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Antibiotic Resistance in the Uropathogenic Enterobacteria Isolated from Patients Attending General Reference Hospital (GRH) of Niamey, Niger

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Abstract

Background: Urinary tract infections (UTIs) are a frequent reason for consultation and lead to a significant and sometimes inappropriate prescription of antibiotics. The latter favors antibiotic resistance and an increase in mortality as well as the cost of treatment. The present study aims to contribute to the fight against antibiotic resistance of enterobacteria. **Methods:** This is a prospective study from January to December, 2021 in the Microbiology laboratory of the General Reference Hospital (GRH) of Niamey including 3369 urine samples. The antibiotic resistance of enterobacteria was determined using the Viteck-2 method. **Results:** At least 280 strains of *Enterobacteriaceae* were isolated from the patient's urine. Among these strains, *Escherichia coli* was the most predominant (74.64%), followed by *Klebsiella pneumoniae* (16.07%) and *Enterobacter cloacae* (7.14%) and other enterobacteria 2.15%. These *Enterobacteriaceae* are more common in community patients than in hospitalized patients. The average age of patients is 52 years and the age group most affected by these enterobacteria is 46 - 60 years (23.33%). The female sex is the most affected sex with (51.07%) against (48.97%) for the male sex with 1.04 as sex ratio. The hospitalization departments most affected by these enterobacteria are Nephrology (29.23%) and Endocrinology (21.54%). Up to 75% of the *Enterobacteriaceae* isolates show high resistance to ampicillin, amoxicillin-clavulanic acid, ticarcillin, piperacillin-tazobactam, cefoxitin, cefixime, ceftazidime, ceftriaxone, cotrimoxazole, nalidixic acid and ofloxacin. **Conclusion**: The high rate of antibiotic resistance among enterobacteria in urine is of concern. Only a few *Enterobacteriaceae* show low resistance to ertapenem, imipenem, amikacin, gentamicin, fosfomycin and nitrofurantoin. Therefore, these antibiotics are recommended as first line treatment for urinary tract infections.

Keywords

Antibiotic Resistance, Urinary Tract Infections, *Enterobacteriaceae*, Viteck-2, Niger

1. Introduction

Urinary tract infections (UIs) are the most common bacterial infections that pose a significant burden on public health [1] [2] [3]. These infections are due to the presence of a pathogenic bacterium within the patient's urinary tract [4]. UIs are common in both hospital and community settings [5] [6] [7] and affect all age groups (children, adults, and the elderly), with women as the predominant group [3] [7] [8]. UTIs are mainly caused by *Enterobacteriaceae* [9] among which *Escherichia coli* is the main causative agent in both infants and adults [10] [11] [12]. *Enterobacteriaceae* urinary tract infections are a frequent reason for consultation and lead to significant and sometimes inappropriate prescriptions of antibiotics [13] [14]. This high consumption of antibiotics favors the emergence of multi-resistant strains of enterobacteria [15] [16]. The spread of resistant *Enterobacteriaceae* may cause economic burden for governments as it will raise health care costs through longer hospital stays, and increase morbidity and mortality among populations [17] [18] [19] [20]. Nowadays, antibiotic resistance is one of the most serious threats to global health. In fact, new resistance mechanisms emerge and spread globally, compromising our ability to treat the most common infectious diseases [21] [22]. Moreover, since *Escherichia coli* accounts for up to 80% of community-acquired uncomplicated UTIs, these bacteria should be targeted when choosing empirical antibiotics [21].

In Africa, particularly in Niger, the resistance of uropathogenic enterobacteria to antibiotics has become a global problem that needs attention and immediate management by using other methods than empirical therapy [23]. Of course, making the diagnosis of urinary tract infection (UTI) and deciding when to initiate antimicrobial therapy remains a challenge to healthcare providers [2]. The aim of this study was to isolate and determine the antibiotic resistance profile of uropathogenic enterobacteria isolates using the Vitek-2 method.

2. Material and Methods

2.1. The Site, Period, and Type of Study

This was a prospective study of the descriptive type carried out in the Microbiology department of the medical biology laboratory of the General Reference Hospital (GRH) of Niamey, Niger. The study covered the period from January to December 2021 (one year).

