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ORIGINAL RESEARCH

A Large Multicenter Prospective Study of Community-Onset Healthcare Associated Bacteremic Urinary Tract Infections in the Era of Multidrug Resistance: Even Worse than Hospital Acquired Infections?

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ABSTRACT

Introduction: Healthcare-associated (HCA) infections represent a growing public health problem. The aim of this study was to compare community-onset healthcare associated (CO-HCA) bacteremic urinary tract infections (BUTI) and hospital-acquired (HA)-BUTI with special focus on multidrug resistances (MDR) and outcomes.

Methods: ITUBRAS-project is a prospective multicenter cohort study of patients with HCA-BUTI. All consecutive hospitalized adult patients with CO-HCA-BUTI or HA-BUTI episode were included in the study. Exclusion criteria were: patients < 18 years old, non-hospitalized patients, bacteremia from another source or primary bacteremia, non-healthcare-related infections and infections caused by unusual pathogens of the urinary tract. The

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main outcome variable was 30-day all-cause mortality with day 1 as the first day of positive blood culture. Logistic regression was used to analyze factors associated with clinical cure at hospital discharge and with receiving inappropriate initial antibiotic treatment. Cox regression was used to evaluate 30-day all-cause mortality.

Results: Four hundred forty-three episodes were included, 223 CO-HCA-BUTI. Patients with CO-HCA-BUTI were older ($p < 0.001$) and had more underlying diseases ($p = 0.029$) than those with HA-BUTI. The severity of the acute illness (Pitt score) was also higher in CO-HCA-BUTI ($p = 0.026$). Overall, a very high rate of MDR profiles (271/443, 61.2%) was observed, with no statistical differences between groups. In multivariable analysis, inadequate empirical treatment was associated with MDR profile (aOR 3.35; 95% CI 1.77–6.35), *Pseudomonas aeruginosa* (aOR 2.86; 95% CI 1.27–6.44) and Charlson index (aOR 1.11; 95% CI 1.01–1.23). Mortality was not associated with the site of acquisition of the infection or the presence of MDR profile. However, in the logistic regression analyses patients with CO-HCA-BUTI (aOR 0.61; 95% CI 0.40–0.93) were less likely to present clinical cure.

Conclusion: The rate of MDR infections was worryingly high in our study. No differences in MDR rates were found between CO-HCA-BUTI and HA-BUTI, in the probability of receiving inappropriate empirical treatment or in 30-day mortality. However, CO-HCA-BUTIs were associated with worse clinical cure.

Keywords: Urinary tract infections; Bloodstream infections; Multidrug resistant; Community-onset healthcare-associated infections; Hospital-acquired infections

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Key Summary Points

Healthcare-associated (HCA) infections represent a growing public health problem.

Community-onset healthcare associated infections are increasing in complexity, but little is known about whether they should be managed as hospital-acquired infections.

We compared hospital-acquired and community-onset HCA bacteremic urinary tract infections (UTIs) with special focus on multidrug resistance (MDR) and clinical outcomes.

Community-onset HCA bacteremic UTIs occurred in eldery and sicker patients and were associated with a worse clinical cure at hospital discharge than hospital-acquired infections.

No differences were found in MDR rates or in mortality between groups.

INTRODUCTION

Urinary tract infections (UTIs) are among the three most frequent healthcare-associated (HCA) infections following respiratory and surgical site infections [1, 2]. They are one of the most common reasons for prescribing antibiotics, with a substantial important economic burden [3].

Antimicrobial resistance represents a growing public health issue with significant impact on antibiotic use and patient outcomes [3–5]. In recent years, there has been an alarming increase in antimicrobial resistance among uropathogens [3]. Infections caused by extended-spectrum β-lactamase (ESBL), AmpC β-lactamase- and carbapenemase-producing *Enterobacterales* are increasing worldwide [3, 4, 6, 7]. Most of the ESBL-producing *Enterobacterales* infections appear after healthcare exposure [6, 8]. Carbapenem-resistant infections have increased in the setting of community-acquired or community-onset infections, with a prevalence ranging from 0.04 to 29.5% [9], while multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Pseudomonas aeruginosa* isolates have disseminated globally with increased rates in recent years [5, 10].

HCA infections include both community onset healthcare-associated (CO-HCA) and hospital-acquired (HA) infections [11, 12]. CO-HCA infections involve a heterogeneous group of patients, such as long-term care facility patients, hemodialysis patients or outpatients receiving intravenous chemotherapy [12]. These infections occur in more complex patients and are associated with worse outcomes than community-acquired infections [13–16]. Nevertheless, little is known about whether CO-HCA infections behave differently from those acquired in the hospital setting [17].

Given the importance of UTI in terms of prevalence, emergence of MDR isolates and the complexity of HCA infections, it is interesting to investigate UTI in the HCA setting. In 2010 our group conducted a multicenter prospective study [18] evaluating bacteremic urinary tract infections (BUTI). It suggested that CO-HCA-BUTIs were more like HA-BUTIs than community-acquired group. Approaching CO-HCA carefully and considering their complexity should be crucial to improve their management. In the present study, we aimed to compare CO-HCA-BUTI and HA-BUTI with special focus on the influence of MDR and clinical outcomes. We hypothesized that CO-HCA-BUTI would be similar to HA-BUTI in terms of clinical outcomes and MDR rates.

METHODS

Study Design and Study Population

This study is part of the ITUBRAS-2 project, which aimed to describe the clinical and microbiological characteristics and outcomes of HCA-BUTIs. A prospective, observational, multicenter cohort study was carried out at 12 university hospitals in the framework of the

Spanish Network for Research in Infectious Diseases (http://www.reipi.org). The patient recruitment was carried out between August 2017 and April 2019.

Adult patients who met Friedman's criteria [12] for CO-HCA-BUTI or HA-BUTI were included. A prospective review of all patients with potential uropathogen isolated in blood cultures at each hospital was conducted. The following were considered as potential uropathogens: *Enterobacterales*, *P. aeruginosa*, other non-fermenting gram-negative bacilli, *Staphylococcus saprophyticus*, *Streptococcus agalactiae* and *Enterococcus* spp. Exclusion criteria were: patients < 18 years old, non-hospitalized patients, bacteremia from another source or primary bacteremia, non-healthcare-related infections and infections caused by unusual pathogens of the urinary tract. Polymicrobial infections were included.

