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RESEARCH ARTICLE

ANTIBIOTIC RESISTANCE OF BACTERIA CAUSING URINARY TRACT INFECTIONS

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ABSTRACT

Background: The development of bacterial resistance to antibiotics makes the fight against the urogenital infections delicate both in hospital and community. The aim of this study was to identify urinary tract infections germs (UTI) and their antibiotic susceptibility in an urban population. **Methods:** At the Army Schooling Hospital, a study on antibiotic resistance of the bacteria was conducted on hospitalized and outpatients. Cytobacteriological tests, identification byVITEK®2 and antibiotics susceptibility were carried out. **Results:** Of 342 patients enrolled with a sex ratio of 1.52,the various tests have helped to isolate the germs such as: *Escherichia coli* (32.78%), *Klebsiella pneumoniae* (16.39%), *Enterobacter cloacae* (11.47%), *Acinetobacter baumannii* (7.46%) for the most important and many other germs found with rates of less than 5%. Enterobacteriaceae and *A. baumannii* strains resistance patterns to different antibiotics were established. Among the Enterobacteriaceae, the isolated *E. coli* strain developed resistance of 65% to ticacilline, 60% to ampicillin, 50% to piperacillin, 35% to amoxicillin, those of *K. pneumoniae* (R: 99% to ampicillin, 80% to ticarcillin, 60% to amoxillin and 40% to piperacillin), and that of *E. cloacae* (R: 57.14% to ampicillline, and amoxillin, R: 42.85% to ticarcillin and R: 14.28% to piperacillin of the Beta-Lactam class). In contrast, *A. baumannii*had ampicillin resistance of 40%, and 20% to amoxillin and ticarcillin respectively. All these bacteria showed a high level of resistance in the beta-lactam group. **Conclusion**: Hence the need for an epidemiological surveillance program by the National Institute for Public Health Surveillance to improve the therapeutic requirements.

Key words: Resistance, Antibiotics, Bacteria, Urinary tract infection.

INTRODUCTION

Normal urine is sterile, with no microbe, virus, or fungus. However, urinary tract infections (UTI) are the most frequent of all infections (genital, digestive, skin, etc.). Indeed, urinary tract infection is one of the most common infections in the community as well as in hospitals (Alaoui *et al*., 1998). Urine has no property to resist microbes, and can therefore be an excellent culture medium for bacteria that come from intestinal flora or perineal flora thus causing infections (Epok, 1999). However, in women they represent the major risk factor for urogenital infections (UGI) whose starting point is usually the vagina. UGI in women includes disorders of the urinary system and those of the genital tract caused by an infectious agent with the main offending agent *Escherichia coli*. Although a simple cytobacteriological test allows detection of these infections, they are growing in recurrent disease in women due to their asymptomatic character in most cases making thus the diagnosis late (Bodika, 1995). Their main complications are related to fertility, reproduction is seen as severely affected. In pregnant women they cause ectopic pregnancies and premature births (Klufio *et al*., 1995). Urogenital infections must be considered as a major problem in society especially for under-populated countries, accentuated since the advent of the HIV pandemic (Djigma *et al*., 2008). Such as Gabon where the population density is 5.5 inhabitants per square kilometer. The female infertility is partly responsible for the observed under-population in Central Africa, a study was conducted in the 90's in Franceville, a town in eastern Gabon, showing the involvement of certain bacterial strains in the cases of female hypo fertility and ectopic pregnancies resulting from acute and chronic genital infections (Roudifre, 1998; Bertherat *et al*., 1998). Usually complications such as infertility occur when the patient is negligent in monitoring the treatment or when treatment is inadequate. Moreover, the microbial strains are multiple, each responsive to a particular way to chemical substances for therapeutic purposes. Indeed, certain strains develop resistance to specific substances, originally phenomenon of ineffective treatment. It would be wise to evaluate the resistance of an infectious agent with therapeutic substances after its identification in a host organism to better guide the administration of treatment. Such diagnostic procedure would be a major contribution in the fight against the development of infections to severe consequences in women.