2.2. Inclusion and Non-Inclusion Criteria

Patients who came to the GRH for a cytobacteriological examination of urine (ECBU), without distinction of sex and age, constituted the targeted population. Any patient with a well-informed report and urine samples under the conditions indicated for an ECBU was taken into account, and any patient whose urine samples were not under these conditions or who brought a sample of urine for a study other than the cytobacteriological study was excluded from the study.

2.3. Data Gathering

We performed accidental non probability sampling based on the arrival of urine samples in the microbiology unit (non probability sampling for convenience). A total of 3369 urines were sampled. The patient's age, gender, and examination results were the main information gathered for this study. Data collection was done on sheets using the laboratory register.

2.4. Cytobacteriological Examination of Urine

The macroscopic appearance of the non-centrifuged urine was first assessed. Then is the examination of fresh urine after centrifugation (microscopic examination). The total urine was homogenized and poured into a hemolysis tube, which was placed in a centrifuge programmed at 3000 rpm for 5 minutes and then centrifuged. At the end of the centrifugation, the supernatant was separated from the pellet and the centrifugation pellet was observed between a slide and a coverslip, under a microscope at X10 and then at X40 in order to look for the figurative elements in the urine. Gram staining was used and made it possible to account for the morphology of the bacteria and their tinctorial affinity.

The urines were inoculated onto non-selective agar media (Cystine-Lactose Electrolyte Deficient (Himedia, India) and onto non-selective agar media UriSelect 4 (Bio-Rad, USA). The latter were incubated in an oven at 37˚C for 24 hours to have bacterial growths and to do the identification and antibiogram on Viteck-2 Compact.

Identification and antimicrobial susceptibility testing

The GN cards of Vitec-2 Compact were used to identify the species of *Enterobacteriaceae* according to the data and knowledge on the germ and the reactions being analyzed on Vitek-2 Compact. First, a bacterial suspension of density

0.5 - 0.63 McFarland (Densicheck plus) was prepared in a first test tube labeled ID containing 3 mL of saline solution (NaCl 0.45%). After thoroughly homogenizing this bacterial suspension, 145 µL was then taken and introduced into a second test tube labeled AST also containing 3 mL of saline solution. An ID card for the identification of Gram-negative *bacilli* was then inserted into the first test tube labeled ID and another AST N-372 card for the antibiotic susceptibility test was placed in the second test tube labeled AST. Instructions were finally followed to load the vitek-2 cards and run the test on the instrument.

A bacterial suspension (0.5 - 0.63 McFarland, Densicheck plus) was used to test the sensitivity and resistance to antibiotics by the vitek-2 system (bioMerieux). The AST N-372 card contains 16 antibiotics that were tested the antibiotic sensitivity and resistance tests on the *Enterobacteriaceae* strains: Ampicillin (4, 8, 32 µg), amoxicillin-clavulanic acid (4/2, 8/2, 32/2 µg), ticarcillin (16, 32, 64 µg), tazocillin (2/4, 8/4, 24/4, 32/4, 32/8, 48/8 µg), cefoxitin (8, 16, 32 µg), cefixime (0.25, 1, 2 µg), ceftazidime (1, 2, 8, 32 µg), ceftriaxone (1, 2, 8, 32 µg), ertapenem 0.03, 0.12, 0.5, 2 µg), amikacin (8, 16, 64 µg), gentamicn (4, 16, 32 µg), nalidixic acid (8, 16, 32 µg), ofloxacin (0.5, 1, 4 µg), fosfomycin (8, 16, 32 µg), nitrofurantoin (16, 32, 64 µg) and trimethorim-sulfametoxazol (1/19, 4/76, 16/304 µg).

Identification and antimicrobial susceptibility testing results were interpreted with CA-SFM EUCAST 2019 V2 integrated in the Viteck-2 system software version 9.02.

2.5. Data Analysis

Data were entered, recorded in the EPI info software version 7.2.2.6. Statistical analyses were performed using the Social Sciences statistical package (SPSS version 16.0). Word software was used for word processing. The comparison of percentages used the Mantel Haenszel Chi-square test or the Yates corrected Chi-square test in case of small numbers. The statistical significance level used was $p = 0.05$.

2.6. Ethics Statement

The Ethics Committee for Health Research of Niger and the General Reference Hospital authorities approved this study. In addition to the consent for participation, individual consent was obtained for sample collection for further research.

