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# The Resistance of Uropathogenic Bacteria to Fosfomycin

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**Abstract:** Urinary tract infection is among bacterial infections that provide antibiotic treatment. The overly systematic use of a single class of antibiotic induces a selection pressure leading to bacterial resistance. The purpose of this study is to evaluate the level of resistance and to follow the evolution of the sensitivity of uropathogenic bacteria to fosfomycin to allow a better antibiotherapy of urinary infections. This is a prospective 3-year study of all positive cytobacteriological urine exam from inpatients or consultants who have arrived at the microbiology laboratory at the Avicenne Military Hospital in Marrakech. Of the 12,116 cytobacteriological urine exam performed, 1788 met the criteria for urinary tract infection. These urinary infections mainly concerned patients followed externally (1471). The sex ratio between men and women is 1.07. Of the isolated uropathogenic bacteria, *E. coli* is the predominant strain (51% isolates). Uropathogenic bacteria were sensitive to fosfomycin in more than 90% of cases, and this sensitivity was favorable during the study period. On the other hand, a high frequency of resistance has been recorded for betalactamines, in particular amoxicillin and amoxicillin-clavulanic acid. Fosfomycin has excellent activity on bacteria of urinary tract infections so its single dose prescription would be effective in uncomplicated urinary tract infections.

**Keywords:** Cytobacteriological Urine Exam, Uropathogenic Bacteria, Fosfomycin, Resistance

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## 1. Introduction

Urinary tract infections are among the most common bacterial infections in both city and hospital medicine and constitute a real public health problem [1]. Urinary tract infections are caused by a limited number of bacterial species, more than 95% of which are monomicrobial. *Escherichia coli* is the most frequently implicated uropathogen reported by virtually all epidemiologic studies worldwide. Other pathogens of the genera *Enterococcus*, *Klebsiella*, *Enterobacter*, *Proteus*, *Morganella*, *Citrobacter*, *Serratia*, *Pseudomonas*, *Streptococcus*, and *Staphylococcus*, and fungi, such as *Candida* spp, are also isolated with variable frequency [2]. The prescription of antibiotics for the treatment of uncomplicated urinary tract infections is common. And the most prescribed molecules in this context most often belong to the same families including fluoroquinolones and sometimes beta-lactams often considered too used for this indication [3]. The reevaluation of older antibiotic agents seems to be an appealing option. Fosfomycin, an old and rather decommissioned antibiotic, which was previously used

mainly as oral (p.o.) treatment for uncomplicated urinary tract infections, currently attracts clinicians' interest worldwide. Particularly, the reported activity against pathogens with advanced resistance suggests that this antibiotic may provide a useful option for the treatment of patients with these difficult-to-treat-infections [4-7].

The purpose of this work is to evaluate the level of resistance and to follow the evolution of the uropathogenic bacteria susceptibility to fosfomycin to allow a better antibiotherapy of urinary infections.

## 2. Patients and Methods

This is a retrospective study on all positive cytobacteriological urine tests from inpatients or consultants who arrived at the microbiology laboratory of the Avicenne Military Hospital in Marrakech for 3 years (2014-2016).

The urine was collected in the middle of the morning urine shot in adults and older children and from collectors in infants and newborns. Sampling conditions (local disinfection, collection time of the collector <30 minutes) and urine preservation conditions were respected.

Cell counting was done using a Mallassez cell. The inoculation was carried out using a wedge calibrated on CLED agar and incubated at a temperature of 37°C for 18-24 hours. Included in this study were urinary specimens that met the criteria for urinary tract infection: leukocyturia greater than  $10^4$  / mL and the bacteriuria threshold was variable depending on the bacterial species and sex of the patient (table 1). The identification of the bacteria was made on the

morphological, cultural and biochemical characters (Api 20E galleries). The study of the sensitivity was carried out according to the technique of diffusion of the disks in an agar medium. Biochemical identification and antibiogram were also performed automatically on Phoenix100 automaton (Becton Dickinson). The interpretation was made according to the standards of The European Committee on Antimicrobial Susceptibility Testing - EUCAST.

**Table 1.** Bacteriuria according to bacterial species and sex [8].

Bacterial species	Threshold of significance	Sex
E. coli, S. saprophyticus	$10^3$ UFC/ml	Man or woman
Enterobacteria other than E. coli, enterococcus,	$10^3$ UFC/ml	Man
C. urealyticum, P. aeruginosa, S. aureus	$10^4$ UFC/ml	Woman

### 3. Results

During this study, 12116 cytobacteriological examinations of the urine were performed, only 1788 met the criteria of urinary infection, which corresponds to 15% of the total cytobacteriological urine. These urinary tract infections included externally followed patients (1471) and hospitalized patients (317). The sex ratio between men and women is 1.07. Escherichia coli still represents the enterobacteria most often found in urine among all isolated uropathogenic bacteria (Table 2).

The study of the sensitivity of uropathogenic bacteria to the main antibiotics used for the treatment of urinary tract infections has shown that only fosfomycin and furans have sensitivity greater than 90% (Table 3). During the study period, fosfomycin showed a favorable evolution of the susceptibility of bacteria to this antibiotic (Figure 1). Of the isolated uropathogenic bacteria, E. coli had the lowest level of resistance to fosfomycin (Table 4).

