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Brief report

Clinical features and outcomes of bacteraemia due to OXA-48-like carbapenemase-producing *Klebsiella pneumoniae* in a tertiary hospital[☆]

Ana Madueño^{a,*}, Jonathan González-García^b, María del Mar Alonso Socas^c,
María Antonia Miguel Gómez^a, María Lecuona^{a,d}

^a Servicio de Microbiología y Control de la Infección, Complejo Hospitalario Universitario de Canarias, La Laguna (Santa Cruz de Tenerife), Spain

^b Servicio de Farmacia, Complejo Hospitalario Universitario de Canarias, La Laguna (Santa Cruz de Tenerife), Spain

^c Sección de Enfermedades Infecciosas, Servicio de Medicina Interna, Complejo Hospitalario Universitario de Canarias, La Laguna (Santa Cruz de Tenerife), Spain

^d Departamento de Medicina Preventiva y Salud Pública, Universidad de La Laguna, La Laguna (Santa Cruz de Tenerife), Spain



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ABSTRACT

Introduction: Limited therapeutic options and high mortality make the management of OXA-48-like carbapenemase-producing *Klebsiella pneumoniae* (KPOXA-48) bacteraemia complicated. The aim of the study was to describe the clinical characteristics of KPOXA-48 bacteraemia between October 2013 and December 2016.

Material and methods: The variables to analyse were retrospectively collected from medical records. Carbapenemase production was confirmed by phenotypic and molecular methods.

Results: A total of 38 patients with bacteraemia were included, mainly classified as hospital-acquired ($n=31$). The majority of cases were secondary bacteraemia ($n=26$), most commonly arising from the urinary tract ($n=11$). All isolates presented a multidrug-resistant profile with the extended spectrum beta-lactamase CTX-M-15 and the carbapenemase OXA-48-like production. The crude mortality rate with adequate targeted antibiotic therapy was 0%, rising to 55% with inadequate treatment ($p=0.0015$).

Conclusions: This study highlights the importance of identifying this resistance mechanism, the patient factors, type of bacteraemia and adequacy of antibiotic therapy in the outcome of bacteraemia.

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Características y evolución clínica de las bacteriemias por *Klebsiella pneumoniae* productora de carbapenemasa tipo OXA-48 en un hospital de tercer nivel

RESUMEN

Introducción: El manejo de las bacteriemias por *Klebsiella pneumoniae* productora de carbapenemasa del tipo OXA-48 (KPOXA-48) es complicado por las escasas opciones terapéuticas y la elevada mortalidad. El objetivo del estudio fue describir las características clínicas de bacteriemia por KPOXA-48 entre octubre de 2013 y diciembre de 2016.

Material y métodos: Se recogieron retrospectivamente de las historias clínicas las variables para analizar. La producción de carbapenemasas se confirmó por métodos fenotípicos y moleculares.

Palabras clave:

Klebsiella pneumoniae

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* Corresponding author.

E-mail address: ana-madueno@hotmail.com (A. Madueño).

Resultados: Se incluyeron 38 pacientes con bacteriemia, mayoritariamente de origen nosocomial ($n = 31$). Un alto porcentaje de las bacteriemias ($n = 26$) fueron secundarias, principalmente de origen urinario ($n = 11$). Todos los aislamientos eran multirresistentes con producción de la beta-lactamasa de espectro extendido CTX-M-15 y carbapenemasa del tipo OXA-48. La mortalidad bruta con antibioterapia dirigida adecuada fue del 0% y la inadecuada del 55% ($p = 0,0015$).

Conclusiones: Se pone de manifiesto la importancia de identificar este mecanismo de resistencia, los factores del paciente, el tipo de bacteriemia y la adecuación de la estrategia terapéutica en la evolución clínica.