The information was entered into a specifically designed electronic research database. All cases were reviewed by a Contract Research Organization (ADKOMA-CRO) and one of the authors (SG-Z), and if controversy was found a double-check was performed by the investigator team at each hospital. The study was approved by the Clinical Research Ethical Committee of Hospital del Mar (registration number 2016/6957/I) and by the local Ethics Committees of each institution (supplementary material). All patients provided written informed consent at the screening. If patients were unable to provide informed consent, they could be entered with the signature of a relative or legal representative. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guideline and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Variables and Definitions

BUTI was considered when the presence of one or more uropathogens in blood cultures was associated with urinary tract symptoms or asymptomatic UTI with the isolation of the same uropathogen in a urine culture and in absence of another source of infection.

CO-HCA-BUTI was defined when the episode was detected at hospital admission or within the first 48 h, which fulfilled any of the following Friedman criteria [12]: (1) receiving intravenous therapy, wound care or specialized nursing care at home by qualified healthcare workers within 30 days prior the episode; (2) attending a hospital, hemodialysis ward or receiving intravenous chemotherapy within 30 days; (3) being hospitalized in an acute care hospital for ≥ 2 days within 90 days; (4) residing in a nursing home or long-term care facility; (5) being subject to an invasive urinary procedure within 30 days of the episode or having a long-term indwelling urethral catheter. HA-BUTI was considered when bacteremia occurred beyond 48 h of hospital admission.

Demographic and clinical characteristics of patients were recorded prospectively. Gender, age, chronic conditions, severity of underlying diseases calculated using the Charlson comorbidity index [19] and the McCabe [20] score were recorded. Patients were considered immunosuppressed if chemotherapy, radiotherapy, corticosteroids and/or other immunosuppressive drugs were administered within the 3 prior months to the bacteremia. Previous urologic history was recorded. Previous use of antibiotic was defined as > 48 h of antibiotic treatment in the 3 months prior to the infection. The severity of acute illness at presentation was calculated using the Pitt bacteremia score [21]. Antimicrobial therapy was considered adequate when the blood culture isolate was susceptible to at least one of the antimicrobial agents prescribed and the dose was in accordance with the current medical standards.

Outcome and Follow-Up

The main outcome variable was 30-day all-cause mortality with day 1 as the first day of positive blood culture. Secondary outcomes were clinical response at hospital discharge, length of hospital stay and rate of inadequate empirical antibiotic treatment. The main variable evaluated was the site of acquisition of the infection

(CO-HCA or HA). Clinical assessment was evaluated 48–72 h after the bacteremia and at hospital discharge. Clinical stability at 48–72 h was considered when the patient was afebrile and with no persistence of signs/symptoms of sepsis attributable to bacteremia at 48–72 h. Clinical cure at hospital discharge was considered when all signs and symptoms of infection were completely resolved at hospital discharge. Clinical improvement was considered when the patient improved but with persistence or recurrence of any signs or symptoms at hospital discharge. Length of hospital stay was defined as stay (days) from the onset of the bacteremia (first day of positive blood culture) until the hospital discharge. Microbiological follow-up was conducted with control blood cultures in case of persistence of fever > 48–72 h after the bacteremia. All patients were followed for 30 days.

Microbiological Studies

All isolates recovered from blood samples were sent to the reference laboratories (Ramón y Cajal, Son Espases), where bacterial identification was confirmed by MALDI-TOF MS (Bruker Daltonics, Bremen, Germany). Antimicrobial susceptibility was studied using the standard broth microdilution method [22]. We defined susceptible isolates combining those categorized as S (susceptible, standard dose regimen) and I (susceptible, increased exposure) according to EUCAST-2019 criteria (http://www.eucast.org/clinical_breakpoints/). The following agents were tested: ampicillin, amoxicillin-clavulanate, piperacillin-tazobactam, ceftazidime, cefotaxime, cefepime, ceftolozane-tazobactam, aztreonam, imipenem, meropenem, ciprofloxacin, gentamicin, tobramycin, amikacin, colistin, fosfomycin, trimethoprim/sulfamethoxazole and vancomycin.

Multidrug-resistant profile was defined in accordance with international definitions [23]. MDR was defined as a strain non-susceptible to at least one agent in ≥ 3 antimicrobial categories. XDR was defined as non-susceptibility to at least one agent in all but ≤ 2 categories. Pandrug resistance (PDR) was defined as resistant to all antimicrobial agents.

ESBL production was screened by the double-disk synergy method and/or the ROSCO ESBL + AMPc Confirm Kit (ROSCO Diagnostica, Taastrup, Denmark) [24, 25]. The screening of carbapenemase production included the colorimetric Carba-NP test (bioMérieux, La Balmes-Grottes, France) and assessment of the inhibition-based profile using the ROSCO KPC/Metallo-β-lactamase (MBL) and OXA-48 Confirm Kit (ROSCO Diagnostica, Taastrup, Denmark) [26, 27]. The presence of horizontally acquired β-lactamases in *P. aeruginosa* was also screened through the ceftazidime/imipenem cloxacillin-inhibition test and the presence of MBLs confirmed by the imipenem/meropenem EDTA double-disk synergy test as described previously [28].

Statistical Analysis

Determining the sample size required (218 patients in each arm) was based on the results of a previous study [18] and in order to detect a 15% difference in the proportion of 30-day mortality between groups, using correction for continuity with a significance level of 95% and power of 80% and considering a patient loss of 10%. Moreover, a post hoc power calculation was conducted regarding the clinical cure as outcome. Accepting an alpha risk of 0.05 in a two-sided test with 223 subjects in the CO-HCA-BUTI group and 220 in the HA-BUTI, the statistical power was 74% to recognize as statistically significant the difference in proportions of MDR profile from 53.4% in the first group to 65.5% in the second group.

