



# Worrisome high frequency of extended-spectrum beta-lactamase-producing *Escherichia coli* in community-acquired urinary tract infections: a case–control study



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## SUMMARY

**Objectives:** There has been a sustained and dramatic increase in community-acquired urinary tract infections (CA-UTI) caused by extended-spectrum beta-lactamase (ESBL)-producing bacteria over recent years. Despite this, no studies have been performed in low- or middle-income countries. The main objective of this case–control study was to describe ESBL CA-UTI and its risk factors.

**Methods:** Outpatients with CA-UTI seen at the Hospital Cayetano Heredia during 2015 were identified. Patients were contacted by telephone. After consent had been obtained, a questionnaire concerning previously identified risk factors was applied. Univariate and multivariate analyses were conducted using Stata version 13.

**Results:** The overall frequency of ESBL-producing *Escherichia coli* was 40.85%. Sixty-seven cases and 105 controls were included in this study. The following main risk factors were identified on multivariate analysis: previous antibiotic use (odds ratio (OR) 3.09), previous hospitalization (OR 2.92), and previous surgery (OR 2.75). Chronic corticosteroid use (OR 24.32, 95% confidence interval 2.39–246.92) was also identified as a risk factor.

**Conclusions:** ESBL *E. coli* accounted for more than 40% of CA-UTIs during 2015. A history of previous hospitalization, surgery, and antibiotic use should be considered when treating this type of infection. Action should be taken to confirm these worrisome results and avoid the major consequences for public health.

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## 1. Introduction

Urinary tract infections (UTI) are a very common healthcare issue and represent the second most common type of infection in humans. In the USA and Latin America, the incidence of UTIs is 0.5–0.7 episodes per year among young women.<sup>1–3</sup> As much as 90% of UTIs are caused by *Escherichia coli*,<sup>4</sup> which is why empiric antimicrobial treatment is directed mostly towards this pathogen. However, the overuse of antibiotics has led to an increase in extended-spectrum beta-lactamase (ESBL)-producing bacteria.

Nowadays, there is an increasingly high prevalence of nosocomial infections caused by ESBL-producing bacteria worldwide. In South America, the frequency varies between 30% and 50%.<sup>5</sup> A study conducted in Lima, Peru in 2008–2009, showed that

the prevalence of positive blood cultures for ESBL-producing *E. coli* was 76.8% for nosocomial infections.<sup>6,7</sup> Risk factors identified for hospital-acquired UTI caused by ESBL bacteria were invasive procedures and antibiotic use.<sup>8</sup>

Regarding community-acquired UTIs (CA-UTIs), there has also been a significant increase in ESBL-producing bacteria. However, publications on CA-UTI caused by ESBL-producing *E. coli* are very limited. Current studies describe small populations, and in most cases risk factors have been non-conclusive. A study performed in Norway during 2013 showed that traveling abroad (especially Asia and Africa), young age, and recent fluoroquinolone use were the most important risk factors for acquiring an ESBL UTI.<sup>9</sup> Another study in Korea during 2010 found a prevalence of 13% for ESBL UTI. It showed that ESBL-producing *E. coli* was responsible for 23.1% of hospital-acquired UTIs and 12.1% of CA-UTIs. Risk factors identified were previous hospitalization, use of a urinary catheter, female sex, and antibiotic exposure.<sup>10</sup> A multinational study performed in 2009 found the following risk factors: recent healthcare-related

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contact, recent antibiotic use, functional dependence, comorbidities, severe disease, age  $\geq 65$  years, and male sex.<sup>11</sup> Although there are several studies describing ESBL infections, no study on ESBL CA-UTIs in Latin America have been published.

The main objective of the current case–control study was to describe ESBL CA-UTI and its risk factors. The identification of specific risk factors in outpatients will allow susceptible patients at risk of developing an infection caused by ESBL-producing *E. coli* to be identified and empiric treatment to be guided. Their identification is important, as infections caused by ESBL-producing bacteria usually have a worse prognosis, because of a delay in starting adequate treatment and the association between antibiotic resistance and virulence genes.<sup>12</sup>

## 2. Materials and methods

### 2.1. Design and study population

This analytical retrospective case–control study was performed in collaboration with the Department of Medicine and the Microbiology Service at Hospital Cayetano Heredia, a main hospital in Lima, Peru. Patients attending the outpatient clinics of the hospital with a diagnosis of CA-UTI and a urine culture positive for *E. coli* during 2015 were considered as the complete study population. Most patients live in the ‘Cono Norte’ (north region) of the city of Lima, which makes up one fourth of the population of Lima. About 39% of families are on a low income and 56% are classified as poor according to local demographic data. Given this, the study population is a representative sample of Peru in terms of social and economic background.<sup>13</sup>

