EVOLUTION OF THE PREVALENCE AND ANTIMICROBIAL RESISTANCE AMONG *Escherichia coli* ISOLATED AS A CAUSE OF INFECTION IN PATIENTS ADMITTED TO A IV-LEVEL HOSPITAL IN LIMA, PERU

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ABSTRACT

The levels and evolution of antimicrobial resistance of *Escherichia coli* during 01/2009-06/2010 (Period 1), 01/2012-06-2013 (Period 2) and 07/2013-12/2014 (Period 3) were analyzed. Identification, susceptibility levels to 13 antibiotics and the presence of extended-spectrum β-lactamases (ESBLs) were determined. Overall, 9,918 microorganisms were isolated as a cause of infection. Of these 3,016 (30.4%) were *E. coli*, with 1,770 (59%), 992 (33%) and 254 (8%), from the Medicine and the Surgery Departments and the Intensive Care Unit (ICU), respectively. There was a significant increase (p=0.0002) of *E. coli* throughout considered periods. The isolates presented high levels of resistance (>60%) to cephalosporins, ciprofloxacin and cotrimoxazole, being only susceptible to imipenem (0.3% of resistance) and tigecycline. Overall the analysis of evolution of antimicrobial resistance showed that resistance to cephalosporins and amikacin significantly increased, while, the ones of piperacillin-tazobactam, cotrimoxazole and gentamicin had significantly decreased. Nevertheless, the ICU isolates showed an inverse scenario for cephalosporins. These findings agree with an increase of ESBLs on the Medicine (56% to 66%; p<0.0001) and on the Surgery (54% to 62%; p=0.0197) departments, with a parallel decrease in the ICU (76% to 68%). In summary, high levels of antimicrobial resistance have been reported among *E. coli*, with worrisome levels of ESBL. A continuous surveillance of antimicrobial resistance levels in the area is needed.

KEY WORDS: *Escherichia coli*; antimicrobial resistance; cephalosporins.

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INTRODUCTION

Antimicrobial resistance is an increasing problem worldwide, affecting all microorganisms regardless of source or whether they are or they are not pathogenic (Bumbangi et al., 2022; Palma et al., 2017; Pons & Ruiz, 2019; Ymaña et al., 2022). This scenario is challenging to medical practices because of the increasing ineffectiveness of the current antibacterial armamentarium. While often under the radar, the development of antimicrobial resistance also has a direct impact on medical practices beyond treatment of infectious diseases. Thus, surgery, transplants, immunosuppressed patients’ prophylaxis among other are directly impaired (Cervera et al., 2014; Teillant et al., 2015). Furthermore, the economy, environment and global development are affected by antimicrobial resistance, with serious concerns related to its negative effect on Sustainable Development Goals (Jasovsky et al., 2016). This problem is clearly visualized in the economical- and life-costs related to infections by these pathogens (Cassini et al., 2019; CDC, 2019).

In this scenario, the so-called ESKAPE group of microorganisms (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp.) are considered of special concern because of the severity of infections and the increasing treatment difficulties related to their high levels of antimicrobial resistance (Pons & Ruiz, 2019; De Oliveira et al., 2020).

In addition to these microorganisms, Escherichia coli is one of the microorganisms most frequently isolated as one of the causes of human infections (Pons & Ruiz, 2019; Vila et al., 2016). Thus, while being a common commensal inhabitant of the human gut, several virulent pathotypes of E. coli play a main role as a cause of infectious diarrhea, leading to different diarrhoeogenic pathotypes of E. coli being considered one of the most relevant causes of children death (Khalil et al., 2018; Levine et al., 2020). Moreover, extraintestinal E. coli are amid the most frequent pathogens involved in other types of infections, such as urinary, wound or systemic infections (Medina & Castillo-Pino, 2019; Poolman & Wacker, 2016).

