AMMI Canada/CACMID 2023, March 28 – March 31, 2023 – Toronto, ON, CANADA

Antimicrobial Resistance of Urinary Tract Pathogens Isolated from Non-Hospitalized Pregnant Patients as Determined by the Novel Weighted-Incidence Syndromic Combination Antibiogram (WISCA) Resistance (WISCA-R) Profiling Method

Shaker Farhat[1*], Andrew E. Simor[1,2,3], George Lim[1], Warren P. Shih[1], Huma Indawala[1], Sirsana Pandit[1], Jyotsna Lamichhane[1], Ivy Dapiosen[1], Nasir Azim[1], Inam Niazi[1], Kaminibahen Rai[1], Ibtesam Marogi[1], Xiao Dan Zhou[1], Yohana Bekele[1]

[1]Alpha Laboratories, Toronto, ON, Canada, [2]Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [3]University of Toronto, Toronto, ON, Canada

* shaker.farhat@alphalabs.ca
http://www.alphalabs.ca

ABSTRACT

Background: The weighted-incidence syndromic combination antibiogram (WISCA) is a recently described novel approach, used to inform empiric therapy decision-making. It displays antimicrobial susceptibilities per drug regimen for a given syndrome, rather than per organism as in traditional antibiograms. Asymptomatic bacteriuria during pregnancy can lead to urinary tract infection (UTI) which if left untreated can progress to serious complications, such as acute pyelonephritis, bacteremia, and fetal loss. We sought to construct a WISCA resistance (R) profile (WISCA-R) per oral agent used in the treatment of UTIs in pregnant patients, to identify agents with low resistance.

Methods: Isolates were identified by conventional methods from urine cultures over a 2-year period ending November 2022 and were tested by disk diffusion or the Vitek-2 system (bioMérieux), according to CLSI guidelines, against amoxicillin-clavulanic acid (AMC), ampicillin (AM), cefazolin (KZ), cefixime (CEF), nitrofurantoin (FM), and trimethoprim/sulfamethoxazole (SXT). WISCA-R was constructed by multiplying the weighted incidence by the corresponding probability of resistance to the studied drug, including intrinsic resistance/imputed susceptibility, followed by the sum of obtained probabilities, to determine the WISCA-R rate for that drug.

Results: Of 170,747 urine specimens processed over 2 years, a total of 318 isolates were recovered from prenatal cultures that yielded ≥ 10^7 CFU/L, including *Escherichia coli* (*n* = 178), *Streptococcus agalactiae* (66), *Enterococcus* (23), *Klebsiella* (22), *Proteus* (13), *Citrobacter* (7), *Staphylococcus* (7), and *Enterobacter* (2) species. WISCA-R rates for AMC, FM, CEF, KZ, AM, and SXT were 4.4%, 10.3%, 12.6%, 18.6%, 35.8%, and 43.1%, respectively.

Conclusions: Of the oral agents commonly used to treat UTIs in pregnancy reported in this study, AMC and FM had the lowest WISCA-R rates among community urinary isolates. These results provide support for AMC and FM as useful agents with low likelihood of resistance, for the empiric treatment of UTIs in non-hospitalized pregnant patients

INTRODUCTION

Asymptomatic bacteriuria during pregnancy can lead to symptomatic urinary tract infection (UTI), which if left untreated can progress to serious complications, such as acute pyelonephritis, sepsis, and fetal loss.[1] Oral agents are the mainstay of UTI treatment in the community. However, there is only a limited selection of oral agents that can be considered safe and effective for UTI treatment during pregnancy.[2]

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.[3,4,5] The main advantage of the WISCA is that it can potentially be useful to inform treatment decision-making at the time of diagnosis, prior to knowing antimicrobial susceptibility test results, while also accounting for polymicrobial infections to provide adequate empirical antimicrobial coverage.[3,5,6]

We sought to construct a WISCA resistance (R) profile (WISCA-R) per oral agent among drugs commonly used for the treatment of UTIs in pregnant patients, to identify agents with low resistance, using the WISCA-R profiling method, as previously described.[7-10]

METHODS

Pregnant patients were identified from test requisitions submitted by clinicians and by use of an in-house software program, which identified additional pregnant cases. Isolates were identified by conventional methods from urine cultures over a 2-year period ending in November 2022 and were tested by disk diffusion or the Vitek-2 system (bioMérieux), according to CLSI guidelines, against amoxicillin-clavulanic acid (AMC), ampicillin (AM), cefazolin (KZ), cefixime (CEF), nitrofurantoin (FM), and trimethoprim/sulfamethoxazole (SXT).[11]

\Each 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.[5] 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 determine the final WISCA-R rate for that drug, as described in Box 1. Box 2 provides an example of how it was constructed.