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The purpose of this study was to establish the profile of microbial strains to the origin of the uro-pathogenic infections and to identify antibiotic resistance of bacteria isolated to improve the care of patients with a review of the therapeutic protocol.

MATERIELS AND METHODS

Area and study population: The study on antibiotic resistance of bacteria infecting the urinary tract was conducted in the laboratory of Army Schooling Hospital Omar Bongo Ondimba (LASH-OBO) in Libreville from August to December 2017.As part of theirs routines activities, these swabs were tested for bacterial infections. The study focused on urinary samples from hospitalized and outpatients. It involved 342 patients suspected of having an urinary tract infection (UTI) confirmed in the laboratory. Were excluded any other additional charges that urine and all other agents (parasites, fungi), isolated in the urine. The recommendations before sampling required: a prior local asepsis, a strict genital hygiene and avoid the proliferation of an accidental bacterium. Sample collection and storage of urine. Urine samples were collected by patients at home and the instructions were given, such as record the identified sample with the name, date and time of collection was taken to the laboratory within two hours of collection. For the preservation of urine the method consists in using tubes containing a stabilizer of bacterial growth such as boric acid, urine could then be stored for 48 hours at room temperature or at + 4°C up to 24 hours before being analyzed.

Cytobacteriolocal tests of urine: The analysis of the urine sample began with a macroscopic examination reflecting the color and appearance of urine. The band at both sides of a tube Uriline Biomérieux was immersed in the urine sample for a seeding Cystine Lactose electrolyte Deficient (CLED), non-selective medium; and on Mc Conkey, a specific medium for Enterobacteria and other Gram (-) bacilli. After incubation at 37°C for a period of 24 hours, a strip with reactive zones was then immersed in the urine sample for the observation of certain parameters such as pH, density, the presence of nitrites, glucose, and proteinuria but also hematuria and leucocyturia made it possible to suspect a urinary tract infection that can be confirmed by cytology. Cytological test was made from the urine sediment obtained after centrifugation of the total urine at 2500 rpm for five minutes. It consisted in detecting under the microscope, the presence of crystals, leucocytes, red blood cells. If leukocyturia, an enumeration is performed using the cell Kova (Pierron pedagogical Scientific Equipment). The inoculated media were revisited for the observation and analysis of colonies grown. If polybacteria growth, environmental contamination is suspected and an additional sample was requested. In the case of a single type of colony, the Urine Germ Count (UGD) is measured to assess the infectious risks of the microorganism present. If significant DGU, confirmation is made for identification of the species with the medium on which the colonies have developed. Reading the API gallery has established a digital profile determined from the scores attributed to positive or negative outcomes tube; this numerical profile corresponds to a determined species.

Identifications by the data processing method: It was done using an automatonVITEK®2 Compact 15 (bioMérieux®, France). The identification of the micro-organisms by the automaton was done by means of the colorimetric cards of identification, containing biochemical tests whose number varies depending on the card. Indeed, the automaton uses several cards to identify the different microorganisms (bacteria and yeasts) contained in the inoculum.

Antibiogram tests: Antimicrobial susceptibility of infectious high-risk species isolated from urine samples was performed after identification of the germ. For the species isolated on EMB (Eosine de Methylen Blue), the antibiogram was performed with the ATB UR EU (08) kit for urine samples. 10 µl of the inoculum prepared at 0.5 McFarland were transferred to a medium suspension ATB ampoule and then 135µl of this solution were inoculated in each well of the gallery about 2×10^5 seeds/ml or 3×10^4 seeds/wells. Using these kits, bacterial resistance to beta-lactams, cephalosporins, aminoglycosides, tetracyclines and sulfonamides could be evaluated. The galleries were incubated for 24 hours at 36 ± 2˚C under aerobic conditions. The reading and interpretation of the API 20 E gallery was made according to the supplier's instructions.

