Rev. Cuerpo Med. HNAAA, Vol 14 (3) - 2021

REVISTA DEL CUERPO MÉDICO HOSPITAL NACIONAL ALMANZOR AGUINAGA ASENJO, CHICLAYO, PERÚ

ISSN | impresa: 2225-5109; Electrónica: 2227-4731

Cross Ref. DOI: 10.35434/rcmhnaaa | OJS https://cmhnaaa.org.pe/ojs

Original Article

Antimicrobial resistance patterns of the Enterobacteriaceae family isolated from urinary tract infections from a Peruvian high-Andean region

Patrones de resistencia antimicrobiana de la familia enterobacteriaceae aisladas de infecciones del tracto urinario de una región alto-andina peruana

DOI
https://doi.org/10.35434/rcmhnaaa.2021.143.1255

Xossé Carreras[1,a*]; Andrea S. Salcedo[1,a*]; Bruno Millones[1,a*]; Valeria S. Paredes[1,a*]; Pamela Carpio-Vargas[1,a*]; Jorge L. Maguiña[1,b*]

ABSTRACT

Background: Antibiotic resistance is considered to be the next worldwide epidemic. Urinary tract infections (UTI) are the second most common cause of infection, which also has the highest resistance frequency. Nevertheless, in high Andean regions, little is known about the antibiotic resistance. **Objectives**: Determine the antimicrobial resistance patterns of the enterobacteriaceae family isolated from urinary tract infections of a Peruvian Andean region. **Material and Methods:** A retrospective cross-sectional review of 1717 records from the microbiology service of a private health institution from Puno - Peru, was done between the years 2014 and 2017. Antibiotic resistance by uropathogens was studied among different age groups. Statistical analysis included Chi2 test with a p<0.05. Poisson regression was used to calculate the prevalence ratio (PR) with a 95% confidence interval. **Results:** There was a wide distribution of antibiotic resistance among all the antibiotics, mainly in *Escherichia coli* and *Proteus spp*. The elderly had the highest prevalence of antibiotic resistance. As age increased, resistance to all drugs also increased (p<0.01). Furthermore, the elderly had a risk probability of resistance of 1.22, 1.42, 1.20 and 1.32 to penicillins, cephalosporins, quinolones and other antibiotics respectively. **Conclusion:** The antimicrobial resistance patterns of the Peruvian Andean region were lower than national and international patterns.

Keywords: Age Groups; Drug Resistance, Bacterial; Urinary Tract Infections; Enterobacteriaceae (Source: DeCS-BIREME).

RESUMEN

Introducción: La resistencia a antibióticos es considerada la próxima epidemia mundial. Las infecciones del tracto urinario (ITU) son la segunda causa más común de infecciones y la que presenta mayor frecuencia de resistencia. Sin embargo, poco se ha reportado en regiones altos-andinas. **Objetivo:** Evaluar los patrones de resistencia antimicrobiana de la familia enterobacteriaceae aisladas de infecciones del tracto urinario de pacientes ambulatorios de una región altoandina peruana y sus factores asociados. **Material y Métodos:** Estudio transversal analítico retrospectivo, a partir de 1717 registros del Servicio de Microbiología de una institución de salud en la región Puno - Perú, entre los años 2014 al 2017. Se estudió la resistencia a antibióticos según uropatógeno en diferentes grupos etarios. Se empleó la prueba de Chi2 de Pearson y un modelo de regresión de Poisson para calcular la razón de prevalencias (RP). En todos los análisis se consideró un valor de p<0.05 como significativo y se estimaron intervalos de confianza al 95%. **Resultados:** Se presentó una amplia distribución de resistencia en todos los fármacos evaluados, siendo mayor en *Escherichia coli* y *Proteus spp*. El grupo etario, ≥ 60 años, presentó la mayor prevalencia de

FILIATION
1. Facultad de Medicina, Universidad Peruana de Ciencias Aplicadas, Lima, Perú.
a. Estudiante de medicina.
b. Candidato Doctoral en Investigación Epidemiológica, Maestro en Epidemiología Clínica, Tecnólogo Médico .

ORCID
1. Xossé Carreras / 0000-0002-6161-217X
2. Andrea S. Salcedo / 0000-0003-1773-4812
3. Bruno Millones / 0000-0001-8682-3048
4. Valeria S. Paredes /0000-0002-4473-1230
5. Pamela Carpio-Vargas / 0000-0003-0217-1770
6. Jorge L. Maguiña /0000-0002-4136-7795

CORRESPONDENCE
Xossé Carreras
Universidad Peruana de Ciencias Aplicadas
Av Alameda San Marcos 11, Chorrillos 15067
Telephone: 983338994

EMAIL
u201511191@upc.edu.pe

CONFLICTS OF INTEREST
There are no conflicts of interest to disclose.

