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Fosfomycin Has the Lowest Resistance Rate among Oral Antimicrobial Agents Tested against Community Uropathogens

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ABSTRACT

Background: Fosfomycin (FOS) has recently attracted increasing interest, largely because of its good activity *in vitro* against multidrug-resistant (MDR) pathogens. However, there have been few studies of FOS in North America, mostly with *Escherichia coli*. In light of current antimicrobial resistance (R) in the community, we sought to assess the R rate of FOS among community urinary isolates, in comparison to those of other oral antimicrobial agents commonly used for the treatment of uncomplicated urinary tract infections (UTIs) in non-hospitalized patients.

Methods: Consecutive isolates were identified by conventional methods from urine cultures processed over a 9 week period ending on January 30, 2015. Organisms not recommended for routine testing (e.g., streptococci) were excluded from the study. Isolates were tested by disk diffusion or the Vitek-2 system (bioMérieux), in accordance with CLSI guidelines, against ampicillin (AM), cefazolin (KZ), ciprofloxacin (CIP), nitrofurantoin (FM), trimethoprim/sulfamethoxazole (SXT), and FOS. Due to lack of FOS interpretive criteria for all organisms, CLSI *E. coli* and *E. faecalis* breakpoints were applied for all organisms, similar to recently published investigations.

Results: Of 11,853 urine specimens processed, a total of 2,455 non-duplicate isolates were tested, including *E. coli* (*n* = 1,617), *E. faecalis* (343), *Klebsiella* (192), *Proteus mirabilis* (144), *Citrobacter* (56), *Enterobacter* (39), *Morganella morganii* (35), *Staphylococcus aureus* (17), *Pseudomonas aeruginosa* (4), *Acinetobacter* (3), *Serratia* (3), *Providencia* (1) species, and *E. faecium* (1). R rates for AM, KZ, CIP, FM, SXT, and FOS were 43%, 25%, 12%, 10%, 30%, and 2%, respectively. FOS R rates among MDR isolates that were R to ≥ 3 antimicrobial classes (*n* = 268), and ESBL producing strains (90 *E. coli*, 2 *Klebsiella*), were 6% and 1%, respectively.

Conclusions: Of the six oral antimicrobial agents reported in this study, FOS had the lowest resistance rate among community urinary isolates. These results provide support for FOS as a useful agent for the treatment of UTIs caused by various organisms.

INTRODUCTION

Fosfomycin (FOS) has recently attracted increasing interest, largely because of its good activity *in vitro* against multidrug-resistant (MDR) pathogens.[1,2] However, there have been few studies of FOS in North America, mostly with *Escherichia coli*.[3,4] While *E. coli* is recognized as the most frequent etiologic agent of urinary tract infections (UTIs),[5] the presence of other organisms accounts for a significant part of positive urine cultures,[6,7] thus supporting the need for investigating FOS activity against these other uropathogens, despite the lack of standardized interpretive criteria for most organism/drug combinations.[4]

UTIs are among the most widely encountered infections in the community setting. In light of continuing multidrug resistance in the community, we sought to assess the resistance rate of FOS among community urinary isolates – comprising the various uropathogens generally encountered in routine practice[4,6] – and compared it to those of other oral antimicrobial agents commonly used for the treatment of uncomplicated UTIs in non-hospitalized patients.

METHODS

Over a 9 week period ending on January 30, 2015, all isolates recovered from positive urine cultures yielding ≥ 10^4 CFU/ml of one or two organisms were identified by standard methods. Organisms not recommended for routine antimicrobial susceptibility testing (such as *Staphylococcus saprophyticus* and beta-hemolytic streptococci) were excluded from the study.

Antimicrobial susceptibility testing was performed by disk diffusion or by the Vitek-2 system (bioMérieux Canada Inc.), in accordance with guidelines of the Clinical and Laboratory Standards Institute (CLSI),[8] against ampicillin (AM), cefazolin (KZ), ciprofloxacin (CIP), nitrofurantoin (FM), trimethoprim/sulfamethoxazole (SXT), and FOS. Due to lack of FOS interpretive criteria for all organisms, CLSI *E. coli* and *E. faecalis* breakpoints were applied for all organisms, similar to recently published investigations.[4,6,9]

Extended-spectrum beta-lactamase (ESBL) and carbapenemase screening tests were performed for *E. coli* and *Klebsiella* spp., and for *Enterobacteriaceae* isolates, respectively, using currently recommended procedures.[8] Multidrug resistant (MDR) strains were defined as isolates resistant to at least three classes of antimicrobial agents.[10]

RESULTS & DISCUSSION

Antimicrobial Resistance: Of 11,853 urine specimens processed, a total of 2,455 non-duplicate isolates were included in this evaluation (Table 1). As can be seen from Figure 1, FOS had the lowest resistance rate (2.2%), compared to those of the other antimicrobial agents, namely, AM (42.6%), CIP (11.6%), FM (10.4%), SXT (30.4%), and KZ (25.2%).