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Introduction

Though not very common, bacteraemia is a clinical entity associated with high morbidity and mortality.¹ The problem of multidrug-resistant microorganisms has been added to this. Notable among them is the rapidly spreading carbapenemase-producing *Klebsiella pneumoniae*.² At present, inter-regional spread is occurring in Spain, with a predominance of OXA-48 (KPOXA-48) and VIM carbapenemase-producing *K. pneumoniae*.³ These often acquire a profile of multidrug resistance⁴ and therefore are associated with high rates of treatment failure and mortality. These rates approach 50% in cases of bacteraemia.⁵

The objective of this paper is to report the clinical, epidemiological, microbiological and therapeutic characteristics as well as the gross intrahospital mortality of patients with KPOXA-48 bacteraemia diagnosed in a tertiary hospital.

Materials and methods

Background

This retrospective study was conducted at the Complejo Hospitalario Universitario de Canarias (Tenerife, Spain), in a tertiary hospital with a reference population of 446,253 inhabitants. Since the first KPOXA-48 outbreak in late 2013, intrahospital spread has been clonal. KPOXA-48 is now endemic. Since then, a surveillance programme⁴ consisting of rectal sampling has been applied in patients hospitalised in units with at least one positive case and systematically in intensive care unit admissions.

Study population

All adult patients (>18 years of age) with bacteraemia due to KPOXA-48 were enrolled between October 2013 and December 2016 and the first episode of bacteraemia due to this same microorganism was considered. In addition, variables were collected from the patients' medical histories to evaluate their influence on the patients' clinical courses.

Bacteraemia was classified as nosocomial or community-acquired. Source of infection was defined according to the criteria of the Centers for Disease Control.⁶

Based on the current recommendations,⁷ adequate antibiotic treatment was defined as the use of two antibiotics active *in vitro* including a carbapenem with an MIC ≤ 8 mg/l. Inadequate treatment was defined as the administration of a single antimicrobial or combination therapy when none or just one of the antimicrobials was active *in vitro*. Similarly, treatment was considered inadequate if the doses used were lower than those recommended based on the patient's kidney function.

Microbiological study

Samples were processed using the BacT/ALERT[®] automatic blood culture analyser (bioMérieux, Marcy-l'Étoile, France). Identification and antibiogram preparation were done with the VITEK-2[®] system (bioMérieux, Marcy-l'Étoile, France). Next, carbapenem susceptibility was confirmed using the gradient diffusion technique, and carbapenemase production was confirmed using the phenotypic method of discs and inhibitors. The susceptibility study was performed in accordance with the criteria of the Clinical and Laboratory Standards Institute.⁸ Finally, the Centro Nacional de Microbiología [Spanish National Centre for Microbiology] (Instituto de Salud Carlos III, Madrid) detected carbapenemase and broad-spectrum β -lactamase genes using polymerase chain reaction.

Statistical analysis

Continuous variables were compared with the Mann–Whitney *U* method and categorical variables were compared using the chi-squared test or Fisher's exact test, as applicable. A *p* value <0.05 was considered statistically significant. All data were analysed with the SPSS 17.0 statistical program (IBM-SPSS Inc., Armonk, NY, United States).

Results

Clinical and epidemiological characteristics

The study enrolled 38 patients with a mean age of 66 years. Of these patients, 89% (34/38) had rectal colonisation by KPOXA-48. In addition, 68% (26/38) had at least one underlying disease. The patients had been admitted mainly to medical and surgical units when they were diagnosed with bacteraemia. Gross intrahospital mortality was 37%. The mean number of days between the first positive blood culture and the date of death was 18. Risk factors for developing bacteraemia included the use of devices such as a urinary catheter or a central venous catheter (Table 1).

Bacteraemia was mainly nosocomial (32/38; 84%), and secondary bacteraemia was mainly of urinary origin (11/38; 29%). All patients with community-acquired bacteraemia had been admitted in the past three months, two of which were institutionalised.

