ORIGINAL RESEARCH

Prevalence of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates in outpatients with urinary tract infection in a Cuban municipality

Prevalencia de aislamientos de Escherichia coli y Klebsiella pneumoniae productoras de β-lactamasas de espectro extendido en pacientes ambulatorios de un municipio de Cuba con infección del tracto urinario

Luis Enrique Cabrera-Rodríguez[1] ⓘ Ana Ibis Miralles-Suárez[1] ⓘ Rosabel Ones-Roque[1] ⓘ Yulian Torres-Herrera[1] ⓘ Magela Pantaleón-Hernández[1] ⓘ

[1] Hospital Clínico-Quirúrgico Docente Aleida Fernández Chardiet - Department of Clinical Microbiology - Güines - Mayabeque - Cuba.

Abstract

Introduction: Community-acquired urinary tract infections (CA-UTI) caused by extended-spectrum β-lactamases (ESBL)-producing *Enterobacteriaceae* are a growing phenomenon worldwide.

Objective: To determine the prevalence of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates obtained from urine samples of outpatients with CA-UTI in a Cuban municipality, as well as the antibiotic resistance profiles associated with the ESBL phenotype.

Materials and methods: Retrospective descriptive study. A total of 304 isolates of *E. coli* and 34 of *K. pneumoniae* obtained from urine cultures of patients with CA-UTI treated between January 1, 2019, and December 31, 2020, at the Hospital Clínico-Quirúrgico Docente Aleida Fernández Chardiet, in the municipality of Güines, Mayabeque province, Cuba, were analyzed. A bivariate analysis (chi-square test) was performed to determine differences in antibiotic resistance rates between ESBL-producing and non-producing bacteria.

Results: 16.77% (51/304) and 17.64% (6/34) of *E. coli* and *K. pneumoniae* isolates were classified as ESBL-producing bacteria. In the case of ESBL-producing *E. coli* isolates, ESBL+ciprofloxacin was the most frequent antibiotic resistance pattern (22/51; 43.13%), followed by ESBL+ciprofloxacin and amikacin (14/51; 27.45%). Moreover, 41.17% (21/51) were multidrug-resistant. In the case of ESBL-producing *K. pneumoniae*, ESBL+ciprofloxacin, amikacin and nitrofurantoin was the predominant antimicrobial resistance pattern (2/6; 33.33%), and 50 % (3/6) were multidrug resistant.

Conclusions: The results reported confirm the presence of ESLB-producing *E. coli* and *K. pneumoniae*, with a high prevalence of multidrug resistance in patients with CA-UTI in the municipality of Güines, Cuba.

Resumen

Introducción. Las infecciones del tracto urinario (ITU) adquiridas en la comunidad y causadas por enterobacterias productoras de β-lactamasas de espectro extendido (BLEE) son un fenómeno creciente a nivel mundial.

Objetivo. Determinar en un municipio de Cuba la prevalencia de aislamientos de *Escherichia coli* y *Klebsiella pneumoniae* productoras de BLEE obtenidos de muestras de orina de pacientes ambulatorios con ITU adquirida en la comunidad, así como los perfiles de resistencia a antibióticos asociados al fenotipo BLEE.

Materiales y métodos. Estudio descriptivo retrospectivo. Se analizaron 304 aislamientos de *E. coli* y 34 de *K. pneumoniae* obtenidos de urocultivos de pacientes con ITU adquirida en la comunidad atendidos entre enero 1 de 2019 y diciembre 31 de 2020 en el Hospital Clínico-Quirúrgico Docente Aleida Fernández Chardiet del municipio de Güines, provincia Mayabeque, Cuba. Se realizó un análisis bivariado (prueba chi-cuadrado) para determinar diferencias en las tasas de resistencia antibiótica entre las bacterias productoras de BLEE y las no productoras.

