 2 + lactato ≥ 2 mmol/L, p=0,1967; qSOFA ≥ 2 + lactato ≥ 3 mmol/L vs frente a qSOFA ≥ 2 y lactato ≥ 4 mmol/L, p=0,0748.

En la figura 2 se observa el rendimiento pronóstico observado al combinar el valor del lactato con el SIRS o el qSOFA.

Tabla 3 **Rendimiento para la predicción de mortalidad a 30 días de las distintas estrategias establecidas.**

	Se	Esp	VPP	VPN	CPP	CPN	ABC	IDI (%)
SIRS ≥ 2	73,63 (64,02-83,23)	52,47 (48,55-56,39)	17,87 (13,86-21,88)	93,41 (90,72-96,09)	1,55 (1,34-1,79)	0,55 (0,35-0,71)	0,637 (0,587-0,688)	-
SIRS ≥ 2 + LACTATO > 2	89,01 (82,04-95,99)	39,04 (35,21-42,88)	17,02 (13,54-20,50)	96,20 (93,70-98,70)	1,46 (1,33-1,61)	0,28 (0,16-0,51)	0,721 (0,666-0,775)	4,8 (<0,001)
SIRS ≥ 2 + LACTATO > 3	85,71 (77,98-93,45)	48,61 (44,69-52,54)	18,98 (15,07-22,89)	96,04 (93,77-98,30)	1,67 (1,49-1,87)	0,29 (0,18-0,49)	0,760 (0,705-0,815)	10,9 (<0,001)
SIRS ≥ 2 + LACTATO > 4	82,42 (74,05-90,79)	50,31 (46,38-54,24)	18,89 (14,92-22,87)	95,32 (92,94-97,71)	1,66 (1,47-1,87)	0,35 (0,22-0,55)	0,720 (0,663-0,778)	7,2 (<0,001)
SIRS ≥ 2 + CHARLSON ≥ 3	89,01 (82,04-95,99)	32,10 (28,43-35,77)	15,55 (12,34-18,75)	95,41 (92,41-98,42)	1,31 (1,20-1,43)	0,34 (0,19-0,62)	0,647 (0,592-0,703)	0,32 (0,124)
QSOFA ≥ 2	58,24 (47,56-68,92)	81,33 (78,25-84,40)	30,46 (23,33-37,59)	93,27 (91,12-95,43)	3,12 (2,46-3,95)	0,51 (0,40-0,66)	0,698 (0,635-0,761)	-
QSOFA ≥ 2 + LACTATO > 2	79,12 (70,22-88,02)	57,25 (53,3761,14)	20,63 (16,24-25,02)	95,13 (92,86-97,39)	1,85 (1,61-2,13)	0,36 (0,24-0,55)	0,749 (0,691-0,807)	3,7 (<0,001)
QSOFA ≥ 2 + LACTATO > 3	72,53 (62,81-82,25)	73,30 (69,82-76,79)	27,62 (21,74-33,49)	95,00 (92,99-97,01)	2,72 (2,27-3,25)	0,37 (0,27-0,53)	0,768 (0,708-0,827)	8,4 (<0,001)
QSOFA ≥ 2 + LACTATO > 4	68,13 (58,01-78-26)	77,16 (73,85-80,47)	29,52 (23,12-35,93)	94,52 (92,48-96,55)	2,98 (2,44-3,64)	0,41 (0,30-0,56)	0,743 (0,683-0,803)	5,0 (0,001)
QSOFA ≥ 2 + CHARLSON ≥ 3	79,12 (70,22-88,02)	48,30 (44,38-52,23)	17,69 (13,86-21,52)	94,28 (91,63-96,93)	1,53 (1,35-1,74)	0,43 (0,29-0,65)	0,715 (0,655-0,775)	0,1 (0,597)

SIRS: síndrome de respuesta inflamatoria sistémica; qSOFA: quick Sequential Sepsis-related Organ Failure Assessment; Se: sensibilidad; Esp: especificidad; VPP: valor predictivo positivo; VPN: valor predictivo negativo; CPP: coeficiente de probabilidad positiva; CPN: coeficiente de probabilidad negativa; ABC: área bajo la curva; IDI: índice de mejoría de la discriminación.

Existe una tendencia estadística a un mejor rendimiento pronóstico de la estrategia qSOFA más lactato (p=0,0727).

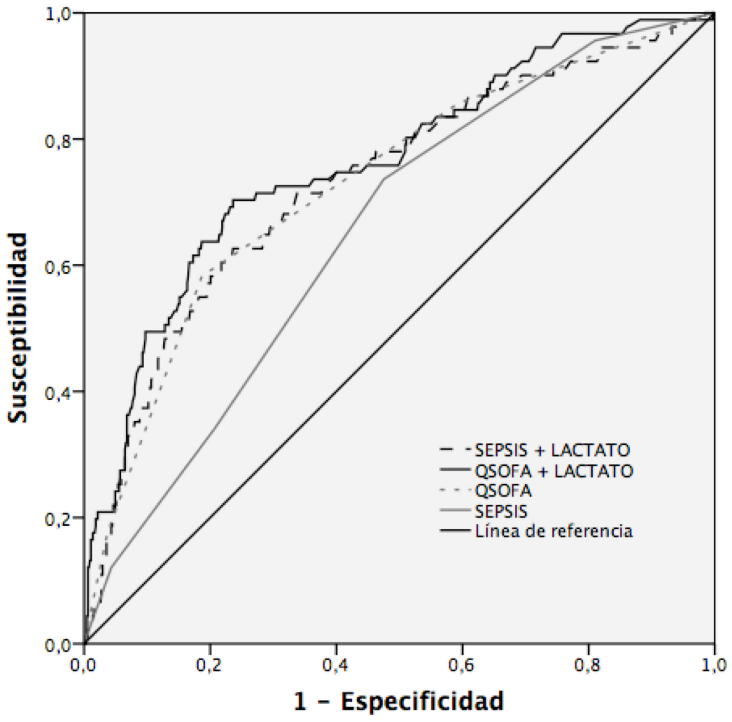
En la figura 3 se muestra la probabilidad post-prueba de mortalidad a 30 días para un resultado positivo y negativo del SIRS ≥ 2 y del QSOFA ≥ 2 de manera aislada y en combinación con el lactato ≥ 3. La probabilidad post-prueba de mortalidad cuando el criterio es positivo para la combinación del lactato ≥ 3 con el qSOFA y SIRS fue de 27,6% y 19,0%, respectivamente, mientras que la probabilidad cuando el criterio fue negativo fue del 3,9% y 4,9%, respectivamente.

DISCUSIÓN

Nuestros resultados muestran una limitada capacidad, tanto del SIRS como del qSOFA, para identificar pacientes infectados mayores de 75 años en riesgo de muerte a corto plazo, con un ABC < 0,70 en ambos casos. La capacidad del qSOFA es, no obstante, superior a la del SIRS. En cualquier caso, ambas muestran un bajo poder predictivo pronóstico para la población estudiada. qSOFA, por otra parte, muestra una menor sensibilidad en comparación con el SIRS, algo ya descrito en otros estudios [15,16].

Añadir en la evaluación del riesgo la cifra de lactato mejora la capacidad de ambas escalas, obteniéndose en ambos casos un ABC por encima de 0,70, siendo el punto de corte óptimo del lactato, aquel que ofrece una mayor ABC e índice de discriminación, de 3 mmol/L en ambas escalas. En este sentido, existe una tendencia estadística a un mejor rendimiento pronóstico para identificar pacientes de alto riesgo con la combinación de la escala qSOFA y la determinación de lactato que con SIRS más lactato (p=0,0727). Además, la estrategia que utiliza el qSOFA en lugar del SIRS resultaría más parsimoniosa, al no requerir esperar a la determinación analítica de los leucocitos, que puede retrasar el cálculo de la escala SIRS.

Una de las críticas más importantes realizadas a la utilización del qSOFA es su limitada sensibilidad. La inclusión de la valoración del lactato mejora sustancialmente la sensibilidad manteniendo una adecuada especificidad. Resaltar que para el punto de corte del lactato de 3 mmol/L, la sensibilidad de la combinación es del 72,52%, manteniendo una especificidad del 73,3%. Las herramientas de estratificación de riesgo con alta sensibilidad y baja especificidad pueden conducir a una asignación inapropiada de recursos, mientras que las he-



	AUC	p	IDI	NRI	NRI (%) evento	NRI (%) no evento
SIRS	0,654					
SIRS + LACTATO	0,732	0,0047	4,9 (p<0,001)	0,73	34,07	39,51
QSOFA	0,730					
QSOFA + LACTATO	0,762	0,0226	3,3 (p<0,001)	0,62 (p<0,001)	38,46	23,15

SIRS: síndrome de respuesta inflamatoria sistémica; AUC: área bajo la curva; IDI: índice de mejoría de la discriminación; NRI: Índice de mejoría de la reclasificación

Figura 2 **Rendimiento para la predicción de mortalidad a 30 días de las distintas estrategias establecidas considerando las variables como continuas (curvas ROC).**

rramientas con baja sensibilidad pueden llevar a los médicos a desconfiar de ellas [17], por lo que es necesario guardar un adecuado equilibrio entre ambos parámetros.

En la línea de nuestro resultados, otros estudios ya han demostrado que el añadir o combinar distintos biomarcadores a las escalas pronosticas condiciona un aumento del poder predictivo de ambos, consiguiendo un mayor rendimiento [18-20]. Otro estudio reciente [17] muestra que con la adición de lactato ≥2 mmol/L como un punto adicional a la escala qSOFA se logra una mayor capacidad predictiva, mejorando la sensibilidad del qSOFA y obteniendo una mejora en la identificación del riesgo de resultados adversos en pacientes con sospecha de sepsis, datos que se asemejan a los nuestros.

El lactato es uno de los biomarcadores que presentan un mejor poder predictivo de mala evolución clínica y de mortalidad, incluso en ausencia de hipotensión [12,13]. Por otra parte, tiene una amplia implantación en los hospitales, es de fácil y rápida obtención, barato y accesible a pie de cama del paciente, por lo que su inclusión en el árbol de decisión no tiene porque retrasar la adopción de las medidas terapéuticas oportunas. Además, ha estado incluido clásicamente dentro de las variables recomendadas para la valoración de los pacientes con sepsis y actualmente esta incluido en la definición de shock séptico.

El disponer de una estrategia de identificación del riesgo de manera rápida y eficaz nos ayuda a la toma inicial de decisiones, como son la extracción de muestras bilógicas para cultivos, la realización de procedimientos invasivos, la administración inmediata del antimicrobiano, así como determinar la necesidad de ingreso o alta hospitalaria.

Un reciente metanálisis [11] muestra una variación muy importante en los resultados de sensibilidad y especificidad entre los 38 estudios evaluados, tanto para el SIRS como para el qSOFA. Esto muestra que probablemente las poblaciones estudiadas sean muy heterogéneas o que el estadio clínico de la infección sea diferente, porque de lo contrario no se puede explicar la dispersión de los resultados informados. La sepsis es un síndrome heterogéneo secundario a diferentes etiologías y con un rango de gravedad y de intervención variables [21-24]. La presentación clínica y el pronóstico depende del modelo de infección, la situación inmunológica del huésped, la edad, la comorbilidad o el tiempo de evolución. El estudio de las poblaciones más homogéneas, como ocurre en nuestro estudio, podría ofrecer resultados más fiables para la población estudiada.

Es importante reseñar que el presente estudio no evalúa la capacidad diagnóstica de infección de las escalas estudiadas, sino tan solo su capacidad pronóstica. Varias revisiones sistemáticas y metanálisis [17,25] han sido publicados recientemente mostrando que la predicción de mortalidad hospitalaria es mayor con el qSOFA, mientras que el SIRS muestra una mejor sensibilidad para el diagnóstico de infección. A raíz de estos datos, existe una propuesta que consiste en combinar el SIRS y el qSOFA, el primero para la identificación del paciente infectado y el segundo de cara a estratificar el pronóstico [25].

No obstante, el SIRS se ha utilizado clásicamente para identificar pacientes infectados susceptibles de peores resultados clínicos, sobre los que actuar desde el punto de vista diagnóstico y terapéutico de una manera más enérgica [26]. El diagnóstico de infección es mucho más complejo y no se pue-

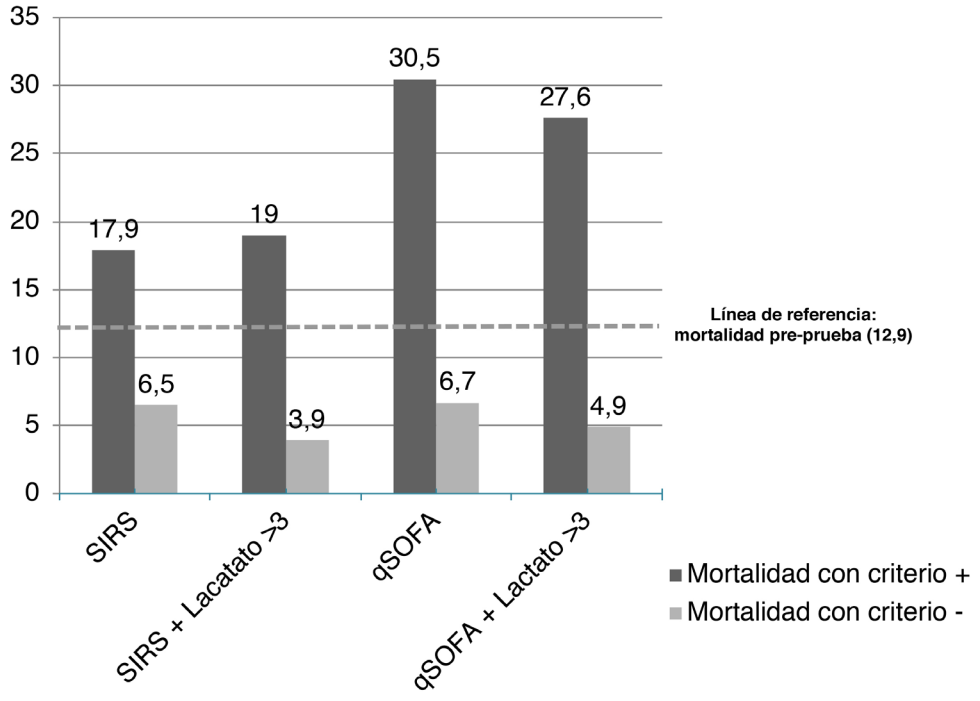


Figura 3 | **Probabilidad de muerte a 30 días basado en la escala de riesgo y el nivel de lactato.**

de establecer con una escala [27]. Es evidente que SIRS puede ayudar a identificar mejor al paciente infectado, al incluir una variable tan específica como la fiebre, pero no debemos olvidar que la fiebre esta ausente en múltiples ocasiones, sobre todo en poblaciones especiales como son los ancianos y los inmunodeprimidos [28]. Las variables incluidas en el SIRS (temperatura, frecuencia respiratoria o PaCO2, recuento de leucocitos y frecuencia cardíaca) podrían ser útiles para aumentar la conciencia de la infección, pero debe tenerse en cuenta su escasa especificidad y su alta prevalencia entre los pacientes hospitalizados [21,28]. Ni los criterios SIRS ni los qSOFA son diagnósticos de infección, pero ofrecen información sobre la reacción inflamatoria del huésped ante un insulto y el grado de perturbación fisiológica, y ambos proporcionan información sobre el pronóstico a corto plazo del paciente [22,25,29].

Nuestros datos muestran también que añadir el índice de Charlson no mejora, en nuestra experiencia, la capacidad pronóstica de las escalas. Esto podría explicarse por la elevada comorbilidad que presenta nuestra población de estudio debido a su avanzada edad. Más de un 40% presentaba un índice de Charlson ≥ 3 lo que puede provocar que el estudio no tenga la suficiente potencia para encontrar estas diferencias.

Nuestro estudio presenta una serie de limitaciones. En primer lugar, existe una gran cantidad de pacientes que han debido ser excluidos por no disponer de todos los datos precisos para el cálculo de las escalas, el índice de Charlson o del lactato. En segundo lugar, excluimos a los pacientes con dependencia funcional grave, ya que la limitación terapéutica puede jugar un papel muy importante en la evolución del paciente lo que puede actuar como un factor de confusión en la estratificación del riesgo. Además, estos pacientes probablemente no sean susceptibles a las terapias intensivas. Por lo tanto, nuestros resultados no deberían aplicarse a esta población específica. En tercer lugar, el momento y el tipo de tratamiento no se evaluaron, y ambos aspectos pueden condicionar el desenlace de la enfermedad. Sin embargo, las pautas de tratamiento locales para los pacientes con este perfil se aplicaron durante el estudio. Finalmente, el criterio de inclusión en el estudio es que existiera un diagnóstico clínico de infección en el SUH, algo que puede o no confirmarse posteriormente durante el ingreso hospitalario. Aunque esto puede representar un sesgo del estudio, pensamos que este enfoque es más similar a la vida real y las decisiones tomadas durante la evaluación inicial de los pacientes durante la atención urgente.

En conclusión, nuestro estudio muestra que en población anciana, sin dependencia grave, atendida por sospecha de infección en urgencias, la adición del lactato a las escalas SIRS y qSOFA mejora su capacidad para identificar pacientes en riesgo de muerte a corto plazo. La estrategia basada en qSOFA más lactato presenta una tendencia estadística a la superioridad y es más sencilla y rápida de calcular al no precisar la determinación de la cifra de leucocitos. Esta estratificación puede ayudar al médico que realiza la atención urgente a seleccionar pacientes que requieren estudios y un manejo más complejos o una terapia más agresiva.

ADENDUM

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CONFLICTOS DE INTERÉS

Los autores declaran que no existen conflictos de interés.

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Original

Information on nosocomial infections in the mainstream media: an opinion document

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ABSTRACT

This paper seeks to explore the reasons for the low impact of nosocomial infection in the mainstream media and the responsibilities of physicians and journalists in terms of this situation. To this end, a small group of 13 experts met for round-table discussions, including physicians with expertise in nosocomial infection, medical lawsuits and ethics, as well as journalists from major mainstream Spanish media outlets. The various participants were asked a series of questions prior to the meeting, which were answered in writing by one of the speakers and discussed during the meeting by the whole group, the aim being to obtain consensual conclusions for each of them. The document was subsequently reviewed, edited and forwarded to all co-authors for their agreement. The opinions expressed are the personal opinions of the participants and not necessarily those of the institutions in which they work or with which they collaborate.

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Key-words: Nosocomial infections, Healthcare associated infections, Healthcare burden, journalists, mass media, journals

Información sobre las infecciones nosocomiales en los principales medios: un documento de opinión

RESUMEN

Este documento busca explorar las razones del bajo impacto de la infección nosocomial en los medios de comunicación tradicionales y las responsabilidades de los médicos y periodistas en esta situación. Con este fin se realizó una mesa redonda con un pequeño grupo de 13 expertos, incluidos médicos con experiencia en infecciones nosocomiales, legislación médica y ética, así como periodistas de los principales medios de comunicación españoles. Antes de la reunión, se les hicieron una serie de preguntas a los participantes, las cuales fueron respondidas por escrito por cada uno y discutidas durante la reunión por todo el grupo, con el objetivo de obtener conclusiones consensuadas para cada una de ellas. El documento fue posteriormente revisado, editado y enviado a todos los coautores para su acuerdo. Las opiniones expresadas por cada participante son propias y no necesariamente de las instituciones en las que trabajan o con las que colaboran.

