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Useful independent factors for distinguish infection and colonization in patients with urinary carbapenemase-producing Enterobacteriaceae isolation

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ABSTRACT

Objective. The aim of this study is to know epidemiologic and clinical differences among those patients colonized or infected by carbapenemase-producing Enterobacteriaceae (CPE) and develop a predictive model to facilitate the clinical approach concerning to start antimicrobial therapy.

Methods. Observational retrospective cohort study was performed involving all patients with Urine carbapenemase-producing Enterobacteriaceae isolation (UCPEI) between November 2013 and July 2015. Patients were classifieds as colonized or infected considering Center for Disease Control and Prevention (CDC) definition for urinary tract infection (UTI).

Results. A total of 72 patients were included, mean age 76.4 (IQR 23-99) years and 40 (55.6%) were women. Thirty-four (47.2%) were colonized and 38 (52.8%) met the criteria of UTI and were considered infected. The independent variables associated to infection were female sex, peripheral vascular disease, admission in medical ward, permanent urinary catheter carrier, previous antimicrobial therapy, and length of stay. Isolation of OXA-48 carbapenemase-producing Enterobacteriaceae behaved as a non UTI (colonization) factor in comparison with KPC or VIM CPE. The developed predictive model showed an area under the curve (AUC) of 0.901 (95% CI: 0.832-0.970; $p < 0.001$).

Conclusion. The predictive model that includes all this factors has demonstrated a good accuracy for infection diagnosis in these patients, an important issue considering that establishing the diagnosis of infection is not always easy in the profile of patients in which a CPE is isolated.

Key words: Carbapenemase-producing Enterobacteriaceae, complicated urinary infection, colonization, urinary catheter, risk factors, therapy

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Factores independientes útiles para distinguir colonización e infección en pacientes con aislamiento urinario de enterobacterias portadoras de carbapenamasas

RESUMEN

Objetivo. El objetivo de este estudio es conocer las diferencias epidemiológicas y clínicas entre los pacientes colonizados e infectados por Enterobacterias productoras de carbapenemasa y desarrollar un modelo predictivo para facilitar el abordaje clínico para iniciar la terapia antimicrobiana.

Métodos. Estudio de cohorte retrospectivo observacional que incluyó a todos los pacientes con aislamiento de Enterobacterias productoras de carbapenemasa de la orina entre noviembre de 2013 y julio de 2015. Los pacientes fueron clasificados como colonizados o infectados considerando la definición de CDC para la infección del tracto urinario (UTI).

Resultados. Se incluyeron un total de 72 pacientes, con edad media de 76,4 años (IQR 23-99) y 40 (55,6%) mujeres. Treinta y cuatro (47,2%) fueron colonizados y 38 (52,8%) cumplieron con los criterios de UTI y se consideraron infectados. Las variables independientes asociadas a la infección fueron el sexo femenino, la enfermedad vascular periférica, el ingreso en una planta de medicina, el ser portador de catéter urinario permanente, haber recibido terapia antimicrobiana previa y una estancia media prolongada. El aislamiento de Enterobacterias productoras de carbapenemasa tipo OXA-48 se comportó como un factor de colonización en comparación con el aislamiento de KPC o VIM. El modelo predictivo desarrollado mostró un área bajo la curva (AUC) de 0,901 (IC del 95%: 0,832-0,970, p <0,001).

Conclusión. El modelo predictivo que incluye todos estos factores ha demostrado una buena precisión para el diagnóstico de infección en estos pacientes, una cuestión importante teniendo en cuenta que establecer el diagnóstico de infección

no siempre es fácil en el perfil clínico de los pacientes con aislamiento de una enterobacteria portadora de carbapenemasa.

Palabras Clave: Enterobacteria portadora de carbapenemasa, infección urinaria, colonización, sonda urinaria, factores de riesgo, tratamiento.

