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Clinical characteristics and outcome of bacteraemia caused by *Enterobacter cloacae* and *Klebsiella aerogenes*: more similarities than differences

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ABSTRACT

Objectives: The genus *Enterobacter* is a common cause of nosocomial infections. Historically, the most frequent *Enterobacter* species were those of *Enterobacter cloacae* complex and *Enterobacter aerogenes*. In 2019, *E. aerogenes* was re-classified as *Klebsiella aerogenes* owing to its higher genotypic similarity with the genus *Klebsiella*. Our objective was to characterise and compare the clinical profiles of bacteraemia caused by *E. cloacae* and *K. aerogenes*.

Methods: This 3-year multicentre, prospective cohort study enrolled consecutive patients with bacteraemia by *E. cloacae* or *K. aerogenes*. Baseline characteristics, bacteraemia features (source, severity, treatment), antibiotic susceptibility, resistance mechanisms and mortality were analysed.

Results: The study included 285 patients with bacteraemia [196 (68.8%) *E. cloacae* and 89 (31.2%) *K. aerogenes*]. The groups showed no differences in age, sex, previous use of invasive devices, place of acquisition, sources or severity at onset. The Charlson score was higher among patients with *E. cloacae* bacteraemia [2 (1–4) vs. 1 (0.5–3); $P = 0.018$], and previous antibiotic therapy was more common in patients with *K.*

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aerogenes bacteraemia (57.3% vs. 41.3%; $P = 0.01$). Mortality was 19.4% for *E. cloacae* and 20.2% for *K. aerogenes* ($P = 0.869$). Antibiotic susceptibility was similar for both species, and the incidence of multidrug resistance or ESBL production was low (6% and 5.3%, respectively), with no differences between species.

Conclusion: Bacteraemias caused by *E. cloacae* and *K. aerogenes* share similar patient profiles, presentation and prognosis. Patients with *E. cloacae* bacteraemia had more co-morbidities and those with *K. aerogenes* bacteraemia had received more antibiotics.

1. Introduction

The genus *Enterobacter* belongs to the family Enterobacteriaceae within the order Enterobacterales [1,2], and some of the species it includes have emerged in recent years as important nosocomial pathogens. *Enterobacter* species can cause many different infections, usually associated with invasive devices or procedures [3,4], and they are among the main aetiologies of nosocomial bloodstream infections (BSIs) [5–7]. Additionally, *Enterobacter* spp. are included in the ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp.) group, defined as the leading aetiologies of hospital-acquired infections caused by resistant pathogens [8].

Until recent taxonomic changes, the genus *Enterobacter* included 22 species sharing diverse phenotypic and genotypic features such as motility facilitated by flagella or the presence of an inducible constitutive AmpC β-lactamase [9]. Among these 22 species, the most frequent in the clinical setting (90–99% of cases) are those belonging to the *Enterobacter cloacae* complex and *Enterobacter aerogenes* [9,10]. However, *E. aerogenes* has recently been reclassified as *Klebsiella aerogenes* [9]. This taxonomic change was based on the genotypic characteristics of this species, as full-genome sequence analyses have revealed that the closest species was *Klebsiella pneumoniae* [9,11].

The new classification separates these species, which have usually been studied together in the clinical setting. Most clinical studies of *Enterobacter* infections have included both *E. cloacae* and *E. aerogenes* without looking for or describing relevant differences between the two [12–14]. Our group recently published the largest European cohort study of *Enterobacter* bacteraemias describing risk factors for the development of this infection and those associated with its mortality [7]. That study included patients with *E. cloacae* and *K. aerogenes* bacteraemia, but their clinical characteristics were not analysed separately. Given the new taxonomic classification, we believe that this analysis is relevant to clarify the potential impact of their genotypic differences on clinical features.

The objective of the present study was to characterise and compare the risk factors, clinical features and prognosis of BSIs caused by *E. cloacae* and *K. aerogenes.* Susceptibility to antibiotics and resistance mechanisms to cephalosporins and quinolones were also studied and compared.

2. Methods

2.1. Study design and patient selection

A multicentre, observational cohort study of consecutive cases of *E. cloacae* and *K. aerogenes* bacteraemia and a nested case–control study with the prospective recruitment of identified patients (post-hoc analysis [7]) was conducted in five Spanish university hospitals with a total of 5976 beds. The local ethics committee approved the study, waiving the requirement to obtain written informed consent owing to the observational nature of the research.

