

Brief Report

Efficacy of Fosfomycin against Extended Spectrum Beta-Lactamase-Producing *Escherichia coli* Isolated from Patient Urinary Cultures in the General Reference Hospital of Niamey, Niger

Alassane Halawen Mohamed ^{1,2,*} , René Dembélé ^{2,3,*} , Alio Mahamadou Fody ⁴ ,
Alix Bénédicte Kagambèga ² , Hiliassa Coulibaly ², Frédéric François Bado ², Chaibou Salaou ¹, Laouali Boubou ⁵,
Alkassoum Ibrahim ^{6,7}, Eric Adehossi Omar ^{7,8}  and Nicolas Barro ²

- ¹ Microbiology Laboratory of the General Reference Hospital (GRH), Niamey BP 12674, Niger; chaiibo@yahoo.fr
 - ² Laboratory of Molecular Biology, Epidemiology and Surveillance of Foodborne Bacteria and Viruses (LaBESTA), University Joseph KI-ZERBO of Ouagadougou, Ouagadougou BP 7021, Burkina Faso; alixbenedictekagambega@gmail.com (A.B.K.); coulhiliassa@gmail.com (H.C.); fredbado94@gmail.com (F.F.B.); barronicolas@yahoo.fr (N.B.)
 - ³ Training and Research Unit in Applied Sciences and Technologies, University of Dedougou, Dedougou 03 BP 176, Burkina Faso
 - ⁴ Superior Normal School, University Abdou Moumouni of Niamey, Niamey BP 10662, Niger; juniorfodym@gmail.com
 - ⁵ Bacteriology Laboratory of the Niamey National Hospital (NNH), Niamey BP 238, Niger; laouali_boubou@yahoo.com
 - ⁶ Direction of Surveillance and Response to Epidemics, Ministry of Public Health, Niamey BP 623, Niger; ibrahim_alkassoum@yahoo.fr
 - ⁷ Faculty of Health Sciences, University Abdou Moumouni of Niamey, Niamey BP 12022, Niger; eadehossi@yahoo.fr
 - ⁸ Center for Medical and Health Research, Niamey BP 10887, Niger
- * Correspondence: mohamed.alassane@outlook.fr (A.H.M.); rene.dembelle@univ-dedougou.bf or simavedemb@gmail.com (R.D.)



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Abstract: Urinary tract infection (UTI) is a common patient infection and a major public health problem today. The rapid spread of antibiotic resistance genes in *Enterobacterales*, particularly in Extended-spectrum beta-lactamases producing *Escherichia coli* (ESBL-*E. coli*), is compromising treatment with the antibiotics that are normally used. The aim of this study was to evaluate the level of susceptibility of uropathogenic ESBL-producing *E. coli* to fosfomycin as an alternative treatment. A total of 3369 samples of urine were received and processed in the Bacteriology Laboratory of the Niamey General Reference Hospital (NGRH) throughout 2021. Synergy testing was performed for phenotypic detection of ESBLs, and fosfomycin sensibility of ESBLs-producing uropathogenic *E. coli* isolates were determined using the Viteck-2 system. Of the 280 enterobacteria identified in the urine samples, 104 *Escherichia coli* isolates were positive to the synergy test. The average age of the patients was 54 ± 17 . The age range of 46–65 years was the most affected by these infections. The female patients predominated over the male ones, with a prevalence of 51.90%, a sex ratio of 1.08. The ESBL-producing *E. coli* isolates were 0.97% resistant to fosfomycin. Fosfomycin is highly effective against uropathogenic ESBL-producing *E. coli* isolates. It could be used as an alternative treatment for both uncomplicated and complicated urinary tract infections.

