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RESEARCH ARTICLE

Antimicrobial Resistance of Uropathogenic *Escherichia coli* from Elderly Patients at a General Hospital, Argentina

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Abstract:

Background:

Urinary Tract Infection (UTI) is a common cause of morbidity and mortality in older adults.

Objective:

To investigate antimicrobial resistance of uropathogenic *Escherichia coli* from elderly patients in a General Hospital, Argentina.

Method:

During the period July 2011-July 2015, patients over 70 years old with urinary tract infections, without urinary catheters and with no antimicrobial therapy the previous week before sampling, were included. Phenotypic characterization was carried out. *In vitro* qualitative and quantitative antimicrobial resistances were investigated. Antimicrobials assayed: ampicillin, amoxicillin-clavulanate, cefazolin, cefuroxime, cefoxitin, cefotaxime, ceftazidime, cefepime, imipenem, ertapenem, gentamicin, nalidixic acid, ciprofloxacin, trimethoprim-sulfamethoxazole (TMS) and nitrofurantoin. Patients' medical records were produced, and risk factors were analyzed by multivariate analysis.

Results:

768 bacterial isolates were identified as *E. coli*. Resistances to ampicillin (80.5%), nalidixic acid (61.7%), ciprofloxacin (42.8%), TMS (37.6%), amoxicillin-clavulanate (28.6%), cefazolin (21.6%), cefuroxime (20.7%), gentamicin (13.8%), cefotaxime (9.7%), ceftazidime (9.7%), cefepime (8.4%), cefoxitin (3.1%) and nitrofurantoin (2.3%) were observed. Resistance to carbapenems was not expressed. Production of extended spectrum β-lactamases was detected (7.6%) in community acquired (96%) and healthcare associated (4%) isolates. The independent risk factors for urinary infections produced by multi-resistant *E. coli* were: diabetes mellitus, recurrent infections, hospitalization during the last year and exposure to β-lactams in the last 3 months.

Conclusion:

A high prevalence of resistance to β-lactams and to other antimicrobials was observed. Detection of antimicrobial multi-resistant isolates highlights the need of antimicrobial resistance surveillance in elderly patients with urinary tract infections.

Keywords: β-lactamases, Elderly patients, *Escherichia coli*, Infections, Resistance, Urinary tract.

1. INTRODUCTION

Urinary Tract Infections (UTI) can be defined as the existence of pathogen microorganisms in the urinary tract with symptoms. Amongst UTI, bacterial etiology (80-90%) is the most frequent. UTI are responsible for an estimated

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7 million office visits, 1 million emergency room visits, and 100,000 hospitalizations each year, accounting for 25% of all infections in geriatric patients [1, 2].

Increased incidence of UTI in elderly patients is due to their immune status and the physiological and anatomical changes linked with aging. While urinary sepsis-associated deaths are globally low, in elderly patients with UTI´s bacteremia, it can reach prevalence rates around 33% [3].

Escherichia coli is one of the bacterial agents with higher prevalence in community-acquired and health care associated urinary infections in elderly patients, followed by other *Enterobacteriaceae* such as *Klebsiella* spp., or Gram positive bacteria [4 - 7].

Worldwide, a rise of Extended Spectrum Beta-Lactamase (ESBL) producing *E. coli* and multi-resistant solates (show resistance to, at least, three antimicrobials from different groups or families of these pharmacological agents). has been reported. This antimicrobial resistance mechanism is highly prevalent in Gram negative bacteria, with significant relevance for Public Health because of its horizontal spread [5, 8 - 11]

Emergence and fast dissemination of ESBL-producing uropatohgenic *E. coli* has resulted in an increase of the employment of carbapenems and non-β-lactams. Usage of these antimicrobial drugs has caused a rise in the prevalence of carbapenemase-synthesizing bacterial strains, and an alarming increase in antimicrobial resistance rates for drugs such as fluoroquinolones and aminoglycosides [2].

