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# Novel Weighted-Incidence Syndromic Combination Antibiogram (WISCA) Resistance (WISCA-R) Profiling of Oral Agents Commonly Used in the Treatment of Community Urinary Tract Infections, and Comparison to Previous WISCA-R Findings

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## ABSTRACT

**Background:** The recently described weighted-incidence syndromic combination antibiogram (WISCA) displays antimicrobial susceptibilities per drug for a given syndrome, rather than per organism as in traditional antibiograms. We sought to (1) construct a WISCA resistance (R) profile (WISCA-R) per oral agent among drugs commonly used in the treatment of community urinary tract infections (UTIs), to identify oral agents with low R, and (2) compare our 2018 vs 2019 WISCA-R profiles.

**Methods:** Isolates were identified by conventional methods from urine cultures over a 2-year period ending in December 2019, and were tested by disk diffusion or Vitek-2 (bioMérieux), according to CLSI guidelines, against amoxicillin-clavulanate (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 -positive organisms, respectively, similar to recently published investigations. WISCA-R was constructed by multiplying the probability of weighted incidence per organism by the corresponding probability of R to the studied drug, including intrinsic R and known/imputed susceptibility per organism/drug combination, followed by the sum of obtained probabilities, to arrive at the WISCA-R rate for that drug. WISCA-R rates for 2018 vs 2019 were compared for each drug.

**Results:** Of 89,787 and 96,186 urine specimens processed in 2018 and 2019, a total of 15,278 and 17,454 isolates were tested, respectively, including *E. coli* (*n* = 9,515; 10,526), Group B *Streptococcus* (1,093; 1,330), *Klebsiella* (1,324; 1,562), *Proteus* (942; 979), *Enterococcus* (786; 1,063), *Staphylococcus* (607; 707), *Citrobacter* (368; 470), *Enterobacter* (281; 334), *Pseudomonas* (134; 174), *Morganella* (124; 195), *Serratia* (42; 50), Group A *Streptococcus* (29; 20), *Providencia* (12; 19), *Acinetobacter* (13; 13) spp, and other uncommon organisms (8; 12). WISCA-R rates for 2018 vs 2019 for FOS, AMC, CIP, FM, KZ, SXT, and AM were 3.3 vs 3.8% (*P* = 0.1106), 8.5 vs 11.8% (*P* < 0.0001), 11.7 vs 12.7% (*P* = 0.0035), 13.8 vs 15.8% (*P* < 0.0001), 18.5 vs 21.3% (*P* < 0.0001), 28.9 vs 29.7% (*P* = 0.0527), and 44.6 vs 45.6% (*P* = 0.0244), respectively.

**Conclusions**: This study provides support for FOS and AMC as oral agents with the lowest WISCA-R rates. WISCA-R rates should be monitored, as a practical tool for guiding timely selection of empiric therapy of UTIs. Further work is underway to investigate the impact of WISCA-R on clinical outcomes.

## INTRODUCTION

The weighted-incidence syndromic combination antibiogram (WISCA) is a recently described novel approach that displays antimicrobial susceptibilities per drug for a given syndrome, rather than per organism as in traditional antibiograms.[1,2,3] The main advantage of WISCA is that it can be potentially useful for informing empiric therapy decision-making at the time of diagnosis prior to knowing antimicrobial susceptibility test results, while also accounting for polymicrobial cultures to provide adequate empirical antimicrobial coverage.[1,3]

Urinary tract infections (UTIs) are among the most commonly encountered infectious diseases worldwide.[4] We sought to (1) construct a WISCA resistance (R) profile (WISCA-R) per oral agent among drugs commonly used in the treatment of community urinary tract infections (UTIs), to identify oral agents with low resistance, and (2) to compare our novel 2019 to our previous 2018 WISCA-R profiles.[5]

