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Occurrence and Susceptibility Rates Among Urinary Tract Infection Pathogens from Europe: A Seven Year Report from the SENTRY Antimicrobial Surveillance Program (1997-2000, 2003)

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AMENDED ABSTRACT

Objectives: To report the occurrence and susceptibility (S) rates for pathogens causing urinary tract infection (UTI) isolated from medical centers in Europe, Turkey, and Israel. The S rates were compared by CLSI and EUCAST breakpoints. The SENTRY Antimicrobial Surveillance Program was utilized as the platform for collecting urine culture isolates during 5 years out of a 10 year period that the program has been in existence.
Methods: A total of 4,507 strains (50 consecutive, non-duplicate per site) were collected from 42 medical centers in 19 countries in Europe, Turkey and Israel (1997-2000, 2003). During the 5 years 31 locations participated in 3 or more years. All isolate identifications were confirmed and S testing performed in a central laboratory using reference broth microdilution methods (M7-A7) and interpretive criteria of CLSI and EUCAST (2006). ESBL phenotype rates were as determined by CLSI criteria.
Results: The 5 most frequent pathogens accounted for 83.3% of the total CA-UTI and the top 7, 90.0%. These 7 pathogens displayed little change in occurrence rates over the 7 year period. *E. coli* remained the dominant UTI pathogen at nearly 50% while enterococci showed a slight decrease from 11.7 to 10.1%. Variations in 1999 were greater due to only 9 participating sites (small sample size). Among commonly isolated Enterobacteriaceae, carbapenems were the most active agents ranging from 99.1% to 100.0% S; lower S was noted for ciprofloxacin (77-89%) and trimethoprim/sulfamethoxazole (T/S; 60-79%). Ceftazidime S rates for *Klebsiella*, *E. coli*, and *P. mirabilis* were 83.4, 97.2, 95.5% (CLSI) and lower at 76.9, 94.7, 92.5% (EUCAST), respectively. ESBL phenotype rates were 28.3, 6.3, and 9.0% for the same organism groups. Polymyxin B was active against *P. aeruginosa* at 99% S, followed by carbapenems and piperacillin/tazobactam at 84% and amikacin at 83%. Vancomycin, teicoplanin, and linezolid remained active against enterococci (99% S).

Table. Variation of rank order in SENTRY Program UTI pathogens by year for Europe.

Rank	Organism	All years	1997	1998	1999	2000	2003
1	*E. coli*	2,175(48.3)	505(51.0)	548(48.0)	68(39.5)	361(46.1)	693(48.8)
2	Enterococci	510(11.3)	116(11.7)	127(11.1)	23(13.4)	100(12.8)	144(10.1)
3	*Klebsiella* spp.	445(9.9)	83(8.4)	120(10.5)	25(11.6)	69(8.8)	153(10.8)
4	*P. aeruginosa*	355(7.9)	65(6.6)	91(8.0)	16(9.3)	71(9.1)	112(7.9)
5	*P. mirabilis*	265(5.9)	52(5.2)	70(6.1)	3(1.7)	56(7.2)	84(5.9)
6	*Enterobacter* spp.	194(4.3)	49(4.9)	36(3.2)	11(6.4)	33(4.2)	65(4.6)
7	Indole + *Proteus* spp.	109(2.4)	21(2.1)	31(2.7)	5(2.9)	27(3.1)	28(2.0)
Total		4,507	991	1,142	172[a]	783	1,419

a. Small sample

Conclusions: This comprehensive report from the SENTRY Program covering 7 years of UTI sampling in Europe, reports minor variation in the most common pathogens between the sample intervals but with significant S differences noted among monitored countries. Emerging resistance is limiting the usefulness of commonly prescribed UTI agents including T/S and FQ, forcing reliance on more potent parenteral broad-spectrum agents and the additional problems inherent in their use.

INTRODUCTION

In primary care settings, between 25 and 35% of women ages 20 to 40 years have experienced a urinary tract infection (UTI). Community-acquired UTIs are responsible for over 8 million office visits per year in the United States (USA) and produce significant morbidity with associated health care costs. Physicians write approximately 11.3 million prescriptions for adult women with UTIs in the USA annually and the cost of treatment has been estimated at $1.6 billion USD per year.

Due to the predictability of pathogens causing UTI and their antimicrobial resistance patterns, empiric therapy without performing a urine culture has become common practice. However, with increasing antimicrobial resistance to the common first-line agents in many countries, knowledge of resistance prevalence in local communities is necessary when choosing appropriate empiric therapy.

Here we summarize the antimicrobial susceptibility profiles of bacterial isolates originating from both community-acquired and nosocomial urinary tract infections, from both women and men, collected by a regular component of the European SENTRY Antimicrobial Surveillance Program over 7 years (1997 to 2000, and 2003).

