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# Implications of the empirical use of antimicrobials against uropathogens resistance found in a military hospital in Rio de Janeiro

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## ABSTRACT
Bacterial resistance is a serious global public health problem, affecting different spheres of society, increasing hospital costs and reducing the patient's chances of cure, since antimicrobials are no longer effective in the treatment of infections caused by such bacteria. Over the years, uropathogens, agents that cause urinary tract infections, have shown increasingly high rates of resistance, making it increasingly necessary to determine the susceptibility profile of such microorganisms. From this, the present study aimed to verify the antimicrobial resistance profile of the main uropathogens found in a military hospital in Rio de Janeiro. For the preparation of this study, all ethical principles were obeyed, being approved by the Research Ethics Committee of the Pedro Ernesto University Hospital, of the State University of Rio de Janeiro, where 825 positive urine culture reports were used, collected between March 2018 and March 2020. Among the main uropathogens identified, Escherichia coli stood out, totaling 72.9% of cases, followed by Klebsiella pneumoniae (13%), Proteus mirabilis (5.7%) and Acinetobacter baumannii (2.09%). Such bacteria can also cause the so- called asymptomatic bacteriuria, whose treatment is empirical and based on broad-spectrum antibiotics. By analyzing the susceptibility profile of these microorganisms, it was possible to identify a trend towards the growth of strains resistant to fluoroquinolones and carbapenems. The development of protocols for the rational use of antimicrobials can be a step forward for evidence-based clinical management.

**Keywords:** Antimicrobials, Bacteriuria, Urinary tract disease, *Escherichia coli*.

## 1 INTRODUCTION

Affecting men and women of different ages, urinary tract infection (UTI) represents one of the most recurrent bacterial infections in humans, where about 150 million people are diagnosed annually, increasing public health costs by more than six billion dollars and contributing to more than thirteen thousand deaths annually (AKOACHERE *et al.,* 2012; MEDINA-POLO *et al.*, 2015; KHOSHNOOD *et al.*, 2017; Waller *et al.*, 2018; SINTSOVA *et al.*, 2019; LI *et al.*, 2022).

UTI can be aggravated by different factors, including the virulence of uropathogens, causing patients to present differentiated symptoms and, consequently, this infection becomes responsible for about seven million medical visits, which can reach the mark of one hundred thousand hospital admissions per year (KUMAR *et al.*, 2015; KÖVES; WULLT, 2016; MAZZARIOL *et al.*, 2017; Waller *et al.*, 2018; BAZZAZ *et al.*, 2021). This fact ends up inducing the exacerbated prescription of antibiotics, whose treatment is based on 15% of the existing antimicrobials (MAZZARIOL *et al.*, 2017; WALLER *et al.*, 2018).

In Brazil, urinary tract infections account for more than half of the cases evaluated (SANTOS *et al.*, 2018). It is estimated that urinary tract infections affect 50% of women at least once in their lives, and among them, about 20 to 30% have recurrent infections within 6 to 12 months (AKOACHERE *et al.*, 2012; VAHLENSIECK *et al.*, 2016; GUGLIETTA *et al.*, 2017; BAZZAZ *et al.*, 2021).

It should be noted that the main methodology for diagnosing a UTI is based on urine culture, where the analysis will depend on the type of infection, the patient's risk factors, and the severity of the infection (KOLMAN, 2019). Together with urine culture, whose diagnosis is quantitative and is based on the presence of bacteria in the urine through the count of colony-forming units (≥100,000 CFU/ml), the antimicrobial susceptibility test (TSA) is the most widely used analysis to identify the susceptibility profile of microorganisms to antibiotic therapy (KONEMAN *et al.*, 2018).

In addition to causing asymptomatic bacteriuria, *Escherichia coli* uropathogen (UPEC) is the main associated agent, corresponding to about 70 to 90% of cases, where at least half of the cases were acquired in a hospital environment (CORTESE *et al.,* 2018; RAMÍREZ-CASTILLO *et al.*, 2018; CAMPOS *et al.,* 2020; ZHANG *et al.*, 2020). However, other uropathogens can be identified, such as *Klebsiella pneumoniae, Proteus mirabilis, Citrobacter* spp., *Enterococcus faecalis*, *Staphylococcus saprophyticus*, *Enterobacter* spp., *Serratia* spp., *Providencia* spp., *Pseudomonas aeruginosa* e *Acinetobacter* spp. (RODRIGUES; BARROSO, 2011; MCLELLAN; HUNSTAD, 2016; OLIVEIRA; SANTOS, 2018; DONKOR *et al.,* 2019; CHOORAMANI *et al.*, 2020).