Resultados. El 16.77% (51/304) y el 17.64 % (6/34) de los aislamientos de *E. coli* y *K. pneumoniae* se clasificaron como bacterias productoras de BLEE, respectivamente. En el caso de los aislados de *E. coli* productoras de BLEE, BLEE+ciprofloxacina fue el patrón de resistencia más frecuente (22/51; 43.13%), seguido por BLEE+ciprofloxacino y amikacina (14/51; 27.45%). Además, 41.17% (21/51) fueron multirresistentes. En el caso de *K. pneumoniae* productoras de BLEE, predominó el patrón de resistencia BLEE+ciprofloxacino, amikacina y nitrofurantoina (2/6; 33.33%), y 50% (3/6) fueron multirresistentes.

Conclusiones. Los resultados confirman la presencia de *E. coli* y *K. pneumoniae* productoras de BLEE, con una alta prevalencia de multirresistencia en pacientes con ITU adquirida en la comunidad en el municipio de Güines.

Introduction

Urinary tract infections (UTIs), both community-acquired and hospital-acquired, are among the most frequent infections in children and adults, thus representing a serious public health problem that results in a high economic burden for healthcare systems worldwide.[1] UTIs are associated with high recurrence rates and when not adequately treated may progress rapidly to severe sepsis. These infections are mostly caused by bacteria of the *Enterobacteriaceae* family, primarily *Escherichia coli*.[2,3]

Enterobacteriaceae pose a therapeutic challenge due to their rapid spread and their resistance to antibiotics.[2,3] In recent years, there has been evidence of substantial changes in the susceptibility patterns of the most important bacterial microorganisms affecting the urinary tract, with a progressive increase in UTIs caused by extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*.[3,4] Unfortunately, the bacteria producing these enzymes are also resistant to other antimicrobials, which considerably reduces therapeutic options and has prompted further changes in the empirical antimicrobial treatment of these infections.[4,5]

Identifying these resistant phenotypes is a priority in clinical microbiology laboratories since such knowledge contributes to selecting the most appropriate antibiotic for treatment and helps to understand the extent of the problem and define strategies for controlling it.[4,5] The epidemiological variation of UTIs is worrisome, as there is a worldwide increase in ESBL-producing bacteria that cause community-acquired urinary tract infections[4,6] with the morbidity, economic and social implications that this entails; Cuba is no exception to this problem.[7,8]

The prevalence of ESBLs varies depending on geographic location, with Latin America (44% for *K. pneumoniae* and 13.5% for *E. coli)* and Asia/Pacific (44% for *K. pneumoniae* and 12.0% for *E. coli)* being the regions with the highest prevalence, followed by Europe (13.3% for *K. pneumoniae* and 7.6% for *E. coli*) and North America (7.5% for *K. pneumoniae* and 2.2% for *E. coli*).[9] Furthermore, according to studies conducted in Peru, it can be established that the frequency of community-acquired ESBL-producing uropathogenic *E. coli* isolates increased from 16.30% in 2016[10] to 55.7% in 2021,[11] which is significant.

Although data on this subject are scarce in Cuba, the results of certain studies point to a high prevalence of ESBL-producing *E. coli* as a cause of community-acquired UTIs. In 2014, Suárez-Trueba *et al.,*[7] in a prospective descriptive study that included all *E. coli* strains isolated from urine cultures collected between March 1 and 31, 2012, at the Hospital Clínico Quirúrgico "Hermanos Ameijeiras" (n=131), established that ESBLs had a frequency of 30.3%. In turn, in 2015, Argüez de Paz *et al.,*[8] in a descriptive observational study that included 150 urine cultures from patients treated between February 2011 and July 2013 in the urology service of the Hospital General Docente "Iván Portuondo" in San Antonio de Los Baños, found that 78.4% of the isolates were ESBLs.

In view of the foregoing, the objective of the present study was to determine the prevalence of ESBL-producing *E. coli* and *K. pneumoniae* isolates obtained from urine samples of outpatients with community-acquired UTIs in a Cuban municipality, as well as the antibiotic resistance profiles associated with the ESBL phenotype.

