

Determination of Oral Antimicrobial Agents with the Lowest Resistance Rates among Community Urinary Isolates

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ABSTRACT

Background: Urinary tract infections (UTIs) are commonly encountered worldwide. Oral antimicrobial agents are the mainstay of treatment in the community. Identifying oral agents with low resistance (R) can be advantageous to informing empirical therapy. Two studies from our lab have identified amoxicillin clavulanate (AMC) or fosfomycin (FOS) as the oral agent with the lowest R rate among urinary isolates from non-hospitalized pregnant women or community patients, respectively. As neither study included both agents and in light of current antimicrobial resistance, we sought to test urinary isolates for their R against AMC, FOS, and five other oral agents commonly used in the treatment of UTIs.

Methods: Consecutive isolates were identified by conventional methods from urine cultures processed over a 2 month period ending December 2017. Isolates were tested by disk diffusion or Vitek-2 system (bioMérieux), in accordance with CLSI guidelines, against AMC, FOS, ampicillin (AM), cefazolin (KZ), ciprofloxacin (CIP), nitrofurantoin (FM), and trimethoprim/sulfamethoxazole (SXT). Due to lack of FOS interpretive criteria for all organisms, CLSI *Escherichia coli* and *Enterococcus faecalis* breakpoints were applied to Gram-negative and -positive organisms, respectively, similar to recently published investigations. Screening was performed for carbapenem-resistant *Enterobacteriaceae* (CRE), extended-spectrum beta-lactamases (ESBLs) in *E. coli* and *Klebsiella* spp, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE), in accordance with CLSI guidelines.

Results: Of 15,949 urine specimens processed, a total of 3,313 non-duplicate isolates were tested, including *E. coli* (n = 2,025), *Streptococcus agalactiae* (283), *Klebsiella* spp (272), *E. faecalis* (232), *E. faecium* (1), *Proteus mirabilis* (160), *Staphylococcus* spp including *S. aureus* (131), *Pseudomonas aeruginosa* (22), *Citrobacter* (84), *Enterobacter* (62), *Morganella* (32), *Serratia* (7), *Providencia* (1), and *Acinetobacter* (1) species. R rates for AMC, FOS, AM, KZ, CIP, FM, and SXT were 9.8%, 3.2%, 43.5%, 20.1%, 12.1%, 12.7%, and 31.8%, respectively. 528 isolates were R to ≥ 3 antimicrobial classes, including 157 ESBL-producing (150 *E. coli*, 7 *Klebsiella*), 4 MRSA and 1 CRE.

Conclusions: Of the oral agents reported in this study, FOS followed by AMC, had the lowest R profile among urinary isolates. These results provide support for FOS and AMC as the most likely useful oral agents for current empirical therapy of UTIs in the community.

INTRODUCTION

Urinary tract infections (UTIs) are among the most frequently encountered infectious diseases worldwide.¹ Oral antimicrobial agents are the mainstay of treatment in the community, and identifying antimicrobials with low resistance can be advantageous for informing the determination of empiric therapy. This can be facilitated by providing susceptibility data per tested drug in addition to that available for specific organisms.^{2,3}

Two studies from our laboratory have identified amoxicillin-clavulanate (AMC) and fosfomycin (FOS) as the oral agents with the lowest resistance rate among urinary isolates recovered from non-hospitalized pregnant women or community patients, respectively.^{4,5} As neither study included both agents and in light of

current antimicrobial resistance, we sought to test urinary isolates for their resistance against AMC, FOS, and five other oral antimicrobial agents commonly used in the treatment of UTIs in the community.

METHODS

Consecutive isolates were identified by conventional methods from urine cultures processed over a two month period to the end of December 2017. Isolates were tested by disk diffusion or the Vitek-2 system (bioMérieux), in accordance with guidelines of the Clinical and Laboratory Standards Institute (CLSI), against AMC, FOS, ampicillin (AM), cefazolin (KZ), ciprofloxacin (CIP), nitrofurantoin (FM), and trimethoprim/sulfamethoxazole (SXT).⁶ Due to lack of FOS interpretive criteria for all organisms, CLSI *Escherichia coli* and *Enterococcus faecalis* breakpoints were applied to Gram-negative and Gram-positive organisms, respectively, similar to recently published investigations.^{7,8,9}

Screening was also performed for carbapenem-resistant *Enterobacteriaceae* (CRE), extended-spectrum beta-lactamases (ESBLs) in *E. coli* and *Klebsiella* spp, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE), using currently recommended procedures.⁶ Multidrug-resistant (MDR) strains were defined as isolates resistant to at least three classes of antimicrobial agents.¹⁰

RESULTS & DISCUSSION

Antimicrobial Resistance Rates: Of the 15,949 urine specimens tested, a total of 3,313 isolates were recovered during the study period. Table 1 lists the organisms and corresponding number of isolates. Overall resistance rates for AM, AMC, CIP, FM, FOS, KZ, and SXT were 43.5%, 9.8%, 12.1%, 12.7%, 3.2%, 20.1%, and 31.8%, respectively (Table 2). Current guidelines recommend FM, FOS, and SXT as first-line agents for uncomplicated UTIs in adult females but reserve AMC to second-line empiric therapy.¹¹ Our data suggest that in the population served by our laboratory, AMC is more likely to be active than SXT against community urinary isolates.

Resistance by Age: Resistance data were plotted by patient age (≤18, >18-30, 31-50, 51-65, >65 years). Interestingly, among all the drugs tested, FOS consistently had the lowest resistance rate in each age group, followed by AMC in every age group except for patients >18-30 years old, where CIP had the second lowest resistance rate (Figure 1).