FINANCING
The development of this study did not receive any kind funding

AUTHOR'S CONTRIBUTIONS
All authors contributed equitably to the development of the research

PEER REVIEW
Received: 04/06/2021
Accepted: 14/09/2021

HOW TO CITE
Carreras, X., Salcedo, A., Millones, B., Paredes, V., Carpio-Vargas, P., & Maguiña, J. Antimicrobial resistance patterns of the Enterobacteriaceae family isolated from urinary tract infections from a Peruvian high-Andean region. Revista Del Cuerpo Médico Hospital Nacional Almanzor Aguinaga Asenjo, 2021, 14(3). https://doi.org/10.35434/rcmhnaaa.2021.143.1255

Printer Version: ISSN: 2225-5109
Electronic Version: ISSN: 2227-4731
Cross Ref. DOI: 10.35434/rcmhnaaa
OJS: https://cmhnaaa.org.pe/ojs

resistencia bacteriana. A medida que la edad aumentaba, la resistencia a todos los fármacos estudiados también aumentó (p <0.01). Así mismo, los pacientes ≥ 60 años presentaron mayor probabilidad de presentar resistencia bacteriana a penicilinas, cefalosporinas y quinolonas. **Conclusión:** El patrón de resistencia a los antibióticos utilizados en ITUs en la zona altoandina peruana incrementa con la edad.

Palabras Clave: Grupos de Edad; Resistencia a medicamentos; Infecciones Urinarias; Enterobacteriaceae. (Fuente: DeCS-BIREME).

INTRODUCTION

Nowadays antimicrobial resistance represents one of the main global health issues[1]. Which is defined as a "phenomenon whereby a microorganism is no longer affected by an antimicrobial to which it was previously sensitive[2], as a consequence of irrational use of antibiotics and wrong dosage[2,3]. According to the World Health Organization (WHO), it has been estimated that between the years 2014 and 2016 one million people died from this phenomenon, and that by 2050 10 million people will die[4]. Another global health problem is Urinary Tract Infections (UTI), being the second most frequent cause of an infectious disease in the female population between 18 and 24 years old[6,7]. Meanwhile, they predominate in the male population in the first year of life and in those older than 50 years, due to prostatic pathologies and a wrongful manipulation of the urinary tract[8].

The Enterobactericeae family englobes the main causative agents as *Klebsiella spp*, *Proteus spp* y *Escherichia coli*[9], the latter is the most prevalent organism both locally and globally[10], and is in the first category of "critical priority" of the WHO for presenting greater resistance[11]. A study made in Spain showed that the most common multidrug resistant uropathogens were *Escherichia coli* and *Klebsiella spp*, which showed a higher resistance pattern in hospitalized patients[12]. In our country in 2014, high resistance to *Escherichia coli* was reported, as in the Andean subregion[13]. There was variation in which age group has the highest prevalence of antibiotic resistance. A study performed in Canada and the US in 2005 found that the age group with highest antimicrobial resistance in UTI's where those over 65 years old[14]. Likewise, another Spanish study carried out in 2011 reported that those over 60 years of age had greater antimicrobial resistance in the same disease[15]. There is no consensus that establishes a defined age group, but there seems to be a vulnerability in the elderly group.

In 2012, the last report about antimicrobial resistance in Peru showed that Escherichia coli was the most frequent isolated bacteria at the hospital level, presenting a resistance to ampicillin greater than 80% and to nalidixic acid greater than 60%[16]. Likewise, one of the most recent studies made in 2014, done by ORAS-CONHU with data from the Andean subregion concluded that the information in our country is scarce due to the absence of national surveillance[13]. Even though the "Instituto Nacional de Salud del Perú (INS)" implemented a national antimicrobial resistance surveillance program, there is no recent data, therefore research in this filed remains pending and forgotten.

National information on antimicrobial resistance is quite limited and unclear, this data absence grows in high-andean regions, as is the case in the department of Puno, where there are few research studies related to the subject. In this regard, it is important that each region has information on the antimicrobial resistance of the area, to guide both empirical and definitive treatment of UTI's, which is often used indiscriminately.

MATERIAL AND METHODS

Design and study population

The present investigation is an observational cross-sectional analytical type, based on a secondary analysis from a level II-I health institution in the department of Puno, Peru. Which is located in the south-eastern part of the country, which has a population of1 268 441 inhabitants, of which 578 383 are men and 594 314 are women. Regarding age groups, the child population (≤ 9 years old) was 255 604, the young population (10 to 24 years old) 393 743, the adult population (25 to 59 years old) 491 431 and the elderly population (≥ 60 years) of 127 663[17].

We used all records that have been registered in the previously mentioned time period. Of the 3926 records included in the database, 1717 fulfilled our eligibility criteria. We included those patient records that: 1) had a complete urine culture and antibiogram, 2) had positive urine culture results, and 3) had bacteria of the Enterobacteriaceae family as uropathogen. We excluded those records that: 1) did not present complete data on our variables of interest such as age and sex, 2) presented a urine culture with a colony count of less than 10,000 CFU and 3) did not comply in the antibiogram with the total number of antibiotics corresponding to group I of the sensitivity diffusion discs described in the "Manual de procedimientos para la prueba de sensibilidad antimicrobiana por el metodo de disco difusión" of the INS[18].