The study recruited all consecutive cases of *E. cloacae* and *K. aerogenes* bacteraemia in patients aged >14 years admitted to the participating hospitals during the 3-year study period. Only the first episode of bacteraemia was included for each patient. After the inclusion of each case, the first two patients with negative blood cultures and of the same sex, age (±10 years) and hospitalisation area were enrolled as controls. The only exclusion criterion for the control patients was a previous episode of BSI during their ongoing hospitalisation. Patients were identified prospectively based on the daily notification of consecutive positive blood cultures by each centre's microbiology department. Clinical information was obtained from electronic charts. Variables were recorded using a standardised form and all patients were followed-up for 30 days or until death or hospital discharge, whichever occurred first.

2.2. Variables and definitions

The following data were recorded: (i) demographic characteristics (age, sex, area of hospitalisation [medical, surgical or intensive care unit (ICU)] and hospital of origin); (ii) baseline clinical conditions, including underlying chronic diseases [heart failure, chronic obstructive pulmonary disease (COPD), diabetes mellitus, liver disease, chronic renal failure, cancer, solid-organ or bone marrow transplantation, human immunodeficiency virus (HIV) infection or other causes of immunosuppression such as neutropenia], Charlson comorbidity index [15] and McCabe index [16], previous antimicrobial therapy (in the preceding 14 days), previous chemotherapy (in the preceding 30 days), previous corticosteroid therapy (defined as ≥10 mg of prednisone or equivalent daily for >10 days), prior admission to an oncology unit or ICU during the ongoing hospital stay, and performance of one or more invasive procedures (insertion of venous catheter, urinary catheter or nasogastric tube; mechanical ventilation; performance of gastroscopy, colonoscopy, bronchoscopy or surgical procedures) during the preceding 10 days; and (iii) clinical variables, including place of acquisition [hospital (onset >48 h after admission or transfer from another hospital; BSIs associated with a surgical site infection if the operation took place within 30 days) [17], healthcare-related (within 48 h from admission and: BSI associated with an ambulatory diagnostic or therapeutic invasive procedure, or outpatients carrying an indwelling urinary catheter or a venous catheter, or patients on chronic dialysis or living in a nursing home) [18], or community (within 48 h from admission and not meeting criteria for hospital or healthcare-related acquisition)], source of the bacteraemia [18], severity at onset of bacteraemia (Pitt bacteremia score [19,20]), presence of sepsis or septic shock at onset of bacteraemia [21] and Acute Physiology and Chronic Health Evaluation (APACHE) II score for ICU patients [22], empirical or pathogen-directed treatment, appropriate empirical treatment (defined as the prescription of at least one antimicrobial active against the strain isolated in

Table 1
Local distribution [*n* (%)] of bacteraemia cases

Hospital of collection	*Enterobacter cloacae* ($n = 196$)	*Klebsiella aerogenes* ($n = 89$)	*P*-value
H. Bellvitge	66 (33.7)	24 (27.0)	0.129
H. Reina Sofía	19 (9.7)	4 (4.5)	
H. Virgen Macarena	21 (10.7)	18 (20.2)	
H. Virgen del Rocío	50 (25.5)	25 (28.1)	
H. Marques de Valdecilla	40 (20.4)	18 (20.2)	

blood cultures in the first 24 h following the onset of the BSI), length of hospital stay (from admission to death or hospital discharge), length of ICU stay (from ICU admission to ICU discharge or death) and mortality (death from any cause during the follow-up period).

