 doi:10.20944/preprints202103.0528.v1

Article

Clinical and economic impact of community-onset urinary tract infections caused by ESBL-producing *Klebsiella pneumoniae* requiring hospitalization: an observational cohort study

D. Rozenkiewicz, [a,b,c] E. Esteve-Palau, [a,b,c] , Arenas-Miras M [a,b,c,f] S. Grau, [c,e,f] X. Duran, [d] L Sorlí, [a,b,c,f] M. Montero, [a,b,c,f] J.P. Horcajada* [a,b,c,f]

[a] Service of Infectious Diseases, Hospital del Mar, Barcelona, Spain
[b] CEXS, Universitat Pompeu Fabra, Universitat Autònoma de Barcelona, Spain
[c] Infectious Pathology and Antimicrobials Research Group (IPAR). Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain
[d] Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain
[e] Pharmacy Service, Hospital del Mar, Barcelona, Spain
[f] REIPI, Instituto de Salud Carlos III (ISCIII), Madrid, Spain
* Correspondence: jhorcajada@psmar.cat

Abstract: *Objective*: To analyze the clinical and economic impact of community-onset urinary tract infections (UTI) caused by extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* requiring hospitalization. *Methods*: A retrospective cohort study included all adults with UTI caused by *K. pneumoniae* admitted to a tertiary care hospital in Barcelona, Spain, between 2011 and 2015. Demographic, clinical and economic data were analyzed. *Results*: One hundred and seventy-three episodes of UTI caused by *K. pneumoniae* were studied; 112 were non-ESBL-producing and 61 ESBL-producing. Multivariate analysis identified ESBL production, acute confusional state associated with UTI, shock, and time to adequate treatment as risk factors for clinical failure during the first 7 days. Economic analysis showed differences between ESBL-producing and non-ESBL-producing *K. pneumoniae* for total cost of hospitalization per episode (mean 6,718 € vs 3,688 € respectively). Multivariate analysis of the higher costs of UTI episodes found statistically significant differences for ESBL production and time to adequate treatment. *Conclusion*: UTI caused by ESBL-producing *K. pneumoniae* requiring hospitalization, and time to adequate antimicrobial therapy are associated with worse clinical and economic outcomes.

Keywords: ESBL -producing Klebsiella pneumoniae, Urinary tract infection, Clinical impact, Economic impact

1. Introduction

Extended-spectrum beta-lactamases (ESBLs) are enzymes produced by Gram-negative bacilli that inactivate oxyimino beta-lactam antibiotics (cephalosporins and aztreonam), but not cephamycins (cefoxitin) or carbapenems. They are generally plasmid-mediated and are derived from other enzymes with a narrower spectrum of hydrolysis. Although many species of Gram-negative bacilli can produce ESBLs, *Escherichia coli* and *Klebsiella pneumoniae* are the major ESBL producers. ESBL-producing bacteria are a major cause of both community-based and healthcare-associated infections and are globally disseminated, although their incidence varies in different parts of the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 March 2021 doi:10.20944/preprints202103.0528.v1

world [1]. *K. pneumoniae* is associated with pneumonia, urinary tract infections (UTI), intra-abdominal infections and sepsis [2]. Data on the incidence of UTI in Spain place *K. pneumoniae* as the second cause of UTI of community origin and the third cause of nosocomial UTI [3].

ESBL-producing *K. pneumoniae* has been considered almost exclusively a nosocomial pathogen due to its epidemiological behavior, although recent data show that it is also an important agent involved in processes of community origin [4]. Data from a multicenter study conducted in 44 hospitals in Spain in 2006 showed a 2-fold increase in the percentage of ESBL-producing strains among *K. pneumoniae* (5.04%) compared to a similar study carried out in 2000 (2.7%). In that study, acquisition was considered community-acquired in 10%, ambulatory healthcare-associated in 18% and hospital-acquired in 68% of cases, with a predominance of acquisition in intensive care units [5].