Palabras clave: Infecciones nosocomiales, infecciones relacionadas con la Atención Sanitaria, carga de la atención médica, periodistas, medios de comunicación, periódicos

INTRODUCTION

Nosocomial infection is one of the greatest challenges to health systems in the developed world. This term refers to infections acquired after admission to a healthcare institution, which were not present or in incubation at the time of admission. They may involve up to 10% of those hospitalised and be responsible for up to 1% of the deaths of all patients admitted, which, when translated into absolute figures, provides unacceptable data, even more so if we bear in mind that a substantial proportion of such infections and deaths are potentially preventable by adopting simple routine measures.

The reasons why this issue does not appear frequently in the media as a reflection of the media's critical work on the government and health institutions was part of the analysis that both the Fundación de Ciencias de la Salud and the Future Day Foundation carried out on the subject at a recent meeting. Questions were raised about whether there is ignorance, lack of interest or other reasons for this and a decision was made to hold a joint meeting between doctors involved in infection control and media professionals, particularly those who report on health issues. All participants were asked a series of questions to review the state of the art of each topic, with particular emphasis on the situation in Spain and opportunities for improvement. The opinions expressed by the speakers are their own and do not necessarily represent those of the institution or institutions to which they belong. This document is not intended to provide recommendations or guidance, but simply to convey opinions.

The meeting was held in Madrid on the 27th June 2018 and this document reflects the main questions, answers and conclusions of the meeting. It has been updated and edited in accordance the literature available up to July 2018.

MATERIAL AND METHODS

Prior to the meeting, questions were sent to the various speakers regarding the situation of nosocomial infections and how they are dealt with by journalists. Each of these questions was formulated by one of the members of the panel and discussed by all the attendees in an attempt for them all to reach a consensus conclusion on the subject.

The questions were essentially divided into two blocks. In the first one, data was presented on the situation of nosocomial infections on a global scale, and specifically in Europe and Spain, in an attempt to find out if the journalists knew all or most of the main data regarding the burden of the problem and how they dealt with such data. In the second block, the position of journalists, their priorities and mechanisms for selecting information and their opinions on how professionals should present information to make it interesting for readers were explored. We also heard opinions regarding the views of readers and the impact that problems related to nosocomial infection have on lawsuits filed against health authorities and covered by insurance companies. Finally, topics relating to ethics pertinent to the issue were addressed.

The document containing the data collected during the conference, which was appropriately edited, was sent back to all the speakers for their corrections and final approval.

We now turn to the different questions that were asked, the data and arguments put forward by the different speakers and a final summary of the responses that was thought to best reflect the overall opinion of the discussion group.

QUESTION 1.

What is nosocomial infection and what is the extent of the problem in terms of figures?

Exposure:

Hospital-acquired infections or nosocomial infections (NIs) are those that are acquired during a hospital stay and as a consequence of healthcare provided. For convenience, we will take them to refer to infections which appear at least 72 hours after admission. NIs will also be considered to be those that, despite being diagnosed within the first 48 hours following admission, meet one of the following criteria: a) involve patients who have been admitted to another hospital within the previous 48 hours; b) relate to deep or space-based surgical infections in patients who have undergone surgery within the previous 30 days or within the previous 90 days in the case of surgery involving implants; c) involve *Clostridium difficile* infections in patients who have been admitted within the previous month; and d) involve infections caused by a device implanted on the first or second day of admission.

It is important to stress that today, healthcare extends beyond acute-care hospitals and there are mixed-care facilities such as dialysis centres, day-care hospitals, home hospitalisation, outpatient chemotherapy, hospitals for the care of chronic diseases, nursing homes, old people's homes, etc. The infections that patients contract when receiving any of these healthcare services or during their stay in a healthcare facility (to receive day care, hospital care, long-term care, etc.) are called healthcare-associated infections (HCAIs).

NIs have a significant impact on healthcare and society in general. They cause significant morbidity and mortality, prolong hospital admissions, increase expenditure and promote antimicrobial resistance. They are considered a quality index of healthcare facilities [1-7].

It is estimated that NIs affect some 4.1 million people in the European Union each year. In Spain, the numerical data can be extracted from the EPINE study, which consists of a prevalence study carried out over the past 25 years in a large proportion of Spanish hospitals [8]. This study has included 313 hospitals and 61,673 patients, of whom 4,772 suffered from NIs. In other words, the prevalence of NIs in our country is 7.74% (7.53-7.95) and this figure has remained practically stable for the past 25 years, fluctuating between 7.7% and 8.5%. Of course, there are differences according to the type of patients analysed, and thus in intensive care the figures for NIs are clearly higher and are close to 20% of patients (17.92% in the 2017 EPINE study and 21.37% in the 2016 study).

When we analyse the results from the Community of Madrid, focusing on hospitals of high complexity, the rate is somewhat lower than the national average, namely 6.45% in 2016. Even so, if we imagine a hospital with 50,000 admissions per year, this nosocomial infection rate means that some 3,500 patients will be affected in a single hospital alone.

Conclusion:

Nosocomial infections are those that are acquired after admission to a healthcare facility which were not in incubation at the time of admission. They affect between 7% and 8% of patients receiving healthcare in Spain.

QUESTION 2.

What are the most prevalent nosocomial infections in Spain?

Exposure:

The main NIs are *Clostridium difficile* infections (CDIs), surgical site infections (SSIs), urinary tract infections (UTIs), respiratory tract infections (RTIs), and catheter-related bloodstream infections (CR-BSIs). The EPINE study shows that the rate of nosocomial UTIs has decreased in recent years, with SSIs becoming the most frequent (prevalence of 2.24%), followed by RTIs (1.74%), UTIs (1.59%) and CR-BSIs (1.18%) [8].

C. difficile (CDI) infection is considered by the Centres for Disease Control (CDC) to be the most common nosocomial infection at present and probably the one associated with the highest economic burden. CDI produces diarrhoea with varying degrees of severity and can be fatal, particularly when caused by hypervirulent strains. Unfortunately, in addition to serious episodes, one of the major problems with CDI is that approximately 20-30% of patients will have recurrent episodes, which often require hospital readmissions and will have a very significant impact on their quality of life. The route of transmission is oral-faecal, person-to-person, or through contaminated fomites or surfaces. We know that the hospital rooms of patients who have had a CDI remain contaminated with spores produced by this microorganism for up to 5 months and proper cleaning is far from easy. In addition to strict cleaning, special emphasis should be placed on the importance of washing hands, as spores are resistant to commonly used alcohol solutions.

In the USA, the CDC reports figures of 250,000 episodes of CDI per year, with 14,000 deaths and a cost of approximately $1 billion. The problem is that the diagnosis of CDI is not simple and not performed uniformly in all hospitals, meaning the rates published do not correctly reflect reality. Only 110 cases of CDI are described in the EPINE study in Spain, representing 2.09% of all NIs and involving 0.17% of the 61,673 patients included. However, we know that the estimated incidence in Spain of CDI is 1-5 cases per 1,000 admissions and 44 episodes per 100,000 inhabitants/year, which would give figures higher than 20,000 episodes per year in Spain alone. In a study carried out in our country we were able to verify that 50% of the episodes are not suspected, so the infra diagnosis in this entity is well demonstrated [9]. Unfortunately, centres with diagnostic excellence are those that logically report the highest incidences, giving the impression they do not have the situation under adequate control.

Surgical site infections (SSIs) affect 4.5% of patients according to the EPINE study and account for 26.5% of all NIs. The rate of NIs clearly varies with the type of surgery, being around 2% in clean surgery (e.g. cardiac surgery), 5.7% in clean-contaminated surgery (e.g. biliary tract surgery), 10.97% in contaminated surgery (e.g. recent traumatic injury) and 6.99% in dirty surgery (e.g. surgery for perforation of the gastrointestinal tract) [8]. More than 25% of patients admitted to a tertiary hospital have a surgical wound, so this NI also represents a significant numerical burden. Surgical wound infections, especially when they are deep or organ/space infections, can lead to readmission, further surgery and even death when accompanied by bacteraemia, or require drainage from spaces such as the mediastinum or abdomen. Also, particularly serious are those associated with infection of prosthetic material, such as heart valves or joint replacements. In any case, they always lead to significant morbidity for the patients involved, as well as a significant increase in health expenditure.

Nosocomial UTIs affect 1.46% of patients admitted and account for 20% of NIs. The incidence is higher in patients with urinary catheterisation (5-25%) and the risk increases with the duration of catheterisation (accumulated 10% per day). Since it is estimated that approximately 15% of all patients admitted to our hospitals have a urinary catheter fitted, the quantitative dimension of the problem is enormous. Of patients with nosocomial UTIs, 2-4% will have secondary bacteraemia, and it is in these patients that mortality is highest.

Catheter-related bloodstream infections (CR-BSIs) occur in 1.17% of patients admitted and account for almost 16% of all NIs. It is estimated that 10% of all hospitalised patients have a central intravenous catheter fitted and 73% a peripheral one. Infection rates increase the longer catheters are in place and are expressed in number of infections per 1,000 catheter-days in order to have comparable figures. Rates range from 0.7-2.3 episodes of CR-BSIs per 1,000 days of catheter use (ICUs 0.4-1.7 and non ICUs 0.9-2.7) [10]. CR-BSIs can be especially severe in patients with prosthetic heart valves or in patients with previous valve injury. Different studies have shown that 31-57% of all nosocomial endocarditis is caused by an IV catheter, many of which were peripheral catheters, not always strictly necessary at the time of infection. Catheters represent a particularly prevalent cause of infectious endocarditis in cancer patients [11]. Mortality from these episodes of nosocomial endocarditis ranges from 25% to 45%. It is important to remember that peripheral venous catheters should not be taken lightly, since, as we have seen, they are much more prevalent than central catheters and also tend to produce *S. aureus* bacteraemias, with the consequent morbidity and mortality caused by this aggressive pathogen.

Finally, regarding RTIs, particularly nosocomial pneumo-

nia, this is the most frequent infection in intensive care units, affecting 10% of intubated patients and resulting in an attributable mortality rate of 15%, an increase in stay of around 8 days and an increase in cost of more than 20,000 euros per case. In the EPINE study, the rate of respiratory infections was 1.43% and accounted for almost 20% of NIs. Pneumonia associated with mechanical ventilation accounted for 23% of nosocomial pneumonia in the study, showing the importance of extending pneumonia prevention campaigns beyond ICUs [10].

Conclusion:

The most frequent nosocomial infections in Spain are, in decreasing order of incidence, *Clostridium difficile* infections, surgical site infections, urinary tract infections, respiratory tract infections and catheter-related bloodstream infections.

QUESTION 3.

What do we know about morbidity and mortality caused by nosocomial infection? What is the economic burden?

Exposure:

NIs are the most common adverse effect of healthcare. Although their effects on patient health and associated costs have been extensively studied, there is a lack of precise knowledge on the global burden due to the absence of comprehensive measurement (monitoring) systems and the heterogeneity of these complications [12, 13].

Direct costs include longer hospital stays, the need for diagnostic tests, treatment by means of antibiotics and other medications, surgery, and ICU admission. Indirect costs include disability, increased avoidable mortality, costs associated with litigation, damage to the image of (reputable) centres, increased resistance of microorganisms to antimicrobials and opportunity costs [14-16]. In addition, NIs have other effects on both the patient and their families and on the general public as a whole, arising from loss of productivity, potential years of life lost, and adjusted years of life lost due to premature death and disability (DALYs) [17]. Multidrug-resistant microorganism (MDRMs) infections represent a significant proportion of nosocomial infections. Recently, they have been given great attention because of their current and future health implications. The most important MDRMs due to their frequency are *Enterobacteriaceae* resistant to third-generation cephalosporins and/or carbapenems, methicillin-resistant *Staphylococcus aureus* (MRSA), and non-fermented Gram-negative bacilli resistant to carbapenems [18]. Another microorganism of epidemiological importance is *C. difficile*, which is associated with both NIs and the use of antibiotics to treat them.

In Europe, according to ECDC data, it is estimated that NIs are responsible for 16 million extra days of hospitalisation, 37,000 attributable deaths and 110,000 contributory deaths at a cost of 7 billion euros, in direct costs alone [19]. The most important social impact (DALYs/100,000 inhabitants) is caused by pneumonia, followed by bacteraemia, urinary tract infections, surgical infections and *C. difficile* infections.

In Spain, the three main MDRMs which cause death are *E. coli* resistant to third-generation cephalosporins, MRSA and *Pseudomonas aeruginosa* resistant to carbapenems. However, in terms of impact on both potential years of life lost and DALYs, the order of importance is carbapenem-resistant *Pseudomonas*, third-generation cephalosporin-resistant *E. coli* and MRSA. According to ECDC calculations, it is estimated that 41,345 cases of MDRM infections occur each year in Spain, causing 1,900 attributable deaths, 40,611 potential years of life lost and another 8,200 years of life with disability [18, 19].

Compared to the top 10 causes of death in Spain, in terms of potential years of life lost, NIs rank 4th only behind ischemic heart disease, lung cancer and Alzheimer's disease. In terms of DALYs, NIs represent the 9th most common cause. According to ECDC estimates, NIs cause 1.5 million extra days of hospitalisation annually in Spain, 3,367 attributable deaths, another 10,011 deaths (as a contributory cause) and direct costs of 637 million euros [18, 19].

Conclusion:

Although we do not know precisely the cost and impact of nosocomial infections on society, both are very significant. In Spain, in terms of the leading causes of death, nosocomial infections are ranked 4th in potential years of life lost, cause more than 13,000 deaths and cost more than 600 million euros per year.

QUESTION 4.

To what extent are nosocomial infections preventable and at what cost?

Exposure:

A high proportion of NIs are preventable and it is our duty and responsibility to consider each of them as a failure of the system, to analyse them as a team, and to determine where we have failed, in order to prevent similar episodes in the future. But preventing NIs is not an easy task because virtually all microorganisms can cause them (viruses, bacteria, fungi and even parasites) and because there are multiple transmission routes (airborne, contact, patient-to-patient, etc.) that require very different measures to be taken.

NI reduction plans are usually coordinated by a hospital's Infection Commission, which establishes targets, looks at the current situation, puts measures into place and then measures their impact. It is essential that the vast majority of their work be focused on action rather than measurement, which is why point prevalence studies are often used.

At practically all facilities, there are training plans in place for patient safety and the prevention of nosocomial infection by staff, and in some of them patients themselves are also being involved, with notable success. Hand hygiene plans, isolation measures, active policies to remove unnecessary catheters and urinary catheters, prevention of surgical wound infection

and ventilator-associated pneumonia and plans to promote the conservative use of antimicrobials are also essential. Of course, swift action is always taken when outbreaks are detected.

To carry out this enormous task, it is necessary to have a multidisciplinary team made up of expert members, such as microbiologists, preventive medicine experts, pharmacists, infectious disease specialists and experts in occupational medicine, as well as representatives from the units/departments with the highest rates of infection, such as intensive care units, surgical departments, paediatrics, internal medicine, nursing and other areas. Management and central departments such as maintenance, engineering, etc. must also be represented. Such a multidisciplinary team is necessary for problems to be dealt with by personnel who have the relevant expertise, this being especially important when faced with issues concerning particularly virulent microorganisms, specific patients, healthcare personnel, or the hospital environment. For this reason, legislation, such as that introduced by the Community of Madrid in 2006, which centralises this task in a single specialty, has been very badly received by scientific societies and by the professionals involved in this task and must therefore be reconsidered.

In addition, we are faced with other added difficulties, such as the lack of visibility of the specialty of clinical microbiology, which, despite its very high level of assistance and scientific recognition internationally, is seriously threatened in our country by voices advocating its integration in core laboratories on economic grounds. It should not be forgotten that microbiologists are the first to diagnose infection and represent the only specialty that has the more precise information on it. They are also experts in infections and resistance and must be essential and well-recognised players in the control of NIs if we are to succeed. On the other hand, Spain continues to be one of the countries in the world without an officially recognised infectious disease specialty. We need to change the laws if we are to move forward.

We have good examples of effective measures that have been endorsed by legislators in other countries. An example of this is the USA, where scientific evidence has shown that the use of a simple checklist with 5 mandatory points followed when inserting a central catheter has practically eliminated catheter-related bactaeremias. Laws were passed to make its implementation mandatory. In addition, this legislation was accompanied by the allocation of funds to each state for its implementation, the aim being to reduce nosocomial infections by 50% over a period of 5 years [20-23].

These measures were followed by a system of incentives and monetary penalties for hospitals based on nosocomial infection rates, which in all cases were considered preventable. It is in this system that the differences in the healthcare model are most significant between Europe and the USA. However, in France, since 2002, hospitals have been responsible for all NIs and patients can seek financial compensation from the ONIAM (Office National d'Indemnisation des Accidents Medicaux, des Affections Iatrogenes et des Infections Nosocomiales), which reports to the Ministry of Health.

This 'carrot and stick' system is a double-edged sword as it punishes the hospitals with the best diagnostic record, these usually being those with the highest degree of excellence as evidenced by recent scientific data. This can lead to an intentional microbiological under-diagnosis, which is not accompanied by a reduction in the actual use of antimicrobials [24].

The change must go deeper and our main goal must be to implement a culture of patient and staff safety. It is not a question of looking for culprits, but of not tolerating deliberate non-compliance with measures proven to be effective (hand hygiene, vaccination of health personnel, etc.). However, this cannot be based on willand sufficient resources must be devoted to carrying out ongoing and sustained campaigns over time, as well as technological innovation being encouraged to help prevent mistakes. Finally, it is essential to stress that the mistaken idea of the situation of zero-risk and zero-infection being immediately feasible must not be conveyed to the public and that the media must work together with health professionals within a framework of meningful, but serious and well-founded campaigns.

Conclusions:

It is possible to significantly reduce nosocomial infections. To this end, we must implement useful and effective campaigns inside and outside ICUs, which are carried out by multidisciplinary teams with the necessary collaboration from microbiology, infectious diseases and preventive medicine departments, among others. A gross estimate from all the experts present is that the current figures for nosocomial infection in Spain could be reduced by at least 50%.

QUESTION 5.

Are nosocomial infections, in the opinion of journalists, an indicator with which to assess and gauge the quality of a health system?

Exposure:

In 1847, Ignaz Semmelweis found that there was a link between the procedures carried out in the necropsy rooms of the University Hospital of Vienna and the high mortality rate in its delivery room, the reason being that the same staff were used, who did not follow proper hygiene measures. He also found that hand hygiene prevented transmission. It is therefore evident that the reduction of nosocomial infection is a parameter of quality of care [25-28].