Materials and methods

Study design and type

Retrospective descriptive study conducted between January 1, 2019, and December 31, 2020.

Bacterial isolates

The study population comprised 2 004 urine cultures from adult patients (over 18 years of age) with a probable diagnosis of community-acquired UTI, which were obtained during the study period at the Clinical Microbiology Laboratory of the Hospital Clínico-Quirúrgico Docente Aleida Fernández Chardiet in the municipality of Güines. The final sample included only urine cultures in which *E. coli* and *K. pneumoniae* growths with counts ≥100 000 colony forming units (CFU)/mL were reported. On the other hand, urine cultures from pregnant women and cases in which growth of other uropathogens was found were excluded. Thus, the final sample consisted of 338 isolates (304 of *E. coli* and 34 of *K. pneumoniae*).

Procedures and instruments

Urine sample collection and isolate identification (genus and species) were performed following conventional methods as established in the standards and procedures recommended for microbiological diagnosis.[12]

Antimicrobial susceptibility testing

Antimicrobial susceptibility was determined using the Bauer-Kirby method following the Clinical Laboratory Standards Institute suggestions.[13] The reading and interpretation of the zone of inhibition was also performed based on the criteria defined by this institution.

The antimicrobials considered in the study were: amoxicillin + clavulanic acid (AUG) 30/10µg, cefazolin (KZ) 30µg, cefoxitin (FOX) 30µg, cefotaxime (CTX) 30µg, ceftazidime (CAZ) 30µg, ceftriaxone (CRO) 30µg, cefepime (FEP) 30µg, aztreonam (ATM) 30µg, amikacin (AK) 30µg, ciprofloxacin (CIP) 5µg, and nitrofurantoin (F) 300µg.

Phenotypic detection of ESBL-producing isolates

Isolates considered as possible ESBL producers were those showing the following diameters in the zones of inhibition: ATM ≤27mm, CTX ≤27mm, CAZ ≤22mm, and CRO ≤25mm, which was confirmed through the double-disk diffusion test.

Double-disk diffusion test

The double-disk test was performed by placing the CTX, CAZ, CRO and ATM disks equidistant on the antibiogram at 2cm from an AUG disc. An enlarged or distorted zone of inhibition around one or all of the cephalosporin and ATM disks was interpreted as synergism. If such a deformation of the zone was present, the isolate was considered to be an ESBL-producing bacterium.[13]

The following control bacteria were used during the study: *Escherichia coli* ATCC 25922 as a negative control, and *Klebsiella pneumoniae* ATCC 700603 as a positive control.

Variables

Antimicrobial susceptibility testing interpretation categories

The isolates were classified into two interpretation categories: susceptible and resistant; the latter included isolates with intermediate susceptibility. Also, multidrug resistance was defined as resistance to antibiotics from 3 or more antibiotic families or groups.[14]

Statistical analysis

Data obtained from the isolates analyzed were entered into a Microsoft Excel database and described using absolute and relative frequencies. Furthermore, a bivariate analysis was performed using the chi-square test to determine differences in antibiotic resistance rates between ESBL-producing and non-producing bacteria, with a statistical significance level of $p<0.05$.

Ethical considerations

The study, which was approved by the Research and Ethics Committee of the Hospital Clínico-Quirúrgico Docente Aleida Fernández Chardiet according to Minutes No. 02/2021 of January 20, 2021, followed the ethical principles for research involving human subjects established in the Declaration of Helsinki.[15] Likewise, anonymity of the participants' data was guaranteed and informed consent was not required because only isolates were analyzed.

Results

Phenotypic detection of ESBL

16.77% (51/304) and 17.64% (6/34) of the *E. coli* and *K. pneumoniae* isolates, respectively, were classified as ESBL-producing bacteria (Table 1).

