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Original Article

Antimicrobial Resistance Profiles of Bacterial Isolates in Patients with Urinary Tract Infections in a Reference Center in Bucaramanga

Perfil de resistencia antimicrobiana de aislamientos bacterianos en pacientes con infección urinaria de un centro de referencia en Bucaramanga

Perfil de resistência antimicrobiana de isulados bacterianos em pacientes com infecção urinária de um centro de referência em Bucaramanga

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ABSTRACT

Introduction. Among the bacterial infections that affect human beings, urinary tract infections are one of the most common, affecting up to 150 million people

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worldwide each year. Indiscriminate use of antibiotics and their improper handling has generated an increase in microbial resistance. This study's objective is to describe the phenotypic patterns of antimicrobial resistance of the most frequent microorganisms in patients with urinary tract infection diagnoses in a reference center in Bucaramanga. **Methodology.** A cross-sectional study with non probability sampling on patients with suspected or diagnosed urinary tract infections who required hospital treatment at a high-complexity health institution during July, 2017 and April, 2018, from whom urine cultures and antibiograms were obtained. **Results.** Out of 120 patients, a report was obtained for 116 urine cultures. The most frequent microorganism was Escherichia coli, followed by Klebsiella pneumoniae. The former presented high sensitivity to carbapenem antibiotics and aminoglycosides and low sensitivity to Ceftriaxone and Ampicillin/Sulbactam. On the other hand, the microorganism Klebsiella pneumoniae presented high sensitivity to carbapenem antibiotics, but elevated resistance to Ceftriaxone and Ampicillin/Sulbactam. The empiric antibiotic used most was Ceftriaxone. **Discussion.** The distribution of isolated microorganisms is comparable to that which has been described nationally and internationally. Antimicrobial resistance profiles have points in common, such as resistance to beta-lactams, but differ in some aspects, such as resistance to cephalosporins and quinolones. **Conclusions.** Isolated microorganisms present high rates of resistance to beta-lactams and cephalosporins, which are widely used. This information must guide developing protocols that allow optimizing clinical decision-making with respect to antibiotic therapy.

Keywords:
Urinary tract infections; Bacterial infection; Antimicrobials; Antimicrobial resistance; Microbial Sensitivity Tests.

RESUMEN

Introducción. Dentro de las infecciones bacterianas que afectan al ser humano, la infección de las vías urinarias es una de las más frecuentes, afectando hasta Perfil de resistencia antimicrobiana de aislamientos bacterianos en pacientes con infección urinaria de un centro de referencia en Bucaramanga 406 150 millones de personas en el mundo cada año. El uso indiscriminado de antibióticos y su manejo inadecuado han generado un aumento en la resistencia antimicrobiana. El objetivo del presente estudio es describir patrones fenotípicos de resistencia antimicrobiana de los microorganismos más frecuentes en pacientes con diagnóstico de infección de vías urinarias en centro de referencia de Bucaramanga. **Metodología.** Estudio de corte transversal, muestreo no probabilístico en pacientes con sospecha o diagnóstico de infecciones de vías urinarias que requirieron manejo intrahospitalario en una institución de salud de alta complejidad durante julio del 2017 y abril del 2018, de quienes se obtuvo urocultivo y antibiograma. **Resultados.** De 120 pacientes incluidos, se obtuvo un reporte de 116 urocultivos. El microorganismo más frecuente fue Escherichia coli, seguido de Klebsiella pneumoniae. El primero presentó alta sensibilidad a carbapenémicos y aminoglucósidos, baja sensibilidad a la Ceftriaxona y a la Ampicilina/Sulbactam. Por otro lado, el microorganismo Klebsiella pneumoniae presentó alta sensibilidad a carbapenémicos, pero resistencia elevada a la Ampicilina/Sulbactam y a la Ceftriaxona. El antibiótico empírico más utilizado fue la Ceftriaxona. **Discusión.** La distribución de microorganismos aislados es comparable con la ya descrita a nivel nacional e internacional. Los perfiles de resistencia antimicrobiana tienen puntos comunes como la resistencia a los betalactámicos, pero difieren en algunos aspectos, como la resistencia a cefalosporinas y quinolonas. **Conclusiones.** Los microorganismos aislados presentan altas tasas de resistencia a los betalactámicos y a las cefalosporinas, las cuales son ampliamente utilizadas. Esta información debe orientar el desarrollo de protocolos que permitan optimizar la toma de decisiones clínicas con respecto a la terapia antibiótica.

