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# Prognosis of urinary tract infection caused by KPC-producing *Klebsiella pneumoniae*: The impact of inappropriate empirical treatment

Jorge Rodriguez-Gómez[a], Elena Pérez-Nadales[b,†], Belen Gutiérrez-Gutiérrez[c,†], Isabel Machuca[d], Luis Martinez-Martinez[e,†], Francisco Rivera[a], Angela Cano[d,†], Juan Jose Castón[d,†], Juan Carlos Robles[a], Carmen de la Fuente[a], Fernando Rodríguez-López[e,†], Jesus Rodriguez-Baño[c,†,*], Julian Torre-Cisneros[d,†], Spanish Network for Research in Infectious Diseases (REIPI), Instituto de Salud Carlos III, Madrid, Spain

[a] *Critical Care Unit, Hospital Universitario Reina Sofia-IMIBIC-Universidad de Cordoba, Cordoba, Spain*
[b] *Spanish Network of Research in Infectious Diseases (REIPI RD16/0016/0008). Maimonides Institute for Biomedical Research (IMIBIC), Cordoba, Spain*
[c] *Infectious Diseases, Microbiology and Preventive Medicine Unit, Hospital Universitario Virgen Macarena/Department of Medicine, Universidad de Seville/Biomedicine Institute of Seville (IBiS), Seville, Spain*
[d] *Infectious Diseases Unit. Hospital Universitario Reina Sofía-IMIBIC-Universidad de Cordoba, Cordoba, Spain*
[e] *Microbiology Unit, Hospital Universitario Reina Sofía-IMIBIC-Universidad de Cordoba, Cordoba, Spain*

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SUMMARY

*Introduction:* There is scarce information on the prognosis of urinary tract infections (UTI) caused by KPC carbapenemase-producing Klebsiella pneumoniae (KPC-Kp).
*Objetive:* To investigate the association between KPC-Kp aetiology and clinical failure and all cause mortality and to explore the impact of inappropriate empirical treatment.
*Material and methods:* This is a retrospective observational study of hospitalized patients with UTI due to K. pneumoniae. We explored clinical failure at day 21 and 30-day all-cause mortality using different models of adjusted analysis.
*Results:* We analyzed 142 episodes of UTI; 46 episodes (32.4%) were due to KPC-Kp and 96 episodes (67.6%) were due to non-KPC-Kp strains (62 wild type and 34 EBSL producer). Clinical failure was more frequent in the KPC-Kp group (41.3% vs. 15.6%, $p = 0.001$). KPC-Kp aetiology and inappropriate empirical therapy were associated in the non-adjusted analysis with clinical failure. When analysed in separate adjusted models, both were found to be associated; inappropriate empirical treatment (OR 2.51; 95% CI, 1.03–6.12; $p = 0.04$) and KPC-Kp (OR 2.73; 95% CI, 1.03–7.22; $p = 0.04$) were associated with increased risk of failure. All-cause 30-day mortality was higher in patients with KPC-Kp UTI (39.1% vs. 15.6%, $p = 0.002$). Bacteraemia was more frequent in patients with KPC-Kp etiology (23.9% vs. 10.4%; $p = 0.034$). In both cases, the association was not confirmed in the adjusted analysis.
*Conclusion:* KPC-Kp UTI is associated with higher clinical failure and may be due to an increase in inappropriate empirical treatment.


## Introduction

*Klebsiella pneumoniae* (Kp) is a common cause of urinary tract infection (UTI). In recent years, numerous centers worldwide have witnessed outbreaks of carbapenemase-producing *Enterobacteriaceae* infections, including *Klebsiella pneumoniae* carbapenemase (KPC) infections, making their adequate control and treatment a global priority.[1] These infections are difficult to treat since they are usually resistant to all first-line drugs, which may explain the high mortality of these infections and the need for combination therapy in high-risk patients.[2–5] inappropriate empirical therapy has been also associated with higher mortality in patients with sepsis and gram-negative bacteremia.[2,3] However, whether UTI due to KPC carbapenemase-producing *K. pneumoniae* (KPC-Kp) is associated with poorer prognosis has not been well determined.

* Corresponding autors.
*E-mail address:* jesusrb@us.es (J. Rodriguez-Baño).
† Authors who are members of the Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0008/REIPI RD16/0016/0001).

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Many of the usually active antibiotics against KPC-Kp have drawbacks, including low urine concentrations (tigecycline), nephrotoxicity (colistin, aminoglycosides) or insufficient data about efficacy (fosfomycin).[6,7] The options are even more limited in areas where colistin-resistant Kp strains with high-level meropenem resistance are prevalent. Additionally, the use of recently approved drugs such as ceftazidime-avibactam may be better reserved for severe infections. In this scenario, it is important to explore the potential efficacy of fosfomycin and gentamicin in clinical practice.

The main objective of this study was to investigate the prognostic impact of KPC-Kp aetiology in the outcomes of UTI due to *K. pneumoniae* (Kp-UTI) in hospitalized patients. Our hypothesis is that KPC-Kp aetiology increases clinical failure and/or all-cause mortality due to a delay in initiating adequate treatment. Additionally, we want to explore the risk factors for KPC-Kp infection and to describe our experience with the use of fosfomycin and gentamicin in the treatment of these infections.