Categorical variables were presented as number of cases and percentages and continuous variables as median and interquartile range (IQR). Comparative analyses were performed with X^2 or Fisher's test for categorical variables and the Mann-Whitney U test for continuous variables, as appropriate. A logistic regression model was used for examining independent variables associated with (1) clinical cure and (2) receiving inappropriate empirical treatment. A bivariate analysis was performed to select potential variables that might affect the response. Variables with a p value < 0.10 were

included in the model as well as those not statistically significant but clinically relevant. Resistance profile and appropriate empirical treatment were considered clinically relevant variables to be forced in the regression model as they may impact clinical outcomes [5, 29–32]. Then, the logistic regression model was built using a stepwise automatic variable selection procedure. Results were expressed as odds ratio (OR) and 95% confidence interval (95% CI). Regarding 30-day mortality, we used a multivariable Cox regression model. Results were reported as hazard ratio (HR) and 95% CI. Multivariable analysis included variables with p value < 0.10 in the unadjusted analysis and/or those clinically relevant. Age was considered a clinically relevant variable as clearly impacting mortality. The site of acquisition of infection was also forced in the multivariable analysis as it was the aggrupation variable. Collinearity diagnostics were applied by controlling the variance inflation factor (VIF). Moreover, for Cox regressions, the proportional hazard assumption, checked by examining Schoenfeld residuals (for overall model and variable by variable), was not violated. All analyses were two-tailed, and $p < 0.05$ was considered statistically significant. Statistical analyses were carried out using STATA.15 software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

RESULTS

Clinical Features According to Site of Acquisition of the Infection

A total of 443 episodes of HCA-BUTI were included. Of these, 223 were CO-HCA-BUTI while 220 were HA-BUTI. Table 1 shows a comparative analysis of baseline data according to the site of acquisition of the infection. Patients with CO-HCA-BUTI were older than those with HA-BUTI [77.0 (IQR: 69.0–83.0) vs. 71.0 (IQR: 61.5–78.5); $p < 0.001$] and had more presence of underlying diseases [209/223 (93.72%) vs. 193/220 (87.72%); $p = 0.029$], although no differences were observed in Charslon index ($p = 0.94$).

In both groups, approximately 70% of the patients had received prior antibiotics; the most frequently used in both group included: non-antipseudomonal penicillins and cephalosporins (mainly amoxicillin, amoxicillin-clavulanate, ceftriaxone, cefixime and cefuroxime). About 20% of patients had received carbapenems. Fluoroquinolones were more frequently used in CO-HCA-BUTI patients than in the HA group [46/223, 20.62% vs. 26/220, 11.81%; $p < 0.012$]. Clinical data and outcomes are shown in Table 2. Pitt score was higher in the CO-HCA-BUTI group ($p = 0.026$). There were no differences between groups in either the rate of appropriate empirical treatment or duration of antibiotic therapy.

Microbiological Studies

Microbiological data are presented in Table 3. Overall, 443 episodes were included; 22 of them (4.97%) were polymicrobial bacteremia (3 of them with 3 strains) with a total of 468 isolates. The causative microorganisms isolated were: *E. coli* 234/468 (50.0%), *Klebsiella pneumoniae* 99/468 (21.2%), *Proteus spp*. 21/468 (4.5%), other *Enterobacterales* 51/468 (10.9%), *P. aeruginosa* 41/468 (8.8%) and *Enterococcus* spp. 22/468 (4.7%): *E. faecalis* 15/22, (68.2%) and *E. faecium* 7/22 (31.8%).

A very high percentage of pathogens with an MDR profile was observed in both groups. Although MDR rates were slightly higher in CO-HCA-BUTI, differences did not reach statistical significance [146/223 (65.47%) CO-HCA-BUTI vs. 125/220 (56.81%) HA-BUTI; $p = 0.11$].

Regarding *Enterobacterales*, among MDR strains, six had XDR profile (4 *K. pneumoniae* and 2 *E. cloacae)* and one PDR pattern (*K. pneumoniae)*. ESBL-producing isolates were identified in 117/405 (28.89%) isolates: 73 *E. coli*, 39 *K. pneumoniae*, 1 *Proteus* spp. and 4 in other *Enterobacterales*. We also identified 12 carbapenemases (1 *E. coli*, 6 *K. pneumoniae*, 1 *K. oxytoca*, 3 *E. cloacae* and 1 *M. morganii*). No differences were observed in the rates of ESBL or carbapenemases-producing isolates when comparing groups. Overall, the more active antibiotics among *Enterobacterales* isolates were:

Table 1 Baseline characteristics of patients with bacteremic urinary tract infections and comparative analysis according to the site of acquisition of the infection

Variable	All cases (n = 443)	Community-onset healthcare-associated BUTI (n = 223)	Hospital-acquired BUTI (n = 220)	p
Baseline features				
Gender (male)	288 (65.0)	145 (65.0)	143 (65.0)	1.00
Age, years, median (IQR)	74.0 (65.0–82.0)	77.0 (69.0–83.0)	71.0 (61.5–78.5)	< 0.001
Charlson index, median (IQR)	3 (2–5)	3 (2–6)	3 (2–5)	0.944
McCabe score II–III	157 (35.5)	76 (34.1)	81 (36.99)	0.552
Any underlying disease	402 (90.7)	209 (93.7)	193 (87.7)	0.029
Diabetes Mellitus	128 (28.9)	65 (29.1)	63 (28.6)	0.91
Chronic renal failure	135 (30.5)	61 (27.4)	74 (33.6)	0.15
Chronic pulmonary disease	59 (13.3)	32 (14.3)	27 (12.3)	0.52
Cardiovascular disease	135 (30.5)	60 (26.9)	75 (34.1)	0.10
Chronic liver disease	26 (5.9)	9 (4.0)	17 (7.7)	0.098
Vascular/degenerative brain disease	94 (21.2)	58 (26.0)	36 (16.4)	0.013
Malignant disease	182 (41.1)	104 (46.6)	78 (35.5)	0.017
Immunosuppressive therapy	121 (27.4)	50 (22.4)	71 (32.4)	0.018
Previous urological history				
Recurrent UTI (> 2 episodes/year)	84 (19.6)	64 (29.8)	20 (9.4)	< 0.001
Structural urinary tract abnormalities	141 (32.1)	84 (38.0)	57 (26.1)	0.008
Indwelling urinary devices	269 (60.7)	120 (53.8)	149 (67.7)	0.003
Urological malignancy	111 (25.1)	74 (33.2)	37 (16.8)	< 0.001
Friedman criteria				
Previous hospitalization (90 days)		146 (65.5)		
Indwelling urinary devices[a]		112 (50.2)		
Residing in long-term care facility		50 (22.4)		
Previous ev. chemotherapy (30 days)		20 (9.0)		
Previous ev. therapy in day hospital (30 days)		10 (4.5)		

