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Impact of an antimicrobial stewardship program on urinary tract infections caused by extended-spectrum β-lactamase-producing *Escherichia coli*

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ABSTRACT

Objective. To analyze the clinical and economic impact of an antimicrobial stewardship program (ASP) targeting urinary tract infections (UTI) caused by extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli.*

Methods. An observational retrospective study that included adults with a diagnosis of UTI caused by ESBL-producing *E. coli* admitted to a tertiary care hospital in Barcelona, Spain, between January 2014 and December 2015. The impact of the ASP was analyzed in terms of clinical and economic outcomes.

Results. A total of 222 patients met the inclusion criteria and an intervention was made by the ASP team in 104 cases (47%). ASP intervention was an independent variable related to clinical cure (p = 0.008). Other variables influencing clinical outcomes were the McCabe Jackson score (p = 0.005) and outpatient status (p < 0.001). The ASP interventions in this study had no economic impact.

Conclusion. Antimicrobial stewardship has a positive clinical impact on UTIs caused by ESBL-producing *E. coli*. Further prospective studies are needed to assess the economic impact of ASPs on UTI caused by ESBL-producing *E. coli.*

Key words: *E. coli*, ESBL, Urinary Tract Infections, Antimicrobial Stewardship

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Impacto de un programa de optimización de antimicrobianos en infecciones urinarias por *Escherichia coli* productor de β-lactamasas de espectro extendido

RESUMEN

Objetivo. Analizar el impacto clínico y económico de un Programa de Optimización de Antimicrobianos (PROA) en las infecciones del tracto urinario (ITU) causadas por *Escherichia coli* productor de β-lactamasas de espectro extendido (BLEE).

Métodos. Estudio observacional retrospectivo que incluye adultos con ITU por *E. coli* BLEE diagnosticados en un hospital terciario en Barcelona, España, entre enero de 2014 y diciembre de 2015. El impacto del PROA se analizó en términos de evolución clínica y consumo de recursos sanitarios.

Resultados. Se incluyeron un total de 222 pacientes, de los cuales se realizó algún tipo de intervención por parte del equipo de PROA en 104 casos (47%). La intervención del PROA resultó ser una variable independiente relacionada con la curación clínica (p = 0,008). Otras variables relacionadas con la evolución clínica fueron la clasificación de McCabe Jackson (p = 0,005) y el manejo ambulatorio (p < 0,001). Las intervenciones del PROA no demostraron tener un impacto económico en este estudio.

Conclusión. Las intervenciones de los PROA tienen un impacto positivo en la evolución clínica de los pacientes con ITU por *E. coli* productor de BLEE. Se necesitan más estudios prospectivos para determinar el impacto económico de los PROA en las ITU por *E. coli* productor de BLEE.

Palabras clave: *E. coli*, BLEE, Infección del tracto urinario, Programa de optimización de antimicrobianos

INTRODUCTION

Extended-spectrum β-lactamase (ESBL) isolates have been increasing in Europe since the first reported case in 1983. The Spanish Hospital Infection Study Group (GEIRAS/GEIH) has conducted several studies on the epidemiology and evolution of this problem in Spain, showing a growing proportion of urinary tract infections (UTI) caused by ESBL-producing *Escherichia coli*, with a high percentage considered to be community-acquired [1]. In our center, in outpatients and inpatients, ESBL-producing *E. coli* increased from 8% and 11.4%, respectively, in 2010, to 10.9% and 15.1% in 2014. Antimicrobial resistance is known to limit treatment options and to increase the cost of healthcare resources [1-6]. Antimicrobial stewardship programs (ASPs) have been developing in Spain in recent years to respond to this problem. The Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC) drafted a consensus document defining the objectives of antimicrobial stewardship and establishing recommendations for their implementation in Spanish hospitals [7]. Based on a previous study conducted by our group, which showed the significant clinical and economic impact of urinary tract infections caused by ESBL *E. coli* [2], it was decided to intensify ASP activities, paying particular attention to multidrug-resistant pathogens, including ESBL producers.

