ASM Microbe 2022, June 09-13, 2022 – Washington, DC, USA

Monitoring 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: A Four-Year Study

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ABSTRACT

Background: The weighted-incidence syndromic combination antibiogram (WISCA) displays antimicrobial susceptibility (S) per drug for a given syndrome, rather than per organism as in traditional antibiograms. We sought to construct a WISCA resistance (R) profile (WISCA-R) per oral agent among drugs commonly used in treatment of urinary tract infections (UTIs), to identify agents with low R, and to monitor WISCA-R profiles over a 4-year period.

Methods: Isolates were identified by conventional methods from urine cultures over a 4-year period ending in December 2021 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 weighted incidence by the corresponding probability of R to the studied drug, including intrinsic R/imputed S, followed by the sum of obtained probabilities, to obtain the WISCA-R rate for that drug. WISCA-R rates were compared year-to-year per drug.

Results: Of 89787, 96186, 70620, and 80186 urines processed in 2018/19/20/21, a total of 15278, 17454,12236, and 11511 isolates were tested, respectively, including *E. coli* (60-64% of isolates/year), *Klebsiella* (9-12%), Group B *Streptococcus* (5-8%), *Proteus* (5-6%), *Enterococcus* (4-6%), and other organisms (each ≤4%). WISCA-R rates compared year-to-year for 2018 vs 2019 vs 2020 vs 2021, respectively, were: for FOS 3.3 vs 3.8% (*P*= 0.1106), 3.8 vs 3.5% (*P*= 0.0886), 3.5 vs 3.1% (*P*= 0.0981); for AMC 8.5 vs 11.8% (*P* < 0.0001), 11.8 vs 10.4% (*P* < 0.0001), 10.4 vs 10.9% (*P*= 0.2014); for CIP 11.7 vs 12.7% (*P* = 0.0035), 12.7 vs 13.7% (*P* = 0.0093), 13.7 vs 15.0% (*P*= 0.0066); for FM 13.8 vs 15.8% (*P* < 0.0001), 15.8 vs 14.1% (*P* < 0.0001), 14.1 vs 14.9% (*P*= 0.0800); for KZ 18.5 vs 21.3% (*P* < 0.0001), 21.3 vs 19.8% (*P* = 0.0008), 19.8 vs 20.3% (*P*= 0.3001); for SXT 28.9 vs 29.7% (*P* = 0.0527), 29.7 vs 27.9% (*P* = 0.0004), 27.9 vs 24.4% (*P* < 0.0001); for AM 44.6 vs 45.6% (*P* = 0.0244), 45.6 vs 45.8% (*P*= 0.3667), 45.8 vs 48.2% (*P*= 0.0003).

Conclusions: This study provides support for FOS and AMC as oral agents with the lowest WISCA-R rates over the past 4 years. WISCA-R rates should be monitored. Further work is underway to study the impact of WISCA-R on decision making for empiric therapy of UTIs.

INTRODUCTION

Urinary tract infections (UTIs) are among the most frequently encountered bacterial infections worldwide.[1] Oral antibiotics are the mainstay of UTI treatment in the community. Knowledge of oral agents with low resistance profiles could be advantageous for informing empiric therapy decision-making.

The weighted-incidence syndromic combination antibiogram (WISCA) is a recently described novel approach that displays antimicrobial susceptibilities per drug/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 laboratory antimicrobial susceptibility test results, while also accounting for polymicrobial cultures to provide adequate empirical antimicrobial coverage.[2,4,5]

We sought to construct a WISCA resistance (R) profile (WISCA-R) per oral agent among drugs commonly used for the treatment of UTIs, to identify single agents with low resistance, and to monitor WISCA-R profiles of oral agents tested over the past 4 years.[6-8]

METHODS

Isolates were identified by conventional methods from urine cultures processed over a 4-year period ending in December 2021, and were tested by disk diffusion or the Vitek-2 system (bioMérieux), in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines, against amoxicillin-clavulanate (AMC), ampicillin (AM), cefazolin (KZ), ciprofloxacin (CIP), fosfomycin (FOS), nitrofurantoin (FM), and trimethoprim/sulfamethoxazole (SXT).[9] For FOS, CLSI *Escherichia coli* and *Enterococcus faecalis* breakpoints were applied to Gram-negative and Gram-positive organisms, respectively, similar to recently published investigations.[10-13]

WISCA-R was constructed by combining resistance data from all organisms per drug, while accounting for intrinsic resistance and known/imputed susceptibility per organism/drug combination.[4] 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 were compared year-to-year per drug.