RESULTS

A total of 342 patients were enrolled, on the cyto bacteriological examinations of the urine, 61 strains of Gram-negative bacteria were identified, in which Enterobacteriaceae were the most representative, 25 of which were men and 38 were women. These infections were diagnosed from inpatients and outpatients. The overall prevalence of infected patients was 36.55%. The analysis showed that women and men had urinary infection rates of 21.76% and 14.53% respectively and 63.71% of the study population was uninfected.

Ecology of germs involved in UTI: Identified uro-pathogenic microorganisms were mainly Enterobacteriaceae *Escherichia coli* (32.78%), *Klebsiella pneumoniae* (16.39%), *Enterobacter cloacae*(11.47%), and *Acinetobacter baumannii* (7.46%).This result also shows a great variety of organisms implicated in urinary tract infections with lower rate to less than 5%, in the case of *Citrobacter koseri*, and *Klebsiella oxytoca* (4.91%), *Staphylococcus haemolyticus* (3.37%) and *Citrobacter freundii*, Pantoea *sp, Kluyvera spp*., *Enterobacter sakazaki*, *Pastorella spp*, *Raoultella orhithinolytica*, *Klebsiella ozenea*, *Enterococcus faecalis*, *Proteus mirabilis*, *Serratia odorifera* and *Pseudomonas spp* were at 1.63% (Figure 1).

Resistance rate: The rate of resistance of the most common urogenital pathogenic bacteria was evaluated, according to the clear or cloudy cups of ATB used, the analyzed species was known respectively sensitive or resistant to the antibiotic tested. The results of antibacterial activity tests of certain reference antibiotics were reported in Table 1. The study on the resistance showed that in *Escherichia coli* the highest rate of resistance was observed with ampicillin (60%) and the acid-amoxicillin clavulanic (35%), as well as ticarcillin (65%). It reached 50% for piperacillin and nalidixic acid, 55% for ofloxacin. The lower resistance rate was obtained with imipenem and cefuroxime, respectively 1 and 0%.In *K. pneumoniae* 60% of strains were resistant to amoxicillin-clavulanic acid, cephalothin, ceftazidime and cefotaxime, 80% to ticarcillin, 50% to cefoxitin, and trimethoprim-sulfamethoxazole. For the *E. cloacae* strain, 85.71% resistance to cefalotine and cefoxitin, 57.14% to ampicillin, amoxicillin-clavulanic acid, cefotaxime and cotrimoxazole were observed. As for *A baumanii*, resistance rates were relatively lower at 40% to ampicillin, fosfomycin, cefixime, cefotaxime, and 20%

