ORIGINAL ARTICLE

Clinical predictors of ceftriaxone resistance in microorganisms causing febrile urinary tract infections in men

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Background and objectives. Because of high rates of resistance to fluoroquinolones, ceftriaxone has become one of the main options for treating febrile urinary tract infection (FUTI). This study aimed to identify predictors of ceftriaxone resistance in community-acquired FUTIs in men.

Methods. Cross-sectional ambispective study enrolling men with FUTIs treated in the emergency department of a local area hospital in Spain.

Results. A total of 552 FUTI episodes were studied; 103 (18.6%) were caused by a ceftriaxone-resistant microorganism. Variables associated with a ceftriaxone-resistant FUTI were older age, health care-associated FUTI, dementia, diabetes mellitus, neoplasms, a history of UTIs, urologic disease, and complicated FUTI. Patients with ceftriaxone-resistant FUTIs also had higher rates of recent antibiotic treatment. Independent variables associated with FUTI due to a ceftriaxone-resistant microorganism were cirrhosis of the liver (odds ratio [OR], 6,00 95% CI, 1.25–28; *P* = .025), health care-associated FUTI (OR, 2.3 95% CI, 1.23–4.27; *P* = .009), and prior treatment with antibiotics (OR, 2.15; 95% CI, 1.23–3.76 *P* = .007). Components of health care-associated FUTI were a history of admission to a long-term residence (OR, 2.90 95% CI, 1.21–7.16; *P* = .017) and use of penicillins with or without beta-lactamase inhibitors (OR, 2.16; 95% CI, 1.05–4.42; *P* = .035).

Conclusion. Cirrhosis of the liver; history of health care-associated FUTI, especially in patients residing in a long-term care facility; and recent use of antibiotics, mainly penicillins with or without beta-lactamase inhibitors, are risk factors for ceftriaxone-resistant FUTI in men.

Keywords: Resistance. Ceftriaxone. Febrile urinary tract infection. Men.

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Article information:
Received: 4-5-2017
Accepted: 2-7-2017
Online: 6-10-2017

Editor in charge:
Agustín Julián-Jiménez, MD, PhD.

Factores clínicos predictivos de resistencia a ceftriaxona en microorganismos causantes de infección del tracto urinario febril en hombres

Objetivo. Las elevadas tasas de resistencia a fluoroquinolonas han hecho de la ceftriaxona una de las principales opciones terapéuticas en las infecciones del tracto urinario febriles (ITUF). El objetivo del estudio es identificar factores predictivos de infección por microorganismos resistentes a ceftriaxona (MRC) en ITUF comunitaria en hombres.

Métodos. Estudio transversal ambispectivo en el que se incluyeron hombres con ITUF atendidos en el servicio de urgencias de un hospital comarcal.

Resultados. Se incluyeron 552 episodios de ITUF, 103 (18,6%) causadas por MRC. Los pacientes con ITUF por MRC tenían mayor edad, más frecuencia de ITUF relacionada con la atención sanitaria (ITUF-AS), demencia, diabetes mellitus, neoplasia, ITU previa, patología urológica, ITUF complicada y antecedente de tratamiento antibiótico reciente. Las variables independientemente asociadas a ITUF por MRC fueron la cirrosis hepática (OR 6,00; IC 95%: 1,25-28; p = 0,025), tener una ITUF-AS (OR 2,3; IC 95%: 1,23-4,27; p = 0,009) y el consumo previo de antibióticos (OR 2,15; IC 95%: 1,23-3,76; p = 0,007). Entre los componentes de la ITUF-AS, el antecedentes de estancia en centro larga estancia (OR 2,90; IC 95%: 1,21-7,16; p = 0,017) y entre los antibióticos el consumo de penicilinas con/sin inhibidores de betalactamasa (OR 2,16; IC 95%: 1,05-4,42; p = 0,035) se asociaron a ITUF por MRC.