Microbiological characteristics

All isolates were *bla*_{OXA-48} carbapenemase-producing and CTX-M-15 broad-spectrum β -lactamase-producing bacteria. All had a profile of multidrug resistance, with the exception of one, identified as pan-resistant.⁹ In general, the most active antibiotics were colistin, amikacin and gentamicin (Table 2). Against 30 isolates, the MIC of at least one carbapenem was ≤ 8 mg/l: imipenem ($n = 28$; 74%), meropenem ($n = 16$; 44%) and ertapenem ($n = 7$; 18%).

Table 1Characteristics of patients with bacteraemia due to OXA-48-positive *K. pneumoniae* during hospitalisation.

Demographics	Total (n = 38)	Patients who survived (n = 24)	Patients who died ^a (n = 14)
Age, years, mean ± SD	66 ± 15	69 ± 14	66 ± 16
Male gender, n (%)	25 (66)	17 (71)	8 (57)
Institutionalisation, n (%)	3 (8)	3 (12)	0 (0)
Prior hospital admission, n (%)^b	23 (61)	14 (58)	9 (64)
Hospitalisation unit, n (%)			
Medical	15 (39)	8 (33)	7 (50)
Intensive care	8 (21)	3 (12)	5 (36)
Surgical	15 (39)	13 (54)	2 (14)
Days of hospital stay, mean ± SD^c	53.5 ± 41.6	60.6 ± 48.1	41.7 ± 25.1
Days to bacteraemia, mean ± SD	29.8 ± 46.2	33.1 ± 55.7	24.2 ± 22.8
ICU admission (%)^d	7 (18)	3 (12)	4 (29)
Comorbidities, n (%)			
Neoplasm	14 (37)	9 (38)	5 (36)
Hepatitis/cirrhosis	3 (8)	2 (8)	1 (7)
Chronic kidney disease	7 (18)	5 (21)	2 (14)
Diabetes mellitus	14 (37)	12 (50)	2 (14)
Chronic obstructive pulmonary disease	2 (5)	1 (4)	1 (7)
Charlson index, mean ± SD	4 ± 2.4	4 ± 2.6	4 ± 1.9
Risk factors, n (%)			
Surgery ^e	16 (42)	10 (42)	6 (43)
Central venous catheter	27 (71)	16 (67)	11 (79)
Mechanical ventilation	9 (24)	4 (17)	5 (36)
Urinary catheter	31 (82)	19 (79)	12 (86)
Origin of bacteraemia, n (%)			
Primary	5 (13)	3 (12)	2 (14)
Catheter-related	7 (16)	6 (25)	1 (7)
Secondary	26 (71)	15 (62)	11 (78)
Urinary	11 (43)	9 (60)	2 (18)
Surgical	4 (15)	2 (13)	2 (18)
Respiratory	4 (15)	2 (13)	2 (18)
Intra-abdominal	4 (15)	1 (7)	3 (28)
Other	3 (12)	1 (7)	2 (18)
Empirical antibiotic treatment (n = 34) n (%)			
Adequate	18 (53)	13 (72)	5 (28)
Inadequate	16 (47)	9 (56)	7 (44)
Targeted antibiotic treatment (n = 34)^f n (%)			
Adequate	12 (35)	12 (100)	0 (0)
Inadequate	22 (65)	10 (45)	12 (55)

^p Value not significant for all comparisons, except for adequate vs inadequate targeted antibiotic treatment ($p = 0.0015$).^a Gross intrahospital mortality.^b Three months before the bacteraemia episode.^c One patient excluded due to ongoing hospital stay at the time of the study.^d During or immediately after bacteraemia.^e 30 days before bacteraemia.^f Four patients were excluded because they did not receive antibiotic treatment, either because they died before the result of the blood culture was received ($n = 2$) or because they were considered to have transient bacteraemia ($n = 2$).**Table 2**Antimicrobial susceptibility of OXA-48-positive *K. pneumoniae* isolates causing bacteraemia.