Multiple studies have clearly demonstrated that implementation of an ASP has a positive impact on the clinical outcomes of patients and on the consumption of healthcare resources and associated costs [8–18], although specific literature on urinary infections caused by ESBL-producing bacteria is scarce.

The study hypothesis was that ASP activities have a positive impact on the clinical outcome of patients with ESBL-producing *E.coli* UTI and on the use of healthcare resources. The Hospital del Mar, Barcelona, recently started to implement these programs. The aim of this study was to study the clinical and economic impact of an ASP on patients with ESBL-producing *E.coli* UTI admitted to our hospital during 2014 and 2015.

METHODS

An observational retrospective study, conducted from January 2014 to December 2015 in a 420-bed, university-affiliated tertiary care hospital in Barcelona (Spain) serving a population of 300,000 people. The study was approved by the Clinical Research Ethical Committee of the Parc de Salut Mar (CEIC - Parc de Salut Mar) (number 2015/6492/I).

A multidisciplinary ASP team started to be built in 2010, comprising a microbiologist, a pharmacist specializing in infectious diseases and two physicians specializing in antimicrobial therapy. Their core strategies include daily review of cultures of clinical samples, informing infection control practitioners and physicians responsible for antimicrobial stewardship by email of multiresistant pathogens and antibiogram once it is available (On Saturdays, the microbiologist, in addition to the email, makes a phone call to the doctor on call in charge of the patient. This activity was performed from Monday to Friday until early 2016, when it was expanded to include the weekends also). In addition, the ASP pharmacist monitors antibiotic use on a daily basis via a computerized system that collects all data related to antibiotic prescriptions. After the daily review of these data, the pharmacist and/or ASP physician review the adequacy of the prescriptions and assess the need for an intervention, which may involve informing the doctor in charge of a culture positive for a multidrug-resistant microorganism and/or making a recommendation to the prescriber to improve the quality of the prescription, as and when necessary. The system of recommendations is based on non-restrictive or imposed strategies and can be made in writing using the electronic medical records, by telephone, and/or directly with the prescriber. Recommendations may include the appropriateness and adequacy of antibiotic treatment, including adjustment of dose, duration of treatment, discontinuation, de-escalation, switching therapy from intravenous to the oral route, change due to adverse events and use of OPAT. These strategies were intensified significantly during the last 4 months included in the study.

Study population and selection criteria

-Inclusion: Symptomatic episodes of UTI in adult patients (over 18 years old) with a positive urine culture for ESBL-producing *E. coli*, graded at the Hospital del Mar, requiring both hospitalization and outpatient treatment.

-Exclusion: patients with a diagnosis of asymptomatic bacteriuria, another concomitant infection that would make it difficult to interpret the UTI, infection caused by a microorganism other than *E. coli* and/or polymicrobial infections.

Data collection and variables analyzed. Data were retrospectively collected from electronic charts. The following variables were recorded: demographic and epidemiological data (age, gender, underlying diseases, use of immunosuppressive therapy, prior antibiotic treatment), clinical and microbiological data (fever, bacteremia, severe sepsis or shock, hospitalization, ICU admission, antibiotic susceptibility patterns, incidence of ESBL-producing *E. coli* isolated from the UTI, empirical treatment, clinical response after 7 days, need for readmission or re-consultation within 30 days of diagnosis, 30-day mortality rate) and risk factors for ESBL-producing *E. coli* (presence of bladder catheters, previous urologic manipulation, acquisition of infection: community vs. healthcare-related vs nosocomial).

The Charlson index was used to classify comorbidities and the McCabe-Jackson index to classify their severity. The following variables concerning use of healthcare resources were analyzed: length of hospital stay, cost of hospitalization, cost of antibiotics, use of outpatient parenteral antimicrobial therapy (OPAT), number of successive consultations and readmissions within 30 days of discharge.