Palabras clave:
Infecciones urinarias; Infecciones bacterianas; Antimicrobianos; Resistencia antimicrobiana; Pruebas de sensibilidad microbiana. Palabras clave: Infecciones urinarias; Infecciones bacterianas; Antimicrobianos; Resistencia antimicrobiana; Pruebas de sensibilidad microbiana.

RESUMO

Introdução. Dentre as infecções bacterianas que afetam o homem, a infecção do trato urinário é uma das mais frequentes, afetando até 150 milhões de pessoas no mundo a cada ano. O uso indiscriminado de antibióticos e seu manejo inadequado têm gerado aumento da resistência antimicrobiana. O objetivo deste estudo é descrever padrões fenotípicos de resistência antimicrobiana dos microrganismos mais frequentes em pacientes com diagnóstico de infecção do trato urinário em um centro de referência em

Bucaramanga. Métodos. Estudo transversal, com amostra não probabilística, em pacientes com suspeita ou diagnóstico de ITU que precisaram de manejo intra-hospitalar em uma instituição de saúde de alta complexidade no período de julho de 2017 a abril de 2018. Foram obtidos urocultura e antibiograma desses pacientes. Resultados. De 120 pacientes incluídos, foi obtido um relatório de 116 uroculturas. O microrganismo mais frequente foi Escherichia coli, seguido por Klebsiella pneumoniae. O primeiro apresentou alta sensibilidade a carbapenêmicos e aminoglicosídeos e baixa sensibilidade a Ceftriaxona e a Ampicilina/Sulbactam. Por outro lado, o microrganismo Klebsiella pneumoniae apresentou alta sensibilidade a carbapenêmicos, mas alta resistência a Ampicilina/Sulbactam e a Ceftriaxona. O antibiótico empírico mais amplamente utilizado foi a Ceftriaxona. Discussão. A distribuição dos microrganismos isolados é comparável àquela já descrita a nível nacional e internacional. Os perfis de resistência antimicrobiana têm pontos comuns como resistência aos beta-lactâmicos, mas diferem em alguns aspectos, como resistência às cefalosporinas e quinolonas. Conclusão. Microrganismos isolados apresentam altas taxas de resistência aos beta-lactâmicos e cefalosporinas, que são amplamente utilizados. Esta informação deve nortear o desenvolvimento de protocolos que permitam otimizar a tomada de decisão clínica em relação à antibioticoterapia.

Palavras-chave:
Infecções urinárias; Infecções bacterianas; Anti-infecciosos; Resistência antimicrobiana; Testes de sensibilidade microbiana.

Introduction

Urinary tract infections (UTI) comprise a set of clinical entities that are common in both outpatient and hospital scenarios (1). They are currently among the most frequent infections, affecting up to 150 million people worldwide every year (2). It has been estimated that between 40% and 50% of women will have a urinary tract infection episode in their lifetime, while infection reports in men are lower, at 12%, with positive cultures of only 5% in this population (3,4). UTIs can clinically manifest themselves as Cystitis (bladder infection) or Pyelonephritis (kidney infection), and the most frequently involved microorganism is uropathogenic *Escherichia coli*. It is responsible for 75% to 95% of UTIs, followed by *Klebsiella pneumoniae* (2,5). In Colombia, various local studies and epidemiological oversight reports have sought to establish the prevalence and populational risk factors, characterization of isolated microorganisms and approximation of their resistance and sensitivity profiles, observing a prevalence of *Escherichia coli and Klebsiella pneumoniae* (6-12). E. coli was the number one infectious agent causing UTI nationally. This was determined in a study that included over 30,000 urine cultures (13).

