Factors Associated with the Presence of Extended-Spectrum Beta-Lactamase-Producing Pathogens in Urinary Tract Infections in a Private Clinic in Lima, Peru

Factores asociados con la presencia de patógenos productores de betalactamasas de espectro extendido en infecciones urinarias en una clínica privada, Lima (Perú)

Fatores associados à presença de patógenos produtores de betalactamases de espectro estendido em infeções urinárias em uma clínica privada, Lima (Peru)

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Received: April 8, 2019 · **Accepted:** February 10, 2020
Doi: https://doi.org/10.12804/revistas.urosario.edu.co/revsalud/a.9255
To cite this article: Remenik-Zarauz V, Díaz-Vélez C, Apolaya-Segura M. Factors associated with the presence of extended-spectrum beta-lactamase-producing pathogens in urinary tract infections in a private clinic in Lima, Peru. Rev Cienc Salud. 2020;18(2):1-11. https://doi.org/10.12804/revistas.urosario.edu.co/revsalud/a.9255

Abstract

Introduction: Urinary tract infections (UTIs) are the second most frequent reason for healthcare visits, and antibiotic resistance among gram-negative bacteria of the *Enterobacteriaceae* family has increased significantly worldwide. The emergence of microorganisms that produce extended-spectrum beta-lactamase (ESBL) is especially problematic. This study aims to identify factors associated with the presence of

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UTI caused by ESBL-producing pathogens. *Material and methods:* An analytical cross-sectional study was conducted, and the urine culture database from a private healthcare clinic was analyzed. Factors possibly associated with the appearance of UTIS due to ESBL-producing pathogens were analyzed, including sex, age, number of hospitalizations, and previous UTIS. *Results:* A total of 1405 positive urine cultures were studied, 85.48% of which belonged to women. The mean age of the subjects was 39.98 ± 24.51 years, 24.13% of whom were over 60 years old. Of these, 55.56% had been attended on an outpatient basis. Almost half (49.18%) of the cultures tested positive for ESBL-related UTI, 96.58% of which had not presented with a previous UTI. A statistically significant association was found between sex and the development of UTI caused by ESBL-producing microorganisms (p = 0.007), with the male sex having the highest association (prevalence ratio, 1.224; 95% confidence interval: 1.035–1.448). In addition, age, number of previous hospitalizations, and prior intensive care unit admissions also showed associations with UTI development. No association was found with the presence of previous UTIS. *Conclusion:* A high frequency of UTIS were ESBL-related, and the factors associated with ESBL-related UTIS were male sex, age >60, and previous hospitalizations.

Keywords: Urinary tract infection; beta-lactamase; antibiotic resistance.

Resumen

Introducción: las infecciones del tracto urinario (ITU) son el segundo motivo más frecuente de atención médica, y la resistencia a los antibióticos entre las enterobacterias gramnegativas ha aumentado de manera importante en todo el mundo, dada la aparición de organismos productores de betalactamasa de espectro extendido (BLEE). Se busca identificar factores asociados a la presencia de ITU por patógeno productor de BLEE. *Materiales y métodos:* se realizó un estudio trasversal analítico, un análisis de la base de datos de urocultivos de una clínica privada y una evaluación de los factores posiblemente asociados a la presentación de ITU por el microorganismo BLEE, como el sexo, la edad, el número de hospitalizaciones e ITU previas. *Resultados:* se estudiaron 1405 urocultivos positivos y se encontró que el 85.48 % fueron de sexo femenino. La edad media de la población fue de 39.98 ± 24.51 años, el 24.13 % de edad mayor a 60 años, y el 55.56 % habían sido atendidos ambulatoriamente. El 49.18 % de los cultivos fue positivo para ITU BLEE, de los cuales el 96,58 % no habían presentado una ITU previa. Se encontró que existe una asociación estadísticamente significativa (0,007; p ≤ 0,05) entre el sexo y el desarrollo de ITU por microorganismo productor de BLEE. El masculino es el de mayor asociación (OR 1,224; IC95 %: 1,035-1,448). También se encontró una asociación con la edad, el número de hospitalizaciones previas y haber estado en UCI. No se encontró ninguna asociación entre la presencia de ITU previas. *Conclusiones:* existe una elevada frecuencia de ITU BLEE, y los factores asociados a dicha infección fueron tener sexo masculino, una edad mayor a 60 años y hospitalizaciones previas.

Palabras clave: infección del tracto urinario; betalactamasa; resistencia antibiótica.