With respect to the ASP, the following variables were collected: appropriateness of empirical treatment, days to appropriate treatment when required, directed antibiotic treatment, ASP team recommendations, time to performance of the recommendation, prescriber acceptance rates of recommendations, adequacy of treatment by dosage and other patient characteristics (allergies, obesity, kidney failure, liver failure, use of extrarrenal purification techniques, etc.) when required, time to correction of inappropriate treatment, appropriate treatment duration, total duration of antibiotic treatment, de-escalation, sequential therapy, incidence of adverse effects, including *Clostridium difficile*-associated diarrhea, incidence of hypersensitivity and toxicity attributable to antibiotic treatment. To be placed in the care of an infectious diseases specialist was considered an intervention, as these patients are discussed with the ASP team and cultures are reviewed daily, although they are not usually reported in the electronic chart.

Definitions. Symptomatic UTI was established when the patient presented at least one of the following symptoms: increased urinary frequency, urgency, dysuria or suprapubic tenderness associated with a positive urine culture (more than 10^5 colony-forming unit (CFU) of uropathogen per mL urine).

Syndromes:

-Cystitis: the presence of dysuria and increased urinary frequency or urgency, with or without hematuria, in patients without fever (axillary temperature < 38ºC).

-Pyelonephritis: presence of fever (axillary temperature ≥38ºC) and back pain or costovertebral angle tenderness.

-Acute prostatitis: a sudden febrile episode characterized by low back or perineal tenderness with increased urination frequency, dysuria and urine retention.

-Orchiepididymitis: a febrile episode accompanied by testicular pain and inflammation.

-Urosepsis: A urine and/or blood culture positive for the study uropathogen (*E. coli*) implying clinical evidence of severe infection of the urinary tract (or male genital tract) and presenting with systemic inflammatory response syndrome (definition adapted for this study) [19].

-Septic shock: urosepsis with hypotension that persists despite intravenous fluid treatment.

Table 1 **Baseline characteristics**

	No ASP N = 118 (%)	ASP N = 104 (%)	p-value
Median age	67	7	0.25
Sex, female	71 (60)	63 (61)	0.95
Charlson	4.9	5.6	0.1
McCabe Jackson	2.4	2.3	0.3
Previous ESBL *E. coli*	35 (30)	35 (34)	0.52
Outpatient	53 (45)	22 (21)	<0.001
Inpatient	65 (55)	82 (79)	<0.001
ICU	2 (2)	4 (4)	0.3
Diabetes mellitus	43 (36)	48 (46)	0.14
Cirrhosis	1 (1)	12 (12)	0.001
Chronic renal failure	28 (24)	26 (25)	0.82
Previous antibiotic	75 (64)	80 (77)	0.04
Immunosupression	14 (12)	18 (17)	0.25
Kidney transplant	5 (4)	4 (4)	0.88
Urinary catheter	15 (13)	22 (21)	0.09
Previous urologic manipulation (3 months)	39 (33)	54 (52)	0.004
Obstructive UTI	6 (5)	2 (2)	0.21
Urological condition	68 (58)	55 (53)	0.48
Recurrent UTI	54 (46)	38 (37)	0.16
Syndrome			
Cystitis	33 (28)	20 (19)	0.13
Pyelonephritis	20 (17)	7 (7)	0.02
Urosepsis	48 (41)	53 (51)	0.13
Septic shock	6 (5)	6 (6)	0.8
Prostatitis	1 (1)	9 (9)	0.01
Orchitis	5 (4)	1 (1)	0.33
Other	7 (6)	8 (8)	0.6
Bacteremia	8 (7)	31 (30)	< 0.001
Acquisition			
Community	54 (46)	23 (22)	<0.001
Health care-related	49 (42)	52 (50)	0.2
Nosocomial	15 (13)	28(27)	0.008
Time to appropriate therapy	1.93	1.14	0.032
OPAT	5 (4)	18 (17)	0.001
De-escalation	12 (34 % of potentials)	30 (71% of potentials)	0,003
Switch to oral route	15 (35% of potentials)	28 (56 % of potentials)	0,052
C. difficile diarrhea	0	2 (2)	0.2
Clinical outcome			
Failure	22 (19)	5 (5)	
Cure	74 (63)	95 (91)	<0.001
Indeterminate	22 (19)	4 (4)	
Microbiological outcome			
Persistence	23 (19)	14 (13)	
Negative	24 (20)	25 (24)	0.4
No control	68 (58)	64 (62)	
Re-consultation	30 (25)	18 (17)	0,08
Re-admission	15 (13)	13 (13)	0.62
Mortality	7 (6)	4 (4)	0.4

