Kafando et al. *Afr. J. Clin. Exper. Microbiol.* 2023; 24 (2): 211 - 216 https://www.afrjcem.org

African Journal of Clinical and Experimental Microbiology. ISSN 1595-689X Apr 2023; Vol.24, No.2
AJCEM/2245. https://www.ajol.info/index.php/ajcem

Short Communication **Open Access**

Antibiotic susceptibility of uropathogenic *Escherichia coli* isolates in a hospital setting in Ouagadougou, Burkina Faso: A twelve-year retrospective analysis

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Abstract:

Background: *Escherichia coli* is the main bacterium responsible for uncomplicated urinary tract infections (UTI). The increasing frequency of antibiotic resistance in *E. coli* isolates from UTI poses concern in their therapeutic management. The aim of this study is to describe the current antibiotic resistance profile of *E. coli* clinical isolates at the Yalgado Ouedraogo University Hospital of Ouagadougou (CHUYO), Burkina Faso, with a view to revising the treatment protocols for bacterial UTI.
Methodology: This was a retrospective review and descriptive study of all *E. coli* isolates from febrile UTI at CHUYO from January 2010 to December 2021. During this period, two techniques were used to perform antibiotic susceptibility test; agar diffusion from 2010 to 2018 and commercial liquid susceptibility testing from 2019 to 2021 using the BD Phoenix M50 automated system. The detection of ESBLs was performed using the Expert System of the automated system or a synergy test combining an amoxicillin-clavulanic acid and a 3rd generation cephalosporin (3GC) disc.
Results: A total of 2055 non-repetitive strains of *E. coli* were isolated from UTI over the period of study, with 62.0% (1274) of isolates resistant to 3GC. Resistance to 3GC by ESBL production was the most dominant mechanism in 83.1% of cases (1059/1274). Among the 781 (38.0%) 3GC-susceptible isolates, there were high resistance rates to ampicillin (75.2%) and cotrimoxazole (60.2%), but these isolates retained full susceptibility to imipenem (carbapenem) and fosfomycin. As for the 3GC-resistant strains, there was high resistance to cotrimoxazole (93.0%) and ciprofloxacin (90.3%) but relatively low to medium resistance to gentamicin (56.0%) and amikacin (26.3%), and low resistance to nitrofurantoin (10.0%), fosfomycin (6.1%) and imipenem (4.2%). About one third (31.7%) of all the isolates tested were resistant to both ceftriaxone and gentamicin.
Conclusion: In view of the results, the implementation of rapid diagnostic tools such as the β-lactamase test to guide empirical antibiotic therapy is essential for an early and efficient management of febrile UTI at the local level in Burkina Faso.

Keywords: Urinary tract infection, susceptibility, resistance, *Escherichia coli*, β-lactamase, Burkina Faso

Received Dec 19, 2022; Revised Mar 14, 2023; Accepted Mar 16, 2023

Sensibilité aux antibiotiques des isolats d'*Escherichia coli* uropathogènes en milieu hospitalier à Ouagadougou, Burkina Faso: une analyse rétrospective sur douze ans

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Résumé:

Contexte: *Escherichia coli* est la principale bactérie responsable des infections des voies urinaires (IU) non compliquées. La fréquence croissante de la résistance aux antibiotiques dans les isolats d'E. coli issus d'infections urinaires pose problème dans leur prise en charge thérapeutique. Le but de cette étude est de décrire le profil actuel de résistance aux antibiotiques des isolats cliniques d'*E. coli* au Centre Hospitalier Universitaire Yalgado Ouedraogo de Ouagadougou (CHUYO), Burkina Faso, en vue de réviser les protocoles de traitement des IU bactériennes.
Méthodologie: Il s'agissait d'une revue rétrospective et d'une étude descriptive de tous les isolats d'E. coli provenant d'infections urinaires fébriles au CHUYO de janvier 2010 à décembre 2021. Au cours de cette période, deux techniques ont été utilisées pour effectuer un test de sensibilité aux antibiotiques; diffusion sur gélose de 2010 à 2018 et tests commerciaux de sensibilité liquide de 2019 à 2021 à l'aide du système automatisé BD Phoenix M50. La détection des BLSE a été réalisée à l'aide du Système Expert de l'automate ou d'un test de synergie associant un amoxicilline-acide clavulanique et un disque de céphalosporine de 3ème génération (C3G).
Résultats: Un total de 2055 souches non répétitives d'*E. coli* ont été isolées d'UTI au cours de la période d'étude, avec 62,0% (1274) d'isolats résistants au C3G. La résistance aux C3G par production de BLSE était le mécanisme le plus dominant dans 83,1% des cas (1059/1274). Parmi les 781 (38,0%) isolats sensibles au C3G, il y avait des taux élevés de résistance à l'ampicilline (75,2%) et au cotrimoxazole (60,2%), mais ces isolats conservaient une sensibilité totale à l'imipénème (carbapénème) et à la fosfomycine. Quant aux souches résistantes au C3G, il y avait une résistance élevée au cotrimoxazole (93,0%) et à la ciprofloxacine (90,3%) mais une résistance relativement faible à moyenne à la gentamicine (56,0%) et à l'amikacine (26,3%), et une faible résistance à la nitrofurantoïne (10,0%), la fosfomycine (6,1%) et l'imipénem (4,2%). Environ un tiers (31,7%) de tous les isolats testés étaient résistants à la fois à la ceftriaxone et à la gentamicine.
Conclusion: Au vu des résultats, la mise en place d'outils de diagnostic rapide comme le test de la β-lactamase pour guider l'antibiothérapie empirique est indispensable pour une prise en charge précoce et efficace des IU fébriles au niveau local au Burkina Faso.