2.3. Microbiological analysis

Enterobacter cloacae and *K. aerogenes* strains were identified and their antimicrobial susceptibility profile was determined according to each participating centre's clinical microbiology laboratory criteria. Isolates from each patient taken after their inclusion in the study were sent to the Virgen del Rocío University Hospital where the following analyses were performed: (i) identification by mass spectrophotometry using a microflex II system (Bruker Daltonik GmbH, Bremen, Germany), with a threshold >2.2 for identification at species level; and (ii) antimicrobial susceptibility testing by broth microdilution based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2011 methods and standard criteria [23]. Multidrug resistance was defined as described by Magiorakos et al. [24]. Several resistance mechanisms were studied: (i) the inductivity of AmpC was tested in all isolates using the cefoxitin–cefotaxime–imipenem antagonism test; (ii) an extended-spectrum β-lactamase (ESBL) phenotypic test was performed in strains with a minimum inhibitory concentration (MIC) of ≥0.25 mg/L, by comparing the MICs of cefotaxime, ceftazidime and cefepime alone and combined with clavulanic acid; and (iii) the genes *qnrA, qnrB, qnrC, qnrD, qnrS, aac(6′)-Ib*-cr, *qepA* and *oqxAB* were screened using a multiplex PCR-based technique and single PCR [25–27]. The amplicons obtained were sequenced.

2.4. Statistical analysis

Categorical variables were expressed as number of cases and percentage, and continuous variables as the median and interquartile range. A bivariate analysis was performed to compare the features of *E. cloacae* and *K. aerogenes* BSIs and the features of each species with their respective controls. Categorical variables were analysed using the χ^2 test or Fisher's test, as appropriate. For comparison of continuous variables, Student's *t*-test or Mann–Whitney *U*-test were used, as appropriate. A *P*-value of ≤0.05 was considered as the threshold for statistical significance. A multivariate analysis to identify risk factors for *E. cloacae* and *K. aerogenes* bacteraemia was performed by logistic regression, including only variables that were statistically significant in the univariate analysis and that did not have collinearity. Odds ratios and their respective 95% confidence intervals were calculated. All statistical analyses were performed using PASW 18.0 Statistics software (SPSS Inc., Chicago, IL, USA).

3. Results

The study included 285 patients, 196 (68.8%) with *E. cloacae* bacteraemia and 89 (31.2%) with *K. aerogenes* bacteraemia. Table 1 presents the distribution of cases by site. During the 3 years of the study, a year-over-year variation was observed, which was higher in the case of *E. cloacae*. With regard to the distribution of species by site, the *E. cloacae:K. aerogenes* ratio was approximately 2.5:1 in three of the participating hospitals, whereas it was 4.75:1 at Reina Sofía Hospital and 1.16:1 at Virgen Macarena Hospital. However, overall the species distribution in the different hospitals showed no significant differences.

Patient profiles were similar for most of the baseline conditions recorded, as shown in Table 2. However, patients with *E. cloacae* bacteraemia had more co-morbidities: they had a higher Charlson comorbidity index and the proportion of haemodialysis patients was also higher. Prior antibiotic therapy was more common in the group of patients with *K. aerogenes* bacteraemia. Regarding specific families of antibiotics, previous use of carbapenems was more common among patients with *K. aerogenes* bacteraemia, but no differences were found for the other groups of drugs.

The risk factor analysis for the acquisition of *E. cloacae* or *K. aerogenes* bacteraemia compared with their controls is provided in Tables 3a and 3b, respectively. An ultimately fatal or rapidly fatal category in the McCabe index, chronic haemodialysis, previous use of corticosteroids, previous ICU stay, invasive devices and previous antibiotic therapy were identified as independent risk factors for the acquisition of *E. cloacae* bacteraemia. For *K. aerogenes*, only previous ICU stay, invasive devices and previous antibiotic therapy were identified as independent risk factors for the development of bacteraemia.

There were no differences in the characteristics of *E. cloacae* and *K. aerogenes* bacteraemia episodes in terms of place of acquisition, source, severity and outcome (Table 4). The most common source for both groups was the use of a vascular catheter, followed by a source of unknown origin. Catheter-related *E. cloacae* bacteraemia was especially common in haemodialysis patients (75% of cases). There were no differences in severity or outcome between *E. cloacae* and *K. aerogenes* bacteraemia. Overall mortality was 19.6%, with no differences between patients with *E. cloacae* bacteraemia and those with *K. aerogenes* bacteraemia. Crude mortality among patients with *E. cloacae* infection was higher than mortality among control patients (19.4% vs. 13%; $P = 0.042$). Mortality did not vary significantly between patients with *K. aerogenes* bacteraemia and control patients (20.2% vs. 14%; $P = 0.195$).