Table 2 Factors related to clinical outcome

	Failure N = 27 (%)	Cure N = 169 (%)	p-value
Sex, female	14 (51.9)	101 (59.8)	0.44
Age > 60	19 (70.4)	127 (75.1)	0.60
MCJ < 2	4 (14.8)	9 (5.3)	0.085
Previous ESBL *E. coli*	7 (25.9)	55 (32.5)	0.50
Outpatient	17 (63)	40 (23.7)	< 0.001
Surgical service	6 (22.2)	35 (20.7)	0.86
DM	9 (33.3)	74 (43.8)	0.31
Chronic renal failure	4 (14.8)	44 (26)	0.24
Immunosuppression	3 (11.1)	24 (14.2)	1.00
Urinary catheter	3 (11.1)	31 (18.3)	0.58
Previous urologic manipulation	8 (29.6)	81 (48.5)	0.095
Septic shock	3 (11.1)	9 (5.3)	0.22
Bacteremia	4 (14.8)	35 (20.7)	0.48
Community	10 (37)	53 (31.4)	0.66
Health care-related	14 (51.9)	77 (45.6)	0.54
Nosocomial	3 (11.1)	38 (22.5)	0.21
Inappropriate empirical treatment	14 (53.8)	74 (44.3)	0.36
No ASP intervention	5 (18.5)	95 (56.2)	< 0.001

MCJ: McCabe Jackson score; DM: Difference in Medians

-Other: evidence of active infection with fever or leukocytosis not attributable to a focus other than urinary (catheter-related UTI, UTI in elderly patients)

Acquisition:

• Community-acquired UTI (CA-UTI) was defined as an episode whose symptoms started either before or within 48 hours of being admitted to hospital, but without criteria for HCA.

• Health care-acquired UTI (HCA-UTI) was defined as an episode whose symptoms appeared in the 48 hours prior to hospital admission and the patient met at least one of the following criteria (adapted from Friedman et al's criteria for bloodstream infections):

- The patient had received specialized treatment (including change of an indwelling urinary catheter) at home by a qualified healthcare worker in the 30 days prior to hospital admission.

- The patient had attended a day hospital, hemodialysis clinic or had received intravenous chemotherapy in the 30 days prior to hospital admission.

- Hospitalization for more than 48 hours in the 90 days preceding the current admission.

- Resident in a long-term care facility or nursing home.

• Hospital-acquired UTI (HA-UTI). More than 48h after admission, within 3 days of discharge or 30 days of an operation [20].

Empirical therapy was defined as the antibiotic given before the *in vitro* susceptibility of the uropathogen causing the episode was known, and was deemed inappropriate if the microorganism was not susceptible according to EUCAST criteria.

-Appropriate antibiotic treatment: defined as use of agents with in vitro activity against the causative pathogens.

-Adequate antibiotic treatment: this required both administration of the correct (appropriate) antibiotic and also the optimal dose and correct route of administration to ensure that the antibiotic penetrated into the site of infection [7].

De-escalation was considered as streamlining or narrowing the spectrum of antibiotics from empiric treatment to a single culture-directed agent with the following ranking: carbapenem > piperacillin / tazobactam or ertapenem > amoxicillin / clavulanate or co-trimoxazole or ciprofloxacin or fosfomycin [21].

Treatment outcome was defined as clinical failure when the patient showed no improvement, or at least one of the initial symptoms worsened, or needed a switch of antimicrobial therapy, or died. Clinical cure was defined as either the absence of symptoms or a consistent improvement in the signs and symptoms of infection.

Statistical analysis. Quantitative variables were analyzed using the Student's t-test or Mann Whitney test and qualitative variables using the Chi-square test or Fisher's exact test, as appropriate. Multivariate logistic and median regression analysis were used to determine the independent variables related to, respectively the clinical and economic impact of the ASP. For the statistical analysis, a P value of <0.05 was considered significant. All data were analyzed using STATA statistical package.