Resumo

Introdução: as infeções do trato urinário (ITU) são o segundo motivo mais frequente de atenção médica e a resistência aos antibióticos entre as enterobactérias gramnegativas tem aumentado de maneira importante no mundo todo; destacado pela aparição de organismos produtores de betalactamase de espectro estendido (BLEE). Busca-se identificar fatores associados à presença de ITU por patógeno produtor de BLEE. *Materiais e métodos:* se realizou estudo transversal analítico, analisando a base de dados de urocultura de uma clínica privada, avaliando fatores possivelmente associados à apresentação de ITU por microrganismo BLEE, como o sexo, a idade, o número de hospitalizações e ITU prévias. *Resultados:* estudaram-se 1405 uroculturas positivas, encontrado que o 85,48% foram de sexo feminino. A idade média da população foi de 39.98 ± 24.51 anos, 24.13% de idade maior a 60 anos, 55.56% tinham sido atendidos ambulatoriamente. O 49.18% dos cultivos foi positivo para ITU BLEE, dos quais 96.58% não tinham apresentado uma ITU prévia. Se encontrou que existe associação estatisticamente significativa (0.007; p ≤

0.05) entre o sexo e o desenvolvimento de ITU por microrganismo produtor de BLEE, sendo o masculino o de maior associação (OR 1,224; IC 95%: 1,035-1,448). Além disso, tanto a idade quanto o número de hospitalizações prévias, e ter estado em UCI também mostraram associação. Não se encontrou associação entre a presença de ITU prévias. *Conclusões:* existe uma elevada frequência de ITU BLEE e os fatores associados a infeção por ITU BLEE foram o sexo masculino, idade > 60 anos e hospitalização prévias.

Palavras-chave: infeção do trato urinário; betalactamase; resistência antibiótica.

Introduction

Currently, urinary tract infections (UTIS) are the second most frequent reason for healthcare visits, and approximately 150 million cases per year are diagnosed worldwide (1). The most common causative pathogen is *Escherichia coli*, which is found in 75%–90% of the urine cultures of community-acquired UTIS (2, 3).

Indiscriminate use of antibiotics in this or other bacterial infections has been associated with high bacterial resistance (4). The development of antibiotic resistance is not new. Within the last two decades, antibiotic resistance among gram-negative bacteria of the *Enterobacteriaceae* family has increased significantly worldwide, with the emergence of organisms producing extended-spectrum beta-lactamase (ESBL) being especially noteworthy (5).

There are several reports on the prevalence of UTIS due to ESBL-producing microorganisms in Latin America. Colombia faces values between 3.1% and 12.5% (6,7). In Brazil, values of 11% were observed (8); however, these values are higher in Mexico, where a study reports that 50% of UTIS due to *E. coli* were caused by ESBL-producing bacteria (9). In Peru, the frequency of UTI due to ESBL-producing microorganisms were high, reaching 40.1% (10); in special populations such as that of pregnant women, a prevalence of 11.8% was found (11). These results show a diverse variability, which may be explained by the various epidemiological factors involved and the level of development of the programs for rational antibiotic use implemented in each health system.

Identifying the sources of transmission of highly-resistant microorganisms is crucial for their prevention. In addition, the importance of identifying risk factors to predict which patients present a higher risk is related with being able to limit the spread of antibiotic-resistant pathogens (3).

Male sex, advanced age, comorbidities (most frequently diabetes), international travel, previous UTIS, recent hospitalizations, and previous use of antibiotics have been described as factors associated with the development of antibiotic resistant and ESBL-producing bacteria (3). A study on the fecal carriage of ESBL-producing *E. coli* in the Dutch population showed an association between the use of antacids and high loads of that microorganism (12). Furthermore, it has been found that the administration of nitrofurantoin in patients with recurrent UTIS

is associated with a twofold increased risk of being a carrier of an ESBL-producing pathogen, and this was also observed in a recent study carried out in the United Kingdom (3, 13).

In this context, the current investigation is aimed at assessing those factors associated with the presence of extended-spectrum beta-lactamase-producing pathogens in urinary infections.

Materials and Methods

A retrospective analytical cross-sectional study was conducted on patients with UTI treated at Clínica Jesús del Norte, Lima, Peru. The study included positive urine cultures from patients treated in the outpatient, emergency, or hospitalization units from July 2016 to July 2017. Data were collated and organized with Excel software. Samples comprised 1542 positive cultures, 137 of which were discarded due to registration errors or insufficient information.