Keywords: ESBL-producing *E. coli*; fosfomycin resistance; Niamey; Niger

1. Introduction

Antimicrobial resistance has increased worldwide, thus leading to infections which are more difficult to treat, with higher mortality, morbidity, and costs. Beta-lactam re-

sistance, particularly, is on the increase, and the production of antibiotic-inactivating enzymes in Gram-negative pathogens is one of the most common mechanisms of drug resistance [1]. The increasing ubiquity of *Escherichia coli* positive for the production of antibiotic-inactivating enzymes in both community and hospital settings has been shown by several studies [2]. ESBL (extended spectrum beta-lactamase)-producing *E. coli* are emerging enterobacteria responsible for urinary tract infections (UTI) in patients [3], and urinary tract infections provoked by these pathogens have become a major public health problem today [4,5]. An uncomplicated UTI is a bacterial infection of the lower urinary tract that is not associated with structural abnormalities of the urinary tract or comorbidities such as diabetes, immunosuppression, or pregnancy, whereas a complicated UTI is associated with structural abnormalities of the urinary tract or comorbidities such as the above [6]. Indeed, the appearance of these bacteria in urinary tract infections is a medical emergency [7,8] requiring long-term monitoring in order to implement appropriate probabilistic treatment [9]. A long time ago, the treatment for UTI was a challenge for physicians due to the emergence of multidrug-resistant uropathogens. In this regard, the treatment of urinary tract infections requires antibiotic therapy, which must be carried out conventionally on the basis of susceptibility test results to avoid the development of resistant mutants or partial cures [10].

At least, the treatment of bacterial infections suffers from the spread of multidrug-resistant (MDR) or extensively drug-resistant (XDR) pathogens and a lack of development of new antibiotics active against such MDR and XDR bacteria [11]. As a result, physicians have turned to older antibiotics. Fosfomycin is a bactericidal antibiotic produced by *Streptomyces fradiae* and classified as a phosphonic acid. It has a broad activity against Gram-positive and Gram-negative pathogens and is particularly active against multi-resistant bacteria such as ESBL-producing *Escherichia coli* [12]. Fosfomycin is used in many countries around the world for a variety of indications, in both of its oral formulations (trometamol or calcium salt), in single doses of 3 g for the treatment of urinary tract infections [13,14]. Fosfomycin acts as a phosphoenolpyruvate analog, preventing the initial stage of cell wall synthesis via the inhibition of MurA (UDP-N-acetylglucosamine enolpyruvyl-transferase enzyme), which catalyzes the initial step of N-acetylmuramic acid and peptidoglycan biosynthesis, leading to bacterial cell death [15]. Fosfomycin is very well tolerated by the body, and adverse reactions vary from 1% to 5% of patients [16,17]. The ESBL-producing *Enterobacteriaceae* family has been detected worldwide, and the risk factors associated to it may be related to hospital care or antibiotic therapy. A recent study showed a high incidence of ESBL resistance genes (73.0% for *bla* TEM, 35.1% for *bla* CTX-M, and 8.1% for *bla* OXA-1) among *E. coli* isolated from urine samples in two hospitals (Hôpital National de Niamey and Hôpital National Lamorde) in Niamey [1]. Therefore, it is imperative that the majority of these bacteria are tested for antibiotic resistance, so that strategies can be put in place to halt the continued spread of these pathogens [18]. The current study intended to assess the effectiveness of fosfomycin against ESBL-producing *Escherichia coli* isolated from patient urine cultures in the General Reference Hospital of Niamey.

2. Materials and Methods

2.1. Study Site, Period, and Data Gathering

To assess the efficacy of fosfomycin against ESBL-producing *Escherichia coli* isolated from patient urinary cultures in the General Reference Hospital of Niamey (GRHN), Niger, we conducted a prospective sampling of urine. The study was held in the Bacteriology Laboratory of the GRHN from January to December 2021. A total of 3369 urinary samples were collected from hospitalized patients and community patients. Only data from ESBL-producing *E. coli* isolates were collected on cards in the Bacteriology Laboratory. The urine cultures yielding growths other than extended spectrum beta-lactamases-producing *E. coli* were eliminated from the study. The request to participate in the study was sent to all the patients and their family members to obtain their positive opinion on the bacteriological analysis of urine.

The macroscopic appearance of the total urine (i.e., non-centrifuged urine) was first assessed. Next, a part of the total urine was introduced into a KOVASLIDE cell to quantify the white blood cells and the red blood cells. Simultaneously, another part of the total urine was centrifuged to qualitatively assess the figurative elements in a pellet placed between a slide and a coverslip under a 40X microscope.