The outcome variable was defined as antibiotic resistance according to uropathogen. The antibiotics were used according to the procedures described above. Each antibiotic was labeled "S, I and R", explaining the level of sensitivity to the antibiotic where "S" is "sensitive", "I" is "intermediate", "R" is "resistant". These antibiotics were recorded according to uropathogen of the Enterobactericea family (*Escherichia coli, Klebsiella Oxytoca and Proteus Vulgaris*). The antibiotics were subsequently grouped according to family, which included penicillins (amoxicillin, clavulanic acid, ampicillin/sulbactam and ampicillin), cephalosporins (cefuroxime, cephalothin, cefotaxime and ceftriaxone), quinolones (nalidixic acid, ciprofloxacin and norfloxacin) and others (gentamicin, nitrofurantoin, trimethropim/sulfamethoxazole and amikacin). Finally, for the multivariate analysis, the outcome variable was dichotomized into Resistant and Non-resistant, the first one including the categories of Intermediate and Resistant. In addition, to calculate the intensity of resistance, the new variables mentioned above were used, and resistance was defined as occurring when there was resistance to at least one of the antibiotics of the corresponding family, and sensitive when there was no resistance.

The exposure variables were age and sex. Age is defined as years of life completed and has been categorized into age groups: infant (0 to ≤ 10 years), young (≥11 to ≤24 years), adult (≥25 to ≤59 years) and elderly (≥60 years). And the sex variable was considered as male and female.

Data recollection and analysis

The present study is secondary to a database analysis compiled between the years 2014 and 2017, performed in the institution's laboratory based on the INS "Procedimientos de Laboratorio" protocol. After obtaining the result, the antibiogram was applied to the uropathogen according to the technique of the “Manual de procedimientos para la prueba de sensibilidad antimicrobiana por el metodo de disco difusión” of the INS.

The data was introduced into Microsoft Excel program and quality control was performed; it was exported to the STATA 15 statistical package for statistical analysis. At the descriptive level, the sociodemographic characteristics of the participants were calculated using absolute and relative frequencies for categorical variables such as age group, sex, uropathogen and sensitivity to antibiotics. In relation to the bivariate analysis, the information was used only for *Escherichia coli* bacteria, using the chi2 test, to analyze the categorical variables of age group and sex, independently, in relation to antibiotic resistance to uropathogens, considering a $p < 0.05$ as significant. Finally, for the multivariate analysis, a generalized linear model with Poisson family and log link function and robust variances was used to calculate the prevalence ratio (PR) with a 95% confidence interval, where resistance to each family of antibiotics was analyzed by age of uropathogens, adjusted for sex.

ethical aspects

The present study was approved by the ethics committee of the Universidad Peruana de Ciencias Aplicadas (UPC), Lima and has the authorization of the medical board of the "Las Kalas" Clinic in Puno. The database does not contain personal information of the patients, so their confidentiality and anonymity are guaranteed.

RESULTS

A total of 1717 records of patients with UTI were analyzed. The majority of the population studied was female (91.6%). In terms of age, the majority (58%) belonged to the adult group, followed by the elderly group (17.1%). The most frequent uropathogen was *Escherichia coli* with 96% of the cases, followed by Proteus Vulgaris with 2.1% (Table 1).

Table 2 showed the total resistance in the penicillin family: amoxicillin/clavulanic acid, ampicillin/sulbactam, ampicillin; presented an overall prevalence of 22.4%, 14.2% and 50.9%, respectively, with a predominance of resistance to ampicillin in *Klebsiella oxytoca* 66.7%. In the cephalosporin family: cefuroxime, cephalothin, cefotaxime, ceftriaxone; a total prevalence of 17.3%, 23.5%, 5.1% and 4.8%, respectively, was observed. Resistance to cefuroxime in Proteus vulgaris 30.5% was the highest. Likewise, resistance to cefolatine was similar in *Escherichia coli* (23.7%) and *Proteus vulgaris* (25.0%). For the quinolone family: nalidixic acid, ciprofloxacin and norfloxacin; an overall prevalence of 29.8%, 19.1% and 19.1%, respectively, was found. Resistance to nalidixic acid was highest in *Escherichia coli* with 29.6% and *Proteus vulgaris* with 44.4%. Finally, with the other antibiotics: gentamicin, nitrofurantoin, trimethoprim/sulfamethoxazole and amikacin, the total prevalence was 7.4%, 4.7%, 26.9% and 0.9%, respectively; resistance to trimethoprim/sulfamethoxazole was predominant in *Escherichia coli, Proteus vulgaris*. *Klebsiella oxytoca* with 25.7%, 33.3% and 33.3%, correspondingly.