RESULTS

A total of 667 positive urine cultures for ESBL-producing *E.coli* were analyzed. The following were excluded from analysis: asymptomatic bacteriuria (253), polymicrobial infections (66), cases with concomitant infection that would make the UTI difficult to interpret (50) and cases with missing data in the medical records (76). A total of 222 patients were finally included.

The baseline characteristics and bivariate analysis of intervention vs non-intervention are shown in table 1.

Of the total of 222 cases, an ASP intervention was performed in 104 (47%). Of these, 27 patients were in the care of an infectious diseases (ID) physician and 28 involved an infectious diseases consultation service from another department. 72 (32%) cases were notifications of a urine culture positive for ESBL *E. coli* received within 72h (communicated by telephone and/or a note in the patient's records when the patient

Table 3 **Univariate and multivariate analysis of factors related to clinical failure**

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p-value	OR (95% CI)	p-value
Sex, female	0.73 (0.32 – 1.64)	0.44	0.82 (0.30 – 2.25)	0.70
Age > 60	0.79 (0.32 – 1.93)	0.6	0.77 (0.24 – 2.46)	0.66
ICC	0.97 (0.85 – 1.11)	0.67		
MCJ < 2	3.09 (0.88 – 10.86)	0.078	9.83 (1.96 – 49.20)	0.005
Previous ESBL	0.73 (0.29 – 1.82)	0.49		
Outpatient	5.48 (2.33 – 12.93)	< 0.001	13.55 (3.5 – 52.43)	< 0.001
Surgical service	1.09 (0.41 – 2.92)	0.86		
Diabetes mellitus	0.64 (0.27 – 1.5)	0.31		
Chronic renal failure	0.49 (0.16 – 1.51)	0.22		
Immunosuppression	0.76 (0.21 – 2.7)	0.67		
Urinary catheter	0.56 (0.16 – 1.97)	0.36		
Previous urologic manipulation	0.45 (0.19 – 1.08)	0.07		
Septic shock	2.22 (0.56 – 8.79)	0.26	2.88 (0.43 – 19.14)	0.28
Bacteremia	0.67 (0.22 – 2.05)	0.48	2.22 (0.45 – 10.89)	0.33
Community	1.29 (0.55 – 3.00)	0.56		
Health care-related	1.29 (0.57 – 2.90)	0.54	2.62 (0.75 – 9.11)	0.13
Nosocomial	0.43 (0.12 – 1.51)	0.19	2.50 (0.39 – 15.84)	0.33
Inappropriate empirical treatment	1.47 (0.64 – 3.36)	0.37	1.30 (0.49 – 3.4)	0.60
No ASP intervention	5.65 (2.04 – 15.63)	0.001	5.04 (1.52 – 16.76)	0.008

was in the charge of a service other than ID; of note, 87 (39%) cultures were received at weekends, correlating with fewer notifications (72% vs 39%; *P* = 0.003). In 51 (23%) patients from a service other than ID, a therapeutic recommendation was made.

Of all recommendations, 44 (86%) were based on susceptibility testing and 22 (43%) involved a recommendation of a change from inappropriate to appropriate treatment. De-escalation was proposed in 12 (24%) of recommendations and switching from the intravenous to oral route in 9 (18%). In 13 cases (25%), dose adjustment was recommended. In one case, a change due to hypersensitivity was proposed, and withdrawal of treatment in another.

With regard to de-escalation, 77 (34%) cases were identified where de-escalation was possible and it was carried out in 58% of them. De-escalation was mostly carried out when a specific recommendation was made (89% vs 36%, P= 0.004). Clinical cure rates were similar in both groups.