INTRODUCTION

Urinary tract infection (UTI) is the most common healthcare-associated infection. In our country, as the ECDC (*European Centre for Disease Prevention and Control*) showed in 2012, UTI represented 18.82% of all nosocomial infections[1]. Nosocomial UTI has been related to the presence of a urinary catheter in more than 80% of the cases, as long as with the duration and the permanent catheterization[2]. In patients undergoing multiple antibiotic treatments or admitted to a social-health centre, isolation of multiresistant gram-negative agents is frequent, such as extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL) and AmpC β-lactamases[3-5].

In the last 3 years, the CPE isolation has emerged in a wide range of infections, including UTI, hospital acquired pneumonia, intra-abdominal infections, and primary bacteriemia[6]. The urine is the sample where the majority of CPE are isolated, such as *Klebsiella pneumoniae,* and displays different types of carbapenemases such as KPC (class A), VIM (class B) and OXA (class D). OXA-48 is by far the most common type of carbapenemase circulating in Spain[5,7]. CPE UTIs represents a growing nosocomial infection.

However, the isolation of a microorganism in urine does not necessarily imply the presence of infection and may simply be related to the status of been colonized. Deciding if a patient is infected or colonized is not always easy in patients with CPE isolation, since they are usually elderly, invasive devices carriers and with significant comorbidity. In this patient profile the clinical and analytical manifestations could be very inexpressive, which makes it difficult to decision-making regarding the initiation or not of antibiotic treatment. Several studies have evaluated the risk factors for infection caused by CPE such as previous antibiotic therapy, presence of an indwelling urinary catheter, surgery, procedures like cardiac catheterization and endoscopy, and admission to an ICU[3]. While lot is known regarding the risk factors for selecting a CPE, little is known to discern among colonization and infection.

Therefore, the aim of this study is to know if there is any different in the epidemiology and clinical characteristics between patients colonized and infected by CPE and develop a predictive model in order to help in the decision-making concerning antibiotic treatment.

MATERIAL AND METHODS

Study design. An observational retrospective cohort study was performed involving all patients with UCPEI in a tertiary hospital between November 2013 and July 2015. Patients were identified through the Microbiology Department database and only a single episode per patient, the first one, was considered during the study period. Study was approved by Ethical Committee in Hospital Clínico San Carlos.

Patient selection. Data were collected from the microbiology laboratory records of patients with UCPEI. Each patient was included only once, at the time of the first UCPEI from clinical samples, and was evaluated and classified either as infected (UTI) or colonized (asymptomatic bacteriuria). UTI was defined as the combination of a positive urine culture growing (≥10^5 CFU/ml) of CPE and ≥ 2 of the following symptoms: urinary symptoms, fever without other demonstrable focus and / or pathological urine analysis (pyuria, leucocytes and nitrites)[8].

Study setting. Hospital Clínico San Carlos is a tertiary, urban, teaching hospital, with an assigned area of approximately 500,000 patients in Madrid.

Definition and collection of variables. Clinical data were obtained by both fulfilling a clinical protocol and consulting medical records, demographic data (age and gender) and comorbidities (Charlson comorbidity index). Severity in comorbidity was defined as a Charlson index ≥3. Risk factors considered selectors of multiresistant pathogens (CPE) were prior antibiotic or hospital admission, indwelling invasive devices, length of stay, type of admission ward, intraabdominal surgery, urological procedures, and selective bowel decontamination. Permanent urinary catheter were defined as urinary catheter with duration of more than 30 days, double J or Pigtail catheter insertion.

Concerning previous antimicrobial therapy, type of antibiotic was also registered (penicillin, penicillin with penicillinase inhibitors, cephalosporines, carbapenems, and fluoroquinolones). It was defined if patients had taken 1 course of antibiotic therapy or more. The ecological impact derived from the usage of carbapenems, define as isolation of carbapenem-resistant *Pseudomonas aeruginosa or Stenotrophomonas maltophilia* within the previous two months, and ESBL-producing Enterobacteriaceae isolation within the previous 6 months of UCPEI were also registered.