Even so, empiric antibiotic therapy continues to be the main treatment of patients affected by urinary tract infections (STEFANIUK *et al.*, 2016; CANTÓN *et al.*, 2019; BADER *et al.*, 2020). Even if the treatment aims to eradicate the bacterium in the urinary tract, the use of these drugs in an experimental way can lead to the so-called bacterial resistance, where uropathogens are no longer susceptible to the action of antibiotics, increasing the prevalence of multidrug-resistant microorganisms (STEFANIUK *et al.*, 2016; GOMILLA *et al.*, 2018; KRANZ *et al.*, 2018; MAJUMDER *et al.*, 2018; BADER *et al.*, 2020).

As it is a major concern for the future of global public health, the monitoring of resistant bacteria, as well as their susceptibility profile, becomes extremely relevant, especially in the control of infections and in the appropriate choice of antimicrobial therapy, thus aiming at the rational use of these drugs and a better quality of patient health care (BAIL *et al.*, 2017).

Therefore, this study aims to verify the main bacteria involved and the profile of resistance to antimicrobials, obtained through positive urine culture reports in a military hospital in Rio de Janeiro, from March 2018 to March 2020.

## 2 MATERIALS AND METHODS

### 2.1 FIELD OF STUDY

This is a retrospective, non-interventional study, carried out in a military hospital located in Campo dos Afonsos, Rio de Janeiro – RJ, called Hospital de Aeronáutica dos Afonsos (HAAF), whose time frame is from March 2018 to March 2020.

### 2.2 OBTAINING SAMPLES

The reports obtained were from outpatients and/or hospitalized at HAAF, referring to urine culture samples whose microbiological analyses were positive for the presence of urinary infection. For each sample, the following variables were recorded: origin, sex, age, origin and type of sample (urinary tract infection or bacteriuria), year of collection, etiologic agent, and antimicrobial susceptibility profile.

All microbiological procedures were performed by the team of the hospital's clinical analysis laboratory, within the bacteriology sector, where the sample processing did not exceed two hours since its collection, where seeding was performed using the depletion technique in transverse striations, using a disposable handle for each sample, in CLED and EMB medium.

The susceptibility test was performed from plate microdilution, using the NC66 panel for Gram-negative bacteria, with twenty-five antimicrobials, through the automated system Macroscan - WalkAway® SL (BECKMAN COULTER), following the standardization criteria of the Clinical and Laboratory Standards Institute (CLSI) (2018), where the strains were classified as resistant or sensitive. The antibiotics selected for analysis, as well as their respective classes and acronyms, can be found in Chart 1.

Table 1 – Antibiotics used in susceptibility testing

| ANTIMICROBIAL CLASS | DRUG | ACRONYM |
|---|---|---|
| Quinolones | - Nalixidic acid | (NAL) |
| Aminoglycoids | Amycin | (AMI) |
| Beta-lactamics | Amoxicilina/K Clavulanato | (AMC) |
| Beta-lactamics | Ampicilin | (AMP) |
| Beta-lactamics | Ampicilina/Sulbactam | (ASB) |
| Beta-lactamics | Aztreonam | (AZT) |
| Cephalosporin (1st Generation) | Cephalotin | (CFL) |
| Cephalosporin (4th Generation) | Cefepime | (CPE) |
| Cephalosporin (3rd Generation) | Cefotaxima | (CTX) |
| Cephalosporin (2nd Generation) | Cefoxitina | (CFO) |
| Cephalosporin (3rd Generation) | Ceftazidima | (CAZ) |
| Cephalosporin (2nd Generation) | Cefuroxime | (CXM) |
| Quinolones | Ciprofloxacin | (CIP) |
| Carbapenems | Early | (ERT) |
| Phosphonics | Phosphomycin | (FOS) |
| Aminoglycoids | Gentamicin | (GEN) |
| Carbapenems | Imipenem | (IPM) |
| Fluoroquinolones (3rd Generation) | Levofloxacin | (LVX) |
| Fluoroquinolones (2nd Generation) | Norfloxacina | (NOR) |
| Carbapenems | Meropenem | (MER) |
| Nitrofurans | Nitrofurantoin | (NIT) |
| Beta-lactamics | Piperacilina/Tazobactam | .PPT) |
| Glycylcyclines | Tigecycline | (TIG) |
| Aminoglycoids | Tobramycin | (TOB) |
| Sulfonamides | Trimethoprima/Sulfamethoxazol | (SXT) |

Source: Prepared by the authors (2023)

## 2.3 INCLUSION AND EXCLUSION CRITERIA FOR SAMPLES

To include the samples, reports from individuals aged 18 years or older, of both sexes, were selected, considering positive urine culture results for mid-stream urine samples or collected by bladder catheterization. In this case, the urine cultures were considered positive when there was bacterial growth greater than 100,000 colony-forming units per milliliter of urine (105 CFU/mL).

