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A Novel Method for Preserving Antibiotic Effectiveness through Predicting Resistance to Agents Used for Empirical Therapy at Point of Diagnosis of Urinary Tract Infections in Non-Hospitalized Patients

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ABSTRACT

Background: Urinary tract infections (UTIs) are widely encountered worldwide. To preserve antibiotic effectiveness and counter antimicrobial resistance, we developed a novel method to predict resistance to agents used for therapy of UTIs, with the objective of guiding prescribers at the point of diagnosis in selecting low-resistance antibiotics for UTI empirical treatment in non-hospitalized patients, aimed at optimizing treatment outcomes and control of resistance transmission.

Methods: Resistance profiles were constructed for amoxicillin-clavulanic acid(AMC), ampicillin(AM), cefazolin(KZ), ciprofloxacin(CIP), fosfomycin(FOS), nitrofurantoin(FM), and trimethoprim/sulfamethoxazole(SXT) tested by disk diffusion or Vitek-2 (bioMérieux), according to CLSI guidelines and study protocol, against organisms identified by conventional methods from urine cultures over a 13-month period ending 01-September-2025. To construct resistance profiles, the incidence proportion(IP) of each organism was multiplied by its corresponding resistance proportion(RP), taking into account intrinsic resistance/imputed susceptibility, followed by the sum of (IPxRP)s, to calculate the resistance rate per agent.

Results: Of 103,796 urines tested, 18,224 isolates grew ≥10^7CFU/L, including *Escherichia coli* (*n*=11,011), *Klebsiella* (2,310), *Enterococcus* (1,299), Group-B *Streptococcus* (1,127), *Proteus* (930), *Citrobacter* (498), *Staphylococcus* (353), *Pseudomonas* (198), *Morganella* (186), *Enterobacter* (177), *Serratia* (45), Group-A *Streptococcus* (31), *Acinetobacter* (27), *Providencia* (16), and other (16) spp. Resistance rates for FOS, AMC, FM, CIP, KZ, SXT, and AM were 4.0%, 9.5%, 9.6%, 16.1%, 24.6%, 25.7%, and 49.0%, respectively.

Conclusions: Due to their low resistance profiles, FOS, AMC, and FM may be useful for UTI empiric treatment at point of diagnosis, for optimal treatment outcomes and control of resistance transmission as part of preserving antibiotic effectiveness.

INTRODUCTION

Urinary tract infections (UTIs) are among the most frequently encountered bacterial infections worldwide, with over 400 million cases diagnosed annually, which if not managed appropriately, can lead to serious complications as well as increased risks for multidrug resistance.[1] Targeting antimicrobial resistance would be desirable to guide appropriate treatment and preserve antibiotic effectiveness.[2]

To counter antimicrobial resistance and preserve the effectiveness of current antimicrobial agents, novel approaches have been proposed, including recently published methods for creating syndromic combination antibiograms displaying antimicrobial susceptibilities per drug regimen, rather than per organism as done in traditional antibiograms, with the aim of guiding antimicrobial therapy with better outcome-driven strategies.[3-5] Upon further work in our laboratory,[2,7-9] we have developed a novel method that could predict resistance to antimicrobial agents, with the objective of guiding clinicians at the point of diagnosis in selecting low-resistance antibiotics for uncomplicated UTI empirical treatment in non-hospitalized patients, aimed at optimizing treatment outcomes as well as better control of resistance transmission.

METHODS

Isolates were identified by conventional methods from urine cultures over a 13-month period ending September 01, 2025 and were tested by disk diffusion or the Vitek-2 system (bioMérieux), according to CLSI guidelines,[10] against amoxicillin-clavulanic acid (AMC), ampicillin (AM), cefazolin (KZ), ciprofloxacin (CIP), fosfomycin (FOS), nitrofurantoin (FM), and trimethoprim/sulfamethoxazole (SXT). For FOS, CLSI *Escherichia coli* and *Enterococcus faecalis* breakpoints were applied to Gram-negative and Gram-positive organisms, respectively, as done in recently published studies.[11-13]

For each antibiotic, the resistance profile was constructed by combining resistance data from all organisms, while accounting for intrinsic resistance and known/imputed susceptibility per organism/drug combination.[5] The incidence proportion (IP) of each organism was multiplied by its corresponding resistance proportion (RP), taking into account intrinsic resistance/imputed susceptibility, followed by the sum of (IPxRP)s, to calculate the resistance rate per agent, as described in Box 1.

