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Construction of Weighted Incidence Syndromic Combination Antibiogram (WISCA) Resistance Profiles of Oral Agents Tested against Community Urinary Isolates, and Comparison to Physician Empiric Choice

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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 for a given syndrome, rather than per organism as in traditional antibiograms. Since urinary tract infections (UTIs) are among the most commonly encountered infections worldwide, and since oral antimicrobial agents are the mainstay of UTI treatment in the community, we sought to (1) construct a WISCA resistance (R) profile (WISCA-R) per oral agent tested against community urinary isolates, and (2) determine if agents with low R rates corresponded to physician empiric choice most frequently prescribed in a subset of patients.

Methods: Isolates were identified by conventional methods from urine cultures over a 1 year period ending December 2018. Isolates were tested by disk diffusion or 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). 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 from combined R data (including intrinsic R) from all organisms for each drug. Information on empiric treatment choice was provided by physicians.

Results: Of 89,787 urine specimens processed, a total of 15,278 isolates were tested, including *E. coli* (*n* =9,515), *Klebsiella* spp (1,324), Group B *Streptococcus* (1,093), *Proteus* spp (942), *Enterococcus* spp (786), *Staphylococcus* spp including *S. aureus* (607), Group A *Streptococcus* (29), *Pseudomonas aeruginosa* (134), *Citrobacter* (368), *Enterobacter* (281), *Morganella* (124), *Serratia* (42), *Acinetobacter* (13), *Providencia* (12), and *Aerococcus* (8) spp. WISCA-R rates for FOS, AMC, CIP, FM, KZ, SXT, and AM were 3.3%, 8.5%, 11.7%, 13.8%, 18.5%, 28.9%, and 44.6%, respectively. Review of files (*n*=419) identified empiric choice to be FOS, FM, CIP, or other in 63%, 34%, 2%, or <1% of cases, respectively. There was concordance between the most frequently selected empiric agent and WISCA-R agent with the lowest R rate.

Conclusions: WISCA-R can be constructed as a practical tool for informing empiric therapy of UTIs in the community at time of diagnosis. Further studies are warranted to investigate its potential impact on clinical outcome.

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 poly-microbial 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 tested against community urinary isolates, and (2) determine if agents with low WISCA-R rates corresponded to physician empiric choice most frequently prescribed in a subset of patients.

METHODS

Isolates were identified by conventional methods from urine cultures over a 1 year period ending in December 2018. Isolates 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).[5] For FOS, CLSI *Escherichia coli* and *Enterococcus faecalis* breakpoints were applied to Gram-negative and -positive organisms, respectively, similar to recently published investigations.[6,7,8]

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 for each drug, to arrive at the final WISCA-R rate for that drug, as described in Box 1.

Information regarding antibiotic therapy prescribed for a subset of patients with positive urine cultures was obtained by review of available clinical records. These patients were identified from physician practices associated with greater than 100 positive urine cultures submitted to the laboratory during the course of this study. Three sources of information were used in the process: (1) test requisition if an empiric therapy choice was indicated or specifically ordered for testing, (2) direct contact with the physician via telephone interview or office visit, and (3) patient record review upon authorization by the physician.

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 for each drug, to arrive at the final WISCA-R rate for that drug.

RESULTS & DISCUSSION

Weighted Incidence of Uropathogens:
Of the 89,787 urine specimens processed in 2018, a total of 15,278 isolates were recovered (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.[9,10]

Construction of the WISCA-R Profiles:
A WISCA-R profile was constructed for each drug as described in Box 1. The WISCA-R rates for FOS, AMC, CIP, FM, KZ, SXT, and AM were 3.3%, 8.5%, 11.7%, 13.8%, 18.5%, 28.9%, and 44.6%, respectively (Figure 1).

Comparison to Physician Empiric Choice:
An initial review of clinical files (*n*=419) identified the physician empiric therapy choice to be FOS, FM, CIP, or other (AM, AMC, KZ, or SXT) in 63%, 34%, 2%, or <1% of cases, respectively. However, the second larger review (*n*=1,226) identified the empiric therapy choice as FOS, FM, CIP, SXT, or other (AM, AMC, or KZ) in 49%, 43%, 6%, 2%, or <1% of cases, respectively. Both reviews showed concordance between the most frequently selected empiric agent and the WISCA-R agent with the lowest R rate; however, in the larger set conducted later, both FOS and FM were identified as being closely the most frequently selected choice of empiric therapy, consistent with current clinical guidelines.[11]

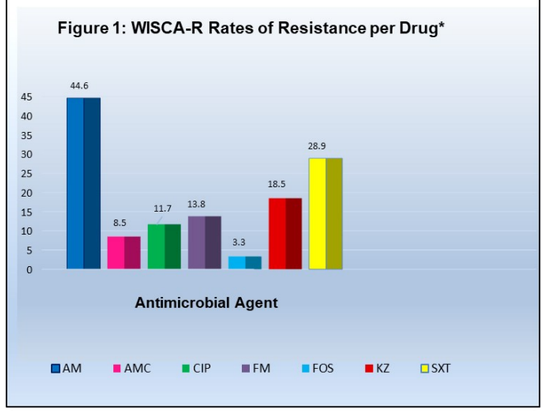
Limitations of the Study and Future Directions:
1. WISCA-R data in this study were derived from testing of patient urine cultures in the laboratory, where distinguishing asymptomatic bacteriuria from symptomatic infection was not always possible. A study currently underway in our laboratory aims to investigate the potential impact of WISCA-R on clinical outcome in patients with UTIs.
2. The data provided here on empiric treatment choice represented only a small portion of the entire study, and therefore would need to be validated in larger investigations.

Table 1: Organisms Isolated from Urine Cultures

Organism	Number of isolates (%)
Escherichia coli	9,515 (62.3)
Klebsiella spp	1,324 (8.7)
Group B *Streptococcus*	1,093 (7.2)
Proteus spp	942 (6.2)
Enterococcus spp	786 (5.1)
Staphylococcus spp*	607 (4.0)
Citrobacter spp	368 (2.4)
Enterobacter spp	281 (1.8)
Pseudomonas aeruginosa	134 (<1)
Morganella morganii	124 (<1)
Serratia spp	42 (<1)
Group A *Streptococcus*	29 (<1)
Acinetobacter spp	13 (<1)
Providencia spp	12 (<1)
Aerococcus spp	8 (<1)
TOTAL	15,278 (100)

**S. aureus*, *n*=96; *S. saprophyticus*, *n*=229

Figure 1: WISCA-R Rates of Resistance per Drug*



AM	AMC	CIP	FM	FOS	KZ	SXT
44.6	**8.5**	**11.7**	**13.8**	**3.3**	**18.5**	**28.9**

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

CONCLUSIONS

To our knowledge, this is the first report of WISCA-R as distinct from WISCA that displays 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. Further studies are currently underway to investigate its potential impact on clinical outcome.

There was concordance between the most frequently selected empiric agent and the WISCA-R agent with the lowest R rate. Both FOS and FM were physicians' most frequently selected choice for the empiric treatment of UTIs in the community.

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