RESULTS & DISCUSSION

Weighted Incidence of Urinary Pathogens

Of 170,747 urine specimens processed in the 2-year period ending in November 2022, a total of 318 isolates were tested (Table 1). *E. coli* was the most frequently identified organism, consistent with previous findings.[7-10]

First WISCA-R Report for Pregnant Patients

To our knowledge, this is the first report using the WISCA-R profiling method to identify low-resistance agents in pregnant patients. The WISCA-R rates for AMC, FM, CEF, KZ, AM, and SXT were 4.4%, 10.3%, 12.6%, 18.6%, 35.8%, and 43.1%, respectively (Figure 1).

Limitations of the Study and Future Directions

WISCA-R data in this study were derived from testing of pregnant patients' 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 as well as clinical outcomes for both pregnant and non-pregnant patient populations in the community setting.

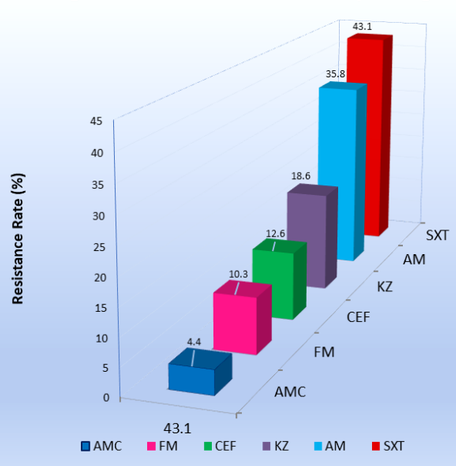
Box 1: Construction of WISCA-R

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).
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 Prenatal Urine Cultures

Organism	Number of isolates (%)
Escherichia coli	178 (56.0)
Streptococcus agalactiae	66 (20.7)
Enterococcus spp	23 (7.2)
Klebsiella spp	22 (6.9)
Proteus spp	13 (4.1)
Citrobacter spp	7 (2.2)
Staphylococcus spp	7 (2.2)
Enterobacter spp	2 (0.6)
TOTAL	318 (100)

Figure 1: WISCA-R Resistance Rate per Drug*



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

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

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	0.55975	0.44944	0.25157
Streptococcus agalactiae/AM	0.20755	0.00000	0.00000
Enterococcus spp/AM	0.07233	0.00000	0.00000
Klebsiella spp/AM	0.06918	1.00000	0.06918
Proteus spp/AM	0.04088	0.07692	0.00314
Citrobacter spp/AM	0.02201	1.00000	0.02201
Staphylococcus spp/AM	0.02201	0.28571	0.00629
Enterobacter spp/AM	0.00629	1.00000	0.00629
TOTAL	1.00000	Non-applicable	0.35848

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 at time of diagnosis.

Our results indicate that of the oral agents commonly used to treat UTIs in pregnancy reported in this study, AMC and FM had the lowest WISCA-R rates among community urinary isolates. These results provide support for AMC and FM as useful agents with low likelihood of resistance, for the empiric treatment of UTIs in non-hospitalized pregnant patients. Further work is underway to study the impact of WISCA-R on clinical decision-making as well as clinical outcomes in both pregnant and non-pregnant patient populations in the community.

REFERENCES

1. Delzell JE and Lefevre ML. 2000. *Am. Fam. Physician* 61: 713-720.
2. Norwitz ER and Greenberg JA. 2009. *Rev. Obstet. Gynecol.* 2: 135-136.
3. Randhawa V, et al. 2014. *Crit.Care* 18(3):R112.1-10.
4. Hughes JS, et al. 2016. *BMJ Open* 6:e012040.1-12.
5. Tandoglu Z, et al. 2019. *PloS ONE* 14 (4):e0214710.
6. Klinker KP, et al. 2021. *Ther. Adv. Infect. Dis.* 8: 1-9.
7. Farhat S, et al. 2019. *ASM Microbe 2019*, San Francisco, CA, USA. FR-844.
8. Farhat S, et al. 2020. *ASM Microbe 2020*, virtual conference. P-4338.
9. Farhat S, et al. 2021. *World Microbe Forum*, virtual conference. WMF21-0720.
10. Farhat S, et al. 2022. *ASM Microbe* 2022, Washington, DC, USA. FR-2826.
11. Clinical and Laboratory Standards Institute. 2020-2022. Performance Standards for Antimicrobial Susceptibility Testing, M100 series. Wayne, PA, USA.

ACKNOWLEDGMENTS

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