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Targeting Antimicrobial Resistance at Point of Diagnosis by a Novel Antibiotic Profiling Method for Guiding Treatment of Urinary Tract Infections and Preventing Urosepsis in Non-Hospitalized Patients

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ABSTRACT

Background: Urinary tract infections (UTIs) are among the most frequently reported infections worldwide. Targeting antimicrobial resistance (AMR) at point of diagnosis is desirable for guiding appropriate treatment and preventing serious complications including urosepsis. We constructed AMR profiles of antibiotics used for UTI treatment in non-hospitalized patients, using the recently described weighted-incidence syndromic combination antibiogram resistance (WISCA-R) profiling method, to identify appropriate antibiotics for empiric treatment at point of diagnosis.

Methods: Isolates were identified by conventional methods from urine cultures over a 16-month period ending 15-September-2024 and were tested by disk diffusion or Vitek-2 (bioMérieux), according to CLSI guidelines, against amoxicillin-clavulanic acid (AMC), ampicillin (AM), cefazolin (KZ), ciprofloxacin (CIP), fosfomycin (FOS), nitrofurantoin (FM), and trimethoprim/sulfamethoxazole (SXT). To construct WISCA-R for a given antibiotic, the weighted incidence (WI) of an organism was multiplied by its corresponding resistance proportion (RP), taking into account intrinsic resistance/imputed susceptibility, followed by the sum of (WIxRP)s, to determine the WISCA-R rate for that antibiotic.

Results: Of 131,078 urine specimens cultured, 23,155 isolates grew ≥ 10^7 CFU/L, including *Escherichia coli* (*n*=14,229), *Klebsiella* (2,455), *Enterococcus* (1,724), Group-B *Streptococcus* (1,345), *Proteus* (1,081), *Citrobacter* (599), *Staphylococcus* (588), *Enterobacter* (451), *Pseudomonas* (236), *Morganella* (198), *Serratia* (54), Group-A *Streptococcus* (54), *Providencia* (25), *Acinetobacter* (18), and other (98) spp. WISCA-R rates for FOS, AMC, FM, CIP, KZ, SXT, and AM were 4.8%, 9.8%, 13.7%, 15.6%, 16.6%, 30.0%, and 46.8%, respectively.

Conclusions: FOS and AMC had the lowest WISCA-R rates. FOS and AMC are the antibiotics of choice for the empiric treatment of uncomplicated UTIs for non-hospitalized patients at point of clinical diagnosis.

INTRODUCTION

Urinary tract infections (UTIs) are among the most frequently encountered bacterial infections worldwide.[1] Targeting antimicrobial resistance (AMR) at point of diagnosis would be desirable for guiding appropriate treatment and preventing serious complications including urosepsis.

The weighted-incidence syndromic combination antibiogram (WISCA) is a recently published novel approach that displays antimicrobial susceptibilities per drug regimen for a given syndrome, rather than per organism as in traditional antibiograms.[2,3,4] The main advantage of the WISCA is that it can be potentially useful at time of diagnosis prior to knowing the pathogen and its susceptibilities. It also has the advantage to provide adequate empirical antimicrobial coverage in polymicrobial infection.[2,4,5]

We sought to construct AMR profiles of antibiotics used for uncomplicated UTI treatment in non-hospitalized patients, using the recently described WISCA resistance (WISCA-R) profiling method.[6-8] The findings could serve as a guide for clinicians to identify appropriate antibiotics for empiric treatment at point of diagnosis.

METHODS

Isolates were identified by conventional methods from urine cultures over a 16-month period ending 15-September-2024 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, WISCA-R was constructed by combining resistance data from all organisms, while accounting for intrinsic resistance and known/imputed susceptibility per organism/drug combination.[4] To construct the WISCA-R for a given antibiotic, the weighted incidence (WI) of an organism was multiplied by its corresponding resistance proportion (RP), followed by the sum of multiplied WIxRPs, to determine the WISCA-R rate for that antibiotic, as described in Box 1. Box 2 provides an example of how it was calculated.

RESULTS & DISCUSSION

Weighted Incidence of Urinary Pathogens:

Of 131,078 urine specimens cultured, 23,155 isolates grew ≥ 10^7 CFU/L, including *Escherichia coli* (*n*=14,229), *Klebsiella* (*n*= 2,455), *Enterococcus* (*n*= 1,724), Group-B *Streptococcus* (*n*= 1,345), *Proteus* (*n*= 1,081), *Citrobacter* (*n*= 599), *Staphylococcus* (*n*= 588), *Enterobacter* (*n*= 451), *Pseudomonas* (*n*= 236), *Morganella* (*n*= 198), *Serratia* (*n*= 54), Group-A *Streptococcus* (*n*= 54), *Providencia* (*n*= 25), *Acinetobacter* (*n*= 18), and other (*n*= 98) spp (Table 1). *E. coli* was the most frequently identified organism, consistent with previous findings.[6-9]

The Weighted Incidence (WI) resulted as determined by the protocol described in Box1. An example of WI calculation is shown in Box 2.

WISCA-R Profiles of Antibiotics:

The WISCA-R rates for FOS, AMC, FM, CIP, KZ, SXT, and AM were 4.8%, 9.8%, 13.7%, 15.6%, 16.6%, 30.0%, and 46.8%, respectively (Figure 1).