A follow-up was carried out, by consulting the electronic clinical history, to determine length of hospital stay, antibiotherapy administered after UTI and the 30-day and 90-day mortality after the index event. The variables were registered in an electronic data collection notebook. The dependent variable consisted on the classification of patients either as colonized or infected.

Microbiological procedures. Enterobacteriaceae strains recovered from urine with imipenem minimum inhibitory concentration (MICs) ≥1 mg/L were prospectively collected. Bacterial identification were performed using MALDI-TOF biotyper mass spectrometry (Bruker, Co), and antibiotic susceptibility testing using Wider® (Fco. Soria Melguizo, Madrid, Spain) or VITEK® (bioMérieux) systems. Imipenem MICs were confirmed by Etest (bioMérieux, Marcy l'Étoile, France). Isolates were categorized as susceptible or resistant to the antibiotics tested according to the interpretative criteria of the CLSI[9]. Breakpoints for tigecycline, fosfomycin and colistin were those of the Euro-

Table 1 **Characteristics of the patients based on the established classification of infected or colonized**

VARIABLE	UTI	COLONIZED	OR (95% CI)	P value
Age (years) [76.4(29-99)]	81.5 (69-84)	80 (68-85)		0.756
Female sex [40 (55.6)]	25 (65.8)	15 (44.1)		0.065
COMORBIDITY				
Charlson Index ≤ 3 [48 (66.6)]	24 (63.2)	24 (70.6)	0.71 (0.26-1.92)	0.504
Diabetes without end-organ damage [10 (13.8)]	3 (7.9)	7 (20.6)	0.33 (0.07-1.39)	0,12
Diabetes with end-organ damage [8 (11.1)]	3 (7.9)	5 (15.2)	0.48 (0.10-2.18)	0,335
Moderate or severe renal disease [13(18)]	7 (18.4)	6 (17.6)	1.05 (0.31-3.51)	0,932
Myocardial infarction [8(11.1)]	4 (10.5)	4 (11.8)	0.88 (0.20-3.83)	0.867
Congestive heart failure [15(20.8)]	11 (28.9)	4 (11.8)	3.05 (0.86-10.73)	0.073
Peripheral vascular disease [13(18)]	5 (13.2)	8 (23.5)	0.49 (0.14-1.68)	0.253
Cerebrovascular disease [6(8.3)]	3 (7.9)	3 (8.8)	0.88 (0.16-4.71)	0.887
Hemiplegia [8(11.1)]	7 (18.4)	1 (2.9)	7.45 (0.86-64.09)	0.037
Connective tissue disease [4(5.5)]	2 (5.3)	2 (5.9)	0.88 (0.11-6.68)	0.909
Dementia [15(20.8)]	7 (18.4)	8 (23.5)	0.73 (0.34-2.29)	0.594
Chronic pulmonary disease[10(13.8)]	7 (18.4)	3 (8.8)	2.33 (0.55-9.86)	0.24
Moderate or severe liver disease [3(4.1)]	1 (2,6)	2 (5.9)	0.43 (0.03-4.99)	0.491
Mild liver disease [5(7)]	2 (5.3)	3 (8.8)	0.57 (0.90-3.66)	0.553
Peptic ulcer disease[3(4.1)]	2 (5.3)	1 (2.9)	1.83 (0.15-21.17)	0.623
Leukemia	0	0		
Lymphoma [3(4.1)]	2 (5.3)	1 (2.9)	1.83(0.15-21.17)	0.623
Tumor without metastasis [15(20.8)]	7 (18.4)	8 (23.5)	0.73 (0.23-2.29)	0.594
Metastatic solid tumor [8(11.1)]	6 (15.8)	2 (5.9)	3 (0.56-15.99)	0.182
AIDS	0	0		
SITE OF ADMISSION				
Medical ward [38(52,8)]	25 (65.8)	13 (38.2)	3.10 (1.18-8.13)	0.019
Surgical ward [19(26.4)]	7 (18.4)	12 (35.3)	0.41 (0.14-1.22)	0.105
Emergency room [4(8.6)]	2 (5.3)	2 (5.9)	0.88 (0.11-6.68)	0.909
Admission in ICU [11(15.2)]	4 (10.5)	7 (20.6)	0.45 (0.12-1.71)	0.236
RISK FACTORS				
SBD [14(19.4)]	7 (18.4)	7 (38.2)	0.36 (0.12-1.06)	0.061
Digestive endoscopy [21(29.1)]	12 (31.6)	9 (26.5)	1.28 (0.46-3.56)	0.634
Mechanical ventilation [19(26.4)]	9 (23.7)	10 (29.4)	0.74 (0.26-2.12)	0.583
Intraabdominal surgery [12(16.6)]	4 (13.2)	8 (23.5)	0.77 (0,30-1,97)	0,598
Urinary catheter [54(75)]	30 (78.9)	24 (70.6)	1.56 (0.53-5.57)	0.413
Permanent urinary catheter [10(13.9)]	8 (21.6)	2 (6.2)	4.13 (0.81-21.14)	0.070
Central venous catheter [25 (34.7)]	14 (36.8)	11 (32.4)	1.22 (0.46-3.23)	0.690

