Variation in Occurrence and Resistance Trends Among Community-Acquired Urinary Tract Infection Pathogens in North America, Latin America and Europe: Report from the SENTRY Antimicrobial Surveillance Program (2003)

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SENTRY ANTIMICROBIAL SURVEILLANCE

AMENDED ABSTRACT

Background: Concern of resistance has led to increasing use of broader spectrum agents for UTI. For the estimated 60% of women having at least 1 UTI occurrence in a lifetime, the use of co-trimoxazole (T/S) and oral ß-lactams are becoming suboptimal. Community-acquired UTI (CA-UTI) pathogens from 3 continents were sampled by the SENTRY Program in 2003.

Methods: A total of 3,448 strains were collected from North America (NA; 1,418; 27 sites), Latin America (LA; 611; 10) and Europe (EU; 1,419; 27). The isolates were tested by NCCLS broth microdilution methods and ESBL rates determined using NCCLS criteria and confirming tests. Epidemic clones were detected by automated ribotyping and PFGE. Linezolid (LZD) target mutations were performed by PCR product sequencing.

Results: Top 5 pathogens (80% of isolates) had a rank order of: *E. coli* (44 - 66%) > enterococci (ENT; 6 - 14%) > *Klebsiella* spp. (KSP; 7 - 13%) > *P. aeruginosa* (PSA; 5 - 8%) > *P. mirabilis* (PM; 5 - 6%). EC was dominant in all regions, highest in LA (66%) where ENT was less prevalent (6%). PSA varied from 4th to 5th in occurrence. 80% of CA-UTI pathogens in LA were Enterobacteriaceae (ca. 20% > NA or EU). ESBL phenotypes were detected in EC (6.2% in EU), KSP (29.1% in EU) and PM (5.1% in LA); confirmed ESBLs were lowest among EC in NA (37%) and highest among KSP in all regions (72 - 100%). PSA ciprofloxacin (CIP)-R rates were 31.5 - 36.6% across all regions. VRE was only seen in NA (5.4%) and LA (2.9%), usually *E. faecium*. 4 epidemic clusters were noted among EC in Turkey, Mexico and USA, and KSP in USA; each with a CIP-R pattern. One LZD-R *E. faecium* (USA) demonstrated a G2576U mutation.

Conclusions: This initial SENTRY Program report of CA-UTI indicates compromised activity/spectrum of primary agents (T/S-R at 20 - 40% in EC), but only 4 - 8% R for nitrofurantoin. CIP-R in EC was 11 (NA) to 22% (LA). Clearly T/S and fluoroquinolones are becoming compromised as first-line agents in CA-UTI in all geographic regions.

INTRODUCTION

Acute uncomplicated cystitis occurs primarily in healthy, premenopausal, nonpregnant, adult women. One in three will have had at least one episode by age 24, and as many as 60% of women will have had a urinary tract infection (UTI) in their lifetime. The 1997 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey estimated that UTI caused seven million office visits and one million emergency room visits resulting in 100,000 hospitalizations. Accurate diagnosis depends upon both the presence of symptoms and a positive culture; however, a diagnosis and subsequent treatment are often made without culture results.

Pathogens isolated from nosocomial and complicated UTI have become increasingly resistant to the commonly prescribed antimicrobial agents. Additionally, antimicrobial resistance has become even more important among pathogens isolated from community-acquired UTIs, due in part to the common practice of treating empirically, without culture results, in the outpatient setting.

In this report, we summarize the antimicrobial susceptibility profiles of bacterial isolates originating from community-acquired UTI collected by SENTRY Program participants on three continents in 2003 (North America, Latin America and Europe).

MATERIALS AND METHODS

A total of 3,448 strains were collected from three continents: North America (1,418 isolates from 22 medical centers in the USA and five in Canada), Latin America (611 isolates from 10 medical centers) and Europe (1,419 isolates from 27 medical centers). All medical centers were chosen to be sentinel sites for each region. Consecutive, non-duplicate isolates were shipped to the central monitor (JMI Laboratories, North Liberty, IA) along with organism identification, date of culture and other patient demographics. Upon receipt, isolates were subcultured, reviewed for identification accuracy and stored in tryptic soy broth with glycerol at -80ºC. Species identification was confirmed by the Vitek System (bio Merieux, Hazelwood, MO) or other biochemical tests as needed. Susceptibility testing was performed according to NCCLS recommendations [NCCLS, 2003]. Quality control was performed using *E. coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *S. pneumoniae* ATCC 49619 and *E. faecalis* ATCC 29212.

E. coli, *Klebsiella* spp. and *P. mirabilis* isolates with ceftazidime or ceftriaxone or aztreonam MICs of ≥ 2 µg/ml [NCCLS, 2004] were screened for ESBL production by the disk approximation method.

Isolates with similar susceptibility patterns isolated in the same medical center and temporally related were typed by automated ribotyping and pulsed-field gel electrophoresis. Linezolid resistance among Gram-positive organisms was verified by Etest and disk diffusion methods. Isolates with confirmed linezolid resistance were evaluated for detection of mutations in the ribosomal gene by PCR and gene sequencing.