Regarding the antimicrobial susceptibility test, bacteria that showed intermediate sensitivity were considered resistant, where those that were resistant to third- and/or fourth-generation cephalosporins were considered beta-lactamase producers, while carbapenemase production was associated with bacteria that were resistant to any carbapenem tested.

However, patients under 18 years of age and/or who had duplicate exams, with the same etiologic agent and sensitivity profile were excluded from the analysis. Samples that showed growth of more than one microorganism and/or contaminants were also removed from the database for this study.

## 2.4 STATISTICAL ANALYSIS

Descriptive data, referring to the demographic information of the patients, as well as the susceptibility profile of the isolated pathogens, were compiled in a Microsoft Excel ® spreadsheet, which was graphically visualized using the Qlik Sense ® program (QlikTech International AB, Pennsylvania USA 1993-2020).

For the statistical analysis, we chose to perform a bivariate analysis for correlation between the demographic variables and the type of samples, using the STATA software version 14 (StataCorp.2015. Stata Statistical Softwere: Release 14. College Station, TX; StataCorp LP). The variables were compared using the chi-square test. Those with values lower than five were chosen to perform the Fischer test. Statistically significant proportions were those with p values lower than 0.05.

## 2.5 RESEARCH ETHICS COMMITTEE

For the elaboration of this study, all ethical principles were obeyed according to Resolution 466/12, of the National Health Council, and it was approved by the Research Ethics Committee of the Pedro Ernesto University Hospital – HUPE, State University of Rio de Janeiro – UERJ, by embodied opinion 3,963,096, on April 9, 2020.

# 3 RESULTS AND DISCUSSION

The present study totaled 4809 reports analyzed, where the incidence of positive urine culture was 17.1% (n=825), whose samples were mostly from patients females (78%, $p \leq 0.05$). Table 1 shows the main demographic characteristics identified, listing the samples divided into asymptomatic bacteriuria and UTI.

Table 1 - Demographic characteristics of positive urine cultures between March 2018 and March 2020.

| **Demographics** | **Total** | **(%)** | **Bacteriuria (%)** | **UTI (%)** | **p- Value** |
|---|---|---|---|---|---|
| Specimens with positive growth | 825 | 100,00 | 243 (29,45) | 582 (70,55) | ≤ 0,05 |
| Sex | | | | | |
| Female | 650 | 78,79 | 202 (24,48) | 448 (54,3) | ≤ 0,05 |
| Male | 175 | 21,21 | 41 (4,97) | 134 (16,24) | ≤ 0,05 |
| Origin | | | | | |
| Community | 639 | 77,45 | 231 (28) | 408 (49,45) | ≤ 0,05 |
| Hospital | 186 | 22,55 | 12 (1,45) | 174 (21,09) | ≤ 0,05 |
| Etiologic Agents | | | | | |
| *Acinetobacter spp* MS | 5 | 0,61 | 2 (0,24) | 3 (0,36) | 0,4 |
| *Acinetobacter spp* RC | 10 | 1,21 | 0 (0) | 10 (1,21) | ≤ 0,05 |
| *Coagulase-negative* Staphylococcus oxaR | 11 | 1,33 | 7 (0,85) | 4 (0,48) | 0,3 |
| *Coagulase-negative* Staphylococcus oxaS | 6 | 0,73 | 4 (0,48) | 2 (0,24) | 0,3 |
| Enterobacterias ESBL + | 94 | 11,39 | 22 (2,67) | 72 (8,73) | 0,06 |
| MS Enterobacteria | 551 | 66,79 | 167 (20,24) | 384 (46,55) | 0,6 |
| RC Enterobacteriaceae | 56 | 6,79 | 9 (1,09) | 47 (5,7) | ≤ 0,05 |
| *Enterococcus* sp. ampS | 22 | 2,67 | 13 (1,58) | 9 (1,09) | ≤ 0,05 |
| *Methicilin resistant* Staphylococcus aureus | 2 | 0,24 | 1 (0,12) | 1 (0,12) | 0,7 |
| *Staphylococcus aureus* sensivel a meticilina | 9 | 1,09 | 3 (0,36) | 6 (0,73) | 0,5 |
| *Pseudomonas aeruginosa* ESBL + | 6 | 0,73 | 0 (0) | 6 (0,73) | 0,06 |
| *Pseudomonas aeruginosa* MS | 28 | 3,39 | 6 (0,73) | 22 (2,67) | 0,5 |
| *Pseudomonas aeruginosa* RC | 16 | 1,94 | 2 (0,24) | 14 (1,7) | ≤ 0,05 |
| *Streptococcus* sp. | 9 | 1,09 | 7 (0,85) | 2 (0,24) | ≤ 0,05 |
| Resistance Profile of Gram Negative Bacilli | | | | | |