## METHODS

Isolates were identified by conventional methods from urine cultures over a 2-year period ending in December 2019, and were tested by disk diffusion or the Vitek-2 system (bioMérieux), according to CLSI guidelines, against amoxicillin-clavulanate (AMC), ampicillin (AM), cefazolin (KZ), ciprofloxacin (CIP), fosfomycin (FOS), nitrofurantoin (FM), and trimethoprim/sulfamethoxazole (SXT).[6] For FOS, CLSI *Escherichia coli* and *Enterococcus faecalis* breakpoints were applied to Gram-negative and -positive organisms, respectively, similar to recently published investigations.[7-9]

WISCA-R was constructed by combining resistance data from all organisms per drug, including accounting for intrinsic resistance and known/imputed susceptibility per organism/drug combination.[3] The probability of incidence of each organism within the cohort was multiplied by the corresponding probability of resistance to the studied drug, followed by the sum of obtained probabilities, to arrive at the final WISCA-R rate for that drug, as described in Box 1. Box 2 shows an example of how it was constructed. WISCA-R rates for 2019 vs 2018 were compared for each drug.

## RESULTS & DISCUSSION

**Weighted Incidence of Uropathogens:**
Of 89,787 and 96,186 urine specimens processed in 2018 and 2019, a total of 15,278 (17.0%) and 17,454 (18.1%) isolates were tested, respectively (Table 1). *E. coli* was the most frequently identified uropathogen, with an incidence similar to that obtained in previous investigations of local community urinary isolates.[10,11]

**Construction and Comparison of the WISCA-R Profiles**:
A WISCA-R profile was constructed for each drug as described in Box 1. Box 2 shows details of constructing a drug WISCA-R from the 2019 data as an example.
WISCA-R rates for 2018 vs 2019 for FOS, AMC, CIP, FM, KZ, SXT, and AM were 3.3 vs 3.8% (*P* = 0.1106), 8.5 vs 11.8% (*P* < 0.0001), 11.7 vs 12.7% (*P* = 0.0035), 13.8 vs 15.8% (*P* < 0.0001), 18.5 vs 21.3% (*P* < 0.0001), 28.9 vs 29.7% (*P* = 0.0527), and 44.6 vs 45.6% (*P* = 0.0244), respectively (Figure 1).

**Limitations of the Study and Future Directions**:
WISCA-R data in this study were derived from testing of patient urine cultures in the laboratory, where distinguishing asymptomatic bacteriuria from symptomatic infection was not always possible. A long-term study currently underway in our laboratory aims to investigate the potential impact of WISCA-R on clinical outcomes in patients with UTIs.

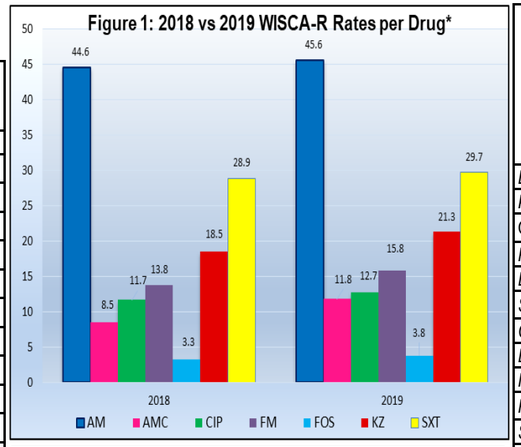
**Box 1: Construction of WISCA-R**

1. Weighted incidence was calculated as the proportion of the incidence of the organism within the cohort, i.e., the proportion of isolates of the same organism divided by the total number of isolates studied.
2. For each drug tested, resistance of each isolate 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 probability of incidence of each organism within the cohort was multiplied by the corresponding probability of resistance to the studied drug, followed by the sum of obtained probabilities, to arrive at the final WISCA-R rate for that drug.