In Perú, reports focused on antimicrobial resistance show a discouraging panorama, with both commensal and clinical isolates of E. coli presenting high levels of antimicrobial resistance to agents such as cephalosporins or fluoroquinolones, and others (Alcedo et al., 2022; Palma et al., 2017; Yabar et al., 2017). Furthermore, E. coli resistance to last-resort antimicrobial agents, such as colistin, has been reported in Peru (Ugarte Silva et al., 2018). Nonetheless, there is a lack of studies focused on the comprehensive evolution of antimicrobial resistance in Peruvian hospital settings. Thus, this present study focuses on the evolution of resistance levels observed in E. coli in a IV-level hospital in Lima, Peru.
MATERIAL AND METHODS

Microorganisms

All E. coli isolates isolated were included in the study from hospitalized patients [on the Medicine and the Surgery Departments and the Intensive Care Unit (ICU)] from January, 2009 to June, 2010 also from January, 2012 to December, 2014 in the Hospital Nacional Guillermo Almenara Irigoyen (HNGAI) of Lima (Peru). Information about samples was extracted from databases of HNGAI. The analysis of data was performed considering 3 periods of 18 months each: Period 1 (January, 2009 - June, 2010), Period 2 (January, 2012 - June, 2013) and Period 3 (July, 2013 - December, 2014).

Bacterial identification and antimicrobial susceptibility

The different samples were processed according to the standard microbiology protocols at the Microbiology Laboratory of HNGAI. Bacterial identification, antibiotic susceptibility and the presence of Extended-Spectrum β-Lactamases (ESBLs) were performed using the automatic MicroScan system (Siemens Medical Solutions Diagnostics, Camberley, UK) in Period 1 and MicroScan and Vitek 2 system (BioMérieux, Marcy l’Etoile, France) in Period 2 and 3.

The antibiotics included in the study were ampicillin, piperacillin-tazobactam, cefazolin, cefotaxime, ceftiraxone, ceftazidime, cefepime, imipenem, cotrimoxazole, amikacin, gentamicin and ciprofloxacin. In addition, susceptibility to tigecycline was established in a subset of 124 isolates from Period 2 and Period 3. Antimicrobial susceptibility levels to all antimicrobial agents, except tigecycline, were established according to Clinical and Laboratory Standards guidelines (CLSI, 2014). Tigecycline susceptibility was determined according to the US Food and Drug Administration criteria (https://www.fda.gov/drugs/development-resources/tigecycline-injection-products)

Statistical analysis

The Chi-squared test was used to analyze statistical associations. A p-value <0.05 was considered as significant.

In all cases intermediate and resistant isolates were classified together for analysis purposes. Coagulase negative Staphylococcus (CoNS) were considered as contamination and were not included in the statistical analysis (Dargere et al, 2018).
RESULTS

Overall, 10,948 microorganisms were recovered from clinical samples from admitted patients: 1,030 were CoNS and were excluded from further analyses. Thus, a total of 9,918 microorganisms were considered for analysis. From these, 3,016 isolates (30.4%) were *E. coli*, with 1,770 (59%) and 992 (33%) being from the Medicine and the Surgery Departments, respectively, and 254 (8%) from the ICU. Most of those *E. coli* were recovered from urine samples (2,188, 72.5% of total *E. coli*), with 287 (9.5%), 201 (6.7%) and 194 (6.4%) from intrabdominal, wounds and blood samples as the most frequent sources. Other sources accounting together for the remaining 4.9% of isolates (Table 1).

Analysis by periods showed that the number of *E. coli* varied from 1,060 (28.1% of the microorganisms considered in Period 1) to 1,123 (31.8% of microorganisms considered in Period 2) and 833 (32.8% of microorganisms considered in Period 3) (p=0.0002). This increase in the number of *E. coli* was observed on the three departments analyzed, being only significant on the Medicine department (Table 2). Nevertheless, considering the overall number of microorganisms recovered/month and the *E. coli*/month, the proportion of *E. coli* from ICU varied around a half and a third of the ones observed on the Medicine and on the Surgery Departments (Table 3).

Analysis of the levels of antimicrobial resistance showed that, overall, *E. coli* isolates from the ICU showed higher levels of antimicrobial resistance. The highest resistance rates found were to ampicillin (90.7%) ciprofloxacin (79.4%) and cefazolin (75.2%). All isolates, with the exception of 8 recovered in the Period 2 from urine samples, were susceptible to imipenem. Similarly, the subset tested for tigecycline showed 0% of resistance (Table 4; Figure 1). When antimicrobial resistance was analyzed considering the original sample, significant differences in the resistance levels of all tested antimicrobial agents, excepting amikacin and imipenem was observed (Table 1). Thus, the isolates from lower respiratory tract samples showed the higher levels of resistance to cephalosporins and aminoglycosides, while those from wounds showed the higher levels of resistance to ciprofloxacin and cotrimoxazole (Table 1). As predictable, significant differences in the origin of isolates were observed among those proceeding from each one of the wards (the Medicine and the Surgery department and ICU) (Table 1).
**Table 1.** Samples analyzed and antimicrobial resistance