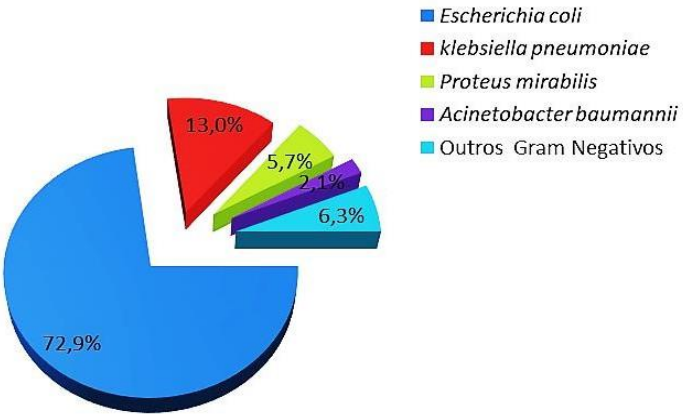
| | | | | | |
|---|---|---|---|---|---|
| ESBL+ | 100 | 12,12 | 22 (2,67) | 78 (9,45) | 0,1 |
| RC | 82 | 9,94 | 11 (1,33) | 71 (8,61) | ≤ 0,01 |

Subtitle: MS = Multisensitive; ESBL + = Extended-spectrum β-lactamase producer; CR = carbapenem-resistant.
Source: Prepared by the authors (2023).

Therefore, approximately 70.5% of the samples were identified as urinary tract infection (n=582) and 29.5% were considered bacteriuria (n=243). Regarding the origin of the samples, 639 were from the community, obtained in the outpatient setting (77.5%, $p \leq 0.05$), while only 186 samples (22.5%, $p \leq 0.05$) were of hospital origin. This study also corroborates what is highlighted in the literature, since 78.8% of the samples analyzed and with UTI were from female patients.

Regarding the identification of pathogens, the highest incidence was of Gram-negative bacteria (n= 766, 92.8%), which were found both in the community and in the hospital environment. The presence of enterobacteria stands out, representing about 91.5% of the identified cases (n=701), including strains of *Escherichia coli* (72.9%), *Klebsiella pneumoniae* (13%), *Proteus mirabilis (5.7%),* Acinetobacter baumannii *(2.1%) and other Gram-negative bacteria (6.3%), such as* Pseudomonas aeruginosa *(Figure 1).*

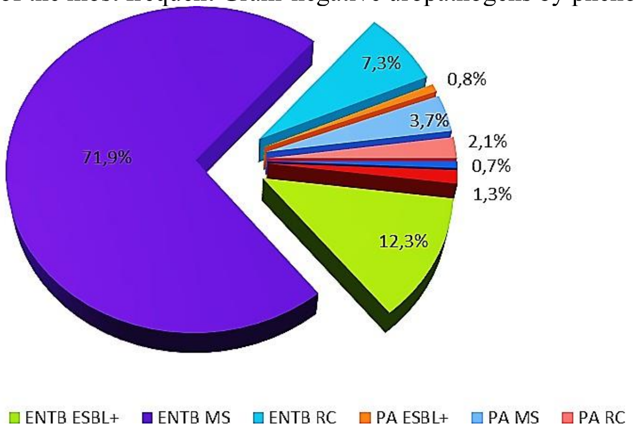
Figure 1 – Frequency of Gram-negative uropathogens isolated in the 766 samples.




Source: Prepared by the authors (2023).

Of these identified bacteria, about 384 isolates (71.9%) were considered multisensitive, i.e., sensitive to different classes of antimicrobials. However, although sensitive phenotypes were the majority, affecting patients for both bacteriuria and UTI, it is noteworthy that carbapenem-resistant bacteria producing extended-spectrum beta-lactamases were also found (Figure 2).