Since then, numerous studies have shown that nosocomial infections are a preventable cause of serious adverse events in healthcare and a patient safety mechanism [10, 21, 29-31]. Infection prevention has been included as one of the parameters for quality control in different clinical situations [10, 21, 32-38]. In addition to the human factor, there is also the aspect of sustainability of health systems, since NIs extend

hospital stays and increase healthcare costs (greater use of medication, more laboratory studies, etc.). According to data from the NNISS in the USA, in 2012 there were 1.7 million nosocomial infections in the country, which resulted in tens of thousands of human lives and a cost of between 28,000 and 45,000 million dollars.

Although already mentioned, a study published in Infection Control and Hospital Epidemiology in 2011 estimated that the implementation of prevention programmes for NIs can prevent around 65% of bacteraemias and urinary tract infections and 55% of pneumonia and surgical infections, which not only saves thousands of lives, but also millions of dollars [39]. Most significantly, the measures to achieve this are relatively simple and include proper hand hygiene and following a series of steps by means of checklists for various medical procedures.

Therefore, from a journalistic point of view, there is no doubt that nosocomial infections and the indicators used to evaluate their incidence are a factor that can be used to assess the quality of care provided. However, when drawing comparisons between facilities, it is necessary to properly weigh up the differences in the basic situations of the populations each one serves and to look at the progress made by each centre, rather than comparing different ones. Hospitals and departments with a higher number of patients with a high-risk profile are therefore more likely to have higher rates of nosocomial infection than other facilities.

Given the size of the problem, it is surprising that nosocomial infection is not extensively reported on by the media, at least by the mainstream media, particularly in comparison to other factors relating to the quality of our health system. For example, despite the fact that the EPINE study has been ongoing since 1990, allowing us to see the trends in terms of prevalence and foci of nosocomial infection, the reality is that its data has received much less media coverage than that provided by other health reports periodically made public, such as those reporting on waiting lists for surgery [8].

Conclusion:

From a journalistic point of view, nosocomial infection figures can be used as an indicator to assess the quality of care in a given sector. However, traditionally they have not received much coverage in the mainstream media.

QUESTION 6.

How does the information on nosocomial infection that reaches the media in the USA, Europe and Spain compare with objective parameters?

Exposure:

One of the advantages of NIs is that their recording and monitoring is both routine and uniform in many countries. The first epidemiological monitoring programme for nosocomial infections was launched in the United States in 1970 and most developed countries now have their own systems, the majority based on the US model. These seek both to monitor and identify the microorganisms responsible for NIs and to compare different hospitals, with the aim of improving the control and prevention of these infections. In Europe, the European Centre for Disease Control (ECDC), based in Stockholm, has been conducting a comprehensive study on the prevalence of NIs and antimicrobial resistance in acute-care hospitals in all Member States since 2011, under the auspices of the European Commission [19].

In the case of Spain, there are several regional models, such as the Catalan and Andalusian models, but the main reference for the monitoring of healthcare related infection is the Study on the Prevalence of Nosocomial Infection in Spain, Epine, launched in 1990 by the Spanish Society of Preventive Medicine, Public Health and Hygiene [8]. There is also a specific study for the monitoring of nosocomial infections in ICUs, Envin-Helics, developed in 1994 by the Spanish Society of Intensive, Critical and Coronary Medicine [40]. There is therefore no shortage of available data.

Having said this, the specific question regarding how the information on this subject is published by the media can only be answered by stating that it is clearly limited. The subject should enjoy more and better coverage in the non-specialised media, this being partly the responsibility of the media and partly that of the institutions, which should improve how and what they communicate. To these, we must add social demand. Since the U.S. Institute of Medicine published the book 'To Err is Human' in 2000, which revealed that adverse medical events were the third leading cause of death in the United States, awareness has increased among the general public, and one of them, nosocomial infections, has emerged as a real public health problem [41]. Sometimes, causing alarm amongst the general public is profitable.

It is clear that there is a growing interplay between the mass media and scientific journals, and that almost every week, the media gather and publish some of the most relevant scientific data that has appeared in leading scientific journals [42]. The relations between the two forms of communication are not always easy and must take into account such things as the need to be newsworthy, the lack of time, the need for prudence and the enormous impact that the mainstream media can have. On the other hand, although some clinical trials have been able to demonstrate the influence of media campaigns in reducing problems such as those surrounding breastfeeding [43], the stigmatisation surrounding HIV amongst young African Americans [44], increasing the use of mosquito nets in Cameroon [45], reducing smoking [46] [47] and encouraging physical exercise [48], in many cases meta-analyses are not conclusive in revealing such an impact. An example of this is the effectiveness of smoking cessation campaigns, where it is not possible to prove a lasting impact as a result of intervention by the media [49], campaigns to discourage risky behaviour in order to prevent the spread of communicable diseases [50] or drug use [51-53]. In places where the consumption of mass media by the general public is scarce, due to their low socio-economic level, the impact will most likely be lower [54].

On the other hand, often the media simply report the facts but only convey a small proportion of the health measures people need to take to protect themselves in outbreaks of communicable diseases [55].

There are general differences in terms of the focus of content published by the media in the United States of America and Europe. In Hallin's opinion, and in terms of political orientation, the European media has a more ideologically oriented position, while the Americans seek greater objectivity in their news [56]. We have not found any data that objectively and quantitatively compares the incidence of nosocomial infection news between the United States and Europe. Daniela Paolotti reviews the major developments in the world of infection between 2008 and 2013 and compares the information, needs of professionals and the public. There was great interest in various outbreaks, particularly *C. difficile* and MRSA infections, although they were more static for the general public than for professionals. The author emphasises the need for collaboration between health authorities, professionals and the media in ensuring the quality of information and its evidence-based rationale [57].

Conclusion:

We are not aware of any studies that specifically compare the quantity and quality of information on nosocomial infections in the mainstream media in the United States, Europe and Spain. In general, information on the subject is well received and followed with interest by readers.

QUESTION 7.

Is the low amount of information in the mainstream media due to ignorance or the fact that it is simply not a priority?

Exposure:

It has been stated that between 7 and 8% of all those hospitalised in Spain acquire an infection that they did not have at the time of admission. The WHO estimates that these figures are still higher and closer to 9% for all those hospitalised in Europe. In addition, a significant proportion of these infections are caused by multidrug-resistant microorganisms (MDRs). We believe that this data, although without much more detail, is known by most media outlets. Having said that, it is not easy to establish the reasons why such information has little or no presence in terms of news published on a daily basis, especially on television. We rely on the news for providing us with new facts and information on topics of general interest. If the outlet in question is specialised, space is made for all types of health-related information, this being part of their philosophy. On the contrary, in the mainstream media, news deals with a wide range of sections: politics, society (with its detachment from events, social facts, scientists, health, education, etc.), culture, sports, economy, etc., and airtime or printed/online space is very limited.

Competition to 'sell' the news of the day, which fills the printed and online pages of newspapers and takes up airtime on TV, is tough and the winner is usually the outlet that provides the stories (whether positive or negative) which are most interesting and most capture the public's attention.

According to the VIII Science Perception Survey 2017 [50], carried out by the Spanish Foundation for Science and Technology (FECYT), public awareness of science has improved substantially. More than half of the general public now answers this question correctly: do antibiotics cure infections caused by bacteria or viruses? It sounds like an anecdote, but it is not. Scientific literacy has increased. A decade ago, less than half of those asked the question on antibiotics knew the answer. Six out of every ten Spaniards who were asked by the FECYT said they are interested in health and science issues, the medium through which the majority of these receive information being television.

Journalists know we cannot give up on health information, but nosocomial infection is often simply not considered to be news. In 2009, a campaign was launched in New York to link sugar-sweetened drinks to obesity. The initiative, published as a scientific study in Jama Internal Medicine, had the effect of significantly reducing the consumption of sugar-sweetened drinks among adults and teenagers [51]. The media can and should be allies of professionals. Many patients turn to the media to complete or check the information they receive from professionals. Nevertheless, the responsibility for promoting good health, health-related campaigns, prevention and health education lies with the public authorities.

Sources are essential when it comes to provide the media with adequate information. These sources should be such that they may be considered to be news, examples being new research, partial or definitive results from a study, new evidence, a warning, a complaint, etc. Of course, those responsible for such news must be willing to collaborate with the media and criticism must be defended and communicated.

For the first time this year, Health Infonometer 2018 was carried out by 'Infoperiodistas y Acceso', with the support of the Federation of Spanish Press Associations (FAPE) and the National Association of Health Informers (ANIS), including more than a hundred journalists from 2,361 media outlets, namely national and local press, radio, television, digital outlets and blogs. The goal was to assess the relationship between the sources of information and health information professionals.

The health sector accounts for 2.8 per cent of all mainstream media coverage. Social networks such as Twitter, or the information on the Internet from specific health websites and Wikipedia itself, account for 44% of information searches. Among the topics of interest are research studies and developments. 70% of the sector's information is published by digital media outlets, despite the fact that they only represent 15% of the media outlets consulted. As a result, 86% of the target audience will be reached.

Conclusions:

Overall, 2.8% of material published comes from the

health sector. The scarcity of information on nosocomial infection is not so much a problem of ignorance as a problem of competition with other 'more newsworthy' topics.

The specialisation of journalists may be the solution to this, something which would allow them to differentiate important information from unimportant information and thus avoid alarm and sensationalism.

QUESTION 8.

What proportion of medical lawsuits are related to infections?

Exposure:

Medical mistakes are frequent and affect 6.2% of patients admitted to Spanish hospitals from our emergency department. According to this study, errors are most common among patients who are admitted with fever and have infectious diseases, where diagnostic or treatment errors are made in 12.8% of all cases [58].

The OCDE has drawn up a list of 21 indicators that it recommends for monitoring in hospitals as a guarantee of patient safety. These are classified into six sections, the first of which is nosocomial infections. In particular, it recommends preventing pneumonia associated with mechanical ventilation, surgical site infection, other infections attributable to medical intervention and pressure ulcers.

Infection is a common cause of medical lawsuits, but hospitals are often only held legally liable if they did not have the usual rules of infection prevention in place and properly implemented, or indirectly if the staff involved did not properly follow such rules, resulting in complications for patients [59].

The British National Health System paid a total of £911 million (0.88% of the total budget) in compensation for malpractice in 2010/2011, figures that have not fallen significantly in recent years. By way of example, between 1996 and 2010 there were 971 lawsuits filed for infections caused by MRSA and *C. difficile*, costing the British taxpayer £35.2 million. Lawsuits for MRSA dropped, but those due to CDI [60] remained.

In Spain, of the 971 medical lawsuits filed in the autonomous communities of Aragon, Cantabria, Extremadura and La Rioja, 2.98% were due to nosocomial infections. At the begining, the emergence of the concept of nosocomial infection in demands was almost synonymous with estimation. Hospital contagion was taken to be the acquisition or spread of a disease due to insufficient sterilisation or lack of antisepsis, involuntarily putting pathogenic microorganisms into contact with people at hospital facilities or health centres. In these lawsuits, the burden of proof is reversed, the respondent being responsible for proving the existence of and compliance with the appropriate rules. Centres must comply with and have their own protocols for the prevention and control of diseases, including the appropriate infrastructure to fight and, above all, prevent infections. However, is it not enough to merely have these protocols in place, centres must also put them into practice and comply with them. It is not having such protocols or not properly implementing them that distinguishes negligence from what may be considered a complication.

In addition to the problems we have mentioned, the lack of specialisation of the judiciary in medical matters complicates decisions. In recent years and given the rise in such lawsuits, rulings have become much more balanced and fairer. We believe that practice and case law tend to suggest that the majority of infections contracted by patients upon admission are caused by basic illnesses or by external agents, which are beyond the responsibility of health centres. More than 85% of contentious-administrative or civil lawsuits are dismissed and more than 99% of criminal lawsuits do not result in convictions.

One of the most common problems for judges is correctly interpreting the concept of 'early' within the context of decisions that depend on 'early' diagnosis or treatment.

Conclusion:

Although nosocomial infection is one of the main causes of preventable problems after admission to hospital, the number of lawsuits relating to nosocomial infections in Spain is low. Overall, 85% of contentious-administrative or civil lawsuits are dismissed and more than 99% of criminal lawsuits do not end in conviction.

Providing judges with specialised training in this area would result in fairer and more balanced outcomes.

QUESTION 9.

What is the role of journalism in presenting to politicians, issues of nosocomial infection, as a state responsibility? The English example.

Exposure:

In the late 1990s, a particular interest in nosocomial infections and their reduction emerged in England with the drafting of the first documents to establish a control plan [61]. The figures of 300,000 hospital-acquired infections per year at a cost of over £1 billion, sometimes resulting in death, were passed on to the public. The data was particularly paradigmatic for two diseases, bacteraemic infections caused by MRSA, which were attributed to some 9,000 deaths per year, and the growing epidemic of *C. difficile* infections, initially with hypertoxigenic strains and involving high morbidity rates and costs. Perhaps an example of this public awareness is the so-called 'Stafford Hospital scandal', which occurred around 2008 when an investigation revealed poor hygiene and infection control conditions going back to 2005, this being related to an increase in deaths. The scandal was so serious that David Cameron had to apologize to the nation.

The coverage of these and other facts by the mainstream media in the UK raised public awareness of the problem, ranging from the general public through to the political class and parliament. The legislation that was drafted to control both

diseases, while at the same time laying down rules to improve hospital hygiene in general and ensuring data is better recorded, has borne fruit with very marked reductions in terms of both problems, reductions that do not have comparisons of the same size in other European countries, where the problem has not reached the political class and has therefore not been translated into legislation [62].

In Spain, the media is provided with information on new developments in this field from groups and societies such as the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Virology, and the Epine study, which is carried out by the Spanish Society of Preventive Medicine and Public Health. In addition, attention is also often paid to what other societies say and to certain information from trade unions involved in the health sector. In Spain, a paradigmatic case that changed the attitude of prevention in many hospitals and represented a real milestone, particularly in terms of prevention as measured by ambient air pollution in the operating room, was the case of an outbreak of invasive aspergillosis associated with major cardiac surgery in a large referral hospital.

The view of the specialised media on nosocomial infections is radically different from that of mainstream media. In order to understand the informative approach of the latter, we must first summarise the changes seen in media outlets throughout the economic crisis, changes which meant a decrease in real health specialists and turned journalists into jacks of all trades, i.e. masters of none. This is a widespread phenomenon that has resulted in a worsening of the quality of information. In general, the approach taken by the mainstream media in terms of nosocomial infections is one of scandal, without any clear intention of actually creating public opinion or giving the legislature a mandate on which to act.

Conclusions:

The role of the media as opinion formers and as vehicles for putting the necessary pressure on the legislative power in terms of issues of major interest for the public, such as hospital infections, is considered essential. The English example is perhaps the most notable one in the last two decades in this regard.

QUESTION 10.

What potential interest could a training programme on nosocomial infections aimed at journalists attract and what would be its conditioning factors?

Exposure:

Nosocomial infection is a relatively recurrent news item in the media with a significantly greater presence in the specialised health media than in the mainstream media. The news which is most often reported (in more than 90% of cases) involves a negative event (news, crisis, study, report, etc.) which focuses on generally worrying, if not alarming, data.

The reliability of the sources of information involved, especially nowadays with the Internet and social media playing a role they should not be playing, but which the general public allows them to play, are in most cases unreliable.

Various studies (American Publishers Federation, WHO, EFPIA) conclude that eight out of ten sources of health information do not offer the reliability that the importance of issues in this field require (or should require).

On a daily basis, journalists receive a whole host of information in different ways and formats and often do not have time to discern in depth what is interesting and what is not. The volume of work and the consequent lack of time also have a decisive impact on the quality of information.

Within this context, specialised journalists and particularly those specialised in health matters are becoming increasingly scarce. Media outlets, both mainstream and specialised ones, have fewer and fewer experienced staff, which is very clearly reflected in the information they publish. The field of health information is paradigmatic in this regard.

There is an unquestionable cause-effect relationship between training and information. The training of those who provide information is a key element in ensuring better quality information.

Faced with such a situation, we believe that specific training is not only appropriate, but essential and should be offered in this and many other areas.

Conclusion:

A training programme for journalists on nosocomial infection and its determinants would not only be interesting, but necessary.

QUESTION 11.

What does the general public expect in terms of health information on infections provided by newspapers and other forms of media?

Exposure:

In order to be able to analyse the preferences of readers of health information and give an informed opinion on the possible interest of readers in nosocomial infection, it is necessary to carry out a review of the issues that have played a leading role in health information in Spain in recent years, in order to identify patterns and compare them with nosocomial infection.

Furthermore, it is important to define the concept of 'health information reader', due to the notable differences between the approach and content of generalist newspapers and their health supplements and those specialised in health information.

The information the media are interested in, investigate and publish is directly related to the interests of those consuming such information. This is why the concerns and interests of the general public are often a determining factor in prioritising certain issues over others [63]. In this sense, health

information has experienced a notable growth in recent years, coinciding with the increase in concerns for health identified in the barometer carried out by the Centre for Sociological Research (Centro de Investigaciones Sociológicas - CIS). By way of example, if we compare the barometer carried out by the CIS in April 2004 with the same period in 2018, we see that the percentage of respondents who consider health as their main concern has almost doubled, from 5.3% to 10.3%, or in other words, from being the tenth most pressing problem for the general public to the fifth [64] [65].

It is interesting to see how often a topic takes priority in such an intense way, either because of the seriousness of the information in question or because of the period of time it covers, that it manages to monopolise the conversation. This is especially true in the field of health, so much so that different studies have been able to relate each year to a health issue that the press focused on more than any other. Although we will not include them all, here are some examples: 2002 - AIDS, boosted by the World Congress held in Barcelona, 2004 - Avian Influenza, 2005 - Smoking Law, 2009 - Influenza A, 2011 and 2012 - funding and sustainability of the NHS, 2014 - Ebola and 2015 - Hepatitis C treatment.

Once the topics of greatest interest have been identified, we find that the vast majority of those that have generated the greatest number of articles and reader demand in the last 18 years have common patterns. Information on infectious diseases with a high impact on the general public stands out above any other. In addition, in the last five years, this news has change and even combined with the discussion on the sustainability of the system and health management (the case of hepatitis C is particularly significant) [66-68].

It can therefore be concluded that nosocomial infection is an issue that may indeed be of interest to readers of health information, insofar as it contains many aspects common to the major health issues that have played a leading role in health information in recent years. Today's reader, much more informed and with vast resources at their disposal, expects more than just mortality figures, prevalence data or various statistics. The nature of nosocomial infection raises questions that any of us would ask ourselves as a patient, and allows us to approach its coverage from different perspectives.

In addition to defining the concept, listing the most common infections and the main routes of infection, it is interesting to address issues such as the safety measures the Autonomous Communities and hospitals are currently implementing, and what costs they entail for the system, as well as the measures that both health professionals and patients can implement on a day-to-day basis in terms of prevention.

Another topic of interest is the extent of the link between reducing the risk of infection and early discharge, and analysing the implications of such measures for patients.