Infections produced by ESBL-producing microorganisms pose important therapeutic challenges. The fact that ESBL-producing bacteria are resistant to all penicillins and cephalosporins, including third- and fourth-generation ones, means that infections due to these bacteria have limited therapeutic options [6]. As a result, infections caused by ESBL-producing bacteria can lead to increased mortality, length of hospital stay and hospital costs compared with infections caused by non-ESBL-producing bacteria of the same species [7,8]. The same phenomenon tends to be significantly stronger among patients with ESBL-producing *K. pneumoniae* infections compared with those with ESBL-producing E. coli infections [9]

A study was recently carried out to assess the clinical impact and consumption of health resources among patients with community-onset UTI due to ESBL-producing E. coli admitted to our hospital. In that study, the presence of ESBL among E. coli strains was associated with higher clinical failure rates in the first 7 days, as well as higher economic costs [10]

Bearing in mind that UTI places an economic burden on both society and the healthcare system, that *K. pneumoniae* is a frequent cause of UTI, and that ESBL-producing Enterobacteriaceae cannot be considered a homogeneous group, the objective of this study was to analyse the clinical and economic impact of ESBL-producing *K. pneumoniae* as a cause of UTI requiring admission to our hospital.

2. Results

One hundred and seventy-three UTI episodes met the criteria for inclusion during the study period and were included: 112 were due to non-ESBL-producing *K. pneumoniae* and 61 to ESBL-producing *K. pneumoniae*. The baseline characteristics of patients, broken down into those with and without ESBL infections are shown in Table 1.

Table 1 Univariate analysis of patient characteristics.

	Non-ESBL	**ESBL**	**p-value**
Total	112	61	
Sex, male	29 (25.9%)	28 (45.9%)	**0.011**
Age (in years)	72.8 ± 18.8	75.8 ± 12.1	0.200
AHA-UTI	34 (30.1%)	38 (63.3%)	**0.000**
Diabetes mellitus	50 (44.6%)	30 (49.2%)	0.633

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 March 2021 doi:10.20944/preprints202103.0528.v1

Dementia	28 (25%)	13 (21.3%)	0.709
Immunosuppressive treatment	40 (35.7%)	25 (41%)	0.515
McCabe Index	2.38 ± 0.67	2.4 ± 0.64	0.105
Charlson Comorbidity Index	6.02 ± 2.7	6.54 ± 2.12	0.198
Urinary catheterization	8 (7%)	10 (16.4%)	0.070
Other urinary catheters	9 (8%)	3 (4.9%)	0.543
Previous urological manipulation	16 (14.3%)	11 (18%)	0.519
Urological pathology	36 (32.1%)	22 (36.1%)	0.617
Kidney transplant	7 (6.3%)	2 (3.3%)	0.496
History of recurrent UTI	39 (34.8%)	25 (41%)	0.510
History of pyelonephritis	16 (14.3%)	7 (11.5%)	0.648
Urinary incontinence	14 (12.5%)	14 (23%)	0.860
Previous antibiotic	38(33.9%)	39(63.9%)	**0.000**
Amoxicillin / clavulanic acid	20 (17.9%)	10 (16.4%)	0.808
Trimethoprim / sulfamethoxazole	1 (0.9%)	2 (3.3%)	0.284
Quinolones	7 (6.3%)	10 (16.4%)	**0.032**
Fosfomycin	4 (3.6%)	3 (4.9%)	0.698
Cephalosporin	2 (1.8%)	6 (9.8%)	**0.024**
Carbapenems	1 (0.9%)	4 (6.6%)	0.053
Aminoglycosides	0 (0%)	1 (1.6%)	0.353
Linezolid	2 (1.8%)	1 (1.6%)	1.000
Others	1 (0.9%)	2 (3.3%)	0.284

AHA-UTI: ambulatory Health Care-Associated Urinaty Tract Infection. HCA-UTI: Health Care-Associated Urinary Tract Infection. CA-UTI: Community-Acquired Urinary Tract Infection.

The bivariate analysis showed a significantly higher prevalence of men, AHA-UTI, and previous antibiotic use (especially quinolones and cephalosporins) in the ESBL group. The clinical characteristics and procedures carried out on the studied patients, comparing ESBL and non-ESBL infections, are shown in Table 2. Among admissions caused by ESBL-producing *K. pneumoniae*, there was a significantly higher clinical prevalence of cystitis, more frequent clinical failure at 7 days, a longer time to adequate treatment, longer hospitalization, and more frequent use of home hospitalization. Among non-ESBL-producing *K. pneumoniae* infections, there was a higher frequency of use of adequate empirical antibiotics, a higher number of positive blood cultures, pyelonephritis and sepsis.

