Decreased Susceptibility Rates Against Orally Administered Antimicrobials for Community-Acquired Urinary Tract Infections in Latin America: Report of the SENTRY Antimicrobial Surveillance Program (2003)

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AMENDED ABSTRACT

Background: Antimicrobial resistance (R) is an emerging problem among community-acquired urinary tract infections (CA-UTI), limiting economic therapeutic options (trimethoprim/sulfamethoxazole [T/S] or ampicillin [AMP]). We have evaluated the contemporary pathogen frequency and susceptibility (S) patterns of CA-UTI in Latin American (LA) medical centers (2003).

Methods: As part of the SENTRY Program, a total of 611 isolates were collected in 2003 from patients with CA-UTI presenting in LA clinics and medical centers. Each strain was tested in a central laboratory using NCCLS broth microdilution methods with appropriate controls.

Results: *E. coli* was the predominant pathogen (66.0%), followed by *Klebsiella* spp. (KSP; 7.0%), *P. mirabilis* (PM; 6.4%), *Enterococcus spp*. (5.6%), and *P. aeruginosa* (PSA; 4.6%). Decreased S rates were detected among *E. coli* for common orally administered agents, such as AMP (46%), cefuroxime (XM; 76%), T/S (60%), ciprofloxacin (CIP; 77%), and gatifloxacin (79%). S rates for AMP, XM, T/S, and CIP were 9, 74, 79 and 81% for KSP, and 59, 90, 72 and 85% for PM, respectively. The rates of ESBL-producing strains were 1.7, 16.3 and 5.1% for *E. coli*, KSP and PM, respectively. For enterococci, S rates for AMP, chloramphenicol, CIP and vancomycin were 88, 85, 56 and 97% respectively; and 24% of strains showed high-level R to gentamicin. PSA exhibited decreased S to CIP (68%), ceftazidime (68%), amikacin (71%), and imipenem (71%).

Conclusions: Bacteria isolated from patients with CA-UTI in LA showed limited S to orally as well as IV administered antimicrobials, especially T/S and the quinolones. Our results highlight the need for continued monitoring of S patterns in geographic regions where R to new and old compounds are elevated, and CA-UTI need regimens with expanded spectrums of activity.

INTRODUCTION

Community-acquired urinary tract infection (CA-UTI) is one of the most frequent infections worldwide. Approximately eight million UTI episodes are reported in the United States every year. These infections are usually caused by *Escherichia coli*, but other uropathogens, such as *Klebsiella* spp. and *S. saprophyticus*, have also been frequently isolated.

Effective management of UTIs in the outpatient setting has been hampered by the development of antimicrobial resistance to most oral antimicrobial agents by the main bacterial pathogens involved in this type of infection. The increasing trimethoprim/sulfamethoxazole resistance is worrisome, since this agent is frequently prescribed for uncomplicated UTIs in many developed and developing countries. The Infectious Disease Society of America (IDSA) guidelines have suggested that fluoroquinolones may be used as a first-line therapy for treatment of uncomplicated bacterial cystitis in women; however, reports of uropathogens resistant to these agents have increasingly been reported.

The current trend of empirically treating CA-UTI episodes poses a great challenge for researchers, since data on uropathogens prevalence and antimicrobial susceptibility have been increasingly more difficult to obtain. In this study, we evaluated the pathogen frequency and susceptibility patterns of CA-UTI in Latin American medical centers as part of the SENTRY Antimicrobial Surveillance Program.

MATERIALS AND METHODS

Bacterial strains. A total of 611 non-duplicate bacterial isolates were collected from patients with CA-UTI in Latin American medical centers (Argentina, Chile, Brazil, Mexico and Venezuela) in 2003. All isolates were identified at the participating institution by the routine methodology in use at each laboratory. Upon receipt at the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA), isolates were subcultured onto blood agar to ensure viability and purity. Confirmation of species identification was performed by the Vitek System (bioMérieux Vitek, St. Louis, MO) or conventional methods as required.