| Sample | Escherichia coli (N=3016) | Percentage of antimicrobial resistance |
|--------|---------------------------|---------------------------------------|
|        | Overall | M | S | ICU | P | Amp | PTZ | Cff | Ctx | Cro | Caz | Fep | Imp | Ak | Gm | Cip | Sxt |
| Urine  | 2188    | 72.5 | 83.2 | 62.0 | 39.4 | <0.0001 | 90.6 | 8.0 | 72.3 | 62.1 | 62.9 | 61.9 | 59.5 | 0.3 | 11.0 | 47.3 | 79.0 | 74.9 |
| IA     | 287     | 9.5 | 2.0 | 19.4 | 23.2 | <0.0001 | 86.4 | 12.9 | 67.9 | 61.7 | 62.4 | 59.6 | 57.5 | 0.0 | 7.3 | 38.3 | 77.0 | 71.4 |
| Wounds | 201     | 6.7 | 4.7 | 10.4 | 5.5 | <0.0001 | 95.0 | 11.9 | 77.7 | 71.6 | 72.6 | 70.6 | 67.6 | 0.0 | 11.9 | 52.2 | 88.1 | 90.5 |
| Blood  | 194     | 6.4 | 5.8 | 4.5 | 19.7 | <0.0001 | 91.8 | 12.9 | 76.3 | 71.6 | 73.7 | 72.2 | 70.1 | 0.0 | 7.2 | 38.1 | 75.2 | 74.7 |
| LRT    | 98      | 3.2 | 3.1 | 2.0 | 9.1 | <0.0001 | 92.9 | 12.2 | 92.9 | 80.1 | 81.6 | 80.6 | 77.6 | 0.0 | 12.2 | 54.1 | 82.7 | 67.3 |
| Other* | 48      | 1.6 | 1.1 | 2.3 | 11.4 | <0.0001 |       |     |     |     |     |     |     |     |     |     |     |

**Table 2.** Number of *Escherichia coli* by ward and period analyzed.

| Sample | Medicine N (%) | Surgery N (%) | ICU N (%) | Overall N (%) |
|--------|----------------|---------------|-----------|---------------|
|        | Period 1 (N=2227) | Period 2 (N=1900) | Period 3 (N=1371) | Period 1 (N=1084) | Period 2 (N=776) | Period 3 (N=663) | Period 1 (N=615) | Period 2 (N=395) | Period 3 (N=3777) | Period 2 (N=3599) | Period 3 (N=2542) |
| E. coli| 672 (30.2) | 620 (32.6) | 478 (34.9) | 296 (33.4) | 403 (37.2) | 293 (37.8) | 92 (13.9) | 100 (16.3) | 62 (15.7) | 1060 (28.1) | 1123 (31.2) | 833 (32.8) |
| P     | 0.0122 | 0.1146 | 0.4691 | 0.0002 |

ICU: Intensive Care Unit; Period 1: January 2009-June 2010; Period 2: January 2012-June 2013; Period 3: July 2013-December 2014

Significant differences referring to the number of *E. coli* isolated in each ward in each Period analyzed.
Overall, significant increases were observed in the resistance to cephalosporins and amikacin, with piperacillin-tazobactam, and gentamicin showing significant reductions in resistance, and imipenem and ciprofloxacin showing no relevant differences between this study periods (Table 4, Figure 2). Regarding cotrimoxazole levels of resistance decreased between Periods 1 and 2, however they tend to recover the original values in Period 3. Nevertheless, the evolution differed when analyzed by department. Isolates from the Medicine and the Surgery Departments tended to agree with above-mentioned data, with some exceptions, as amikacin in the Surgery Department, with the resistance levels remaining unaltered among the 3 analyzed periods. Meanwhile, isolates from the ICU showed a different scenario when tested for cephalosporins. Thus, in the Period 2 amid the ICU isolates the resistance rates of all cephalosporins decreased towards values similar or slightly over to those observed in the other two departments. They tend to increase again in the Period 3 over values detected on the Medicine and on the Surgery Departments, with these fluctuations being significant in the case of cefotaxime (p=0.0047) and ceftriaxone (p=0.0161), (Table 4; Figure 2).