Table 2. Univariate analysis of clinical data

	Non-ESBL	**ESBL**	**p-value**
Cystitis	17 (15.2%)	23 (37.7%)	**0.001**
Pyelonephritis	39 (34.8%)	12 (19.7%)	**0.038**
Confusion syndrome associated with UTI	34 (30.4%)	21 (34.4%)	0.611
Prostatitis	6 (5.4%)	2 (3.3%)	0.714

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 March 2021 doi:10.20944/preprints202103.0528.v1

Sepsis	40 (35.7%)	12 (19.7%)	**0.037**
Shock	6 (5.4%)	0 (0%)	0.091
Positive blood culture	45 (40.2%)	13 (21.3%)	**0.012**
Infectious diseases intervention	32 (28.6%)	43 (70.5%)	**0.000**
Pharmacy intervention	9 (8%)	13 (21.3%)	**0.017**
Appropriate empirical treatment	104 (92.9%)	23 (37.7%)	0.000
Time to adequate treatment (days)	0.54 ± 1.4	1.59 ± 2.1	**0.000**
Duration of hospital treatment (days)	4.57 ± 2.64	4.06 ± 4.1	0.956
Clinical response at 7 days	82 (73.2%)	31 (50.8%)	**0.004**
Days of hospitalization	8.43 ± 6.42	11.62 ± 7.1	**0.003**
Readmission for the same UTI	24 (21.4%)	17 (27.9%)	0.355
Emergency consultation [a]	25 (22.3%)	18 (29.5%)	0.358
Home hospitalization	5 (4.5%)	10 (16.4%)	**0.011**
ICU admission	6 (5.4%)	0 (0%)	0.091
Mortality within 30 days	12 (10.7%)	3 (4.9%)	0.263

[a] Reconsult in the emergency room within 30 days after discharge

In the non-ESBL-producing group, the most commonly used empiric antibiotics were cephalosporins (32.1%), amoxicillin/clavulanate (30.4%) and carbapenems (11.6%) and adequate coverage was achieved in 92.9% of cases. In the ESBL-producing group, the most commonly used empiric treatments were amoxicillin/clavulanate (26.2%), cephalosporins (19.7%) and carbapenems (18%), and adequate coverage was achieved in only 37.7% of cases. The antibiotics most commonly used as directed therapy in the non-ESBL-producing group were ciprofloxacin (45.5%) and amoxicillin/clavulanate (19.6%), and in the ESBL-producing group, ertapenem (45.6%) and imipenem (29.5%).

Table 3 shows the multivariate analysis of factors associated with clinical failure at 7 days. ESBL production, acute confusional state associated with UTI, shock, and time to adequate therapy were factors independently associated with clinical failure at 7 days.

Table 3. Univariate and multivariate analysis of factors associated with a clinical failure at 7 days.

	OR (95%CI)	**p-value**	**Adjusted OR**	**p-value**
Sex, male	1.230 (0.626,2.415)	0.548	1.182 (0.501,2.785)	0.702
Age > 77	1.155 (0.886,1.505)	0.286	1.129 (0.856,1.487)	0.388
Infectious diseases intervention	1.676 (0.891,3.154)	0.109		
Pharmacy intervention	1.683 (0.681,4.161)	0.259		
Previous antibiotic	1.314 (0.700,2.465)	0.396	1.763 (0.756,4.114)	0.189
Immunosuppressive treatment	2.001 (1.052,3.805)	**0.034**		
Urinary catheterization	0.505 (0.159,1.609)	0.248		
Other catheters	0.157 (0.020,1.248)	0.080		
Previous urological manipulation	0.280 (0.092,0.851)	**0.025**		
Urological pathology	0.543 (0.270,1.089)	0.086		
History of recurrent UTI	1.092 (0.572,2.084)	0.790		
DM	0.679 (0.360,1.280)	0.231		

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 March 2021 doi:10.20944/preprints202103.0528.v1