Susceptibility testing. Antimicrobial susceptibility testing was performed and interpreted following the guidelines for reference broth microdilution method as described by the NCCLS. Dry-form microdilution panels and broth for inoculation were purchased from Trek Diagnostic Systems (Cleveland, OH, USA). Testing of quality control strains *E. coli* ATCC 25922 and 35218, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, and *Enterococcus faecalis* ATCC 29212 was performed for quality assurance purposes.

Isolates of *E. coli* and *Klebsiella* spp. with increased MICs (≥ 2 µg/ml) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as extended-spectrum ß-lactamase (ESBL)-producing phenotypes. Production of ESBL was confirmed by disk approximation test.

RESULTS

- *E. coli* was the most frequently isolated pathogen from CA-UTI (66.0%), followed by *Klebsiella* spp. (7.0%), *P. mirabilis* (6.4%), *Enterococcus spp*. (5.6%), and *P. aeruginosa* (4.6%). The strains were collected mainly from patients with complicated UTI or previous treatment failure.
- Decreased susceptibility rates were detected among *E. coli* for common orally administered agents, such as ampicillin (46.2%), ciprofloxacin (77.4%), gatifloxacin (79.2%), levofloxacin (78.7%), and trimethoprim/sulfamethoxazole (59.6%). The production of ESBL was detected in only 1.7% of strains and nitrofurantoin showed excellent activity against *E. coli* isolates (93.1% susceptibility).
- The most active oral agents against *Klebsiella* spp. were the fluoroquinolones gatifloxacin (83.7% susceptibility), levofloxacin (81.4%), and ciprofloxacin (81.4%); followed by trimethoprim/sulfamethoxazole (79.1%), cefuroxime (74.4%) and nalidixic acid (74.4%). The production of ESBL was detected in 16.3% of *Klebsiella* spp. strains and nitrofurantoin was active against only 51.2% of isolates at the susceptible breakpoint. Only imipenem and meropenem were active against 100.0% of *Klebsiella* spp.
- Against *P. mirabilis*, amoxicillin/clavulanate was the most active compound (94.9% susceptibility) among the orally administered antimicrobials, followed by levofloxacin (92.3%), cefuroxime (89.7%), and gatifloxacin (87.2%). Trimethoprim/sulfamethoxazole inhibited only 71.8% of *P. mirabilis* strains at the susceptibility breakpoint and 5.1% of strains were considered ESBL-producers.
- All isolates of *E. coli, Klebsiella* spp., and *P. mirabilis* with increased MICs (≥ 2 µg/ml) for ceftazidime and/or ceftriaxone and/or aztreonam (ESBL-phenotype) had a positive confirmatory disk approximation test for ESBL production.
- *P. aeruginosa* showed elevated resistance rates to most antimicrobials evaluated. The most active compound was polymyxin B (96.4% susceptibility), followed by meropenem, imipenem and amikacin (71.4%). The most active oral compound was ciprofloxacin (67.9% susceptibility).
- Linezolid was the most active compound against *Enterococcus* spp. (100% susceptibility). Resistance rates to glycopeptides were relatively low (2.9% for both vancomycin and teicoplanin) and ampicillin was active against 88.2% of strains at the NCCLS breakpoint. High-level resistance to gentamicin or streptomycin was observed in 23.5 and 29.4% of strains, respectively.

Table 1. Occurrence of the top 10 pathogens isolated from community-acquired urinary tract infections in Latin American medical centers (SENTRY Program, 2003).

	Organism or group	No. of isolates	% of total
1.	*E. coli*	403	66.0
2.	*Klebsiella* spp.	43	7.0
3.	*P. mirabilis*	39	6.4
4.	*Enterococcus* spp.	34	5.6
5.	*P. aeruginosa*	28	4.6
6.	group B streptococci	14	2.3
7.	*S. saprophyticus*	8	1.3
8.	*K. oxytoca*	7	1.1
9.	*E. cloacae*	6	1.0
10.	*S. marcescens*	5	0.8

Table 1. Antimicrobial susceptibility of CA-UTI isolates collected from Latin American medical centers (SENTRY Antimicrobial Surveillance Program, 2003).