## Methods

### *Study design and population*

This is a retrospective cohort study of Kp-UTI in hospitalized patients performed at a university hospital (> 40,000 annual admissions) in Córdoba, Spain, during a hospital outbreak and subsequent endemicity of KPC-Kp (ST512 clone).[8] All Kp-UTI episodes diagnosed between December 2012 and October 2015 in our center were eligible. Cases that occurred after this date are not analyzed since they have been included in a preregistered international prospective cohort (European Prospective Cohort Study on Enterobacteriaceae Showing Resistance to Carbapenems, EURECA, ClinicalTrials.gov identifier: NCT02709408).

Patients were identified by a search in our microbiology database. The following inclusion criteria were used: (i) UTI in hospitalized patients according to the Food and Drug Administration/Center for Drug Evaluation and Research (FDA/CDER) definition[9]: clinical syndrome characterized by pyuria and a documented microbial pathogen on culture, accompanied by local and systemic signs and symptoms, including fever (i.e., oral or tympanic temperature greater than 38 °Celsius), chills, malaise, flank pain, back pain, and/or costo-vertebral angle pain or tenderness; (ii) isolation of *K. pneumoniae* in urine culture; (iii) age ≥ 18 years; (iv) administration of a targeted treatment in the first 72 h after the urine culture, including at least one active antibiotic in vitro. Patients with polymicrobial UTI, patients under palliative care, patients with non-resuscitation orders and patients with any previous Kp-UTI episode in the previous years were excluded. Day 0 was defined as the day of collection of the urine culture in which the microorganism was isolated. In patients with a urinary catheter, the catheter was removed or replaced before taking the index urine culture.

This report is in accordance with the STROBE recommendations[10] (see Table S1 in the supplementary material). The study was approved by the Spanish Agency for Medicines and Health Products (AEMPS, code FIC-KPC-2015-01) and by the local Ethics Committee (code 2848), which exempted the need to seek written informed consent due to the observational nature of the study. A database designed for this study was used. All the data collected were anonymized.

### *Outcome variables*

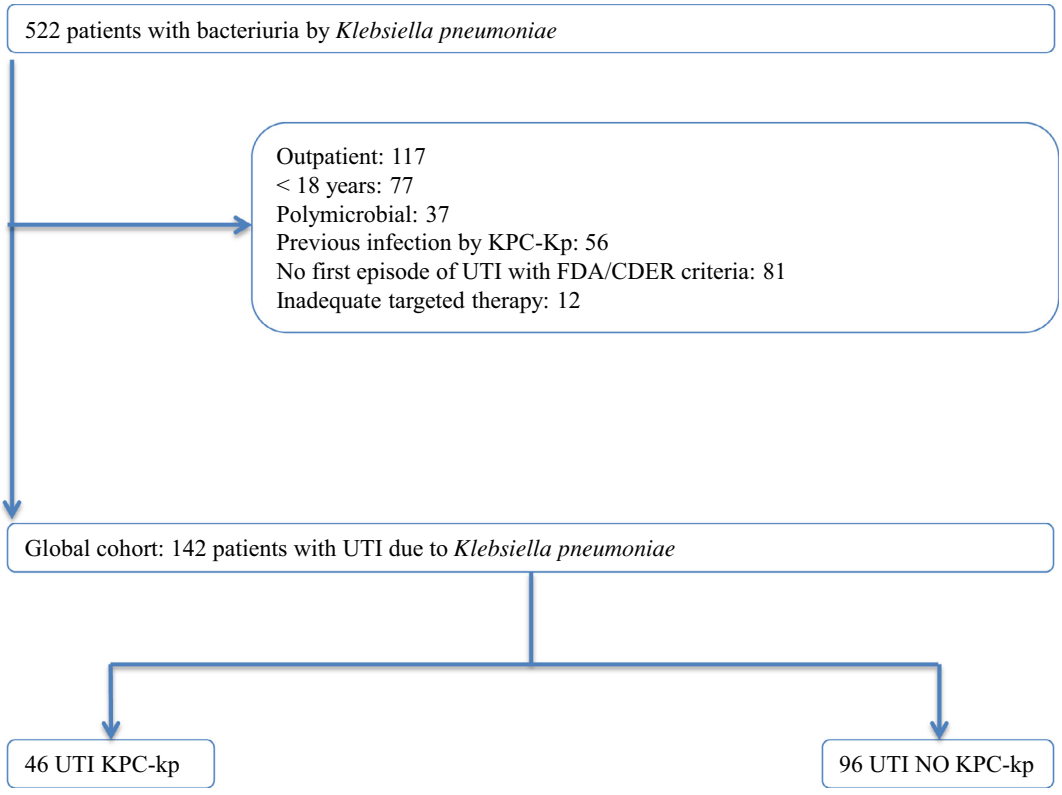
The primary outcome variable was clinical failure at day 21. Other secondary outcome variables were 30-day all-cause mortality, microbiological failure at day 14 and recurrence after clinical response in the 3 months after end of treatment (EOT). Clinical failure was defined as persistence/recurrence of signs or symptoms present at baseline. Patients who died before day 21 without clinical response were considered clinical failure. Survival status of patients discharged before day 30 was determined by telephone call. Microbiological failure was defined as persistence of the index bacteria in a urine sample collected in the 5 days after EOT. Recurrence was defined as the presence of a Kp-UTI in the 3 months after clinical response (see previous definition of UTI). The presence of a positive urinary culture in an asymptomatic patient was not considered recurrence.