Due to comorbility factors, people over 70 years old are frequent users of Public Health settings. This exposes them to a high consumption of antimicrobial drugs widely used for the treatment of infections, which leads to an increment of resistance to these antimicrobial agents. Elderly patients are expected to show a higher incidence of UTI; since it has been proven that it increases with aging [12].

In Argentina, for elderly patients, *E. coli* is the most frequently multi-resistant bacteria associated with UTI. Resistance profiles of these strains include antimicrobials widely used for infections therapy. However, there is scarce recent information about elderly patients with community-origin UTI [13].

The aim of this study was to investigate antimicrobial resistance of uropathogenic *Escherichia coli* from elderly patients in a General Hospital, Argentina.

2. MATHERIAL AND METHODS

2.1. Study Design

During the period July 2011-July 2015, an observational, prospective study was carried out.

2.2. Epidemiology of Patients and Clinical Setting

Patients with the following criteria were included: over 70 years old, with no urinary catheters, no antimicrobial therapy the previous week before sampling, attending a General Hospital in Tandil (Argentina), presenting UTI´s signs and symptoms and having only monomicrobial cultures.

In Tandil, Argentina, there is a Public Health system that assists the population of the central region of the Buenos Aires province, including the city of Tandil and its surrounding districts. This region comprises middle-sized cities and small towns, as well as rural settings.

Over 40% of the district´s population attends Public Health system facilities. During the last years, a significant increase of elderly patients at the district´s General Hospital has been registered. Most of these patients are female and male over 70 years old people with documented comorbidities such as diabetes mellitus, recurrent UTIs, history of hospitalization, chronic renal failure, autoimmune diseases and exposure to antimicrobials widely used in the clinical settings (*e.g* β-lactams and quinolones).

2.3. Sampling and Initial Microbiological Processing

Urine samples, N: 3,920 (from every July to the following June, each period had 980, 930, 995 and 1015 urine samples respectively obtained under medical prescription), were sent to the Microbiology laboratory for their analysis. An initial isolation for *Enterobacteriaceae* was performed in a selective and differential culture media, EMB Levine agar (Lab. Britania, Buenos Aires, Argentina). For Gram positive cocci, initial cultures were carried out in Triptein Soy Agar (Lab. Britania), sheep blood-agar (Lab. Britania), and Sabouraud-dextrose agar (Lab. Britania) for yeasts. Isolates

were stored (-70ºC) by triplicate in Brain Heart Infusion broth (Lab. Britania) with glycerol (30%).

2.4. Phenotypic Characterization

Phenotypic characterization of isolates at species level was carried out with biochemical tests [14]. VITEK 2® Compact automated system (BioMérieux, Buenos Aires, Argentina) was used for the validation of characterization.

2.5. Antimicrobial Susceptibility Testing

Disk diffusion method: *In vitro* qualitative antimicrobial resistance profiles were investigated according to the Clinical and Laboratory Standards Institute´s recommendations, CLSI [15]. Assayed disks (Lab. Britania): ampicillin (10 μg), Amoxicillin-clavulanate (20/10 μg), cefazolin (30 μg), cefuroxime (30 μg), cefoxitin (30 μg), cefotaxime (30 μg), ceftazidime (30 μg), cefepime (30 μg), imipenem (10 μg), ertapenem (10 μg), gentamicin (10 μg), nalidixic acid (30 μg), ciprofloxacin (5 μg), trimethoprim-sulfamethoxazole (TMS, 1.25/23.75 μg) and nitrofurantoin (300 μg).

Minimum Inhibitory Concentration (MIC): it was determined by the broth microdilution method according to CLSI [15]. Quality control strains: *E. coli* ATCC 25922, *E. coli* ATCC 35218 and *Pseudomonas aeruginosa* ATCC 27853.

2.6. Detection of ESBL

For detection of ESBL in *E. coli*, disk diffusion method was performed in Mueller-Hinton agar (Lab. Britania), employing cefotaxime, cefotaxime-clavulanate (30/10 μg), ceftazidime and ceftazidime-clavulanate (30/10 μg), respectively. A ≥ 5-mm increase in diameter for either antimicrobial agent tested in combination with clavulanate *versus* the diameter of the agent when tested alone was considered as an ESBL´s producer isolate [15].