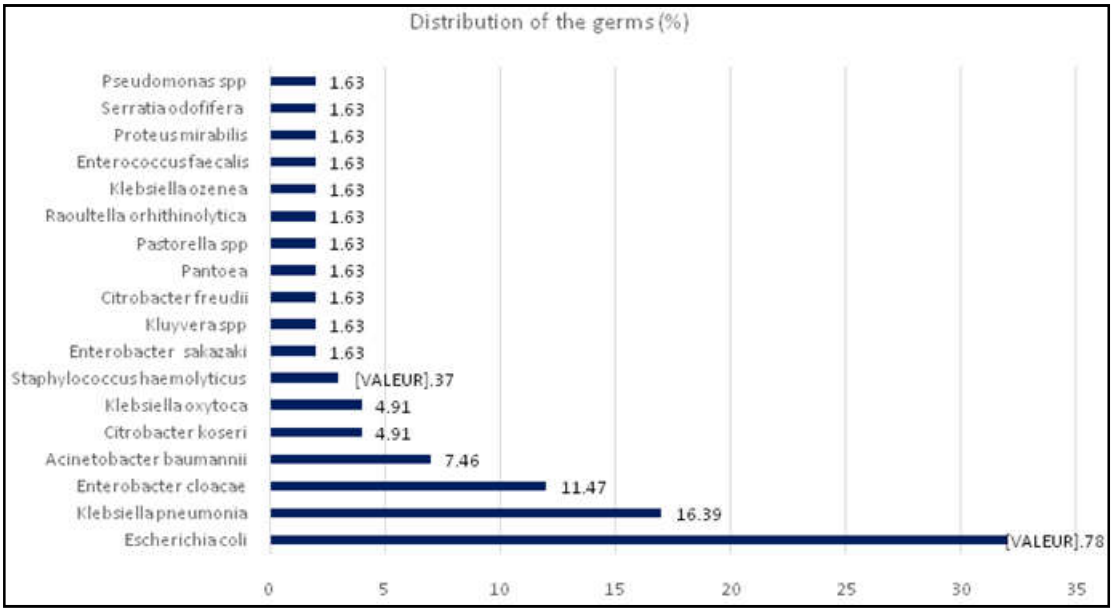

Figure 1. Distribution of germs infecting the urinary tract

Table 1. Mean resistance rate (%) of bacterial agents isolated from urine, tested with standard antibiotics

Antibiotics	Mean resistance rate (%) of bacterial agents isolated from urine			
	E. coli	*K. pneumoniae*	*E. cloacae*	*A. baumannii*
AMP	60	99	57.14	40
AMC	35	60	57.14	20
TIC	65	80	42.85	20
PIC	50	40	14.28	ND
CIP	25	10	14.28	ND
TSU	25	30	57.14	20
FOS	0	10	28.57	40
NOR	15	20	42.85	40
CXT	5	50	85.71	40
CX32	1	1	1	40
CAZ	10	60	28.57	ND
FEP	1	1	28.57	ND
IMI	1	1	ND	ND
CFT	5	60	85.71	40
CXM	0	10	1	ND
CFM	5	30	28.57	40
CTX	5	60	57.14	40
TET	25	10	28.57	20
NAL	25	ND	42.85	20
FUC	50	10	28.57	20
OFL	55	ND	28.57	20
LVX	10	10	14.28	20
MERO	ND	ND	1	20
GEN	ND	30	28.57	20
TOB	ND	20	1	20
AKN	ND	ND	1	ND
ERY	ND	ND	1	ND
SXT	20	50	1	ND

to amoxicillin-clavulanic acid, ciprofloxacin, cefotaxime and gentamicin. ND: Not Done.AMP: Ampicillin, AMC: Amoxillin, TIC: Ticarcillin, in, PIC: Piperacillin, CIP: Ciprofloxacin, TSU: Cotrmoxazol, FOS:Fosfomycin, NOR: Norfloxacin, CXT: Cefoxitin, CX32: Cefoxitin 32, CAZ: Ceftazidim, FEP: Cefepim, IMI: Imipenem, CFT: Cefalotin, CXM: Cefuroxin, CFM: Cefixin, CTX: Cefotaxim, TET: Tetracyclin, NAL: Nalid CA-SFM Ac, FUC: Nalidixic CLSI Ac, OFL: Ofloxacin, LUX: Levofloxacin, MERO: Meropenem, GEN: Gentamicin, TOB: Trobamycin, AKN: Amikacin, ERY: Erythromicin, SXT: Trimethoprim sulfa.

DISCUSSION

The urinary tract infections affect all age groups and gender (Omigie *et al*., 2009; Ahmed *et al*., 2014). A higher prevalence among women during pregnancy and among those who are sexually very active is observed (Verstraelen *et al*., 2010). Indeed, the urogenital infections in women are usually bottom-that is to say start at the urethra or vagina. Regarding genital infections, their propagation emanates from an imbalance in the vaginal flora favoring the proliferation of infectious mucosal microorganisms. In pregnant women, the hormonal imbalance origin associated with changes in the morphology of the uterus increases the occurrence of infection (Xia *et al*., 2004; Yan *et al*., 2009). The upward pathophysiology of UI as well as the strong colonization of the perineum by enterobacteria of digestive origin, and in particular *Escherichia coli*, associated with specific factors of uropathogenicity such as bacterial adhesins able to bind to the urinary epithelium explain this preponderance (Alvarez *et al*., 1992). The female predominance (21.76%) is thought to be related to the