Conclusiones. La cirrosis, presentar una ITUF-AS, especialmente provenir de un centro de larga estancia, y el consumo reciente de antibióticos, principalmente de penicilinas con/sin inhibidores de betalactamasa, son factores de riesgo de ITUF por MRC en hombres.

Palabras clave: Resistencia. Ceftriaxona. Infección tracto urinaria febril. Hombres.

Introduction

Urinary tract infections occupy the second place, after respiratory infections, among the most prevalent infections in hospital emergency services (HES)[1]. Acute cystitis is the most common form of presentation followed by acute pyelonephritis (APN). Acute prostatitis (AP) would occupy the third place[1], although its frequency could be higher. The use of different diagnostic methods in men with febrile urinary tract infection (FU-

TI) has shown that a high percentage have prostatic involvement, which is why they should be considered as AP[2,3]. Since fluoroquinolones (FQ) have adequate penetration into prostate tissue, they are considered the treatment of choice in AP[4].

Most of the FUTIs in men are caused by *Escherichia coli (E. coli)*, with FQ resistance rates ranging from 26% in community acquired FUTI (CA-FUTI) to 71% in those related to healthcare associated (HCA-FUTI)[5]. Resistance rates greater than 10% discourage the empirical use of FQ[6].

Ceftriaxone is a therapeutic alternative, since it reaches an adequate prostatic concentration, especially in the initial stages of infection[4]. When a single daily administration is required, it is an option of great interest for the treatment of FUTIs in outpatients parenteral antibiotic treatment units (OPAT)[7]. In addition, it is active against most strains of *E. coli* that cause FUTI in men, with resistance rates of around 5%[8]. However, in recent years there has been a progressive increase in ceftriaxone resistance in Europe, mainly due to the production of extended-spectrum beta-lactamases (ESBL)[9]. ESBL has recently been described in 10.8% of *E. coli* strains causing AP[10]. In the etiological assessment of the FUTIs, in addition, it is necessary to consider the possible participation of other microorganisms with natural resistance to ceftriaxone, such as *Enterococcus spp.* and *Pseudomonas aeruginosa (P. aeruginosa)*. The inadequacy of antibiotic therapy in the ED has a negative impact on both the hospital stay and the morbidity and mortality of the patients[11]. The administration of ceftriaxone in APN caused by *E. coli* with ESBL has been associated with persistent fever and prolongation of hospital admission[12]. The identification of risk factors for inadequate antibiotic treatment is key to the development of antibiotic treatment guidelines within the framework of programs to optimize the use of antimicrobials. The objective of this study is the identification of clinical variables predictive of presenting an FUTI due to microorganisms resistant to ceftriaxone (MRC).

Method

Cross-sectional, ambispective study in which episodes of FUTI of community origin were analysed in men aged 18 years and older treated between January 2008 and December 2015 in the ED of a regional hospital. The FUTI was defined as the presence of an axillary temperature equal to or greater than 38ºC, one or more symptoms of UTI (urgent urination, frequency or dysuria) and a positive urine culture. In patients without urinary symptoms, the diagnosis of FUTI was accepted in the absence of other foci of infection. In the case of recurrent FUTI, only the first episode was analyzed. Nosocomial FUTI and those with negative or polymicrobial urine culture were excluded. The study was approved by the Clinical Research Ethics Committee of the Fundació Unió Catalana d'Hospitals.

For each episode of FUTI, the following variables were collected: age, place of infection acquisition (CA-FUTI or HCA-FUTI), dementia, diabetes mellitus, renal failure, liver cirrhosis, neoplasia, pulmonary disease, heart failure, use of immunosuppressants or antibiotic therapy in the previous 30 days, Charlson's index, urological pathology and history of previous urinary tract infections.

The presence of urological abnormalities, urinary catheter, recent urinary manipulation or of certain diseases such as diabetes mellitus was considered as complicated FUTI (FUTIc). The diagnostic criteria for severe sepsis and septic shock were those established in 2001[13].