Organism (no. tested)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	% S	% R
E. coli (403)				
Ampicillin[a]	>16	>16	46.2	53.6
Ampicillin/sulbactam	8	32	56.6	23.3
Amoxicillin/clavulanate[a]	8	16	83.6	1.2
Piperacillin/tazobactam	2	4	97.3	0.2
Cefoxitin	4	8	93.1	1.7
Cefuroxime[a]	4	8	76.4	2.2
Ceftriaxone	≤0.25	≤0.25	98.5	1.2 (1.7)[b]
Ceftazidime	≤1	≤1	98.3	1.5 (1.7)[b]
Cefepime	≤0.12	≤0.12	98.8	1.0
Aztreonam	≤0.12	≤0.12	98.3	1.7 (1.7)[b]
Imipenem	≤0.5	≤0.5	100.0	0.0
Amikacin	2	4	100.0	0.0
Gentamicin	≤2	4	90.1	8.4
Nalidixic acid[a]	4	>32	72.7	29.3
Ciprofloxacin[a]	≤0.03	>4	77.4	21.6
Gatifloxacin[a]	≤0.03	>4	79.2	17.1
Levofloxacin[a]	≤0.03	>4	78.7	18.6
Nitrofurantoin[a]	≤16	32	93.1	6.9[d]
Trimethoprim/sulfamethoxazole[a]	≤0.5	>2	59.6	40.4
Klebsiella spp. (43)				
Ampicillin[a]	>16	>16	9.3	74.4
Ampicillin/sulbactam	8	>32	67.4	25.6
Amoxicillin/clavulanate[a]	2	16	76.7	7.0
Piperacillin/tazobactam	2	32	88.4	9.3
Cefuroxime[a]	2	>16	74.4	16.3
Ceftriaxone	≤0.25	32	86.0	9.3 (16.3)[b]
Ceftazidime	≤1	16	88.4	4.7 (13.9)[b]
Cefepime	≤0.12	2	90.7	7.0
Aztreonam	≤0.12	>16	83.7	11.6 (16.3)[b]
Imipenem	≤0.5	≤0.5	100.0	0.0
Amikacin	2	16	95.3	4.7
Gentamicin	≤2	>8	86.0	14.0
Nalidixic acid[a]	4	>32	74.4	25.6
Ciprofloxacin[a]	0.12	>4	81.4	18.6
Gatifloxacin[a]	0.06	>4	83.7	16.3
Levofloxacin[a]	0.06	>4	81.4	16.3
Nitrofurantoin[a]	32	>32	51.2	48.8[d]
Trimethoprim/sulfamethoxazole[a]	≤0.5	>2	79.1	20.9
P. mirabilis (39)				
Ampicillin[a]	≤1	>16	59.0	41.0
Ampicillin/sulbactam	1	32	76.9	10.3
Amoxicillin/clavulanate[a]	≤1	8	94.9	0.0
Piperacillin/tazobactam	≤0.5	1	100.0	0.0
Cefuroxime[a]	2	8	89.7	7.7
Ceftriaxone	≤0.25	≤0.25	94.9	5.1 (5.1)[b]
Ceftazidime	≤1	≤1	100.0	0.0 (2.5)[b]
Cefepime	≤0.12	0.5	94.9	5.1
Aztreonam	≤0.12	≤0.12	100.0	0.0 (5.1)[b]
Imipenem	1	2	100.0	0.0
Meropenem	≤0.06	≤0.06	100.0	0.0
Amikacin	4	8	97.4	2.6
Gentamicin	≤2	>8	79.5	20.5
Nalidixic acid[a]	4	>32	84.6	15.4
Ciprofloxacin[a]	≤0.03	4	84.6	10.3
Gatifloxacin[a]	0.12	4	87.2	7.7
Levofloxacin[a]	0.06	2	92.3	5.1
Nitrofurantoin[a]	>32	>32	2.6	97.4[d]
Trimethoprim/sulfamethoxazole[a]	≤0.5	>2	71.8	28.2
P. aeruginosa (28)				
Ceftazidime	4	>16	67.9	32.1
Cefepime	4	>16	64.3	14.3
Aztreonam	8	>16	57.1	39.3
Imipenem	1	>8	71.4	25.0
Meropenem	0.5	>8	71.4	14.3
Piperacillin/tazobactam	8	>64	67.9	32.1
Amikacin	4	>32	71.4	21.4
Gentamicin	4	>8	60.7	35.7
Nalidixic acid[a,c]	> 32	>32	3.6	96.4
Ciprofloxacin[a]	0.25	>4	67.9	32.2
Gatifloxacin[a]	2	>4	60.7	32.1
Levofloxacin[a]	1	>4	60.7	32.1
Nitrofurantoin[a,c]	>32	>32	0.0	100.0
Polymyxin B	≤1	≤1	96.4	3.6
Enterococcus spp. (34)				
Ampicillin[a]	≤1	>16	88.2	11.8
Chloramphenicol[a]	8	>16	85.3	11.8
Ciprofloxacin[a]	1	>4	55.9	35.3
Gatifloxacin[a]	0.5	>4	64.7	35.3
Levofloxacin[a]	1	>4	64.7	35.3
Linezolid[a]	≤2	≤2	100.0	0.0
Nitrofurantoin[a]	≤16	≤16	94.1	5.9
Quinupristin/Dalfopristin	>2	>2	11.8	76.5
Gentamicin HL	≤500	>1000	76.5	23.5
Streptomycin HL	≤1000	>2000	70.6	29.4
Teicoplanin	2	2	97.1	2.9
Vancomycin	≤2	≤2	97.1	2.9