Table 3 presents the antibiotic resistance in Escherichia coli samples and its relationship with age categorized by age groups and sex. All the antibiotics evaluated presented a significant association, both for age ($p<0.001$) and sex ($p<0.001$). Likewise, an increase in resistance was observed as age increased with the exception of ampicillin-sulbactam, cephalothin, cefotaxime, ceftriaxone, amikacin, nitrofurantoin and trimethropim/sulfamethoxazole. In addition, in males the prevalence of resistance was higher in all antibiotics, being up to 6 times higher in some drugs, such as: ceftriaxone, amikacin and nitrofurantoin.

Finally, Table 4 shows the multivariate regression analysis, having as an outcome variable the prevalence of resistance to at least one antibiotic to Escherichia coli in each family. For this analysis, it was decided to classify the variable Resistant/Non-resistant by incorporating the category Intermediate in the Resistant category. The analysis showed that according to age and adjusted for sex, the elderly group was 1.22, 1.42, 1.20 and 1.39 times more likely to be resistant to penicillins, cephalosporins, quinolones, and other antibiotics, respectively, compared to infants.

Table 1. Sociodemographic features and frequency of isolated uropathogens in patients with UTI's.

Characteristics	N	%
Year		
2014	395	23
2015	305	17.8
2016	520	30.3
2017	497	29
Age (years)		
Child (0-10)	227	13.2
Young (10-24)	201	11.7
Adult (25-59)	996	58
Elderly (>60)	293	17.1
Sex		
Feminine	1572	91.6
Masculine	145	8.4
Uropathogen		
Escherichia coli	1648	96
Klebsiella Oxytoca	33	1.9
Proteus Vulgaris	36	2.1

Table 2. Antimicrobial resistance frequency by uropathogen.

Antimicrobial family		Total			*Escherichia coli*		*Klebsiella Oxytoca*		*Proteus Vulgaris*	
		n	%	IC 95%	n	%	n	%	n	%
Penicillins										
Amoxicillin/Clavulanic Acid										
	S	970	56.5		933	56.6	19	57.6	18	50
	I	363	21.1	20.5 - 24.4	346	21	7	21.2	10	27.8
	R	384	22.4		369	22.4	7	21.2	8	22.2
Ampicillin/Sulbactam										
	S	1153	67.2		1103	66.9	27	81.8	23	63.9
	I	320	18.6	12.6 - 16.0	310	18.8	5	15.2	5	13.9
	R	244	14.2		235	14.3	1	3	8	22.2
Ampicillin										
	S	551	32.2		535	32.5	7	21.2	9	25
	I	291	16.9	48.6 - 53.3	279	16.9	4	12.1	8	22.2
	R	875	50.9		834	50.6	22	66.7	19	52.8
Cephalosporins										
Cefuroxime										
	S	1087	63.3		1043	63.3	25	75.7	19	52.8
	I	333	19.4	15.6 - 19.2	321	19.5	6	18.2	6	16.7
	R	297	17.3		284	17.2	2	6.1	11	30.5
Cefalotin										
	S	1047	61		1006	61.1	23	69.7	18	50
	I	266	15.5	21.6 - 25.6	251	15.2	6	18.2	9	25
	R	404	23.5		391	23.7	4	12.1	9	25
Cefotaxime										
	S	1542	89.8		1486	90.2	29	87.8	27	75
	I	87	5.1	4.2 - 6.3	81	4.9	2	6.1	4	11.1
	R	88	5.1		81	4.9	2	6.1	5	13.9
Ceftriaxone										
	S	1538	89.5		1482	89.9	28	84.8	28	77.8
	I	97	5.7	3.9 - 5.9	90	5.5	2	6.1	5	13.9
	R	82	4.8		76	4.6	3	9.1	3	8.3
Quinolones										
Nalidixic Acid										
	S	802	46.7		774	47	16	48.5	12	33.3
	I	403	23.5	27.7 - 32.0	386	23.9	9	27.3	8	22.2
	R	512	29.8		488	29.6	8	24.2	16	44.4
Ciprofloxacin										
	S	1191	69.4		1149	69.7	18	54.6	24	66.6
	I	197	11.5	17.4 - 21. 1	185	11.2	6	18.2	6	16.7
	R	329	19.1		314	19.1	9	27.2	6	16.7
Norfloxacin										
	S	1208	70.4		1167	70.8	18	54.6	23	63.9
	I	181	10.5	17.4 - 21.1	170	10.3	4	12.1	7	19.4
	R	328	19.1		311	18.9	11	33.3	6	16.7
Others										
Gentamicin										
	S	1447	84.3		1398	84.8	21	63.6	28	77.8
	I	142	8.3	6.3 - 8.8	136	8.3	3	9.1	3	8.3
	R	128	7.4		114	6.9	9	27.3	5	13.9
Nitrofurantoin										
	S	1312	76.4		1272	77.2	23	69.7	17	47.2
	I	324	18.9	3.8 - 5.8	305	18.5	8	24.2	11	30.6
	R	81	4.7		71	4.3	2	6.1	8	22.2
Trimethoprim/Sulfamethoxazole										
	S	896	52.2		866	52.6	13	36.1	13	36.1
	I	360	20.9	24.8 - 29.0	342	20.6	11	30.6	11	30.6
	R	461	26.9		440	25.7	12	33.3	12	33.3
Amikacin										
	S	1668	97.2		1600	97.1	33	100	35	97.2
	I	33	1.9	0.1- 1.5	32	1.9	0	0	1	2.8
	R	16	0.9		16	1	0	0	0	0