UTI: urinary tract infection; OR: odds ratio; CI: confidence interval; IQR: Interquartile range; UCPEI: Urine carbapenem-producing Enterobacteriaceae isolation; ICU: intensive care unit; SBD: Selective bowel decontamination; ESBL: extended-spectrum β-lactamase-producing Enterobacteriaceae.

pean Committee on Antimicrobial Susceptibility Testing (EUCAST) for Enterobacteriaceae[10].

Carbapenemase production was screened by the modified Hodge test (MHT). The presence of MBL was detected by the combined disk test with imipenem and EDTA (10 µL, 100 mM), and the combined disk test with meropenem and phenylboronic acid (PBA) (10 µL/µL, 40 µg/µL) was used to screen for production of class A carbapenemases. All of the isolates in which carbapenemase production was detected were characterised by molecular methods. PCR was used for identification of the carbapenemase genes *bla*KPC, *bla*VIM, *bla*IMP, *bla*NDM-1and *bla*OXA-48[11,12].

Statistical analysis. To analyse all variables between colonized and infected patients univariate analysis were carried out. The Student t and Mann-Whitney U tests were used to compare normally and non-normally distributed continuous variables, respectively. Comparison of proportions for categorical variables was performed by Fisher's exact test or chi-square test. Odds ratio (OR) and 95% confidence interval (CI) were calculated for all valid associations. Multivariate logistic regression models (backward stepwise) were performed using the presence of infection as the dependent variable and including those significantly ($p \leq 0.20$) associated in the univariate analysis as independent variables. To identify the variables independently associated with infection, a significance level of $p \leq 0.05$ was considered. The power of the logistic regression model to discriminate between colonized and infected patients was expressed as the area under the receiver-operating characteristics curve (AUROC). The statistical analyses were performed using the statistical package SPSS 20.0 software (SPSS Inc., Chicago, Illinois, USA).

Table 1 **Characteristics of the patients based on the established classification of infected or colonized (cont.)**