**Table 2.** Distribution of bacteria isolated in the urine.

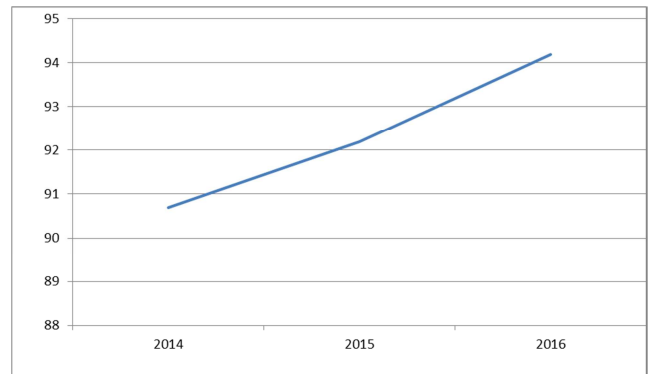
Bacteria	Number
Enterobacteriaceae	1488
Escherichia coli	1056
Klebsiella pneumoniae	254
Enterobacter cloacae	64
Proteus mirabilis	46
Other	58
Non-fermenting gram-negative bacillus	78
Acinetobacter	20
Pseudomonas	58
Gram positive cocci	205
Enterococcus	70
Streptococcus	68
Staphylococcus	67

**Table 3.** Percentage of sensitivity of bacteria isolated from urinary tract infections.

Antibiotics	Sensitive	Resistant
Amoxicillin	30%	70%
Amoxicillin-clavulanic acid	42,8%	57,2%
Fosfomycin	92%	8%
Nitrofurantoin	93%	7%
Ciprofloxacin	71,3%	28,7%
Trimethoprim-sulfamethoxazole	61,5%	38,5%

**Table 4.** Percentage of sensitivity to fosfomycin urinary tract.

	Sensibilité	Résistance
Escherichia coli	96%	4%
Klebsiella pneumoniae	84%	16%
Enterobacter cloacae	93,8%	6,2%
Proteus mirabilis	85%	15%



**Figure 1.** Evolution of percentages of susceptibility to fosfomycin.

### 4. Discussion

The high frequency of urinary tract infection and its potential gravity have led city practitioners and hospital doctors to prescribe very many molecules [9]. Extensive use of broad-spectrum antibiotic therapy may lead to the resistance of strains previously sensitive to a class of antibiotics, which is illustrated in the example of amoxicillin[10]: its frequent use and that of amoxicillin / Clavulanic acid in urinary tract infection during the 1990s contributed to the evolution of E. coli towards resistance rates > 30% of strains [11]. In our series, the resistance of uropathogenic bacteria to amoxicillin and amoxicillin-clavulanic acid is 70% and 57.2% respectively, which is consistent with several local and foreign studies [1, 12, 13]. Resistance to fluoroquinolones was recorded in nearly 30% of cases, a high rate compared with resistance reported by other authors [13, 14]. Fluoroquinolones are often prescribed sometimes in an abusive way which maintains the evolution of the resistance of the bacteria for this family of antibiotics [15]. The frequency of resistance to fosfomycin was the lowest of all (93%) and had a favorable evolution over the

three years of study (90% in 2014 and 94% in 2016). This high level of antibiotic sensitivity of most uropathogenic bacteria does not appear to be observed with other antibiotics used in the treatment of urinary tract infections [16]. This can be explained by the use of fosfomycin monodose, limited to the treatment of cystitis, by its early and powerful bactericidal and the absence of cross resistance with other antibiotics [17]. The ARESC (Antimicrobial Resistance Epidemiological Survey on Cystitis) study group [18] collected clinical data from 4264 eligible patients. A positive urine culture was found in 74.6%, and *E. coli* was most frequent (76.7%) with the highest rate of susceptibility to fosfomycin (98.1%). In all countries, a susceptibility rate of *E. coli* above 90% was found only for fosfomycin, mecillinam and nitrofurantoin. The conclusions of the ARESC study were that fosfomycin, mecillinam and nitrofurantoin have preserved their in vitro activity in all countries investigated, representing good options for empiric therapy of female patients with uncomplicated cystitis. Falagas et al. [19] published a meta-analysis of 27 randomized controlled trials (eight were blind) on fosfomycin versus other antibiotics for the treatment of cystitis. The conclusion was that in an era with high drug resistance rates, even among community-acquired uropathogens, fosfomycin may provide a valuable alternative option for the treatment of cystitis in women (non-pregnant and pregnant) and in elderly and paediatric patients.

## 5. Conclusion

In this study, we observe a good in vitro efficacy of fosfomycin which is above 90% sensitivity throughout the years of follow-up. On the other hand, it confirms the progression of bacterial resistance to betalactamines as well as to fluoroquinolones. Fosfomycin monodose offers by its brevity of administration a reduction in the risk of appearance of resistant strains and has an ecological advantage compared to long treatments. It therefore seems legitimate to update the use of this old molecule within a well-defined prescription, particularly simple cystitis. This is in line with the recommendations of learned societies that are promoting the prescription of fosfomycin for uncomplicated urinary tract infections.

## Conflict of Interest

The authors declare that they have no competing interests.

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