MATERIALS AND METHODS

Organism Collection: A total of 4,507 strains were submitted for testing from 42 medical centers in 19 countries in Europe, Turkey and Israel (1997-2000, 2003) as part of the global SENTRY Program. Over the seven year period, eight sites participated in all years, 14 participated in all except for 1999, and 31 sites participated in 3 or more years. The number of participating sites/countries per year was: 21/12, 22/13, 9/5, 16/12 (1997-2000) and 27/14 (2003).

Participating medical centers were directed to send 50 consecutive, non-duplicate isolates along with organism identification, date of culture, source (community acquired or nosocomial), and other patient demographics to the central monitor (JMI Laboratories, IA, USA). Isolates were transported on Amies charcoal swabs, subcultured on receipt, reviewed for identification accuracy and stored in tryptic soy broth with glycerol or defibrinated rabbit blood (for fastidious species) at -80ºC. Where indicated, identifications were confirmed by biochemical tests and/or the Vitek System (bioMerieux, Hazelwood, MO, USA).

Susceptibility Testing: MIC testing was performed by reference broth microdilution methods (CLSI M7-A7, 2006) on validated dry-form panels (TREK Diagnostics, OH, USA) with interpretive criteria being those of the CLSI (M100-S17, 2007) and EUCAST (2006). Quality control (QC) 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.

ESBL phenotypes of *E. coli*, *Klebsiella* spp. and *P. mirabilis* isolates were identified by having MIC values of ≥2 mg/L for ceftazidime or ceftriaxone or aztreonam (CLSI M100-S17, 2007). Confirmation screening of ESBL producers was performed by a disk approximation method or by Etest (AB BIODISK, Solna, Sweden).

RESULTS

- The 7 most frequent isolates accounted for 90% of UTI, of which *E. coli* was nearly 50%. Overall rank order was *E. coli* (48.3%) > enterococci (11.3%) > *Klebsiella* spp. (9.9%) > *P. aeruginosa* (7.9%) > *P. mirabilis* (5.9%) > *Enterobacter* spp. (4.3%) > indole-positive *Proteae* (2.4%; see Table 1).
- Over the study period, only minimal changes in occurrence rates were noted: *E. coli* was dominant each year with enterococci and *Klebsiella* spp. variably ranked second and third (Table 1).
- Among the Enterobacteriaceae, carbapenems were the most active class with susceptibility rates of 99.1 to 100.0% (CLSI breakpoints) and 87.2 to 100.0% (EUCAST; see Table 2).
- Susceptibility of Enterobacteriaceae to commonly used oral agents such as ciprofloxacin (76.8 to 89.0%, CLSI; 75.2-87.6%, EUCAST) and trimethoprim/sulfamethoxazole (1999 and 2003 data only; 60.6% to 78.9%, CLSI) is increasingly being compromised.
- ESBL phenotype rates for *Klebsiella* spp., *E. coli* and *P. mirabilis* were 28.3, 6.3 and 9.0% by CLSI criteria; and by EUCAST breakpoints, all CLSI phenotypic ESBLs would automatically be classified as non-susceptible.
- *Klebsiella* and *E. coli* ESBL phenotypes have increased from 26.5 to 32.0% and 4.2 to 6.6%, respectively; ESBL phenotypes for *P. mirabilis* have varied over the course of the study from lows of 3.6-3.8% (1997 and 2003) to a high of 17.1% (1998; Table 3).
- Ranking of the most active agents against *P. aeruginosa* was polymyxin B (99.1% susceptible) > carbapenems and piperacillin/tazobactam (83.9-84.8%) > amikacin (82.8%, CLSI; 77.7%, EUCAST).
- Among the enterococci, vancomycin, teicoplanin and linezolid remained highly active at 98.8, 99.2 and 99.0-100%, respectively (CLSI and EUCAST criteria).

Table 1. Variation of rank order in UTI pathogens by year for European patients (SENTRY Program 1997-2000, 2003).

Rank	Organism	All years	1997	1998	1999	2000	2003
1	*E. coli*	2,175(48.3)	505(51.0)	548(48.0)	68(39.5)	361(46.1)	693(48.8)
2	Enterococci	510(11.3)	116(11.7)	127(11.1)	23(13.4)	100(12.8)	144(10.1)
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4	*P. aeruginosa*	355(7.9)	65(6.6)	91(8.0)	16(9.3)	71(9.1)	112(7.9)
5	*P. mirabilis*	265(5.9)	52(5.2)	70(6.1)	3(1.7)	56(7.2)	84(5.9)
6	*Enterobacter* spp.	194(4.3)	49(4.9)	36(3.2)	11(6.4)	33(4.2)	65(4.6)
7	Indole + *Proteus* spp.	109(2.4)	21(2.1)	31(2.7)	5(2.9)	27(3.1)	28(2.0)
Total		4,507	991	1,142	172[a]	783	1,419

a. Limited sample size.