Table 3. Antimicrobial resistance in Escherichia coli by age and sex (n = 1717).

Antimicrobial family		Age									Sexo				
		Child		Young		Adult		Elderly		P value	Masculine		Feminine		P value
		n	%	n	%	n	%	n	%		n	%	n	%	
Penicillins															
Amoxicillin/Clavulanic Acid															
	S	129	59.5	117	61.2	575	60	112	39.7		61	43.3	872	57.8	
	I	51	23.5	37	19.4	185	19.3	73	26	<0.001	30	21.2	316	21	<0.001
	R	37	17	37	19.4	198	20.7	97	34.3		50	35.5	319	21.2	
Ampicillin/Sulbactam															
	S	153	70.5	135	70.7	662	69.1	153	54.2		68	48.2	1035	68.6	
	I	34	15.7	36	18.8	176	18.4	64	22.7	<0.001	29	20.6	281	18.7	<0.001
	R	30	13.8	20	10.5	120	12.5	65	23.1		44	31.2	191	12.7	
Ampicillin															
	S	90	41.5	67	35.1	319	33.3	59	20.9		28	19.9	507	33.6	
	I	47	21.7	36	18.9	162	16.9	34	12.1	<0.001	14	9.9	265	17.6	<0.001
	R	80	36.8	88	46	477	49.8	189	67		99	70.2	735	48.8	
Cephalosporins															
Cefuroxime															
	S	151	69.6	127	66.6	616	64.3	149	52.8		70	49.7	973	64.5	
	I	36	16.6	37	19.8	194	20.2	54	19.2	<0.001	26	18.4	295	19.6	<0.001
	R	30	13.8	27	14.1	148	15.5	79	28		45	31.9	239	15.9	
Cefalotin															
	S	145	66.8	119	62.3	617	64.4	125	44.3		69	48.9	937	62.1	
	I	31	14.3	30	15.7	138	14.4	52	18.5	<0.001	18	12.8	233	15.5	<0.001
	R	41	18.9	42	22	203	21.2	105	37.2		54	38.3	337	22.4	
Cefotaxime															
	S	206	94.9	180	94.2	878	91.7	222	78.7		99	70.2	1387	92	
	I	5	2.3	4	2.1	45	4.7	27	9.6	<0.001	15	10.6	66	4.4	<0.001
	R	6	2.8	7	3.7	35	3.6	33	11.7		27	19.2	54	3.6	
Ceftriaxone															
	S	208	95.9	179	93.7	874	91.2	221	78.4		99	70.2	1383	91.7	
	I	5	2.3	5	2.6	50	5.2	30	10.6	<0.001	16	11.4	74	5	<0.001
	R	4	1.8	7	3.7	34	3.6	31	11		26	18.4	50	3.3	
Quinolones															
Nalidixic Acid															
	S	111	51.2	100	52.4	466	48.6	97	34.4		59	41.8	715	47.5	
	I	59	27.2	47	24.6	220	23	60	21.3	<0.001	20	14.2	366	24.3	<0.001
	R	47	21.6	220	23	272	28.4	125	44.3		62	44	426	28.2	
Ciprofloxacin															
	S	186	85.7	148	77.5	668	69.7	147	52.1		69	49	1080	71.7	
	I	14	6.5	14	7.3	107	11.2	50	17.8	<0.001	20	14.1	165	11	<0.001
	R	17	7.8	29	15.2	183	19.1	85	30.1		52	36.9	262	17.3	
Norfloxacin															
	S	186	85.7	152	79.6	680	71	149	52.8		67	47.5	1100	73	
	I	11	5.1	11	5.7	97	10.1	51	18.1	<0.001	21	14.9	149	9.9	<0.001
	R	20	9.2	28	14.7	181	18.9	82	29.1		53	37.6	258	17.1	
Others															
Amikacin															
	S	212	97.7	190	99.5	935	97.6	263	93.3		124	87.9	1476	97.9	
	I	4	1.8	1	0.5	16	1.7	11	3.9	<0.001	10	7.1	22	1.5	<0.001
	R	1	0.5	0	0	7	0.7	8	2.8		7	5	9	0.6	
Gentamicin															
	S	202	93.1	172	90.1	817	85.2	207	73.4		90	63.8	1308	86.8	
	I	11	5.1	10	5.3	82	8.6	33	11.7	<0.001	20	14.2	136	7.7	<0.001
	R	4	1.8	9	4.7	59	6.2	42	14.9		31	22	114	5.5	
Nitrofurantoin															
	S	183	84.3	150	78.5	750	78.3	189	67		92	65.2	1180	78.2	
	I	28	12.9	33	17.3	179	18.7	65	23.1	<0.001	22	15.6	283	18.8	<0.001
	R	6	2.8	8	4.2	29	3	28	9.9		27	19.2	44	3	
Trimethoprim/Sulfamethoxazole															
	S	118	54.4	107	56	533	55.7	108	38.3		60	42.5	806	53.5	
	I	37	17	43	22.5	211	22	51	18.1	<0.001	21	14.9	321	21.3	<0.001
	R	62	28.6	41	21.5	214	22.3	123	43.6		60	42.6	380	25.2	