### *Exposure variables*

The main exposure variable of interest was KPC-Kp aetiology (for microbiological characteristics of the isolates, see below). Antimicrobial treatment initiated or maintained after receiving the susceptibility results was considered targeted therapy. Antibiotic therapy was considered appropriate when the isolate was susceptible in vitro to at least one of the prescribed antibiotics. In patients with KPC-Kp UTI, and because of the susceptibility pattern of the isolates, gentamicin and fosfomycin were used for targeted therapy either alone or in combination. Gentamicin was administered intravenously as a single daily dose of 5 mg/kg and adjusted according to blood level concentrations; for patients with intermediated strains to gentamicin (MIC=8 mg/L), this antibiotic was used only in combination regimens with other active drugs. Fosfomycin was administered at an intravenous dose of 4 g every 6 h and adjusted according to renal function. The duration of treatment ranged from 7 to 14 days according to the judgment of the attending physician. Tigecycline was considered an inactive antibiotic for UTI. Ceftazidime-avibactam was not available during the study period. A therapeutic regimen including a single in vitro active drug was considered as monotherapy, and those including two or more in vitro active drugs were considered as combination therapy. To classify patients as receiving a specific targeted therapy, the regimen should have been initiated in the first 72 h following the index culture and maintained for at least 50% of the total duration of the treatment.

Other recorded variables were (i) demographics: age and gender; (ii) previous conditions: residence in a nursing home, number of hospitalisation days in the previous 6 months, previous colonisation by KPC-Kp, underlying conditions, Charlson comorbidity index,[11] surgery in the previous week and antibiotic therapy in the previous month; (iii) clinical characteristics: acquisition (community, healthcare-associated, nosocomial),[12] ward type at diagnosis (medical, surgical, intensive care unit), complicated UTI (cUTI) defined by FDA/CDER (UTI criteria in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization indwelling urinary catheter, 100 mL or more of residual urine after voiding, obstructive uropathy, azotemia caused by intrinsic renal disease and urinary retention; all cases of pyelonephritis are considered cUTI),[9] bacteraemia at diagnosis, Pitt bacteremia score,[13] septic shock at diagnosis[14] and acute renal failure; (iv) microbiological characteristics: *K. pneumoniae* phenotype (wild type, extended-spectrum beta-lactamase producer (ESBL-producer, KPC-producer) and in vitro resistance (fosfomycin, gentamicin, colistin, meropenem); (v) treatment: inappropriate empirical therapy and targeted combination therapy. The Pitt bacteremia score was applied to all patients with sepsis criteria and/or bacteremia. For all other patients, the Pitt score was considered to be 0.

The policy of the center established that rectal colonisation by carbapenem-resistant *Enterobacteriaceae* be investigated in patients at risk and in patients with active infection by these bacteria. Consequently, the variable colonisation by KPC-Kp was only available in patients with KPC-Kp UTI. Therefore, rectal colonization by carbapenem-resistant *Enterobacteriaceae* was evaluated in:




UTI: urinary tract infection; FDA/CDER: Food and Drug Administration/Center for Drug Evaluation and Research; NO KPC-Kp: No KPC-producing *Klebsiella pneumoniae*; KPC-Kp: KPC-producing *Klebsiella pneumoniae*.

**Fig. 1.** Flowchart of included patients with urinary tract infections due to *Klebsiella pneumoniae*.
UTI: urinary tract infection; FDA/CDER: Food and Drug Administration/Center for Drug Evaluation and Research; NO KPC-Kp: No KPC-producing *Klebsiella pneumoniae*; KPC-Kp: KPC-producing *Klebsiella pneumoniae*.

(i) all patients admitted to the intensive care or hematology units; (ii) hospitalized patients undergoing abdominal interventions and transplantation previously admitted to units affected by the outbreak; (iii) patients with active infections.

The Cockroft-Gault formula was used to calculate creatinine clearance (CrCL). The presence of CrCl < 60 mL/min was considered renal failure. Empirical therapy was defined as treatment administered within the first 24 h following the collection of urine culture and prior to determining the susceptibility of the isolate. At least one active antibiotic must be included in the empirical regimen to be considered active.

### *Microbiological studies*

Identification and susceptibility studies of the isolates were performed using the Wider panel MIC/UD gram-negative urocult (Siemens Healthcare Diagnostics Inc., West Sacramento, CA 95,691) and/or the MicroScan Panel NC-54 (Siemens Healthcare Diagnostics Inc. West Sacramento, CA 95,691). Minimal inhibitory concentrations (MICs) were interpreted according to the breakpoint of the Clinical and Laboratory Standards Institute (CLSI) standard criteria for broth microdilution.[15,16] Gentamicin, fosfomycin and colistin were considered active when MIC was ≤ 4 mg/L, ≤ 64 mg/L and ≤ 2 mg/L, respectively. Meropenem was not considered active against any isolate because the MIC was ≥ 64 mg/L in all cases of KPC-kp. Confirmatory tests for ESBL production were performed with a double-disc synergy test using ceftazidime or cefotaxime with and without clavulanic acid on Mueller Hinton agar supplemented with cloxacillin when appropriate according to CLSI recommendations.[15]

The KPC-Kp index isolates in the outbreak were characterized as belonging to the ST512 clone and producing the KPC-3 by the reference laboratory of the Virgen Macarena University Hospital of Seville, Spain. The characteristics of the strain have been previously reported.[8] Colistin resistance was checked in selected KPC-producing strains using a broth dilution method (MIC > 2 mg/L). Selected strains yielded negative screening for the *mcr-1* and *mcr-2* genes using polymerase chain reaction with specific primers.