RESULTS & DISCUSSION

Weighted Incidence of Urinary Pathogens:

Of 89787, 96186, 70620, and 80186 urine specimens processed in 2018, 2019, 2020, and 2021, a total of 15278, 17454,12236, and 11511 isolates were tested, respectively (Table 1). *E. coli* was the most frequently identified organism, consistent with previous findings.[6-8]

Comparison of the WISCA-R Profiles:

WISCA-R rates compared year-to-year for 2018 vs 2019 vs 2020 vs 2021, respectively, were: for FOS 3.3 vs 3.8% (*P*= 0.1106), 3.8 vs 3.5% (*P*= 0.0886), 3.5 vs 3.1% (*P*= 0.0981); for AMC 8.5 vs 11.8% (*P* < 0.0001), 11.8 vs 10.4% (*P* < 0.0001), 10.4 vs 10.9% (*P*= 0.2014); for CIP 11.7 vs 12.7% (*P* = 0.0035), 12.7 vs 13.7% (*P* = 0.0093), 13.7 vs 15.0% (*P*= 0.0066); for FM 13.8 vs 15.8% (*P* < 0.0001), 15.8 vs 14.1% (*P* < 0.0001), 14.1 vs 14.9% (*P*= 0.0800); for KZ 18.5 vs 21.3% (*P* < 0.0001), 21.3 vs 19.8% (*P* = 0.0008), 19.8 vs 20.3% (*P*= 0.3001); for SXT 28.9 vs 29.7% (*P* = 0.0527), 29.7 vs 27.9% (*P* = 0.0004), 27.9 vs 24.4% (*P* < 0.0001); for AM 44.6 vs 45.6% (*P* = 0.0244), 45.6 vs 45.8% (*P*= 0.3667), 45.8 vs 48.2% (*P*= 0.0003).
The fluctuation of WISCA-R rates emphasizes the need for monitoring rate changes per drug over time.

Limitations of the Study and Future Directions:

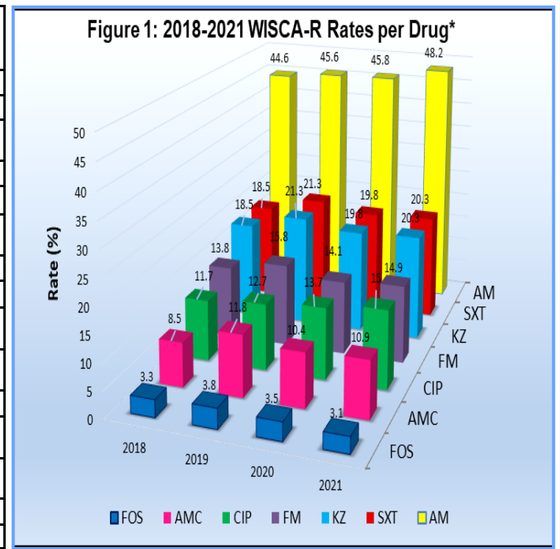
WISCA-R data in this study were derived from testing of patient urine cultures in the laboratory, where it was not always possible to distinguish asymptomatic bacteriuria from symptomatic infection. A long-term study currently underway in our laboratory aims to investigate the potential impact of WISCA-R on clinical decision making for empiric therapy of UTIs at time of diagnosis in the community setting.

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; *Enterococcus* spp always R to all cephalosporins; *Pseudomonas aeruginosa* always R to SXT).
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 (2018 - 2021)