**Table 1: Organisms Isolated from Urine Cultures in 2018 vs 2019**

| Organism | Number of isolates (%) **2018** | Number of isolates (%) **2019** |
|---|---|---|
| *Escherichia coli* | 9,515 (62.3) | 10,526 (60.3) |
| *Klebsiella* spp | 1,324 (8.7) | 1,562 (8.9) |
| Group B *Streptococcus* | 1,093 (7.2) | 1,330 (7.6) |
| *Proteus* spp | 942 (6.2) | 979 (5.6) |
| *Enterococcus* spp | 786 (5.1) | 1,063 (6.1) |
| *Staphylococcus* spp | 607 (4.0) | 707 (4.1) |
| *Citrobacter* spp | 368 (2.4) | 470 (2.7) |
| *Enterobacter* spp | 281 (1.8) | 334 (1.9) |
| *Morganella morganii* | 124 (<1) | 195 (1.1) |
| *Pseudomonas aeruginosa* | 134 (<1) | 174 (<1) |
| *Serratia* spp | 42 (<1) | 42 (<1) |
| Group A *Streptococcus* | 29 (<1) | 20 (<1) |
| *Acinetobacter* spp | 13 (<1) | 13 (<1) |
| *Providencia* spp | 12 (<1) | 19 (<1) |
| Other rare organisms | 8 (<1) | 12 (<1) |
| TOTAL | 15,278 (100) | 17,454 (100) |

**Figure 1: 2018 vs 2019 WISCA-R Rates per Drug***




| Year | AM | AMC | CIP | FM | FOS | KZ | SXT |
|---|---|---|---|---|---|---|---|
| **2018** | **44.6** | **8.5** | **11.7** | **13.8** | **3.3** | **18.5** | **28.9** |
| **2019** | **45.6** | **11.8** | **12.7** | **15.8** | **3.8** | **21.3** | **29.7** |
| ***P*** | **0.0244** | **<0.0001** | **0.0035** | **<0.0001** | **0.1106** | **<0.0001** | **0.0527** |

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

**Box 2: Example of WISCA-R Construction Ampicillin (AM) WISCA-R (2019)**

| Organism/AM Combination | Proportion of Incidence (Number of isolates/ total number tested) (A) | Proportion of isolates R to AM (Number of R isolates/ number of isolates tested) (B) | Weighted Resistance for AM (A)×(B) |
|---|---|---|---|
| *E. coli* /AM | 0.60307 | 0.43844 | 0.26441 |
| *Klebsiella* spp/AM | 0.08949 | 1.00000 | 0.08949 |
| Group B *Streptococcus*/AM | 0.07620 | 0.00000 | 0.00000 |
| *Proteus* spp/AM | 0.05609 | 0.15117 | 0.00848 |
| *Enterococcus* spp/AM | 0.06090 | 0.01317 | 0.00080 |
| *Staphylococcus* spp/AM | 0.04051 | 0.51768 | 0.02097 |
| *Citrobacter* spp/AM | 0.02693 | 1.00000 | 0.02693 |
| *Enterobacter* spp/AM | 0.01914 | 1.00000 | 0.01914 |
| *Morganella morganii*/AM | 0.01117 | 1.00000 | 0.01117 |
| *Pseudomonas aeruginosa*/AM | 0.00997 | 1.00000 | 0.00997 |
| *Serratia* spp/AM | 0.00241 | 1.00000 | 0.00241 |
| Group A *Streptococcus*/AM | 0.00115 | 0.00000 | 0.00000 |
| *Acinetobacter* spp/AM | 0.00074 | 1.00000 | 0.00074 |
| *Providencia* spp/AM | 0.00109 | 1.00000 | 0.00109 |
| Other rare organisms/AM | 0.00069 | 0.08333 | 0.00006 |
| TOTAL | 1.00000 | Non-applicable | 0.45566 |

## CONCLUSIONS

This 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. Due to physiological concentration of antibiotics in urine, we propose WISCA-R as a more clinically useful tool than WISCA for informing empiric therapy of UTIs in the community at time of diagnosis.

Our study provides support for FOS and AMC as oral agents with the lowest WISCA-R rates. WISCA-R rates should be monitored, as a practical tool for guiding timely selection of empiric therapy of UTIs. Further work is underway to investigate the impact of WISCA-R on clinical outcomes.

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