2.7. Definition of Urinary Tract Infection

Symptomatic UTI in older adults is defined as the presence of localized genitourinary symptoms, urinary tract inflammation demonstrated by leukocyturia, and a urine culture with an identified urinary pathogen, with a minimum level of bacteriuria of 10^3 cfu/mL. Recurrent UTI refers to ≥2 infections in six months or ≥3 infections in one year [16, 17].

2.8. Epidemiological Features

Patients' medical records were produced. With the reception of each urine sample a pre-designed form was completed. It included the following data: gender, diabetes mellitus, recurrent urinary tract infection, hospitalization in the last year, chronic kidney disease, autoimmune disease and exposure to antimicrobials in the last 3 months (global expousure and specific expousure to β-lactams and quinolones).

2.9. Statistical Analysis of Epidemiological Features from Patients

XLSTAT (version 2018.1) software package was used for the analysis of patients´ epidemiological features. Potential risk factors for ESBL-producing *E. coli* UTI were identified by univariate analysis. Multi-variate analysis was performed by a multiple regression test and Odd Ratios (OR) with a confidence interval (95%) were calculated by a logistic regression test. Ratio was calculated for the variable genre. Categorical variables were expressed in absolute numbers and percentages. The Chi-square test was used for categorical variables. Independent risk factors were determined. $p < 0.05$ values were considered as statistically significant.

3. RESULTS

Of the analyzed urine samples, *n:* 1,024 were positive with one cultured microorganism. In patients with monomicrobial cultures, etiological agents of urinary infections were initially characterized as Gram negative bacilli (88%), Gram positive cocci (9%) and yeasts (3%). Phenotypic characterization showed that *n*: 768 bacterial isolates were identified as *E. coli* (75%).

Amongst this bacterial species, 335/768 (43.6%) isolates were multi-resistant to antimicrobials, while 433/768 (56.4%) showed susceptibility or non-multiple resistance. Non multi-resistant *E. coli* expressed resistance to: β-lactams alone (176, 40.7%), β-lactams and quinolones (82, 18.9%), quinolones alone (81, 18.7%), β-lactams and TMS (36, 8.3%), TMS alone (13, 3%), aminoglycosides and quinolones (1, 0.2%), and resistance to no antimicrobial (44, 10.2%).

Highest antimicrobial resistance prevalence frequencies were detected for β-lactams, followed by quinolones.

Uropathogenic *E. coli* isolates showed resistance to ampicillin (618/768), cefazolin (166/768), nalidixic acid (474/768), ciprofloxacin (329/768), TMS (289/768), amoxicillin-clavulanate (220/768), cefuroxime (159/768), gentamicin (106/768), cefoxitin (24/768), cefotaxime (74/768), ceftazidime (74/768), cefepime (65/768) and nitrofurantoin (18/768). Resistance to imipenem and/or ertapenem was not observed in any of the investigated *E. coli* (Table **1**).

Table 1. Antimicrobial resistance in *Escherichia coli* isolated from elderly patients with urinary tract infections.

ATM	I (%)	R (%)	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Ampicillin	0	80.5	≤2-64	32	64
AMC[a]	3.1	28.6	≤2-64	4.0	64
Cefazolin	46.2	21.6	≤1-64	4.0	32
Cefuroxime	0	20.7	1-32	2.0	32
Cefoxitin	11.2	3.1	1-32	1.0	32
Cefotaxime	0	9.7	≤1-64	0.25	2.0
Ceftazidime	0	9.7	≤4-64	0.25	2.0
Cefepime	0	8.4	0.5-32	0.50	8.0
Ertapenem	0	0	≤0.25-0.5	0.12	0.5
Imipenem	0	0	≤0.25-1	0.12	0.50
Gentamicin	0.9	13.8	≤0.5-128	0.50	64
Nalidixic acid	0.1	61.7	≤16-64	32	64
Ciprofloxacin	3.0	42.8	≤0.25-8	0.12	8.0
TMS[b]	0.1	37.6	2-320	2.0	160
Nitrofurantoin	0	2.3	2-128	4.0	32

ATM, antimicrobial; I, intermediate susceptibility; R, resistance; AMC, amoxicillin-clavulanate; TMS, trimethoprim-sulfamethoxazole. MIC, Minimum inhibitory concentration. [a]For MICs determination, the concentration of clavulanic acid was fixed at 2 µg/mL. [b]TMS in the ratio 1:19. MICs values are expressed as the trimethoprim concentration.