Table 4 **Patients with non-evaluable outcome.**

	Missing UTI data in medical record	Lost to Follow-up	Death not related to UTI[a]	Total
Cystitis	5	5	0	10
Pyelonephritis	0	2	0	2
Prostatitis	1	1	0	2
Urosepsis	4	3	4	11
Other	0	0	1	1
Total	10	9	5	26

[a]All were patients with a severe chronic disease and 4 (80%) were aged ≥ 80

With respect to switching therapy from the intravenous to the oral route, 92 (41%) potential cases were identified for a switch to oral therapy, and the conversion was performed in 47%. There were more conversions to oral therapy when a specific recommendation was made (88% vs 39%; p= 0.019). There were no differences in clinical cure between switch to oral therapy vs non-switch patients.

Table 2 shows factors related to clinical failure and table 3 the univariate and multivariate analyses of variables involved in the clinical outcome of patients. Twenty-six patients were excluded from the analysis because the outcome was not evaluable (table 4). In multivariate analysis, ASP intervention and inpatient status were independent variables related to clinical cure, while patients with septic shock were related to clinical failure.

Table 5 **Univariate analysis of patient costs: intervention versus no intervention**

	No ASP med [P25-P75]	ASP med [P25-P75]	p-value
Hospital stay cost	3,807.93 (2,403.96 – 6,973.3)	5,423.16 (3,684.11 – 9,674.61)	0.056
Cost of antibiotics	22.6 (9.62 – 112.55)	98.28 (14.6 – 288.53)	0.002

It should be noted that during the intensive period when a person was in charge of revising cultures and making recommendations systematically (September to December 2015), the number of interventions was significantly higher than the rest of the study period (74% vs 42%, P < 0.001).

Table 6 Univariate and multivariate analyses of costs of hospital stay and antibiotics

	DM (95% CI)	p-value	Adjusted	p-value
Hospital stay costs				
Intervention	1,615.23 (33.14 - 3,197.32)	0.045	1,351.17 (-234.26 - 2,936.60)	0.094
Age	3.26 (-53.83 - 60.36)	0.91	-1.89 (-69.40 - 65.62)	0.956
Sex	-1,047.19 (-2,699.65 - 605.27)	0.21	-691.61 (-2,165.26 - 782.05)	0.355
MCJ	-208.94 (-1,542.48 - 1,124.60)	0.757	608.16 (-952.14 - 2,168.46)	0.442
Shock	2,446.63 (-705.35 - 5,598.61)	0.127	706.32 (-2,087.67 - 3,500.29)	0.618
Bacteremia	53.55 (-2,061.50 - 2,168.50)	0.96	-339.58 (-2,148.91 - 1,469.76)	0.711
HCA or HA	2,081.02 (43.82 - 4,118.22)	0.045	2,089.32 (88.50 - 4,090.13)	0.041
Alternative to carbapenem	-1,043.48 (-3,373.5 - 1,286.54)	0.38	-109.85 (-2,055.35 - 1,835.65)	0.911
OPAT	-805.56 (-3,153.23 - 1,542.11)	0.50	-1,173.23 (-3,179.80 - 833.34)	0.249
Cost of antibiotics				
Intervention	75.68 (29.98 - 121.37)	0.001	-5.2325 (-62.62 - 52.16)	0.857
Age	0.82 (-0.64 - 2.28)	0.27	-0.065 (-2.03 - 1.90)	0.948
Sex	-74.49 (-119.97 - -29.00)	0.001	-14.665 (-70.44 - 41.11)	0.605
MCJ	-45.08 (-78.52 - 11.64)	0.008	-6.5175 (-62.30 - 49.27)	0.818
Shock	146.44 (57.01 - 235.87)	0.001	38.69 (-77.21 - 154.59)	0.51
Bacteremia	168.09 (113.94 - 222.24)	< 0.001	127.31 (51.08 - 203.54)	0.001
HCA or HA	79.23 (28.49 - 129.97)	0.002	3.42 (-66.72 - 73.55)	0.92
Alternative to carbapenem	-254.06 (-327.56 - -180.56)	< 0.001	-96.29 (-176.74 - -15.84)	0.019
OPAT	147.49 (83.53 - 211.45)	< 0.001	119.57 (32.94 - 206.20)	0.007
Inpatient	104 (50.62 - 157.38)	< 0.001	40.81 (-32.14 - 113.76)	0.27

DM: Difference in Medians; MCJ: McCabe Jackson score

In spite of this, the sample is too small to show conclusive results (data not shown).