Susceptibility to antibiotics and resistance mechanisms are summarised in Supplementary Table S1. A higher proportion of *K. aerogenes* isolates were susceptible to cefepime (84.3% vs. 73.5%; $P = 0.050$) and imipenem (93.3% vs. 83.7%; $P = 0.037$). Susceptibility profiles were similar for all of the other antibiotics tested. Multidrug resistance and ESBL production were uncommon and were homogeneous in both groups. Different plasmid-mediated quinolone resistance mechanisms were detected. The resistance patterns of the isolates exhibiting these mechanisms are summarised in Supplementary Table S2.

4. Discussion

The present study shows that the clinical behaviour of *E. cloacae* and *K. aerogenes* BSIs is very similar. This similarity contrasts with the microbiological differences that have led to the taxonomic reclassification of *E. aerogenes* to *K. aerogenes*. Several fea-

Table 2
Baseline clinical and demographic characteristics of patients with *Enterobacter cloacae* and *Klebsiella aerogenes* bacteraemia

Variable	*E. cloacae* (n = 196)	*K. aerogenes* (n = 89)	Bivariate analysis (P-value)	Multivariate analysis [OR (95% CI); P-value]
Age (years) [median (IQR)]	67.81 (56.75–77.43)	67.22 (52.84–77.03)	0.513	–
Female sex	70 (35.7)	26 (29.2)	0.282	–
McCabe UF/RF	78 (39.8)	25 (28.1)	0.057	–
Charlson comorbidity index [median (IQR)]	**2 (1–4)**	**1 (0.5–3)**	**0.025**	**0.86 (0.76–0.97); 0.018**
Diabetes mellitus	50 (25.5)	18 (20.2)	0.332	–
Chronic hepatopathy	87 (44.4)	46 (51.7)	0.252	–
COPD	26 (13.3)	12 (13.5)	0.960	–
Chronic heart failure	32 (16.3)	12 (13.5)	0.538	–
Chronic renal failure	108 (55.1)	44 (49.4)	0.374	–
Haemodialysis	**28 (14.3)**	**1 (1.1)**	**<0.001**	–
Solid-organ transplantation	12 (6.1)	3 (3.4)	0.405	–
HIV infection	2 (1.0)	1 (1.1)	1	–
Cancer	58 (29.6)	18 (20.2)	0.097	–
Haematological malignancy	16 (8.2)	3 (3.4)	0.199	–
Solid tumour	42 (21.4)	15 (16.9)	0.371	–
Neutropenia	10 (5.1)	4 (4.5)	1	–
Previous chemotherapy	20 (10.2)	5 (5.6)	0.261	–
Previous corticosteroids	22 (11.2)	7 (7.9)	0.385	–
Other causes of immunosuppression	6 (3.1)	1 (1.1)	0.441	–
Previous conditions or procedures during the ongoing hospital stay				
ICU stay	72 (36.7)	40 (44.9)	0.189	–
Stay in an oncology unit	17 (8.7)	6 (6.7)	0.579	–
Invasive procedure	152 (77.6)	75 (84.3)	0.192	–
Catheter insertion	156 (79.6)	72 (80.9)	0.798	–
Urinary catheter	107 (54.6)	48 (53.9)	0.918	–
Nasogastric tube	55 (28.1)	31 (34.8)	0.249	–
Mechanical ventilation	52 (26.5)	33 (37.1)	0.071	–
Gastroscopy	12 (6.1)	4 (4.5)	0.783	–
Colonoscopy	5 (2.6)	0 (0)	0.329	–
Bronchoscopy	3 (1.5)	0 (0)	0.554	–
Clean surgery	29 (14.8)	15 (16.9)	0.656	–
Contaminated surgery	20 (10.2)	15 (16.9)	0.113	–
Dirty surgery	14 (7.1)	4 (4.5)	0.600	–
Previous antibiotic therapy	**81 (41.3)**	**51 (57.3)**	**0.012**	**1.97 (1.18–3.29); 0.010**
Penicillins	45 (23.0)	27 (30.3)	0.184	–
Cephalosporins	24 (12.2)	13 (14.6)	0.582	–
Carbapenems	**11 (5.6)**	**11 (12.4)**	**0.048**	–
Quinolones	8 (4.1)	3 (3.4)	1	–
Other drugs	29 (14.8)	18 (20.2)	0.301	–
Length of stay prior to blood culture collection (days) [median (IQR)]	7 (1–16.75)	9 (1–22)	0.104	–

NOTE: Data are n (%) unless otherwise stated.
OR, odds ratio; CI, confidence interval; IQR, interquartile range; UF/RF, ultimately fatal/rapidly fatal; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit.

tures make this species phenotypically and genotypically closer to the *Klebsiella* genus, and various authors had proposed this taxonomic change since 1971. This species was finally reclassified in 2019 after obtaining cumulative results from full-genome sequence analysis [9].