VARIABLE	UTI	COLONIZED	OR (95% CI)	P value
MICROBIOLOGICAL RESULTS				
Length of stay to UCPEI (days) [22.21(0-96)]	21.5 (7-34)	15.5 (9-30)		0.520
Isolation of ESBL- producing bacteria [17(23.6)]	9 (23.7)	8 (23.5)	1 (0.33-2.99)	0.988
Carbapenem resistant *Pseudomonas aeruginosa* [5(6.9)]	2 (5.3)	3 (8.8)	0.57 (0.90-3.66)	0.553
Stenotrophomonas maltophilia [2 (2.8)]	1 (2.6)	1 (2.9)	0.89 (0.54-14.83)	0.936
KPC [31 (43.1)]	17 (44.7)	14 (42.2)	1.15 (0.45-2.94)	0,761
VIM [10 (13.9)]	7 (18.4)	3 (8.8)	2.33 (0.55-9.86)	0.240
OXA [30 (41.7)]	13 (34.2)	17 (50)	0.52 (0.20-1.34)	0.175
ANTIBIOTIC THERAPY				
One full course of antibiotics [53(73.6%)]	31 (81.6)	22 (64.7)	2.41 (0.82-7.11)	0.105
Penicilin [3(4.1)]	0 (0)	3 (7.9)	0.39 (0.30-0.50)	0.036
Penicillin with penicillinase inhibitors [16(22.2)]	9 (16.7)	7 (18.4)	0.88 (0.29-2.63)	0.827
Cephalosporines[17(23.6)]	11 (20.4)	6 (15.8)	1.36 (0.45-4.07)	0.577
Carbapenems [31(43)]	20 (37)	11 (28.9)	1.44 (0.59-3.52)	0.419
Fluoroquinolones [25(34.7)]	14 (25.9)	11 (28.9)	0.85 (0.34-2.17)	0.748
CLINICAL OUTCOME				
Length of stay (days) [34.19(1-100)]	34.5 (21-53)	25.5 (13-41)		0.112
30-day-mortality [17(23.6)]	13 (34.2)	4 (11.8)	1.36 (0.45-4.07)	0.577
90-day-mortality [10(13.9)]	7 (18.4)	3 (8.8)	1.44 (0.59-3.52)	0.419

UTI: urinary tract infection; OR: odds ratio; CI: confidence interval; IQR: Interquartile range; UCPEI: Urine carbapenem-producing Enterobacteriaceae isolation; ICU: intensive care unit; SBD: Selective bowel decontamination; ESBL: extended-spectrum β-lactamase-producing Enterobacteriaceae.

RESULTS

Seventy-two patients with CPE isolates from urine samples were finally included. The mean age was 76.4 (IQR 23-99) years and 40 (55.6%) were women. Moreover, 38 (52.8%) isolates corresponded to patients hospitalized in medical wards, 19 (26.4%) to patients from surgical wards, 11 (15.2%) from the ICU, and 4 (8.6%) from the emergency room. Thirty-four (47.2%) patients were colonized and 38 (52.8%) met the criteria of UTI and were considered infected.

Concerning the evolution of the clinical processes, a total of 27 (37.5%) patients died, 17 (23.6%) of them within 30 days from admission and 10 (13.9%) within 90 days. After adjusted by comorbidity using the Charlson score, the mortality rate was higher among the patients admitted to medical wards than those admitted to surgical wards (13 of 38 vs 4 of 36; p=0.017).

Our study showed that 24 (33.3%) patients had a Charlson index ≥ 3. Among patients that had suffered instrumentalization, 54 (75%) an indwelling urinary catheter, 10 (13.9%) a permanent urinary catheter, 21 (29.1%) undergone digestive endoscopy, 12 (16.6%) intraabdominal surgery, and 3 (4.1%) undergone urological procedures. Moreover, 14 (19.4%) patients received selective bowel decontamination, 19 (26.4%) underwent mechanical ventilation, and 25 (34.7%) bore central venous catheter. The median length of stay was 34.19 (IQR: 1-100) days. Mean time from admission to UCPEI was 22.21 (IQR: 0-96) days. Twenty-four (33.3%) patients had been admitted in the ICU, and the mean stay was 8.18 (IQR: 0-95) days.

Regarding the previous antibiotic therapy, 53 (73.6%) patients had received at least one full course of antibiotics, mainly with carbapenems [31 (43%) patients], followed by fluoroquinolones [25 (34.7%) patients], cephalosporines [17 (23.6%) patients], penicillin with penicillinase inhibitors [16 (22.2%) patients], and penicillins [3 (4.1%) patients]. ESBL-producing Enterobacteriaceae were isolated in 17 (23.6%) of patients within the previous 6 months to UCPEI, carbapenem-resistant *P. aeruginosa* in 5 (6.9%) and *S. maltophilia* in 2 (2.8%), both two last within the previous 2 months to UCPEI.