RESULTS

- *E. coli* was dominant and represented approximately 50% of all organisms tested (**Table 1**). The overall rank order was: *E. coli* (44 - 66%) > enterococci (6 - 14%) > *Klebsiella* spp. (7 - 13%) > *P. aeruginosa* (5 - 8%) > *P. mirabilis* (5 - 6%). The top five pathogens accounted for over 83% of the total for North America and Latin America and nearly 90% for Europe.
- The prevalence of *E. coli* was much higher in Latin America (66%) when compared to Europe (49%) or North America (44%). Conversely, enterococci showed a lower prevalence in Latin America (5% versus 10% in Europe and 14% in North America).
- Resistance of *E. coli* to trimethoprim/sulfamethoxazole varied from 20 to 40% by region whereas resistance to nitrofurantoin remained low (4 to 8%). *E. coli* showed high rates of resistance to ampicillin (41.2 - 53.6%) and trimethoprim/sulfamethoxazole (20.3 - 40.4%). In general, resistance rates were highest in Latin America, followed by Europe and North America (**Table 2**).
- The emergence of ciprofloxacin resistance among *E. coli* is especially worrisome, varying from 11% in North America to 14% in Europe and 22% in Latin America (**Table 2**).
- Nitrofurantoin (4.2 - 7.9% resistance) and cefuroxime (2.2 - 6.5% resistance) were the most active oral agents tested (**Table 2**).
- Ciprofloxacin resistance rates among *P. aeruginosa* were 31.5% in North America, 32.2% in Latin America and 36.6% in Europe (**Table 2**). *P. aeruginosa* showed higher resistance rates to multiple drug classes in Latin America compared to North America or Europe.
- Ampicillin was highly active against *E. faecalis* (0.0 - 1.7% resistance), but *E. faecium* showed high resistance rates (83.3 - 100.0%).
- Four epidemic clusters of *E. coli* were detected in Turkey, Mexico and the USA, and one of *Klebsiella* spp. in the USA; all clones displayed a fluoroquinolone-resistant pattern.
- Vancomycin-resistant enterococci were detected only in North America (5.4%) and Latin America (2.9%; **Table 2**). Among *E. faecium* from North America, 39.5% of isolates were resistant to vancomycin. Only one linezolid-resistant enterococcal strain was detected. This *E. faecium* strain was isolated in North America and had a G2576U ribosomal DNA mutation.
- Isolates with ESBL phenotypes were predominantly recovered from European sites with rates of 29.1% for *Klebsiella* spp. and 6.2% for *E. coli* (**Table 3**). The prevalence of ESBL-producing *P. mirabilis* was highest in Latin America at 5.1%. ESBL confirmation rates for *E. coli* and *Klebsiella* spp. were highest in Latin America (100%) > Europe (78.3 and 86.6%, respectively) > North America (36.8 and 72.2%).

Table 1. Variation of rank order for community-acquired UTI by region (North America, Europe, Latin America).

	North America		Europe		Latin America	
Organism	Rank	No. of strains (%)	Rank	No. of strains (%)	Rank	No. of strains (%)
E. coli	1	617 (44.0)	1	694 (48.9)	1	403 (66.0)
Enterococcus spp.	2	204 (14.4)	3	144 (10.1)	4	34 (5.6)
Klebsiella spp.	3	181 (12.8)	2	153 (10.8)	2	43 (7.0)
P. aeruginosa	4	108 (7.6)	4	112 (7.9)	5	28 (4.6)
P. mirabilis	5	73 (5.1)	5	85 (6.0)	3	39 (6.4)
TOTAL		1,183 (83.4)		1,188 (89.6)		547 (83.7)

Table 2. Key resistance markers for community-acquired UTI pathogens in North America, Latin America and Europe.

		% resistant		
Organism	Antimicrobial agent	North America	Latin America	Europe
E. coli	Ampicillin	41.2	53.6	47.1
	Cefuroxime	3.6	2.2	6.5
	Ciprofloxacin	11.0	21.6	14.0
	Trimethoprim/Sulfamethoxazole	20.3	40.4	28.8
	Nitrofurantoin	4.2	6.9	7.9
P. aeruginosa	Ciprofloxacin	31.5	32.2	36.6
	Tobramycin	1.9	32.1	27.7
	Amikacin	0.9	21.4	7.1
	Ceftazidime	5.6	32.1	18.8
	Cefepime	1.9	14.3	9.8
	Imipenem	6.5	25.0	13.4
	Meropenem	0.9	14.3	2.7
E. faecium	Ampicillin	95.7	100.0	83.3
	Ciprofloxacin	95.7	100.0	58.3
	Vancomycin	39.1	0.0	0.0
	Linezolid	4.3	0.0	0.0
E. faecalis	Ampicillin	1.7	0.0	0.8
	Ciprofloxacin	45.0	26.7	27.9
	Vancomycin	1.1	3.3	0.0
	Linezolid	0.0	0.0	0.0

Table 3. ESBL phenotype and confirmation rates by region (North America, Europe, Latin America).

	ESBL phenotype[a] (%)			ESBL confirmation[b] (%)		
Organism	Europe	North America	Latin America	Europe	North America	Latin America
E. coli	6.2	3.6	1.7	78.3	36.8	100.0
Klebsiella spp.	29.1	8.8	16.3	86.6	72.2	100.0
P. mirabilis	3.5	2.7	5.1	66.7	100.0	100.0

a. Percentage based on ceftazidime, or ceftriaxone or aztreonam MICs ≥ 2 µg/ml [NCCLS, 2004].
b. Confirmation by disk approximation method.

CONCLUSIONS

- Clearly, trimethoprim/sulfamethoxazole, ampicillin and fluoroquinolones are becoming compromised as first-line agents in community-acquired UTI in all geographic regions.
- The development of a strategy to encourage use of fluoroquinolone-sparing agents for uncomplicated UTI is critical to preserve this important antimicrobial class.
- Surveillance programs such as the SENTRY Program and others are critical in providing local, regional, national and international data that can be used to assist in guideline development aimed at optimizing and extending the useful life of available therapeutics.

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