MDR Isolates: We investigated the incidence of MDR isolates in this cohort. Of the 3,313 isolates, there were a total of 528 (15.9%) that were resistant to ≥ 3 antimicrobial classes, including 157 ESBL-producing organisms (150 *E. coli*, 7 *Klebsiella*), 4 MRSA, and 1 CRE. There were no VRE strains detected in this study.

Comparative Resistance per Organism: We compared resistance rates per organism against the seven agents tested. As can be seen from Figure 2, most organisms with the largest number of isolates had low FOS and AMC resistance rates, an observation that supports the usefulness of both agents for the empirical treatment of UTIs in the community.

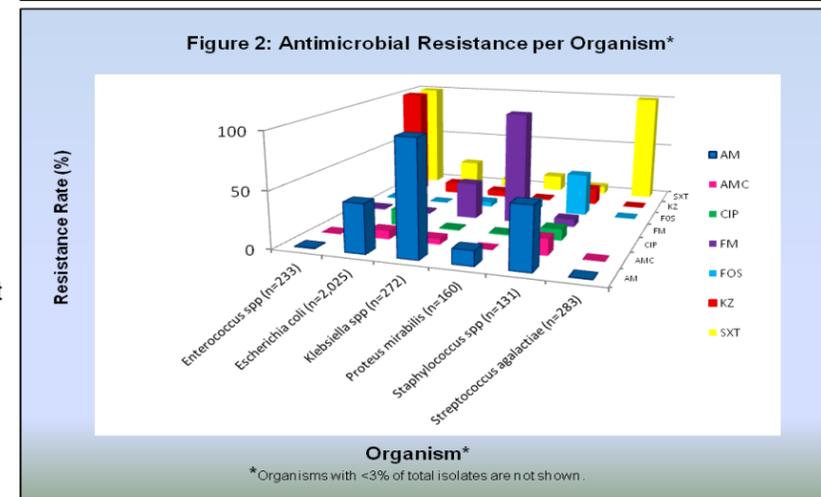
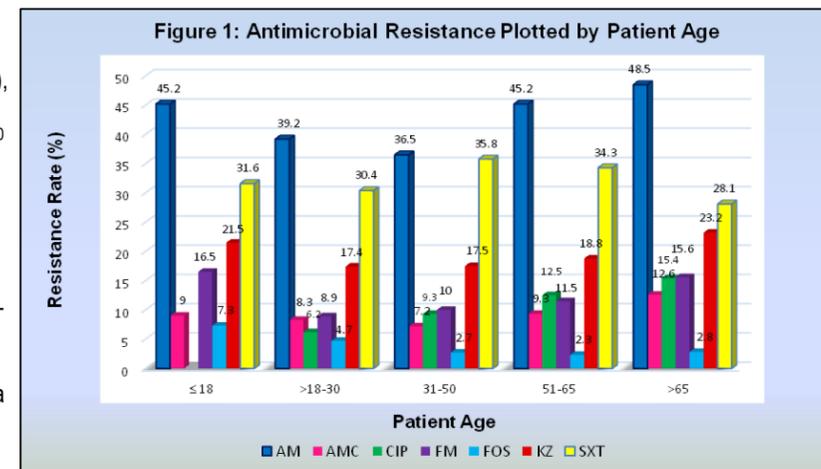
Table 1: Organisms Isolated from Urine Cultures

Organism	Number of isolates (%)
<i>Escherichia coli</i>	2,025 (61.1)
<i>Streptococcus agalactiae</i>	283 (8.5)
<i>Klebsiella</i> spp.	272 (8.2)
<i>Enterococcus faecalis</i>	232 (7.0)
<i>Proteus mirabilis</i>	160 (4.8)
<i>Staphylococcus</i> spp., coagulase-negative	115 (3.5)
<i>Citrobacter</i> spp.	84 (2.5)
<i>Enterobacter</i> spp.	62 (<2)
<i>Morganella morganii</i>	32 (<1)
<i>Pseudomonas aeruginosa</i>	22 (<1)
<i>Staphylococcus aureus</i>	16 (<0.5)
<i>Serratia</i> spp.	7 (<0.5)
<i>Acinetobacter baumannii</i>	1 (<0.1)
<i>Enterococcus faecium</i>	1 (<0.1)
<i>Providencia rettgeri</i>	1 (<0.1)
TOTAL	3,313 (100)

Table 2: Number of Resistant Isolates and Rates of Resistance*

Agent	AM		AMC		CIP		FM		FOS		KZ		SXT	
	R/T	%R	R/T	%R	R/T	%R	R/T	%R	R/T	%R	R/T	%R	R/T	%R
Total	1,442/ 3,313	43.5	326/ 3,313	9.8	342/ 2,832	12.1	381/ 3,007	12.7	105/ 3,313	3.2	665/ 3,313	20.1	1,052/ 3,313	31.8

* Abbreviations: %R, percent rate of resistance; AM, ampicillin; AMC, amoxicillin-clavulanate; CIP, ciprofloxacin; FM, nitrofurantoin; FOS, fosfomycin; KZ, cefazolin; R/T, number of resistant isolates/ number of isolates tested; SXT, trimethoprim/sulfamethoxazole.



CONCLUSIONS

- Of the oral agents reported in this study, FOS followed by AMC, had the lowest resistance profile among urinary isolates.
- These results provide support for FOS and AMC as useful oral agents for current empirical therapy of UTIs in the community.

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