It is also important to inform readers about the potential legal responsibility of hospitals, in addition to the treatment that health insurance companies provide for this type of infection. It is also important to clarify that there are treatments available for this type of infection, and how this relates to drug resistance, given that this is a current issue in which the European Union is involved, and which it is closely related to the treatment of nosocomial infections.

The approach that can be taken to nosocomial infection is broad and involves different approaches. How information if prioritised is decided by the readers themselves. As far as health information is concerned, there is no single yardstick, although there are succinct differences between those who read mainstream newspapers and those who regularly read specialised newspapers.

Conclusion:

Nosocomial infection is of potential interest for readers of health information. The nature of nosocomial infection makes it possible to provide readers, whether of mainstream or specialised media, with interesting information on aspects ranging from legal to clinical issues, and also to relate it to other current news such as drug resistance or early discharge.

QUESTION 12.

What aspects would an expert in Ethics consider about the missions that health professionals and journalists must fulfill to help reduce Nosocomial Infection?

Exposure:

The ethics of journalism and the media is a widely developed discipline of exceptional importance, given the great influence of the media on people's behaviour. It is not for nothing that they are called "the fourth estate".

The first problem that arises is that of what its functions are. The first, which is universally accepted, is that of "informing". Reporting means reporting what happens. The journalist would be, in this case, a mere transmitter, who makes public what in principle is not. The publicity of life's events undoubtedly has an important ethical component, since it allows corruption to be uncovered that would otherwise go unnoticed. But it also has another highly negative component, especially when things or behaviors come to light that belong to people's private lives, and therefore threaten their intimacy and privacy.

It follows from the above that publicising events cannot be considered good in itself, nor can one take refuge in the argument that the function of journalism is simply to "report", as if it were possible to put oneself in a position of pure "neutrality". No matter how often it is stated, this supposed neutrality does not exist, because it cannot exist. In fact, the journalist does not report everything he hears or sees. He selects what he thinks is "newsworthy" and can give him a "headline", the more flashy or even scandalous the better. Thus, it completely breaks any purported neutrality slogan.

The journalist is an informer, but an informer who has the enormous capacity and responsibility to create "public opinion". I do not think that it is possible to distinguish clearly,

however much one may claim, between information and opinion. The former is not neutral or value-free, unlike the latter, which is value-laden. It's all value-laden, whether we want it or not. And professional responsibility always consists of the same thing, in the way we handle the specific values of each profession. This happens to the judge, the doctor, the politician and, of course, to the journalist. There is no doubt that values related to health, life and well-being are of great concern to society, which is also looking for information in the media. So there is a demand. The problem is in the supply. First of all, because much of the information found, for example, on networks, is in most cases unreliable. On the other hand, the media, which are commercial companies, are more interested in the "news" that may be profitable for them than in the other that may be more valuable or more useful for the citizen.

Here is an example. Medical errors will always be more "newsworthy" than adverse event prevention programmes, even though the health and social importance of the latter is far greater than that of the former. This shows that the aims of journalism and health care are not only not the same, but often not the same, and may even be antagonistic.

Is it possible to reconcile the two, to make them converge in a middle point that can be satisfactory for both parties? Of course it is. That is the role of meetings such as the one that has led to this opinion document. Only mutual knowledge, the exchange of opinions and points of view, health education for journalism professionals and journalism education for health professionals can increase awareness on both sides and create a "culture" of this type of problem. Which is probably what we're missing.

Conclusion:

Information is never neutral. It is always "loaded with values". Hence, their quality will depend on how they are handled. Only collaboration between journalists and health professionals can avoid biases in assessment and thus improve information on health issues, and more specifically on hospital infections. A field in which truthful and careful information is extremely important, because only it can put an end to the myth, so widespread today, that in the age of antibiotic therapy it is no longer necessary to take the universal precautions of prevention and asepsis that many people today consider to be typical of times happily overcome.

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CONFLICTS OF INTEREST

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Broncoespasmo y *flushing* tras la vacunación con neumococo polisacárida de 23 serotipos en pacientes crónicos

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RESUMEN

Objetivos. Describir las características clínico-epidemiológicas en una serie de casos de sospecha de reacciones adversas sistémicas registradas tras la administración de la vacuna frente a neumococo polisacárida de 23 serotipos (PNEUMOVAX23®). Calcular la incidencia acumulada de dicha reacción y conocer si se han descrito casos similares y/o compatibles en la literatura científica o en Farmacovigilancia.

Métodos. Estudio observacional retrospectivo realizado entre 01/12/2015 y 30/09/2017 en la Unidad de Vacunas de un hospital autonómico de referencia. Se calculó la incidencia acumulada de la reacción adversa sistémica para esa vacuna. Se consultó la base de datos del Sistema Español de Farmacovigilancia (FEDRA).

Resultados. Se registraron 9 sospechas de reacciones adversas sistémicas inmediatas (*flushing* + broncoespasmo + SatO_2<95%). La incidencia acumulada fue 1,036%. El desenlace fué recuperado/resuelto para todos. No se encontraron casos similares y/o compatibles.

Conclusiones. Las reacciones descritas no constan en la ficha técnica de PNEUMOVAX23®. Epidemiológicamente no se puede establecer ninguna relación causal entre la aparición de los síntomas y las variables estudiadas. Esta información podría ser la base de investigaciones más amplias que supusieran la posible modificación de la ficha técnica.

Palabras clave: vacuna, *Streptococcus pneumoniae*, farmacovigilancia, vacuna neumococo polisacárida de 23 serotipos.

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Bronchospasm and flushing after vaccination with 23 serotype pneumococcal polysaccharide in chronic patients.

ABSTRACT

Objectives. To describe the clinical-epidemiological characteristics of a series of suspected systemic adverse reactions registered with the 23 serotype pneumococcal polysaccharide vaccine (PNEUMOVAX23®). Calculate the cumulative incidence of the reaction and know if similar and/or compatible cases have been described in the scientific literature or in pharmacovigilance.

Methods. Observational and retrospective study realized between 01/12/2015 and 30/09/2017 in the Vaccines Unit of an autonomic reference hospital. We calculated the cumulative incidence of the adverse reaction for that vaccine. The common pharmacovigilance database (FEDRA) was consulted.

Results. Nine systemic adverse reactions were recorded (flushing + bronchospasm + SatO2<95%). The cumulative incidence was 1.036%. The outcome was recovered/resolved for everyone. No similar and/or compatible cases were found.

Conclusions. The reactions described do not appear in the PNEUMOVAX23® data sheet. Epidemiologically, no causal relationship can be established between the symptoms and the variables studied. This study could be the basis for more detailed research that could modify the vaccine data sheet.

Keywords: vaccine, *Streptococcus pneumoniae*, pharmacovigilance, 23 serotype pneumococcal polysaccharide vaccine.

INTRODUCCIÓN

Las infecciones por *Streptococcus pneumoniae* suponen, a día de hoy, una elevada morbilidad a nivel poblacional [1]. La inmadurez del sistema inmune durante la infancia, las enfermedades hematológicas, la inmunodeficiencia congénita o

adquirida, la *diabetes mellitus*, la insuficiencia renal crónica y la asplenia funcional o anatómica representan, entre otros, los factores de riesgo más importantes para desarrollar enfermedad neumocócica invasora [2].

Es sabido que la vacunación en general constituye una medida preventiva y de Salud Pública que mejora y aumenta la calidad y esperanza de vida de la población [3]. Concretamente, la administración de las vacunas antineumocócicas se ha extendido tanto en población adulta por encima de cierta edad como en grupos de riesgo tanto por indicación del Ministerio de Sanidad, Consumo y Bienestar Social como previamente por parte de algunas Comunidades Autónomas (CCAA) en España [4-6].

Los numerosos ensayos clínicos realizados en vacunas previa comercialización, así como los rigurosos controles de calidad durante los procesos de fabricación, hacen que estas se hayan convertido en fármacos muy seguros [7, 8]. En la mayoría de las ocasiones, las reacciones adversas que son infrecuentes o las que se dan en subpoblaciones específicas de pacientes, no son identificadas en las fases previas a la comercialización por lo que los estudios post-comercialización son imprescindibles para la detección de reacciones farmacológicas adversas [9].

La notificación a los Sistemas de Farmacovigilancia de cualquier sospecha o confirmación de reacción adversa es clave con cualquier medicamento, pero más aún en el caso de las vacunas ya que se aborda de manera sistemática la población infantil que, en general, representan una población sana [10].

Por tanto, el objetivo principal de la presente investigación es describir las características clínicas y epidemiológicas de una serie de casos de sospecha de reacciones adversas sistémicas relacionadas con la vacuna de neumococo polisacárida de 23 serotipos (PNEUMOVAX23®) en pacientes inmunodeprimidos y en situaciones especiales. Los objetivos secundarios son calcular la incidencia acumulada de dicha reacción adversa para esta vacuna en el período de tiempo de estudio y conocer si se han descrito casos similares y/o compatibles con los aquí expuestos.

MÉTODOS

Estudio descriptivo retrospectivo de la sospecha de reacciones adversas sistémicas relacionadas con la vacuna PNEUMOVAX23® identificada entre el 1 de diciembre de 2015 (mes del primer caso) y el 30 de septiembre de 2017 (mes del último caso) en la Unidad de Vacunas de un hospital autonómico de referencia.

La vacunación se llevó a cabo siguiendo las indicaciones del Calendario de Vacunación del Adulto y Vacunación en Situaciones Especiales oficial de la CCAA.

Se tuvieron en cuenta las siguientes variables: edad, sexo, diagnóstico principal, tratamiento farmacológico activo, vacunación previa con neumococo conjugada de 13 serotipos, tiempo transcurrido entre la administración de neumococo conjugada de 13 serotipos y PNEUMOVAX23®, número de dosis previas de PNEUMOVAX23®, coadministración con otras vacunas, enfermera que administra la vacuna y lote de la vacuna.

Se calculó la incidencia acumulada de dicha reacción adversa para esa vacuna en el período comprendido entre la aparición de la primera y la última reacción adversa.

Para la búsqueda de notificaciones de reacciones adversas se consultó en la base de datos de FEDRA (Farmacovigilancia Española, Datos de Reacciones Adversas) y las notificaciones realizadas al Centro de Farmacovigilancia de la CCAA por parte de la Unidad de Vacunas en el periodo de tiempo anteriormente mencionado.

RESULTADOS

Se identificaron un total de 9 sospechas de reacciones adversas sistémicas relacionadas con PNEUMOVAX23® en la Unidad de Vacunas del hospital de estudio. De ellas, cinco tuvieron lugar en mujeres y las edades estuvieron comprendidas entre los 12 y los 73 años. Todos ellos eran pacientes en situaciones especiales aunque, desde el punto de vista farmacológico solamente uno tenía prescrito tratamiento inmunomodulador en el momento de administración de la vacuna. Todos los casos habían recibido previamente la vacuna conjugada frente a neumococo de 13 serotipos y la reacción se produjo siendo la primera vez que recibían PNEUMOVAX23®. En 7 de los 9 casos esta vacuna fue coadministrada con otras, siempre en el brazo opuesto. El lote de las vacunas coincidió en cuatro pacientes. La tabla 1 recoge las principales variables de estudio.

Desde el punto de vista clínico, la figura 1 describe la secuencia de los síntomas. Destaca el inicio inmediato tras la vacunación (primeros 60 segundos), el rubor facial y tronco (*flushing*) y la clínica respiratoria (broncoespamo) con descenso rápido de la saturación de oxígeno en sangre. En todos los casos se administró oxigenoterapia mediante mascarilla con reservorio a un flujo de 15 lpm observando mejoría a los 2 minutos. El desenlace fue recuperado/resuelto para todos ellos.

Desde la fecha de aparición del primer y el último caso se administraron un total de 868 dosis. Por tanto, la incidencia acumulada de esta reacción adversa fue 1,036%.

Todos los casos fueron notificados al Sistema Español de Farmacovigilancia. No se encontraron casos similares y/o compatibles mediante la búsqueda en FEDRA. El Departamento de Farmacovigilancia del laboratorio responsable de la vacuna fue informado tras la aparición del segundo caso. No obstante, tras un análisis general de la situación no se consideró por su parte poner en marcha ningún tipo de medida específica adicional a la notificación.

DISCUSIÓN

En el presente trabajo se ha descrito una serie de casos relacionados con la sospecha de una reacción adversa sistémica no descrita en la ficha técnica de PNEUMOVAX23®. A pesar de

Tabla 1 Características clínicas de los pacientes que presentaron una reacción adversa sistémica tras la vacuna de neumococo polisacárida de 23 serotipos (PNEUMOVAX23®)

Caso	Edad sexo	Diagnóstico principal	Tratamiento inmunosupresor / inmunomodulador activo	Fecha VNC13	Fecha VNP23	Tiempo entre VNC13 y VNP233	1ª o 2ª dosis de VNP23	Coadministración con otras vacunas	Lote vacuna	Enfermera que administra la vacuna
1	12 H	TRASPLANTE DE PROGENITORES HEMATOPOYÉTICOS	NO	24/06/2015 29/07/2015 27/08/2015	21/12/2015	114 DÍAS	1ª DOSIS	NO	PNEUMOVAX23® AK011922	Enfermera 1
2	21 M	FIBROSIS QUÍSTICA	NO	26/11/2015	16/03/2016	110 DÍAS	1ª DOSIS	NO	PNEUMOVAX23® L005688	Enfermera 2
3	59 H	TRASPLANTE RENAL	NO	26/02/2016	06/05/2016	71 DÍAS	1ª DOSIS	Hepatitis B (FENDRIX®)	PNEUMOVAX23® L032310	Enfermera 3
4	33 H	ENFERMEDAD DE CROHN	SÍ (azatioprina)	19/01/2016	08/06/2016	140 DÍAS	1ª DOSIS	Hepatitis B (FENDRIX®)	PNEUMOVAX23® L032310	Enfermera 3
5	58 H	PSORIASIS	NO	19/04/2016	22/06/2016	63 DÍAS	1ª DOSIS	Hepatitis B (FENDRIX®)	PNEUMOVAX23® L032310	Enfermera 3
6	54 M	TRASPLANTE RENAL	NO	28/04/2016	26/06/2016	58 DÍAS	1ª DOSIS	Difteria-tétanos (DIFTAVAX®) Meningococo C (NEISVAC-C®)	PNEUMOVAX23® L032310	Enfermera 3
7	38 M	PSORIASIS	NO	12/04/2016	26/10/2016	196 DÍAS	1ª DOSIS	Hepatitis B (FENDRIX®)	PNEUMOVAX23® L045657	Enfermera 3
8	23 M	FIBROSIS QUÍSTICA	NO	23/11/2016	13/02/2017	80 DIAS	1ª DOSIS	Hepatitis B (ENGERIXB20®)	PNEUMOVAX23® L045657	Enfermera 4
9	73 M	ESCLEROSIS MÚLTIPLE	NO	30/05/2017	05/09/2017	96 DÍAS	1ª DOSIS	Hepatitis B (FENDRIX®)	PNEUMOVAX23® N010182	Enfermera 4

H: hombre; M: mujer; VNC13: vacuna neumocócica conjugada 13 serotipos; VNP23: vacuna de neumococo polisacárida de 23 serotipos

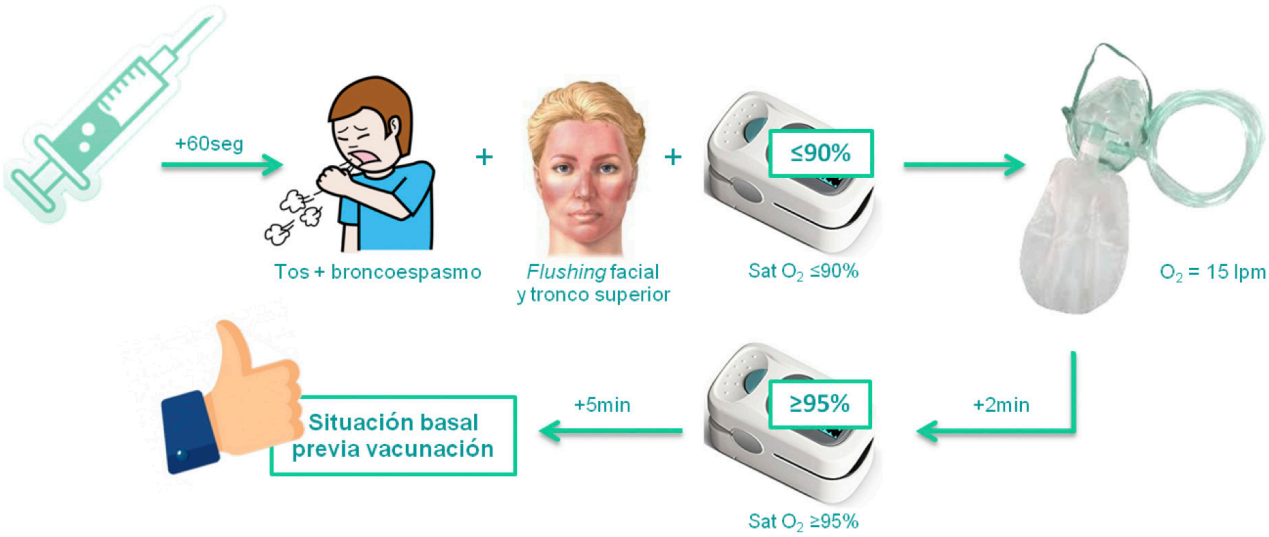

Figura 1 | **Secuencia de la sintomatología clínica observada tras la vacunación con neumococo polisacárida de 23 serotipos (PNEUMOVAX23®).**

que esta vacuna ha sido estudiada en pacientes con enfermedades autoinmunes, trasplantados de órgano sólido y progenitores hematopoyéticos, VIH y artritis idiopática juvenil, entre otros [11], no se han encontrado publicaciones científicas ni notificaciones a Farmacovigilancia similares.

En general, la incidencia acumulada de esta reacción adversa fue baja en comparación con otros fármacos (2,25% en el caso del acenocumarol [12] y hasta 4% en la carbamacepina [13], por ejemplo), sin embargo, no es despreciable cuando se compara con las reacciones descritas con otras vacunas [14].

Desde el punto de vista epidemiológico y con las variables recogidas para el estudio no se puede establecer ningún tipo de relación causal que explique la aparición de los síntomas, sin embargo, llama la atención que lo descrito parece haber tenido lugar solamente en pacientes en situaciones especiales y esto refuerza la necesidad de mejora de la Farmacovigilancia en este grupo. Además, es sabido que los adyuvantes utilizados para mejorar la respuesta inmunológica a las vacunas están relacionados con una mayor frecuencia de reacciones de tipo local [15], sin embargo, esta hipótesis se descarta ya que PNEUMOVAX23® no contiene ningún tipo de adyuvante y las reacciones adversas fueron sistémicas.

Pese a que este estudio describe una serie limitada de casos los autores consideran que su principal valor redunda en el reconocimiento, abordaje y notificación de las reacciones adversas sistémicas asociadas a PNEUMOVAX23® que previamente no habían sido descritas en la literatura científica ni notificadas a Farmacovigilancia y que podrían ser la base de un estudio de mayor magnitud y la posible modificación de la ficha técnica.