Based on the definitions of bacteremia related to health care[14], the HCA-FUTI was defined in the presence of any of the following criteria: admission to an acute care hospital for 2 years. or more days in the previous 90 days; come from a long stay care (LSC); intravenous treatment at home or day hospital, hemodialysis, specialized nursing care or invasive procedures of the urinary tract in the previous 30 days; and patients with a urinary catheter or withdrawal within 48 hours prior to the FUTI. In the absence of the above criteria, the patient was considered to have an CA-FUTI.

Urine samples were obtained by spontaneous average urination or through urinary catheters and were cultured in CLED medium and MacConkey agar. The urine culture was considered as positive against bacterial counts equal to or higher than 103 colony forming units (CFU)/mL. The microbiological identification was carried out by conventional biochemical means. The susceptibility to amoxicillin, amoxicillin-clavulanate, cefuroxime, ceftriaxone, imipenem, gentamicin, pipemidic acid, ciprofloxacin, cotrimoxazole and fosfomycin was determined by disc diffusion techniques, following the criteria of the Clinical and Laboratory Standards Institute (CLSI). The resistant or intermediate susceptible strains were grouped for statistical analysis. The phenotypic identification of the ESBL was performed in case of resistance to third-generation cephalosporins (3G Ceph), susceptibility to cefoxitin and evidence of synergism between amoxicillin-clavulanic acid and 3G Ceph. AmpC were identified in case of resistance to 3G Ceph, resistance to cefoxitin and synergism between cloxacillin or boronic acid and 3G Ceph. If you suspect the presence of a carbapenemasae the Hodge test was carried out. The patient was considered to have had a FUTI due to MRC if the infection was caused by microorganisms with decreased susceptibility (*Staphylococcus spp.*), Natural resistance (*P. aeruginosa, Acinetobacter spp., Enterococcus spp., Candida spp.*) Or acquired to ceftriaxone. Inappropriate antibiotic therapy (IAT) was defined if the causative organism was resistant to the first antimicrobial administered.

The qualitative data were expressed as the number of patients (percentages) and the quantitative data in the form of mean and standard deviation (SD). The study of the association between the qualitative variables was performed using the chi-square test and Fisher's exact test. The continuous variables were compared

with the Student's t test or the Mann-Whitney U test. A $p < 0.05$ was considered statistically significant. A logistic regression analysis was performed to identify the variables associated with FUTI due to MRC, including those variables with $p < 0.1$ in the univariate analysis. The statistical analysis was carried out with the statistical program SPSS version 20.0.

Results

The study included 552 men treated in the ED for an FUTI. The baseline characteristics of the patients are shown in Table 1. In the HCA-FUTI, hospital admission and previous urological manipulation were the most common forms of contact with the health system. Of the patients who were treated with antibiotics in the previous month, most received beta-lactam with or without beta-lactamase inhibitor (BI) or FQ. *E. coli* was the main isolated microorganism, followed by *Klebsiella spp*. (Table 2). Of the patients included, 103 (18.6%) had an FUTI by MRC. The isolated MRCs, in descending order of frequency, were: microorganisms with natural resistance (*P. aeruginosa, Acinetobacter spp., Enterococcus spp., Candida spp.*) Or decreased susceptibility to ceftriaxone (*Staphylococcus spp.*) In 51 (49.5%) of the cases, acquired resistance to ceftriaxone (*E. coli, Klebsiella spp.*) in 47 (45.6%) and infection by microor-

Table 1. Description of the patients included in the study and univariate analysis of the cases according to whether or not they had an infection with microorganisms resistant to ceftriaxone