### *Statistical analysis*

Continuous variables were compared using the Mann-Whitney U test and categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Multivariate analyses were performed using logistic regression for KPC-kp aetiology and clinical failure. Cox modeling regression without censoring, after assessing the proportional hazard assumption, was applied for 30-day all-cause mortality.

The variables included in the models were selected manually in a backward stepwise manner according to their association (p 0.2 or lower) and biological value. To study whether the association between KPC-Kp aetiology and prognosis (clinical failure or all-cause mortality) depends on the use of inappropriate empirical treatment, two multivariable models were constructed. In model 1, the KPC-Kp aetiology was adjusted for the potentially confounding variables and in model 2 the analysis was repeated adjusting for

**Table 1**
Clinical characteristics of patients with urinary tract infection caused by *Klebsiella pneumoniae*.

| *Number of cases* | Total 142 | Non-KPC-Kp 96 | KPC-Kp 46 | *P* |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age, median (IQR) | 78 (68–83) | 75 (64–84) | 79 (75–83) | 0.12 |
| Female gender | 81 (57) | 54 (56.2) | 27 (58.7) | 0.78 |
| **Previous conditions** | | | | |
| Residence in a nursing home | 30 (21.1) | 20 (20.8) | 10 (21.7) | 0.90 |
| Number of hospitalization days in previous 6 months, median (IQR) | 12 (5–25) | 8 (5–18) | 24 (10–37) | **<0.001** |
| Previous colonization by KPC-Kp | NA | NA | 13 (28.3) | |
| Underlying conditions | | | | |
| Chronic renal failure | 43 (30.3) | 29 (30.2) | 14 (30.4) | 0.9 |
| Hemodialysis | 7 (4.9) | 7 (7.3) | 0 (0) | 0.09 |
| Solid organ transplantation | 11 (7.7) | 10 (10.4) | 1 (2.2) | 0.10 |
| Diabetes mellitus | 69 (48.6) | 43 (44.8) | 26 (56.5) | 0.19 |
| Chronic heart failure | 51 (35.9) | 35 (36.5) | 16 (34.8) | 0.84 |
| Charlson comorbidity index, median (IQR) | 4 (2–6) | 3 (2–5) | 6 (4–8) | **<0.001** |
| Surgery in the previous week | 10 (7) | 9 (9.4) | 1 (2.2) | 0.16 |
| Antibiotic therapy in the previous month. | 65 (45.8) | 35 (36.5) | 30 (65.2) | **0.001** |
| **Clinical characteristics of the urinary tract infection** | | | | |
| Acquisition | | | | |
| Community-acquired | 54 (38) | 44 (45.8) | 10 (21.7) | 0.06 |
| Healthcare-associated | 23 (16.2) | 16 (16.7) | 7 (15.2) | 0.82 |
| Nosocomial | 65 (45.8) | 36 (37.5) | 29 (63) | **0.004** |
| Ward type at diagnosis | | | | |
| Medical | 117 (82.4) | 74 (77.1) | 43 (93.5) | **0.01** |
| Surgical | 12 (8.5) | 10 (10.4) | 2 (4.3) | 0.33 |
| Intensive Care Unit | 13 (9.2) | 12 (12.5) | 1 (2.2) | 0.06 |
| Complicated urinary tract infection | 104 (73.2) | 66 (68.8) | 42 (91.3) | **0.003** |
| Pyelonephritis. | 13 (9.2) | 8 (8.3) | 5 (10.9) | 0.75 |
| Indwelling-catheter previous week | 82 (57.7) | 47 (49) | 35 (76.1) | **0.002** |
| Obstruction or retention | 14 (9.9) | 10 (10.4) | 4 (8.7) | 1 |
| Urinary procedures previous month | 19 (13.4) | 13 (13.5) | 6 (13) | 0.93 |
| Bacteraemia at diagnosis | 21 (14.8) | 10 (10.4) | 11 (23.9) | **0.034** |
| Pitt bacteremia score, median (IQR)* | 1 (0–2) | 1 (0–2) | 1 (0–3) | 0.13 |
| Septic shock at diagnosis | 24 (16.9) | 18 (18.8) | 6 (13) | 0.39 |
| Acute renal failure | 60 (42.3) | 40 (41.7) | 20 (43.5) | 0.83 |
| **Microbiological characteristics** | | | | |
| Phenotype of the *Klebsiella pneumoniae* | | | | |
| Wild type | 62 (43.7) | 62 (64.6) | 0 (0) | |
| ESBL-producer | 34 (23.9) | 34 (35.4) | 0 (0) | |
| KPC producer | 46 (32.4) | 0 (0) | 46 (100) | |
| In vitro resistance | | | | |
| Fosfomycin | 32 (22.5) | 17 (17.7) | 15 (32.6) | 0.04 |
| Gentamicin | 8 (5.6) | 7 (7.3) | 1 (2.2) | 0.43 |
| Colistin | 47 (33.1) | 6 (6.2) | 41 (89.1) | **<0.001** |
| Meropenem | 48 (33.8) | 2 (2.1) | 46 (100) | **<0.001** |
| **Treatment** | | | | |
| Inappropriate empirical therapy | 71 (50.0) | 37 (38.5) | 34 (73.9) | **<0.001** |
| Targeted combination therapy | 24 (17.8) | 13 (13.5) | 11 (23.9) | 0.12 |
| **Outcome** | | | | |
| Clinical failure at day 21 | 34 (23.9) | 15 (15.6) | 19 (41.3) | **0.001** |
| Microbiological failure at day 14 ($n = 68$) | 8/68 (11.8) | 5/42 (11.9) | 3/26 (11.5) | 1 |
| All-cause mortality at day 30 | 33 (23.2) | 15 (15.6) | 18 (39.1) | **0.002** |
| Recurrence after clinical response | 7/108 (6.5) | 5/81 (6.2) | 2/27 (7.4) | 1 |