Table 1 continued

Variable	All cases (n = 443)	Community-onset healthcare-associated BUTI (n = 223)	Hospital-acquired BUTI (n = 220)	p
Hemodialysis program		4 (1.8)		
Specialized ambulatory nursing care (30 days)		10 (4.5)		
Prior antimicrobial therapy				
Any antibiotic (90 days)	315 (71.1)	163 (73.1)	152 (69.1)	0.353
Fluoroquinolones	72 (16.3)	46 (20.6)	26 (11.8)	0.012
Trimethoprim/sulfamethoxazole	35 (7.9)	13 (5.8)	22 (10.0)	0.104
Fosfomycin	59 (13.3)	26 (11.7)	33 (15)	0.30
Non antipseudomonal penicillins	130 (29.3)	63 (28.3)	67 (30.5)	0.61
Antipseudomonal penicillins	58 (13.1)	20 (9.0)	38 (17.3)	0.010
Non-antipseudomonal cephalosporins	121 (27.3)	67 (30.0)	54 (24.5)	0.194
Antipseudomonal cephalosporins	64 (14.5)	37 (16.6)	27 (12.3)	0.196
Carbapenems	87 (19.6)	41 (18.4)	46 (20.9)	0.50
Aminoglycosides	12 (2.7)	8 (3.6)	4 (1.8)	0.25
Ceftolozane-tazobactam	12 (2.7)	1 (0.5)	11 (5)	0.003

Data are presented as no. (%) unless otherwise specified

BUTI, bacteremic urinary tract infection; IQR, interquartile range; UTI, urinary tract infection

[a] Indwelling urinary devices or had conducted an invasive urinary procedure within the last 30 days

colistin (5.96% of resistance excluding isolates of intrinsically resistant species, respectively), amikacin (5.99% resistance) and ceftolozane-tazobactam (7.20% resistance).

Regarding *P. aeruginosa*, MDR phenotype was documented in 12/41 (29.27%) isolates; among them, 5 (12.20%) were XDR. Only two isolates produced MBLs. Antibiotics with lower rates of resistance for *P. aeruginosa* were: colistin (0%), amikacin (0%) and ceftolozane/tazobactam (5.3%). Only the two MBL-producing isolates were resistant to ceftolozane/tazobactam. Finally, among episodes caused by enterococci (n = 22), all *E. faecium* strains (n = 7) showed an MDR phenotype.

Clinical Outcomes

Mortality Analysis

Thirty-day mortality occurred in 29 patients (6.55%), and no differences were observed between the two groups. Unadjusted and adjusted 30-day mortality is shown in Table 4. The McCabe score was not included in the multivariable model to avoid collinearity. After adjustment, mortality was associated with the severity of the underlying disease according to the Charlson index (aHR1.19 [95% CI, 1.04–1.37]) and with being immunosuppressed (aHR 2.24 [95% CI, 1.00–5.00]). In the multivariable analysis, mortality was not associated

Table 2 Clinical characteristics and outcome of patients according to the site of acquisition of the bacteremic urinary tract infection

Variable	All cases (n = 443)	Community-onset healthcare-associated BUTI (n = 223)	Hospital-acquired BUTI (n = 220)	p
Clinical presentation				
Pitt score > 2	160 (36.2)	92 (41.3)	68 (31.1)	0.026
Septic shock	59 (14.0)	36 (16.9)	23 (11.1)	0.088
ICU admission required	82 (18.7)	22 (9.9)	60 (27.9)	< 0.001
Irritative urinary symptoms	134 (31.9)	86 (40.4)	48 (23.2)	< 0.001
Renal pain	47 (11.2)	32 (15)	15 (7.2)	0.011
Prostate pain in DRE	6 (2.8)	2 (1.0)	8 (1.9)	0.165
Temperature > 38 °C	352 (83.8)	186 (87.3)	166 (80.2)	0.047
Leukocytes (10^3/ul), median (IQR)	12 (8.3–16.8)	12.1 (8.5–17.7)	11.2 (7.8–16.3)	0.316
Polimicrobial infection	22 (4.97)	14 (6.3)	13 (5.9)	0.364
MDR profile	271 (61.2)	146 (65.5)	125 (56.8)	0.062
Treatment				
Appropriate empirical treatment	359 (81.0)	183 (82.1)	176 (80.0)	0.580
Fluoroquinolones	134 (30.3)	61 (27.3)	73 (33.2)	0.182
Ampicillin	39 (8.8)	25 (11.2)	14 (6.4)	0.072
Amoxicillin-clavulanate	98 (22.1)	55 (25.0)	43 (19.3)	0.147
Non-antipseudomonal cephalosporins	159 (35.9)	102 (45.7)	57 (25.9)	< 0.001
Antipseudomonal cephalosporins	61 (13.8)	35 (15.7)	26 (11.8)	0.236
Piperacillin-tazobactam	108 (24.4)	49 (22.0)	59 (26.8)	0.235
Ertapenem	116 (26.2)	67 (30.0)	49 (22.3)	0.063
Imipenem	40 (9.0)	23 (10.3)	17 (7.7)	0.342
Meropenem	157 (35.44)	68 (30.5)	89 (40.5)	0.028
Aztreonam	9 (2.0)	3 (1.4)	6 (2.8)	0.303
Aminoglycosides	53 (12.0)	27 (12.1)	26 (11.8)	0.925
Vancomycin	12 (2.7)	4 (1.79)	8 (3.6)	0.232
Ceftolozane-tazobactam	3 (0.67)	0 (0)	3 (1.4)	0.080
Antibiotic treatment duration (days), mean ± SD	15.43 ± 6.57	15.08 ± 5.67	15.78 ± 7.18	0.255

Table 2 continued

Variable	All cases (n = 443)	Community-onset healthcare-associated BUTI (n = 223)	Hospital-acquired BUTI (n = 220)	p
Urological intervention required	116 (26.2)	60 (26.9)	56 (25.6)	0.750
Outcome				
Clinical assessment at 48-72 h				
Afebrile	393 (89.5)	193 (87.3)	200 (91.7)	0.131
Persistence of sepsis signs/ symptoms	49 (11.2)			0.686
Clinical cure	263 (59.4)	119 (53.4)	144 (65.5)	0.010
Median hospital stay since BUTI, d (IQR)	12 (8–20)	10 (7–14)	16 (10–29.5)	< 0.001
Mortality at day 30	32 (7.2)	17 (7.6)	15 (6.8)	0.743
Mortality related with infection	9 (2)	6 (2.7)	3 (1.4)	0.322

Data are presented as no. (%) unless otherwise specified
IQR, interquatile range; SD, standard deviation. BUTI, bacteremic urinary tract infection; ICU, intensive care unit; irritative urinary symptoms include dysuria, frequency, gross hematuria and urgency; DRE, digital rectal examination; urological intervention required included endoscopic, percutaneous or surgical drainage; MDR, multidrug resistant

with the site of acquisition or the presence of MDR profile.