Variable	Total N = 552 n (%)	FUTI MSC N = 449 n (%)	FUTI MRC N = 103 n (%)	p Value
Baseline characteristics				
Age in years [mean (SD)]	66 (17)	65 (17)	73 (14)	< 0.001
HCA- FUTI	203 (36.8)	135 (30.1)	68 (66)	< 0.001
Hospital admission	130 (23.6)	91 (20.3)	39 (37.9)	< 0.001
Long stay center	46 (8.3)	23 (5.1)	23 (22.3)	< 0.001
IV-EH Treatment	70 (12.7)	46 (10.2)	24 (23.3)	< 0.001
Nursing care	7 (1.3)	6 (1.3)	1 (1)	1
Urological manipulation	110 (19.9)	78 (17.4)	32 (31.1)	0.002
Urinary catheter	77 (13.9)	51 (11.4)	26 (25.2)	< 0.001
Dementia	64 (11.6)	44 (9.8)	20 (19.4)	0.006
Diabetes mellitus	148 (26.8)	110 (24.5)	38 (36.9)	0.01
Chronic renal failure	54 (9.8)	41 (9.1)	13 (12.6)	0.28
Liver cirrhosis	9 (1.6)	5 (1.1)	4 (3.9)	0.067
Active neoplasia	81 (14.7)	58 (12.9)	23 (22.3)	0.015
Heart failure	8 (1.4)	5 (1.1)	3 (2.9)	0.17
COPD	100 (18.1)	75 (16.7)	25 (24.3)	0.072
Immunosuppressant treatment	11 (2)	10 (2.2)	1 (1)	0.70
Charlson's index points [mean (SD)]	3.6 (2.5)	3.3 (2.4)	4.7 (2.4)	< 0.001
Previous ITU	222 (45.5)	171 (42.4)	51 (60)	0.003
Urological pathology	339 (61.5)	266 (59.2)	73 (71.6)	0.021
FUTIc	375 (68.1)	292 (65.2)	83 (80.6)	0.002
Previous antibiotic treatment	179 (32.6)	124 (27.7)	55 (53.9)	< 0.001
Penicillins with/without IB	60 (11)	42 (9.5)	18 (17.6)	0.018
Fluoroquinolones	54 (9.9)	35 (7.9)	19 (18.6)	0.001
3G Ceph	16 (2.9)	9 (2)	7 (6.9)	0.017
Phosphomycin	10 (1.8)	6 (1.4)	4 (3.9)	0.098
Clinic presentation				
Severe sepsis or septic shock	17 (3.1)	11 (2.4)	6 (5.8)	0.10
Urinary syndrome	359 (65.3)	318 (71)	41 (40.2)	< 0.001
Low back pain	89 (16.2)	76 (17)	13 (12.7)	0.29
Physical exploration				
Mean arterial pressure in mmHg [mean (SD)]	93.4 (15.3)	94.3 (15.5)	89.5 (14.1)	0.003
Positive	94 (22.1)	79 (22.4)	15 (20.5)	0.73
Painful DRE	81 (42.6)	74 (44)	7 (31.8)	0.27
Laboratory				
Creatinine in mg/dL [mean (SD)]	1.2 (0.7)	1.2 (0.5)	1.5 (1)	0.015
PCR in mg/l [mean (SD)]	142.8 (81.3)	145.3 (78.3)	135.1 (90.5)	0.45
Bacteremia	120 (31.6)	93 (30.6)	27 (35.5)	0.40
Evolution				
Conventional admission	266 (48.2)	196 (43.7)	70 (68)	< 0.001
Admission in OPAT	71 (12.9)	47 (10.5)	24 (23.3)	< 0.001
Income days [average (DE)]*	3.5 (5.2)	2.5 (4.1)	7.5 (7)	< 0.001

* In a conventional hospitalization facility or in an outpatient parenteral antibiotic treatment unit.
SD: standard deviation; UTI: urinary tract infection; FUTI: febrile urinary tract infection; MSC: microorganisms sensitive to ceftriaxone; MRC: microorganisms resistant to ceftriaxone; HCA-FUTI: Healthcare associated FUTI; IV-EH: intravenous-extrahospitalary; COPD: chronic obstructive pulmonary disease; FUTIc: complicated FUTI; 3G Ceph: 3rd generation cephalosporins; IB; beta-lactamase inhibitor; LFP: lumbar fist percussion; PCR: C-reactive protein; DRE: digital rectal examination; OPAT: outpatients parenteral antibiotic therapy.