The most frequent antimicrobial treatments used were fosfomycin (23%), in combinations with extended infusion of meropenem (EIM) (18%), or tigecycline (12%) prescribed at high dose (100 mg twice a day).

Microbiological results. In relation to the isolated pathogens, 58 (80.6%) were *K. pneumoniae*, 2 (2.8%) *Klebsiella oxytoca*, 7 (9.7%) *Enterobacter cloacae*, 2 (2.8%) *Enterobacter aerogenes*, 2 (2.8%) *Serratia marcescens*, and 1 (1.4%) *Providencia stuartii*.

The genotyping testing characterized 31 (43.1%) isolates as positive for KPC, 30 (41.7%) isolates as OXA-48 enzyme, 10 (13.9%) as VIM, and 1 (2.1%) as KPC + VIM. About antimicrobial resistance, 70 (97.2%) isolates showed imipenem resistance, and in 37 (51.4%) isolates MICs were ≤ 8 mg/L. Ciprofloxacin resistance was found in 69 (95.8%) of the isolates. Twenty-four (33.3%) isolates were resistant to colistin, 32 (44.4%) to tigecycline, 26 (36.1%) to fosfomycin and 7 (9.7%) to amikacin.

Infection and colonization. Table 1 shows the characteristics of the patients and the univariate analyses based on the established classification of infected or colonized.

UTI was more frequent among women (62.5% vs 40.6%,

Table 2 Independent variables associated to infection in patients with UCPEI

VARIABLE	OR (95% CI)	P value
Sex	8,595 (1,776-41,592)	0.007
Peripheral vascular disease	0.055 (0.006-0.5)	0.010
Medical ward admission	24,599 (2,605-232,260)	0.005
Permanent urinary catheter	41,216 (2,348-723,443)	0.011
One course of antibiotic	11,957 (1,752-81,604)	0.011
Length of stay	1,049 (1-1,101)	0.049
OXA-48	0.027 (0.002-0.355)	0.006

UCPEI: Urine carbapenem-producing Enterobacteriaceae isolation

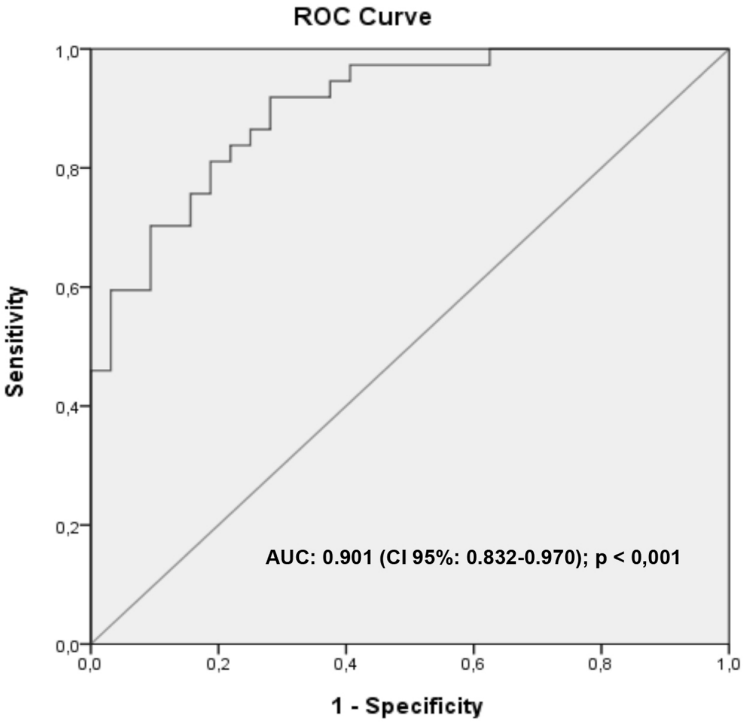

Figure 1 (a) ROC curve and area under curve (AUC) of the predictive model of infection in patients with patients with UCPEI.