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CONFLICTOS DE INTERESES

Los autores declaran que no tienen conflictos de intereses

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Brief report

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Postantifungal effect of anidulafungin against *Candida albicans*, *Candida dubliniensis*, *Candida africana*, *Candida parapsilosis*, *Candida metapsilosis* and *Candida orthopsilosis*

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ABSTRACT

Objectives. *Candida albicans* remains the most common aetiology of invasive candidiasis, leading to high morbidity and mortality. Nevertheless, the incidence of candidiasis due to non-*C. albicans* species, such as *Candida parapsilosis*, is increasing. Postantifungal effect (PAFE) is relevant for establishing dosage schedules in antifungal therapy, as the frequency of antifungal administration could change depending on PAFE. The aim of this study was to evaluate the PAFE of anidulafungin against *C. albicans*, *Candida dubliniensis*, *Candida africana*, *C. parapsilosis*, *Candida metapsilosis* and *Candida orthopsilosis*.

Material and methods. Twenty-one *Candida* strains were evaluated. Cells were exposed to anidulafungin for 1 h at concentrations ranging from 0.12 to 8 mg/L for PAFE studies. Time-kill experiments (TK) were conducted at the same concentrations. The experiments were performed using an inoculum of 1-5 x 10^5 cells/mL and 48 h incubation. Readings of PAFE and TK were done at 0, 2, 4, 6, 24 and 48 h.

Results. Anidulafungin was fungicidal against 2 out of 14 (14%) strains of *C. albicans* related species in PAFE experiments. Moreover, 2 mg/L of anidulafungin exerted a prolonged PAFE (≥ 33.6 h) against 13 out of 14 (93%) strains. Similarly, fungicidal endpoint was achieved against 1 out of 7 (14%) strains of *C. parapsilosis* complex, being PAFE prolonged (≥ 42 h) against 6 out of 7 (86%) strains.

Conclusions. Anidulafungin induced a significant and prolonged PAFE against *C. albicans* and *C. parapsilosis* and their related species.

Keywords: Postantifungal effect; anidulafungin; *Candida*

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Efecto postantifúngico de anidulafungina contra *Candida albicans, Candida dubliniensis, Candida africana, Candida parapsilosis, Candida metapsilosis* y *Candida orthopsilosis*

RESUMEN

Objetivos. *Candida albicans* continúa siendo la causa más frecuente de candidiasis invasiva; sin embargo, la incidencia de candidiasis causadas por especies diferentes a *C. albicans*, como *Candida parapsilosis*, está aumentando. El efecto postantifúngico (PAFE) es relevante para establecer pautas de dosificación en la terapia antifúngica, ya que la frecuencia de administración de los fármacos antifúngicos podría cambiar dependiendo del PAFE. El objetivo de este estudio fue evaluar el PAFE de anidulafungina contra *C. albicans*, *Candida dubliniensis*, *Candida africana*, *C. parapsilosis*, *Candida metapsilosis* y *Candida orthopsilosis*.

Material y métodos. Se evaluaron 21 cepas de *Candida*. Para llevar a cabo los estudios PAFE, las células se expusieron durante 1 h a concentraciones entre 0,12 y 8 mg/L de anidulafungina. Las curvas de letalidad (TK) se obtuvieron empleando las mismas concentraciones. Los experimentos se realizaron utilizando un inóculo de 1-5 x 10^5 células/mL, durante 48 h de incubación. Las lecturas de PAFE y TK se realizaron a las 0, 2, 4, 6, 24 y 48 h.

Resultados. Anidulafungina, en los experimentos PAFE, fue fungicida contra 2 de 14 (14%) cepas de las especies relacionadas con *C. albicans* y ejerció un PAFE prolongado (≥ 33,6 h) contra 13 de 14 (93%) cepas (2 mg/L). El límite fungicida de anidulafungina se alcanzó contra 1 de 7 (14%) cepas del complejo *C. parapsilosis*, con un PAFE prolongado (≥ 42 h) contra 6 de 7 (86%) cepas.

Conclusiones. Anidulafungina produce un PAFE significativo y prolongado contra *C. albicans* y *C. parapsilosis* y las especies relacionadas con estas.

Palabras clave: Efecto postantifúngico; anidulafungina; *Candida*

INTRODUCTION

Invasive candidiasis is a significant cause of morbidity and mortality, especially among patients suffering from severe immunodeficiency. Although *Candida albicans* remains the most common aetiology, the incidence of candidiasis due to non-*C. albicans* species is increasing. Most *Candida* bloodstream infections are caused by *C. albicans*, *Candida parapsilosis*, *Candida glabrata, Candida tropicalis*, and *Candida krusei* [1,2]. Moreover, *C. albicans* and *C. parapsilosis* have close-related species, such as *Candida dubliniensis* and *Candida africana* (*C. albicans* related species) or *Candida orthopsilosis* and *Candida metapsilosis* (*C. parapsilosis* complex). Differences and variability in the prevalence and antifungal susceptibility of these species have been reported [3,4].

Postantifungal effect (PAFE) describes how long an antifungal drug continues acting after it has been removed. This effect depends on both the fungal species and antifungal drug, and it may be relevant for antifungal therapy, having clinical relevance for establishing dosage schedules. Echinocandins and amphotericin B (fungicidal drugs) exert prolonged PAFE against *C. albicans* while triazoles (fungistatic drugs) possess shorter PAFE. Theoretically, antifungal drugs with long PAFE will require less frequent administration than those with shorter PAFEs [5,6]. The aim of this study has been to evaluate the PAFE of clinically relevant concentrations of anidulafungin against *C. albicans* and *C. parapsilosis* related species.

MATERIAL AND METHODS

Microorganisms. Twenty-one *Candida* clinical isolates and culture collection strains were studied (table 1). The clinical isolates were identified as previously described [7,8].

***In vitro* susceptibility testing.** Anidulafungin (Pfizer SLU, Spain) was dissolved in dimethyl sulfoxide. Further dilutions were done in standard RPMI 1640 medium (Sigma-Aldrich, Spain). Minimum concentrations that produce ≥ 50% growth reductions (MICs) after 24 h of incubation were determined according to the M27-A3, M27-S4 and M60 documents [9,10].

Time-kill procedures. Time-kill studies (TK) were performed out in microtiter plates in a computer-controlled microbiological incubator (BioScreen C MBR, LabSystems, Finland) in RPMI (200 µl) using an inoculum of 1-5 x 10^5 cells/ml, as previously described [11]. The concentrations assayed were 0.125, 0.5 and 2 mg/L for *C. albicans* related species, and 0.25, 2 and 8 mg/L for *C. parapsilosis* complex. Aliquots were removed from each well at 0, 2, 4, 6, 24 and 48 h, after dilution in phosphate buffered saline (PBS), the samples were inoculated onto Sabouraud dextrose agar (SDA) plates. Colonies were counted after incubation of the plates (36 ± 1 ˚C) for 48 h. All experiments were performed in duplicate. The limit of quantification was 20 colony forming units (CFU).

Postantifungal effect. PAFE was evaluated as previously described [12-14]. After an incubation period of 1 h, anidulafungin was removed by serial washing in PBS and centrifuged at 2000 rpm x 10 min. Tested concentrations, incubations, sample collection times and inoculations onto SDA plates were the same as described for TK assay. PAFE was calculated according to the equation PAFE= T - C (T: time required to increase by 1 log the counts in treated culture; C: time required to increase by 1 log the counts following the last washing) [15].

Fungicidal activity was defined as a growth reduction ≥ 3 log (99.9%), and fungistatic activity, as a reduction < 3 log (< 99.9%) in CFU from the starting inoculum. The ratios of the log killing during PAFE assays to the log killing during TK assays were also calculated [16].

Statistical analysis. The differences in PAFEs among the anidulafungin different concentrations and species were evaluated by ANOVA (GraphPad Software, USA). A P value < 0.05 was considered significant.

Table 1 **Anidulafungin MICs against strains from species related with *C. albicans* and *C. parapsilosis***

Isolate	Origin	MIC (mg/L)
Candida albicans NCPF 3153	Reference	0.03
Candida albicans NCPF 3156	Reference	0.03
Candida albicans UPV/EHU 99-101	Blood	0.06
Candida albicans UPV/EHU 99-102	Blood	0.03
Candida albicans UPV/EHU 99-103	Blood	0.03
Candida albicans UPV/EHU 99-104	Blood	0.06
Candida albicans UPV/EHU 99-105	Blood	0.06
Candida dubliniensis NCPF 3949	Reference	0.06
Candida dubliniensis UPV/EHU 00-131	Blood	0.06
Candida dubliniensis UPV/EHU 00-132	Blood	0.06
Candida dubliniensis UPV/EHU 00-133	Blood	0.03
Candida dubliniensis UPV/EHU 00-135	Blood	0.03
Candida africana UPV/EHU 97-135	Vaginal	0.03
Candida africana ATCC 2669	Reference	0.06
Candida parapsilosis ATCC 22019	Reference	1
Candida parapsilosis ATCC 90018	Reference	2
Candida parapsilosis UPV/EHU 09-378	Blood	2
Candida metapsilosis ATCC 96143	Reference	1
Candida metapsilosis UPV/EHU 07-045	Blood	1
Candida orthopsilosis ATCC 96139	Reference	1
Candida orthopsilosis UPV/EHU 07-035	Blood	1

RESULTS

Anidulafungin MICs are summarized in table 1. Anidulafungin (2 mg/L) exhibited a prolonged and significant

Table 2 **Reductions in starting inocula of *Candida* during TK and PAFE experiments and PAFE in hours against fourteen strains of species related with *C. albicans***

Isolate	AND (mg/L)	Killing (log)		PAFE/TK killing[a]	PAFE (h)
		TK	PAFE		
Candida albicans NCPF 3153	0.12	0.27	0.2	85.11	2
	0.5	0.39	0.01	41.69	20
	2	0.05	0.66	100	> 44
Candida albicans NCPF 3156	0.12	1.35	0.15	6.31	0
	0.5	≥ 4	0.04	0.01	0
	2	≥ 4	2.05	1.12	> 42
Candida albicans UPV/EHU 99-101	0.12	2.7	0.36	0.46	0
	0.5	≥ 4	0.51	0.03	0
	2	≥ 4	≥ 4	100	> 43
Candida albicans UPV/EHU 99-102	0.12	0.92	0.30	24	3.2
	0.5	2.02	1.6	38.02	> 39.1
	2	≥ 4	1.3	0.19	> 39.1
Candida albicans UPV/EHU 99-103	0.12	NA[b]	0.1		> 43
	0.5	NA	0.05		19
	2	2.03	1.24	16.22	> 43
Candida albicans UPV/EHU 99-104	0.12	NA	0.35		> 42
	0.5	NA	0.44		> 42
	2	1.1	0.41	20.42	> 42
Candida albicans UPV/EHU 99-105	0.12	≥ 4	0.42	0.02	0
	0.5	≥ 4	0.5	0.03	0
	2	≥ 4	1.82	0.66	> 42
Candida dubliniensis NCPF 3949	0.12	NA	NA		0
	0.5	0.04	0.04	100	0
	2	0.57	0.92	100	> 42
Candida dubliniensis UPV/EHU 00-131	0.12	NA	NA		0
	0.5	NA	NA		2
	2	0.54	1.16	100	> 44
Candida dubliniensis UPV/EHU 00-132	0.12	NA	NA		0
	0.5	NA	0.08		0
	2	0.53	0.03	31.62	> 42
Candida dubliniensis UPV/EHU 00-133	0.12	NA	0.13		0
	0.5	0.39	0.39	100	18
	2	0.72	1.03	100	18
Candida dubliniensis UPV/EHU 00-135	0.12	≥ 4	NA		0
	0.5	≥ 4	≥ 4	100	> 42
	2	≥ 4	1.32	0.21	> 42
Candida africana ATCC 2669	0.12	NA	0.23		2.8
	0.5	0.12	0.25	100	> 37.7
	2	0.15	0.4	100	> 37.7
Candida africana UPV/EHU 97-135	0.12	0.02	0.3	100	0.7
	0.5	0.36	0.34	95.5	2
	2	0.6	0.42	66.07	> 33.6

AND, anidulafungin; TK, time-kill; PAFE, postantifungal effect. [a]Ratio of the log killing during PAFE experiments to the log killing during TK experiments. [b]NA, not applicable (without any reduction in colony counts compared with the starting inoculum)

PAFE (≥ 33.6 h) against most strains of *C. albicans* related species (13 out of 14, 93%) (table 2). Besides, prolonged PAFE (> 37.7 h) with ≤ 0.5 mg/L of anidulafungin was observed against 5 out 14 (36%) of these strains. In TK experiments, anidulafungin (2 mg/L) was fungicidal against 5 out of 14 (36%) strains of *C. albicans* related species. Fungicidal endpoint was achieved against 2 out of 14 (14%) strains of *C. albicans* related species in PAFE experiments (strains *C. albicans* UPV/EHU 99-101 and *C. dubliniensis* UPV/EHU 00-135). This fungicidal effect was even achieved when 0.5 mg/L of anidulafungin was tested against strain *C. dubliniensis* UPV/EHU 00-135. The mean value of PAFE/TK ratio was 52.61 (2 mg/L) for *C. albicans* related species. Although there were no significant differences between the PAFE against *C. albicans*, *C. dubliniensis* and *C. africana*, it could be observed that anidulafungin presented slightly higher PAFE than against *C. dubliniensis* or *C. africana* (table 2).

A significant and prolonged PAFE (≥ 42 h) against 6 out of 7 (86%) strains of *C. parapsilosis* complex was observed with 8 mg/L of anidulafungin ($P < 0.05$) (table 3), but fungicidal endpoint was achieved only against *C. metapsilosis* UPV/EHU 07-045. This concentration was fungicidal against 6 out 7 (86%) strains from the *C. parapsilosis* complex and fungistatic against 1 *C. orthopsilosis*, in TK experiments. The mean value of PAFE/TK ratio was 15.48 (8 mg/L) for *C. parapsilosis* complex. There were no significant differences between the PAFE of anidulafungin against *C. parapsilosis*, *C. metapsilosis* and *C. orthopsilosis* (table 3).

Mean anidulafungin PAFE against *C. albicans* related species (39.6 ± 26.81 h) (2 mg/L) did not differ from that one against *C. parapsilosis* complex (37.6 ± 14.32 h) (8 mg/L) (figure 1 and 2).

DISCUSSION

C. albicans and *C. parapsilosis* are the most frequent aetiological agents of invasive candidiasis in Spain and in many Mediterranean and Latin-American countries [1]. *C. orthopsilosis* and *C. dubliniensis* represent relatively frequent aetiolog-

Table 3 **Reductions in starting inocula of *Candida* isolates during TK and PAFE experiments and PAFE in hours against seven strains of species related with *C. parapsilosis***

Isolate	AND (mg/L)	Killing (log)		PAFE/TK killing[a]	PAFE (h)
		TK	PAFE		
Candida parapsilosis ATCC 22019	0.25	NA[b]	NA		0
	2	0.88	0.11	16.98	0
	8	≥ 4	0.36	0.02	42
Candida parapsilosis ATCC 90018	0.25	NA	NA		0
	2	NA	NA		3.6
	8	≥ 4	0.18	0.02	42
Candida parapsilosis UPV/EHU 09-378	0.25	0.15	NA		0
	2	0.08	0.19	100	5.7
	8	≥ 4	NA		5.2
Candida metapsilosis ATCC 96143	0.25	NA	NA		0
	2	≥ 4	NA		0
	8	≥ 4	2.36	2.29	> 44
Candida metapsilosis UPV/EHU 07-045	0.25	NA	NA		0
	2	1.12	NA		0
	8	≥ 4	≥ 4	100	> 44
Candida orthopsilosis ATCC 96139	0.25	NA	NA		0
	2	3.05	NA		2
	8	≥ 4	2.67	4.68	> 44
Candida orthopsilosis UPV/EHU 07-035	0.25	NA	NA		0
	2	1.73	NA		0
	8	2.06	0.19	1.35	42

AND, anidulafungin; TK, time-kill; PAFE, postantifungal effect. [a]Ratio of the log killing during PAFE experiments to the log killing during TK experiments. [b]NA, not applicable (without any reduction in colony counts compared with the starting inoculum)

ical agents of invasive candidiasis, being in some institutions more prevalent than *C. krusei* [17]. To our knowledge, this is the first study that shows and compares the PAFE of anidulafungin against the emerging species *C. dubliniensis*, *C. africana*, *C. metapsilosis* and *C. orthopsilosis*. PAFE and TK experiments of anidulafungin against *C. albicans* and *C. parapsilosis* have not been widely evaluated and most studies included low numbers of isolates [5,12,15]. Moreover, this study provides a comparison among the in vitro activities of anidulafungin, caspofungin and micafungin [13,14].

Anidulafungin MICs were consistent with those reported in previous studies [8,18]. In the current study, anidulafungin exerted good fungicidal activity against most strains of *C. parapsilosis* complex but this activity was lower against *C. albicans* related species (with 8 mg/L and 2 mg/L, respectively). This discrepancy in the activity of the echinocandins against different species of *Candida* has been reported previously [11,12,16,19]; anidulafungin is considered fungicide against *Candida* but does not achieve this effect against all isolates. This effect depends on isolate, species, antifungal concentration and test conditions [5,11,19]. Similarly, Clancy et al. reported prolonged PAFE of caspofungin against *C. albicans*, *C. parapsilosis* and *C. glabrata*, but fungicidal activity was not observed in TK or PAFE experiments [16]. For this reason, it would be advisable to perform in vitro susceptibly testing, such as TK and PAFE studies, since killing curves are tools that provide much information about the antifungal activity.

Smith et al. [15] described fungicidal activity of anidulafungin in TK and in PAFE against *C. glabrata* and *C. parapsilosis* at similar concentrations. Moreover, Nguyen et al. [12] evaluated the anidulafungin PAFE against several *Candida* species, reporting fungicidal PAFE against the former species. However, we only observed fungicidal activity against *C. parapsilosis* in TK experiments, except for one strain of *C. metapsilosis* with fungicidal PAFE.

In the current study, there were not significant differences in anidulafungin activity among the species related to *C. albicans* and *C. parapsilosis*. However, we have observed previously statistically significant differences between species related to against *C. albicans* and *C. parapsilosis* in the duration of micafungin and caspofungin PAFEs, which were longer against *C. albicans* related species than against *C. parapsilosis* complex [13,14]. Anidulafungin is the echinocandin with greater PAFE against *C. parapsilosis*. Conversely, micafungin was the echinocandin that displayed the lowest PAFE against the *C. parapsilosis* complex. However, all echinocandins showed a similar PAFE against the *C. albicans* related species, with a slightly but non-significant higher PAFE with micafungin [13,14]. In PAFE experiments anidulafungin (≤ 2 mg/L) and micafungin (2 mg/L) achieved the fungicidal endpoint against 2 out 14 (14%) strains of *C. albicans* related species (*C. albicans* UPV/EHU 99-101, *C. dubliniensis* UPV/EHU 00-135 and *C. albicans* UPV/EHU 99-102, and *C. dubliniensis* UPV/EHU 00-135, respectively). Caspofungin (2 mg/L) only achieved this endpoint against 1 out of 14 (7%) strains (*C. albicans* UPV/EHU 99-101). Only anidulafungin (8 mg/L) displayed a fungicidal PAFE against the *C. parapsilosis* complex (1 out 7, 14% strains, *C. metapsilosis* UPV/EHU 07-045) [13,14]. Fungal growth characteristics or binding affinities of each drug could be possible explanations for PAFE differences [12]. PAFE may have clinical relevance to the design of dosing regimens for antifungal agents, as those antifungal drugs with longer PAFEs may be administered less frequently than those ones with shorter PAFEs [5,20].