All data are expressed as n (%) unless otherwise indicated. IQR: interquartile range; Non-KPC-Kp: *Klebsiella pneumoniae* strain; not producing KPC-Kp: KPC-producing *Klebsiella pneumoniae* strain; Kp: *Klebsiella pneumonia*; NA, not available; ESBL: Extended spectrum beta lactamase.

* The Pitt bacteraemia score was applied to all patients whit sepsis criteria and/or bacteremia; for all other patients, the Pitt score was considered to be 0.

inappropriate empirical treatment without KPC-Kp. The predictive ability (validity) of each multivariate model was studied by calculating the area under the ROC curve (AUROC). The analyses were performed using SPSS software (SSPS 15.0, IBM Corp, Armonk, New York, USA).

## Results

### *Descriptive data and variables associated with KPC-Kp UTI*

During the study period, 522 patients with isolation of *K. pneumoniae* in urine cultures were identified, but only 142 met the criteria to be included in the analysis. The causes of exclusion are shown in Fig. 1; the main cause of exclusion was the isolation of the bacteria in an outpatient (117 cases). The clinical characteristics of the cohort are described in Table 1. Overall, 46 episodes (32.4%) were due to KPC-Kp strains and 96 episodes (67.6%) were due to non-KPC-Kp strains (62 wild type and 34 EBSL-producers). The median of the Charlson comorbidity index was 4 (range, 2–6), 45.8% (65 cases) received antibiotics in the previous month, 73.2% (104 cases) were complicated UTI (more frequently indwelling catheter) and 62% (88 cases) were either nosocomial or health-care associated.

Previous colonisation with KPC-Kp was observed in 13 cases of KPC-Kp UTI (28.3%). Patients with KPC-Kp UTI had more hospitalisation days in the previous 6 months (median, 24 vs. 8, $p < 0.001$), a higher Charlson comorbidity index (median, 6 vs. 3, $p < 0.001$), antibiotic therapy in the previous month (65.2% vs. 36.5%, $p < 0.001$), nosocomial acquisition (63% vs. 37.5%, $p = 0.004$), complicated UTI (91.3% vs. 66.8%, $p = 0.003$) or bacteraemia at diagnosis

**Table 2**
Adjusted analysis of the association between different variables and urinary tract infection due to KPC-producing *Klebsiella pneumoniae*.

| Variable | Total Kp Cohort | | Crude analysis | | Adjusted analysis[a] | |
|---|---|---|---|---|---|---|
| | Non-KPC-Kp ($n=96$) | KPC-Kp ($n=42$) | OR (95% CI) | $p$ | OR (95% CI) | $p$ |
| Female gender | 54 (56.2) | 27 (58.7) | 1.10 (0.54–2.25) | 0.78 | | |
| Residence in a nursing home | 20 (20.8) | 10 (21.7) | 1.05 (0.44–2.48) | 0.90 | | |
| Number of hospitalization days in previous 6 months, median (IQR)* | 8 (5–18) | 24 (10–37) | 1.04 (1.02–1.07) | **<0.001** | 1.04 (1.01–1.07) | **0.004** |
| Charlson comorbidity index, median (IQR) | 3 (2–5) | 6 (4–8) | 1.55 (1.30–1.84) | **<0.001** | 1.65 (1.34–2.02) | **<0.001** |
| Surgery in the previous week | 9 (9.4) | 1 (2.2) | 0.21 (0.02–1.74) | 0.15 | | |
| Antibiotic therapy in the previous month* | 35 (36.5) | 30 (65.2) | 3.26 (1.56–6.81) | **0.002** | 4.51(1.66–12.29) | **0.003** |
| Indwelling-catheter in the previous week | 47 (49) | 35 (76.1) | 3.31 (1.51–7.28) | **0.003** | 2.88 (1.03–8.00) | **0.04** |
| Septic shock at diagnosis | 18 (18.8) | 6 (13) | 0.65 (0.23–1.76) | 0.39 | | |

All data are expressed as n (%) unless otherwise indicated. Kp: *Klebsiella pneumoniae* strain; IQR: interquartile range; Non-KPC-Kp: No KPC-producing *Klebsiella pneumoniae*; KPC-Kp: KPC-producing *Klebsiella pneumoniae*; OR, odds ratio; CI: confidence interval.
* No differences were observed when groups of antibiotics were analyzed.
[a] Area under ROC curve (AUROC) = 0.883.

(23.9% vs. 10.4%, $p=0.034$). The presence of indwelling catheter in the previous week was the most frequent cause of complicated UTI (76.1% vs. 49%, $p=0.002$). The frequency of septic shock at diagnosis was similar in both groups (13% vs. 18.8%, $p=0.39$).