Table 4. Resistance to antimicrobial families in Escherichia Coli, regression model adjusted by sex (n=1648).

Antimicrobial family	Penicillins			Cephalosporines			Quinolones			Others		
	PR	IC 95%	P value	PR	IC 95%	P value	PR	IC 95%	P value	PR	IC 95%	P value
Age*												
Child	Ref.			Ref.			Ref.			Ref.		
Young	1.04	0.92-1.18	0.543	1.13	0.92-1.39	0.254	1.07	0.90-1.27	0.459	1.03	0.87-1.23	0.721
Adult	1.06	0.96-1.17	0.235	1.09	0.92-1.29	0.266	1.2	1.05-1.38	0.007	1.05	0.92-1.20	0.445
Elderly	1.22	1.10-1.35	<0.001	1.42	1.19-1.69	<0.001	1.39	1.20-1.60	<0.001	1.31	1.14-1.52	<0.001

*Models adjusted by sex

DISCUSSION

This study found a prevalence of 22.4% resistance to amoxicillin/clavulanic acid in *Escherichia coli*, very similar to a previous study in Colombia by Castrillon et al. where 28.3% resistance was reported[19]. However, this differs from other studies where Abbas et al[20] reported a lower percentage of resistance (11.2%), or the study by Castro-Orozco et al[21], which presented a higher resistance (62.0%). Theoretically, it is established that any antimicrobial that presents a resistance of less than 20% can be used as a therapeutic option empirically, a concept that should be carefully analyzed with this antibiotic[22].

Resistance to third generation cephalosporins such as ceftriaxone was low in *Escherichia coli* (4.6%) similar to the study by Gómez et al[23], who reported 2.8%, which could justify its empirical use in the treatment of urinary tract infections. However, it should be remarked that this study found a high resistance to cefuroxime (17.2%) compared to other studies such as that of Castro-Orozco et al[21] with a resistance of 7.7% and that of Gómez et al[23] of 5.6%, which could be controversial and, therefore, opens the need to conduct more studies in Puno and other high Andean regions to make decisions regarding its use.

We found that gentamycin, nitrofurantoin and amikacin have a lower resistance pattern in all of the uropathogens compared to the studies from Abbas et al[20], Castro-Orozco et al[21] and Castrillon et al[19]. The high rate of resistance to trimethoprim-sulfamethoxazole by all of the analyzed uropathogens has been widely reported in various investigations that show high bacterial resistance to this antibiotic, despite numerous recommendations on its exclusive use after obtaining an antibiogram that demonstrates its sensibility. For this reason, Puno should reconsider its therapeutic use in UTI.

There is scarce information about the antimicrobial resistance in the peruvian high-andean regions. Escherichia coli had a 19.1% resistance to ciprofloxacin, 26.9% to trimethoprim-sulfamethoxazole and 4.3% to nitrofurantoin, results similar to that reported by Marcos-Carabajal et al[24], in which a 18.4%, 25.5% and 6.1% resistance was respectively observed. Nonetheless, the resistance to ceftriaxone (4.6%) and gentamycin (6.9%) was lower compared to Marcos Carabajl et al[24], who showed an 14.3% and 13.3% resistance respectively.

The present study found that the elderly group had 1.22 times greater probability of being resistant to penicillin, when compared to the infant group, a result similar to that reported by Sanchez et al[25], who found that women older than 65 years had 1.46 times greater probability of presenting resistance to amoxicillin/ clavulanic acid as found by Lee et al[26], where adults over 60 years are 1.07 times more likely to have resistance compared to those under 60. On the other hand, Sotto et al[27], reported that people older than 65 years were 2.19 times more likely to present antimicrobial resistance compared to those below 64. Another antimicrobial family used in the UTI's treatment are the cephalosporins, our study showed that the elderly group had 1.42 times more probability of presenting resistance to this family when compared to the infant population. Similar to what has been described by Sanchez et al[25], where women of the elderly age group were 1.50 and 2.60 times more likely to present resistance to ceftriaxone and cefuroxime respectively, compared to women below 64.