In addition, in 7.6% of the resistant isolates the production of ESBL was detected. Most of the enzymes were synthesized by community acquired *E. coli* (96%).

Also, patients´ epidemiological features were analysed in order to detect independent risk factors of UTI produced by *E. coli* (Table **2**).

Table 2. Epidemiological features and statistical analysis of elderly patients with urinary tract infections produced by *Escherichia coli*.

Antimicrobial Resistance Phenotype				
Epidemiological feature	**Non-Multi Resistant (*n*: 433)**	**Multi-Resistant (*n*: 335)**	**OR (CI 95%)**	**Multi-Variate Analysis (*p*)**
Female patients (F:M)	323 (2.9:1)	207 (1.6:1)	0,64 (0.45-0.92)	*0.019*
Diabetes mellitus (%)	25 (5.8)	68 (20.3)	4.56 (2.95-7.05)	*<0.0001*
Recurrent urinary tract infections (%)	37 (8.5)	108 (32.2)	2.94 (1.94-4.45)	*<0.0001*
Hospitalization during the last year (%)	53 (12.2)	123 (36.7)	2.37 (1.23-4.57)	*0.0076*
Chronic renal failure (%)	17 (3.9)	63 (18.8)	1.52 (0.52-4.38)	0.5987
Autoimmune disease (%)	8 (1.8)	25 (7.5)	0.25 (0.06-1.05)	0.0779
Exposure to antimicrobials in the last 3 months (%)	73 (16.9)	132 (39.4)	1.23 (0.64-2.37)	0.4671
Exposure to β-lactams in the last 3 months (%)	36 (8.3)	98 (29.3)	2.68 (1.36-5.26)	*0.0027*
Exposure to quinolones in the last 3 months (%)	52 (12)	93 (27.8)	1.05 (0.72-1.51)	0.8477

OR, odd ratio. CI, confidence interval. *p* values < 0.05 are showed in cursive letter. F:M. female/male patients ratio.

According to the statistical analysis, independent risk factors for UTI produced by multi-resistant *E. coli* were: diabetes mellitus (OR 4.56, 95% CI 2.95-7.05), recurrent UTI (OR 2.94, 95% CI 1.94-4.45), hospitalization during the last year (OR 2.37 95% CI 1.23-4.57) and exposure to β-lactams in the last 3 months (OR 2.68 95% CI 1.36-5.26).

4. DISCUSSION

Over the last years, in South America, predominance of Gram negative bacilli as etiological agents of UTI has been reported [16, 17]. In Argentina, a previous study reported that 76.3% of UTI in outpatients and hospitalized patients were associated with Gram negative bacilli, where 62.7% of the isolates were identified as *E. coli*. In a more recent investigation, *E. coli* was responsible for 67.7% of the community-acquired UTI [13, 18].

In this study, in 100% of the analyzed strains, resistance to imipenem or ertapenem was not detected. Previously, in Argentina, other authors have communicated the abscense of resistance to carbapenems in *E. coli* from patients over 65 years old with UTI [13].

Uropathogenic *E. coli* isolates showed resistance to ampicillin (80.5%) and to ampicillin-clavulanate (28.6%). In Argentina, during 2013, in a general hospital a lower prevalence of ampicillin resistance (70.5%) was observed in patients with community-onset UTI caused by *E. coli*, while a higher frequency of ampicillin-sulbactam resistance was reported (52.7%). Conversely, in Uruguay, in low-UTI patients, lower percentages of ampicillin (52%) and ampicillin-sulbactam resistance were detected for *E. coli*. A similar prevalence of ampicillin resistance (ca. 80%) was observed for uropathogenic Gram negative bacilli isolated from non-hospitalized elderly in Italy [13, 16, 19].