The adjusted analysis of the association between selected variables and KPC-Kp aetiology is shown in Table 2. We considered only epidemiological or clinical variables that were evaluable before the urine culture was available. Previous KPC-Kp colonisation was not considered in this analysis since it was not available in the non-KPC-Kp group. Bacteraemia was not included since it was not available before the urine culture when empirical treatment was indicated. The variables included in the final adjusted model were: (i) number of hospitalisation days in previous 6 months (odds ratio [OR] 1.04; 95% confidence interval [CI], 1.01–1.07; $p=0.004$); (ii) Charlson comorbidity index (OR 1.65; 95% CI, 1.34–2.02; $p < 0.001$); (iii) antibiotic therapy in the previous month (OR, 4.51; 95% CI, 1.66–12.29; $p=0.003$); and (iv) indwelling catheter in the previous week (OR 2.88; 95% CI, 1.03–8.00; $p=0.04$). The area under ROC curve (AUROC) of the model was 0.88.

### *Association of KPC-Kp aetiology and clinical failure: implication of delay in initiating adequate treatment*

Clinical failure at day 21 was more frequent in the KPC-Kp group (41.3% vs. 15.6%; $p=0.001$). Resistance to colistin was observed in 41 KPC-Kp isolates (89.1%). All KPC-Kp strains were susceptible to either fosfomycin or gentamicin, 15 (32.6%) were resistant to fosfomycin and only 1 (2.2%) was resistant to gentamicin. In this particular phenotypic scenario, inappropriate empirical treatment was more frequent in patients with KPC-Kp UTI (73.9% vs. 38.5%; $p < 0.001$) (Table 1).

Table 3 shows the two models of adjusted analysis designed to explore the association of KPC-Kp aetiology with clinical failure at day 21. In the unadjusted analysis, the variables KPC-Kp aetiology (OR 3.8; 95% CI, 1.69–8.49; $p=0.001$), female gender (OR 2.58; 95% CI, 1.1–6.03; $p=0.02$), Charlson comorbidity index (OR 1.15; 95% CI, 1.01–1.30; $p=0.02$), Pitt bacteraemia score (OR 1.51; 95% CI, 1.15–1.98; $p=0.003$) and inappropriate empirical treatment (OR 2.61; 95% CI, 1.16–5.89; $p=0.02$) were associated with clinical failure. The variables inappropriate empirical therapy and KPC-Kp aetiology were correlated, since 58/94 (61.7%) patients with non-KPC-Kp received appropriate empirical treatment and 28/40 (70%) patients with KPC-Kp received inappropriate empirical treatment. Because we considered that KPC-Kp aetiology would increase the probability of inappropriate empirical treatment but would not have a direct causal effect on failure by itself, it would not be a confounder. Therefore, we did not include both in the same model but performed two, one with each variable, to evaluate their predictive ability for failure. In their respective models of adjusted analysis, KPC-Kp was associated with increased risk of failure (OR 2.73; 95% CI, 1.03–7.22; $p=0.04$) and inappropriate empirical treatment was protective of failure (OR 2.51; 95% CI, 1.03–6.12; $p=0.04$).

### *Association between KPC-Kp aetiology and secondary outcome variables: implication of delay in initiating adequate treatment*

All-cause mortality at day 30 was higher in KPC-Kp group (39.1% vs. 15.6%; $p=0.002$). Urine cultures at the end of the treatment were performed in 42.7% (42/96) of patients in the non-KPC-Kp UTI group versus 56.5% (26/46) in the KPC-Kp UTI group. The frequency of microbiological failure did not differ between the groups (11.5% vs. 11.9%; $p=1$). Recurrence after clinical response was also similar (7.4% vs. 6.2%; $p=1$). (Table 1)

In the unadjusted analysis, the variables KPC-Kp aetiology (HR 2.83; 95% CI; 1.42–5.63; $p=0.003$), female gender (HR 3.23; 95% CI, 1.40–7.45; $p=0.006$), Charlson comorbidity index (HR 1.13; 95% CI, 1.03–1.24; $p=0.007$), Pitt bacteraemia score (HR 1.37; 95% CI, 1.18–1.59; $p \leq 0.001$) and inappropriate empirical treatment (HR 2.10, 95% CI, 1.02–4.34, $p=0.04$) were associated with all-cause mortality. In the model without inappropriate empirical therapy, KPC-Kp aetiology could not be found to be clearly associated with all-cause mortality, and in the model without KPC-Kp, the estimation of the impact of inappropriate empirical treatment was not significant but was informative that a potential protective effect cannot be discarded (Table 4).

Bacteraemia at diagnosis was more frequent in the KPC-Kp group (23.9% vs. 10.4%; OR 2.70; 95% CI, 1.05–6.93; $p=0.03$). Nevertheless, this association was not observed when the analysis was adjusted by other variables associated with bacteraemia (OR 1.51; 95% CI, 0.49–4.66; $p=0.46$).

### *Impact of different antibiotic regimens on KPC-Kp UTI prognosis*

KPC-Kp UTI was treated with fosfomycin in 23 cases, gentamicin in 28 cases and with a combination of both in 11 cases. The clinical failure, all-cause mortality, microbiological failure and recurrence observed with the different antibiotic treatment regimens (fosfomycin, gentamicin or a combination of both) are shown in Table 5. We could not demonstrate the advantage of any particular antibiotic regimen over the others in the prognosis of KPC-Kp UTI.

