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Epidemiology and Antibiotic Resistance of Uropathogenic Bacteria Isolated at Thierno Birahim Ndao Regional Hospital Center in Kaffrine (Senegal)

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ABSTRACT

Introduction: *Urinary tract infection is very common in hospital and community settings. This study aims to determine bacteriological profile and to study sensitivity to antibiotics of bacteria isolated at Thierno Birahim Ndao Regional Hospital Center in Kaffrine.*

Methods: *A cross-sectional study with an epidemiological aim over a period of three years was conducted concerning all bacteria isolated from urine samples of patients suffering from benign prostatic hypertrophy hospitalised or outpatient. Culture was done according to the usual techniques and antibiogram was carried out by the method of diffusion disk in Mueller-Hinton agar medium according to the recommendations of EUCAST 2023.*

Results: *A total of 537 samples were analysed from patients with an average age of 70 years, 61-80 age group was most represented with 75.8%. Samples came from outpatients (7.3%) and inpatients (92.7%), mainly from urology department (69.3%). Bacteriological study showed that enterobacteria were the most frequently isolated germs, including Escherichia coli (52.43%) followed by Klebsiella pneumoniae (12.62%). With regard to antibiotic sensitivity of strains, out of a total of 172 enterobacteria (83.9%), 61.05% (n=105) produced an extended-spectrum ß-lactamase (ESBL), with a predominance of Escherichia coli (41.28%) and Klebsiella pneumoniae (9.88%) (p<0.001). Antibiotic resistance in ESBLE over the three-year period revealed co-resistance to ciprofloxacin, levofloxacin (80%), gentamicin (39.05%) and tobramycin (40%).*

Conclusion: *Bacterial epidemiology of UTIs has not changed much in recent years, and remains dominated by Enterobacteriaceae. However, the level of antibiotic resistance is becoming increasingly high, reaching worrying levels, particularly in relation to beta-lactams and fluoroquinolones.*

Keywords
Urinary tract infections, Enterobacteria, ESBL, Antimicrobial resistance.

Introduction
Throughout the world, urinary tract infection (UTI) is one of the main reasons for consultations, microbiological investigations and the intensive use of antibiotics, with the consequences for the cost of care and selection of multi-resistant strains in both hospital and community settings [1].

According to World Health Organisation (WHO), human and economic impact of antimicrobial resistance between now and 2050 will be considerable. The continued increase in resistance between now and 2050 would lead to the deaths of 10 million people each year and a reduction of between 2% and 3.5% in gross domestic product. This would cost the world up to 100 billion dollars [2]. According to projections by a group of international experts, the emergence and steady increase in antibiotic resistance will be the leading cause of death in the world, ahead of cancer (8.2 million deaths), diabetes (1.5 million), diarrhoeal diseases (1.4 million) and road accidents (1.2 million), with 10 million deaths by 2050 [3]. The situation is alarming in countries with limited resources, where infectious diseases, poverty and malnutrition are endemic. The development of antibiotic resistance is a complex process, often involving host, pathogen and environmental factors. In recent years, there has been an increase in incidence of antibiotic resistance in germs responsible for urinary tract infections, particularly with the emergence of *Enterobacteriaceae* producing extended-spectrum beta-lactamase (ESBL) [4,5]. These enzymes (TEM, SHV, CTX-M and derivatives) give enterobacteria resistance to all beta-lactam antibiotics with the exception of cephamycins and carbapenems, in addition to associated resistance to other families of antibiotic [1]. The mainly plasmid transmission of genes coding for ESBLs is responsible for their rapid dissemination and thus for the increase in prevalence of ESBL-producing bacteria throughout the world [6].

The incidence of UTIs and the economic burden of managing them in a context of antibiotic resistance make this a public health issue. The aim of our work was therefore to use up-to-date data to propose the microbial ecology of urinary tract infections and to monitor antibiotic susceptibility profile of uropathogenic bacteria, against a background of changes in the epidemiology of antibiotic resistance.