Mots clés: Infection urinaire, sensibilité, résistance, *Escherichia coli*, β-lactamase, Burkina Faso

Introduction:

Urinary tract infection (UTI) is one of the most common infections in the world, and one of the first reasons for consultation, making the urine cytobacteriological examination by far the most prescribed bacteriological examination(1). The Gram-negative bacilli (GNB), especially *Enterobacteriaceae*, occupy important place among the bacteria responsible for UTI (2). *Escherichia coli* is both a commensal of the human gastrointestinal tract and the main pathogen responsible for UTI, representing 60-80% of uropathogenic enterobacteria in both the developed and developing countries (3,4). Its high frequency in infections makes it a priority for surveillance and assessment of its level of antibiotic resistance.

The last decades have been marked by a steady increase in antibiotic resistance in clinical *E. coli* strains due to the emergence and dissemination of CTX-M ESBLs worldwide (5,6). The frequent use of carbapenems which are reserved antibiotics for the treatment of severe *E. coli* ESBL infections, is associated with the emergence of carbapenem-resistant strains through production of carbapenemases, membrane impermeability or efflux mechanisms (7).

The third generation cephalosporins (3GC), either as monotherapy or in combination with an aminoglycoside (such as gentamicin), are used in the presumptive treatment of febrile UTI at Yalgado Ouedraogo University Hospital of Ouagadougou (CHUYO), Burkina Faso. These therapeutic protocols developed on the basis of recommendations from other countries are not always in line with the microbial ecology of our countries. The aim of this study therefore was to describe the antibiotic resistance profiles of *E. coli* strains isolated from UTIs over the last decade to verify the validity of these first-line treatment protocols and to propose adaptive solutions.

Materials and method:

Study setting design and period of study:

This was a retrospective study over the period of 12 years (1 January 2010 to 31 December 2021) on all patients who presented with UTI and confirmed by a urine culture in the Bacteriology-Virology Department of the CHUYO.

Inclusion and exclusion criteria:

Patients whose urine samples met the criteria for UTI were included in this study; leukocyturia greater than 10^4 leukocytes /ml and bacteriuria greater than or equal to 10^3, 10^4 or 10^5 CFU/ml, depending on the uropathogenic nature of the bacterial species identified (8,9,10,11). All patients with a negative or positive urine on cytobacteriological examination but associated with candidiasis were excluded. Clearly identified duplicates were also excluded (isolation of the same species

with the same susceptibility profile from the same patient).

Culture and identification of bacteria:

Bacteria were isolated on CLED and EMB or URISELECT® agar media, depending on their availability. From 2010 to August 2019, bacterial identification was mainly performed by conventional methods including the use of API20E or minimal galleries depending on the availability of inputs. From September 2019 to December 2021, identification and susceptibility testing was performed on the BD Phoenix M50 (Becton Dickinson; New Jersey).