Urological neoplasms	0.176 (0.051,0.609)	**0.006**		
McCabe Jackson Index > 2	0.899 (0.684,1.181)	0.446	1.108 (0.848,1.447)	0.451
Charlson Comobilidity Index >5.8	1.062 (0.862,1.308)	0.571	1.695 (0.921,3.120)	0.090
Bacteremia	1.936 (1.006,3.724)	**0.048**	2.412 (0.351,16.538)	0.370
Cystitis	1.018 (0.485,2.138)	0.962	1.656 (0.562,4.877)	0.360
Pyelonephritis	0.410 (0.192,0.875)	**0.021**	0.782 (0.246,2.487)	0.678
Prostatitis	0 (0,0)	0.999		
Confusion syndrome associated with UTI	2.215 (1.142,4.296)	**0.019**	5.155 (1.670,15.906)	**0.004**
Sepsis	2.275 (1.163,4.451)	**0.016**	3.758 (0.519,27.208)	0.190
Shock	3.964 (0.705,22.306)	0.118	7.239 (1.008,51.983)	**0.049**
ESBL	2.645 (1.376,5.084)	**0.004**	2.622 (1.086,6.328)	**0.032**
Time to adequate treatment	1.359 (1.092,1.692)	**0.006**	1.364 (1.059,1.755)	**0.016**
Appropriate empirical treatment	0.217 (0.106,0.443)	**0.000**		
Duration of hospital treatment	1.285 (1.161,1.422)	**0.000**		
CA-UTI	0.997 (0.528,1.881)	0.993		

CA-UTI: Community-Acquired Urinary Tract Infection

An analysis of economic data can be found in Table 4. The analysis showed a mean difference of 3.030€ (EUR) between the two groups for total cost of hospitalization, in favour of the ESBL-producing group. Costs associated with medication, nursing and antibiotics accounted for this difference.

Tabla 4. Univariate analysis of the economic impact ESBL and non-ESBL-producing *K. pneumoniae* in Euros.

	Non-ESBL med[P_{25},P_{75}]	**ESBL med[P_{25},P_{75}]**	**p-value**
Cost of hospitalization	3688 [1783,4141]	6718 [3322,9611]	**0.000**
Cost of pharmacy	457 [174,577]	888 [325,1158]	**0.001**
Cost of antibiotics	47 [7,31]	380 [87,544]	**0.000**
Cost of nursery	1809 [880,2294]	4581 [2375,6630]	**0.000**
Cost of laboratory	165 [39,201]	171 [81,192]	0.852
Cost of radiology	94 [0,111]	62 [1,72]	0.205
Cost of inter consultations	60 [0,33]	65 [0,71]	0.818
Cost of Urgency	341 [0,760]	463 [0,663]	0.218

Table 5 shows the multivariate analysis of costs. The presence of ESBL, shock at admission, time to adequate treatment, and length of hospitalization were variables independently associated with higher hospitalization costs.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 March 2021 doi:10.20944/preprints202103.0528.v1

Table 5. Univariate and multivariate analysis of the cost of the UTI episode.

	DM (95%CI)	p-value	Adjusted DM	p-value
ESBL	3446 (2330,4561)	0.000	2569 (993,4144)	**0.002**
Sex, male	417 (-1126,1960)	0.594	-285 (-1578,1008)	0.663
Age > 77	-117 (-727,373)	0.526	-101 (-1578,1008)	0.602
Infectious diseases intervention	2718 (1582,3854)	0.000		
Pharmacy intervention	2977 (814,5140)	0.007		
Previous antibiotic	957 (-592,2508)	0.224		
Immunosuppressive treatment	2304 (703,3904)	0.005		
Previous urological manipulation	-1202 (-3073,668)	0.206		
Urological pathology	-1353 (-2706,-1)	0.050		
History of recurrent UTI	647 (-1013,2308)	0.442		
Urological neoplasms	-1648 (-3347,51)	0.057	-413 (-1953,1127)	0.596
McCabe Jackson Index > 2	39 (-421,501)	0.865		
Charlson Comorbidity Index >5.8	0.56 (-714,715)	0.999		
Bacteriemia	2031 (114,3949)	0.038	1617 (-762,3996)	0.181
Cystitis	1847 (115,3579)	0.037		
Pyelonephritis	401 (-1371,2173)	0.655		
Prostatitis	-1653 (-4984,1677)	0.328		
Sepsis	1772 (-144,3690)	0.070	-479 (-2944-1985)	0.701
Shock	8750 (4680,12820)	0.000	6812 (3925-9699)	**0.000**
Others	-413 (-2001,1174)	0.608		
Time to adequate treatment	612 (117,1107)	0.016	546 (82,1010)	**0.021**
Appropriate empirical treatment	-3552 (-4928,-2177)	0.000	157 (-1635,1950)	0.862
Duration of hospital treatment	494 (298,629)	0.000	266 (140,392)	**0.000**
CA-UTI	-827 (-2371,717)	0.291	788 (-1101,1391)	0.818