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 both FM and SXT against urinary isolates in non-hospitalized patients. Further future studies are being planned in our laboratory to investigate this observation in relation to actual clinical outcome.

Limitations of the Study and Future Directions:

The WISCA-R data in this study were derived from testing of patient urine cultures in the laboratory, where it was not always possible to distinguish asymptomatic bacteriuria from symptomatic infection based on available test ordering information.

A long-term study currently underway in our laboratory aims to investigate the potential impact of WISCA-R on clinical outcomes in non-hospitalized patients.

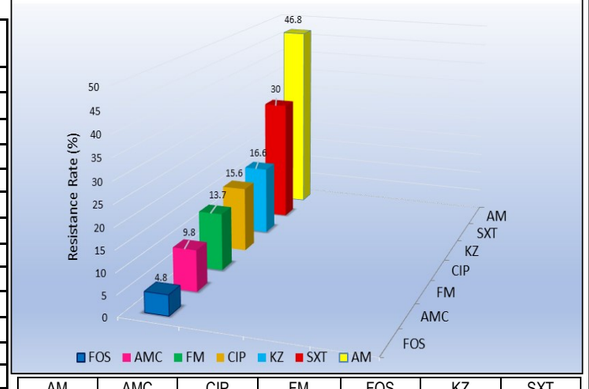
Box 1: Construction of WISCA-R (AMR 2024)

1. The Weighted Incidence (WI) 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 studied.
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 (e.g., *Enterobacter* spp always R to AM; *Pseudomonas aeruginosa* always R to SXT; *Enterococcus* spp always R to all cephalosporins).
3. To construct the WISCA-R profile for each drug, the WI was multiplied by the corresponding probability of resistance (Resistance Proportion [RP]), to determine the Weighted Resistance [WR]) of the organism obtained against the studied drug, followed by the sum of WRs ([WIxRP]s), to arrive at the final WISCA-R rate for that antibiotic.

Table 1: Organisms Isolated from Prenatal Urine Cultures

Organism	Number of isolates (%)
Escherichia coli	14,229 (61.5)
Klebsiella spp	2,455 (10.6)
Enterococcus spp	1,724 (7.4)
Group B *Streptococcus*	1,345 (5.8)
Proteus spp	1,081 (4.7)
Citrobacter spp	599 (2.6)
Staphylococcus spp	588 (2.5)
Enterobacter spp	451 (1.9)
Pseudomonas spp	236 (1.0)
Morganella morganii	198 (<1)
Serratia spp	54 (<1)
Group A *Streptococcus*	54 (<1)
Acinetobacter spp	18 (<1)
Providencia spp	25 (<1)
Other spp	98 (<1)
TOTAL	23,155 (100)

Figure 1: WISCA-R Resistance Rate per Drug*



AM	AMC	CIP	FM	FOS	KZ	SXT
46.8	9.8	15.6	13.7	4.8	16.6	30.0

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

Box 2: Example of WISCA-R Construction: Construction of Ampicillin (AM) WISCA-R

Organism/ AM Combination	Weighted Incidence (Number of isolates/ total number tested) (A)	Resistance Proportion (Number of R isolates/ number of isolates tested) (B)	Weighted Resistance for AM (A)×(B)
Escherichia coli /AM	0.61451	0.44768	0.27510
Klebsiella spp/AM	0.10602	1.00000	0.10602
Enterococcus spp/AM	0.07445	0.00290	0.00022
Group B *Streptococcus*/AM	0.05809	0.00000	0.00000
Proteus spp/AM	0.04669	0.14524	0.00678
Citrobacter spp/AM	0.02587	1.00000	0.02587
Staphylococcus spp/AM	0.02539	0.38265	0.00972
Enterobacter spp/AM	0.01948	1.00000	0.01948
P. aeruginosa/AM	0.01019	1.00000	0.01019
Morganella morganii/AM	0.00856	1.00000	0.00856
Serratia spp/AM	0.00233	1.00000	0.00233
Group A *Streptococcus*/AM	0.00233	0.00000	0.00000
Acinetobacter spp/AM	0.00078	1.00000	0.00078
Providencia spp/AM	0.00108	1.00000	0.00108
Other spp/AM	0.00423	0.33570	0.00142
TOTAL	1.00000	Non-applicable	0.46755 (WISCA-R)

CONCLUSIONS

The present report follows our earlier findings of WISCA-R as distinct from WISCA, in displaying weighted resistance rather than susceptibility per drug in community urinary isolates. Given that an "Intermediate" test result would still imply clinical efficacy due to physiological concentration of the antibiotic in urine,[10] we propose WISCA-R as a more comprehensive clinically useful tool than WISCA for alerting the clinician to the antibiotic resistance profile, thus guiding appropriate empiric therapy of UTIs at time of diagnosis.[6-9]

Our results indicate that among the antibiotics commonly used to treat UTIs reported in this study, FOS and AMC had the lowest WISCA-R rates. These results provide support for FOS and AMC as useful agents with low likelihood of resistance, for the empiric treatment of uncomplicated UTIs in non-hospitalized patients at the point of clinical diagnosis. Further work is underway to study the impact of WISCA-R on clinical outcomes in non-hospitalized patients.

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