Antibiotic susceptibility testing and resistance detection:

With the exception of antibiotic susceptibility tests performed after the acquisition of the BD Phoenix automated system from 2019, all other tests were performed by the agar diffusion method. The following antibiotic discs (ThermoFisher Diagnostics, Oxoid, France) were used; ampicillin (AM) 10µg, amoxicillin-clavulanic acid (AMC) 20-10µg, ceftriaxone (CRO) 30µg, ceftazidime (CAZ) 10µg, cefepime (FEP) 30µg, cefoxitin (FOX) 30µg, imipenem (IMP) 10µg, gentamicin (GN) 10µg, amikacin (AK) 30µg, ciprofloxacin (CIP) 5µg, trimethoprim-sulfamethoxazole (SXT) 1.25 - 23.75µg, nitrofurantoin (NR) 100µg, and fosfomycin (FOS) 200µg.

ESBL screening was performed by a synergy test involving a central disc of amoxicillin/clavulanic acid 30 mm from a disc of 3GC (ceftazidime, ceftriaxone) or 4GC (cefepime). For liquid antibiotic susceptibility testing, ESBL detection was performed using the BD Phoenix M50 Expert System (Becton Dickinson; New Jersey) but the cartridges used for antibiotic susceptibility testing did not allow the detection of carbapenemases or cephalosporinases (ampC). The interpretation of the susceptibility test was performed according to the 2019 guideline of the European Committee for Antimicrobial Susceptibility Testing

Statistical analysis:

The data for this study were entered into Excel 2013 and analysed with EPI-INFO 7.2.4.0. Tables and graphs were produced. The Chi-square test used to measure association between the different proportions, with value of $p<0.05$ considered as statistical significance.

Ethical considerations:

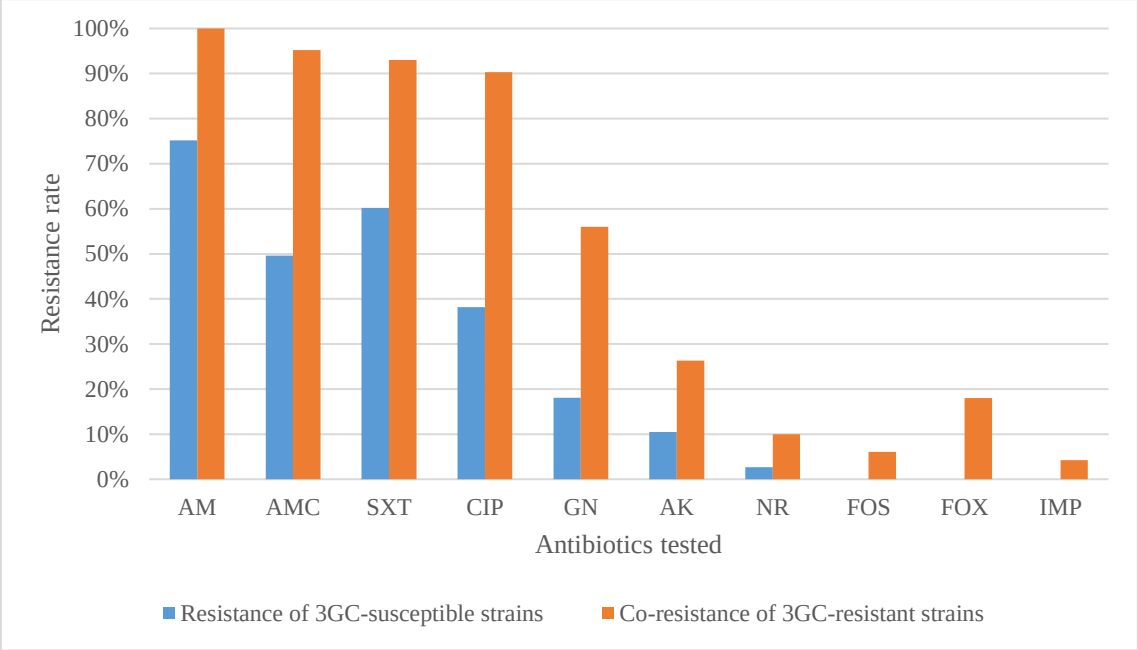
Personal data collected from patients were not disclosed.

Results:

A total of 2947 family *Enterobacteriaceae* were isolated out of which 2055 (69.7%) were non-repetitive *E. coli* isolates. A total of 1274 (62%) *E. coli* isolates were resistant to 3GCs while 781 (38%) were susceptible. Resistance by beta-lactamase production (78.4%, 1611/2055) was the main mechanism of resistance, of which 51.5% (1059/2055) were by ESBLs and 26.9% (552/2055) penicillinases. Resistance to 3GC by ESBL production was the dominant mechanism (1059/1274; 83.1%).