Table 1. Frequency of *Escherichia coli* and *Klebsiella pneumoniae* isolates in extended-spectrum β-lactamase-producing and non-producing enterobacteria.

Isolates	*Escherichia coli* n (%)	*Klebsiella pneumoniae* n (%)
ESBL-producing bacteria	51 (16.77%)	6 (17.64%)
Bacteria that do not produce ESBL	253 (83.23%)	28 (82.36%)
Total	304 (100%)	34 (100%)

ESBL: extended-spectrum β-lactamase-producing enterobacteria.
Source: Own elaboration.

Antimicrobial resistance analysis

In general, resistance to the antibiotics considered was higher in ESBL-producing *E. coli* isolates than in non-producing ones, with statistically significant differences observed for all antibiotics with the exception of F ($p>0.05$). In the case of *K. pneumoniae* isolates,

the frequency of antimicrobial resistance was higher for ESBL-producing isolates compared to non-producing isolates, with statistically significant differences observed in resistance to CTX, CRO, FEP, ATM, AK, and F ($p<0.05$). Detailed information is provided in Table 2.

Table 2. Distribution of antimicrobial resistance in *Escherichia coli* and *Klebsiella pneumoniae* isolates (extended spectrum β-lactamase-producing and non-producing enterobacteria).

Antibiotics	*Escherichia coli* no ESBL (n=253) n (%)	*Escherichia coli* ESBL (n=51) n (%)	*p*-value	*Klebsiella pneumoniae* no ESBL (n=28) n (%)	*Klebsiella pneumoniae* ESBL (n=6) n (%)	*p*-value
Amoxicillin + clavulanic acid	175 (69.16)	46 (90.19)	$p<0.01$	25 (89.28)	5 (83.33)	$p>0.05$
Cefazolin	115 (45.45)	50 (98.03)	$p<0.001$	19 (67.85)	6 (100.0)	$p>0.05$
Cefotaxime	63 (24.90)	50 (98.03)	$p<0.001$	16 (57.14)	6 (100.0)	$p<0.05$
Ceftazidime	57 (22.52)	50 (98.03)	$p<0.001$	15 (53.57)	5 (83.33)	$p>0.05$
Ceftriaxone	56 (22.13)	51 (100.0)	$p<0.001$	15 (53.57)	6 (100.0)	$p<0.05$
Cefepime	50 (19.76)	51 (100.0)	$p<0.001$	13 (46.42)	6 (100.0)	$p<0.05$
Aztreonam	61 (24.11)	48 (94.11)	$p<0.001$	15 (53.57)	6 (100.0)	$p<0.05$
Amikacin	25 (9.88)	22 (43.13)	$p<0.001$	11 (39.28)	3 (50.00)	$p<0.05$
Ciprofloxacin	98 (38.73)	43 (84.31)	$p<0.001$	17 (60.71)	4 (66.66)	$p>0.05$
Nitrofurantoin	26 (10.27)	7 (13.72)	$p>0.05$	10 (35.71)	2 (33.33)	$p<0.05$

ESBL: extended-spectrum β-lactamase-producing enterobacteria.
Source: Own elaboration.

Antimicrobial resistance profiles associated with the ESBL phenotype

According to the distribution of resistance profiles, ESBL-producing *E. coli* isolates (n=51) were grouped into 4 resistance patterns (Table 3), with pattern III (ESBL+CIP) being the most frequent (43.13%), followed by pattern II (ESBL+CIP, AK) (27.45%). In addition, 41.17% of the isolates were multidrug-resistant.

Table 3. Antimicrobial resistance profile in *Escherichia coli* isolates producing extended-spectrum β-lactamase-producing enterobacteria.