Resistance (21.6%) to cefazolin in the studied isolates was observed. In UTI-producing *E. coli* from Colombia, a higher resistance (42.8%) to first-generation cephalosporins in primary care patients was detected. In Argentina, in another surveillance study that included *E. coli* recovered from 2004 to 2007, resistance to first-generation cephalosporins ranged from 6.8% to 15.8% [17, 18].

Cefoxitin resistance (3.1%) was detected in this study. In Colombian patients, *E. coli* showed slightly higher resistance to cephalotin (4.8%). During the years 2005, 2009 and 2011, in Spanish patients with UTI produced by *E. coli*, resistance to this antimicrobial comprised a range from 1.7% to 8.2%, with lower and higher frequencies than the isolates included in this investigation [20, 21].

Resistance to cefuroxime was expressed by 20.7% of the uropathogen *E. coli* isolated from elderly patients. A significant lower prevalence (1%) was communicated for patients with community-acquired low-UTI in Uruguay. However, in urinary *E. coli* from Colombian patients, cefuroxime resistance was considerably higher (63%) than the reported in this study [16, 22]. A mean cefuroxime resistance of 17.7% was observed in uropathogen *E. coli* isolates from Mexico. In addition, resistance (27%) to this second-generation cephalosporin was expressed by community-acquired *E. coli* recovered from Cuban patients [23, 24].

In this study, resistance to cefotaxime (9.7%) and ceftazidime (9.7%), in *E. coli* was observed. A recent surveillance carried out in Argentina, showed a higher prevalence of cefotaxime (12.9%) and ceftazidime (10.2%) in *E. coli* from elderly patients with UTI [13]. In a previous research carried out in Romania, 20% of the elderly patients studied expressed resistance to ceftazidime. A different epidemiological situation was seen in community-onset UTI patients´ from Uruguay, where *E .coli* showed no resistance to third-generation cephalosporins [16, 25].

Cefepime-resistant *E. coli* (8.4%) were recovered from elderly patients with UTI. When prevalence of community-acquired UTI produced by *Enterobacteriaceae* was investigated, in a US-prospective-observational study that analyzed the occurrence of UTI by community-acquired *E. coli*, 12.5% of the isolates showed resistance to cefepime [9].

In this research, resistance to gentamicin was detected (13.8%). Previously, a higher frequency of gentamicin resistance (22.6%) was reported for *E. coli* in elderly Argentinian patients and in *Enterobacteriaceae* from Italian elderly (over 30%). In contrast, a significantly lower average prevalence (3.7%) of gentamicin resistance was detected during a 5-year period for community urinary *E. coli* isolates from Australia [13, 19, 26].

Nalidixic acid (61.7%) and ciprofloxacin (42.8%) were the most prevalent among non-β-lactams antimicrobials. In Argentina, from 2009 to 2013, an increasing ciprofloxacin resistance frequency (20-29.8%) was detected in UTI-producing *E. coli*. In 2017, 51.9% of UTI in non-hospitalized elderly patients were reported to be caused by *E. coli* resistant to this drug [13, 18]. In Italy and Romania, ciprofloxacin resistance presented a similar prevalence than the one in this study, 41.4% and over 50%, respectively. In Brazil, 33/49 nalidixic-resistant *E.coli* isolates also expressed resistance to ciprofloxacin, showing that nalidic acid is still a marker for quinolones susceptibility [19, 25, 27]

Resistance to TMS was osberved by *E.coli* isolates in this investigation (37.6%). In Argentina, on recent years, resistance to this antimicrobial showed a preavalence range between 28.1% and 45.7% in eldery patients with UTI. However, at continental level, higher rates of resistance were informed, as was the case of low-UTI strains (70%) in

Uruguay. In Australia, the main resistance prevalence to trimethoprim from 2009 to 2013 was still lower (20.6%) than what was reported in this research [13, 16, 18, 26].