Methods

Study Design

This was a three-year retrospective epidemiological study of all bacteria isolated from urinary samples taken from patients with benign prostatic hyperplasia, whether inpatients or outpatients, referred to medical biology laboratory of Regional Hospital Center of Kaffrine.

Study Population

The study concerned all patients with prostatic problems hospitalized in the urology department or in other departments or outpatients.

Sample collection and identification

Urine samples were collected in the various hospital departments, mainly urology, in sterile jars and transported directly to laboratory in suitable conditions. As soon as the sample was received, the bottle was checked for conformity with request, and the macroscopic appearance was noted. Each urine sample undergoes a cytobacteriological examination, including microscopic examination using Fast Read® cell, in order to note any elements that may be present: leukocytes, red blood cells, epithelial cells, cylinders and crystals. Samples are inoculated using the calibrated loop method on CLED (Cystine Lactose Electrolyte Deficient) medium.

Interpretation used is standard and takes into account urinary infection parameters: leucocyturia > 10^4/mL, bacteriuria in colony forming units (CFU) per mL >10^5/mL bearing in mind that *Escherichia coli* and *Staphylococcus saprophyticus* are considered specific uropathogens, so their threshold is lowered to 10^3/ CFU/mL. Identification of isolated bacteria is based on the use of BioMérieux™ Api 20 galeries (E, NE, Staph, Strep) and immunological identifications by latex agglutination (*Staphylococcus aureus, Streptococcus B*,...).

Antimicrobial Susceptibility Testing

Antibiotic susceptibility was tested by diffusion on Mueller-Hinton agar and interpreted in accordance with the recommendations EUCAST 2023 [7]. ESBLs were detected using the synergy method between amoxicillin+clavulanic acid (ACA) and ceftriaxone (CRO) or cefotaxime (CTX), characterised by a 'champagne cork' image indicating the presence of an ESBL.

Data Analysis

Statistical analysis was carried out using STATA 14.0 software (Stata Corp, USA). Descriptive analysis consisted of calculating frequencies for categorical variables. To compare percentages in a bivariate analysis, Pearson's Chi-square test was used, and Fischer's if necessary. Significance threshold was $p<0.05$.

Ethical Considerations

The isolates were obtained as part of the routine activities of the microbiology laboratory of Thierno Birahim Ndao Regional Hospital Center in Kaffrine. Demographic data were extracted from the computer database anonymously. Approval of ethics and informed consent were therefore not necessary.

Results

Descriptive Analysis

A total of 537 samples were analysed from patients with an average age of 70 years, ranging from 47 to 95 years. Age group 61-80 was the most represented with 75.8%. The samples came from outpatients (7.3%) and inpatients (92.7%), mainly from the urology department (69.3%), followed by the surgery department (16.2%), the emergency department (5.2%) and the internal medicine department (2%) (Figure 1). Concerning the reason for hospitalisation or consultation, 98.9% of patients suffered from benign prostatic hyperplasia (BPH), one patient (0.6%) suffered from a prostate tumor. Of these samples, 205 met the criteria for urinary tract infection, i.e. 38.2%. Bacteriological study showed that enterobacteria were the most frequently isolated germs, including *Escherichia coli* (52.43%), followed by *Klebsiella pneumoniae* (12.62%), *Enterobacter spp* (8.25%) and *Pseudomonas aeruginosa* (7.28%); however, the urinary tract infection was fungal in origin in 2.91% of patients and was due to *Candida spp* (Figure 2).