Figure 2 – Distribution of the most frequent Gram-negative uropathogens by phenotypes.

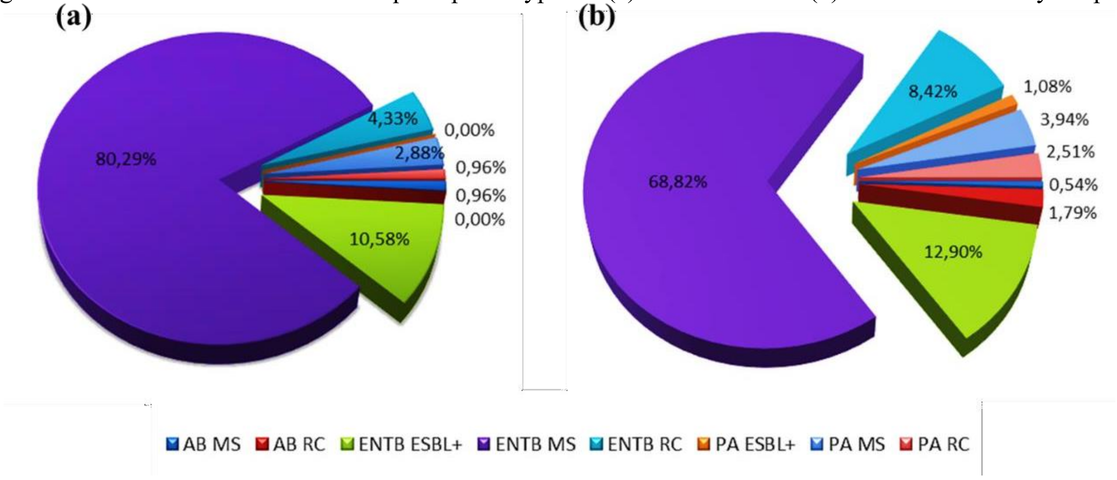



Legend: ENTB MS = Multisensitive Enterobacterium; ENTB ESBL + = Extended-spectrum β-lactamase-producing Enterobacterium; ENTB RC = Carbapenem-resistant enterobacterium; PA MS=Pseudomonas aeruginosa Multisensitive; PA RC= Carbapenem-resistant *Pseudomonas aeruginosa*; AB RC=carbapenem-resistant Acinetobacter baumannii. Source: Prepared by the authors (2023).

When analyzing the etiology of the causative agents of asymptomatic bacteriuria (n=208), as shown in Figure 3, we found 167 cases of multisensitive enterobacteriaceae (80.3%), 22 cases of extended-spectrum beta-lactamase-producing enterobacteriaceae (10.6%), 9 carbapenem-resistant enterobacteriaceae (4.3%), and 6 cases of multisensitive *Pseudomonas aeruginosa* (2.9%).

On the other hand, for patients affected by urinary tract infections (n=558, Figure 3b), 384 cases of multisensitive enterobacteriaceae (68.8%), 72 cases of extended-spectrum beta-lactamase-producing enterobacteriaceae (12.9%), 47 patients affected by carbapenem-resistant enterobacteriaceae (8.4%), 22 cases of multisensitive Pseudomonas aeruginosa *(3.9%), 14 cases of* Pseudomonas aeruginosa resistant to carbapenem (2.5%), 6 cases of *Pseudomonas* sp. ESBL positive *(1.1%), 10 cases of carbapenem-resistant Acinetobacter baumannii (1.8%) and 3 cases of* multisensitive Acinetobacter baumannii *(0.5%).*