All the urinary samples were inoculated into Cystine–Lactose–Electrolyte-Deficient (CLED) (Himedia, Dindori, Nashik, India) agar and non-selective agar media UriSelect 4 (Bio-Rad, Redmond, WA, USA) following standard bacteriology protocols. The culture media were then placed in a 37 °C incubator for 18–24 h.

2.2. Identification and Antimicrobial Susceptibility Testing

Vitek GN cards were used to identify *E. coli* isolates and an AST-N372 card was used to determine the *E. coli* isolates' sensitivity and resistance to fosfomycin [19]. Each AST card contains a selection of antibiotics in varying concentrations, together with a dehydrated culture medium. In our study, fosfomycin was the focus of attention, with variable concentrations of 8, 16, and 32 µg in different wells of the AST. The results were categorized using the CA-SFM EUCAST 2019 V2 version 9.02 software [20]. ESBL testing was carried out on all C3G-resistant *E. coli* isolates. A synergy test was performed for the ESBL phenotypic research, which resulted in champagne cork images, using antibiotic discs, amoxicillin-clavulanic acid (20/10 µg), ceftazidime (10 µg), cefepime (30 µg), and cefotaxime (5 µg) on single Mueller–Hinton agar, incubated at 37 °C for 24 h according to the CA-SFM 2019 recommendations [21]. For the *E. coli* isolates that did not express champagne cork images on the single Mueller–Hinton agar, an additional synergy test was performed by adding 250 mg/L of the cephalosporinase inhibitor cloxacillin to single Mueller–Hinton agar to test for champagne cork images [21].

2.3. Data Analysis and Processing

The data were collected and analyzed with the EPI Info Version 7.2.2.6 software. A *p*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Prevalence of ESBL-Producing *E. coli* Isolates

A total of 3369 urinary samples, i.e., 1651 samples (49%) from male patients and 1718 samples (51%) from female patients, were received in the Bacteriology Laboratory. In these samples, 280 enterobacteria were implicated in urinary tract infections. According to our findings, *Escherichia coli* was the most common *Enterobacteriales* associated with urinary tract infections. Indeed, out of the 280 enterobacteria, 209 were *E. coli* isolates, of which 104 were ESBL-producing *E. coli* (Figure 1), with a frequency of 37.14%, against 105 non-ESBL-producing *E. coli* isolates, i.e., 37.50%. The other enterobacteria isolates represented were 71, with a frequency of 25.36%.

The patients' average age was 54 ± 17 years. The age range most affected by ESBL-producing *E. coli* and urinary tract infections was 46–65 years, with frequencies of 58.65% and 48.19%, respectively, followed by the age group over 66 years, with frequencies of 21.15% and 26.51% (Table 1). This suggested that the age range that is most affected by urinary tract infections is also the age range which shows more ESBL-producing *E. coli*.

Considering the gender distribution, the ESBL-producing *E. coli* isolates were found more in the female patients, with a frequency of 51.90%, than in the male patients, with a frequency of 48.10%, i.e., a sex ratio of 1.08 (Table 1).

It was also shown that urinary tract infections due to ESBL-producing *E. coli* isolates were more frequent (75.96%) in the community outpatients compared to the hospitalized inpatients (24.04%) (Table 1).