Likewise, the overall prevalence of ESBLs has increased in the three periods analyzed, from 57.1% (Period 1) to 67.1% (Period 3) (p<0.0001), with an increase of 56.1% (Period 1) to 67.8% (Period 3) (p=0.0001) on the Medicine Department and 54.1% (Period 1) to 64.8% (Period 3) (p=0.0278) on the Surgical Department. Meanwhile, the prevalence of ESBLs on the ICU showed a non-significant reduction between the first and second period from 76.1% to 65.0%, returning to values of 74.2% in the Period 3.

Table 3. Differences in positivity among Periods.

|          | Medicine | Surgery | ICU | Overall |
|----------|----------|---------|-----|---------|
|          | P1       | P2      | P3  | P1      | P2      | P3  | P1       | P2       | P3       |
| MM       | 123.7    | 105.3   | 76.1| 49.3    | 60.2    | 43.1| 36.8     | 40.8     | 21.8     |
| EcM      | 37.3     | 34.4    | 26.5| 16.4    | 22.4    | 16.3| 5.1      | 5.5      | 3.4      |
| EcM/M  | 0.30     | 0.33    | 0.35| 0.33    | 0.37    | 0.38| 0.14     | 0.13     | 0.16     |

ICU: Intensive Care Unit; P1: Period 1 (January 2009-June-2010); P2: Period 2 (January 2012-June-2013); P3: Period 3 (July-2013-December-2014); EcM: E. coli per month; MM: Microorganisms per month.
### Table 4. Antimicrobial resistance levels

| N     | Period               | Amp  | PTZ  | Cfz  | Ctx  | Cro  | Caz  | Fep  | Imp  | Ak   | Gm   | Cip  | Sxt  | Tgc |
|-------|----------------------|------|------|------|------|------|------|------|------|------|------|------|------|-----|
| 3016  | Overall              | 90.7 | 8.7  | 75.2 | 64.5 | 65.2 | 64.0 | 61.4 | 0.3  | 10.5 | 47.2 | 79.4 | 74.7 | --- |
| 1060  | 01/2009-06/2010       | 92.0 | 13.7 | 66.8 | 61.0 | 61.6 | 59.6 | 57.2 | 0.0  | 8.3  | 51.0 | 80.7 | 77.1 | --- |
| 1123  | 01/2012-06/2013       | 89.7 | 6.1  | 74.6 | 65.3 | 65.7 | 64.2 | 61.3 | 0.5  | 10.5 | 46.7 | 78.1 | 72.0 | 0.0 |
| 833   | 07/2013/12/2014       | 90.9 | 5.9  | 86.8 | 67.8 | 69.1 | 69.4 | 67.1 | 0.2  | 13.2 | 43.2 | 79.6 | 75.3 | 0.0 |
|       | P                    | NS   | <0.0001 | <0.0001 | 0.0072 | <0.0001 | <0.0001 | NS   | 0.0025 | 0.0029 | NS   | 0.0233 | NS |
| 1770  | Overall              | 91.1 | 8.9  | 73.6 | 64.1 | 65.4 | 64.4 | 61.9 | 0.3  | 10.8 | 48.0 | 79.6 | 75.8 | --- |
| 672   | 01/2009-06/2010       | 92.1 | 12.5 | 75.5 | 59.5 | 60.0 | 58.6 | 56.1 | 0.0  | 7.7  | 50.7 | 80.8 | 79.0 | --- |
| 620   | 01/2012-06/2013       | 90.8 | 6.5  | 73.0 | 66.1 | 67.6 | 66.3 | 63.4 | 0.5  | 10.8 | 48.2 | 79.8 | 73.2 | 0.0 |
| 478   | 07/2013/12/2014       | 90.4 | 7.2  | 89.1 | 68.0 | 70.1 | 69.9 | 68.0 | 0.4  | 15.3 | 43.9 | 77.6 | 74.7 | 0.0 |
|       | P                    | NS   | 0.0002 | <0.0001 | 0.0056 | 0.0006 | 0.0002 | 0.0002 | NS   | 0.0003 | BS   | NS   | 0.0416 | NS |
| 992   | Overall              | 91.1 | 7.6  | 73.4 | 62.8 | 62.5 | 61.4 | 58.1 | 0.2  | 9.6  | 45.6 | 78.2 | 72.9 | --- |
| 296   | 01/2009-06/2010       | 89.9 | 15.2 | 62.8 | 57.1 | 58.1 | 55.4 | 53.0 | 0.0  | 9.5  | 49.7 | 78.7 | 73.6 | --- |
| 403   | 01/2012-06/2013       | 86.8 | 4.5  | 73.0 | 64.3 | 62.5 | 61.0 | 57.1 | 0.5  | 9.4  | 44.9 | 75.2 | 70.5 | 0.0 |
| 293   | 07/2013/12/2014       | 91.1 | 4.1  | 84.6 | 66.6 | 66.9 | 67.9 | 64.5 | 0.0  | 9.9  | 42.3 | 81.9 | 75.4 | 0.0 |
|       | P                    | NS   | <0.0001 | <0.0001 | 0.0437 | 0.0885 | 0.0076 | 0.0164 | NS   | NS   | NS   | NS   | NS   | NS |
| 254   | Overall              | 94.1 | 11.4 | 79.9 | 73.6 | 74.8 | 72.0 | 71.7 | 0.4  | 11.4 | 48.4 | 82.7 | 74.0 | --- |
| 92    | 01/2009-06/2010       | 95.0 | 17.4 | 84.8 | 84.8 | 84.8 | 80.4 | 78.3 | 0.0  | 8.7  | 57.6 | 85.8 | 73.9 | --- |
| 100   | 01/2012-06/2013       | 93.0 | 10.0 | 76.0 | 64.0 | 67.0 | 64.0 | 65.0 | 1.0  | 10.0 | 44.0 | 79.0 | 71.0 | 0.0 |
| 62    | 07/2013/12/2014       | 93.5 | 4.8  | 79.0 | 72.6 | 72.6 | 72.6 | 72.6 | 0.0  | 12.9 | 41.9 | 83.9 | 79.0 | 0.0 |
|       | P                    | NS   | 0.0474 | NS   | 0.0047 | 0.0161 | NS   | NS   | BS   | NS   | BS   | NS   | NS   | NS |