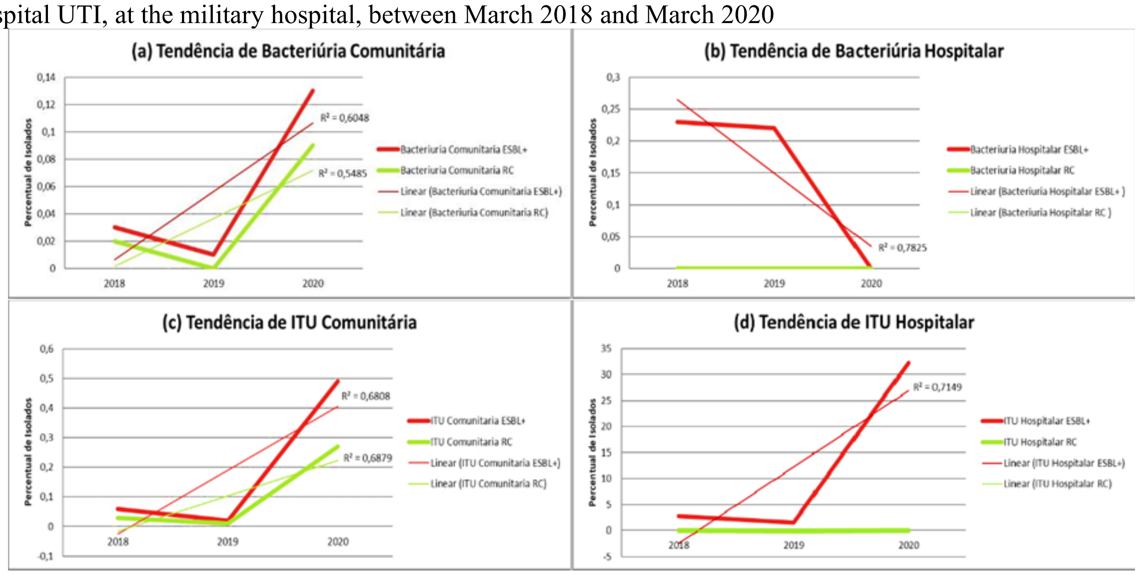
Figure 3 – Distribution of the most frequent phenotypes in (a) bacteriuria and (b) UTI of the military hospital




Legend: ENTB MS = Multisensitive Enterobacteriaceae; ENTB ESBL + = Extended-spectrum β-lactamase-producing enterobacterium; ENTB RC = Carbapenem-resistant enterobacterium; PA MS=Pseudomonas aeruginosa Multisensitive; PA RC= Carbapenem-resistant *Pseudomonas aeruginosa*; AB RC=carbapenem-resistant Acinetobacter baumannii. Source: Prepared by the authors (2023).

Based on these results, it is important to emphasize that the advance of bacterial resistance in the community served by the Hospital de Aeronáutica dos Afonsos (HAAF) demands attention, since there is a tendency for resistance to increase in cases of bacteriuria and UTI (Figure 4). Nevertheless, infections caused by resistant bacteria have a direct and negative impact on the patient's chances of cure, increasing not only hospital costs related to care, but also increasing morbidity and mortality rates (SILVA, 2023).

Figure 4 – Resistance trend of Gram-negative isolates in (a) Community BA, (b) Hospital BA, (c) Community UTI, and (d) Hospital UTI, at the military hospital, between March 2018 and March 2020




Legend: ESBL + = Extended-spectrum β-lactamase producer; UTI = Urinary tract infection; CR = carbapenem-resistant. Source: Prepared by the authors (2023).

The negative trend found for bacterial resistance in cases of nosocomial bacteriuria is justified by the closure of the hospital's inpatient and intensive care unit (ICU) units, since these sectors were under construction during the period from 2019 to 2020, thus constituting a limitation of the study.

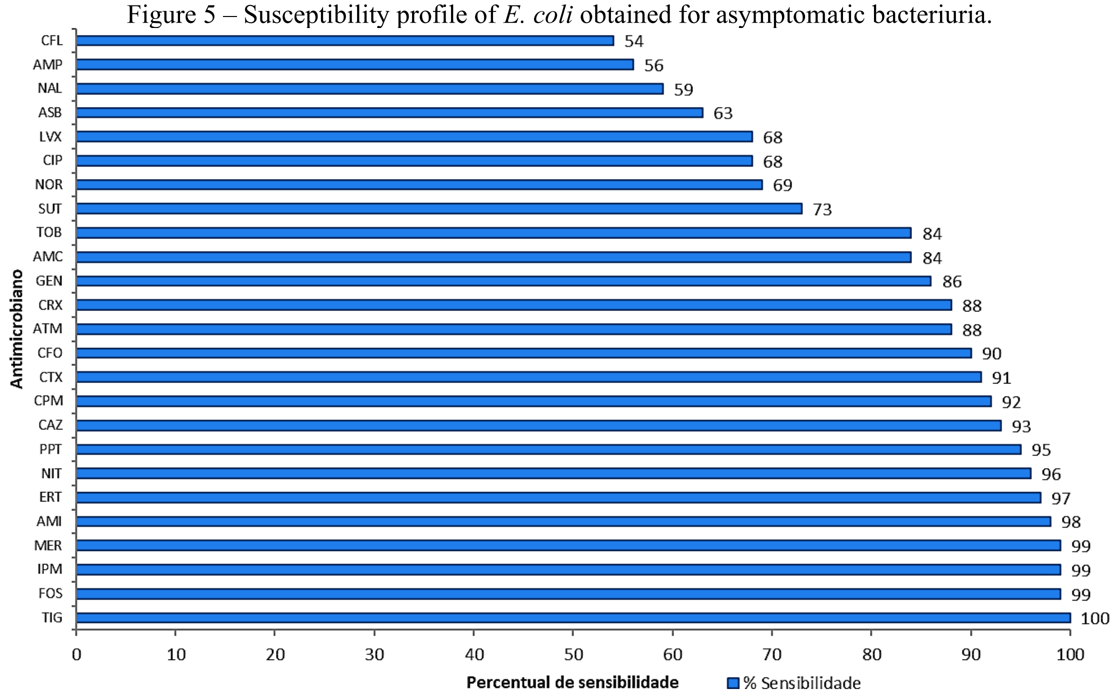
As mentioned above, *Escherichia coli* was the most present enterobacterium among the strains of isolates in the HAAF samples, corroborating what has been reported in the literature (MACHADO *et al.*, 2019; PEREIRA *et al.*, 2019; CHIBELEAN *et al.*, 2020; CHOORAMANI