Resistance pattern	Resistance profiles	n (%)
I	ESBL + CIP, AK, F	7 (13.72%)
II	ESBL + CIP, AK	14 (27.45%)
III	ESBL + CIP	22 (43.13%)
IV	ESBL + AK	1 (1.96%)
Multi-resistant isolates		21 (41.17%)

ESBL: extended spectrum β-lactamase-producing enterobacteria; AK: amikacin; CIP: ciprofloxacin; F: nitrofurantoin.
Source: Own elaboration.

In ESBL-producing *K. pneumoniae* isolates (n=6), 3 resistance patterns were identified, with a predominance of pattern I (ESBL + CIP, AK, F) (33.33%). There were 3 multi-drug-resistant isolates (50.00%) (Table 4).

Table 4. Antimicrobial resistance profile in *Klebsiella pneumoniae* isolates producing extended-spectrum β-lactamase-producing enterobacteria.

Resistance pattern	Resistance profiles	n (%)
I	ESBL + CIP, AK, F	2 (33.33%)
II	ESBL + CIP, AK	1 (16.66%)
III	ESBL + CIP	1 (16.66%)
Multi-resistant isolates		3 (50.00%)

ESBL: extended spectrum β-lactamase-producing enterobacteria; AK: amikacin; CIP: ciprofloxacin; F: nitrofurantoin.
Source: Own elaboration.

Discussion

ESBLs are a mechanism of antibiotic resistance in bacteria of the *Enterobacteriaceae* family[2,3] and, in recent years, an increasing number of reports have demonstrated their presence in isolates of community-acquired infections.[4-11]

In the present study, the prevalence of ESBL-producing *E. coli* was 16.77%, a figure higher than that reported in studies of ESBL detection in uropathogenic *E. coli* isolates from Brazil (7.1%),[16] Colombia (12.52%),[17] and Paraguay (13%).[18] Nevertheless, the prevalence described in the present study is similar to the 16.30% reported in 2012 by Galván *et al.*[10] in a phenotypic and molecular characterization study that included 53 *E. coli* isolates from outpatients in Lima, Peru, and to the 17.92% described in 2016 by Alviz-Amador *et al.*[19] in a cross-sectional study that included 396 uropathogen-positive urine cultures, in which the susceptibility profile of a hospital in Cartagena, Colombia, was determined. However, in a study conducted by Miranda *et al.*[20] on 1 026 *E. coli* isolates from adult patients treated at a private clinic in Lima between January 2014 and October 2016 (927 outpatients and 99 inpatients), a higher prevalence than that of the present study was reported: 41.7% overall, 40.8% for outpatients, and 50.5% for inpatients.

In the Cuban case, Suárez-Trueba *et al.*,[7] in a study on antibiotic susceptibility and resistance mechanisms carried out on 131 isolates of *E. coli* obtained from urine cultures of patients treated at a tertiary hospital in Havana, reported that the proportion of ESBL-producing phenotypes in isolates from outpatients (n=11) was 30.3%. However, Argüez de *Paz et al.,*[8] in a study on beta-lactamase production carried out in San Antonio de Los Baños that included 150 positive urine cultures (51 of *E. coli* and 22 of *K. pneumoniae*) from patients with UTIs, reported that the prevalence of ESBL among *E. coli* isolates was 78.4.

With regard to *K. pneumoniae* isolates, in the present study the ESBL phenotype was detected in 17.6% of the isolates, a figure higher than the 3.54% reported in 2016 by Alviz-Amador *et al.*[19] in Colombia, but much lower than the 77.2% described by Argüez de Paz *et al.*[8] This finding was also much lower than the one reported by Miranda *et al.*,[20] whose study included 108 *K. pneumoniae* isolates (93 outpatients and 15 inpatients), with an overall prevalence of these microorganisms of 50.92% (53.8% for outpatients and 33.3% for inpatients).

