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Resistance Profiles of Oral Agents Used in the Treatment of Urinary Tract Infections as Determined by the Novel Weighted-Incidence Syndromic Combination Antibiogram (WISCA) Resistance (WISCA-R) Profiling Method, 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) to compare results to previous year WISCA-R profiles.

Methods: Isolates were identified by conventional methods from urine cultures over a 2-year period ending in December 2020 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 2019 vs 2020 were compared for each drug.

Results: Of 96,186 and 70,620 urine specimens processed in 2019 and 2020, a total of 17,454 and 12,236 isolates were tested, respectively, including *E. coli* (*n* = 10,526; 7,544), *Klebsiella* (1,562; 1,123), Group B *Streptococcus* (1,330; 848), *Proteus* (979; 745), *Enterococcus* (1,063; 653), *Staphylococcus* (707; 538), *Citrobacter* (470; 257), *Enterobacter* (334; 225), *Pseudomonas* (174; 135), *Morganella* (195; 94), *Serratia* (50; 36), Group A *Streptococcus* (29; 11), *Providencia* (19; 9), *Acinetobacter* (13; 12) spp, and other uncommon organisms (8; 6). WISCA-R rates for 2019 vs 2020 for FOS, AMC, CIP, FM, KZ, SXT, and AM were 3.8 vs 3.5% (*P* = 0.08857), 11.8 vs 10.4% (*P* = 0.00008), 12.7 vs 13.7% (*P* = 0.00934), 15.8 vs 14.1% (*P* < 0.00006), 21.3 vs 19.8% (*P* = 0.00084), 29.7 vs 27.9% (*P* = 0.00038), and 45.6 vs 45.8% (*P* = 0.36673), 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

Identifying antimicrobial agents that could be effective and appropriate at the point of diagnosis would be advantageous for informing appropriate empiric therapy decision-making. 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 at the time of diagnosis prior to knowing laboratory 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 2020 to our previous 2019 WISCA-R profiles.[5]

METHODS

Isolates were identified by conventional methods from urine cultures over a 2-year period ending in December 2020, 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 provides an example of how it was constructed. WISCA-R rates for 2020 vs 2019 were compared for each drug.

RESULTS & DISCUSSION

Weighted Incidence of Uropathogens:
Of 96,186 and 70,620 urine specimens processed in 2019 and 2020, a total of 17,454 (18.1%) and 12,236 (17.3%) 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.[5,10-12]

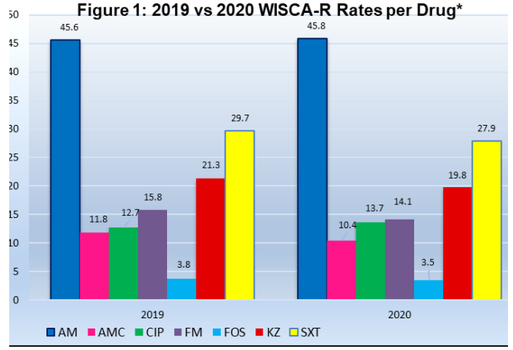
Construction and Comparison of the WISCA-R Profiles:
A WISCA-R profile was constructed for each drug as described in Box 1. Box 2 shows details of constructing a drug WISCA-R from the 2020 data as an example.
WISCA-R rates for 2019 vs 2020 for FOS, AMC, CIP, FM, KZ, SXT, and AM were 3.8 vs 3.5% (*P* = 0.08857), 11.8 vs 10.4% (*P* = 0.00008), 12.7 vs 13.7% (*P* = 0.00934), 15.8 vs 14.1% (*P* < 0.00006), 21.3 vs 19.8% (*P* = 0.00084), 29.7 vs 27.9% (*P* = 0.00038), and 45.6 vs 45.8% (*P* = 0.36673), respectively.
Our previous study[5] had compared WISCA-R rates for 2018 vs 2019 for FOS, AMC, CIP, FM, KZ, SXT, and AM, and found them to be 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.
The fluctuation of WISCA-R rates emphasizes the need for monitoring rate changes per drug over time, as a practical tool for guiding timely selection of empiric therapy of UTIs in the community at the time of diagnosis.

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 it was not always possible to distinguish asymptomatic bacteriuria from symptomatic infection. 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.

Table 1: Organisms Isolated from Urine Cultures in 2019 vs 2020

Organism	Number of isolates (%) **2019**	Number of isolates (%) **2020**
Escherichia coli	10,526 (60.3)	7,544 (61.7)
Klebsiella spp	1,562 (8.9)	1,123 (9.2)
Group B *Streptococcus*	1,330 (7.6)	848 (6.9)
Proteus spp	979 (5.6)	745 (6.1)
Enterococcus spp	1,063 (6.1)	653 (5.3)
Staphylococcus spp	707 (4.1)	538 (4.4)
Citrobacter spp	470 (2.7)	257 (2.1)
Enterobacter spp	334 (1.9)	225 (1.8)
Morganella morganii	195 (1.1)	94 (<1)
Pseudomonas aeruginosa	174 (<1)	135 (1.1)
Serratia spp	42 (<1)	36 (<1)
Group A *Streptococcus*	20 (<1)	11 (<1)
Acinetobacter spp	13 (<1)	12 (<1)
Providencia spp	19 (<1)	9 (<1)
Other organisms	12 (<1)	6 (<1)
TOTAL	17,454 (100)	12,236 (100)

Figure 1: 2019 vs 2020 WISCA-R Rates per Drug*



Year	AM	AMC	CIP	FM	FOS	KZ	SXT
2019	**45.6**	**11.8**	**12.7**	**15.8**	**3.8**	**21.3**	**29.7**
2020	**45.8**	**10.4**	**13.7**	**14.1**	**3.5**	**19.8**	**27.9**
P	**0.36673**	**0.00008**	**0.00934**	**0.00006**	**0.08857**	**0.00084**	**0.00038**

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

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.

Box 2: Example of WISCA-R Construction: Ampicillin (AM) WISCA-R (2020)

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	0.61654	0.44406	0.27378
Klebsiella spp/AM	0.09178	1.00000	0.09178
Group B *Streptococcus*/AM	0.06930	0.00000	0.00000
Proteus spp/AM	0.06089	0.13557	0.00825
Enterococcus spp/AM	0.05337	0.01838	0.00098
Staphylococcus spp/AM	0.04397	0.46654	0.02051
Citrobacter spp/AM	0.02100	1.00000	0.02100
Enterobacter spp/AM	0.01839	1.00000	0.01839
Morganella morganii/AM	0.00768	1.00000	0.00768
Pseudomonas aeruginosa/AM	0.01103	1.00000	0.01103
Serratia spp/AM	0.00294	1.00000	0.00294
Group A *Streptococcus*/AM	0.00090	0.00000	0.00000
Acinetobacter spp/AM	0.00098	1.00000	0.00098
Providencia spp/AM	0.00074	1.00000	0.00074
Other organisms/AM	0.00049	0.16666	0.00008
TOTAL	1.00000	Non-applicable	0.45814

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

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