In conclusion, anidulafungin showed a significant and

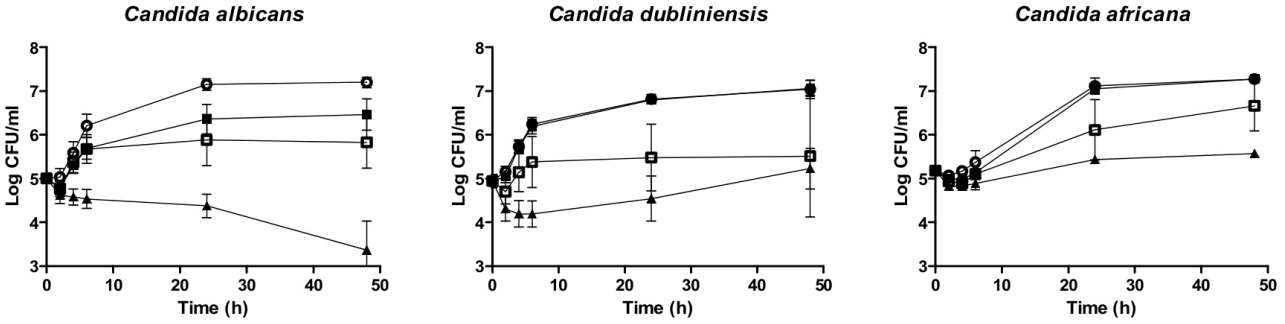

Figure 1 Mean time-kill curves from the PAFE assays against seven *C. albicans*, five *C. dubliniensis* and two *C. africana* strains. Each point represents the mean count ± standard deviation (error bars). Open circles (○): control; filled squares (■): 0.12 mg/L anidulafungin; open squares (□): 0.5 mg/L anidulafungin; and filled triangles (▲): 2 mg/L anidulafungin

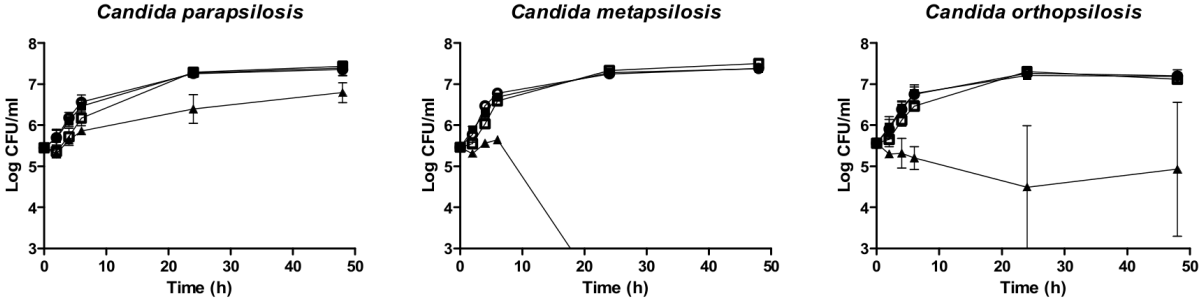

Figure 2 Mean time-kill curves from the PAFE assays against three *C. parapsilosis*, two *C. metapsilosis* and two *C. orthopsilosis* strains. Each point represents the mean count ± standard deviation (error bars). Open circles (○): control; filled squares (■): 0.25 mg/L anidulafungin; open squares (□): 2 mg/L anidulafungin; and filled triangles (▲): 8 mg/L anidulafungin

prolonged PAFE against the species closely related to *C. albicans* and *C. parapsilosis*, being the echinocandin with greater PAFE against *C. parapsilosis* complex. Although the clinical implications of in vitro killing and PAFE need further research, the current findings represent an initial step towards improving dosage regimen in clinical setting.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest related to the current manuscript, but declare the following: G.Q. has received research grants from Astellas Pharma, Pfizer, Merck Sharp & Dohme, and Scynexis. G.Q. has served on advisory/consultant boards for Merck, Sharp & Dohme, and Scynexis, and he has received speaker honoraria from Abbvie, Astellas Pharma, Merck Sharp & Dohme, Pfizer, and Scynexis.

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Carta al Director

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Estudio de las infecciones del tracto urinario por *Streptococcus gallolyticus* subespecie *pasteurianus*

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Sr. Editor: Las infecciones del tracto urinario (ITU) son las más frecuentes en España en la actualidad, seguidas por las del aparato respiratorio. Se estima que el 50% de todas las mujeres presentarán al menos un episodio de ITU durante su vida [1]. En líneas generales, la etiología probable de las ITUs está bien establecida, así como su prevalencia, pero no ocurre lo mismo con los microorganismos menos habituales. Es el caso del *Streptococcus gallolyticus* subespecie *pasteurianus* (SGP), del que existen escasos estudios que profundicen en la repercusión clínica que tiene la presencia de esta bacteria en los urocultivos significativos [2, 3], ya que previamente fueron considerados dentro de los *Streptococccus* del grupo *bovis* (SGB) [4-7]. En este trabajo se analiza el significado clínico de los SGB en urocultivos, su sensibilidad a los antibióticos y la evolución de los pacientes después de recibir tratamiento antibiótico.

Se revisaron retrospectivamente los urocultivos con recuento significativo de SGB durante un periodo de dos años (2015-2016) procedentes del Servicio de Microbiología del Complejo Hospitalario Universitario Virgen de las Nieves de Granada (España). Las muestras estudiadas incluyeron orina de micción media, orina de pacientes con sonda permanente u orina de sondaje vesical. El procedimiento de recogida, transporte y procesamiento en el laboratorio se realizó según protocolo previamente descrito [8]. Además, se identificaron los SGB mediante MALDI-TOF (Bruker Daltonics, Billerica, EE. UU.). Los aislados se clasificaron como sensible, intermedio o resistentes para cada antibiótico siguiendo las recomendaciones del EUCAST del año 2016 y se utilizaron los puntos de corte epidemiológicos (ECOFF) para daptomicina, levofloxacino y linezolid. Los datos clínicos de los pacientes, incluyendo el índice de Charlson [9], se obtuvieron de la revisión de la Historia de Salud Digital en Diraya® (sistema utilizado en el Sistema Sanitario Público de Andalucía como soporte de la historia clínica electrónica).

Durante el periodo de estudio se analizaron un total de 20.916 urocultivos: 17.242 (82,43%) procedentes de atención primaria y 3.674 (17,57%) de atención especializada; 4.652 (22,25%) de varones (edad media: 57 años; rango: 2 meses a 93 años); 16.264 (77,75%) de mujeres (edad media: 44 años; rango: 15 días a 98 años); 326 (1,56%) de niños; 11.610 (55,51%) de adultos; 6.511 (31,13%) de gestantes para estudios de cribado; 1.251 (5,98%) de adultos inmunocomprometidos; 14.138 (67,59%) con un resultado negativo; 4.287 (20,49%) con aislamiento clínicamente significativo de microorganismos; 870 (4,16%) con crecimiento mixto de microorganismos en cultivo, interpretada como orina contaminada; 860 (4,11%) con crecimiento de microbiota del epitelio genitourinario; 761 (3,64%) con aislamiento en recuento clínicamente presuntivo de microorganismos.

De las anteriores 39 (0,9%) resultaron positivos para SGB, de adquisición comunitaria en 38 pacientes, y un caso que fue nosocomial durante un ingreso en cardiología. De estos 38 fueron SGP y hubo un caso de *Streptococcus infantarius* ssp. *coli* (*Streptococcus lutetiensis*); SGB se aisló de forma monomicrobiana en 35 urocultivos, en 3 junto con *Escherichia coli* y en 1 junto con *Staphylococcus aureus*. Los datos de sensibilidad antibiótica se muestran en la tabla1, con indicación de la categoría clínica o epidemiológica. El 100% de los aislados fueron sensibles a penicilina (CMI≤0,25mg/l), ampicilina (CMI≤0,5mg/l) y teicoplanina (CMI≤2mg/l); el 98% fueron sensibles a vancomicina (CMI≤0,5mg/l) y el 55% sensibles a clindamicina (CMI≤ 0,5mg/l). El 97% de las cepas fueron epidemiológicamente sensibles a levofloxacino, y el 100% a linezolid y a daptomicina. La edad de los pacientes osciló entre 15 días y 93 años (68 ± 25,65 años), incluyendo 5 con menos de 14 años; 27 (70%) casos eran mujeres y 12 (30%) hombres. Los antecedentes clínicos fueron urológicos (12, 31%), diabetes mellitus

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Tabla 1 **Sensibilidad acumulada para los antibióticos de las cepas de *Streptococcus* grupo *bovis*, con indicación de la categoría clínica y epidemiológica, para aquellos sin punto de corte clínico, siguiendo las recomendaciones establecidas por EUCAST.**

Antibiótico	Nº Cepas	CMI acumulada (mg/L)	Categoría Clínica	Punto de Corte Epidemiológico (ECOFF)	Sensible (%) según ECOFF
Ampicilina	39	≤0,5	Sensible	-	-
Penicilina	39	≤0,03	Sensible	-	-
Ciprofloxacino	19	1			
	16	2	Ininterpretable	ND	ND
	4	>2			
Levofloxacino	38	≤1	Ininterpretable	2,0	97
	1	>4			
Teicoplanina	39	≤1	Sensible	-	-
Vancomicina	39	≤1	Sensible	-	-
Eritromicina	24	≤0,25	Ininterpretable	ND	ND
	15	>4			
Clindamicina	25	≤0,25	Sensible	-	-
	14	4	Resistente		
Tetraciclina	12	≤1	Ininterpretable	ND	ND
	1	8			
	26	>8			
Linezolid	39	≤1	Ininterpretable	2,0	100
Daptomicina	39	≤0,5	Ininterpretable	0,25	100

(7, 18%), neoplasias (4, 10%), trasplante renal (4, 10%), trasplante hepático (2, 5%) y hemodiálisis (2, 5%). La media del Índice de Charlson fue de 2,5. Se realizó colonoscopia en 2 pacientes, siendo uno diagnosticado de enfermedad de Crohn. En 12 (31%) pacientes no se reflejó en la historia la clínica relacionada con la presencia del SGB; pero en 14 (52%) presentaron síntomas de infección urinaria, de ellos 13 con piuria, 9 con cistitis y 5 con pielonefritis. El antibiótico administrado no fue recogido en la historia de 20 (51,3%) pacientes. La mayoría fueron tratados durante 7 días (9 pacientes), en los demás el tiempo de tratamiento osciló de 5 a 14 días, siendo desconocido en 22 (56%) pacientes. La mayoría, 30 (76%), alcanzaron la curación completa y en 2 (5%) no, ya que en los urocultivos de control continuó apareciendo el SGB; y en los 7 (17%) restantes no se reflejó en la historia. Respecto a la erradicación del SGB, en 19 pacientes se consiguió tras el tratamiento antibiótico, activo según el antibiograma; en otros 5 se erradicó la infección pero desconocemos que antibiótico se empleó; y en 14 pacientes no hubo urocultivo de control. El caso de peor evolución fue el de una paciente de 69 años, con antecedentes de hipertensión arterial, diabetes mellitus y cirrosis hepática, con varios episodios de hemorragia digestiva alta, dependiente para ABVD, que acude al servicio de urgencias, consciente y orientada, por malestar general, constatándose hiperglucemia, ITU y encefalopatía hepática. Fue tratada con ceftriaxona y clindamicina, presentando un urocultivo positivo para SGB y *S. aureus* meticilin sensible no estando sondada previamente. La paciente falleció con infección urinaria, descompensación de la encefalopatía hepática y fallo multiorgánico posterior, desenlace en principio relacionado presuntivamente con la sepsis urológica (no documentada o confirmada), ya que durante el ingreso no se encontraron otros desencadenantes. El único caso de infección por *S. lutetiensis* ocurrió en una mujer de 85 años, que presentó clínica en domicilio de hematuria. Se pautó en urgencias cefuroxima, 500 mg. cada 12 horas, durante 5 días. Tras este episodio es derivada al Servicio Urología que valoró la ITU por *S. lutetiensis*, pautó medicación antibiótica, y se realizó urocultivo de control al mes que fue negativo. Finalmente, se realizó el diagnóstico de carcinoma urotelial de alto grado. Posiblemente se trata de una ITU por *S. lutetiensis*, aunque por el hallazgo que implica el carcinoma urotelial no es posible garantizar que se trate de una ITU verdadera.

Este trabajo confirma que la mayoría de los pacientes donde se aisló SGP eran mujeres [6, 7], a diferencia de otro tipos etiológicos de infecciones por *Pseudomonas* y *Acinetobacter*, más frecuentes en varones [10]. El tratamiento de las infecciones por SGB se fundamenta en el estudio de sensibilidad a los distintos antibióticos, existiendo puntos de corte

clínicos sólo para ampicilina, penicilina, vancomicina, teicoplanina y clindamicina, aunque esta no es activa en la orina. En nuestro caso la sensibilidad para todos ellos fue del 100%, excepto para clindamicina que presentó un 36% de aislados resistentes, con resultados similares a otros estudios [3,4]. La falta de puntos de corte clínicos para el resto de antibióticos hace que el arsenal terapéutico sea limitado y se utilicen puntos de corte epidemiológicos, de ahí la importancia de seguir realizando estudios en este campo. En nuestro caso el 97% fue epidemiológicamente sensible a levofloxacino, y el 100% sensible a linezolid y daptomicina, aunque estos antibióticos no son activos en la orina.

En resumen, los datos obtenidos en nuestra serie, a pesar de que en un número importante de los casos no se pudieron analizar debido a la falta de información en la historia clínica, nos hace pensar que SGP es un potencial agente responsable de bacteriuria, sobre todo en mujeres, con patología urológica y/o diabetes, pudiendo ocasionar tanto bacteriurias asintomáticas como sintomáticas, y que, por tanto, son necesarios más estudio al respecto para establecer el riesgo potencial de desarrollo posterior de bacteriemia.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Carta al Director

Peritonitis por *Clostridium innocuum* asociada a diálisis peritoneal

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Sr. Editor: La peritonitis es una de las principales complicaciones de la diálisis peritoneal y una causa importante de morbilidad y mortalidad. Estas infecciones se engloban dentro de las peritonitis primarias ya que, no están asociadas a una solución de continuidad en el tracto gastrointestinal [1]. El desarrollo de la infección peritoneal se produce por la llegada de los microorganismos a la cavidad peritoneal por distintas vías: intraluminal, pericatéter, migración transmural y hematógena [2].

Su incidencia es de 0,24-1,67 episodios/paciente/año [3]. En el 90% de los casos son monomicrobianas y su principal origen es la contaminación del catéter por microbiota cutánea [1]. En el 39% de los casos están producidas por estafilococos coagulasa negativos, en el 13% por estreptococos, 6% por enterococos, 4% por *Staphylococcus aureus* y en menos del 5% por corinebacterias [4]. Los bacilos gramnegativos son responsables de 10-30% de los casos, donde *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp. y *Pseudomonas* spp., se aíslan con mayor frecuencia [5]. Los hongos ocasionan un 3-5% de los casos [4], siendo el 90% de ellos por levaduras [5]. Tanto los microorganismos anaerobios, como las micobacterias (tuberculosas y no tuberculosas) se asocian con menos de un 0,5% de los casos cada uno [6].

Presentamos un caso de peritonitis asociada a diálisis peritoneal por *Clostridium innocuum*.

Mujer de 44 años, alérgica a la penicilina, diagnosticada de Arteritis de Takayasu tipo III hace 25 años y con enfermedad renal crónica. Hace 11 años comenzó a precisar terapia renal sustitutiva en programa de hemodiálisis inicialmente, transfiriéndose meses después a diálisis peritoneal. Acude al hospital refiriendo dolor abdominal difuso de 48 horas de evolución, asociado a hipotensión arterial, negando fiebre o líquido turbio en su domicilio. En la analítica de sangre destacó: Leucocitos 21,20 x 10^3/µL (91,8% PMN), Lactato 3,32 mM/L y Procalcitonina 6,22 ng/mL. Se realizó drenaje de líquido peritoneal presentando turbidez y un recuento celular de 6,67 x 10^3/µL leucocitos (90,8% PMN). Se enviaron al Servicio de Microbiología muestras para cultivo de líquido peritoneal en tubo estéril y en frascos de hemocultivos. Se decidió ingreso iniciando tratamiento empírico con vancomicina y ceftazidima intraperitoneal y profilaxis fúngica con fluconazol vía oral, siguiendo las pautas del protocolo de la Unidad de Diálisis peritoneal.

La muestra en tubo estéril se sembró en los medios sólidos habituales y en caldo de enriquecimiento (tioglicolato), siendo el cultivo negativo a las 48 horas de incubación. La botella anaerobia del frasco de hemocultivo fue positiva tras 25 horas de incubación, por lo que se sembró en los medios habituales y se realizó la tinción de gram donde se observaron bacilos grampositivos de extremos rectos. En esta situación, se cambió la cobertura antibiótica a cefotaxima, ampicilina y clindamicina intraperitoneal, manteniendo profilaxis antifúngica, y, se realizó un TAC abdominal no visualizándose la existencia de perforación intestinal.

A las 48 horas se observó crecimiento de unas colonias gris brillante en agar Brucella con hemina y vitamina K1 (Becton Dickinson) incubado en atmósfera de anaerobiosis. Mediante espectrometría de masas MALDI-TOF (Bruker), el microorganismo se identificó como *C. innocuum*.

El estudio de sensibilidad antibiótica se realizó mediante Etest (bioMérieux) en placas de agar Brucella con hemina y vitamina K1, incubadas en atmósfera anaerobia que se leyeron a las 24 y 48 horas. La sensibilidad fue la siguiente: amoxicilina/ácido clavulánico CMI= 0,58mg/L (sensible), imipenem CMI= 0,5mg/L (sensible), vancomicina CMI= 8mg/L (resistente), clindamicina CMI= 0,25mg/L (sensible) y metronidazol CMI= 0,125mg/L (sensible).

A las 24 horas del cambio terapéutico mencionado, se ob-

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servó que el drenaje del líquido peritoneal era fecaloideo. Se realizó un TAC abdominal en el que se observó perforación intestinal, cuadro clínico que se sospechaba desde el momento inicial. La permanencia en el programa de diálisis peritoneal facilitó su diagnóstico. Se realizó sigmectomía y derivación tipo Hartman. Dos días después debido a su evolución fue reintervenida, realizándose resección parcial del muñón rectal que estaba perforado. La paciente continuó con mala evolución falleciendo a los 15 días de ingreso. Mencionar que, a pesar del tratamiento con cefalosporinas y carbapenémicos, la paciente no tuvo ninguna reacción cruzada durante el tratamiento.