An increasing problem is the rising antimicrobial resistance, which has reduced empiric therapy options (5). This is due to various factors, such as irrational use of antibiotics and a lack of adherence to therapy (14). These factors represent a high risk of therapeutic failure, especially in patients susceptible to acquiring these germs, such as people with a chronic kidney disease, previous antibiotic use, recent hospitalization, pyelonephritis or diabetes (15). Antimicrobial resistance in UTIs has increased, and it varies greatly depending on each region (16). However, global, national and local resistance trends to traditionally used antibiotics, such as Ampicillin, Cyprofloxacin or Trimethoprim-Sulfamethoxazole, have made urinary infections a challenge to health-care personnel (13,17) in both the general population and different groups of patients. This is the case for people diagnosed with diabetes *mellitus*, in which a high prevalence of the strains that produce extended-spectrum beta-lactamases and carbapenemases (18). This is also the case for pregnant patients, in whom enterobacteriaceae resistant to third-generation cephalosporins has been reported (19).

The increase in antimicrobial resistance rates is a health-care problem, since it could compromise the effectiveness of empiric therapy and increase rates of recurrence, hospital stay and death (7,8). Therefore, identifying and updating local resistance profiles is necessary to optimize antimicrobial therapy.

Information on these profiles in Bucaramanga is scarce, reason why this study is proposed in order to describe the resistance patterns to antibiotics of isolated microorganisms in patients diagnosed with a urinary tract infection in a reference center in the city.

Methodology

A cross-sectional study was performed based on an analytical, longitudinal study, in which all patients of legal age attended by the emergency room with suspected or diagnosed urinary tract infections, who required hospital attention at a high-complexity health-

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care institution during the period between July, 2017 and April, 2018, were included by means of non-probability sampling by convenience. Patients at a very early stage of development and the pediatric population were excluded.

A form prepared by the research team with the support of professionals with experience in infectious diseases was designed to collect information. This form was completed by a trained interviewer based on direct patient interviews and a subsequent review of their clinical history. In addition to sociodemographic data, records, clinical presentations and paraclinical results of blood samples, this form included the urine culture report and its respective antibiogram with a sensitivity report, when it was available.

Antibiograms were processed through an automated method with Vitek 2XL devices from trading house Biomerieux, with Minimum Inhibitory Concentration (MIC) cut-off points according to the CLSI standard. Sensitive, Intermediate and Resistant categories were taken into account for the descriptive analysis.

A database for processing data was developed on Excel based on information stated in the physical patient recruitment form. The information was recorded by two trained medical students in two independent files. It was then verified by one of the researchers to consolidate a single document.

A univariate analysis was performed for the statistical analysis. Qualitative variables were described by frequencies with their respective percentage and proportions, while quantitative variables were described with central tendency measures, in accordance with the sample's distribution.

This study was approved by the Ethics Committee of Universidad Autónoma de Bucaramanga and Fundación Oftalmológica de Santander Clínica Carlos Ardila Lulle (FOSCAL), and was performed taking into account the Declaration of Helsinki and Resolution 8430 of 1993, according to which the study is research without risk, since laboratory records were obtained from medical records. In addition, each patient provided written informed consent.

Results

One hundred and twenty patients diagnosed with UTI, who were attended at the institution's emergency room, were included. The group had an average age of 65 and was predominantly female. Of these patients, most had histories of urinary tract infections, and the most frequent systemic comorbidity was high blood pressure, among others, such as diabetes *mellitus* and chronic kidney disease. The demographic and clinical characteristics are described in table 1.