Finally, our analysis reflected that the elderly age group had 1.39 times more probability to present antimicrobial resistance to other antibiotics compared to the infant population. This result was similar to what has been reported in literature by Lee et al[26], where adults older than 60 years had 1.14 more probability of presenting resistance to amikacin compared to those under 60. Similarly, Treviño et al[28], reported that adults older than 65 years are 1.79 more likely to present resistance to gentamicin compared to those younger than 64 years. On the other hand, Sanchez et al[25] reported that women older than 65 years were 3.14 times more likely to present resistance to nitrofurantoin, compared to those under 64 years of age. The greater antimicrobial resistance in the elderly group may be explained by multiple factors, like a prolonged exposure to antibiotics, which leads to an alteration of their microbiome and vulnerability to a possible later colonization by resistant bacteria[29].

This study has some limitations as the fact of ignoring the clinical context and outcome from the patient, underlying chronic diseases, current status, possible gestation, immunodepression, hospitalization, use of urinary catheter, etc. There is also no clinical diagnosis of the patient. Likewise, the location where the infection was acquired is unknown. Finally, the obtained results can't be extrapolated to other populations outside from the analyzed area. The bivariate and multivariate analysis of the uropathogens *Klebsiella oxytoca* and Proteus vulgaris was not performed because the results were not statistically significant. Among the strengths of the study, we must mention that we have a large sample size. Likewise, we found that the robust regression model used has been rarely used in high Andean areas that seek to characterize resistance patterns and identify associated factors. Lastly, the collection urine culture samples allow us to have reliable information about the results, because the international results were met, in turn, specific methods were used for the characterization of sensitivity or resistance, which avoid the possibility of error in the results.

The collected information in this study, in a high Andean area, indicates that the antimicrobial resistance pattern utilized to treat UTI's, despite being lower than in other areas of the region, is still high and worrisome. Finding that the penicillin family has the highest resistance pattern, therefore it must be used with caution as empirical treatment in this disease.

Recommendations

The results presented in this study allow us to evaluate and demonstrate that the current situation, regarding antibacterial resistance, is similar to the situation at the national or international level, where elderly people present the highest resistance. Research in this area should be improved and applied to other regions of the country in an effort to have more information and be able to create public policies for the appropriate management of antibiotics. In an era where antibiotic resistance is on the rise, the proper use of these drugs is essential to prolong the efficacy of therapeutic agents.