Among the 781 3GC-susceptible isolates, the rate of resistance was high to ampicillin (75.2%) and cotrimoxazole (60.2%), moderate resistance to amoxicillin/clavulanic acid (49.6%) and ciprofloxacin (38.2%), and low resistance to gentamicin (18.1%), amikacin (10.5%) and nitrofurantoin (2.7%). These isolates showed no resistance to carbapenems, cephamycins and fosfomycin (Fig 1).

The 3GC-resistant isolates showed a high resistance rate to amoxicillin-clavulanic acid (95.2%), cotrimoxazole (93.0%) and ciprofloxacin (90.3%), moderate resistance rates to aminoglycosides, with a large disparity between gentamicin (56%) and amikacin (26.3%). However, the resistance rate was low to cefoxitin (18%), nitrofurantoin (10%), fosfomycin (6.1%) and imipenem (4.2%) (Fig 1). Of the 1800 isolates tested for susceptibility to both gentamicin and ceftriaxone, one third of were resistant to both antibiotics and less than 30.0% of the isolates were susceptible to both (Table 1).



AM: ampicillin, AMC: amoxicillin-clavulanic acid, SXT: cotrimoxazole, CIP: ciprofloxacin, GN: gentamicin, AK: amikacin, NR: nitrofurantoin, FOS: fosfomycin, FOX: cefoxitin, IMP: imipenem

Fig 1: Comparison of the resistance rates of 3GC-resistant versus 3GC-sensitive *Escherichia coli* isolates to different antimicrobial agents

Table 1: *In vitro* efficacy of combined ceftriaxone and gentamicin against *Escherichia coli* isolates

Phenotypes	**Number of isolates**	**Percentage**
CRO^S and GN^R	243	13.5
CRO^R and GN^S	448	24.9
CRO^S and GN^S	538	29.9
CRO^R and GN^R	571	31.7
Total	**1800**	**100.0**

GN: Gentamicin; CRO: Ceftriaxone; S: Susceptible; R: Resistant

Discussion:

The resistance profiles of uropathogenic *E. coli* isolates vary considerably in time, and space. The knowledge of the local epidemiology and its evolution is necessary for the choice of an effective and adapted empirical antibiotic therapy. The result of our study showed a predominance of *E. coli* (69.7%) in UTIs caused by enterobacteria. The predominance of *E. coli* in the bacteriological profile of UTIs has been reported in several studies in proportions ranging from 60% to more than 80% of enterobacteria (4,12). This predominance can be explained by the presence of virulence factors such as adhesins (fimbriae or pili) and toxins in the strains responsible for extra-intestinal pathologies (13). The role of type 1 pili of *E. coli* in lower UTI such as cystitis has been widely documented. Indeed, its adhesin, FimH, attached to the top of the pili, specifically binds to D-mannose residues attached to the surface of membrane glycoproteins lining perineal and bladder cells resulting in bacterial persistence and enhanced inflammatory response to infection (14).

The main mechanism of antibiotic resistance in *E. coli* observed in this study was enzymatic resistance through the production of beta-lactamases. Indeed, analysis of the data shows that resistance by ESBL production (51.5%) and penicillinases (26.9%) were the most frequent mechanisms. Similar results were reported in Antananarivo, Madagascar on uropathogenic *E. coli* strains with respec tive frequencies of 22.5% of ESBL-producing strains against 55.9% of penicillinase-producing strains, 50% of which was high-level resistance penicillinases (15).

Aminopenicillin (ampicillin and amoxicillin/clavulanic acid) resistance was the most common, with a rate of 75.2% among 3GC-susceptible isolates for ampicillin and 49.6% for amoxicillin/clavulanic acid, with 100% and

95.0% among 3GC-resistant isolates respectively. Penicillinase resistance in *E. coli* has long been described and is most commonly associated with TEM penicillinases (15,16). However, the emergence and spread of this acquired resistance is thought to be a consequence of the overuse of aminopenicillins through selection pressure.

About 62% of the *E. coli* isolates were resistant to 3GCs and in 83.1% of cases, this resistance was associated with ESBL production. Sbiti et al., (17) reported high rates of 3GC resistance of up to 80% among ESBL producing strains. The emergence and spread of ESBLs in *E. coli* is thought to be due to the advent of CTX-M ESBLs in the 1990s, which are genetically supported by a plasmid, but also due to the selection pressure caused by the overuse of antibiotics (6). The high incidence of resistance to 3GCs considerably reduces the therapeutic options and maintains a continuous increase in the prescription of carbapenems which retain good activity in most cases (18). Indeed, over the study period 1.9% of *E. coli* isolates were resistant to imipenem. These data show the emergence of pan-resistance phenotype to beta lactam antibiotics, often combining several mechanisms, including production of ESBLs or the co-production of ESBLs and carbapenemases, as well as impermeability of bacteria to antibiotics (19). The use of rapid diagnostic tools such as the β-lacta test (Bio-Rad, France) for the early detection of bacteria resistant to 3GCs through production of beta-lactamases will allow an appropriate choice of first-line antibiotics and the preservation of last-resort drugs (20).