Antibiotics	Susceptibility, n (%)	MIC range (mg/l)	MIC ₅₀ (mg/l)	MIC ₉₀ (mg/l)
Colistin (n = 37)	31 (84)	0.125 to ≥16	≤0.5	≤0.5
Fosfomycin (n = 34)	8 (24)	≤16 to ≥256	64	≥256
Tigecycline (n = 38)	11 (29)	≤0.5 to ≥8	4	≥8
Imipenem ^a (n = 38)	6 (16)	0.25 to ≥32	4	≥16
Meropenem ^a (n = 37)	6 (17)	0.5 to ≥32	16	≥32
Ertapenem ^a (n = 38)	0 (0)	1 to ≥32	≥16	≥32
Amikacin (n = 36)	26 (72)	≤2 to ≥64	4	≥64
Gentamicin (n = 38)	27 (71)	≤1 to ≥16	≤1	≥16
Tobramycin (n = 30)	3 (10)	1 to ≥16	≥16	≥16
Co-trimoxazole ^a (n = 38)	0 (0)	≤0.02 to >32	≥32	≥32
Ciprofloxacin (n = 38)	0 (0)	1 to ≥4	≥4	≥4

^a Results obtained using gradient diffusion method.

Treatment

In 53% of cases, empirical antibiotic treatment was adequate. Targeted antibiotic treatment was adequate in 35% of patients and inadequate in 65%. Intrahospital mortality was 55% (12/22) in the group of patients in which targeted antibiotic therapy had been inadequate; no patient died with adequate targeted treatment (0/12) ($p = 0.0015$) (Table 1).

Discussion

There are few studies on experience with KPOXA-48 bacteraemia. This study provides new data on the clinical, epidemiological, microbiological and therapeutic characteristics of KPOXA-48 bacteraemia in a hospital endemic context.

Overall mortality in infections due to carbapenemase-producing enterobacteriaceae (CPE) is generally high.^{5,10} However, the mortality data published do vary. For example, in a Spanish study,¹¹ mortality during admission for bacteraemia due to OXA-48-producing enterobacteriaceae was 65%. Recently, a meta-analysis⁵ on infections caused by carbapenemase-producing *K. pneumoniae* placed gross mortality in bacteraemia at 54.30% (range: 47.51–61.02). In addition, mortality was linked to factors concerning the host, infection and antibiotic treatment.¹²

In our study, gross intrahospital mortality was 37%, which is lower than the data published. This could be due to various factors. First, our patients had few comorbidities with no serious underlying diseases and moderately serious infection. Second, the source of infection in our bacteraemia cohort was predominantly with low inoculum or in contexts in which management of the focus could be achieved.

Definitive antibiotic treatment, together with management of the focus of infection and prompt establishment of effective empirical antibiotic treatment, are the factors that determine the rate of mortality due to this type of infection.^{7,12} However, at present, definitive antibiotic treatment in serious infections due to carbapenemase-producing *K. pneumoniae* remains a subject of much debate due to a limited number of therapeutic options and a lack of randomised clinical trials. Recently, Paño-Pardo's working group¹³ demonstrated that combination therapy was associated with a lower mortality rate only in seriously ill patients, in whom the risk of mortality was very high. In less seriously ill patients, the use of combination therapy did not seem to show any advantages over monotherapy in terms of mortality. Contrasting with these results, our study found the use of combination therapy to be significantly associated with a lower mortality rate.

Regarding microbiological characteristics, in accordance with other case series published,^{11,14} our isolates had high resistance *in vitro* to all antibiotics; colistin, amikacin and gentamicin had the highest percentages of activity. In addition, awareness of the risk factors associated with CPE infections would aid in improving prevention and clinical management. Consistent with the findings of other authors,^{14,15} our patients had a long hospital stay, use of invasive procedures, prior surgery and KPOXA-48 rectal colonisation, which aided in guiding empirical treatment.

The limitations of the study are those inherent to its retrospective design and small number of patients enrolled. In addition, survival might have been overestimated as follow-up was limited to the time of the hospital stay and as gross intrahospital mortality was analysed. Finally, the limited variables collected in relation to treatment response made it difficult to evaluate treatment efficacy.