C. innocuum es un bacilo grampositivo anaerobio e inmóvil, que pertenece al denominado grupo RIC, junto a *Clostridium ramosum* y *Clostridium clostridioforme* [7,8]. Los miembros de este grupo se caracterizan por carecer de la morfología típica del género Clostridium y por no presentar esporas [7,8]. La principal peculiaridad de *C. innocuum* es su resistencia moderada a vancomicina (MIC 4-16 mg/L) sin extensión a teicoplanina [9]. El mecanismo de resistencia es intrínseco y se asocia con la síntesis de precursores del peptidoglicano con baja afinidad por este antibiótico [9]. La alta resistencia a vancomicina se relaciona con tratamiento previo con este fármaco, en el que se seleccionan mutantes con CMI >16mg/L [9].

Las peritonitis causadas por microorganismos anaerobios en pacientes en diálisis peritoneal son raras, suelen ser parte de cultivos mixtos y están asociadas, en la mayoría de los casos, a lesiones intraabdominales [6]. La mayor parte de las peritonitis por anaerobios están producidas por especies del género *Bacteroides* [6].

En el caso descrito, la vía más probable de entrada fue la migración transmural desde el tracto gastrointestinal. Creemos que la infección por *C. innocuum*, especie intrínsecamente resistente a vancomicina, fue un agravante que pudo favorecer el difícil control de la peritonitis, por lo que consideramos muy importante el diagnóstico diferencial de peritonitis asociadas a diálisis peritoneal por microorganismos anaerobios. Asimismo, recordamos la importancia de la recogida de la muestra en frascos de hemocultivos para la recuperación de los microorganismos, sobre todo en los casos de bajo inóculo.

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CONFLICTO DE INTERESES

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Utilidad de la PCR-múltiple (*FilmArray Blood Culture Identification*) en otros líquidos biológicos. Detección de *Streptococcus pyogenes* en absceso cerebral y líquido sinovial

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Aunque este sistema está diseñado para la detección de patógenos en sangre, nosotros describimos dos casos clínicos donde se utilizó en otras muestras clínicas, identificando *Streptococcus pyogenes* en el pus de un absceso cerebral y en el líquido sinovial de un paciente con una grave fascitis necrotizante. El estudio fue aprobado por el Comité de Ética del Hospital Universitario Central de Asturias (número 237/18).

Caso 1

Mujer de 53 años con antecedentes de adenocarcinoma de endometrio tratado con cirugía y quimioradioterapia. Cuadro de malestar general, otitis derecha de un mes de evolución a tratamiento con ciprofloxacino, movimientos involuntarios en extremidad inferior izquierda y afasia. Escala de Glasgow 11, parálisis facial central izquierda y paresia de miembro superior izquierdo. En TC craneal lesión temporal derecha sugestiva de absceso cerebral, con importante efecto masa y desviación de línea media (figura 1). Se inicia tratamiento anticomicial, corticoides, antibioterapia empírica con meropenem y linezolid y drenaje quirúrgico urgente obteniéndose 55 cc de líquido purulento donde se realizó FilmArray® BCID, con resultado positivo para *S. pyogenes* que posteriormente se confirmó en el cultivo del pus cerebral. Los hemocultivos fueron negativos.

Evolución desfavorable con status epiléptico refractario precisando tratamiento con múltiples fármacos anticomiciales. Afebril desde su ingreso hasta el decimotercer día que presentó 38ºC y ascenso de leucocitosis. En TC persistía imagen de absceso cerebral por lo que se realizó nuevo drenaje quirúrgico. En la TC postquirúrgica, edema cerebral y hematoma en el lecho quirúrgico siendo reintervenida para realizar craniectomía descompresiva, evacuación del hematoma y monitorización de presión intracraneal (PIC). A partir de ese momento presentó una evolución favorable, con buen control de la PIC, del status epiléptico y del nivel neurológico lo que permitió la retirada de la ventilación mecánica. Tras 35 días de estancia en UCI, fue trasladada a neurocirugía consciente, orientada temporoespacialmente, con lenguaje comprensible y ligera paresia de la extremidad inferior izquierda. La paciente fue dada de alta a su domicilio tras 61 días de ingreso, con buen nivel neurológico, hipoestesia en mano izquierda y caminando de forma autónoma. En el último TC se observa área de encefalomalacia temporal derecha (figura 2)

Caso 2

Varón de 51 años, con hipertensión portal no cirrótica, enfisema pulmonar y esófago de Barret. Sin traumatismo previo, comenzó con fiebre, malestar general, dolor e inflamación en la 5ª articulación metatarsofalángica izquierda y en el hombro izquierdo que fue tratada con una infiltración local. 24 horas después progresión del dolor hasta el muslo e impotencia funcional a tratamiento con AINEs. En Urgencias se objetiva aumento del perímetro de la pierna izquierda y signos de derrame articular en la rodilla. Hemodinámicamente estable y afebril. En la analítica destaca, creatininfosfoquinasa 1.999 u/l, proteína C reactiva 24,2 mg/dl, procalcitonina 7,14 ng/ml, D-dímero 1.897 ng/ml y acidosis metabólica compensada.

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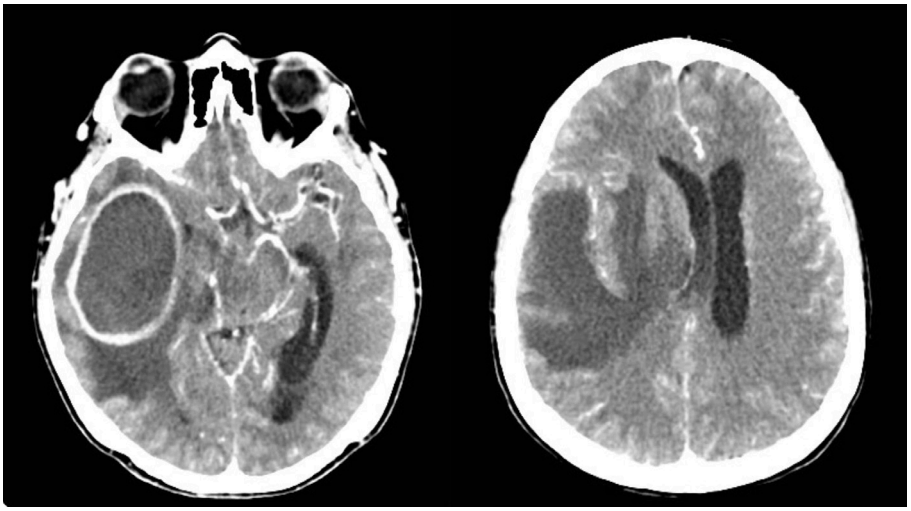

Figura 1 **Corte axial de TC craneal con contraste . Se objetiva lesión hipodensa con realce en anillo correspondiente a absceso cerebral y edema perilesional que condiciona efecto masa. Edema cerebral con borramiento de surcos, colapso parcial de asta frontal y occipital de ventrículo derecho y desviación de línea media.**

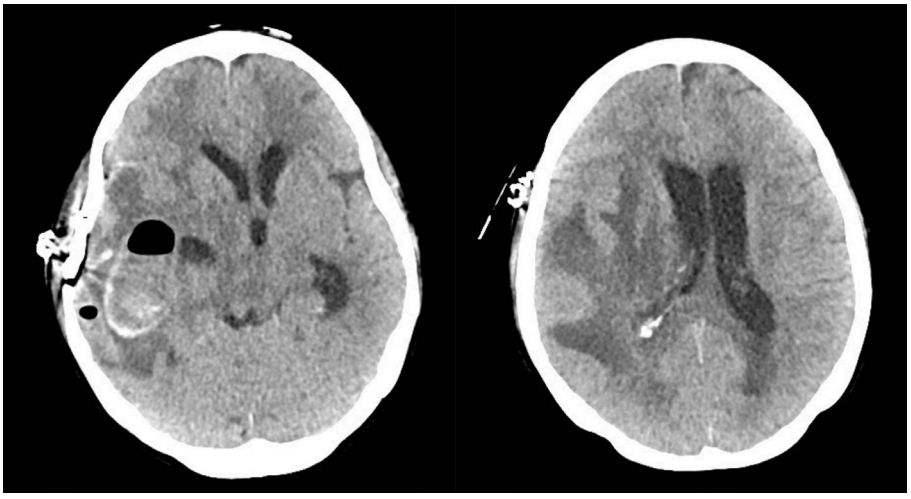

Figura 2 **Craniectomía descompresiva temporal derecha y alteraciones postquirúrgicas. Área de encefalomalacia temporal derecha y burbujas de neumoencéfalo.**

Leucocitos 9.666/mm^3 (88,8 % neutrófilos, 5,3% linfocitos). Plaquetas 88.000/ mm^3. Coagulación normal. Ante la sospecha de trombosis venosa profunda se realiza angio-TC que muestra signos de fascitis y miositis aguda en compartimento anterior del muslo, afectando fundamentalmente al cuadriceps femoral. Se inicia tratamiento con meropenem, metronidazol, linezolid e intervención quirúrgica urgente, realizando exéresis y limpieza de tejidos necróticos. Se realiza punción intraarticular de la rodilla obteniéndose líquido purulento en el cual se realiza FilmArray® BCID siendo positivo para *S. pyogenes*, que posteriormente se confirma en hemocultivos, cultivo de líquido sinovial y del exudado muscular. Tras la identificación del *S. pyogenes* se trató con meropenem, clindamicina y linezolid. Mala evolución con rápido deterioro hemodinámico y de la función renal, aumento de procalcitonina a 38 ng/ml, leucopenia de 1.450/mm^3, acidosis láctica y aparición de nuevas lesiones necróticas en raíz de muslo. Ante la mala situación clínica y la rápida progresión de la fascitis necrotizante, se decide intervención quirúrgica con desarticulación de la extremidad inferior izquierda sin cerrar los bordes quirúrgicos (figura 3),

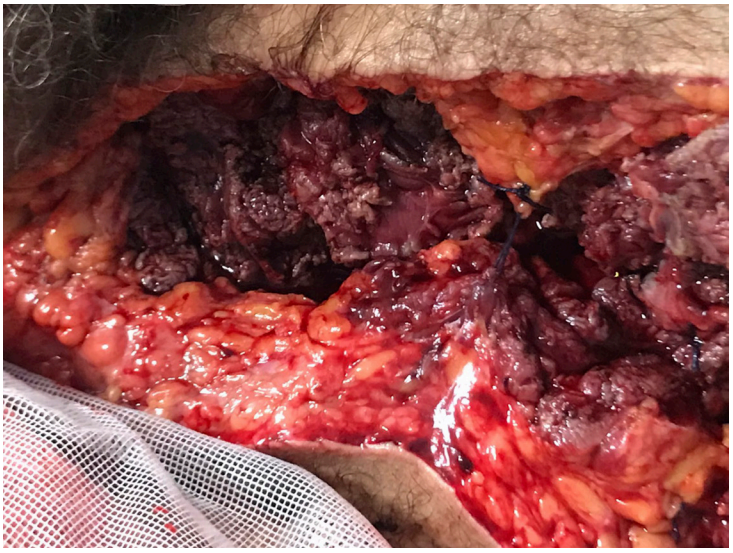

Figura 3 | **Áreas de necrosis muscular y zona expuesta tras la desarticulación de la extremidad inferior izquierda.**

se mantiene soporte hemodinámico con dosis altas de noradrenalina, fluidos y hemodiafiltración, aumentando la necrosis muscular y la acidosis metabólica (ácido láctico de 16 ng/ml). Evoluciona de forma fulminante a una situación de fallo multiorgánico refractario, siendo éxitus a las 27 horas de su ingreso en UCI.

En el paciente crítico, identificar el patógeno e iniciar precozmente un tratamiento antibiótico dirigido es primordial para disminuir morbimortalidad. El sistema de PCR-múltiple utilizado, ha sido diseñado para el diagnóstico de la sepsis y permite en una hora identificar simultáneamente 24 patógenos y tres genes de resistencia en sangre con una alta sensibilidad y especificidad [9, 10]. Las referencias bibliográficas sobre su uso en otras muestras clínicas distintas a la sangre son muy escasas, pero algunos estudios han confirmado su utilidad en la identificación en líquidos biológicos como líquido cefalorraquídeo, sinovial, pleural, ascitis, aspirado traqueal y fluidos de material protésico infectado [2, 8, 11, 12], permitiendo hacer el diagnóstico microbiológico en un tiempo sensiblemente menor a los métodos de cultivo tradicionales.

En nuestros pacientes este sistema de PCR múltiple identificó en ambos casos *S. pyogenes* lo que fue posteriormente confirmado en los cultivos convencionales.

Estos dos casos clínicos muestran que el panel FilmArray® BCID, puede ser utilizado también con buenos resultados en muestras clínicas distintas a la sangre. Esta aplicación está fuera de las indicaciones del fabricante, pero consideramos que puede tener un impacto considerable en la práctica clínica en la UCI, ya que permitiría identificar de forma muy rápida una gran variedad de patógenos infecciosos en diferentes tipos de líquidos biológicos y patologías, lo que facilitaría un rápido tratamiento antibiótico dirigido, algo fundamental en el manejo de las infecciones graves. Será necesario realizar estudios prospectivos más amplios para confirmar estos hallazgos.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Official journal of the Spanish Society of Chemotherapy

Carta al Director

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Queratitis fúngica por *Colletotrichum gloeosporioides*: A propósito de un caso.

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Received: 5 November 2018; Revision Requested: 21 December 2018; Revision Received: 10 January 2019; Accepted: 21 January 2019

Sr Editor*:* El género *Colletotrichum* está formado por hongos filamentosos causantes de la *"antracnosis"*, una infección propia de vegetales que afecta principalmente al género *Cytrus* en países de clima templado [1]. En humanos, las especies del género *Colletotrichum* rara vez producen infecciones y, aunque en los últimos años haya aumentado el número de casos publicados de infecciones oftálmicas y subcutáneas por este tipo de hongo [2,3], la incidencia en humanos es baja.

Presentamos el caso de un varón de 45 años de origen ecuatoguineano que acude a la consulta de oftalmología por un absceso corneal en el ojo derecho tras traumatismo con rama de naranjo. El paciente había estado en seguimiento en atención primaria durante un mes sin presentar buena evolución tras tratamiento con dexametasona/tobramicina, moxifloxacino y ciclopéjico. En la consulta no refirió ninguna enfermedad sistémica, intervención quirúrgica previa o tratamiento farmacológico de forma habitual. Tampoco era portador de lentes de contacto.

En la exploración se observó hiperemia conjuntival, gran absceso corneal de 4-5 mm con lisis celular e infiltrado purulento en la cámara anterior del ojo (hipopion) de 2 mm. El fondo vítreo se observaba claro y transparente sin condensaciones fúngicas. Tras la exploración, se decidió pautar ciclopéjico, prednisona, ácido hialurónico, doxiciclina, moxifloxacino y colirios reforzados con ceftazidima y vancomicina, además de tomar muestras de humor acuoso del hipopion y de raspado corneal para cultivo microbiológico. El raspado corneal fue inoculado directamente en agar sangre, chocolate y caldo de enriquecimiento de tioglicolato, mientras que el humor acuoso únicamente en caldo de enriquecimiento. Las muestras se incubaron a 37ºC en atmosfera de CO_2.

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Al quinto día de incubación se observó crecimiento únicamente en el tioglicolato del raspado corneal, visualizándose en la tinción de gram hifas septadas no ramificadas. En el subcultivo realizado en placa de Sabouraud con cloranfenicol a 30ºC en aerobiosis, se observó crecimiento de un hongo filamentoso a las 72 horas. El paciente fue diagnosticado de queratitis fúngica, iniciándose tratamiento con 200 mg de voriconazol oral cada 12 horas y en colirio al 1% cada 2 horas. El resto de los fármacos fueron retirados.

En el subcultivo del raspado, tras 72 horas de incubación a 30ºC en aerobiosis, se observó macroscópicamente una colonia grisácea con el reverso marrón oscuro al tercer día. Microscópicamente con la tinción de azul de lactofenol se observaron hifas septadas no ramificadas, sin ninguna otra estructura característica que pudiera ayudar a su identificación. Debido a esto se decidió realizar diferentes subcultivos y enviar una muestra de la cepa aislada al Centro Nacional de Microbiología del Instituto de Salud Carlos III, donde fue identificada como *C. gloeosporioides*.

A los 7 días de iniciar tratamiento antifúngico, el paciente presentaba hiperemia corneal de predominio inferior con adelgazamiento de esta (dellen) y neovascularización superficial, aunque no se apreciaba hipopion. Se mantuvo tratamiento con voriconazol tanto oral como en colirio y se citó al paciente para observar evolución. A la semana siguiente se observaba una hiperemia corneal moderada, con un dellen menor y sin hipopion. Tras indicar el paciente el regreso a su país, se decidió realizar un lavado intracameral con voriconazol. En el mismo procedimiento quirúrgico se le tomó muestra de humor acuoso para cultivo microbiológico, no visualizándose microorganismos en la tinción de Gram y siendo el cultivo negativo a los 30 días. Finalmente, se pautó voriconazol oral durante dos meses para que pudiera finalizar el tratamiento en su país.

C. gloeosporioides es un hongo filamentoso que de forma excepcional pueden producir infecciones en humanos, siendo su principal presentación infecciones oftálmicas secundarias a

traumatismos producidos con material vegetal. La amplia mayoría de los casos publicados en la literatura son de regiones tropicales o subtropicales [2, 4], aunque en los últimos años también se han publicado algunos casos en nuestro país [5–8]. Las queratitis por *Colletotrichum* spp. se caracterizan por una progresión tórpida que, si no se tratan inmediatamente, pueden originar complicaciones que precisan en ocasiones de una intervención quirúrgica [5,6]. En este sentido, la no siempre fácil identificación de *Colletotrichum* spp. requiere, en muchos casos, la utilización de técnicas moleculares en laboratorios externos que demoran la identificación y, por consiguiente, un tratamiento dirigido [7]. Actualmente no existe un consenso en la terapia antifúngica, aunque se ha observado buena respuesta a natamicina, anfotericina B y voriconazol [4, 7, 9]. En estudios in vitro se ha observado resistencia a nistatina e itraconazol [9]. En este caso, la lenta progresión de la infección del paciente pudo deberse a la demora diagnóstica ocasionada por la tardía toma de muestras. Por otra parte, el tratamiento inicial y posterior con corticoides, factor de riesgo asociado a este tipo de infecciones [2], posiblemente agravó la evolución. Una vez diagnosticada la queratitis fúngica se retiró el tratamiento antibiótico y se pautó voriconazol tópico, sistémico e intracameral y al igual que en otros casos publicados [4,10], el hipopion desapareció una vez iniciado el tratamiento, pudiendo indicar que el hipopion era consecuencia de una respuesta inflamatoria a la infección. La evolución final del paciente se desconoce debido al retorno a su país de origen.