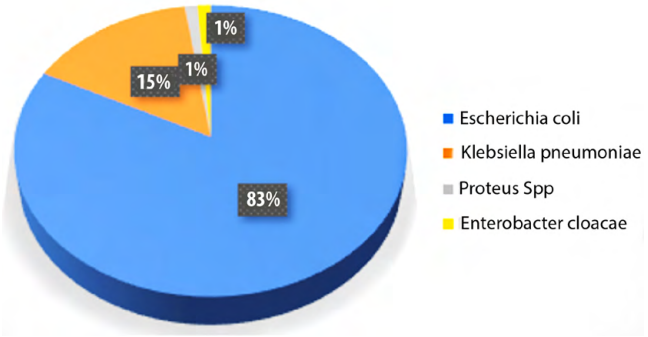
Table 1. Demographic and clinical characteristics of the studied population

Population Characteristics	Number (%)	CI (95%)
Gender		
Male	47 (39.17%)	30.74-48.28
Female	73 (60.83%)	51.71-69.25
Previous UTI	68 (57.14%)	47.98-65.83
Previous antimicrobial use	51 (42.86%)	34.16-52.01
Associated comorbidities		
Diabetes mellitus	34 (28.81%)	(21.26-37.74)
Chronic kidney disease	22 (18.64%)	12.52-26.83
High blood pressure	58 (49.15%)	40.12-58.23
Oncological disease	17 (14.53%)	9.16-22.26

Source: prepared by author

Out of the entire group, antibiograms were not taken for 4 patients because their UTI was not complicated. During hospital stay, a report on 116 urine cultures was obtained, of which 95 were positive (81.90%). The most frequently isolated microorganism was *Escherichia coli* (n = 79), followed by *Klebsiella pneumoniae* (n = 14). A minimal percentage of *Proteus spp and de Enterobacter cloacae* were also isolated (figure 1).

Figure 1. Isolated microorganisms during the hospital stay of patients with urinary tract infection.



Source: prepared by author

Table 2 shows the medications introduced in the emergency room. The antibiotic medication used most was Ceftriaxone, present in 68.4% of cases, followed by Ertapenem, with an 8.6% frequency.

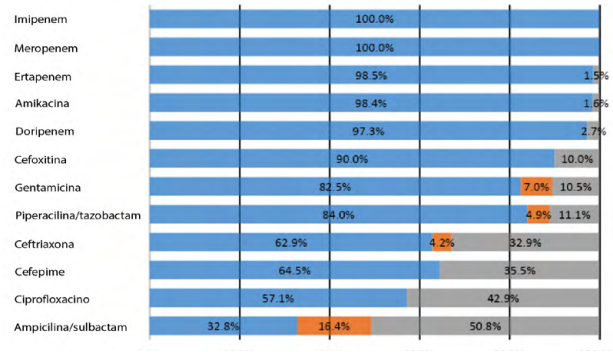
Table 2. Empiric therapy with antibiotics.

Started empiric therapy with antibiotics	n: 116 (%)	CI
Ceftriaxone	79 (68.1%)	(58.95-76.03)
Piperacillin-Tazobactam	7 (6%)	(2.87-12.24)
Meropenem	4 (3.4%)	(1.28-8.94)
Amikacin	3 (2.5%)	(0.82-7.83)
Ciprofloxacin	2 (1.7%)	(0.42-6.76)
Cefoxitin	2 (1.7%)	(0.42-6.76)
Cefazolin	2 (1.7%)	(0.42-6.76)
Ertapenem	10 (8.6%)	(4.65-15.41)
Gentamicin	1 (0.8%)	(0.11-6.02)
Cefotetan	1 (0.8%)	(0.11-6.02)
Cefepime	1 (0.8%)	(0.11-6.02)
Cefalotin	1 (0.8%)	(0.11-6.02)
Ampicillin	1 (0.8%)	(0.11-6.02)
Ampicilina	1 (0.8%)	(0.11-6.02)

Source: prepared by author

Moreover, the antimicrobial susceptibility profiles of the most frequently observed germs were analyzed. Figure 2 shows the antimicrobial resistance profile of *Escherichia coli,* and antibiotics are regrouped, filtered into three categories: Sensitive, Intermediate and Resistant. It was observed that the group of carbapenem antibiotics had the highest sensitivity profile, with a resistance of under 5%, highlighting Imipenem, in which no resistance was recorded. On the other hand, the antibiotic to which the most resistance was observed was Ampicillin-Sulbactam. Fifty point eight percent of microorganisms were resistant, and 16.4% of them had intermediate sensitivity.