The ASP interventions did not have a significant impact on length of hospital stay, treatment duration, microbiological eradication, re-admissions or mortality. There was no economic impact as a result of ASP interventions for these infections (tables 5 and 6).

DISCUSSION

This study reviewed cases of UTI caused by ESBL-producing *E. coli* in 2014 and 2015 and the effect of an antimicrobial stewardship program on clinical outcomes and costs. In terms of the clinical outcomes of patients, the results showed a clearly positive impact in cases where there was some kind of intervention compared to those where none was made. Overall, we observed little differences between both groups regarding basal characteristics. However, the prevalence of conditions potentially involving an increased risk of treatment failure (cirrhosis, bacteremia, previous urologic manipulation, previous antibiotic therapy, nosocomial infection) was significantly higher in the ASP group (table 1). In this context, the results we observed in this group suggests that therapeutic intervention in the framework of an ASP might improve the prognosis of high-risk patients.

A previous quasi-experimental study evaluating the impact of an Antimicrobial Stewardship Program (ASP) on the management of UTI showed improvements in the number of discontinuations of treatment, duration of treatment and adherence to local guidelines. There were no differences with respect to de-escalation, switching therapy from the intravenous to oral route, re-admissions, length of stay and hospitalization costs [22]. In our study, there was only one discontinuation for unnecessary treatment and treatment duration was similar in both groups. This may have been due to the small sample size and its heterogeneity, or to the fact that, after a recommendation was made, the prescription was not exhaustively followed in most cases.

In our study, a higher rate of de-escalation therapy was observed when there was a specific ASP recommendation for de-escalation than when there was none. Similar rates of clinical cure were observed for de-escalated and not de-escalated groups, and the duration of carbapenem therapy was shorter when de-escalated. This is consistent with other studies [13]. Early switching from intravenous to oral routes has been shown to reduce the economic costs of antimicrobial treatment, the side effects and complications of parenteral therapy and length of hospital stay without compromising the effectiveness of treating infections when it is used [23]. Other studies have shown that early sequential therapy is just as effective for the treatment of acute pyelonephritis and has fewer side effects [24,25]. In our study, a significant reduction in intravenous therapy and length of stay was observed when patients switched from the intravenous to oral route, with a similar rate of clinical cure. Switch therapy was mostly carried out when the ASP team made the recommendation. Despite a higher rate of de-escalation and sequencing in cases of intervention, our study failed to show an overall reduction in carbapenem use or hospital stay when an ASP intervention was performed.

The costs attributable to antimicrobial resistance are considerable, hence the potential economic benefit of prevention programs [26]. Despite the fact that multiple studies have shown that antimicrobial stewardship programs make a positive impact on the consumption of health resources and economic outcomes [8–10,17,27–30], it was not possible to demonstrate this impact in our study.

Our study has several limitations, mainly related to its retrospective nature. The main limitation of the study lies in the potential bias between the groups studied, since during a long period of the study the team worked on ASP only part-time and therefore there is no clear division between candidates and non-candidates for ASP recommendations. Further, since data collection in based on reviewing patients' medical records, all the data may not be available in all cases. Another limitation is the small sample size. It is difficult to assess the long-term benefits of an ASP in a single study. In cases where any intervention is made, the prevention of possible future infections caused by multiresistant pathogens should be considered [31]. In addition, the lack of dedicated full-time staff makes it difficult to optimize the number and quality of interventions. A prospective intervention study with more dedicated staff will be required to overcome these limitations. The costs of implementation should be offset by reductions in the consumption of health care resources and antimicrobial costs.

In our study, there was less clinical failure when some kind of ASP intervention was applied to patients with ESBL-producing *E. coli* UTI. We conclude therefore that antimicrobial stewardship has a positive clinical impact on these urinary tract infections. Further prospective studies are needed to assess the impact on the consumption of health care resources, as well as the long-term ecological impact.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest

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