anatomical configuration; shortness of the urethra, proximity of anal and vaginal openings, poor hygiene practices, sexual intercourse and pregnancy (Amaoui *et al*., 2003). The irrational and indiscriminate use of antibiotics as well as counterfeit products, including antibiotics is common in developing countries (Abubakar, 2009; Wilson and Fenoff, 2011). The prevalence of Enterobacteriaceae, *Escherichia coli* (32.78%) of *K. pneumoniae* (16.39%) and *E. cloacae* (11.47) in the case of UTIs has already been shown and confirmed in this study (Sheela and Rajkumar, 2012; Subramaniam *et al*., 2016; Ndong Atome *et al*., 2017). *Escherichia coli* and *Klebsiellapneumoniae* are saprophytes of the gastrointestinal tract and upper airway capable of being harmful under certain conditions. *Klebsiella pneumoniae* is naturally resistant to beta-lactams from the penicillin subfamily through the secretion of penicillinases whereas *Escherichia coli* is resistant to this through non-enzymatic mechanisms such as membrane permeability, these results are consistent with those obtained in 2005 (Seck, 2005). On the other hand, these two species have a high susceptibility to fosfomycin with 100% for *E. coli* and 90% for *K. pneumoniae*. This antibiotic could be recommended in the treatment of UTI. The finding that isolates of *E. coli* and *K. pneumoniae* were resistant to ampicillin (R: 60% and 99%) and amoxicillin (R: 35% and 60%), states that enzyme production is the main, if not, the most effective mechanism for inducing bacterial resistance to beta-lactams.

This implies that these antibiotics cannot be used as empirical therapy for urinary tract infection (Beyene and Tsegaye, 2011). High rates observed resistance in *E. coli* on Beta-lactam mainly aminopenicillin (ampicillin, 60%), the carboxypenicillines (ticarcillin, 65%), and ureidopenicillies (piperacillin 50%), tries to demonstrate that are acquired resistance and would be the consequence of the selection pressure linked to the excessive consumption of these antibiotics (Prere *et al*., 2004). Acquired resistance of *E. coli* to amoxicillin by producing penicillase was 60% according to data obtained in 2015 (Benhiba *et al*., 2015). With rates reported in a study in the Marrakech military hospital (65%) (El Bouamri *et al*., 2014). And therefore below that of the Meknes military hospital (85%) (Lahlou Amine *et al*., 2009). These high levels of uropathogenic *E. coli* resistance to amoxicillin justify that aminopenicillins are no longer recommended for probabilistic UI treatment (*www.jle.com*). *E. coli* resistance rate to ciprofloxacin (Quinolones) was 25% among patients seen in the hospital, almost equivalent to those of Morocco 20% (Nadmi *et al*., 2010) and 27% in Rabat (Tagajdid *et al*., 2010). The global epidemiological situation of the resistance of *E. coli* strains to fluoroquinolones remains variable with 10% resistance rate in the United States (Neuhauser *et al*., 2003).

In addition, there is 55% resistance rate of *E. coli* to Ofloxacin and 50% to Nalidixic Acid. Acquired resistance to quinolones is conventionally due to chromosomal mutations by minor changes of the target, the to poisomerases of type II (DNA gyrase) and IV and its diffusion is limited. Resistance by decreasing the intracellular concentration of these antibiotics membrane impermeability and/or over-expression of efflux systems is rare (Hooper, 2001). The resistance rate of *K. pneumoniae* recorded was 60% for cefotaxime and 50% for cefoxitin in the second and third generation cephalosporin group. However in Bamako, the sensitivity was 84% for cefoxitin and 58% for cefotaxime (Tahirou, 2005).This higher sensitivity rate to cefoxitin compared with cefotaxime may be explained by the large number of strains producing ESBL (extended-spectrum beta lactamase) among isolated*Klebsiella* strains. *K. pneumoniae* expressed a relatively low resistance rates of 1% to imipenem, but the higher rate of 12% was observed (Akram *et al*., 2007), 10% of uropathogenic ESBL enterobacteria isolated in the hospital laboratory Avicenna military of Marrakech were resistant to imipenem. All of these imipenem-resistant strains belonged to the species *K. pneumoniae*, ie 20% of all strains of *K. pneumoniae* producing ESBLs were isolated during the same year (El Bouamri *et al*., 2014). Another point to note is the emergence of multiresistant strains *E.cloacae*. In fact, among the main isolated enterobacteria, the species *E. cloacae* presented the resistance levels for the majority of the antibiotics tested, despite its low frequency of isolation (11.47%). The percentage of *E cloacae* resistant to 3rd generation cephalosporins obtained in this analysis was 39.04%. This finding is also reported at the Moulay-Ismail Hospital (Meknes, Morocco) where 52% of strains of *E. cloacae* are resistant to cephalosporin of third generation (Lahlou Amine *et al*., 2009). *Acinetobacter baumannii* is a non-fermenting Gram-negative bacillus, often with multi-resistance to antibiotics such as beta-lactams (40% ampicillin, 20% ticarcillin and amoxicillin), with higher levels of 90-100% for beta-lactams already listed, for cephalosporins 3rd and 4th generation (40% to cefotaxime), 20% resistance to amino glycosides and fluoroquinolones against 55.5% in hospitals (Qingling, Kong *et al*., 2018).