3. Results

3.1. Sociodemographic Data and Prevalence of *Enterobacteriaceae*

A total of 3369 urines samples were taken from patients with urinary tract infections and analyzed. These samples came from 1651 men and 1718 women, with respective proportions of 49% and 51% (a sex ratio of 0.96). The average age of the patients was 52 years. The age group most affected by urinary tract infections was 46 - 60 years with 23.33%, followed by 61 - 75 years and 36 - 45 years with

21.25% and 11.25% respectively.

Escherichia coli, *Klebsiella pneumoniae and Enterobacter cloacae* were the three main enterobacteria in the present study. *Escherichia coli* was the most predominant enterobacteria species with a prevalence rate of 74.64% (95% CI, 69.12 - 79.63), followed by *Klebsiella pneumoniae* with a prevalence rate of 16.07% (95% CI, 11.97 - 20.91) and *Enterobacter cloacae* with a prevalence rate of 7.14% (95% CI, 4.42 - 10.82). Likely, the *Enterobacteriaceae* were mosly isolated in these three age groups (**Figure 1**).

Escherichia coli species were found in all hospital wards and the wards most affected by this species were Nephrology and Endocrinology with 29% and 22% respectively (**Figure 2**).

In patients with urinary tract infections, *Escherichia coli* was the most predominant species of enterobacteria with 69.57%, followed by *Klebsiella pneumoniae* and *Enterobacter cloacae* with 17.39% and 8.70% respectively. In patients for an infectious workup, *Escherichia coli* predominated with 67.60%, followed by *Klebsiella pneumoniae* and *Enterobacter cloacae* with 14.89% and 8.51% respectively. In patients after antibiotic therapy, *Escherichia coli* predominated with 84.62%, followed by *Klebsiella pneumoniae* with 15.38%. At least, the enterobacteria isolated were prevalent in communauty patients than in hospitalized (**Figure 3**).

3.2. Antibiotic Resistance Profile of Enterobacterial Strains

Given the high prevalence of *Escherichia coli* in the spectrum of enterobacteria that cause UTIs, this species was of particular interest to study antibiotic resistance. A large proportion of *Escherichia coli* species showed high rates of resistance to ampicillin (95.22%), amoxicillin-clavulanic acid (72.25%), ticarcillin (95.22%), trimethoprim-sulfamethoxazole (92.43%), fluoroquinolones: nalidixic acid (87.56%), ofloxacin (87.56%), to 3rd generation cephalosporins: cefixime

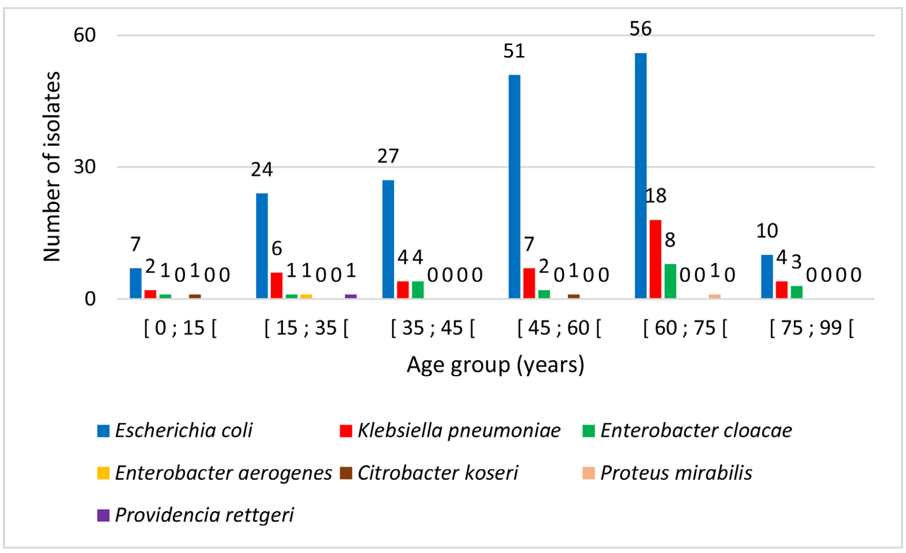

Figure 1. Number of enterobacteria isloated according to the age groups.