With regard to risk factors for these infections, patients with *E. cloacae* bacteraemia had more co-morbidities, a higher Charlson index and a higher number were on chronic haemodialysis. On the other hand, patients with *K. aerogenes* bacteraemia had a higher exposure to previous antibiotic therapies, especially carbapenems. Both characteristics (co-morbidities and previous antibiotics) have been described as risk factors for the acquisition of *Enterobacter* spp. bacteraemia, including *E. cloacae* and *K. aerogenes* [28,29]. However, comparison of these cases with their controls showed that the most important risk factors for developing either *E. cloacae* or *K. aerogenes* bacteraemia were healthcare procedures (ICU stay, invasive procedures or devices, previous antibiotic therapy). Baseline conditions, classified according to the McCabe index, were a risk factor only for *E. cloacae* bacteraemia. This is in line with a previously published analysis of the whole cohort [7] and, along with the low proportion (4.5%) of community-acquired bacteraemia, reflects how these micro-organisms are typically associated with healthcare procedures.

The clinical presentation of the BSIs caused by *E. cloacae* and *K. aerogenes* did not show any differences in terms of place of acquisition, severity, source or outcome. A difference in APACHE II score was found (only in ICU patients), with a higher median score in *E. cloacae* than in *K. aerogenes* bacteraemia patients. To our knowledge, there has only been one study comparing the clinical features of *E. cloacae* and *K. aerogenes* BSIs in which Song et al. compared 172 *E. cloacae* bacteraemia cases with 67 *K. aerogenes* bacteraemia cases (then *E. aerogenes*) from a single Korean centre [10]. In their cohort, patients with *E. cloacae* bacteraemia also had more co-morbidities, and patients with *K. aerogenes* bacteraemia showed a higher incidence of septic shock, presence of invasive devices and mortality. *Klebsiella aerogenes* was identified as an independent risk factor for mortality in the multivariate analysis, along with septic shock and inappropriate empirical treatment. This indicated that *K. aerogenes* could be more virulent, although their data showed that certain baseline characteristics of patients with *K. aerogenes* bacteraemia may have differed from those of patients with *E. cloacae* bacteraemia (e.g. the presence of invasive devices was higher, potentially indicating that there was a higher proportion of patients who had previously been admitted to the ICU). In addition, because of the single-centre design of the study, the findings may have reflected the local presence of a more virulent

Table 3
Risk factor analysis for acquisition of *Enterobacter cloacae* or *Klebsiella aerogenes* bacteraemia compared with controls

(a) Risk factors for acquisition of *Enterobacter cloacae* bacteraemia compared with controls