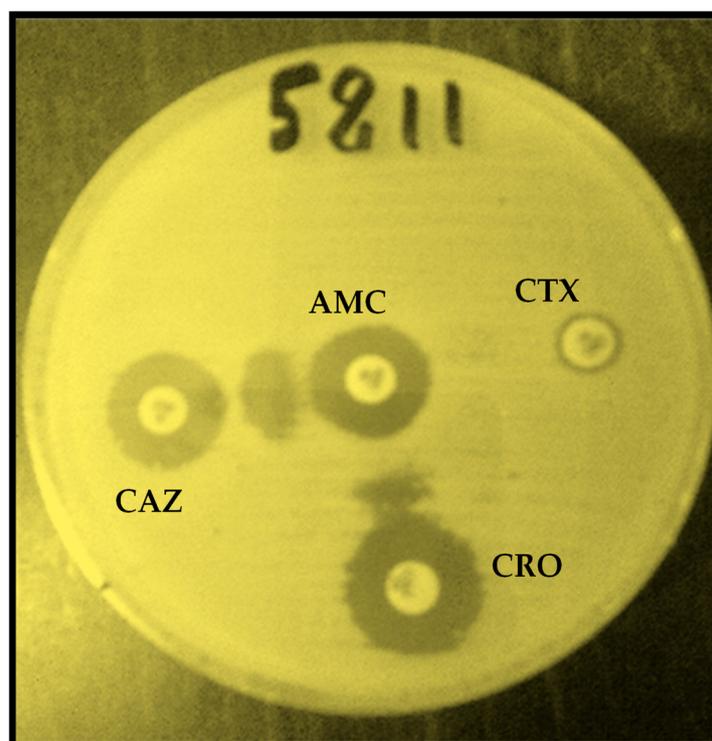


Figure 1. Synergy confirmation test for ESBL-producing *Escherichia coli*. **Legend:** AMC = amoxicillin-clavulanic acid, CTX = cefotaxime, CAZ = ceftazidime, and CRO = ceftriaxone.

Table 1. Distribution of ESBL-producing *Escherichia coli* according to socio-demographic aspects and patient status.

Age (Years)		≤5 N (%)	6–25 N (%)	26–45 N (%)	46–65 N (%)	≥66 N (%)	Total N (%)
Sexe	Male	0 (0)	0 (0)	6 (42.86)	28 (45.90)	16 (72.73)	50 (48.10)
	Female	1 (100)	6 (100)	8 (57.14)	33 (54.10)	6 (27.27)	54 (51.90)
Status	Inpatients	0 (0)	1 (16.67)	2 (14.30)	18 (29.51)	4 (18.19)	25 (24.04)
	Outpatients	1 (100)	5 (83.33)	12 (85.70)	43 (70.49)	18 (81.81)	79 (75.96)

Legend: N = number.

3.2. Susceptibility of ESBL-Producing *E. coli* to Fosfomycin

All the isolates were tested for susceptibility to twelve antibiotics belonging to seven classes: amoxicillin-clavulanic acid, temocillin, cefoxitin, ertapenem, imipenem, nalidixic acid, ofloxacin, amikacin, gentamicin, trimethoprim-sulfamethoxazole, fosfomycin, and nitrofurantoin. The ESBL-producing *E. coli* showed a 99.03% sensibility to fosfomycin compared to a 0.97% resistance. There was no statistically significant difference between the sexes for fosfomycin sensitivity ($p = 1.000$).

3.3. Antibiotic Resistance Profile of ESBL-Producing *Escherichia coli*

As far as the antibiotics-resistance profile is concerned, the ESBL-producing *E. coli* isolates revealed a high degree of *E. coli* resistance to various antibiotics. Indeed, in contrast with fosfomycin, as shown above, the ESBL-producing *E. coli* isolates showed high rates of resistance to cotrimoxazole (99.03%), fluoroquinolones (99.03%), and amoxicillin-clavulanic acid (85.58%). However, a low rate of resistance was observed towards cefoxitin (32.69%), amikacin (36.54%), temocillin (46.15%), and gentamicin (55.77%). Antibiotics such as ofloxacin (from the fluoroquinolones group) showed only a 0.97% sensitivity, while the sensitivity patterns of other oral antibiotics were 14.42% for amoxicillin-clavulanate and 0.97% for sulfamethoxazole-trimethoprim.

Interestingly, our findings showed very low resistance rates towards fosfomycin (0.97%), carbapenems (2.88%), and nitrofurantoin (10.58%) (Figure 2).