Length of Stay and Clinical Cure

The median hospital length of stay after the onset of bacteremia was higher in those patients with HA-BUTI ($p > 0.001$). No significant differences were observed in the rate of clinical stability reached at 48–72 h when comparing CO-HCA-BUTI and HA-BUTI [177/223 (79.37%) CO-HCA-BUTI vs. 181/220 (82.23%) HA-BUTI; $p = 0.42$]. In multivariable logistic regression analysis (Table 5) of clinical cure at hospital discharge, both CO-HCA-BUTI (aOR 0.61 [95% CI, 0.40–0.93]) and urinary tract abnormalities (aOR 0.56 [95% CI, 0.36–0.88]) were associated with lower odds of achieving clinical cure at hospital discharge. MDR profile was not associated with a worse clinical cure.

Empirical Antibiotic Treatment

Table S1 in Supplementary Material summarizes the parameters related to receiving inadequate empirical antibiotic treatment. Overall, 85 patients (19.18%) received inadequate initial therapy. Among them, the most frequently used antibiotics were: non-antipseudomonal cephalosporins (26 patients), penicillins plus β-lactamase inhibitors (18 patients), antipseudomonal penicillins plus β-lactamase inhibitors (13 patients) and fluoroquinolones (13 patients). The median time until receiving an active therapy was 3 days. No differences in length of stay were observed between patients who received adequate and inadequate empirical treatment, although the median hospital stay after the onset of BUTI (days) was slightly longer in those who received inadequate empirical treatment [11 (IQR 8–20) vs. 13 (8–22); $p = 0.43$]. In a multivariable analysis, MDR profile (aOR 3.35 [1.77–6.35]), *P. aeruginosa* (OR 2.86 [1.27–6.44]) and Charlson index

Table 3 Microorganisms isolated from blood cultures of patients with bacteremic urinary tract infection: antimicrobial susceptibility, resistance profile and resistance mechanisms

Uropathogen isolated *N* (% global)	**Antibiotic resistance rate (*n*, %)**	**All cases, *n* = 446 Antibiotic resistance (*n*, %)**	**Community-onset healthcare associated BUTI (*n* = 226)**	**Hospital-acquired BUTI (*n* = 220)**	***p***
Escherichia coli		234	132	102	
	Penicillins	191 (81.6)	110 (83.3)	81 (79.4)	0.50
	Penicillins + β-lactamase inhibitor	82 (35.0)	45 (34.1)	37 (36.3)	0.78
	Antipseudomonal penicillins + β-lactamase inhibitor	52 (22.2)	31 (23.5)	21 (20.6)	0.6
	Non antipseudomonal cephalosporins	76 (32.5)	47 (35.6)	29 (28.4)	0.32
	Antipseudomonal cephalosporins	73 (31.2)	46 (34.8)	27 (26.5)	0.20
	Ceftolozane/tazobactam	0	0	0	–
	Monobactams (Aztreonam)	69 (29.5)	42 (31.8)	27 (26.5)	0.38
	Group 1 Carbapenems	1 (0.4)	0	1 (1)	0.44
	Group 2 Carbapenems	0	0	0	–
	Fluoroquinolones	129 (55.1)	81 (61.4)	48 (47.1)	0.034
	Aminoglycosides	67 (28.6)	13 (35.6)	20 (19.6)	0.009
	Trimethoprim-sulfamethoxazole	101 (43.2)	55 (41.7)	46 (45.1)	0.69
	Fosfomycin	83 (35.5)	50 (37.9)	33 (32.4)	0.41
	Polymyxins (Colistin)	1 (0.4)	1 (0.8)	0	1.00
	MDR profile (*n*, % MDR)	172 (73.5)	104 (78.8)	68 (66.7)	0.052
Klebsiella pneumoniae		99	37	62	
	Penicillins + β-lactamase inhibitor	61 (61.6)	19 (51.4%)	42 (67.7)	0.14
	Antipseudomonal penicillins + β-lactamase inhibitor	36 (36.4)	13 (35.1)	23 (37.1)	1.00
	Non antipseudomonal cephalosporins	41 (41.8)	14 (37.8)	27 (44.3)	0.67

Table 3 continued

Uropathogen isolated *N* (% global)	Antibiotic resistance rate (*n*, %)	All cases, *n* = 446 Antibiotic resistance (*n*, %)	Community-onset healthcare associated BUTI (*n* = 226)	Hospital-acquired BUTI (*n* = 220)	*p*
	Antipseudomonal cephalosporins	42 (42.4)	14 (37.8)	28 (45.2)	0.53
	Ceftolozane/tazobactam	17 (17.7)	4 (10.8)	13 (22.0)	0.18
	Monobactam (Aztreonam)	41 (42.3)	14 (37.8)	27 (45.0)	0.53
	Group 1 Carbapenems	9 (9.1)	2 (5.4)	7 (11.3)	0.48
	Group 2 Carbapenems	3 (3.0)	0 (0.0)	3 (4.8)	0.29
	Fluoroquinolones	47 (47.5)	15 (40.5)	32 (51.6)	0.31
	Aminoglycosides	39 (39.4)	14 (37.8)	25 (40.3)	0.84
	Trimethoprim-sulphamethoxazole	44 (44.4)	16 (43.2)	28 (45.2)	1.00
	Fosfomycin	84 (87.5)	33 (89.2)	51 (86.4)	0.76
	Polymyxins (Colistin)	5 (5.2)	1 (2.7)	4 (6.8)	0.65
	MDR profile (*n*, % MDR)	56 (56.6)	19 (51.4)	37 (59.7)	0.53
Proteus spp.		21	14	7	
	Penicillins + β-lactamase inhibitor	9 (42.9)	9 (64.3)	0	0.007
	Antipseudomonal penicillins + β-lactamase inhibitor	0	0	0	–
	Non antipseudomonal cephalosporins	1 (4.8)	0	1 (14.3)	1.00
	Antipseudomonal cephalosporins	1 (4.8)	0	1 (14.3)	1.00
	Monobactams (Aztreonam)	1 (4.8)	0	1 (14.3)	1.00
	Group 1 and group 2 carbapenems	0	0	0	–
	Fluoroquinolones	11 (52.4)	10 (71.4)	1 (14.3)	0.02
	Aminoglycosides	10 (47.6)	7 (50.0)	3 (42.9)	1.00