RESULTS & DISCUSSION

Incidence of Urinary Pathogens:

Of 103,796 urine samples tested, 18,224 isolates grew ≥10^7CFU/L, including *Escherichia coli* (*n*=11,011), *Klebsiella* (2,310), *Enterococcus* (1,299), Group-B *Streptococcus* (1,127), *Proteus* (930), *Citrobacter* (498), *Staphylococcus* (353), *Pseudomonas* (198), *Morganella* (186), *Enterobacter* (177), *Serratia* (45), Group-A *Streptococcus* (31), *Acinetobacter* (27), *Providencia* (16), and other (16) spp (Table 1).
E. coli was the most frequently identified organism, consistent with previous findings.[2,7-9]

Resistance Profiles of Antibiotics:

Resistance rates for FOS, AMC, FM, CIP, KZ, SXT, and AM were 4.0%, 9.5%, 9.6%, 16.1%, 24.6%, 25.7%, and 49.0%, respectively.
Current guidelines recommend FM, FOS, and SXT, as first-line agents for uncomplicated UTIs but reserve AMC to second-line empiric therapy.[14] The data from this study show that AMC was more likely to be active than SXT against urinary isolates in non-hospitalized patients. Further future studies are underway in our laboratory to investigate this observation in relation to actual clinical outcome.

Limitations of the Study and Future Directions:

The data in this study were derived from testing of patient urine samples in the laboratory, where it was not always possible to distinguish asymptomatic bacteriuria from symptomatic infection, based on test-ordering information provided by clinicians.
Several long-term studies currently underway in our laboratory aim to investigate potential application of our findings in relation to clinical outcomes and their impact on control of resistance transmission as part of preserving antibiotic effectiveness.

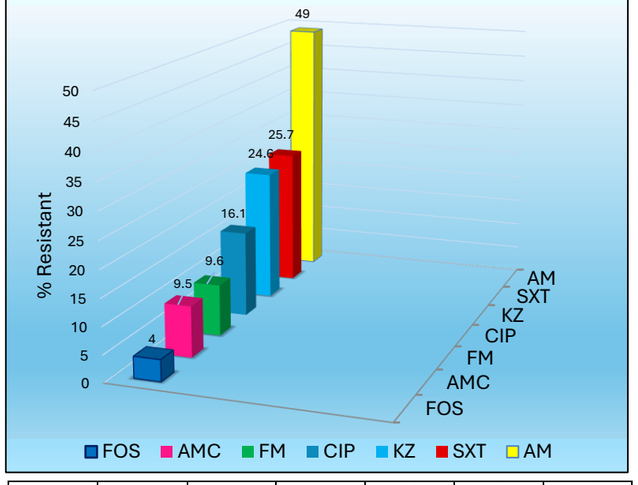
Table 1: Organisms Isolated from Urine Cultures

Organism	Number of isolates (%)
Escherichia coli	11,011 (60.4)
Klebsiella spp	2,310 (12.7)
Enterococcus spp	1,299 (7.1)
Group B *Streptococcus*	1,127 (6.2)
Proteus spp	930 (5.1)
Citrobacter spp	498 (2.7)
Staphylococcus spp	353 (1.9)
Pseudomonas spp	198 (1.1)
Morganella morganii	186 (1.0)
Enterobacter spp	177 (<1.0)
Serratia spp	45 (<0.3)
Group A *Streptococcus*	31 (<0.2)
Acinetobacter spp	27 (<0.2)
Providencia spp	16 (<0.2)
Other spp	16 (<0.2)
TOTAL	**18,224 (100)**

Box 1: Construction of Resistance Profile per Agent

1. The incidence proportion (IP) was calculated as the proportion of the incidence of the organism within the cohort, i.e., the number of isolates of the same organism divided by the total number of isolates for which a test result has been confirmed upon final review.
2. For each drug tested, resistance of each organism to the drug was determined, including any intrinsic resistance and known/imputed susceptibility per organism/drug combination, even if not tested or required to be tested, in accordance with CLSI guidelines. Rules were created to apply the effect for each organism/drug combination.
3. To construct the resistance profile for each drug, the IP of the organism was multiplied by its corresponding resistance probability (RP), followed by the sum of (IPxRP)s, to calculate the resistance rate per agent.

Figure 1: Resistance Rate per Drug*



AM	AMC	CIP	FM	FOS	KZ	SXT
49.0	9.5	16.1	9.6	4.0	24.6	25.7

*Resistance rates (%); AM, ampicillin; AMC, amoxicillin-clavulanic acid; CIP, ciprofloxacin; FM, nitrofurantoin; FOS, fosfomycin; KZ, cefazolin; SXT, trimethoprim/sulfamethoxazole.

CONCLUSIONS

Our results indicate that among the antibiotics tested in this study, FOS, AMC, and FM are the agents most likely to be useful for uncomplicated UTI empiric treatment at the point of clinical diagnosis. Further work is underway to study their future impact on patient outcomes and control of resistance transmission as part of preserving antibiotic effectiveness.

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