DM: Difference of the median of the group that presents the variable less the median of the group that does not present it. The positivity of the value indicates increase of the cost in the presence of the variable and the negativity decrease of the cost;; CA-UTI: Community-Acquired Urinary Tract Infection

3. Discussion

The present study showed that clinical outcomes were worse and hospital costs higher for community-onset UTI caused by ESBL-producing *K. pneumoniae* requiring hospitalization, compared to UTI caused by non-ESBL-producing *K. pneumoniae*.

 doi:10.20944/preprints202103.0528.v1

There are several risk factors for acquisition of UTI caused by ESBL-producing microorganisms, including healthcare contact, previous antibiotic use, recurrent UTI, urinary catheter, old age and male gender [12]. Our study identified a higher prevalence of ambulatory healthcare-associated infections, previous antibiotic use and male gender in the ESBL-producing group. Ambulatory healthcare-associated UTIs have previously been identified as more frequently caused by antibiotic-resistant microorganisms than community-acquired UTIs and have important clinical consequences [13] Higher male gender prevalence could be attributed to the fact that UTIs in males tend to have more hospitalization criteria.

There was a significant difference in clinical response (22.4%) between the two groups, with lower response rates in the ESBL-producing group, similar to previous studies performed with E. coli.[9]. The presence of ESBL was identified as one of the independent variables responsible for this difference. Other variables associated with worse clinical response were clinical presentation with confusional state and shock, time to receipt of adequate antimicrobial therapy was also an independent factor associated with a worse clinical response. Previous studies have shown that patients who received adequate empirical treatment were more likely to have a better clinical course. [14] Hospital stay was significantly longer in ESBL-UTI patients. This is another important clinical consequence that could probably be avoided or reduced by improving initial or early antimicrobial management. Our data confirm that inadequate antimicrobial therapy is associated with a worse prognosis for patients with *K. pneumoniae* UTI requiring hospital admission without differences in mortality. These findings are similar to those from a recent study from Denmark [15].

Interestingly, we observed that among patients with ESBL-producing *K. pneumoniae* infections, there was a higher prevalence of cystitis, whereas among patients with non-ESBL-producing *K. pneumoniae* UTI, clinical symptoms of pyelonephritis, positive blood cultures, sepsis and ICU admission were more prevalent. These data seem to indicate lower virulence in ESBL strains, a phenomenon that has already been reported in other studies involving E. coli, in which acquisition of quinolone resistance was associated with loss of virulence factors [16]. The relationship between resistance and bacterial virulence has also been studied in recent years. For instance, acquisition by E.coli of the OXA-10, OXA-24 or SFO-1 family of beta-lactamases is known to be associated with loss of virulence due to alterations in the formation of peptidoglycan, probably caused by residual enzymatic activity in the β-lactamases similar to that of penicillin-binding proteins. [17]. In the case of *K. pneumoniae*, there are studies describing the role of mechanisms such as the deletion of ompK36 and ompK36 porins in loss of virulence and acquisition of resistance.[18] Our cohort comprised community-acquired and ambulatory healthcare-associated UTIs, which are environments in which the selective pressure of antibiotics is not as high as in the nosocomial setting. It is likely that loss of virulence in these environments due to the acquisition of resistance is better tolerated by microorganisms.