ROC: Receiver-operating characteristics
UCPEI: Urine carbapenem-producing Enterobacteriaceae isolation

p=0.065) and patients with co-morbid conditions at the time of admission (58.5% vs 45.2%, p=0.260). The percentage of patients presenting permanent urinary catheter was higher in infected than in those CPE carriers (80% vs 49.2%, p=0.07). Infections were more frequent among medical wards (65.8% vs 38.2%, p=0.019). The median hospital stay prior to culture collection (40.21 vs 32.35 days, p=0.112) and prior antibiotic exposure rate was higher among patients with infection than colonized (58.5% vs 36.8%, p=0.105). Percentage of deaths was higher among infected patients than among colonized in the first 30 days (76.5% vs 45.5%, p=0.025).

Table 2 shows the results of the multivariate analyses. The independent variables selected by the logistic regression model (Nagelkerke R-square = 0.607; p<0,001), Hosmer & Lemeshow: p= 0.966, AUC= 90.1%, associated to infection were sex, peripheral vascular disease, admission in medical ward, length of stay, permanent urinary catheter carrier, and previous antimicrobial therapy.

Isolate of OXA-48 behaved as a factor related to colonization, not to infection (table 2). The logistic regression model displayed a good predictive power, with an overall predictive accuracy of 0.901% (95% CI: 0.832-0.970; $p < 0.001$) (figure 1).

DISCUSSION

The present study has shown some risk factors independently associated with infection in patients with UCPEI like permanent urinary catheter, female gender, prior antibiotic exposure, medical ward admission, length of stay and peripheral vascular disease. OXA-48 producing Enterobacteriaceae isolation was related to colonization, not to infection. The predictive model that includes all these elements has demonstrated a good accuracy for infection diagnosis in these patients.

Firstly, most of studies published about describing risk factors associated to UCPEI, without assessing its clinical signification[6-8,10]. Second, to differentiate colonization from an infection in some clinical profiles is difficult. Frequently these patients have important comorbidities, are immunosuppressed or elderly, factors that can induce atypical clinical manifestations hindering the initial approach. Thirdly, it is well known that early and appropriate treatment has been associated to a better clinical outcomes, both in survival and reduction of health costs, especially but not only, in those patients with worse clinical course. On the other hand, there is a trend of broad-spectrum antimicrobial prescription in this kind of patients due to the complexity of their diagnosis, which can lead in over-cost and ecological impact as a result of unnecessary antibiotic use. Lastly, the treatment of these infections usually requires high doses of antimicrobials, which could increase risks of toxicity[13,14]. Therefore, we need tools to help us in clinical decisions, especially in those patients on which clinical or analytical signs are not enough suggestive of infection, to start antimicrobial therapy in those having these factors, which are independently associated with a higher risk of UTI.

UTI by multidrug-resistant microorganisms are frequently related to the presence of permanent urological devices (catheter, pig-tail, double J), because an adequate environment is generated, favoured by the antibiotic pressure in which the physiological mechanisms of urinary clearance are also avoided. This situation of antibiotic pressure favours selection of resistant strains capable of transferring this resistance to other Enterobacteriaceae in mobile genetic elements. Sometimes this situation also occurs favoured by cross-transmission by hands of health personnel[2,15,16]. In our serie, permanent catheterization had statistical significance as a risk factor for developing CPE UTI and the duration of catheterization was the most important risk factor in any kind of UTI. These data have already been communicated[2,8,15]. Given the difficulty in establishing a diagnosis of UTI in patients with permanent urinary catheter, because of the non-specific symptoms, after UCPEI in patients with permanent urinary devices who have fever and/or leucocytosis, antimicrobial therapy may be justified in the absence of another infectious foci[17,18]. Therefore, it is of great importance for clinicians to consider daily the need of keeping the urinary catheter, in order to avoid unnecessary antibiotic overtreatment and to prevent transferring of resistance genes in these clinical reservoirs. Lastly, any broad-spectrum antibiotic, not only carbapenems, can contribute to CPE selection[5,17] and in our population studied, the majority of patients with CPE UTI had received antibiotic treatment with β-lactam/β-lactamase inhibitor combinations, fluoroquinolones or carbapenems. Thus, the urinary catheterization, especially in female (because of the anatomic proximity to the rectum), and in elderly patients (who are frequently comorbid) with previous antimicrobial treatment and admission in medical wards were main predisposing combination to suffer a CPE UTI[3,6,9].