The rate of resistance to fluoroquinolones (ciprofloxacin) was very high in 3GC resistant isolates (90.3%) in contrast to the 3GC-sensitive strains (38.2%). Similar results were reported by Sbiti et al., (17) and El Bouamri et al., (21) who reported in their studies, rates of ciprofloxacin co-resistance ranging from 82% to 92.5% in ESBL producing strains. The co-resistance of ESBL-producing strains is thought to be linked to the presence of mobile *qnr* genetic elements (A, B, S alleles) and especially the *aac(6')-Ib-cr* gene which most often co-exists with CTXM-type ESBL genes and confers dual aminoglycoside-piperazinylamine-quinolone resistance (22). In addition, the high prescription of fluoroquinolones in the treatment of UTIs caused by enterobacteria, in this case *E. coli*, is not to be outdone (12). High-level resistance in all fluoroquinolones is most often related to cumulative mutations in DNA gyrase A or B (*gyrA/gyrB*) and *parC* (23).

Almost all family *Enterobacteriaceae* are naturally susceptible to aminoglycosides. Most of the observed resistance is attributable to the acquisition of modifier enzymes. Aminoglycoside co-resistance in our study varied significantly depending on the molecule and the bacterial phenotype towards beta-lactams. Indeed, 3GC-resistant isolates had relatively high rates of associated resistance, 56.0% for gentamicin versus 18.1% for amikacin. The 3GC-sensitive isolates had resistance rates to aminoglycosides of 26.3% and 10.5% for gentamicin and amikacin respectively. Belmonte et al., (24) and Sbiti et al., (17) reported that 67.2%-75% of 3GC-resistant strains of family *Enterobacteriaceae* through ESBL production were resistant to gentamicin compared to 6%-18% for amikacin. However, a low rate of resistance to amikacin (14.3%) was observed overall in our study. This pattern was reported by Sbiti et al., (17) and Nana et al., (1) with rates of 6.1% and 10.4% respectively. The high variability of resistance to gentamicin and amikacin is thought to be associated with aminoglycoside acetylases of the AAC(3) type that spare amikacin and/or AAC(6') with amikacin AAC(6')-I and gentamicin AAC(6')-II as substrates. The high resistance to gentamicin in our study is thought to be due to the presence of AAC(3) and or AAC(6')-II acetylases.

Analysis of combined *in vitro* efficacy of ceftriaxone and gentamicin commonly used as empirical treatment for febrile UTIs showed that less than 30% of *E. coli* isolates were sensitive to both drugs, compared to 31.7% of cases of associated resistance. This combined antibiotics, long considered as the empirical antibiotic therapy of choice during invasive infections in many departments of the CHUYO, is now experiencing enormous limitations due to the multi-resistance of bacteria, in this case *E. coli*.

Conclusion:

Escherichia coli is the main uropathogenic bacterium observed at the CHUYO in Ouagadougou, Burkina Faso. The production of beta-lactamases is its main mechanism of resistance to beta-lactams. Antibiotics for the treatment of uncomplicated UTIs, notably fosfomycin and nitrofurantoin remained active on *E. coli* isolates in the present study but about one third of the isolates were resistant to both ceftriaxone and gentamicin, which are generally used in synergy for therapy of febrile UTIs at UHYO.

The implementation of rapid diagnostic tools such as the β-lacta test (Bio-Rad, France) for rapid identification of resistance, will guide empirical antibiotic therapy, which is essential for early and effective management of febrile UTIs at local level in Burkina Faso.

Contributions of authors:

HK was involved in data compilation, analysis, writing of the manuscript; MO was involved in data compilation; MK, YDC, KO,

RO, MS and CG were involved in sample analysis; LS was involved in supervision of the project and correction of the manuscript; ASO was involved in coordination of the surveillance of antibiotic resistance throughout the national territory and correction of the manuscript; and IS was involved in correction of the manuscript. All authors approved the final manuscript submitted.

Source of fundings:

No funding was received for the study

Conflicts of interest:

Authors declare no conflict of interest

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