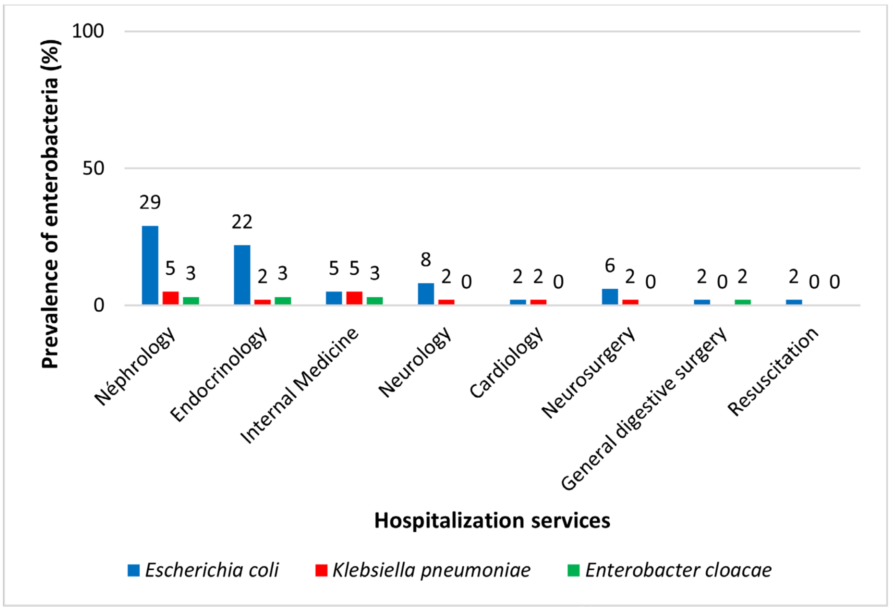

Figure 2. Prevalence of enterobacteria isloated according hospitalization service.

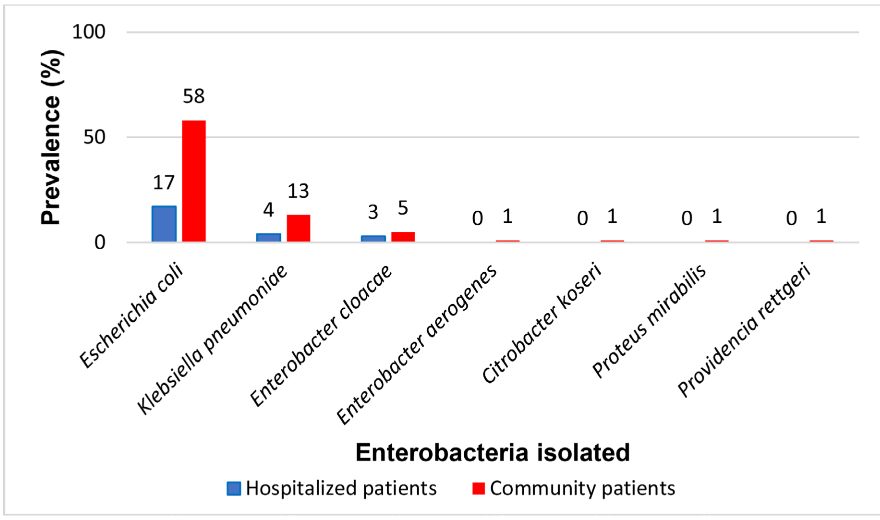

Figure 3. Comparative prevalence of enterobacteria in hospitalized and community patients.

(62.02%), ceftriaxone (58.85%), ceftazidime (55.98%). Combinations of penicillins, 2nd generation cephalosporins and other antibiotics showed a low rate of resistance against *Escherichia coli*: piperacillin-tazobactam (34.13%), cefoxitin (25.36%), amikacin (22.97%), gentamicin (39.23%). Very low rates of resistance in *Escherichia coli* were observed for ertapenem (7.66%), imipenem (7.66%), fosfomycin (0.97%), nitrofurantoin (6.70%). Relatively high rates of resistance in *Klebsiella pneumoniae* were observed against amoxicillin-clavulanic acid (62.22%), piperacillin-tazobactam (51.11%), fosfomycin (54.55%), 3rd generation cephalosporins (55.56% to 62.22%) fluoroquinolones (62.22%), trimethoprim-sulfamethoxazole (60%). Low rates of resistance to *Klebsiella pneumoniae* were observed against the following antibiotic agents: cefoxitin (22.22%), carbapenem (18.18%), amikacin