From a microbiological point of view, isolation of an OXA-48-producing Enterobacteriaceae in the urine samples of our hospitals is becoming increasingly frequent, often among patients without symptoms. This could be due to the efficient dissemination of the *bla*OXA-48 gene among the faecal flora of our hospitalized patients facilitating a high rate of colonization that leads to an increased dispersion of this enzyme producing a complex epidemiological situation with a high number of colonized individuals[7,19]. The *bla*OXA-48 gene is housed in a conjugated plasmid whose gene encodes a protein that inhibits bacterial conjugation, which leads to an increase in the frequency of plasmid conjugation and efficient dissemination of the *bla*OXA-48 gene[20]. This may be probably the key factor for the successful diffusion of this plasmid[21,22]. Although there are no differences in virulence between the different species of CPE, our results showed that OXA-48 was more frequently associated with the non-infection (colonization) group.

Majority of isolates corresponded to *K. pneumoniae*, most of which expressed KPC and OXA-48. There has been an epidemiological change with respect to CPE in our hospital, being KPC and VIM predominant from 2010 to 2012[23], KPC and OXA during the present study analysis period (2013-2015), emerging OXA-48 from 2015 to present time, as it has been the case in other hospitals in the country[24]. In recent years, outbreaks of KPC-producing strains have been reported in some Spanish hospitals presenting limited therapeutic alternatives[25,26] and new molecules such as ceftazidime-avibactam have already been used in some cases with good results. This new therapeutic option, ceftazidime-avibactam, is highly active against CPE class A, has variability in activity against CPE Class D and none against those harbouring metalloenzymes (Class B)[27]. To complicate this therapeutic scenario, new mechanisms of resistance to colistin have recently been reported such as the horizontal transfer of the *mcr*-1 gene[28].

These reduced susceptibility profiles have therapeutic implications. Thus, combinations of meropenem in extended perfusion, high dose tigecycline and fosfomycin were the most chosen strategies, as reported another authors[14,25]. Although some of these therapeutic regimens are not standardized and have suboptimal pharmacokinetics in UTI, they were used because of therapeutic needs. Specifically in the case of tigecycline at high doses, with which hepatic toxicity has been described[29], we observed in our treated patients an elevation of 3-5 times the value of the liver enzymes, but the withdrawal of the drug was not necessary. Similarly, withdrawal of colistin by standard dose toxicity of 4.5 million units twice daily in cycles of 5-7 days was not required either.

Given that the therapeutic complexity of infections caused by CPE is one of the most difficult challenges in current infectious diseases and due to its rapid spread through the hospitals, it is important to maximize infection control measures and optimize antibiotic policies[30]. Further studies are also needed to specify UTI risk factors after UCPEI that allow us to avoid unnecessary antibiotic treatments that favour the selection of resistant strains.

The present study has certain limitations. First, its retrospective nature may limit the application of some conclusions. Secondly, it is a unicentric study. Despite all of this, we can conclude that the present study emphasize the importance of the permanent urinary catheter, female gender, peripheral vascular disease, prior antibiotic exposure, medical ward admission and length of stay as clinically relevant risk factors to develop a CPE UTI, and can help in a decision-making not always easy.

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CONFLICTS OF INTEREST

None to declare

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