With respect to the economic impact, we showed that total hospitalization costs associated with patients with ESBL-producing *K. pneumoniae* UTI admitted to hospital were almost double those of patients with non-ESBL-producing *K. pneumoniae* UTI. The cost of medication and nursing costs accounted for the difference in total cost. The difference in medication cost was mainly due to the use of more expensive antibiotics such as carbapenems. Time to adequate treatment was also identified as a variable related to the increased total cost of hospitalization, and was probably an indirect effect of a worse clinical response, as seen in previous studies. [10, 19]

The main limitation of our study is its retrospective design. However, this design permits to study a higher number of patients in less time.

 doi:10.20944/preprints202103.0528.v1

4. Materials and Methods

A retrospective cohort study was conducted from January 2011 to January 2016 at Hospital del Mar, a tertiary university hospital with 420 beds serving a population of 340,000 people in the City of Barcelona (Spain). The study included all adults (older than 17 years) admitted to Hospital del Mar during the study period with urinary tract infection and a urine culture positive for *K. pneumoniae*. The only UTI origins considered were strictly community-acquired (CA) and ambulatory healthcare-associated (AHA). Hospital-acquired UTIs were excluded. In case of multiple episodes requiring admission, only the first episode was studied. UTIs caused by microorganisms other than *K. pneumoniae*, cultures showing mixed flora, and patients with asymptomatic bacteriuria were excluded.

4.1. Variables

Patient data was collected retrospectively from hospital electronic medical records. The following variables were collected: demographic and epidemiological factors (age, gender, underlying diseases, use of immunosuppressive therapy, prior antibiotic treatment), clinical and microbiological data (UTI symptoms, sepsis, shock, empirical and definitive antibiotic treatment, time to adequate treatment, clinical response at 7 days, infectious diseases and/or pharmacy services interventions, ICU admission, emergency room visits after discharge, hospital readmissions, convalescent or subacute hospitalization after discharge, mortality at 30 days) and risk factors for ESBL-producing *K. pneumoniae* (urinary catheter, urological manipulation, urologic conditions, type of acquisition: community-acquired (CA) versus ambulatory healthcare-associated (AHA). The Charlson Index was used to classify comorbidities and the McCabe-Jackson index to classify their severity. The main variable used to analyse clinical impact was clinical response 7 days after admission. Variables selected to study use of clinical resources were: duration of hospitalization, cost of hospitalization, use and cost of antibiotic treatment, emergency room visits, use of home hospitalization and need for re-admission after 30 days. Costs of hospitalization were obtained from hospital data base and were broken down into cost of medication, cost of antibiotics, cost of nursing, laboratory, radiology, pharmacy, specialist consultations and emergency visits.

4.2. Definitions

A diagnosis of symptomatic UTI was established if the patient presented one of the following signs or symptoms: fever >38ºC, urinary urgency, polyuria, dysuria or suprapubic pain, and a positive urine culture (more than 105 CFU of uropathogen per mL of urine). Five UTI syndromes were considered:

1. Cystitis: the presence of dysuria, urinary frequency, urgency and occasionally hematuria in patients without fever (axillary temperature <38 ºC).
2. Pyelonephritis: presence of fever (axillary temperature >38 ºC) and spontaneous lumbar pain or pain on costovertebral percussion, with or without increased urinary frequency, dysuria or urine retention.
3. Acute prostatitis: sudden febrile episode in men accompanied by lower back and perineal pain with polyuria or dysuria, and/or urinary retention.
4. Confusional state associated with UTI was defined as an episode of confusion attributed to an underlying UTI after excluding other infectious foci and other causes.
5. Urinary sepsis: systemic inflammatory response syndrome with a positive urine culture or blood culture for an uropathogen with no other apparent source of infection [11].

CA-UTI was defined as UTI detected within the first 48 hours of hospital admission that did not meet the criteria for AHA-UTI. AHA-UTI was defined as UTI detected within the first 48 hours of hospital admission and met one of the following criteria [12]:

 doi:10.20944/preprints202103.0528.v1

1. The patient had received specialized treatment at home by qualified healthcare workers within 30 days prior to hospital admission.
2. The patient had attended a day hospital, hemodialysis clinic or had received intravenous chemotherapy within 30 days prior to hospital admission
3. Hospitalization for more than 48 h during the 90 days preceding the current admission.
4. Resident in a long-term care facility or nursing home.
5. The patient underwent an invasive urinary procedure within 30 days of the episode or had a long-term indwelling urethral catheter.