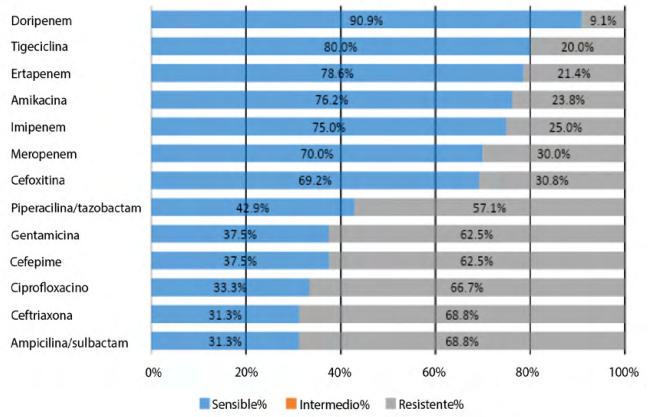
Figure 2. *Escherichia coli's* sensitivity profile to antimicrobials in microbiological isolates of patients with urinary tract infections



Source: prepared by author

On its part, figure 3 shows the antibiotic resistance profile of the second most frequent germ, *Klebsiella pneumoniae.* The antibiotic with the best profile was observed to be Doripenem, with a sensitivity of 90.9% (n = 13). In contrast, two antibiotics were found with the highest antimicrobial resistance - Ampicillin/ Sulbactam and Ceftriaxone, with a 68.8% resistance. No antibiogram reports with intermediate sensitivity to any medication were recorded for this microorganism.

Figure 3. *Klebsiella pneumoniae's* sensitivity profile to antimicrobials in urinary tract infections



Source: prepared by author

Discussion

This study was proposed in order to make a first approximation of the phenotypic antimicrobial resistance patterns of microorganisms isolated most frequently in patients with UTI diagnoses at a reference center in the city of Bucaramanga. Thus, with respect to isolated microorganisms, this work observed a distribution similar to that which was reported previously by numerous international studies, which observed that the most prevalent germ is *Escherichia coli,* followed by species of *Klebsiella,* within which the most frequent is *Klebsiella pneumoniae* (20-22). In the same way, this microorganism distribution has been reported in various national studies (23-25). The work developed by Pardo *et al*. (13) is especially relevant, who followed up on over 30 thousand patients for 5 years and reported an E coli prevalence of 70% and a *K. pneumoniae* prevalence of 10%.

On their part, in a study performed in Cartagena, the main etiologic agents were: E. coli (46.7%), *E. coli* (BLEE) (17.9%) and *Pseudomona aeruginosa* (10.85%), associated with populations in highly vulnerable conditions (11). Another study in Bogotá reported isolation of E. coli (62.58%), *Enterococcus*

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faecalis (12.33%), Proteus spp. (8.74%) and Klebsiella pneumoniae (6.83%) (10).

The following facts stand out from the above: that gram-negative bacteria continue leading characters in urinary tract infections and *Klebsiella pneumoniae* has become important due to its rising prevalence as an etiologic agent, as reported in the work by Pardo *et al.*, which shows how *Proteus* species has yielded second place (13). This must be taken into account when selecting empiric therapy. Despite the above, it is worth highlighting that empiric therapy is mainly based on *Escherichia coli's* sensitivity profile in recent treatment protocols (26,27).

With respect to the phenotypic resistance patterns of the most frequent microorganisms, when it comes to *E. coli,* this study highlights high sensitivity to carbapenems and aminoglycosides. However, it is important to clarify that these antibiotics are not the first choice due to their broad spectrums of action, which can lead to selective pressure and greater resistance, especially in the case of carbapenems (26-29), as well as aminoglycoside safety profiles, which must be used cautiously on patients with kidney disease. Use should be reserved for non-critical, simple UTIs (28-30).