*et al.*, 2020; TIGABU *et al.*, 2020). However, although E. coli usually has low pathogenicity, *it* has a great capacity to accumulate resistance genes, and is even able to spread this genetic information to other Gram-negative bacteria, facilitating its dissemination in susceptible populations (FARIA *et al.*, 2022).

In the present study, approximately 552 E. *coli samples were isolated, mainly from female patients (n= 452; 86.6%) whose age was over 60 years (n=349;* 66.8%). Furthermore, because it is a common enterobacterium of the intestinal microbiota of humans and animals (FARIAS *et al., 2022), uropathogenic* E. coli *(UPEC) is one of the main causes of UTI and asymptomatic bacteriuria, mainly caused by resistant strains, mainly ESBL-producing ones (CAMPOS* et al., *2020).*

It is also noteworthy that the empirical treatment of asymptomatic bacteriuria has been recognized as an important factor for the indiscriminate use of antimicrobials, which can result in the worsening of bacterial resistance through the selection of resistant strains (NICOLLE *et al.*, 2019; SILVA, 2023). However, among the E. *coli* isolates from BA samples, it was possible to observe a low resistance profile, being mostly multisensitive (Figure 5).

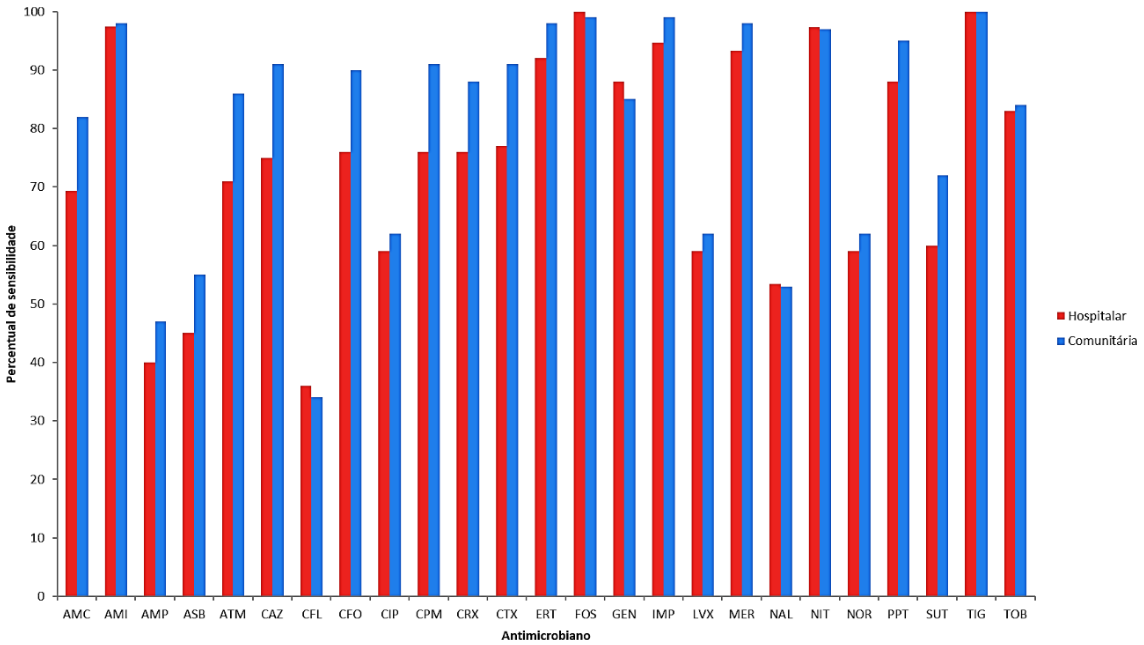
Figure 5 – Susceptibility profile of *E. coli* obtained for asymptomatic bacteriuria.