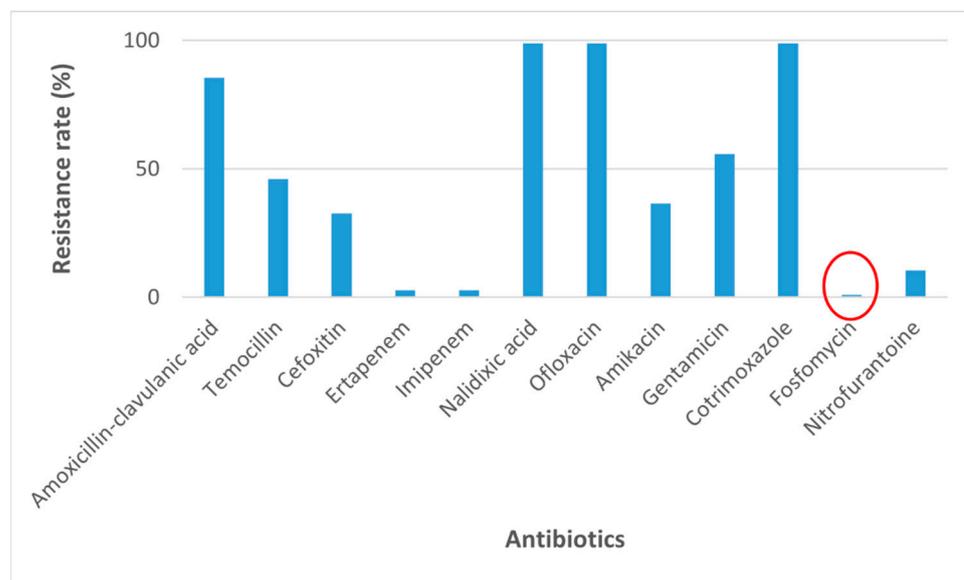


Figure 2. Resistance to individual antimicrobial agents among ESBL-producing *E. coli*.

4. Discussion

The present study showed the resistance to probabilistic antibiotics used to treat urinary infections due to *Escherichia coli* isolates. Our findings showed a high resistance to the sulfamethoxazole-trimethoprim combination (anti-folates family), the amoxicillin-clavulanic acid combination, and fluoroquinolones (nalidixic acid, ofloxacin). These results are also consistent with those reported by other researchers in different parts of the world [22,23], meaning that many antibiotics once used to treat urinary tract infections are now ineffective because of the development of antimicrobial resistance. Nonetheless, this increase in resistance to traditional antibiotic molecules will lead clinicians to a few new antibiotics, some of which have been recently approved, mostly for intravenous use, like meropenem/vaborbactam, imipenem/cilastatin-relebactam, sulopenem, ceftazidime-avibactam, ceftolozane-tazobactam, and aminoglycosides including plazomicin, cefideroc, sitafloxacin, and finafloxacin [24].

The mean age of the patients with urinary tract infections caused by ESBL-producing *Escherichia coli* isolates was 54 ± 17 years. This result was similar to those reported in 2021 by different authors in studies conducted in India and Morocco [25,26]. The age group of 46–65 years was the most affected by these ESBL-producing *Escherichia coli* isolates, and this corroborated what had been found by Jia et al. in China during a clinical study [27]. Our results differ slightly from a greater prevalence reported in the age groups of 61–70 (23.9%) and 71–80 (20.7%) years, in Pakistan [2]. However, the patients in both their study and ours are at an increased risk of developing chronic UTI, since they are elderly patients with low immunity and are generally diabetics, kidney patients, or suffering from other pathologies. Therefore, they must be managed with a better antimicrobial agent with fewer side effects.

When analyzing UTI prevalence according to gender, our results showed that 49% of the patients were male and 51% were female. Reasons such as female anatomy, particularly with regard to the urethra, i.e., the tube which carries urine from the bladder out of the body, may justify this difference. Indeed, the urethra is much shorter in length in women than it is in men, and pathogenic bacteria could easily enter the urinary tract through the urethra.