Variable	Patients with *E. cloacae* bacteraemia (n = 196)	Controls (n = 392)	Bivariate analysis (P-value)	Multivariate analysis [OR (95% CI); P-value]
Age (years) [median (IQR)]	67.8 (56.7–77.4)	67.1 (55.6–76.4)	0.901	–
McCabe UF/RF	**78 (39.8)**	**118 (30.1)**	**0.019**	**1.58 (1.08–2.33); 0.019**
Charlson comorbidity index [median (IQR)]	2 (1–4)	2 (1–4)	0.310	–
Diabetes mellitus	50 (25.5)	104 (26.5)	0.791	–
Chronic hepatopathy	87 (44.4)	173 (44.1)	0.953	–
COPD	26 (13.3)	66 (16.8)	0.261	–
Chronic heart failure	32 (16.3)	52 (13.3)	0.317	–
Chronic renal failure	108 (55.1)	190 (48.5)	0.129	–
Haemodialysis	**28 (14.3)**	**15 (3.8)**	**<0.001**	**5.20 (2.59–10.41) <0.001**
Solid-organ transplantation	12 (6.1)	26 (6.6)	0.812	–
HIV infection	2 (1.0)	2 (0.5)	0.604	–
Cancer	58 (29.6)	121 (30.9)	0.751	–
Haematological malignancy	16 (8.2)	32 (8.2)	1	–
Solid tumour	42 (21.4)	88 (22.4)	0.779	–
Neutropenia	10 (5.1)	11 (2.8)	0.157	–
Previous corticosteroids	**22 (11.2)**	**10 (2.6)**	**<0.001**	**3.81 (1.71–8.52) 0.001**
Other causes of immunosuppression	6 (3.1)	6 (1.5)	0.228	–
ICU stay	**72 (36.7)**	**93 (23.7)**	**0.001**	**1.61 (1.05–2.46) 0.027**
Stay in an oncology unit	17 (8.7)	26 (6.6)	0.370	–
Invasive procedure	**152 (77.6)**	**226 (57.7)**	**<0.001**	**1.71 (1.09–2.68) 0.020**
Catheter insertion	156 (79.6)	222 (56.6)	<0.001	–
Urinary catheter	107 (54.6)	136 (34.7)	<0.001	–
Nasogastric tube	55 (28.1)	65 (16.6)	0.001	–
Mechanical ventilation	52 (26.5)	49 (12.5)	<0.001	–
Surgical drainage device	23 (11.7)	37 (9.4)	0.386	–
Gastroscopy	12 (6.1)	17 (4.3)	0.346	–
Colonoscopy	5 (2.6)	6 (1.5)	0.389	–
Bronchoscopy	3 (1.5)	7 (1.8)	1	–
Clean surgery	29 (14.8)	34 (8.7)	0.024	–
Contaminated surgery	20 (10.2)	24 (6.1)	0.096	–
Dirty surgery	14 (7.1)	19 (4.8)	0.254	–
Previous antibiotic therapy	**81 (41.3)**	**94 (24.0)**	**<0.001**	**1.77 (1.17–2.66) 0.006**
Penicillins	45 (23)	48 (12.2)	0.001	–
Cephalosporins	24 (12.2)	22 (5.6)	0.005	–
Carbapenems	11 (5.6)	22 (5.6)	1	–
Quinolones	8 (4.1)	14 (3.6)	0.759	–
Other drugs	29 (14.8)	22 (5.6)	<0.001	–

(b) Risk factors for acquisition of *Klebsiella aerogenes* bacteraemia compared with controls

Variable	Patients with *K. aerogenes* bacteraemia (n = 89)	Controls (n = 178)	Bivariate analysis (P-value)	Multivariate analysis [OR (95% CI); P-value]
Age (years) [median (IQR)]	67.2 (52.8–77.0)	66.6 (55.3–75.7)	0.848	–
McCabe UF/RF	25 (28.1)	57 (32.0)	0.511	–
Charlson comorbidity index [median (IQR)]	1 (0.5–3)	2 (0–3)	0.392	–
Diabetes mellitus	18 (20.2)	45 (25.3)	0.359	–
Chronic hepatopathy	46 (51.7)	86 (48.3)	0.604	–
COPD	12 (13.5)	27 (15.2)	0.713	–
Chronic heart failure	12 (13.5)	17 (9.6)	0.330	–
Chronic renal failure	44 (49.4)	84 (47.2)	0.729	–
Haemodialysis	1 (1.1)	0 (0)	0.333	–
Solid-organ transplantation	3 (3.4)	6 (3.4)	1	–
HIV infection	1 (1.1)	2 (1.1)	1	–
Cancer	18 (20.2)	53 (29.8)	0.096	–
Haematological malignancy	3 (3.4)	9 (5.1)	0.531	–
Solid tumour	15 (16.9)	44 (24.7)	0.144	–
Neutropenia	4 (4.5)	3 (1.7)	0.227	–
Previous corticosteroids	7 (7.9)	9 (5.1)	0.362	–
Other causes of immunosuppression	1 (1.1)	4 (2.2)	0.523	–
ICU stay	**40 (44.9)**	**57 (32.0)**	**0.039**	**0.98 (0.54–1.77); 0.955**
Stay in an oncology unit	6 (6.7)	10 (5.6)	0.715	–
Invasive procedures	**75 (84.3)**	**109 (61.2)**	**<0.001**	**2.45 (1.22–4.92); 0.012**
Catheter insertion	72 (80.9)	109 (61.2)	0.001	–
Urinary catheter	48 (53.9)	69 (38.8)	0.019	–
Nasogastric tube	31 (34.8)	37 (20.8)	0.013	–
Mechanical ventilation	33 (37.1)	31 (17.4)	0.001	–
Surgical drainage device	7 (7.9)	16 (9.0)	0.758	–
Gastroscopy	4 (4.5)	2 (1.1)	0.098	–
Colonoscopy	0 (0)	2 (1.1)	0.554	–
Bronchoscopy	0 (0)	4 (2.2)	0.305	–
Clean surgery	15 (16.9)	22 (12.4)	0.349	–
Contaminated surgery	15 (16.9)	13 (7.3)	0.016	–
Dirty surgery	4 (4.5)	8 (4.5)	1	–
Previous antibiotic therapy	**51 (57.3)**	**48 (27.0)**	**<0.001**	**2.93 (1–65–5.19) <0.001**
Penicillins	27 (30.3)	22 (12.4)	<0.001	–
Cephalosporins	13 (14.6)	15 (8.4)	0.120	–
Carbapenems	11 (12.4)	4 (2.2)	0.001	–
Quinolones	3 (3.4)	9 (5.1)	0.756	–
Other drugs	18 (20.2)	11 (6.2)	0.001	–