BIBLIOGRAPHIC REFERENCES

1. Organización Mundial de la Salud. Resistencia a los antibióticos [homepage on the Internet]. 2018 [updated 2020 July 31; cited 2021 April 12]. Available from: http://www.who.int/es/news-room/fact-sheets/detail/resistencia-a-los-antibi%C3%B3ticos
2. Serna LFC, Dávila CE, Bernal GB, Gómez C, Uribe AG. Plan Nacional de respuesta a la resistencia a los antimicrobianos. 2018;1:66.
3. World Health Organization. Causes of antibiotic resistance [homepage on the Internet]. 2015 [updated 2015 October 10; cited 2021 April 11]. Available from: http://www.who.int/mediacentre/events/2015/world-antibiotic-awareness-week/infographic-causes.pdf?ua=1
4. Jim O'Neill. Tackling drug-resistant infections globally: Final report and recommendations. AMR. 2016;1:84.
5. Echevarría-Zarate J, Sarmiento Aguilar E, Osores-Plenge F. Infección del tracto urinario y manejo antibiótico. Acta méd. peruana. 2006;23(1):26-31.
6. Organización Panamericana de la Salud. Informe Anual de la Red de Monitoreo/ Vigilancia de la Resistencia a los Antibióticos. 2010;1(1):210
7. Ignacio Alós J. Epidemiología y etiología de la infección urinaria comunitaria. Sensibilidad antimicrobiana de los principales patógenos y significado clínico de la resistencia. Enferm Infecc Microbiol Clin. 2005;23:3-8. DOI: https://doi.org/10.1157/13091442
8. Delgado Mallén, P. Infecciones Urinarias. Nefrologia al dia [Internet] 2019 [cited 7 March 2021]. Available from: <https://www.nefrologiaaldia.org/es-articulo-255>
9. Machado-Alba JE. Evaluación de sensibilidad antibiótica en urocultivos de pacientes en primer nivel de atención en salud de Pereira. Rev Salud Pública. 2012;10.
10. Ferrer LMV. Etiologia y perfil de resistencia a antimicrobianos de uropatogenos aislados en 2 hospitales de Cartagena. Cienc Salud Virtual. 2013;5(1):18-25. DOI-. https://doi.org/10.22519/21455333.343
11. Tacconelli E. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. OPS. 2017;1(1):7.
12. Arana DM, Rubio M, Alós J-I. Evolution of antibiotic multiresistance in Escherichia coli and Klebsiella pneumoniae isolates from urinary tract infections: A 12-year analysis (2003-2014). Enferm Infecc Microbiol Clin. 2017;35(5):293-8. DOI: 10.1016/j.eimc.2016.02.018.
13. Gabriel Levy Hara. Recopilación y análisis de los estudios de resistencia antimicrobiana para el diagnóstico de la situación y elaboración del plan de acción parta contener la resistencia antimicrobiana en la sub región andina. ORAS CONHU. 2014;97.
14. Zhanel GG, Hisanaga TL, Laing NM, DeCorby MR, Nichol KA, Palatnick LP, et al. Antibiotic resistance in outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). Int J Antimicrob Agents. 2005;26(5):380-8. DOI: 10.1016/j.ijantimicag.2005.08.003
15. Álvarez G, Caamaño Troitiño AB, Sánchez Hernández, C. Estudio de resistencias en atención primaria de las infecciones del tracto urinario. Cad Aten Primaria. 2011;18:181-7.
16. Ministerio de Salud. Plan Nacional para enfrentar la resistencia a los antimicrobianos 2017 - 2021. Lima; 2016.
17. Francisco Costa Aponte. Resultados definitivos de los censos nacionales 2017, Puno. Puno, Peru; 2017.
18. Sacsaquispe Contreras RE, Velásquez Poma J. Manual de procedimientos para la prueba de sensibilidad antimicrobiana por el método de disco disfusión. INS; 2002.
19. Spitia JDC, Machado-Alba JE, Idarraga SG, Gutierrez MG, León NR, Gallego JJR. Etiología y perfil de resistencia antimicrobiana en pacientes con infección urinaria. Infectio. 2018;23(1):45-51. DOI: http://dx.doi.org/10.22354/in.v23i1.755
20. Mihankhah A, Khoshbakht R, Raeisi M, Raeisi V. Prevalence and antibiotic resistance pattern of bacteria isolated from urinary tract infections in Northern Iran. J Res Med Sci Off J Isfahan Univ Med Sci. 2017;22:108-108. DOI: https://dx.doi.org/10.4103%2Fjrms.JRMS_889_16
21. Castro-Orozco R, Barreto-Maya AC, Guzmán-Álvarez H, Ortega-Quiroz RJ, Benítez-Peña L. Patrones de resistencia antimicrobiana en uropatógenos gramnegativos aislados de pacientes ambulatorios y hospitalizados Cartagena, 2005-2008. Rev Salud Pública. 2010;12(6):1010-9.
22. Orrego-Marin CP, Henao-Mejia CP, Cardona-Arias JA. Prevalencia de infección urinaria, uropatógenos y perfil de susceptibilidad antimicrobiana. Acta Médica Colomb. 2014;39(4).
23. Gómez E. CP, Plata S. M, Sejnaui J, Rico Villegas CL, Vanegas González S. Resistencia de la E.coli en urocultivos de pacientes con sospecha de infección urinaria intr y extra-hospitalaria en la Fundación Santa Fe de Bogotá. Rev Urol Colomb. 2009;XVIII(1):53-8.
24. Marcos-Carbajal P, Galarza-Perez M, Huancahuire-Vega S, Otiniano-Trujillo M, Soto-Pastrana J. Comparación 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. Biomedica. 2020;40(Suppl 1):139–47 DOI: https://dx.doi.org/10.7705%2Fbiomedica.4772
25. Sanchez G V, Babiker A, Master RN, Luu T, Mathur A, Bordon J. Antibiotic Resistance among Urinary Isolates from Female Outpatients in the United States in 2003 and 2012. Antimicrob Agents Chemother. 2016;15. DOI: https://dx.doi.org/10.1128%2FAAC.02897-15
26. Lee DS, Choe H-S, Kim HY, Yoo JM, Bae WJ, Cho YH, et al. Role of age and sex in determining antibiotic resistance in febrile urinary tract infections. Int J Infect Dis. 2016;51:89-96. DOI: 10.1016/j.ijid.2016.08.015
27. Sotto A, De Boever CM, Fabbro-Peray P, Gouby A, Sirot D, Jourdan J. Risk factors for antibiotic-resistant Escherichia coli isolated from hospitalized patients with urinary tract infections: a prospective study. J Clin Microbiol. 2001;39(2):438-44. DOI: 10.1128/JCM.39.2.438-444.2001.
28. Treviño M, Losada I, Fernández-Perez B, Coira A, Pea-Rodríguez MF, Hervada X. Vigilancia de la sensibilidad a antimicrobianos de Escherichia coli productor de infecciones del tracto urinario comunitarias en Galicia. Rev Esp Quimioter. 2016;29:86-90.
29. Beckett CL, Harbarth S, Huttner B. Special considerations of antibiotic prescription in the geriatric population. Clin Microbiol Infect. 2015;21(1):3–9 DOI: 10.1016/j.cmi.2014.08.018.