In this study, the lowest antimicrobial resistance prevalence was observed for nitrofurantoin (2.3%). Other studies carried out in South and Central America reported frequencies of nitrofurantoin resistance below 10% in *E. coli* identified as etiologic agents of UTI, as was communicated in Argentina (0.9-6%), Colombia (4.2%) and Cuba (1.8%). However, in Mexico, in community-acquired UTI it was shown that resistance to this antimicrobial was higher (40%) than the reported in this investigation [16, 17, 23, 24].

Production of ESBL (96%, community origin and 4% health-care associated origin) was detected in 7.6% of *E. coli* isolates. In Mexico, it was reported that 10.2% of 4,375 *E. coli* identified as agents of community-acquired UTI was ESBL-producing strains. In other countries from the northern hemisphere, prevalence of ESBL-producing *E. coli* was higher (36.8%, US) or similar (8.7%, Spain) to the ESBL frequency communicated in this study. On the contrary, in Australia ESBL production until 2013 still remained significantly lower (1.9%) than in Argentina or other American countries [9, 10, 21, 26].

In this research, independent risk factors for UTI produced by multi-resistant *E. coli* were: diabetes mellitus, recurrent UTI, hospitalization during the last year and exposure to β-lactams in the last 3 months. A retrospective case–control study carried out in an Australian tertiary referral hospital during 2003 to 2009 discovered that the factors associated with UTI produced by ESBL-Gram negative bacteria were: recent travels, previous exposure to antibiotics, residency at a nursing home, and length of hospital inpatient [28].

In a prospective cohort study, conducted from December 2010 to January 2012, a total of 376 patients were enrolled and 393 isolates from urine culture were analyzed; nasogastric tube placement and hospitalization within the previous 3 months were statistically significant for the acquisition of ESBL-producing pathogens in community-onset UTI [29].

Elderly patients are more likely to be immunocompromised, have co-morbidities, are hospitalized more frequently than younger patients and are more likely to develop infections with multi-drug resistant pathogens [30]. For similar reasons, patients with diabetes are at risk of recurrent UTIs that, over time, pose more risk of resistances [31, 32].

A common and preventable risk factor for multi-drug resistant UTIs is the prior use of antimicrobials. In our investigation, exposure to β-lactams in the last 3 months was an independent risk factor for multi-resistant *E. coli´*s ITU. Recent studies have demonstrated that the use of antimicrobials from 4 weeks to 1 year preceding the index infection increases the probability of multi-drug resistance. Uses of fluoroquinolones and anti-pseudomonal penicillin, as well as more cumulative days of treatment with any antimicrobial prior to UTI presentation, were most strongly associated with resistance [30 - 32].

CONCLUSION

In this study, a high prevalence of resistance to β-lactams as well as to other antimicrobials were observed in *E. coli* isolates from elderly patients with UTI. Statistical analysis of patients´ epidemiological features showed the existence of independent risk factors for UTI produced by multi-resistant *E.coli*. Based on the results of this research. we suggest to avoid using quinolones or TMS for patients older than 70 years old with at least one of the previously mentioned independent risk factors. These findings might help physicians to choose empirical antibiotics in an overall high-rate setting of ESBL-producing *E. coli*. Detection of these strains represents an alarm signal that motivates a continuous surveillance of antimicrobial resistance in adult patients with urinary infections produced by *E. coli*.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not Applicable.

HUMAN AND ANIMAL RIGHTS

This investigation was carried in accordance with the Helsinki's Declaration and the Argentinian Bill for protection of personal data. Results were analyzed in an anonymous fashion.

CONSENT FOR PUBLICATION

Absolute confidentiality of the obtained information and its exclusive use for research purposes were guaranteed to the participants.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Authors` contribution

- Gastón Delpech contributed with sample processing, antimicrobial susceptibility testing, analysis of results and writing of manuscript.
- Natalia Garcia Allende contributed with the design and statistical analysis of results, and writing of the manuscript.
- Sabina Lissarrague contributed with the sample processing, characterization of isolates and antimicrobial susceptibility testing.
- Mónica Sparo coordinated procedures, contributed with characterization of isolates, analysis of results, writing and editing of the manuscript.

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