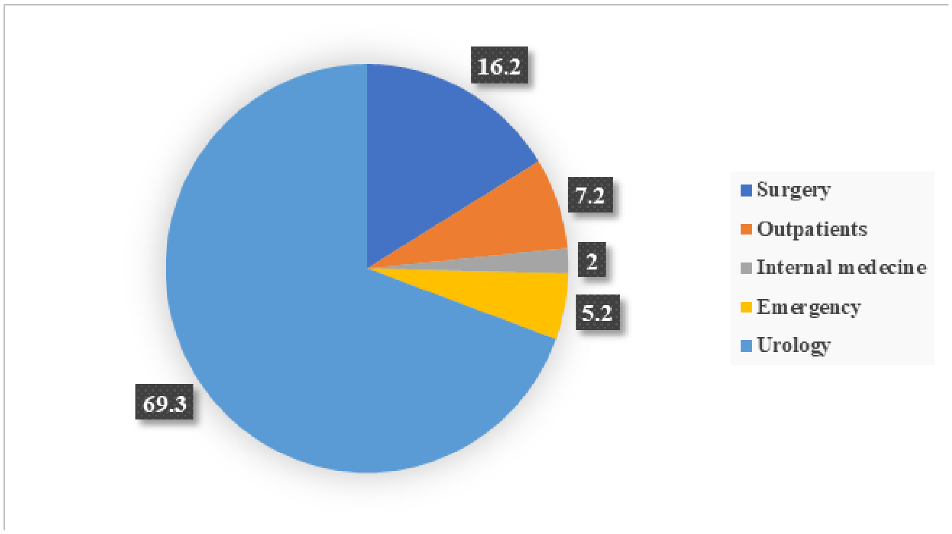

Figure 1: Breakdown of patients by department.

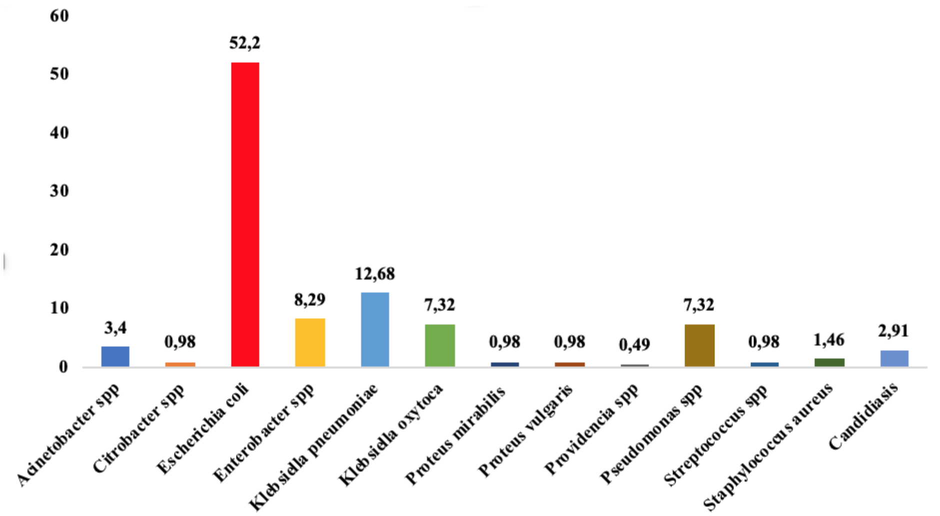

Figure 2: Distribution of strains isolated.