N: Number; Amp: ampicillin; PTZ: piperacillin-tazobactam; Cfz: cefazolin; Ctx: cefotaxime; Cro: ceftriaxone; Caz: ceftazidime; Fep: cefepime; Imp: imipenem; Ak: amikacin; Gm: gentamicin; Cip: ciprofloxacin; Sxt: cotrimoxazole; Tgc: tigecycline; HNGAI: Hospital Nacional Guillermo Almenara Irigoyen; ICU: intensive care unit; BS: bordering significance (0.05<p<0.09); NS: no significant; --: No data.

Significant differences established among levels of resistance of each antibiotic in each ward among the analyzed periods.

* Tested in 124 isolates.
Figure 1: Heat map of antimicrobial resistance by period and department analyzed.

1: Period 01/2009-06/2010; 2: Period 01/2012-06/2013; 3: Period 07/2013-12/2014; M: Medicine; S: Surgery; I: Intensive Care Unit; O: Overall; Amp: ampicillin; Cfz: cefazolin; Ctx: cefotaxime; Cro: ceftriaxone; Caz: ceftazidime; Fep: cefepime; PTZ: piperacillin-tazobactam; Imp: imipenem; Gm: gentamicin; Ak: amikacin; Cip: ciprofloxacin; Sxt: cotrimoxazole; Tgc: Tigecycline Ab: Antibiotic; Ab-C: Antibiotic category defined by Magiorakos et al (2012); β: β-lactam antibiotics (penicillins); nesCph: non extended-spectrum cephalosporins; APβ: anti-Pseudomonal β-lactam; βLI: β-lactam plus β-lactamase inhibitors; CBP: carbapenems; AMG: aminoglycosides; Q: quinolones; PI: pholate inhibitors; GLC: glycylycyclines. ND: No data
Figure 2: Evolutive trends in antimicrobial resistance between the study periods.