Table 2. Isolated uropathogens and antimicrobial resistance rate

	Total N = 552 n (%)	FUTI MSC N = 449 n (%)	FUTI MRC N = 103 n (%)	p Value
Escherichia coli	393 (71.2)	358 (79.7)	35 (34)	< 0.001
Amoxicillin	254 (69.2)	220 (66.1)	34 (100)	< 0.001
Amoxicillin clavulanic	52 (13.3)	33 (9.2)	19 (55.9)	< 0.001
Cefuroxime	38 (9.7)	3 (0.8)	35 (100)	< 0.001
Ceftriaxone[1]	35 (8.9)	0	35 (100)	CS
Gentamicin	30 (7.7)	18 (5)	12 (34.3)	< 0.001
Fluoroquinolones	152 (38.7)	122 (34.1)	30 (85.7)	< 0.001
Cotrimoxazole	102 (26.9)	80 (23.3)	22 (62.9)	< 0.001
Fosfomycin	15 (4)	9 (2.6)	6 (18.8)	0.001
Klebsiella spp.[2]	56 (10.1)	44 (9.8)	12 (11.7)	0.57
Amoxicillin clavulanic	13 (23.2)	4 (9.1)	9 (75)	< 0.001
Ceftriaxone[3]	12 (21.4)	0	12 (100)	CS
Fluoroquinolones	15 (26.8)	5 (11.4)	10 (83.3)	< 0.001
Cotrimoxazole	11 (20.8)	2 (4.9)	9 (75)	< 0.001
Enterobacter spp.[4]	21 (3.8)	16 (3.6)	5 (4.9)	0.56
Ceftriaxone	5 (23.8)	0	5 (100)	CS
Fluoroquinolones	0	0	0	–
Serratia spp.	4 (0.7)	4 (0.9)	0	1
Citrobacter spp.	4 (0.7)	4 (0.9)	0	1
Morganella spp.	5 (0.9)	5 (1.1)	0	0.59
Proteus mirabilis	17 (3.1)	17 (3.8)	0	0.053
Pseudomona aeruginosa	25 (4.5)	0	25 (24.3)	CS
Fluoroquinolones	7 (28)	0	7 (28)	CS
Other Gram-negative bacteria[5]	2 (0.4)	1 (0.2)	1 (1)	0.34
Gram-positive bacteria	22 (4)	0	22 (21.4)	CS
Enterococcus spp.[6]	16 (2.9)	0	16 (15.5)	CS
Staphylococcus spp.[7]	6 (1.1)	0	6 (5.8)	CS
Candida spp.[8]	3 (0.5)	0	3 (2.9)	CS

[1]Includes 32 (91.4%) strains producing ESBL and 3 (8.6%) strains producing AmpC. [2]Includes 47 (84%) strains of *K. pneumoniae* and 9 (16%) of *K. oxytoca.* [3]Include 9 (75%) strains that produce ESBL and 3 (25%) strains that produce AmpC. [4]Includes 18 (85.7%) strains of E. cloacae and 3 (14.3%) of E. aerogenes. [5]One strain of P. *stuartii* in the MSC group and 1 strain of *A. baumannii* in the MRC group. [6]Includes 11 strains (68.7%) of *E. faecalis,* 4 (25%) strains of *Enterococcus spp.* and 1 (6.3%) strain of *E. faecium.* [7]Includes 5 strains of *S. aureus* (83.3%) and 1 (16.7%) strain of *S. capitis.* [8]Includes 2 (66.7%) strains of *C. albicans* and 1 strain (33.3%) of *C. tropicalis.*
FUTI: febrile urinary tract infection; MSC: microorganisms sensitive to ceftriaxone; MRC: microorganisms resistant to ceftriaxone; ESBL: extended-spectrum beta-lactamases; SC: selection criteria.

ganisms with inducible AmpC (*Enterobacter spp.*) in 5 (4.9%) patients. The cases with an MRC infection were older, an increased frequency of HCA-FUTI, dementia, diabetes mellitus and neoplasia. None of the patients received hemodialysis. The frequency of previous urinary tract infection, urological pathology, FUTIc and recent antibiotic treatment was significantly higher in MRC infections.