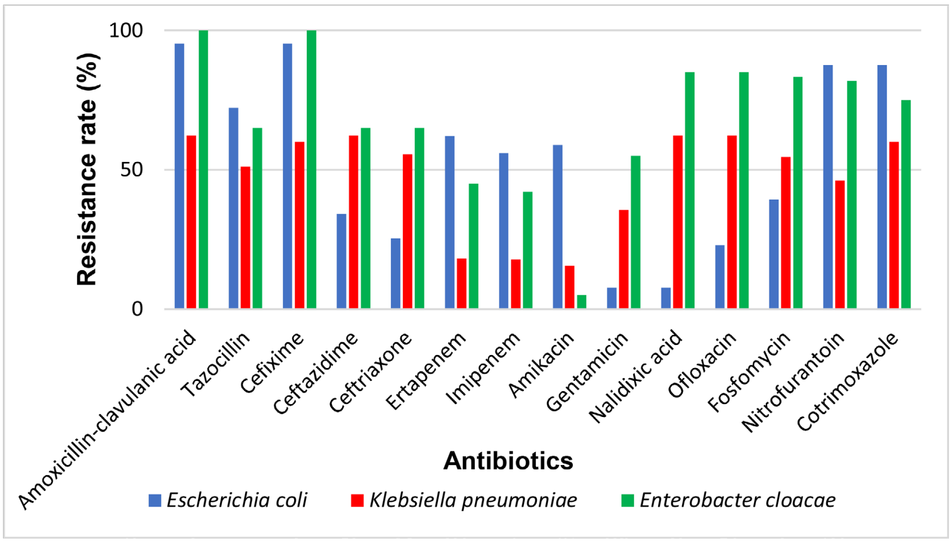

Figure 4. Resistance to individual antimicrobial among enterobacteria isolates.

(17.78%), gentamicin (35.56%), nitrofurantoin (46.15%). The prevalence of resistance was high in *Enterobacter cloacae*: ticarcillin (75%), piperacillin-tazobactam (65%), 3rd generation cephalosporins (65% to 100%), gentamicin (55%), fluoroquinolones (85%), fosfomycin (83.33%), nitrofurantoin (81.82%), trimethoprim-sulfamethoxazole (75%). A moderate level of resistance to *Enterobacter cloacae*, was detected with carbapenems (42% to 45%) while those against amikacin is very low (5%). The other enterobacteria isolated showed resistance rates as follow: all the two *Citrobacter koseri* were resistant to ticarcillin; the *Enterobacter aerogenes* was resistant to ampicillin, amoxicillin-clavulanic acid, cefoxitin and cefixime; the *Proteus mirabilis* strain was resistant to piperacillin-tazobactam, cefoxitin, cefixime, ceftazidime, ceftriaxone, nalidixic acid, ofloxacin, nitrofurantoin and cotrimoxazole; the *Providencia rettgeri* strain was resistant to ampicillin, amoxicillin-clavulanic acid, nalidixic acid, ofloxacin and cotrimoxazole. The antibiotic resistance profile of the three main isolates is given in Figure 4.

4. Discussion

The method of Vitek-2 is regarded as an automatic identification system for microorganisms to show the phenotype of the isolates tested and able to determine the sensitivity or resistance of an isolate to antibiotics [24].

According to the results of our study *Escherichia coli* was the most predominant species of enterobacteria with 74.64%, followed by *Klebsiella pneumoniae* (16.07%). This is in line with the literature data from different countries [13] [25] [26]. The age group most affected by these urinary tract infections was 46 - 60 years with 23.33%. This result was consistent with those reported in other countries of the world [27]. The female sex was the most affected by enterobacterial urinary tract infections with 51.07% against 48.97% for the male sex. Several previous studies and today have shown that the female sex was the most affected

[28] [29]. The proximity of the gastrointestinal tract to the urogenital tract and the short urethra would explain the predominance of UTI in the female sex. In addition, the vagina has commensal flora that can be pathogenic to the urinary tract.