M: Medicine; S: Surgery; I: Intensive Care Unit; O: Overall; Amp: ampicillin; Cfz: cefazolin; Ctx: cefotaxime; Cro: ceftriaxone; Caz: ceftazidime; Fep: cefepime; PTZ: piperacillin-tazobactam; Imp: imipenem; Gm: gentamicin; Ak: amikacin; Cip: ciprofloxacin; Sxt: cotrimoxazole; Tgc: Tigecycline; Ab: Antibiotic; Ab-C: Antibiotic categories defined by Magiorakos et al (2012); β: β-lactam antibiotics (penicillins); nesCph: non extended-spectrum cephalosporins; APβ: anti-Pseudomonal β-lactam; βLI: β-lactam plus β-lactamase inhibitors; CBP: carbapenems; AMG: aminoglycosides; Q: Quinolones; PI: pholate inhibitors.

Grey: No significant differences; White: Significant decrease; Black: Significant increase
DISCUSSION

While *E. coli* is a common inhabitant of the human gut, a series of these microorganisms are relevant human pathogens and they are frequently isolated as a cause of severe life-threatening infections (Simonsen et al., 2014). In those cases, an early and adequate antibiotic treatment is the key for good patient outcomes (Bonine et al., 2019). Nevertheless, the increasing levels of antimicrobial resistance are challenging the current antibiotic schedules, having a direct impact on fatal outcomes (ARC, 2022; Cassini et al., 2019; CDC, 2019). In most low- and middle-income countries, this scenario is aggravated by socioeconomic and cultural factors such as lack of adequate and sufficient health infrastructures, the treatment costs, the over-the-counter access to antibiotics or (especially in low-income countries) a limited number of antibiotic alternatives, and others (Mandomando et al., 2010; Mills, 2014; Nusair et al., 2021; Worku et al., 2003)

Antimicrobial resistance differs among isolates from different samples. Of note, as the burden of each sample within each ward differs, this finding probably contributes to the differences in the levels of resistance observed among isolates recovered from the ICU, the Medicine and the Surgery departments.

Overall, the present data shows high rates of resistance to β-lactams excepting carbapenems and piperacillin-tazobactam. These data are directly related to the high levels of ESBLs found in our study also in accordance with the frequency of ESBLs in *E. coli* and other pathogenic microorganisms reported in previous studies in Peru (Alcedo et al., 2022; García et al., 2016; Palma et al., 2017; Castillo-Tokumori et al., 2017; Granda et al., 2019).

In addition to older β-lactam agents (ampicillin and cefazolin), the highest levels of antimicrobial resistance were to ciprofloxacin and cotrimoxazole, with ESBL prevalence being >50% in all Departments and periods analyzed. For years, quinolones have been a commonly used agent to treat the community and hospital infections and it can be easily obtained over-the-counter in Peru (Rojas-Adrianzén et al., 2018; Ruiz, 2019). Furthermore, quinolones, such as enrofloxacin, have been largely used in veterinary health for therapeutic, prophylaxis or growth promoter purposes (Ruiz, 2019). The levels of quinolone resistance found in this study agree with previous data in the country. Thus, Palma et al (2017), reported 71% of ciprofloxacin non-susceptible *E.coli* isolated from children with bacteremia, and García et al. (2012) reported 85.6% of ciprofloxacin resistance by bacteremic *E. coli*. Quinolone resistance is mainly mediated by chromosomal mechanisms, mainly mutations in quinolone targets, in addition to chromosomal efflux pumps, cell wall alterations and native chromosomal qnr genes (Ruiz, 2003, 2019). Additionally, a series of transferable genes able to produce low-level quinolone resistance and favoring further selection of full quinolone-resistance have been described (Ruiz, 2019). Of these, while scarcely sought, previous reports have shown at least the...
circulation of aac (6′) Ib-cr, qnrB, qnrS and qnrVC resistance genes among *E. coli* isolated in Peru (Palma et al., 2017; Pons et al., 2014; Tamariz et al., 2018). Meanwhile, for many years cotrimoxazole has been largely used in the treatment of community-acquired infections, with *E. coli* usually presenting high levels of resistance worldwide (Benmessaoud et al., 2016; Mandomando et al., 2010; Ruiz et al., 2007; Yabar et al., 2017).