As mentioned above, the prevalence of ESBL-producing *E. coli* and *K. pneumoniae* varies from country to country, and even among studies, as is the case between the present study

and others conducted in Cuba.[7,8] This phenomenon could be explained by differences in the sample sizes of the studies, the methods used for detection, the previous use of antimicrobials in the included patients, and the patients' own risk factors. These variations have serious therapeutic implications, as they make it difficult to establish a standard treatment for UTIs since these bacteria present intrinsic resistance to beta-lactams and sometimes co-resistance with other first-line antibiotics (fluoroquinolones and aminoglycosides). Therefore, it is suggested to be aware of the importance of an appropriate reading of the antibiogram to identify ESBL-producing bacteria at an early stage and, consequently, to implement an adequate use of antibiotics and take pertinent measures to control the development of infections by this type of microorganisms, both in the community and in the hospital environment.

Furthermore, in the present study, 84.31% of ESBL-producing *E. coli* isolates were found to be resistant to IPC, with a significant difference with non-ESBL-producing *E. coli* isolates ($p<0.001$). This figure was much higher than the 26.5% resistance to this antibiotic found in 28 ESBL-producing *E. coli* isolates by Marcos-Carbajal *et al.*,[21] who conducted a comparative study evaluating the antimicrobial resistance profiles of uropathogenic *E. coli* and the incidence of ESBL production in 98 *E. coli* isolates collected in 3 private health care facilities in Peru, or the 40% reported by Montañez-Valverde *et al.*[22] in a study conducted in Peru with 81 ESBL-producing *E. coli* isolates from patients with UTI, but the figure is lower than the 97.3% described by Alviz-Amador *et al.*[19] in Colombia in isolates with this phenotype. Likewise, in the present study, 43.13% of ESBL-producing *E. coli* isolates were resistant to AK, a result that differs from the low levels of resistance to this antibiotic reported by Montañez-Valverde *et al.*[22] and Alviz-Amador *et al.*,[19] which were 3.5% and 12%, respectively. The high resistance rates to IPC and AK have a clinical impact, limiting their use in patients with infections caused by ESBL-producing bacteria.

Likewise, in the present study, 66.66% of ESBL-producing *K. pneumoniae* isolates showed resistance to CIP. This finding is similar, although slightly lower, to the 77.78% resistance rate to this antibiotic found in 27 ESBL-producing *K. pneumoniae* isolates analyzed in the study by Chero-Vargas *et al.*,[23] which was conducted using data from 567 urine cultures from older adults (60 years or older) treated in 2017 at a private clinic in Lima in different levels of care (emergency, outpatient, inpatient, and ICU).

Similarly, in the present study, AK resistance was observed in 50% of ESBL-producing *K. pneumoniae* isolates. This is much higher than the 18.5% of resistance to this antibiotic in this type of isolates reported by Chero-Vargas *et al.*,[23] but similar to the 43.3% found in 12 ESBL-producing *K. pneumoniae* isolates described by Guevara *et al.*,[24] in a study on antimicrobial susceptibility patterns of gram-negative bacteria isolated from urinary tract infections in Venezuela.

Finally, the results concerning resistance profiles in ESBL-producing *E. coli* and *K. pneumoniae* isolates reported here, i.e., the change in the resistance profile, can be explained by many reasons, including indiscriminate use of antibiotics, spontaneous mutations, transfer of deoxyribonucleic acid (DNA) between bacteria, among others. This finding may indicate the possible circulation of genetic elements that encode information about resistance mechanisms to several families of antimicrobials, an aspect that should be corroborated in further studies.

Notably, the main limitation of the present study was that virulence and molecular studies (determination of genes encoding ESBLs) were not performed.

Conclusions

The results of the present study, the first of its kind to be carried out in Güines, confirm the presence of ESBL-producing *E. coli* and *K. pneumoniae* in uropathogenic isolates obtained from patients with community-acquired UTIs in this municipality. These results should be considered as a warning to health authorities about the need to establish the real prevalence in other regions of the country in order to implement the necessary actions to control the circulation of multidrug-resistant bacteria, carry out studies on risk factors in outpatients, and develop policies to prevent infections caused by this type of bacteria.