This germ is considered an opportunistic pathogen responsible for occasional sporadic nosocomial infections or epidemic. The most commonly encountered infections are pulmonary infections septicemia, wound infections and urinary tract infections (Jans *et al*., 2014). Antibiotic resistance of beta-lactam is made by increased degradation by beta-lactamases, mutations that alter cell targets or functions (alterations of penicillin-binding proteins (PBP), reduced access to bacterial targets due to the decrease in the permeability of the outer membrane caused by the loss or reduced expression of porins, and the expulsion of antibiotics out of the cell by the flow pump (Davies and Davies, 2010). *A. baumannii* produces inherent an AmpC-type cephalosporinase, also known as Acinetobacter-derived cephalosporinases (ADC) (Bou and Martínez-Beltrán, 2000; Hujer *et al*., 2005). ADC hydrolyze amino-penicillins and cephalosporins extended spectrum. While the main mechanism for quinolone resistance is made via mutations in the gyrA and parC genes, which results in phenotypic changes in DNA gyrase and topoisomerase IV, leading to reduced drug affinity (Ugolotti *et al*., 2016). This evolution of bacterial resistance to antibiotics gradually over time is the result of the inappropriate use of antibiotics.

It is foreseeable that new bacterial resistance will emerge in the future, including the acquisition of new resistance mechanisms allowing the bacterium to sophisticate its physiological and enzymatic equipment in order to fight against the lethal effect of new antibiotics (Moukrad *et al*., 2012). Therefore, the choice of an antibiotic must take into account the field (pregnant woman, elderly, kidney or liver failure, allergic or intolerance), always choose the least toxic antibiotic and monitor this potential toxicity by appropriate means. In addition, it is necessary to respect the durations of treatments, the current tendency is the shortening of the durations of treatment to reduce the selection of the multi-resistant bacteria. The need to verify that the prescribed treatment was followed by the patient is an obligation (Bruyère *et al*., 2008).

Conclusion

This study helped to raise the emergence and spread of bacteria involved in urinary tract infections and their resistance to antibiotics. Ultimately, urinary tract infections lead specifically to urogenital infections in women and include disorders related to the female urogenital tract. The analysis of the germs of the urinary tract made it possible to determine the prevalence of pathogenic tropics found such as *E. coli*, *K. pneumoniae* and *E. cloacae*. A big step in the fight against these infectious agents has been made with the discovery of antibiotics but a regression is felt since the emergence of bacterial resistance. Unfortunately, this phenomenon of natural origin induces acquired resistance that tends to grow due to overconsumption of antibiotics and/or non-compliance with antibiotic treatment protocols. Therefore, we must adopt a policy for the appropriate use of antibiotics; updated by regular antibiotic susceptibility surveillance programs to stop the spread of this bacterial resistance. Alternative treatment options reside in the identification of medicinal plants with antibacterial and antifungal properties and can suppress resistant strains and/or multi-resistant to current molecules commonly distributed in pharmacies in order to improve the care of patients.

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