The findings above are similar to those reported in other work: in a prospective, multicentric international study in which women with uncomplicated UTIs were included, *E. coli* demonstrated a low sensitivity to Ampicillin (48.3%), Trimethoprim/Sulfamethoxazole (29.4%) and nalidixic acid (18.6%), while other medications, such as Cefuroxime and Ciprofloxacin, with resistances lower than 10%, were most active against isolated strains (31). They also correspond to that which was reported in a literature review that summarizes the epidemiologic evidence of UTIs. For *E. coli's* resistance profile between 2003 and 2006, it found that Ampicillin obtained the highest rate of resistance, surpassing 60% in most reports (32). In addition, in a cross-sectional study performed in 2 hospitals in 2014, it was observed that *E. coli's* sensitivity to Ampicillin-Sulbactam decreased, with a sensitivity of 47%. The fact that the highest antibiotic sensitivity was to Meropenem, at 87%, followed by Piperacillin/Tazobactam, at 83% (33), stands out, with the caveat, once again, that these antibiotics must be reserved for critically ill patients. They are not first-line antibiotics according to most scientific positions (26,28). In the case of Colombia, *E. coli* has been recorded to show close to 38% resistance to Ceftriaxone, 75% to Ampicillin, and 95% to Amoxicillin/Clavulanate in general hospitalization halls in Bogotá, Antioquia and Valle del Cauca (12). Resistances of 54% to Ampicillin, 39% to Trimethoprim-Sulfamethoxazole and 28% to Ciprofloxacin have also been recorded (13). This distribution is similar to this study's reports.

For *Klebsiella pneumoniae*, this study demonstrated that the highest sensitivity was recorded for carbapenems, while other commonly used antibiotics, such as Ampicillin/Sulbactam and Ceftriaxone showed elevated resistances. This resistance profile is comparable to that which was reported in a Chinese study, where *K. penumoniae* demonstrated a greater resistance to Cefazolin (35.1%) and Ampicillin/Sulbactam (32.6%), and lower resistance to Ertapenem (2.7%) (34). Another study performed in Morocco reported K. pneumoniae isolation in 22% of urine samples, with a 61% resistance to Trimethoprim-Sulfamethoxazole, followed by Amoxicillin/Clavulanate, with a 51% rate (35).

On a national level, it was observed that this germ's highest resistance was to Ampicillin, with a resistance of up to 85%, followed by Ampicillin/Sulbactam (up to 43%) and Ceftriaxone, with a resistance of around 30%, with low resistance to Ciprofloxacin (12,13), which is also similar to this study. It is worth highlighting that high local resistance to Ciprofloxacin was identified here, which is related to the previously mentioned studies and reinforces the trend of avoiding using quinolones empirically.

With this in mind, the high rate of resistance to beta-lactam antibiotics, even associated with beta-lactamase inhibitors, is not surprising. There were high rates of resistance to Ceftriaxone in the institution (35.5% for E. coli, 68.8% for beta-lactams). This, added to the high rate at which this antimicrobial is empirically prescribed, invites those in charge of designing institutional protocols to reconsider using third-generation cephalosporins as empiric therapy in patients with urinary tract infections.

Lastly, this work observed that almost half of all patients had received previous antibiotic therapy, which reflects an excessive use of antimicrobials. This increases the problem of resistance, which is more frequent in low and middle-income countries in which UTIs are one of the main causes of self-medication with antibiotics (36,37). The general community is called to avoid self-medication, and the medical community is called to have better prescription guidelines.

Some of this work's limitations include a relatively low sample size compared to other studies, as well as convenience sampling, which limits the sample's representativity and the study's replicability.

Finally, resistance rates to antibiotic markers allow concluding a low prevalence of *E. coli* strains that produce broad spectrum beta-lactamases, as well as a high prevalence of *K. pneumoniae* with this resistance profile. However, the limitation to characterizing this population of microorganisms better is recognized, since this information was not differentiated in the data registry forms.

Conclusions

The most frequently isolated microorganisms were E. coli and *K. peumoniae,* which present a high resistance to beta-lactamsm intermediate resistance to third-generation cephalosporins and low resistance to aminoglycosides and carbapenems.

Therefore, it is important to perform studies based on these results with a larger sample selected by non-probability sampling, including patients with various infectious pathologies in order to define institutional protocols adjusted to local resistance profiles, in addition to developing health-care education strategies that allow addressing this issue with a more comprehensive approach.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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