Conflicts of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgments

None stated by the authors.

References

1. Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-resistant Gram-negative bacteria causing urinary tract infections: a review. J Chemother. 2017;29(Suppl 1):2-9. https://doi.org/ghw9gd.

2. Shrestha R, Khanal S, Poudel P, Khadayat K, Ghaju S, Bhandari A, *et al.* Extended spectrum β-lactamase producing uropathogenic Escherichia coli and the correlation of biofilm with antibiotics resistance in Nepal. Ann Clin Microbiol Antimicrob. 2019;18(1):42. https://doi.org/kj9q.

3. Ibrahim Y, Sani Y, Saleh Q, Saleh A, Hakeem G. Phenotypic Detection of Extended Spectrum Beta lactamase and Carbapenemase Co-producing Clinical Isolates from Two Tertiary Hospitals in Kano, North West Nigeria. Ethiop J Health Sci. 2017;27(1):3-10. https://doi.org/kj9r.

4. Fatima S, Muhammad IN, Usman S, Jamil S, Khan MN, Khan SI. Incidence of multidrug resistance and extended-spectrum beta-lactamase expression in community-acquired urinary tract infection among different age groups of patients. Indian J Pharmacol. 2018;50(2):69-74. https://doi.org/gd3cdh.

5. Bader MS, Loeb M, Leto D, Brooks AA. Treatment of urinary tract infections in the era of antimicrobial resistance and new antimicrobial agents. Postgrad Med. 2020;132(3):234-50. https://doi.org/kj9s.

6. Gajdács M, Ábrók M, Lázár A, Burián K. Comparative Epidemiology and Resistance Trends of Common Urinary Pathogens in a Tertiary-Care Hospital: A 10-Year Surveillance Study. Medicina (Kaunas). 2019;55(7):356. https://doi.org/gjnvs6.

7. Suárez-Trueba B, Milián-Samper Y, Espinosa-Rivera F, Hart-Casares M, Llanes-Rodríguez N, Martínez-Batista ML. Susceptibilidad antimicrobiana y mecanismos de resistencia de *Escherichia coli* aisladas a partir de urocultivos en un hospital de tercer nivel. Rev Cubana Med. 2014;53(1):3-13.

8. Argüez de Paz AR, Rodríguez-Chávez A, Rojas-Hernández N. *Klebsiella pneumoniae* y *Escherichia coli* productoras de betalactamasas en pacientes con infección del tracto urinario. Rev Cub Med Int Emerg. 2015;14(4):16-29.

9. Reinert RR, Low DE, Rossi F, Zhang X, Wattal C, Dowzicky M. Antimicrobial susceptibility among organisms from the Asia/Pacific Rim, Europe and Latin and North America collected as part of TEST and the in vitro activity of tigecycline. J antimicrob chemoth. 2007;60(5):1018-29. https://doi.org/ck8343.

10. Galván F, Agapito J, Bravo N, Lagos J, Tamariz J. Caracterización fenotípica y molecular de *Escherichia coli* productoras de β-Lactamasas de espectro extendido en pacientes ambulatorios de Lima, Perú. Rev Med Hered. 2016;27(1):22-9.

11.   Marcos-Carbajal P, Salvatierra G, Yareta J, Pino J, Vásquez N, Díaz P, *et al.* Caracterización microbiológica y molecular de la resistencia antimicrobiana de *Escherichia coli* uropatógenas de hospitales públicos peruanos. Rev Peru Med Exp Salud Pública. 2021;38(1):119-23. https://doi.org/kj82.

12.   Koneman E, Allen S, Dowell VR, Sommers H. Diagnóstico microbiológico. Buenos Aires: Editorial Medica Panamericana; 2006.

13.   Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Suscepti-bility Test. 26th ed. Wayne: CLSI; 2018.