The result of the cultures and the antimicrobial resistance pattern is detailed in Table 2. *E. coli* was isolated less frequently among patients with a FUTI by MRC. The rates of resistance to the different antibiotics not used as selection criteria were higher among strains of *E. coli and Klebsiella spp.* isolated from patients with MRC infection. Most of the FUTIs caused by strains of *E. coli* or Klebsiella spp. resistant to ceftiaxone was due to the production of ESBL. No strains were identified with carbapenemases. 23.8% of strains of *Enterobacter spp.* was resistant to ceftriaxone.

Of the total number of patients evaluated, 286 (51.8%) were managed exclusively from the ED. Of these, 141 (49.3%) were discharged from the ED and 121 (42.3%) from the observation area. Of the remaining 24 patients, 5 (1.7%) required transfer and 19 (6.6%) entered into OPAT units. Of the 266 (48.2%) hospitalized patients, 1 (0.4%) moved and 52 (19.5%) entered into OPAT units. Patients with FITU due to MRC more frequently required admission to a conventional hospital ward or OPAT units, and the duration of admission was longer (Table 1).

Regarding the empirical antibiotic treatment administered, 307 (55.6%) patients received a 3G Ceph, 98 (17.7%) FQ, 59 (10.7%) a carbapenem or piperacillin-tazobactam, 51 (9.2%) amoxicillin-clavulanic and 37 (6.7%) other antibiotics or combination treatments. A total of 95 patients (17.2%) received a IAT. Table 3 shows the main reasons for IAT and its impact on the evolution of patients. Treatment with 3G Ceph was the main cause of IAT. The duration of hospital admission, overall mortality and that related to the FITU were higher among patients who received a IAT.

In relation to the role of ceftriaxone as the most used therapeutic option and main cause of IAT, a multivariate analysis was carried out in order to determine the variables independently associated with FUTI by MRC (Table 4). In the general multivariate analysis, having an HCA-FUTI, liver cirrhosis and previous antibiotic use were associated with FUTI due to MRC. In a second model, of the defining components of HCA-FUTI with $p < 0.1$ in the univariate analysis, only the history of stay in LSC was associated with MRC infection. In the third model, among the different antibiotics with a

Table 3. Empirical treatment administered and evolution of patients with inadequate antibiotic treatment

	Total N = 552 n (%)	No IAT N = 457 n (%)	IAT N = 95 n (%)	p Value
Empirical treatment				
3rd generation cephalosporins	307 (55.6)	258 (56.5)	49 (51.6)	0.38
Fluoroquinolones	98 (17.8)	75 (16.4)	23 (24.2)	0.07
Amoxicillin-clavulanic	51 (9.2)	39 (8.5)	12 (12.6)	0.21
Carbapenemes or PT	59 (10.7)	55 (12)	4 (4.2)	0.025
Combined treatment	12 (2.2)	11 (2.4)	1 (1.1)	0.70
Others	25 (4.5)	19 (4.2)	6 (6.3)	0.41
Evolution				
Severe sepsis or septic shock	17 (3.1)	13 (2.8)	4 (4.2)	0.51
Bacteremia	120 (31.6)	104 (33)	16 (24.6)	0.18
Hospitalization*	285 (51.6)	232 (50.8)	53 (55.8)	0.37
Duration of hospital admission in days [mean (SD)]	3.5 (5.2)	3.2 (5.1)	4.7 (5.8)	0.016
Duration of antibiotic treatment in days [mean (SD)]	16.3 (6.7)	16.4 (7)	15.7 (5)	0.56
Overall hospital mortality	15 (2.7)	7 (1.5)	8 (8.4)	0.001
Hospital mortality related to the FUTI	8 (1.4)	3 (0.7)	5 (5.3)	0.005