Two patients treated with fosfomycin acquired resistance during treatment and developed microbiological failure. Two patients developed recurrence and the strain in both patients was susceptible to the antibiotic previously used (fosfomycin and gentamicin in monotherapy).

**Table 3**
Adjusted analysis of the association of KPC-producing *Klebsiella pneumoniae* aetiology and clinical failure at day 21 in patients with urinary tract infections due to *Klebsiella pneumoniae*.

| | Clinical Cure 108 (76.1) | Clinical Failure 34 (23.9) | Crude analysis | | Adjusted analysis (Model 1)[a] | | Adjusted analysis (Model 2)[b] | |
|---|---|---|---|---|---|---|---|---|
| | | | OR (95% CI) | p | OR (95% CI) | *p* | OR (95% CI) | *p* |
| **KPC-Kp aetiology.** | 27 (25) | 19 (55.9) | 3.8 (1.69–8.49) | **0.001** | 2.73 (1.03–7.22) | **0.04** | | |
| Female gender | 56 (51.9) | 25 (73.5) | 2.58 (1.10–6.03) | **0.02** | 2.91 (1.15–7.35) | **0.02** | 2.97 (1.17–7.52) | **0.02** |
| Charlson comorbidity index, median (IQR) | 4 (2–6) | 5 (3–8) | 1.15 (1.01–1.30) | **0.02** | 1.10 (0.94–1.29) | 0.21 | 1.16 (1.01–1.34) | **0.03** |
| Nosocomial UTI | 53 (49.1) | 12 (35.3) | 0.75 (0.50–1.12) | 0.16 | | | | |
| Complicated UTI | 81 (75) | 25 (79.4) | 1.28 (0.50–3.28) | 0.60 | | | | |
| Pitt bacteraemia score*, median (IQR) | 1 (0–2) | 2 (1–3) | 1.51 (1.15–1.98) | **0.003** | 1.52 (1.14–2.04) | **0.004** | 1.56 (1.17–2.08) | **0.02** |
| Inappropriate empirical therapy | 48 (44.4) | 23 (67.6) | 2.61 (1.16–5.89) | **0.02** | | | 2.51 (1.03–6.12) | **0.04** |
| Targeted combination therapy | 18 (16.7) | 6 (17.6) | 1.07 (0.38–2.96) | 0.89 | | | | |

All data are expressed as n (%) unless otherwise indicated. OR: odds ratio; CI: confidence interval; KPC-Kp: KPC-producing *Klebsiella pneumoniae*; IQR: interquartile range; UTI: urinary tract infection.
* The Pitt bacteraemia score was applied to all patients whit sepsis criteria and/or bacteremia; for all other patients, the Pitt score was considered to be 0.

**Table 4**
Adjusted analysis of the association of KPC-producing *Klebsiella pneumoniae* aetiology and all-cause mortality at day 30 in patients with urinary tract infections due to *Klebsiella pneumoniae*.

| Variables | Alive 96 (67.6) | All-cause mortality 46 (32.4) | Crude analysis | | Adjusted analysis (Model 1)[a] | | Adjusted analysis (Model 2)[b] | |
|---|---|---|---|---|---|---|---|---|
| | | | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| **KPC-Kp aetiology.** | 28 (25.7) | 18 (54.5) | 2.83 (1.42–5.63) | **0.003** | 1.87 (0.83–4.23) | 0.13 | | |
| Gender, female | 55 (50.5) | 26 (78.8) | 3.23 (1.40–7.45) | **0.006** | 3.43 (1.47–7.99) | **0.004** | 3.46 (1.49–8.04) | **0.004** |
| Charlson comorbidity index, median (IQR) | 4 (2–6) | 6 (4–8) | 1.13 (1.03–1.24) | **0.007** | 1.12 (0.99–1.26) | 0.05 | 1.15 (1.04–1.28) | **0.005** |
| Nosocomial UTI | 52 (47.7) | 13 (39.4) | 0.86 (0.60–1.22) | 0.39 | | | | |
| Complicated UTI | 83 (76.1) | 25 (75.8) | 0.95 (0.43–2.11) | 0.91 | | | | |
| Bacteraemia at diagnosis | 14 (12.8) | 7 (21.2) | 1.70 (0.73–3.92) | 0.21 | | | | |
| Pitt bacteremia score*, median (IQR) | 1 (0–2) | 2 (1–3) | 1.37 (1.18–1.59) | **<0.001** | 1.40 (1.19–1.65) | **<0.001** | 1.42 (1.21–1.68) | **<0.001** |
| Inappropriate empirical therapy | 49 (45) | 22 (66.7) | 2.10 (1.02–4.34) | **0.04** | | | 1.99 (0.94–4.21) | 0.07 |
| Targeted combination therapy | 18 (16.5) | 6 (18.2) | 1.08 (0.44–2.61) | 0.86 | | | | |

All data are expressed as n (%) unless otherwise indicated. HR: Hazard ratio; CI: confidence interval; KPC-Kp: KPC-producing *Klebsiella pneumoniae;* IQR: interquartile range; UTI: urinary tract infection.
* The Pitt bacteraemia score was applied to all patients whit sepsis criteria and/or bacteremia; for all other patients, the Pitt score was considered to be 0.