The ampicillin resistance rate of *Escherichia coli* strains was 95.22%. Comparable results have been reported from different parts of the world. For example, results reported from Iran, India and Antananarivo [30] [31]. Studies conducted in Nigeria and Ivory Coast had reported 100% resistance to ampicillin [8] [32]. This resistance to ampicillin in *Escherichia coli* strains is acquired and would be the consequence of the selection pressure linked to the abusive consumption of these antibiotics in developing countries [6] [33]. The rate of resistance to amoxicillin-clavulanic acid was 72.25%. Studies have reported similar results [34]. The beta-lactamase inhibitor, clavulanic acid, both blocks the activity of beta-lactamase enzymes produced by enterobacteria and also acts as a bactericide. The ticarcillin resistance rate was 95.22%. This is higher than that reported in a study by Jamila *et al.* on antibiotic resistance in uropathogenic enterobacteria [35]. However, the resistance rate to piperacillin + tazobactam was 34.13%. Michno performed a study in which he brought 13% resistance to this antibiotic [36]. The cefoxitin resistance rate was 25.36%. A previous study in Guinea reported lower results [37]. Cefoxitin resistance in *Escherichia coli* strains was low in Niger compared to data from other countries. The rate of resistance to third generation cephalosporins ranged from 55.98% to 62.02%. This rate is slightly higher than that reported by Koita *et al.* [38]. The carbapenem resistance rate was 7.66%. This result corroborated that reported in Gabon [39] [40]. The rate of resistance to amikacin was 22.97% in our study and was also low in studies conducted in other parts of the world [6]. However, the rate of gentamicin resistance was 39.23%, while in another study it was 67.2% [14]. The rate of resistance to quinolones was 87.56%. This result is perfectly consistent with those reported by other researchers [41] [42]. The high rate of resistance to quinolones worldwide compromises the use of this class of anti-infectives widely used in daily practice. This can be mainly explained by the massive use of these antibiotics to treat first-line urinary tract infections without prior documentation [14]. The rate of resistance to fosfomycin was 0.97%. This rate is consistent with that reported in a study on Experiments in fosfomycin susceptibility testing and determination of resistance mechanism in *Escherichia coli* from urinary tract infections in the United Kingdom [43]. Fosfomycin remains a viable option for the treatment of uncomplicated urinary tract infections [44]. In the present study, it was shown that the rate of resistance to nitrofurantoin was 6.70% among *Escherichia coli* strains. This resistance rate was similar to those reported in other previous studies [41] [45]. However, increasing rates of resistance to nitrofurantoin 9.4% and 12.4% were reported by Haindongo *et al.* (2022) [25]. Despite the non-significant growth in the rate of resistance to nitrofurantoin, it appears to be a good antibiotic for the treatment of urinary tract infections caused by *Escherichia coli*, but it should be considered that unlimited use of nitrofurantoin may gradually lead to an increase in resistance to this antibiotic. trimethoprim/sulfamethoxazole is an important and widely used first-line antimicrobial for the treatment of uncomplicated cystitis [17]. The rate of resistance to trimethoprim-sulfamethoxazole was 92.43%. This rate was consistent with those reported in other studies [14] [46]. However in a study conducted by Koita in 2019, had brought 97% resistance to trimethoprim/sulfamethoxazole [38].

5. Conclusions

This study allowed us to identify the isolates of enterobacteria involved in urinary tract infections of patients attending the microbiology laboratory of the General Reference Hospital of Niamey, with a predominance of the female sex (sex ratio F/M = 0.96). This study also allowed us to study the antibiotic resistance of enterobacteria. The data showed that the prevalence of urinary tract infections due to enterobacteria is higher than in other groups of bacteria. The most common enterobacteria isolates were *Escherichia coli* and *Klebsiella pneumoniae.* High antibiotic resistance was identified for frequently used antibiotics. Lower antibiotic resistance was observed for some broad-spectrum antibiotics. Amikacin, gentamicin, ertapenem, imipenem, nitrofurantoin, and fosfomycin remain useful antibiotic choices for treating UTIs with enterobacteria, with an overall sensitivity of greater than 70%.

The alarming problem of antibiotic resistance in uropathogens requires awareness. The best ways to fight against urinary tract infections are prevention through hygiene measures in the population, performing antibiograms before treating patients, respecting the prescription of antibiotics and raising awareness to avoid self-medication before coming to the hospital.

Disclosure

The funders had no role in the study design, data collection, data analysis and interpretation, writing of the manuscript, and publication decision.

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Contributions of the Authors

All authors contributed to the design of the study, data analysis, writing and editing of the document and agreed to be responsible for all aspects of the work. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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