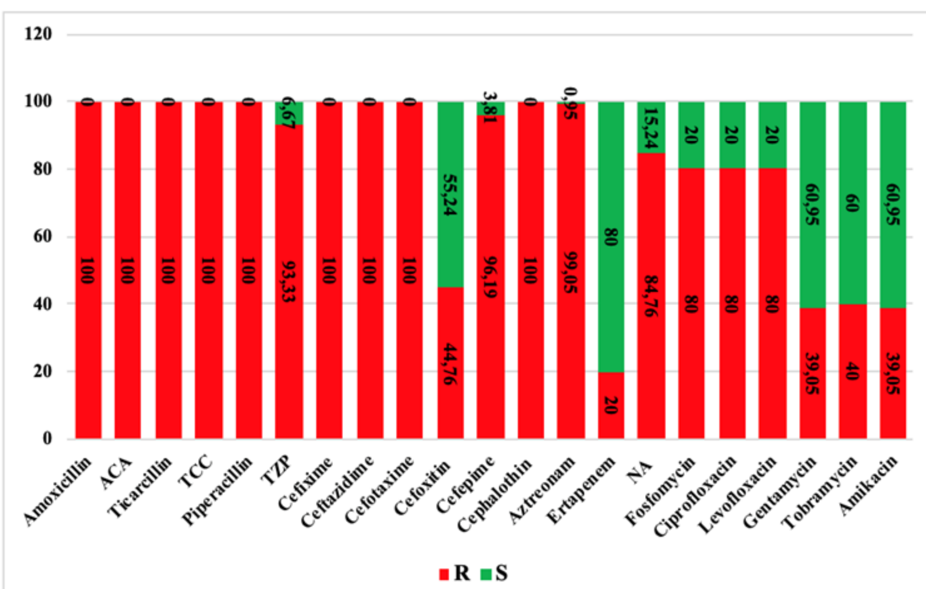

Figure 3: Susceptibility profile of ESBLE to the main antibiotics.

With regard to antibiotic sensitivity of the strains, out of a total of 172 enterobacteria (83.9%), 61.05% (n=105) produced an extended-spectrum β-lactamase (ESBL), 24.42% (n=42) a high-level penicillinase (HLP), 7.56% (n=13) a low-level penicillinase, 2.33% (n=4) a cephalosporinase and 1.74% (n=3) had a TRI-type mechanism. Only 2.91% (n=5) were wild-type. With regard to antibiotic resistance in ESBLE, analysis of the cases showed considerable resistance to fluroquinolones, in particular ciprofloxacin and levofloxacin (80%). Gentamicin resistance in EBLSE was 39.05%. These strains also showed resistance of around 20% and 80% to ertapenem and fosfomycin. These ESBLE strains also showed good sensitivity to amikacin (39.05%) (Figure 3). This makes it the aminoglycoside of choice when a combination of antibiotics is required for treatment.

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Bivariate Analysis

The distribution of *Enterobacteriaceae* producing extended-spectrum beta-lactamase (ESBLE) showed a predominance of *Escherichia coli* accounting for approximately 41.28% of cases, followed by *Klebsiella pneumoniae* 9.88%. Distribution of these phenotypes according to the *Enterobacteriaceae* isolated showed a statistically significant difference (p<001) (Table 1).

Phenotypes	**BLSE**	**Case**	**Wild type**	**PBN**	**PHN**	**TRI**	**p-value**
Bacteria							
Citrobacter spp	0	0	0	0	1,16	0	
E.coli	41,28	1,74	1,16	3,49	12,79	1,74	
Enterobacter spp	4,07	0,58	0,58	1,16	3,49	0	
K.oxytoca	5,23	0	0	2,33	1,16	0	p<0,001
K.pneumoniae	9,88	0	0	0,58	4,65	0	
P.mirabilis	0	0	1,16	0	0	0	
P.vulgaris	0	0	0	0	1,16	0	
Providencia	0,58	0	0	0	0	0	

Table 1: Distribution of *Enterobacteriaceae* phenotypes according to bacteria isolated.

Discussion

Urinary tract infection (UTI) is a frequent reason for hospitalisation and antibiotic prescriptions, and has been the subject of a number of studies, notably on the high incidence of antibiotic resistance associated with UTIs, and the remarkable trends in recent years [8,9]. This study highlights the problem of urinary tract infections among urology patients in hospitals, leading to the emergence of new bacterial strains that are increasingly resistant to broad-spectrum antimicrobials.

In this study, the frequency of UTIs in urology was 38.2%. At Marrakech University Hospital, two studies conducted in 2017 and 2018 by Hamdani et al. and Mouayche et al. respectively showed prevalences of 25.6% [10] and 31% [11]. At the Hassan II University Hospital in Fez, an incidence study carried out on patients hospitalised in urology department revealed a rate of 39%, similar to that in our study.

In this study, a high frequency of UTIs was found in people in the 40-60 age group, in line with the findings of Gonthier [12], who highlighted the role of advanced age in the occurrence of UTIs in hospitalised patients.

Escherichia coli dominated epidemiological profile (52.2%), followed by *Klebsiella pneumoniae* (12.68%), *Enterobacter spp* (8.29) [13] and *Pseudomonas aeruginosa* (7.32%).