Our results show that as many ESBL-producing *Escherichia coli* isolates are involved in urinary tract infections as non-ESBL-producing *Escherichia coli*. Additionally, the female sex

was more favorable to ESBL-producing *E. coli*, with a frequency of 51.90% against the 48.10% observed for the male sex. In accordance with this finding, the *E. coli*-produced enzymes extended spectrum beta-lactamases (ESBLs) have been recognized as significant pathogens causing UTI. This pathogenicity is related to the fact that ESBLs are enzymes able to hydrolyze all penicillins, cephalosporins, and monobactams [28]. ESBLs are also responsible for the cross-resistance to co-trimoxazole, fluoroquinolones, and amino glycosides [29]. For all these reasons, ESBLs-producing bacteria commonly pose serious problems in UTI management. Notably, antibiotics such as ofloxacin (fluoroquinolones group) showed only a 0.97% sensitivity, meaning that their use in treating urinary tract infections has decreased. The sensitivity patterns of other oral antibiotics were 14.42% for amoxicillin-clavulanate and 0.97% for sulfamethoxazole-trimethoprim. Indeed, this also explains the response failure of those antibiotics during treatment on an empirical basis. Similar susceptibility patterns were found in a study conducted in Pakistan [2].

The ESBL-producing *Escherichia coli* isolated in our study presented low rates of resistance to fosfomycin (0.97%). This result is slightly higher than the zero resistance rate reported by other researchers in different parts of the world, such as Sri Lanka in 2019 [30], Morocco in 2021 [26], and India in 2022 [31]. However, other long-term, single-center and multi-center studies reported a 3% fosfomycin resistance rate in 2019 [32] and a 4.6% resistance rate in 2021, respectively [27]. Fosfomycin may be the treatment of choice for urinary tract infections caused by ESBL-producing *E. coli* isolates in patients. Indeed, fosfomycin has shown a good effectiveness in the laboratory compared to the other first-line antibiotics used [2]. Moreover, fosfomycin comes in the form of a single-dose oral tablet, is easily absorbed in the stomach before food intake, and is eliminated via urine [23]. Fosfomycin has no harmful effects on the body and its microbiota, so several clinical studies have demonstrated an excellent effectiveness of this antibiotic in the treatment of urinary infections compared to the use of other first-line antibiotics. [33–35]. It is interesting to note that this antibiotic was introduced into the list of antibiotics to be used as first-line treatments of urinary infections in European countries [36]. In addition, fosfomycin is part of the latest list of first-line antibiotics in the probabilistic treatment of urinary tract infections recommended by the European Association of Urology [37–39]. For example, in France, fosfomycin is indicated as a single oral dose for the first-line treatment of cystitis [40]. The data from our study on the effectiveness of fosfomycin against ESBL-producing *E. coli* confirm the conclusions of previous studies reported by researchers [23,41,42]. Interestingly, our results showed that up to 99.03% of the ESBL-producing *E. coli* isolates tested for susceptibility were susceptible to fosfomycin, demonstrating an increased efficacy of fosfomycin against isolates of multidrug-resistant *Escherichia coli*. In line with this, a mini-review of existing data showed that fosfomycin had a high efficacy against *Enterobacterales* in general, including those expressing enzymes for protection [43]. Despite decades of use, up to the present day, fosfomycin is resistant to the pathogenicity of ESBL-producing *E. coli* isolates, and this may explain the low resistance rates observed in several studies [44]. Other reasons also explaining the low rate of resistance to fosfomycin in ESBL-producing *Escherichia coli* isolates may include, certainly, the rapid contact time of the antibiotic with the isolates and its high elimination via urine, in its active form [45].

5. Conclusions

In the present study, fosfomycin showed a high rate of resistance against ESBL-producing *Escherichia coli* isolates. Our findings suggest that fosfomycin remains the best viable option for the treatment of urinary infections caused by ESBL-producing *Escherichia coli* isolates. Indeed, fosfomycin is absorbed rapidly in the stomach and presents no negative effects on the microbiota. In addition, it is eliminated in high concentration in urine, in its active form.

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review and editing, R.D., A.M.F., A.B.K., H.C., F.F.B., C.S. and L.B.; and supervision, A.I., E.A.O. and N.B. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all the subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding authors.

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Conflicts of Interest: The authors declare no conflict of interest.

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