*In a conventional hospitalization facility or in an outpatient parenteral antibiotic treatment unit.
IAT: inappropriate antibiotic treatment; FUTI: febrile urinary tract infection; PT: piperacillin-tazobactam; SD: standard deviation.

p < 0.1 in the univariate analysis, only penicillin consumption with or without IB was associated with FUTI by MRC.

Discussion

Ceftriaxone is one of the most widely used antibiotics for the treatment of FUTIs in ED[15]. The risk factors for 3G Ceph resistance in *E. coli* have already been evaluated in the literature. Our study aims to answer the most common therapeutic question of the emergency physicians facing a patient with a FUTI: can I treat the patient with ceftriaxone or should I use antibiotics of a wider spectrum? 18.6% of the analysed FUTI were caused by MRC, data similar to those found in patients with spontaneous bacterial peritonitis (SBP), an entity in which 3G Ceph, as in the FUTIs, represent the main therapeutic option[16].

Regarding the characteristics of the patients, those with an FUTI by MRC were older and had higher Charlson and urological conditions. These data probably reflect the higher frequency of HCA-FUTI among MRC infections[17]. An interesting aspect is the ability of the FUTIc or HCA-FUTI criteria to predict MRC infection. In our study, both were equally useful, unlike the recently observed in which the frequency of Enterobacteriaceae with ESBL did not prove to be higher among the FUTIc[15]. To emphasize that the FUTI have not been considered complicated due to the simple fact of occurring in men, in accordance with the latest guidelines[18]. Recent exposure to antibiotics was also more frequent among the FUTI by MRC. The ability of antibiotic treatment to select resistant microorganisms is well established, and the effect is directly proportional to the duration and number of previous treatment cycles[19].

E. coli was the main microorganism isolated in MRC infections. The ceftriaxone resistance rate among *E. coli* strains was similar to that previously observed in patients with AP and SBP and was mainly due to the presence of ESBL[10,16]. The indices of resistance to the rest of antibiotics in the strains of *E. coli* and *Klebsiella spp.* resistant to 3G Ceph were higher, due to the coexistence of other resistance mechanisms among the isolates ESBL[20]. Ceftriaxone resistance rates between strains of

Table 4. Multivariate analysis of the factors associated with febrile urinary tract infection by microorganisms resistant to ceftriaxone

Model[1]	OR (95% CI)	P Value
General model		
Age (years)		NS
HCA-FUTI	2.30 (1.23-4.27)	0.009
Dementia		NS
Diabetes mellitus		NS
Liver cirrhosis	6.00 (1.25-28)	0.025
Active neoplasia		NS
COPD		NS
Previous UTI		NS
Urological pathology		NS
Previous antibiotic	2.15 (1.23-3.76)	0.007
Model with the different components of HCA-FUTI[2]		
Hepatic cirrhosis		NS
Hospital admission		NS
Residence or LSC	2.90 (1.21-7.16)	0.017
Treatment IV-EH		NS
Urological manipulation		NS
Urinary catheter		NS
Model with different antibiotics[2]		
Liver cirrhosis	6.14 (1.33-28.25)	0.02
Penicillins with/without IB	2.16 (1.05-4.42)	0.035
Fluoroquinolones		NS
Cephalosporins 3rd generation		NS
Fosfomycin		NS

[1]Three models are presented. In the general model, the "HCA-FUTI" and the "previous Antibiotic" were analysed as dichotomous variables. In the other two models, these two variables were replaced by the components of HCA-FUTI and by the consumption of the different antibiotics that reached a P < 0.1 in the univariate analysis. 2The rest of the significant variables in the general model are not shown when presenting similar OR and P.
OR: odds ratio; IC: confidence interval; HCA-FUTI: febrile urinary tract infection related to health care; COPD: chronic obstructive pulmonary disease; LSC: long stay center; IV-EH: intravenous-extrahospitalary; IB: beta-lactamase inhibitors; NS: not significant.