The ascending pathophysiology of UTI and heavy colonisation of perineum by enterobacteria of digestive origin, and in particular *Escherichia coli*, combined with specific uropathogenic factors such as bacterial adhesins capable of binding to the urinary epithelium, explain their predominance [14].

In Senegal, a retrospective study carried out between 2003 and 2013 found that these same bacteria predominated in urinary tract infections [15]. Another retrospective study carried out between January 1999 and December 2000 in Dakar showed the predominance of *Escherichia coli*, followed by *Klebsiella pneumoniae* and *Streptococcus agalactiae* [16]. Our results show a worrying trend in frequency of isolation of uropathogenic EBLSE in our region, with 62.05%. In fact, this rate varies from one country to another and from one centre to another. For example, southern European countries recorded rates in excess of 10%, while northern European countries recorded rates of less than 5% [17]. In Morocco, Lahlou et al. found a rate of 9% [18]. In 2010, a study carried out in a urology department at Ibn Sina hospital in Rabat showed a rate of 17.5% [19]. Similar frequencies (in excess of 10%) have been recorded in Greece, Turkey, Italy and Portugal [17]. In France and on the island of Réunion, frequency of ESBLE isolation was 5.8% in 2006/2007 [20]. This is higher than rates reported in Germany and UK (2.6% and 2% respectively) [21], but lower than those reported in Algeria (37.1%) in 2011 and Tunisia (30.8%) in 2010 [22,23].

According to the results of our study, 41.28% of the ESBLE identified were strains of *Escherichia coli* and 9.88% of *Klebsiella pneumonia*. This is consistent with the results of several studies which have shown that these two species are the most frequently responsible for production of ESBLs [4,17,18,24]. In addition, *Klebsiella pneumoniae* remains the most common ESBL producer within its genus, with a prevalence of expression of 65.38% (17/26). For Ben Haj Khalifa and Khedher, *Klebsiella pneumoniae* produced ESBL in 20.2% of cases [25]. However, some authors report a decline in this dominance in favour of *E. coli* [26].

The study of antibiotic resistance in isolated uropathogenic ESBLE revealed high rates of co-resistance for ciprofloxacin and levofloxacin (80%), gentamycin and amikacin (39.05%) and tobramycin (40%). These rates of co-resistance are similar to those reported in results published in Morocco in 2009 in Meknes, in 2012 in Rabat and in 2014 in Marrakech [5,18,24].

This high level of ESBLE co-resistance severely limits the therapeutic arsenal and increases the risk of treatment deadlock [27]. The high rate of co-resistance of ESBLE to quinolones worldwide compromises the use of this class of anti-infectives, which are widely used in daily practice. The main reasons for this are, firstly, the widespread use of these antibiotics as first-line treatment for urinary tract infections without prior documentation. Secondly, by the recent emergence of 3 plasmid resistance mechanisms to fluoroquinolones: the 'Qnr' quinolone resistance gene, the genes coding respectively for an N-acetyltransferase, ACC-(6')-Ibcr and the genes coding for the QepA efflux pump [28].

Over three years, 20% of uropathogenic ESBLEs isolated were resistant to ertapenem. This is evidence of the emergence of strains combining ESBL and carbapenem impermeability or co-production of ESBL and carbapenemases, thus showing a 'pan-resistance' phenotype to betalactam antibiotics [29]. As a result, the rational use of carbapenems is essential, as they represent the last-line therapeutic tool for the treatment of infections by ESBL-producing Gram-negative bacilli [30].

Conclusion

The profile of local and up-to-date bacteriological data is essential for the effective application of the new consensus in the management of UTIs, which involves in particular prescribing first-line antibiotic therapy effective against uropathogenic bacteria. Our results show that the bacterial epidemiology of UTIs has not changed significantly in recent years, and remains dominated by Enterobacteriaceae. However, the level of antibiotic resistance is becoming increasingly high, reaching worrying levels, particularly in relation to beta-lactams and fluoroquinolones. Carbapenems, however, continue to have good activity, which is why it is

Competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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