NOTE: Data are n (%) unless otherwise stated.
OR, odds ratio; CI, confidence interval; IQR, interquartile range; UF/RF, ultimately fatal/rapidly fatal; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit.

Table 4
Characteristics of the presentation and outcome of bloodstream infections caused by *Enterobacter cloacae* and *Klebsiella aerogenes*

Variable	*E. cloacae* (n = 196)	*K. aerogenes* (n = 89)	*P*-value
Acquisition			
Nosocomial	143 (73.0)	66 (74.2)	0.832
Healthcare-related	46 (23.5)	16 (18.0)	0.298
Community	7 (3.6)	7 (7.9)	0.120
Hospitalisation area			
Medical ward	83 (42.3)	34 (38.2)	0.519
Surgical ward	47 (24.0)	21 (23.6)	1
ICU	66 (33.7)	34 (38.2)	0.458
Source			
Urinary tract	26 (13.3)	18 (20.2)	0.157
Digestive tract	34 (17.3)	10 (11.2)	0.186
Respiratory tract	12 (6.1)	9 (10.1)	0.232
Catheter	61 (31.1)	26 (29.2)	0.783
Surgical site	17 (8.7)	5 (5.6)	0.476
Burn	3 (1.5)	0 (0)	0.554
Unknown	43 (21.9)	21 (23.6)	0.761
Positive blood cultures after 3 days	9 (4.6)	6 (6.7)	0.451
Positive blood cultures after 7 days	4 (2.0)	1 (1.1)	1
Polymicrobial bacteraemia	31 (15.8)	10 (11.2)	0.307
Presentation			
Sepsis	55 (28.1)	30 (33.7)	0.334
Septic shock	19 (9.7)	6 (6.7)	0.414
Multiorgan failure	10 (5.1)	3 (3.4)	0.761
Pitt bacteremia score [median (IQR)]	1 (0–3)	1 (0–4)	0.561
APACHE II score [median (IQR)] [a]	18.5 (13.7–22.2)	14 (8–18)	0.029
Mortality at 7 days	21 (10.7)	8 (9.0)	0.655
Mortality at 14 days	29 (14.8)	14 (15.7)	0.838
Mortality at 30 days	38 (19.4)	18 (20.2)	0.869
Length of hospital stay (days) [median (IQR)]	22 (10.25–41.75)	27 (13.5–49.5)	0.396
Length of ICU stay (days) [median (IQR)] [a]	11.5 (7–23.5)	13 (8–20)	0.982

NOTE: Data are *n* (%) unless otherwise stated.
ICU, intensive care unit; IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation.
[a] Only among patients admitted to the ICU.

clone of *K. aerogenes*. Our study cohort included a higher number of patients and is the largest cohort to date in which the clinical profiles of *E. cloacae* and *K. aerogenes* BSIs have been characterised and compared. Furthermore, its multicentre design should have contributed to avoid the bias derived from a single-centre design with regard to the potential presence of virulent clones of *K. aerogenes*.