a. Orally administered antimicrobial agents.
b. Percentage of ESBL-producing strains.
c. Susceptibility breakpoints for Enterobacteriaceae were used (NCCLS, 2004).
d. Includes intermediate and resistant strains.

CONCLUSIONS

- Bacterial pathogens isolated from CA-UTI in Latin American medical centers showed decreased susceptibility rates to commonly prescribed oral antimicrobials, especially trimethoprim/sulfamethoxazole, ampicillin and ciprofloxacin.
- Although nitrofurantoin exhibited excellent in vitro activity against *E. coli* (93.1% susceptibility), elevated rates of resistance among other pathogens frequently isolated from CA-UTI, such as *Klebsiella* spp. and *P. mirabilis,* may limit the use of this compound as a first-line agent for the treatment of CA-UTI.
- High rates of resistance to oral and IV administered antimicrobials recorded among these isolates highlights the need of continuing monitoring of the pathogen frequency and susceptibility profile of CA-UTI in the Latin America region.

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SELECTED REFERENCES

Blondeau JM. (2004). Current issues in the management of urinary tract infections: extended-release ciprofloxacin as a novel treatment option. *Drugs* 64:611-628.

Gales AC, Sader HS, Jones RN; SENTRY Participants Group (Latin America). (2002). Urinary tract infection trends in Latin American hospitals: report from the SENTRY antimicrobial surveillance program (1997-2000). *Diagnostic Microbiology Infectious Diseases* 44:289-299.

Gupta K, Stamm WE. (2002). Outcomes associated with trimethoprim/sulphamethoxazole (TMP/SMX) therapy in TMP/SMX resistant community-acquired UTI. *International Journal of Antimicrobial Agents* 19:554-556.

National Committee for Clinical Laboratory Standards. (2003). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - sixth edition. Approved document M7-A6*. Wayne, PA:NCCLS.

National Committee for Clinical Laboratory Standards. (2004). *Performance standards for antimicrobial susceptibility testing. 14th informational supplement M100-S14*. Wayne, PA:NCCLS.

Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. (1999). Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clinical Infectious Diseases* 29:745-758.