FOS Resistance among MDR Isolates: Figure 1 also shows the resistance rates of the MDR isolates that were resistant to at least three antimicrobial classes (*n* = 268), showing FOS with a low resistance rate of 6.3%. Of these isolates, 90 *E. coli* and 2 *Klebsiella* strains were identified as ESBL-producing, with a combined FOS resistance rate of 1.1%, included in the MDR data. No carbapenemase-producing isolates were identified during this period.

FOS Resistance by Age: Resistance data of FOS versus those of the other agents were plotted by patient age groups (<18, 19-30, 31-50, 51-65, >65 years). FOS retained the lowest resistance rate in each age group (Figure 2).

Comparative Resistance per Organism: For most organisms, FOS retained a low resistance rate per organism, ranging from <1% to 5.9% (Figure 3). Taken together, the vast majority of isolates belonged to organisms that had a low FOS resistance rate, an observation that supports the usefulness of FOS for the empirical treatment of UTIs caused by various organisms in the community.

Table 1: Organisms Tested in this Study

Organism	Number of isolates (%)
Escherichia coli	1,617 (66)
Enterococcus faecalis	343 (14)
Klebsiella spp.	192 (8)
Proteus mirabilis	144 (6)
Citrobacter spp.	56 (2)
Enterobacter spp.	39 (<2)
Morganella morganii	35 (<2)
Staphylococcus aureus	17 (<1)
Pseudomonas aeruginosa	4 (<0.5)
Acinetobacter spp.	3 (<0.5)
Serratia spp.	3 (<0.5)
Providencia spp.	1 (<0.5)
Enterococcus faecium	1 (<0.5)
Total	2,455 (100)

Figure 1: Rates of Resistance of All Isolates vs MDR Isolates

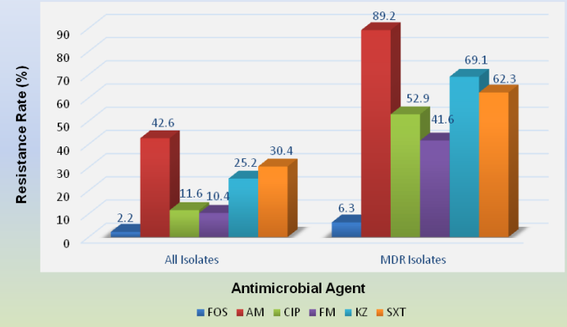


Figure 2: Antimicrobial Resistance Shown by Patient Age

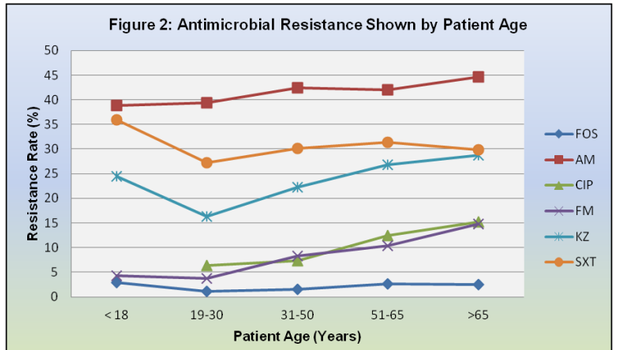
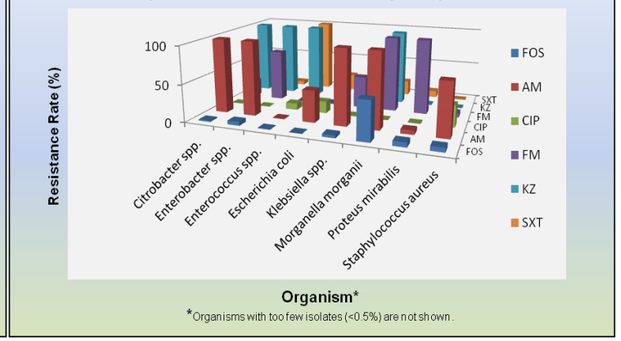


Figure 3: Antimicrobial Resistance per Organism



*Organisms with too few isolates (<0.5%) are not shown.

CONCLUSIONS

- Of the six oral antimicrobial agents tested in this study, FOS had the lowest resistance rate among community urinary isolates, including multidrug resistant strains.
- Among the various patient age groups, FOS continued to retain the lowest resistance rate in each age group.
- These results support the usefulness of FOS for the treatment of uncomplicated lower UTIs that may be caused by various organisms in the community.

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