The description of a high prevalence of ESBLs is not a surprising fact. Thus, different reports showed a high prevalence of ESBL-producing *E. coli* in Peru, which can be up to 76.8% reported by Garcia et al (2012). Most recent reports in the country described around 40% of ESBL-producing *E. coli* around 40%. Thus, Palma et al. (2017), showed a 43.5% of ESBL-producing *E. coli* in the blood samples. In the same line, Castillo-Tokumori et al. (2017) and Ormeño et al. (2022) reported a 40.8% and 42.5%, respectively, of ESBL-producing *E. coli* among uropathogenic *E. coli*. In Peru, the presence of ESBLs has also been reported among healthy people, as well as in non-human samples, from the environment, the food, the livestock and from wild animals (Alcedo et al., 2022; Castillo et al., 2022).

Descriptions of antimicrobial-resistant microorganisms have expanded from all Latin America, including microorganisms from the environment, animals, food and human origins (Castillo et al., 2022; García-Betancur et al., 2021; Medina-Pizzalli et al., 2021). Regarding *E. coli*, similar data have been reported in different countries, with descriptions of high level of antimicrobial resistance (Finello et al., 2021; Garza-González et al., 2019), which includes the description of *E. coli* isolates showing resistance to last resort antibacterial agents (Paiva et al., 2021) and high levels of ESBLs (Ponce-de-Leon et al., 2018).

Of note, these antimicrobial resistance values, with the exception of those for ciprofloxacin, are also in accordance with most modern CLSI guidelines (CLSI, 2021), as no change in breakpoints have been done. Regarding ciprofloxacin, as current breakpoints are more restrictive, it is predictable that under current considerations ciprofloxacin resistance levels will be higher. Unfortunately, in the database no exact minimal inhibitory concentration values were recorded.

The evolution of antimicrobial resistance over time has shown a general trend to increase, especially when regarding cephalosporins. This finding is not so surprising, as this trend has been reported worldwide which lead the World Health Organization to issue an alert to this trend (WHO, 2019).

Of note, albeit modest, an overall significant increase in the levels of resistance to amikacin has been observed. Amikacin resistance is mostly associated with the presence of transferable genes (Ruiz et al., 2005; Seward et al., 1998), and then with the potential to be horizontally disseminated (Seward et al., 1998). This finding highlights the need to preserve functional antibiotics to avoid the presence of untreatable infections. When the evolution was analyzed by the
hospital departments, an unexpected scenario was observed in which \textit{E. coli} isolates from the ICU showed a decrease in resistance levels and the prevalence of ESBLs in Period 2 towards values present in the Medicine and the Surgery Departments, then increasing again in Period 3. There is no clear explanation for this phenomenon, other than a possible increase in fluxes of microorganisms between different hospital departments resulting in the mix of bacterial populations, thus leading to increasing antimicrobial resistance levels in the Medicine and the Surgery Departments and an inverse phenomena in the ICU. While this scenario may favor a transient decrease of antimicrobial resistance in the ICU, over medium or long term it may lead to a rise in antimicrobial resistance in all hospital settings.

While their use is well established, the fact that two different automated methods were used during the time of the study may be considered as a limitation. Other limitations on the present study are the lack of data about patient outcomes and the uncertain role of CoNS as a cause of infection. Nevertheless, different reports have described a series of negative impacts of antibiotic resistance on patient outcomes, including the prolonged hospitalization, the expensive treatment costs as well as an effect on poor outcomes increasing (Cassini et al., 2019; CDC, 2019; Pons & Ruiz, 2019). Meanwhile, CoNS were classified as contaminants (Dargère et al., 2018), however a small fraction of them might act as a true infective agent (Quispe et al., 2020). In addition, no data on colistin resistance was available, with colistin being considered as the last resort treatment (Thomas et al., 2019). Finally, while antimicrobial resistance levels were established using the CLSI (2014) criteria, these breakpoints, except for ciprofloxacin, have not been modified (CLSI, 2021), thereby ciprofloxacin resistance might be underestimated as for current breakpoints.

In summary, high levels of resistance have been reported among \textit{E. coli}, with worrisome levels of ESBL. While the levels of cephalosporin resistance tended to increase, those from the ICU isolates showed a transient inverse trend, suggesting a reduction on the controlling measures between different departments, which favors a higher circulation of isolates between departments. A close control of antibiotics used together with a continuous and an active surveillance on the antibiotic resistance’s development is needed to preserve the activity of these antibiotics.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests to disclose.

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