Table 3 continued

Uropathogen isolated *N* (% global)	Antibiotic resistance rate (*n*, %)	All cases, *n* = 446 Antibiotic resistance (*n*, %)	Community-onset healthcare associated BUTI (*n* = 226)	Hospital-acquired BUTI (*n* = 220)	*p*
	Trimethoprim-sulfamethoxazole				
	Fosfomycin	9 (42.9)	7 (50.0)	2 (28.6)	0.64
	MDR profile (*n*, % MDR)	11 (52.4)	10 (71.4)	1 (14.3)	0.02
Other *Enterobacterales*		51	21	30	
	Antipseudomonal penicillins + β-lactamase inhibitor	13 (25.5)	4 (19.0)	9 (30.0)	0.52
	Non antipseudomonal cephalosporins	15 (29.4)	3 (14.3)	12 (40.0)	0.064
	Antipseudomonal cephalosporins	12 (23.5)	3 (14.3)	9 (30.0)	0.32
	Ceftolozane/tazobactam	11 (21.6)	2 (9.5)	9 (30.0)	0.098
	Monobactam (Aztreonam)	12 (23.5)	3 (14.3)	9 (30.0)	0.32
	Group 1 Carbapenems	8 (15.7)	2 (9.5)	6 (20.0)	0.445
	Group 2 Carbapenems	1 (2.0)	0 (0.0)	1 (3.3)	1.00
	Fluoroquinolones	11 (21.6)	7 (33.3)	4 (13.3)	0.17
	Aminoglycosides	10 (19.6)	3 (14.3)	7 (23.3)	0.50
	Trimethoprim-sulphamethoxazole	11 (21.6)	7 (33.3)	4 (13.3)	0.17
	Fosfomycin	41 (80.4)	18 (85.7)	23 (76.7)	0.50
	Polymyxins (Colistin)	16 (31.4)	5 (23.8)	11 (36.7)	0.375
	MDR profile (*n*, % MDR)	18 (35.3)	7 (33.3)	11 (36.7)	1.00
Pseudomonas aeruginosa		41	22	19	
	Antipseudomonal penicillins + β-lactamase inhibitor	14 (34.14)	8 (36.4)	6 (31.6)	1.00
	Antipseudomonal cephalosporins	13 (31.7)	7 (31.8)	6 (31.6)	1.00

Table 3 continued

Uropathogen isolated *N* (% global)	Antibiotic resistance rate (*n*, %)	All cases, *n* = 446 Antibiotic resistance (*n*, %)	Community-onset healthcare associated BUTI (*n* = 226)	Hospital-acquired BUTI (*n* = 220)	*p*
	Ceftolozane/tazobactam	2 (4.9)	1 (4.5)	1 (5.2)	1.00
	Monobactams (Aztreonam)	4 (9.8)	2 (9.1)	2 (10.5)	1.00
	Group 2 Carbapenems	17 (41.5)	7 (31.8)	10 (52.6)	0.22
	Fluoroquinolones	15 (36.6)	7 (31.8)	8 (42.1)	0.53
	Aminoglycosides	7 (17.1)	3 (13.6)	4 (21.1)	0.69
	Polymyxins (Colistin)	0 (0)	0 (0)	0 (0)	-
	MDR profile (*n*, % MDR)	12 (29.3)	6 (27.3)	6 (31.6)	1.00

Data are presented as no. (%)

Antimicrobial categories (antimicrobial agents tested and included): penicillins (ampicillin), penicillins + β-lactamase inhibitor (amoxicillin-clavunalate), antipseudomonal penicillins + β-lactamase inhibitor (piperacillin-tazobactam), non-antipseudomonal cephalosporines (cefotaxime), antipseudomonal cephalosporines (ceftazidime, cefepime), group 1 carbapenems (ertapenem), group 2 carbapenems (imipenem, meropenem), monobactam (aztreonam) fluoroquinolones (ciprofloxacin), aminoglycosides (gentamicin, tobramycin, amikacin), polymyxins (colistin). *Proteus* spp. included: 19 *P. mirabilis*, 1 *P. vulgaris* and 1 *Proteus spp*. Other *Enterobacterales* included: 15 *Enterobacter cloacae* complex, 9 K. *aerogenes*, 7 K. *oxytoca*, 8 *Serratia marcescens*, 4 *Morganella morganii*, 1 *Providencia stuartii*, 3 *Citrobacter koseri*, 2 *C. freundii* and 1 *C. amalonatycus*. MDR, multidrug resistance profile was defined as a strain non-susceptible to at least one agent in ≥ 3 antimicrobial categories

BUTI, bacteremic urinary tract infection; MDR, multidrug-resistant

(aOR 1.11 [1.01–1.23]) were the independent predictors of receiving inadequate empirical treatment, whereas the initial presentation with septic shock was a protective factor (aOR 0.38 [0.15–0.96]).

DISCUSSION

Healthcare-associated infections represent a current major health problem [2]. Demographic changes, aging and a higher grade of complexity of medical treatments are among the reasons for the increasing number of HCA infections during recent years [7, 16]. Furthermore, many patients with multiple underlying diseases and/or invasive devices, who were traditionally treated in acute care hospitals, are currently managed in primary care centers, in long-term care facilities or even at home [33]. Previous studies have shown that CO-HCA infections represent a different entity from other community-acquired infections [17, 18]. However, few studies have aimed to clarify whether CO-HCA infections should be managed as HA infections [18, 34, 35]. We carried out a multicenter prospective study to gain a better understanding of CO-HCA and HA infections. Due to the huge clinical and economic burden of UTI on the healthcare systems [3, 8], and to avoid bias derived from including different sources of infection, we focused our study on BUTI.