The virulence of *Enterobacter* spp., including *K. aerogenes*, remains poorly understood owing to the limited number of studies performed in this field. However, differences in the pathogenicity of *K. aerogenes* (formerly *E. aerogenes*) and *E. cloacae* have been reported [30]. In particular, several authors have found some virulence-encoding genes in *K. aerogenes* related to bacterial adhesion and biofilm formation (*fimH, mrkD, ycfM*) [31] and genes involved in the production of siderophores (*kfu, entB, ybtS*) [32]. These genes have also been identified in *K. pneumoniae* [30], but none have been described in *E. cloacae* or other *Enterobacter* species [9]. None the less, we did not find differences in the clinical course or the prognosis of *K. aerogenes* bacteraemia, and the multicentre design should have avoided some of the mentioned potential biases of the study by Song et al. [10]. Our findings support the view that both micro-organisms have similar virulence and clinical behaviour, but further studies are needed to clarify the role of the virulence factors of *K. aerogenes* and their impact on clinical features.

The antibiotic susceptibility profile was similar for *E. cloacae* and *K. aerogenes*, except for a higher susceptibility of *K. aerogenes* to cefepime and imipenem. The incidences of multidrug resistance and ESBL-producing isolates were low, and no strains producing a carbapenemase were identified, in line with a previous cohort study that has also reported a mortality similar to ours [33]. Multidrug resistance [34] and resistance to cephalosporins [28] have been described as risk factors for mortality in patients with *Enterobacter* spp. (including *K. aerogenes*) bacteraemia.

Enterobacterales acquire resistance to quinolones through mutations in different chromosomal genes. However, several plasmid-mediated resistance mechanisms have been described that do not confer clinical resistance but facilitate survival during quinolone exposure and the selection of resistant mutants [35]. The most common resistance mechanisms involve the presence of plasmid-mediated quinolone resistance *qnr* genes (comprising five families, *qnrA, qnrB, qnrC, qnrD* and *qnrS*), which encode proteins that protect DNA gyrase and topoisomerase IV from quinolone action. The presence of *qnr* genes has been described both in *E. cloacae* and *K. aerogenes*, as well as their frequent transmission together with ESBLs [36,37]. Another plasmid-mediated quinolone resistance mechanism is the production of Aac(6′)-Ib-cr, which reduces the activity of fluoroquinolones through acetylation of the drug molecule [38]. In our cohort, 8/13 ESBL-producing *E. cloacae* isolates also showed a plasmid-mediated quinolone resistance mechanism. Notably, they all came from the same centre, suggesting horizontal transmission of strains or plasmids. As previously mentioned, not all isolates with these resistance mechanisms showed clinical resistance to ciprofloxacin.

This study had several limitations. Some were inherent to its observational design and the post-hoc analysis, while others resulted from the fact that the sample size determination and variable selection were not made specifically for comparison of the clinical profiles between *E. cloacae* and *K. aerogenes*. However, to our knowledge, this is the largest study comparing these two species, and the only one with a multicentre design, which increases its strength. Additionally, the absence of a third cohort of patients with *K. pneumoniae* bacteraemia may in fact represent the main limitation of the study. This option was ruled out because of

the risk of bias irrespective of whether a retrospective cohort or a prospective cohort study design had been used. To date, there are no published clinical studies comparing these three pathogens and this is undoubtedly an area worthy of future research. The criteria established to select control patients may also represent a matter of discussion. A similar control group selection has been successfully used in previous studies of BSIs [7,39] but certain authors have used as controls patients with bacteraemia caused by other pathogens (e.g. *Escherichia coli*) [40]. The latter option may provide a more homogeneous control group, but our strategy avoided ascribing attributable mortality of *E. cloacae* or *K. aerogenes* to other pathogens.

In conclusion, BSIs caused by *E. cloacae* and *K. aerogenes* have a similar clinical presentation and prognosis. Patients with *E. cloacae* bacteraemia had a higher rate of co-morbidities, while those with *K. aerogenes* bacteraemia had a higher rate of previous antibiotic use. Risk factors for acquiring both entities were similar, namely previous antibiotic therapy and use of invasive devices in hospital settings.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2021.04.008.

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