Community-onset UTI was defined as any CA-UTI or AHA-UTI.

Previous antibiotic therapy was defined as use of antibiotics in the three months prior to diagnosis of UTI. Empirical therapy was administered before the in vitro susceptibility of the uropathogen that caused the episode was known. Empirical therapy was considered inadequate if the microorganism causing UTI was not fully susceptible to the antibiotic used.

Response to treatment at 7 days was considered satisfactory if the patient was asymptomatic or there was a significant improvement in the signs and symptoms of infection; treatment response was unsatisfactory if there was persistence or progression of signs and symptoms of infection, a change of pharmacological agent was required after three days of treatment, or infection-related death occurred.

4.3. Statistical analysis

Data from patients with and without ESBL-producing *K. pneumoniae* were compared. Quantitative variables were compared using the Student's t-test, or the Mann Whitney U test if the distribution of data was not normal. Qualitative variables were compared using the Chi-square test. Bivariate and multivariate analyses were performed to elucidate variables independently related to clinical failure at 7 days and to higher hospital costs. Clinical response was analyzed by binary logistic regression. With respect to hospital costs, the normality of the variables was assessed by histogram inspection, testing for normality with a QQ-plot, and applying the Shapiro-Wilk W-test. Once non-normality was established ($p<0.001$), hospital costs were analyzed by median regression. Associations with p-values <0.05 were regarded as statistically significant. Statistical analyses were performed using the SPSS v.22 and STATA v.15.1 packages.

5. Conclusions

In conclusion, our study shows that the production of ESBL by *K. pneumoniae* causing community-onset UTI and time to adequate antimicrobial therapy are independent factors for a worse clinical response and higher healthcare costs. It is important to identify risk factors in order to categorize these patients earlier so that they benefit from the appropriate empirical treatment that leads to a better clinical response and reduced hospitalization costs. Rapid diagnostic tests are also important in this scenario.

More studies of infections caused by multidrug-resistant bacteria in the community should be performed in order to prevent acquisition and to optimize management of infection in an attempt to reduce their clinical and economic burden. This section is not mandatory but can be added to the manuscript if the discussion is unusually long or complex.

Author Contributions: "Conceptualization: JPH.; methodology: JPH, EEP, DR.; validation, JPH, EEP, LS, MM, SG; formal analysis: XD, JPH; investigation: DR, EEP; data curation: DR, XD.; writing—original draft preparation: DR, JPH; writing—review and editing: MAM, JPH, LS, MM, SG; supervision: JPH; All authors have read and agreed to the published version of the manuscript."

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics for Clinical Research (Nr. 2010/41221 / I) of the IMIM-Parc de Salut MAR, Barcelona, Spain. The study followed legal regulations on the confidentiality of data (Spanish Organic Law 15/1999 of 13 December on the Protection of Personal Data [LOPD]).

Informed Consent Statement: Informed consent was waived due to the retrospective observational nature of the study.

Conflicts of Interest: JPH has received honoraria for speaker activities and advisory boards from MSD, Pfizer, Angelini, Menarini. All the other authors declare no conflict of interest.