In our study, patients with CO-HCA infections were older and had more underlying

Table 4 Univariate and multivariable analysis of parameters predicting overall mortality in bacteremic urinary tract infection

	Overall mortality (*n* = 443, 30-day mortality = 29)					
	Deceased (*n* = 29)	**Alive (*n* = 414)**	**Unadjusted HR (95% CI)**	***p***	**Adjusted HR (95% CI)**	***p***
Gender (male)	21 (72.41)	267 (64.49)	1.43 (0.63–3.23)	0.39		
Age, years, median (IQR)	79 (66–84)	74 (65–82)	1.02 (0.99–1.05)	0.27	1.02 (0.99–1.06)	0.23
Charlson index, median (IQR)	6 (2–7)	3 (2–5)	1.24 (1.09–1.40)	0.001	1.19 (1.04–1.37)	0.012
McCabe score II–III	26 (89.66)	131 (31.64)	16.89 (5.11–55.80)	< 0.001	–	–
Diabetes mellitus	8 (27.59)	120 (28.99)	0.94 (0.42–2.12)	0.88		
Chronic renal failure	11 (37.93)	124 (29.95)	1.44 (0.68–3.05)	0.34		
Chronic pulmonary disease	4 (13.79)	55 (132.85)	1.06 (0.37–3.04)	0.92		
Cardiovascular disease	10 (34.48)	125 (30.19)	1.23 (0.57–2.64)	0.60		
Chronic liver disease	3 (10.34)	23 (5.56)	1.86 (0.56–6.16)	0.31		
Vascular/degenerative brain disease	8 (27.59)	86 (20.77)	1.45 (0.64–3.26)	0.38		
Malignant disease	15 (51.72)	167 (40.34)	1.54 (0.74–3.20)	0.24		
Immunosuppressive therapy	13 (44.83)	108 (26.09)	2.18 (1.05–4.53)	0.037	2.23 (1.00–5.00)	0.05
Recurrent UTI (> 2 episodes/year)	7 (24.14)	77 (18.60)	1.53 (0.64–3.65)	0.33		
Structural urinary tract abnormalities	15 (51.72)	126 (30.43)	2.53 (1.20–5.31)	0.014	2.11 (0.98–4.55)	0.06
Indwelling urinary devices	20 (68.97)	249 ((60.14)	1.46 (0.66–3.20)	0.35		
Site of infection (CO-HCA)	16 (55.17)	207 (50.00)	1.23 (0.59–2.55)	0.58	1.01 (0.46–2.19)	0.99
Previous antibiotic use (3 months)	24 (82.76)	291 (70.29)	1.98 (0.76–5.20)	0.16		
Pitt score > 2	12 (41.38)	148 (35.75)	1.25 (0.60–2.62)	0.55		
Septic shock	5 (17.24)	54 (13.04)	1.48 (0.56–3.93)	0.43		
ICU admission required	5 (17.24)	77 (18.60)	0.90 (0.34–2.36)	0.83		
Polimicrobial infection	1 (3.45)	21 (5.07)	0.68 (0.09–4.98)	0.70		
Resistance profile (MDR)	22 (75.86)	249 (60.14)	2.04 (0.87–4.78)	0.10	1.80 (0.75–4.33)	0.19
Appropriate empirical treatment	18 (62.07)	340 (82.13)	0.37 (0.17–0.78)	0.009	0.61 (0.27–1.38)	0.23
Persistence of sepsis signs/symptoms at 48–72 h	5 (17.24)	44 (10.63)	1.90 (0.72–5.02)	0.20		
Escherichia coli	16 (55.17)	214 (51.69)	1.15 (0.55–2.39)	0.71		
Klebsiella pneumoniae	5 (17.24)	94 (22.70)	0.72 (0.28–1.89)	0.51		

Table 4 continued

	Overall mortality (n = 443, 30-day mortality = 29)					
	Deceased (n = 29)	Alive (n = 414)	Unadjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
Proteus spp.	2 (6.90)	19 (4.59)	1.56(0.37–6.54)	0.55		
Other Enterobacterales	2 (6.90)	49 (11.84)	0.57 (0.13–2.38)	0.44		
Pseudomonas aeruginosa	4 (13.79)	37 (8.94)	1.55 (0.54–4.44)	0.83		
Enterococcus spp.	2 (6.90)	20 (4.83)	1.41 (0.33–5.91)	0.64		

diseases than those with HA-BUTI. The MDR rate was high, but similar between the two groups. Several studies have also shown that CO-HCA infections occur in vulnerable populations [13, 14, 17, 18, 35]. The rising rates of elderly and complex patients managed in the community setting could explain this fact. In line with our results, previous studies have found high rates of antibiotic resistance in CO-HCA infections [17, 18, 33]. Therefore, although CO-HCA infections were initially considered an intermediate entity between community-acquired and HA infections [35], it seems they are more prone to HA infections, at least in terms of patients' characteristics and microbiology [17, 18]. Although no differences were found in mortality rates, patients with HA-BUTI had a better clinical cure than those with CO-HCA infection. As UTIs are usually associated with a low mortality rate [29], clinical cure could be a more accurate outcome to assess BUTI prognosis.

Worryingly, our study shows a high rate of healthcare-related patients with previous use of antimicrobial agents. In fact, the European Centre for Disease Prevention and Control data demonstrated high antibiotic consumption rates in Spain, being the fifth country in Europe in consumption of systemic antimicrobials in the community and hospital sector in 2019 [36]. Several studies have demonstrated that previous antibiotic exposure is a strong risk factor for colonization and infection with a drug-resistant pathogen [37, 38]. The high percentages of prior antibiotic may explain, at least in part, the high rates of MDR infections observed in our study. In this scenario, Antimicrobial Stewardship programs are essential to enhance appropriate use of antimicrobial therapy.

Of relevance is the dramatic increase of multidrug resistance rates compared with previous studies carried out in our country [16, 18]. In recent years MDR *Enterobacterales*, mainly ESBL producers, have emerged as important causes of community-onset pathogens worldwide [39]. In this context, developing public health strategies to control and reduce the spread of MDR strains in healthcare settings, such as long-term care facilities, is essential [40].