En conclusión, aunque sea un patógeno raro en nuestro medio, sería aconsejable incluir a *C. gloeosporioides* en el diagnóstico diferencial de cualquier queratitis infecciosa secundaria a un traumatismo con material vegetal, evitando así una demora en el tratamiento antifúngico que ocasione complicaciones de cierta gravedad.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Letter to the Editor

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Breast abscess due to *Trueperella bernardiae* and *Actinotignum sanguinis*

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Sir,

Trueperella bernardiae is a facultative anaerobic gram-positive coccobacillus which is part of the normal microbiota of human skin and the oropharynx. This microorganism has been reported in only few cases of human infection, especially in wound and prosthetic joint infections [1-3]. On the other hand, *Actinotignum sanguinis* is a small facultative anaerobic gram-positive rod which forms part of the normal urogenital flora. They grow slowly and especially under anaerobic or in atmosphere enriched with CO_2. *Actinotignum* species have been rarely associated with urinary tract infections [4] and bacteremia [5].

We report a rare case of breast abscess caused by these two pathogens. To our best knowledge, this is the first report of breast abscess caused by these two microorganisms together. Table 1 shows all published cases of *T. bernardiae* and/or *A. sanguinis* infections.

A 39-year-old woman refers ten days history of pain and local swelling in her right breast. Her clinical history was unremarkable, and she was in treatment with cloxacillin (1g /8h) for seven days. The abscess was drained by puncture and the fluid obtained sent to the microbiology laboratory for culture. The sample was inoculated in blood agar (both aerobic and anaerobic) (BD Columbia Agar 5% Sheepblood®, Becton Dickinson) chocolate agar (BD Choco Agar, Becton Dickinson), thioglycolate broth (BD™ Fluid Thioglycolate Medium, Becton Dickinson), Mannitol agar (BD Mannitol Salt, Becton Dickinson) and MacConkey (BD Mac Conkey II, Becton Dickinson).

Gram stain of the abscess showed gram positive bacilli, and on the second day of incubation two types of colonies grew on both aerobic and anaerobic blood agar and chocolate agar. They were identified with MALDI-TOF MS (Bruker Biotyper, Billerica, MA, USA) as *Trueperella bernardiae* (score 2,13) and *Actinotignum sanguinis* (score 2,22). The MIC of different antibiotics was carried out by the E-test method in Brucella agar supplemented with hemin, vitamin K1 and lacked sheep blood incubated at 37°C. As no specific clinical breakpoints have been established for *T. bernardiae* and *A. sanguinis*, we used the EUCAST PK/PD (non-species related) clinical breakpoints. *T. bernardiae* was susceptible to ciprofloxacin (0.5 mg/L), gentamicin (1.5 mg/L), imipenem (0.016 mg/L), linezolid (0.25 mg/L), penicillin (0.032 mg/L), rifampicin (<0.016 mg/L), tetracycline (0.094 mg/L), vancomycin (0.19 mg/L), and resistant to trimethoprim-sulfamethoxazole (>32 mg/L), clindamycin (1 mg/L) and erythromycin (1 mg/L). *A. sanguinis* was susceptible to ciprofloxacin (0.5 mg/L), gentamicin (<0.016 mg/L), linezolid (0.047 mg/L), penicillin (<0.016 mg/L), vancomycin (<0.016 mg/L), and resistant to trimethoprim/sulfamethoxazole (>32 mg/L), clindamycin (>256 mg/L) and erythromycin (>256 mg/L). Antimicrobial treatment was changed to amoxicillin-clavulanic (875/125 mg/8h) for 10 days, and at three months of follow-up the woman was asymptomatic.

The diagnosis of *T. bernardiae* and *A. sanguinis* is based on culture of an adequate sample. Identification using conventional laboratory methods could be difficult and when isolated in clinical samples these microorganisms are usually not identified, especially *T. bernardiae* due to it coryneform aspect. The recent introduction of mass spectrometry for routine analysis in the clinical laboratories may help in the final identification of these pathogens, and can help to know the true incidence of infections with these bacteria. For this reason it is highly recommended to use the MALDI-TOF method for identification.

Overall, drug resistance in *T. bernardiae* and *A. sanguinis* may be not considered still a problem. According to different studies, *T. bernardiae* was susceptible to all antimicrobials tested, except to ciprofloxacin [6, 7]. On the other hand, the genus *Actinotignum* has demonstrated high

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Table 1 **Cases with infection caused by *Trueperella bernardiae* and/or *Actinotignum sanguinis.***

Patient (year of publication) Author	Age (years)/sex	Microorganism	Localization of infection	Microbiological diagnosis
1 (1996) Ieven M	69/M	*Actinomyces bernardiae*	Urinary tract	Urine, perirenal abscess and necrotic tissue cultures Blood culture (+)
2 (1998) Adderson EE	19/F	*Arcanobacterium bernardiae*	Hip	Synovial fluid culture
3 (1998) Lepargneur JP	75/M	*Arcanobacterium bernardiae*	Urinary tract	Urine culture
4 (2009) Bemer P	63/M	*Arcanobacterium bernardiae* *Staphylococcus. aureus*	Knee	Intraoperatory specimen
5 (2009) Loïez C	78/M	*Arcanobacterium bernardiae*	Hip prosthesis	Intraoperatory specimen
6 (2010) Sirijatuphat R	60/M	*Arcanobacterium bernardiae*	Kidney Pleura	Perinephric drainage culture
7 (2010) Clarke TM	62/F	*Arcanobacterium bernardiae* *Morganella morganii*	Skin abscess	Abscess and tissue cultures
8 (2011) Weitzel T	72/F	*Arcanobacterium bernardiae*	Blood	Blood cultures (+)
9 (2013) Otto MP	78/F	*Trueperella bernardiae* *Bacteroides fragilis* *Enterococcus avium*	Wound	Ulcer culture Blood cultures (+)
10 (2015) Parha E	68/F	*Trueperella bernardiae* *Peptoniphilus harei*	Brain	Abscess culture
11 (2015) Schneider UV	45/M	*Trueperella bernardiae* *Peptoniphilus lacrimalis*	Skin ulcers	Ulcer tissue culture
12 (2016) Rattes ALR	24/F	*Trueperella bernardiae*	Wound	Umbilical secretion culture
13 (2016) Gilarranz R	73/F	*Trueperella bernardiae*	Knee prosthesis	Synovial fluid Blood cultures (+)
14 (2016) VanGorder B	77/F	*Trueperella bernardiae*	Skin	Drainage abscess culture
15 (2017) Cobo F	69/F	*Trueperella bernardiae*	Wound	Wound secretion culture
16 (2017) Cobo F	70/F	*Trueperella bernardiae* *Escherichia coli*	Inguinal granuloma	Wound secretion culture
17 (2017) Pedersen H.	NR	*Actinotignum sanguinis*	Blood	Blood cultures (+)
18 (PR/2018) Calatrava E	39/F	*Trueperella bernardiae* *Actinotignum sanguinis*	Breast abscess	Drainage abscess culture

M: male; F: female; NR: not reported; PR: present report

susceptibility to ß-lactams and vancomycin [5]. In other study, 12 isolates of *Actinotignum* spp. were susceptible to penicillin [8]. However, treatment of choice for these microorganisms has not been clearly established due to the scarcity of data and the absence of breakpoints for these bacteria. Further studies are necessary in order to establish the best therapeutic option.

In summary, it is still unknown the true clinical implications of *T. bernardiae* and *A. sanguinis*, but with the generalized use of MALDI-TOF in the majority of laboratories, the diagnosis of these pathogens implicated in human infections probably will increase. Microbiologists should be aware of these microorganisms especially if the new diagnostic techniques area applied.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest

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Carta al Director

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Tratamiento prolongado con dalbavancina en infección protésica de cadera por *Staphylocuccus epidermidis* resistente a meticilina

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Sr. Editor: Dalbavancina es un antibiótico bactericida del grupo de los lipoglucopeptídicos aprobado en ficha técnica para el uso en infecciones bacterianas de piel y partes blandas en adultos. Debido a su larga vida media (372 horas), su posología es de 1.500 mg administrados como perfusión única o 1.000 mg, seguidos de 500 mg una semana después. Esta característica farmacocinética, abre nuevas puertas en cuanto al manejo extrahospitalario de los pacientes [1,2].

A continuación, exponemos un caso de infección protésica producida por *Enterobacter cloacae* y *Staphylococcus epidermidis* tratada con dalbavancina en combinación con ciprofloxacino y rifampicina, en condiciones diferentes a las aprobadas por ficha técnica.

Mujer de 84 años con antecedentes de poliartrosis, hipertensión arterial, cardiopatía isquémica, infarto agudo de miocardio y trombocitopenia esencial.

En febrero de 2017 fue sometida a una intervención de prótesis total de cadera (PTC) derecha, a los dos meses de la intervención, la herida quirúrgica seguía sin cicatrizar y se aisló *Escherichia coli* en ella y en líquido articular. La paciente continuó en seguimiento por infección activa hasta julio de 2018, en la que tras fractura periprotésica se decide recambio en un tiempo de la PTC y toma de muestra quirúrgica. En las muestras, se aisló *E. cloacae* sin ningún mecanismo de resistencia adquirido y *S. epidermidis*, cuya concentración mínima inhibitoria (CMI) para cada antibiótico fue de: sensible a gentamicina (CMI ≤ 0,5 mg/L), teicoplanina (CMI = 4 mg/L), vancomicina (CMI = 1 mg/L), rifampicina (≤ 0,5 mg/L) y linezolid (CMI = 1 mg/L); resistente a oxacilina (CMI ≥ 4 mg/L), clindamicina (CMI ≤ 0,25 mg/L), levofloxacino (CMI ≥ 8 mg/L) y trimetoprim/sulfametoxazol (CMI = 80 mg/L).

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Se decide empezar tratamiento con: vancomicina 1.000 mg cada 12 horas intravenoso, ciprofloxacino 500 mg cada 12 horas oral y rifampicina 300 mg en por la mañana 600 mg por la noche oral durante 4 meses. Tras 4 semanas de ingreso se decide dar de alta a un centro sociosanitario y el tratamiento es modificado a linezolid 600 mg cada 12 horas oral y rifampicina 600 mg cada 24 horas oral, manteniendo la misma pauta de ciprofloxacino.

A las 4 semanas la paciente presentó alteraciones hematológicas (hemoglobina 8 g/dL, hematocrito 23,8 %, plaquetas 44.000 u/L) debidas al uso de linezolid. Por tanto, se solicitó al Servicio de Farmacia el uso de dalbavancina a dosis inicial de 1.000 mg intravenosa seguido de 500 mg semanales intravenosas durante 3 semanas, junto con el tratamiento ya existente con ciprofloxacino y rifampicina. Tras finalizar los ciclos de antibióticos, la paciente presentó mejoría hematológica (hemoglobina 10g/dL, hematocrito 33,7%, plaquetas 88.000 u/L), la herida cicatrizó por completo, la PCR descendió (20,52 mg/dL al inicio y 2,57 mg/dL cinco días después de finalizar el tratamiento) y desaparecieron los signos de infección.

Las infecciones de prótesis articulares, aunque infrecuentes, son unas de las complicaciones más graves de la artroplastia, generando reingresos, uso prolongado de antibióticos e incluso reintervenciones quirúrgicas, como en el caso de nuestra paciente. En nuestro entorno, la incidencia de infecciones protésicas de cadera es del 1%, siendo los microorganismos más predominantes los cocos grampositivos (30-40% los estafilococos coagulasa negativa y 12-23% *S. aureus*) [3,4].

En los estudios pivotales, en términos de no inferioridad, dalbavancina ha demostrado ser igual de eficaz respecto a los comparadores (linezolid/vancomicina) [2].

Aunque la indicación de dalbavancina en ficha técnica es en infección aguda de piel y partes blandas, ya se ha puesto de manifiesto en diversos estudios, el uso de la misma, en infecciones protésicas y del tejido osteoarticular, usando posologías más prolongadas que las aprobadas en dicha ficha [5-7].

En nuestro caso, utilizamos la combinación de dalbavancina con ciprofloxacino y rifampicina, debido a los antecedentes de infección de la paciente tras la primera intervención y al aislamiento de dos microorganismos (*E. cloacae y S. epidermidis* resistente a meticilina) tras el recambio. En los estudios publicados, utilizan dalbavancina en monoterapia con una posología prolongada, pero en infecciones de un solo microorganismo; *S. aureus* resistente a meticilina en osteomielitis en un caso y en el otro *S. epidermidis* resistente a oxacilina en infección de prótesis de rodilla [5,7].

Con nuestra experiencia podemos confirmar que dalbavancina es una buena alternativa para infecciones protésicas que requieran antibióticos de uso prolongado, como alternativas a otros antibióticos comercializados, ya sea bien por efectos adversos de los mismos o por mejorar el manejo extrahospitalario del paciente.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Letter to the Editor

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Is it reasonable to perform Fecal Microbiota Transplantation for recurrent *Clostridium difficile* Infection in patients with liver cirrhosis?

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Sir,

Fecal Microbiota Transplantation (FMT) is a successful procedure that in recent years has been accelerated and oversimplified, to the point that in the near future it will be probably used in more patients and much earlier in the natural history of CDI [1, 2].

Advanced liver cirrhosis (LC) is a well-known cause of bacterial translocation and bacteremia [3-5] and also in LC patients CDI is frequent, severe and recurrent [6]. Even when LC is not a formal contraindication of FMT, the number of patients with LC who underwent a FMT that have been reported in the medical literature are very scarce and the few episodes reported appear only listed and not described in detail [7].

We report four cases of LC patients with multiple recurrent CDI who received FMT and their clinical outcome (table 1).

Case 1

A 72-year-old woman with LC and hepatocellular carcinoma due to Hepatitis C virus (HCV) had a MELD score of 13 and was classified as Child Pugh C. She had suffered hepatic encephalopathy several times as a result to different infections and received several courses of antimicrobial agents over the course of three months. Other comorbid conditions included multifactorial pancytopenia, esophageal variceal bleeding and severe malnutrition.

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In January 2015, she had a first episode of CDI caused by a strain of ribotype 027 which was treated with full dose oral vancomycin, followed by vancomycin tapering. She had four more recurrences and the patient received vancomycin tapering in the first, third and fourth recurrences and fidaxomicin in the second one. Finally, the patient ended up with continuous low doses of vancomycin to control the diarrhea, to enable her to perform her basic activities of daily life. She received a FMT by colonoscopy from which she recovered uneventfully, without any further episodes of CDI during the five months of follow up, with a clear-cut increase in her quality of life.

Case 2

A 60-year-old woman had cirrhosis and hepatocellular carcinoma due to HCV. She had a MELD score of 9 and was classified as Child Pugh C. She also suffered hepatic encephalopathy. Her first episode of 027 CDI was treated with vancomycin tapering. She had a first recurrence that was treated with fidaxomicin and the second one was treated with vancomycin, followed by a FMT via colonoscopy. Three days after the FMT, she developed a single episode of fever with *Escherichia coli* bacteremia without a clear focus of origin other than bacterial translocation. She received ceftriaxone for 10 days with a favorable outcome and no further recurrences of CDI were detected after eleven months follow-up. It should be noted that the patient never had episodes of bacteremia or spontaneous bacterial peritonitis previously.

Case 3

A 57-year-old man had alcoholic cirrhosis with a MELD score of 9 and was classified as Child Pugh B. He had suffered gastrointestinal bleeding due to esophageal varices. In April 2017, he had a Fournier´s gangrene requiring surgery and received long-term antibiotics. He had his first episode of CDI treated with metronidazole; subsequently, he had four recurrences which were treated with metronidazole, vancomy-

Table 1 **Clinical cases**

Case	Age (years)	Sex	Causes	Comorbidities	Child-Pugh score	MELD score	Ribotype	Number of recurrences	Treatment received	Route of administration	Complications	Follow up (months)
1	72	F	Hepatitis C virus	Hepatocellular carcinoma, Pancytopenia, Esophageal variceal bleeding, Encephalopathy, Malnutrition	C	13	27	4	Vancomycin tapering, Fidaxomicin	Colonoscopy	No	5
2	60	F	Hepatitis C virus	Encephalopathy episodes, Hepatocellular carcinoma	C	19	27	2	Vancomycin tapering, Fidaxomicin	Colonoscopy	*Escherichia coli* bacteremia	11
3	57	M	Alcohol	Esophageal varices	B	9	no 027	4	Metronidazole, Vancomicycin tapering, Fidaxomicin	Colonoscopy	No	4
4	84	F	Hepatitis C virus	Hepatocellular carcinoma , Hepatopulmonar syndrome, Cholangitis	C	11	no 027	5	Metronidazole, Vancomycin tapering, Fidaxomicin	Nasogastric tube	Death due to collangitis	N.A.

cin, fidaxomicin and vancomycin tapering respectively. In the last recurrence, he received a FMT via colonoscopy. No complications have been seen during the recent four months of follow-up.

Case 4

An 84 year-old woman with LC and hepatocellular carcinoma had a MELD score of 11 and was classified as Child Pugh C. She also suffered from hepatopulmonar syndrome and choledocolitiasis with several cholangitis episodes.

In June 2013, she had a first episode of CDI that was treated with metronidazole. She had six recurrences; three were treated with vancomycin standard dose, the fourth with fidaxomicin, the fifth with vancomycin tapering and in the last one treated with vancomycin followed by FMT by nasogastric tube. Seven days later, the patient died due to a new episode of cholangitis but blood cultures had not been obtained.

Advanced liver cirrhosis (LC) was present as an underlying condition in approximately 25% of our patients who received a FMT.

Out of our four cases with advanced LC that were treated with FMT, in our report, two patients had severe complications post procedure and one of them died.

There is no question that the severity of the previous underlying conditions of our four candidates can explain episodes of superinfection at any time which may endanger their lives.

Bacterial translocation and bacteremia is relatively common in advanced LC without the contribution of FMT but the coincidence of FMT in our second patient is a cause of concern. We were surprised by the very low number of LC patients that appear in large series of patients with FMT. We speculate that the risk aversion towards some complications seen in some of our patients may have accounted for a reluctance of some physicians to perform the FMT.

Our literature research highlights one clinical trial that used FMT in LC patients to treat hepatic encephalopathy. However, it is not applicable to our possible future patients, as the methodology was not designed to treat CDI, used a small quantity of stool and an antibiotic prophylaxis prior to FMT [8].

Bacteremia, as a complication of FMT has been reported only anecdotally [3].

Cholangitis after FMT in the fourth patient, it is quite possible that it was a mere coincidence. However, focusing in the second case, a proven episode of superinfection out of our four cases appears to be striking.

As a contrast to our concerns, the three cases who survived the FMT, were free of recurrent CDI episodes in the ongoing follow up periods of eleven, five and one months.

Despite the fact that the advanced LC is not a formal contraindication of FMT, this report is advisory in its intent and

recommends the need for a careful follow up with a systematic review of complications of FMT in cirrhotic patients.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

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