References

1. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: A clinical update. Clin Microbiol Rev 2005;18:657-86.
2. Podschun R, Ullmann U. Klebsiella spp. as nosocomial pathogens: epidemiology, taxonomy, typing methods, and pathogenicity factors. Clin Microbiol Rev 1998;11:589-603.
3. Medina,Polo J, Guerrero,Ramos F, Pérez,Cadavid S, Arrébola,Pajares A, Sopeña,Sutil R, et al. Community,associated urinary infections requiring hospitalization: risk factors, microbiological characteristics and patterns of antibiotic resistance. Actas Urol Esp. 2015;39:104-11.
4. Boix-Palop L, Xercavins M, Badia C, Obradors M, Riera M, Freixas N, et al. Emerging extended-spectrum β-lactamase-producing Klebsiella pneumoniae causing community-onset urinary tract infections: a case–control–control study. International Journal of Antimicrobial Agents. 2017;50:197-202.
5. Díaz MA, Hernández JR, Martínez,Martínez L, Rodríguez,Baño J. Pascual A. Extended Spectrum Betalactamase producing Escherichia coli and Klebsiella pneumoniae in Spanish hospitals. Second multicenter study (GEIH,BLEE 2006 Project). Enferm Infecc Microbiol Clin 2009;27:503-10.
6. Paterson DL. Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum-lactamases (ESBLs). Clin Microbiol Infect 2000;6:460-3.
7. MacVane SH, Tuttle LO, Nicolau DP. Impact of extended-spectrum B-lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. J Hosp Med 2014;4;232-238.
8. Lautenbach E, Patel JB, Bilker WB, Edelstein PH, Fishman NO. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. Clin Infect Dis 2001;32:1162-71.
9. Scheuerman O, Schechner V, Carmeli Y, Gutiérrez-Gutiérrez B, Calbo E, Almirante B, et al. Comparison of Predictors and Mortality Between Bloodstream Infections Caused by ESBL-Producing Escherichia coli and ESBL-Producing Klebsiella pneumoniae. Infect Control Hosp Epidemiol 2018;39(6), 660-667.
10. Esteve Palau E, Solande G, Sánchez F, Sorlí L, Montero M, Güerri R, Villar J, Graus S, Horcajada JP. Clinical and economic impact of urinary tract infections causes by ESBL, producing Escherichia coli requiring hospitalization: A matched cohort study. J Infect 2015: 71, 667-674.
11. Levy MM, Fink MP, Marshall JC et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31:1250-1256.
12. Horcajada JP, Shaw E, Padilla B, Pintado V, Calbo E, Benito N, et al. ITUBRAS group; Grupo de Estudio de Infección Hospitalaria (GEIH); Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC). Healthcare-associated, community-acquired and hospital-acquired bacteraemic urinary tract infections in hospitalized patients: a prospective multicentre cohort study in the era of antimicrobial resistance. Clin Microbiol Infect 2013;19:962-8.
13. Medina, Polo J, Guerrero, Ramos F, Pérez,Cadavid S, Arrébola,Pajares A, Sopeña,Sutil R, Benítez,Sala R, et al. Infecciones urinarias adquiridas en la comunidad que requieren hospitalización: factores de riesgo, características microbiológicas y resistencia a antibióticos. Actas Urol Esp. 2015;39:104-111.
14. Lee SY, Kotapati S, Kuti JL, Nightingale CH, Nicolau DP. Impact of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species on clinical outcomes and hospital costs: a matched cohort study. Infect Control Hosp Epidemiol 2006;27:1226-32.
15. Richelsen R, Smit J, Schønheyder HC, Laxsen Anru P, Gutiérrez-Gutiérrez B, Rodríguez-Bãno J, Nielsen H. Outcome of community-onset ESBL-producing Escherichia coli and Klebsiella pneumoniae bacteraemia and urinary tract infection: a population-based cohort study in Denmark. J Antimicrob Chemother. 2020 Dec 1;75(12):3656-3664.
16. Horcajada JP, Soto S, Gajewski A, et al. Quinolone-Resistant Uropathogenic Escherichia coli Strains from Phylogenetic Group B2 Have Fewer Virulence Factors than Their Susceptible Counterparts J Clin Microbiol 2005;43:2962-2964.
17. Fernandez A, Perez A, Ayala JA, Mallo S, Rumbo,Feal S, Tomas M, Poza M, Bou G. 2012. Expression of OXA-type and SFO-1 beta-lactamases induces changes in peptidoglycan composition and affects bacterial fitness. Antimicrob Agents Chemother 2012;56:1877-1884.

18. Tsai Y,K, Fung C,P, Lin J,C, et al. Klebsiella pneumoniae Outer Membrane Porins OmpK35 and OmpK36 Play Roles in both Antimicrobial Resistance and Virulence . Antimicrob Agents Chemother. 2011;55:1485-1493.
19. MacVane Shawn H, Tuttle Lindsay O, Nicolau David P. Impact of extended-spectrum-B-lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. J Hosp Med April 2014;9:232-8.