Organism	Number of isolates (%) **2018**	Number of isolates (%) **2019**	Number of isolates (%) **2020**	Number of isolates (%) **2021**
Escherichia coli	9,515 (62.3)	10,526 (60.3)	7,544 (61.7)	7,408 (64.4)
Klebsiella spp	1,324 (8.7)	1,562 (8.9)	1,123 (9.2)	1,345 (11.7)
Group B *Streptococcus*	1,093 (7.2)	1,330 (7.6)	848 (6.9)	542 (4.7)
Proteus spp	942 (6.2)	979 (5.4)	745 (6.1)	660 (5.7)
Enterococcus spp	786 (5.1)	1,063 (6.1)	653 (5.3)	427 (3.7)
Staphylococcus spp	607 (4.0)	707 (4.1)	538 (4.4)	253 (2.2)
Citrobacter spp	368 (2.4)	470 (2.7)	257 (2.1)	299 (2.6)
Enterobacter spp	281 (1.8)	334 (1.9)	225 (1.8)	276 (2.4)
Pseudomonas aeruginosa	134 (<1)	174 (<1)	135 (1.1)	148 (1.3)
Morganella morganii	124 (<1)	195 (1.1)	94 (<1)	77 (<1)
Serratia spp	42 (<1)	42 (<1)	36 (<1)	42 (<1)
Group A *Streptococcus*	29 (<1)	20 (<1)	11 (<1)	2 (<1)
Acinetobacter spp	13 (<1)	13 (<1)	12 (<1)	17 (<1)
Providencia spp	12 (<1)	19 (<1)	9 (<1)	8 (<1)
Other organisms	8 (<1)	12 (<1)	6 (<1)	7 (<1)
TOTAL	15,278 (100)	17,454 (100)	12,236 (100)	11,511 (100)



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

Box 2: Example of WISCA-R Construction
Ampicillin (AM) WISCA-R (2021)

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	0.64356	0.43278	0.27852
Klebsiella spp/AM	0.11684	1.00000	0.11684
Group B *Streptococcus*/AM	0.04709	0.00000	0.00000
Proteus spp/AM	0.05734	0.10758	0.00617
Enterococcus spp/AM	0.03709	0.00937	0.00035
Staphylococcus spp/AM	0.02198	0.19331	0.00425
Citrobacter spp/AM	0.02598	1.00000	0.02598
Enterobacter spp/AM	0.02398	1.00000	0.02398
Pseudomonas aeruginosa/AM	0.01286	1.00000	0.01286
Morganella morganii/AM	0.00669	1.00000	0.00669
Serratia spp/AM	0.00365	1.00000	0.00365
Group A *Streptococcus*/AM	0.00017	0.00000	0.00000
Acinetobacter spp/AM	0.00148	1.00000	0.00148
Providencia spp/AM	0.00069	1.00000	0.00069
Other organisms/AM	0.00061	0.14286	0.00009
TOTAL	1.00000	Non-Applicable	0.48155

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 lends further support to our previous work for FOS and AMC as oral agents with the lowest WISCA-R rates over the past 4 years. WISCA-R rates should continue to be monitored per drug over time. Further work is underway to study the impact of WISCA-R on clinical decision making for empiric therapy of UTIs.

REFERENCES

1. Gupta K, et al. 2017. *Ann.Intern.Med.* 167(7):ITC49-ITC64.
2. Randhawa V, et al. 2014. *Crit.Care* 18 (3):R112.1-10.
3. Hughes JS, et al. 2016. *BMJ Open* 6:e012040.1-12.
4. Tandoglu Z, et al. 2019. *PloS ONE* 14 (4):e0214710.
5. Klinker KP, et al. 2021. *Ther. Adv. Infect. Dis.* 8: 1-9.
6. Farhat S, et al. 2019. *ASM Microbe 2019*, San Francisco, CA, USA. FR-844.
7. Farhat S, et al. 2020. *ASM Microbe 2020,* virtual conference. P-4338.
8. Farhat S, et al. 2021. *World Microbe Forum,* virtual conference. WMF21-0720.
9. Clinical and Laboratory Standards Institute. 2018-2021. Performance Standards for Antimicrobial Susceptibility Testing, M100 series. Wayne, PA, USA.
10. Hirsch EB, et al. 2015. *Int. J. Antimicrob. Agents* 46: 642-647.
11. Sorlozano A, et al. 2014. *Am. J. Infect. Control* 42: 1033-1038.
12. Michalopoulos AS, et al. 2011. *Int. J. Infect. Dis.* 15: e732- e739.
13. Sreenivasan S, et al. 2019. *J. Lab. Physicians* 11(3): 249-252.

ACKNOWLEDGMENTS

We thank Ranjeet Bharji and Tommy Li for their assistance with data mining and layout production of this study.