14.   Jiménez-Pearson MA, Galas M, Corso A, Hormazábal JC, Duarte-Valderrama C, Salgado-Marcano N, *et al.* Consenso latinoamericano para definir, categorizar y notificar patógenos multirresistentes, con resistencia extendida o panresistentes. Rev Panam Salud Pública. 2019;43:e65. https://doi.org/gk7v5j.

15.   World Medical Association (WMA). WMA Declaration of Helsinki - Ethical principles for medical research involving human subjects. Fortaleza: 64th WMA General Assembly; 2013.

16.   Gonçalves LF, de Oliveira Martins-Júnior P, de Melo ABF, da Silva RCRM, de Paulo Martins V, Pitondo-Silva A, *et al.* Multidrug resistance dissemination by extended-spectrum β-lactamase-producing *Escherichia coli* causing community-acquired urinary tract infection in the Central-Western Region, Brazil. J Glob Antimicrob Resist. 2016;6:1-4. https://doi.org/gqwghd.

17.   Blanco VM, Maya JJ, Correa A, Perenguez M, Muñoz JS, Motoa G, *et al.* Prevalencia y factores de riesgo para infecciones del tracto urinario de inicio en la comunidad causadas por *Escherichia coli* productor de betalactamasas de espectro extendido en Colombia. Enferm Infecc Microbiol Clin. 2016;34(9):559-65. https://doi.org/gqwghz.

18.   Cáceres-Rojas R, Galeano-Burgos A, Legal-Arias J, Monges-Alonso C, Battaglia-Petersen P, Santa Cruz-Segovia F. Perfil de sensibilidad de Escherichia coli aislados de infecciones del tracto urinario de pacientes del Hospital Regional de Villarrica en el periodo de julio 2013 a agosto 2015. An. Fac. Cienc. Méd. (Asunción). 2019;52(2):17-22. https://doi.org/kj9t.

19.   Alviz-Amador A, Gamero-Tafur K, Caraballo-Marimon R, Gamero-Tafur J. Prevalencia de infección del tracto urinario, uropatógenos y perfil de susceptibilidad en un hospital de Cartagena, Colombia. 2016. Rev. Fac. Med. 2018;66(3):313-7. https://doi.org/kj9v.

20.   Miranda J, Pinto J, Faustino M, Sánchez-Jacinto B, Ramirez F. Resistencia antimicrobiana de uropatógenos en adultos mayores de una clínica privada de Lima, Peru. Rev Peru Med Exp Salud Pública. 2019;36(1):87-92. https://doi.org/gqwghn.

21.   Marcos-Carbajal P, Galarza-Pérez M, Huancahuire-Vega S, Otiniano-Trujillo S, Soto-Pastrana J. Com-paración de los perfiles de resistencia antimicrobiana de *Escherichia coli* uropatógena e incidencia de la producción de betalactamasas de espectro extendido en tres establecimientos privados de salud de Perú. Biomédica. 2020;40(Suppl 1):139-47. https://doi.org/kj9w.

22.   Montañez-Valverde RA, Montenegro-Idrogo JJ, Arenas-Significación FR, Vásquez-Alva R. Infección urinaria alta comunitaria por *E. coli* resistente a ciprofloxacino: características asociadas en pacientes de un hospital nacional en Perú. An. Fac. med. 2015;76(4):385-91. https://doi.org/kj9x.

23.   Chero-Vargas J, Bravo-Osorio I, Apolaya-Segura M. Resistencia antimicrobiana de uropatógenos en adultos mayores. Rev Cubana Med. 2021;60(4):e2634.

24.   Guevara N, Guzmán M, Merentes A, Rizzi A, Papaptzikos J, Rivero N, *et al.* Patrones de susceptibilidad antimicrobiana de bacterias gramnegativas aisladas de infecciones del tracto urinario en Venezuela: Resultados del estudio SMART 2009-2012. Rev. Chil. Infectol. 2015;32(6):639-48. https://doi.org/gqwghf.