The main study variables were demographic aspects including: Patient age and sex, healthcare unit in which they were treated, previous hospitalizations, and number of UTIS before the appearance of a positive culture for ESBL-producing pathogens.

Urine culture collection: Urine samples were collected from mid-stream urine after urogenital cleaning with tap water and soap. Calibrated loops were used to perform semiquantitative urine cultures. Isolation of ESBL-producing *Enterobacteriaceae* was carried out by disk diffusion, and the minimal inhibitory concentration was determined by broth microdilution.

Statistical analysis was performed with STATA 14.0 software. Univariate analysis was conducted using relative and absolute frequencies as well as means and standard deviation; for the bivariate analysis, Poisson regression was used to find the prevalence ratio (PR) of the different variables in relation to the presence of UTI caused by ESBL-producing microorganisms. A 95% confidence interval (CI) and a $p < 0.05$ significance level were considered for this study. Permission was requested from the clinic to access the clinical laboratory database. Because it was a secondary data source analysis, no informed consent was obtained; however, confidentiality of information was kept using a correlative number to identify the cases.

Results

A total of 1405 patients with positive urine cultures met the study inclusion criteria. The mean age was 39.9 ±24.5 years, 85.48% belonged to women, and 24.13% were over 60 years. Of these, 55.56% were treated on an outpatient basis. Furthermore, 3.42% had presented previous UTIS, and only 10.25% had been hospitalized before their current visit. Of the total positive urine cultures, 49.18% tested positive for ESBL UTI (table 1).

Table 1. Clinical features of patients with urinary infection

Features		n	%
Sex	Female	1201	85.48
	Male	204	14.52
Age	Under 10	222	15.80
	Between 11 and 20	43	3.06
	Between 21 and 40	473	33.67
	Between 41 and 60	328	23.35
	Over 60	339	24.13
Healthcare unit	Ambulatory	780	55.56
	Emergency	546	38.89
	Hospitalization	64	4.56
	ICU	14	1.00
UTI caused by ESBL	No	714	50.82
	Yes	691	49.18
Previous UTIS	No	1357	96.58
	Yes	48	3.42
Previous hospitalization	No	1261	89.75
	Yes	144	10.25

The most frequently isolated microorganism was *E. coli* (85.41%), followed by *Klebsiella pneumoniae* (4.48%) and *Staphylococcus saprophyticus* (3.13%) (table 2). Of the 714 patients that tested positive for ESBL UTI, 92.1% presented ESBL-producing *E. coli*, 5.7% presented ESBL-producing *K. pneumoniae,* and 2.6% were positive for ESBL-producing *Proteus mirabilis* (table 3).

Table 2. Etiologic agents isolated in urinary tract infections

Isolated microorganisms	n	%
Escherichia coli	1200	85.41
Klebsiella pneumoniae	63	4.48
Staphylococcus saprophyticus	44	3.13
Proteus mirabilis	41	2.92
Enterococcus sp.	18	1.28
Streptococcus agalactiae	8	0.57
Pseudomona aeruginosa	8	0.57
Alpha-hemolytic streptococci	5	0.36
Klebsiella oxytoca	5	0.36

Continue

Isolated microorganisms	n	%
Morganella morganii	3	0.21
Enterobacter cloacae	2	0.14
Proteus vulgaris	2	0.14
Enterobacter aerogenes	2	0.14
Citrobacter freundii	1	0.07
Methicillin-resistant Staphylococcus aureus	1	0.07
Shigella flexneri	1	0.07
Salmonella enteritidis	1	0.07

Table 3. Main etiologic ESBL agents causing urinary tract infections

Germ	n	%
Escherichia coli-ESBL	644	92.13
Klebsiella pneumoniae-ESBL	40	5.72
Proteus mirabilis-ESBL	18	2.58
Klebsiella oxytoca-ESBL	3	0.43
Proteus vulgaris-ESBL	2	0.29

A statistically significant association was found between the male sex and the development of UTI caused by ESBL-producing microorganisms (PR: 1.224; 95% CI: 1.035–1.448; p = 0.007). In addition, age, number of previous hospitalizations, and specific care unit (i.e., coming from hospitalization or ICU), also showed a statistically significant association ($p \leq 0.05$) with ESBL-associated UTI. However, no significant association was found between ESBL-associated UTI and previous UTIs, having been treated by the emergency unit, or having been an outpatient ($p \geq 0.05$) (table 4).