In our study, receiving inadequate empirical antibiotic treatment was independently associated with MDR profile and with *P. aeruginosa*. Doubtlessly, one of the main consequences of multidrug resistance is that patients are at higher risk of receiving inadequate empirical antibiotic treatment. The delay in receiving effective antibiotics has been linked to worse outcomes, including mortality [29, 30]. However, inadequate empirical treatment was not associated with worse outcomes in our cohort. The small number of patients who received inadequate empirical treatment might contribute to finding any statistically significant differences. On the other hand, this finding could be partly explained because patients who were less likely to receive inadequate empirical treatments were those with septic shock, in whom time is a critical factor [41]. Another possible explanation is the relatively low

Table 5 Univariate and multivariable analysis of parameters predicting clinical cure in bacteremic urinary tract infection

	Clinical cure (*n* = 443, clinical cure = 263)					
	Cure (*n* = 263)	**Failure (*N* = 180)**	**Unadjusted OR (95% CI)**	***p***	**Adjusted OR (95% CI)**	***p***
Gender (male)	158 (60.07)	130 (72.22)	0.58 (0.38–0.87)	0.009	0.67 (0.43–1.06)	0.09
Age, years, median (IQR)	75 (66–82)	73 (64–82)	1.00 (0.99–1.02)	0.68		
Charlson index, median (IQR)	3 (2–5)	3 (2–6)	1.00 (0.93–1.07)	0.94		
McCabe score II–III	96 (36.50)	61 (33.89)	1.11 (0.75–1.66)	0.60		
Diabetes mellitus	80 (30.42)	48 (26.67)	1.20 (0.79- 1.83)	0.39		
Chronic renal failure	83 (31.56)	52 (28.89)	1.14 (0.75–1.72)	0.55		
Chronic pulmonary disease	36 (13.69)	23 (12.78)	1.08 (0.62–1.90)	0.78		
Cardiovascular disease	83 (31.56)	52 (28.89)	1.14 (0.75–1.72)	0.55		
Chronic liver disease	15 (5.70)	11(6.11)	0.93 (0.42–2.07)	0.86		
Vascular/degenerative brain disease	59 (22.43)	35 (19.44)	1.20 (0.75–1.92)	0.45		
Malignant disease	98 (37.26)	84 (46.67)	0.68 (0.46–1.00)	0.049	0.72 (0.48–1.09)	0.12
Immunosuppressive therapy	77 (29.28)	44 (24.44)	1.27 (0.82–1.96)	0.28		
Recurrent UTI (> 2 episodes/year)	54 (20.53)	30 (16.67)	1.27 (0.77–2.08)	0.35		
Structural urinary tract abnormalities	66 (17.36)	75 (41.67)	0.46 (0.31–0.70)	< 0.001	0.56 (0.36–0.88)	0.01
Indwelling urinary devices	161 (61.22)	108 (60.00)	1.05 (0.71–1.55)	0.80		
Site of infection (CO-HCA)	119 (45.24)	104 (57.7)	0.60 (0.41–0.89)	0.010	0.61 (0.40–0.93)	0.02
Previous antibiotic use (3 months)	187 (71.10)	128 (71.11)	1.00 (0.66–1.52)	1.00		
Pitt score > 2	101 (38.40)	59 (32.78)	1.27 (0.85–1.89)	0.24		
Septic shock	41 (15.59)	18 (10.00)	1.62 (0.90–2.93)	0.11		
ICU admission required	58 (22.05)	24 (13.33)	1.78 (1.06–2.99)	0.03	1.74 (0.96–3.05)	0.052
Polimicrobial infection	14 (5.32)	8 (4.44)	1.21 (0.50–2.94)	0.68		
Resistance profile (MDR)	164 (62.35)	107 (59.44)	1.13 (0.77–1.67)	0.53	1.17 (0.75–1.83)	0.49
Appropriate empirical treatment	218 (82.89)	140 (77.78)	1.38 (0.86–2.23)	0.18	1.39 (0.82–2.33)	0.22
Persistence of sepsis signs/symptoms at 48–72 h	26 (9.89)	23 (12.78)	0.74 (0.41–1.34)	0.32		
Escherichia coli	146 (55.51)	84 (46.67)	1.43 (0.97–2.09)	0.07	1.01 (0.60–1.69)	0.98
Klebsiella pneumoniae	51 (19.39)	48 (26.27)	0.66 (0.42–1.04)	0.07	0.59 (0.33–1.05)	0.08
Proteus spp.	11 (4.18)	10 (5.56)	0.74 (0.31–1.79)	0.51		

Table 5 continued

	Clinical cure (n = 443, clinical cure = 263)					
	Cure (n = 263)	**Failure (N = 180)**	**Unadjusted OR (95% CI)**	p	**Adjusted OR (95% CI)**	p
Other Enterobacterales	30 (11.41)	21 (11.67)	0.97 (0.54–1.76)	0.93		
Pseudomonas aeruginosa	24 (9.13)	17 (9.44)	0.96 (0.50–1.85)	0.91		
Enterococcus spp.	12 (4.56)	10 (5.56)	0.81 (0.31–1.92)	0.64		

mortality rate of UTI compared with other sources of infections [29].

Some limitations of our study should be recognized. First, we did not include non-hospitalized patients, so our results cannot be extrapolated to outpatients. Second, the comparator groups may be imbalanced in terms of bacteremia duration. Although the community-onset group is likely to have a more prolonged duration before the hospital admission, in routine clinical practice, determining the exact difference in bacteremia duration between groups is very complicated. Third, the observation period for clinical cure at hospital discharge may be biased between groups as lengths of stay may differ for other reasons beyond the BUTI episode. Fourth, our results may not be generalizable to other countries with a different epidemiology. Finally, antibiotic dosing was not recorded. Antibiotic dosing is associated with appropriate treatment; thus, not collecting this information may represent a lost opportunity to evaluate the role of timely and appropriate antibiotic exposures.

CONCLUSIONS

In summary, the present study represents the largest study published to date with the aim of evaluating differences between CO-HCA-BUTI and HA-BUTI. Our study shed light on the burden of CO-HCA infections, at least regarding UTI. CO-HCA-BUTIs occur in complex patients, who are more elderly and have more underlying comorbidities. The rate of MDR infections was similar in both groups, and worryingly high overall. We did not find differences in either mortality or the probability of receiving inappropriate empirical antibiotic treatment between the two groups. However, CO-HCA-BUTIs were associated with a worse clinical cure. Our results suggest that CO-HCAs are similar or even worse than HA-BUTIs. These results should be considered when prescribing empirical antibiotic treatments. However, it should be noted that CO-HCA infections include a very heterogeneous group of patients and, in the face of antimicrobial stewardship strategies, an important challenge will be to differentiate which patients are at a higher risk of developing a MDR infections within this huge group.

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Compliance with Ethics guidelines. Protocol and informed consent form were approved by the Clinical Research Ethical Committee of Hospital del Mar (registration number 2016/6957/I) and by the local Ethics Committees of each institution (information in Supplementary Material). Prior to initiation the study, an informed consent form was signed by the patient or guardian/legal representative. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guideline and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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