**Table 5**
Prognosis of urinary tract infection due to KPC-producing *Klebsiella* pneumoniae ($n = 40$) treated with fosfomycin, gentamicin of combination of both.

| | Fosfomycin (23 cases) | P[a] | Gentamicin (28 cases) | P[b] | Combination (11 cases) | P[c] |
|---|---|---|---|---|---|---|
| Clinical failure, day 21 | 6 (26.1) | 0.31 | 10 (35.7) | 0.71 | 3 (27.3) | 1 |
| All-cause mortality, day 30 | 6 (26.1) | 0.53 | 8 (28.6) | 1 | 2 (18.2) | 0.45 |
| Microbiologic failure, day 14 (26 cases) | 2/26 (14.3) | 1 | 2/26 (10.5) | 1 | 1/7 (14.3) | 1 |
| Recurrence after clinical response, month 3 (2 cases). | 1 (4.3) | 1 | 1 (3.6) | 1 | 0 (0) | 1 |

[a] Fosfomycin vs. Non Fosfomycin.
[b] Gentamicin vs. Non Gentamicin.
[c] Monotherapy vs. Combined therapy.

## Discussion

To the best of our knowledge, this is the first study to analyze the prognosis of KPC-Kp UTI and the impact of inappropriate empirical treatment. The main conclusion of our study is that if KPC-Kp aetiology is associated with clinical failure, it is mostly due to a high rate of inappropriate empirical treatment. Our conclusion is based on the adjusted analysis designed to test our hypothesis. Inappropriate empirical therapy and KPC-Kp aetiology were associated with clinical failure in their respective adjusted models analysis (Table 3). Both seems to be correlated; taking in to account the hypothetical causally direction, we hypothesize that it is the delay in initiating an active treatment what is causalty associated with an increased risk of failure, while KPC-Kp aetiology is associated because it increases the probability of receiving inappropriate empirical treatment.

In a previous study that included not only UTI but also other severe infections caused by carbapenem-resistant microorganisms treated with ceftazidime-avibactam, the delayed onset of this antibiotic was associated with worse clinical and microbiological outcomes.[17]

Surely, empirical therapy is not the only factor determining clinical response of patients with KPC-Kp. We have not investigated whether there are intrinsic factors to this strain that would make it more virulent. In the crude analysis, bacteraemia was more frequent in patients with KPC-Kp aetiology, but the adjusted analysis showed no association between KPC-Kp aetiology and bacteraemia. However, the Pitt bacteraemia score was associated with

clinical failure in the adjusted analysis. This variable takes into account not only bacteremia but also the acute severity of the baseline situation.

It may be possible to improve the targeted treatment. Our patients received treatment with fosfomycin or gentamicin in monotherapy or combination therapy. Although new drugs are available that could improve clinical response,[17–22] such as ceftazidime-avibactam or meropenem-vaborbactam, our results show the importance of prescribing early adequate treatment, which is not easy with the first cases of an outbreak or when only sporadic cases occur. In our series, the profile of hospitalized patients with KPC-Kp UTI was very similar to that of patients with carbapenem-susceptible strains. Nevertheless, there are some variables that may be helpful to identify these patients. In fact, antibiotic therapy in the previous month was associated in adjusted analysis with KPC-Kp aetiology (OR 4.51; CI 95% 1.66–12.29; $p = 0.003$), and 13 patients among those with KPC-Kp UTI (28.3%) were previously known to be colonised. Certain centers with outbreaks must consider empirical treatment of KPC-Kp in selected cases of UTI in addition to standard treatment of cephalosporin-resistant strains. We have recently proposed an algorithm that can help to indicate adequate empirical treatment in this scenario.[23]

Based on our data, we cannot state that KPC-Kp aetiology and inappropriate empirical treatment are associated with higher 30-day all-cause mortality. In general, it is accepted that early and adequate empirical treatment reduces mortality in septic patients.[24] It should be noted that studies on KPC-Kp bacteraemia have shown lower mortality when the source is the urinary tract.[25] Our observation is relevant for centers with sporadic cases of KPC-Kp UTI, since the usual empirical treatment protocols do not cover these isolates. It seems that 30-day all-cause mortality is associated with the comorbidities of the patient (Charlson comorbidity index), the presence of bacteraemia and its severity (Pitt bacteremia score).

Our study has the obvious and important limitation of our sample size due to the number of available cases. This means that our estimates have low precision and that the results of the adjusted analysis should be interpreted with caution. Our study has other limitations inherent in observational retrospective cohorts. Although the confounding variables have been controlled for, they may be subject to the usual biases. However, in the absence of controlled trials, these analyses of clinical practice are the best available evidence to manage patients. Finally, the Pitt bacteremia score has not been validated for patients without bacteremia.

Despite this, our study provides some insights about the association between KPC-Kp aetiology and clinical failure, as well as the implications of inappropriate empirical treatment. It is necessary to insist on the need to initiate appropriate early treatment using, whenever possible, an objective algorithm[23] that helps to indicate empirical antibiotic coverage of KPC-Kp.

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## Conflict of interest

JRB has served as scientific advisor for a research project for AstraZeneca and InfectoPharm and has been a speaker in unrestricted accredited educational activities funded by Merck. JTC has served as scientific advisor for a research/consensus projects for Pfizer and as an expert in a consensus document for Infecto-Pharm. He has received honoraria for lectures including service on speakers bureaus and for the development of educational presentations for Pfizer, AstraZeneca and Merck. AC has received honoraria for the development of educational presentations for Pfizer. All other authors declare no conflicts of interest.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.06.014.

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