Inclusion criteria were the following: (1) patient with a urine culture positive for *E. coli* ( $\geq 10^5$  CFU/ml), (2) age  $\geq 18$  years, and (3) patient agreed to verbal informed consent. Exclusion criteria were (1) patient with a healthcare-associated UTI (patients who had been hospitalized for  $\geq 2$  days during the 90 days prior to urine culture, patients who had received hemodialysis, intravenous treatment, wound care, or specialized nursing care during the 30 days prior to urine culture, residents in healthcare/long-term care/specialized care facilities, and patients who had a bladder catheter or had undergone an invasive urinary tract procedure during the 30 days prior to urine culture), and (2) patient with a hospital-acquired UTI (UTI diagnosis 48 h after admission to hospital).<sup>14,15</sup>

Cases were defined as patients with a diagnosis of CA-UTI and urine culture positive for ESBL-producing *E. coli*. Controls were defined as patients with a CA-UTI and urine culture positive for a non-ESBL-producing *E. coli*.

The GRANMO statistical calculator was used to determine the study sample size.<sup>16</sup> The odds ratio (OR) calculation model was used (case–control study). An alpha risk of 0.05 and a beta risk of 0.20 were used for bilateral contrast. The proportion of controls exposed to the factor was 0.61 according to the available preliminary data. An expected OR of 3 was used.<sup>5,9,10,15</sup> The minimum expected OR was calculated based on previous studies. The ratio between controls and cases was 51.57. With these data, the study sample size was calculated as 172 patients, requiring 67 cases and 105 controls.

### 2.2. Data collection

Urine culture was performed on Mueller–Hinton agar, by simple sowing method. Antimicrobial susceptibility was tested by agar disk diffusion method using Centers for Disease Control and Prevention (CDC) established minimum inhibitory concentrations (MICs).<sup>9</sup> ESBL-producing bacteria were defined as any culture with

antimicrobial resistance to penicillin, cephalosporins, and aztreonam.<sup>17</sup>

Study patients were identified through a review of the urine culture database of the Microbiology Laboratory of the Hospital Cayetano Heredia. Data were registered in WHONET 5.5 software, where general information about the patients can be found. A total 1158 eligible patients were identified; telephone contact information was available for 498 (42.97%) of these. One hundred and seventy-two patients were selected by simple randomization using the randomize function in Microsoft Excel 2016 (67 cases and 105 controls) and these subjects were contacted by telephone. However, some patients could not be reached due to an outdated telephone number registry and some were not willing to participate in the study or fulfilled an exclusion criterion. New patients were added in a randomized manner from the remaining 326 until the study sample size was reached. A total of 288 telephone calls were made to reach the necessary sample size – approximately 24.87% of all eligible patients. Patients received the study information orally (by telephone). Informed consent was also obtained this way (orally), after which data were collected using a simple questionnaire.

The questionnaire took into account risk factors identified in previous studies.<sup>9–11</sup> Questions were focused on general information concerning the patient (age, sex) and important past medical history: previous hospitalization or previous surgery (3–12 months prior to urine culture), bladder catheter (3–12 months prior to urine culture), antibiotic use during the 30 days prior to urine culture (penicillins, cephalosporins, carbapenems, fluoroquinolones),<sup>15,18</sup> history of pulmonary disease (chronic pulmonary disease or chronic respiratory insufficiency), cardiovascular disease (hypertension or heart failure), type 2 diabetes mellitus, renal disease (chronic renal failure or structural anomaly), previous cerebrovascular accident, malignancy, or chronic corticosteroid use (more than 6 months, not specifying continuous use or dose).<sup>5,9–11,19</sup>

### 2.3. Ethics statement

The study protocol was reviewed and approved by the institutional ethics committee of the Universidad Peruana Cayetano Heredia, and by the institutional research ethics committee of Hospital Cayetano Heredia. The study was performed with the approved time lapse.

### 2.4. Statistical analysis

Stata version 13 statistical software (StataCorp LP, College Station, TX, USA) was used for the statistical analysis. ORs were calculated by univariate analysis for each possible risk factor identified; the Chi-square test was used. Factors that did not have controls or cases were excluded from the analysis. The 95% confidence interval (CI) was calculated, and a *p*-value of  $< 0.05$  was used to indicate statistical significance.<sup>9</sup>

Multivariate analysis was used to identify risk factors associated with ESBL-producing *E. coli* CA-UTI. The frequency of positive urine cultures for ESBL-producing *E. coli* in patients attending the outpatient clinics during 2015 was also calculated, using data available in the Microbiology Laboratory.

## 3. Results

A total of 1158 *E. coli* isolates were identified in outpatient urine cultures at the Hospital Cayetano Heredia during 2015. The study population was selected randomly and comprised 172 patients with *E. coli* CA-UTI. Sixty-seven had ESBL-producing *E. coli* cultures (cases) and 105 had non-ESBL-producing *E. coli* cultures (controls).

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