Legend: NAL = Nalidixic Acid; AMI = amikacin; AMC = Amoxilin/Clavulanate; AMP = Ampicillin/Sulbactam; AMP = Ampicillin; ATM = Aztreonam; CFL= Cephalothin; COM = Cefepime; CTX = Cefotaxime; CFO = Cefoxitin; CAZ = Ceftazidime; CRX = Cefuroxime; CIP = Ciprofloxacin; ERT = Ertapenem; FOS = Fosfomycin; GEN = Gentamicin; IPM = Imipenem; LVX = Levofloxacin; MER = Meropenem; NIT = Nitrofurantoin; NOR = Norfloxacin; PPT = Piperacillin/Tazobactam; TIG = Tigecycline; TOB = Tobramycin; SUT = Trimetroprim/Sulfamethoxazole. Source: Prepared by the authors (2023).

From this, it is noted that Nalidixic Acid (59%), Ampicillin (56%) and Cephalothin (54%) were the antimicrobials with the lowest sensitivity rates, and may be considered less effective when compared to the other drugs tested. In contrast, tigecycline (100%), fosfomycin (99%) and imipenem (99%) were the antimicrobials with the highest sensitivity rates, and therefore the most effective for the E. coli strains found in patients with asymptomatic bacteriuria.

Regarding the results obtained for UTI, Figure 6 shows the susceptibility profile of *E. coli* against different antimicrobials tested in HAAF, where drugs such as Tigecycline, Fosfomycin (99%), Imipenem (99%), Meropenem (99%), Amikacin (98%), Ertapenem and Nitrofurantoin (97%) presented the highest sensitivity rates Figure 6 – Sensitivity profile of *E. coli* obtained for Community and Hospital UTI.




Legend: NAL = Nalidixic Acid; AMI = amikacin; AMC = Amoxilin/Clavulanate; AMP = Ampicillin/Sulbactam; AMP = Ampicillin; ATM = Aztreonam; CFL= Cephalothin; COM = Cefepime; CTX = Cefotaxime; CFO = Cefoxitin; CAZ = Ceftazidime; CRX = Cefuroxime; CIP = Ciprofloxacin; ERT = Ertapenem; FOS = Fosfomycin; GEN = Gentamicin; IPM = Imipenem; LVX = Levofloxacin; MER = Meropenem; NIT = Nitrofurantoin; NOR = Norfloxacin; PPT = Piperacillin/Tazobactam; TIG = Tigecycline; TOB = Tobramycin; SUT = Trimetroprim/Sulfamethoxazole. Source: Prepared by the authors (2023).

When comparing the results obtained for the community samples with the hospital samples, there is a reduction in the efficacy of the treatment in cases of nosocomial UTI for most of the antimicrobials tested, which corroborates the majority presence of positive (18.6%) and carbapenem-resistant (9.3%) ESBL strains in hospitals, while for community samples, Only 8.8% of ESBL-positive isolates and 3.7% of carbapenem-resistant isolates were found.

Finally, the present study highlights the importance of knowing how to discriminate cases of asymptomatic bacteriuria from urinary tract infections, in order to favor advances in clinical management, aiming at the rational use of antimicrobials and, consequently, minimize their impact on bacterial resistance. In addition, it is necessary to develop an up-to-date information network, whose data on antimicrobial resistance patterns will allow an increasingly effective and evidence-based therapeutic decision.

## 4 FINAL THOUGHTS

Based on everything described and presented in this article, it is extremely important to differentiate cases of asymptomatic bacteriuria from urinary tract infections, since it was possible to identify the advance of antimicrobial resistance, where uropathogens spread They were mainly resistant to treatment based on fluoroquinolones and carbapenems, broad-spectrum antibiotics that are used empirically in cases of asymptomatic bacteriuria. This scenario evidences, therefore, the attention of the medical community regarding its exacerbated and indiscriminate prescription, where antimicrobial management and management programs can help reduce the impact of bacterial resistance in the long term. Finally, the authors emphasize the need for the development of an information network, whose data regarding antimicrobial resistance patterns are constantly updated, favoring evidence-based decision-making.

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