Table 4. Factors associated with the presence of ESBL-producing pathogens in urinary tract infections

Variable	PR	95% CI	p value
Male sex	1.200	1.051–1.369	**0.007**
Age (over 60)	1.007	1.005–1.009	**<0.001**
Previous UTI	0.973	0.721–1.313	0.86
Previous hospitalization	1.395	1.224–1.591	**<0.001**
Healthcare unit:			
Ambulatory	1.333	1.101–1.613	**0.003**
ICU	1.595	1.202–2.117	**0.001**
Emergency	0.944	0.842–1.059	0.334

Discussion

This study, in addition to other studies, showed that UTI episodes occur more frequently in women (14-16). Whereas some literature indicates that the average age of the most frequently affected patients is 65 years, other studies report ages from 35 to 40 years (17, 18). This study, as well as various international studies, found that the age group with the highest incidence of UTIS was that over 60 years, with the mean age of cases of UTI patients being 37 years.

Among publications that were reviewed herein, the most frequently isolated UTI pathogen was *E. coli* (3, 19-22). This represents approximately 50%–80% of uncomplicated UTIS in women (23). The present study identified *E. coli* in 8 out of 10 positive cultures, being more frequently found in women, which is consistent with findings from other research studies (2, 3, 6).

ESBL is an emerging health concern worldwide, and Peru is no exception (3-5, 16, 20). This investigation found that more than half of the cultures tested positive for ESBL UTI, a figure that exceeds previous studies in this field (5, 21). In addition, 92.1% of all ESBL pathogen-positive cultures corresponded to ESBL-producing *E. coli*, followed by ESBL-producing *K. pneumoniae*.

The concern about resistance to multiple drugs was first detected in enteric bacteria such as *E. coli, Shigella,* and *Salmonella* between 1950 and 1960 (4). There are variable patterns of antibiotic resistance; genes responsible for it can be transferred among different bacteria through elements such as bacteriophages, plasmids, DNA, or transposons. These genes often show resistance to a specific antibiotic, but several genes may accumulate in a single bacterial cell, with each gene presenting a different type of resistance (4). With bacterial genetic endowment, in the case of ESBL, these bacteria develop enzymes that are capable of hydrolyzing latest-generation cephalosporins and aztreonam.

UTI recurrence has been proposed as a risk factor in previous studies (7, 19); however, the present study found that more than 90% of patients with a positive urine culture for ESBL UTI had no previous UTIS. Although the results of this investigation differ from those of previous studies, it is important to emphasize that this could be due to data under-reporting or to patients having been previously treated in other health institutions.

As in other research studies, this study found a significant association between the presence of UTIS due to ESBL-producing pathogens and male sex, age, number of previous hospitalizations, and healthcare unit (22, 23). An explanation for this could be that adult male patients, probably with prostate pathology, require more invasive procedures in the urinary tract and may also suffer from alterations in the bladder function and anatomy. As a result, they present a greater predisposition to UTIS caused by ESBL-producing pathogens. Furthermore, patients with previous hospitalizations are exposed to the hostile environment of health centers, where there is a greater presence of resistant pathogen strains. Likewise,

older patients tend to visit hospital centers more often and are more vulnerable to infections due to their physiological conditions (24-26).

Finally, it should be mentioned that this study had certain limitations such as the lack of assessment of diagnoses from previous hospitalizations or the use of antibiotics during hospitalization. Although the information was obtained from a single-center database and the cases found were numerous, extrapolation of the results to the general population of the country may correspond to certain socioeconomic strata with a higher purchasing power, and, therefore, large-scale results could vary.

In conclusion, although the presence of UTI is associated with female sex and patient age, the development of UTIs caused by an ESBL-producing pathogen is usually significantly associated with the male sex, number of previous hospitalizations, and the healthcare unit in which the patient was attended.

Author contributions

Vania Remenik Zarauz and Moises Apolaya-Segura participated in the conception and design of this paper, in the data analysis and interpretation processes, in the drafting and critical review of this paper and in the approval of its final version.

Cristian Diaz Velez participated in the data analysis and interpretation processes, in the conception and design of this paper, and in the approval of its final version.

Acknowledgements

We thank Crimson Interactive Pvt. Ltd. (Enago) – https://www.enago.com/es/, for their assistance in manuscript translation and editing.

Disclaimers

The authors declare that they have no conflicts of interest. The opinions expressed correspond to the personal title of the authors and not necessarily to the institutions that we belong to.

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