In conclusion, this study shows how KPOXA-48 may be involved in bacteraemia of nosocomial origin. It demonstrates the importance of suspecting and identifying this mechanism of resistance, as well as the risk factors of the patient, the type of bacteraemia and the adequacy of the treatment strategy in the clinical course of bacteraemia. Similarly, taking into account the seriousness of the infection, the identification of carriers and the strengthening of infection management practices are vitally important for preventing the spread of these microorganisms.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

- Wheeler AP, Bernard GR. Treating patients with severe sepsis. *N Engl J Med*. 1999;340:207–14.
- Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. *Lancet Infect Dis*. 2013;13:785–96.
- Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DL. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. *Euro Surveill*. 2015;20, <http://dx.doi.org/10.2807/1560-7917.ES.2015.20.45.30062>.
- Comunidad de Madrid. Plan de prevención y control frente a la infección por enterobacterias productoras de carbapenemasas (EPC) en la Comunidad de Madrid. Available from: http://www.madrid.org/cs/Satellite?blobcol=urldata&blobheader=application%2Fpdf&blobheadername1=Content-Disposition&blobheadername2=cadena&blobheadervalue1=filename%3DPLAN+PREVENCIÓN+Y+CONTROL+EPC+CM.v1_sept+2013.pdf&blobheadervalue2=language%3Des%26site%3DPortalSalud&blobkey=id&blobtable=MungoBlobs&blobwhere=1352838664739&ssbinary=true [accessed 10.04.17].
- Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant *Klebsiella pneumoniae*. *Ann Clin Microbiol Antimicrob*. 2017;16:18.
- Definitions S. CDC/NHSN surveillance definitions for specific types of infections; 2016. Available from: <http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef.current.pdf> [accessed 10.04.17].
- Rodríguez-Baño J, Cisneros JM, Cobos-Trigueros N, Fresco G, Navarro-San Francisco C, Gudiol C, et al. Study Group of Nosocomial Infections (GEIH) of the Spanish Society of Infectious Diseases, Infectious Diseases (SEIMC). Executive summary of the diagnosis and antimicrobial treatment of invasive infections due to multidrug-resistant Enterobacteriaceae. Guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). *Enferm Infecc Microbiol Clin*. 2015;33:338–41.
- Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. In: Twenty-fourth informational supplement. M100-S24. 2014.
- Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18:268–81.
- Viale P, Giannella M, Lewis R, Trecarichi EM, Petrosillo N, Tumbarello M. Predictors of mortality in multidrug-resistant *Klebsiella pneumoniae* bloodstream infections. *Expert Rev Anti Infect Ther*. 2013;11:1053–63.
- Navarro-San Francisco C, Mora-Rillo M, Romero-Gómez MP, Moreno-Ramos F, Rico-Nieto A, Ruiz-Carrascosa G, et al. Bacteraemia due to OXA-48-carbapenemase-producing Enterobacteriaceae: a major clinical challenge. *Clin Microbiol Infect*. 2013;19:E72–9.
- Paño Pardo JR, Serrano Villar S, Ramos Ramos JC, Pintado V. Infections caused by carbapenemase-producing Enterobacteriaceae: risk factors, clinical features and prognosis. *Enferm Infecc Microbiol Clin*. 2014;32 Suppl. 4:41–8.
- Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo JR, et al. REIPI/ESGBIS/INCREMENT Investigators. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. *Lancet Infect Dis*. 2017;17:726–34.
- Liu P, Li X, Luo M, Xu X, Su K, Chen S, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection: a meta-analysis. *Microb Drug Resist*. 2017. <http://dx.doi.org/10.1089/mdr.2017.0061>.
- Madueño A, González García J, Ramos MJ, Pedroso Y, Díaz Z, Oteo J, et al. Risk factors associated with carbapenemase-producing *Klebsiella pneumoniae* fecal carriage: a case-control study in a Spanish tertiary care hospital. *Am J Infect Control*. 2017;45:77–9.