Enterobacter spp. were lower than those described[16,21]. *P. aeruginosa* was the second microorganism most frequently isolated in the FUTI by MRC and was mostly sensitive to FQ.

Half of the patients were managed from the ED, with a relevant role in the observation area. Previous studies have shown how these areas can decrease income in the APN[22]. The number of patients admitted to OPAT units was also relevant. Most of the income in these units is usually made from the hospitalization areas, followed by the ED[23], data similar to those observed in our study. In addition to reducing costs, OPAT has proven to be a safe option in the treatment of infections by multiresistant microorganisms[24,25].

In our study, FUTI due to MRC more frequently required admission to OPAT units, with the potential cost savings and cross-transmission of multiresistant microorganisms among patients.

Regarding empirical treatment, the majority of patients received a 3G Ceph, in line with what was recommended in the APN[18]. Ceftriaxone is one of the most widely used antibiotics for the treatment of FUTIs in ED, so it is important to establish risk factors for MRC infection. It should be remembered that IAT, as we have noted, is associated with prolongation of hospital admission[11,12,26]. The relationship observed between IAT and mortality in the FUTI has not been demonstrated in other studies[12,26].

In the general multivariate model, the variables independently associated with MRC infection were cirrhosis, having an HCA-FUTI and previous antibiotic consumption. There are few studies that have established the association between cirrhosis and MRC infection. In one of them, cirrhosis was associated with colonization by ESBL producing *E. coli* and *Klebsiella pneumoniae* in hospitalized patients, which could explain the higher frequency of MRC infection among SBP of nosocomial acquisition[16,27]. Having an HCA-FUTI and prior exposure to antibiotics are risk factors for MRC infection and, especially, for enterobacteria with ESBL[17,19,20].

Of the defining components of HCA-FUTI, the history of stay in LSC, as in previous studies, was associated with MRC infection[20]. In this sense it has been observed that 36% of residents in LSC carriers of muti-resistant microorganisms[28]. Regarding exposure to antibiotics, the association between the consumption of FQ or 3G Ceph and infection with ESBL enterobacteria is well documented[16,20,29]. In spite of this, in the multivariate model with the different antibiotics, only exposure to penicillins with or without IBs was associated with the FUTI by MRC, which could perhaps be explained by the under-documented consumption of antimicrobials in the reports. In any case, this association is not new, since the taking of amoxicillin-clavulanic acid in the community has been associated with enterobacterial infection with ESBL[30].

This study has different limitations. First, it was carried out in a single hospital over several years and includes a retrospective component. Secondly, unfortunately, urine culture was not performed in all the FUTI during the study period, which could have generated a selection bias. Finally, the isolated uropathogens and their resistance pattern could be different from those found in other geographical areas.

The results of our study suggest that men with an FUTI by MRC have different clinical characteristics. Cirrhosis, the HCA-FUTI, especially if the patient comes from a LSC, and the recent consumption of antibiotics, mainly of penicillins with or without IB, are risk factors of FUTI by MRC.

Conflicting interests

The authors declare no conflict of interest in relation to this article.

Financing

The authors declare the non-existence of external financing of this article.

Ethical Responsibilitiess

The study was authorized by the Clinical Research Ethics Committee of the Fundació Unió Catalana d'Hospitals (CEIC 16/58). All patients included prospectively gave their informed consent to participate in the study.

All authors have confirmed the maintenance of confidentiality and respect for patients' rights in the author's responsibilities document, publication agreement and assignment of rights to EMERGENCIAS.

Article not commissioned by the Editorial Committee and with external peer review

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