Table 2. Susceptibility rates of urinary tract pathogens recovered from European patients (SENTRY Program; 1997-2000, 2003).

Organism (no. tested)	MIC (mg/L): 50%	MIC (mg/L): 90%	% Susceptible: CLSI	% Susceptible: EUCAST
E. coli (2175)				
Amoxicillin/clavulanate	4	16	76.5	-[a]
Ampicillin	16	>16	49.9	-
Cefepime	≤0.12	≤0.12	98.0	96.5
Ceftazidime	≤1	≤1	97.2	94.7
Ceftriaxone	≤0.25	≤0.25	96.7	95.4
Cefuroxime	4	8	91.5	91.5
Ciprofloxacin	≤0.25	>2	85.7	85.0
Gentamicin	≤2	2	92.7	91.8
Imipenem	≤0.5	0.5	100.0	99.9
Nitrofurantoin	≤32	32	91.6	-
Piperacillin/tazobactam	1	8	94.9	-
Tetracycline	≤4	>8	59.4	-
Trimethoprim/sulfamethoxazole	≤0.5	>2	70.3[b]	-
Enterococcus spp. (510)				
Ampicillin	1	8	90.6	-
Ciprofloxacin	1	>2	58.8	-
Doxycycline	>4	>4	34.9	-
Gentamicin (HL)[c]	≤500	>1000	73.5	-
Linezolid	2	2	99.0	100.0
Nitrofurantoin	≤32	≤32	91.0	-
Quinupristin/dalfopristin	>2	>2	10.2	-
Teicoplanin	≤2	≤2	99.2	99.2
Tigecycline	0.12	0.5	85.6[d]	85.6
Vancomycin	1	2	98.8	98.8
Klebsiella spp. (445)				
Amoxicillin/clavulanate	4	>16	70.1	-
Cefepime	≤0.12	16	88.8	78.0
Ceftazidime	≤1	>16	83.4	76.9
Ceftriaxone	≤0.25	>32	80.7	5.5
Cefuroxime	2	>16	72.4	72.4
Ciprofloxacin	≤0.25	2	89.0	87.6
Gentamicin	≤2	>8	80.9	79.3
Imipenem	≤0.5	0.5	99.8	99.6
Nitrofurantoin	≤32	64	65.8	-
Piperacillin/tazobactam	2	>64	79.8	-
Tetracycline	≤4	>8	68.5	-
Trimethoprim/sulfamethoxazole	≤0.5	>1	64.2[b]	-
P. aeruginosa (355)				
Amikacin	4	>32	82.8	77.7
Cefepime	4	>16	73.5	56.1
Ceftazidime	4	>16	73.2	66.8
Ciprofloxacin	0.25	>2	62.8	60.6
Gentamicin	≤2	>8	63.9	63.9
Imipenem	1	>8	83.9	83.9
Piperacillin/tazobactam	8	>64	84.8	-
Polymyxin B	≤1	≤1	99.1	-
P. mirabilis (265)				
Amoxicillin/clavulanate	≤2	16	85.3	-
Ampicillin	2	>16	58.1	-
Cefepime	≤0.12	0.5	94.7	92.5
Ceftazidime	≤1	≤1	95.5	92.5
Ceftriaxone	≤0.25	≤0.25	94.0	92.5
Cefuroxime	1	16	89.8	89.8
Ciprofloxacin	≤0.25	>2	90.0	75.8
Gentamicin	≤2	>8	83.8	82.3
Imipenem	1	2	99.6	93.2
Nitrofurantoin	64	>64	0.8	-
Piperacillin/tazobactam	≤0.5	2	96.2	-
Trimethoprim/sulfamethoxazole	≤0.5	>1	66.7[b]	-
Enterobacter spp. (194)				
Amoxicillin/clavulanate	>16	>16	4.1	-
Ampicillin	>16	>16	10.3	-
Cefepime	≤0.12	8	93.3	77.3
Ceftazidime	≤1	>16	66.5	56.2
Ceftriaxone	≤0.25	>32	66.5	56.7
Cefuroxime	>16	>16	39.7	39.7
Ciprofloxacin	≤0.25	>2	76.8	75.3
Gentamicin	≤2	>8	79.9	78.4
Imipenem	0.5	2	100.0	100.0
Nitrofurantoin	>32	>32	41.2	-
Piperacillin/tazobactam	4	>64	69.6	-
Tetracycline	≤4	>8	74.7	-
Trimethoprim/sulfamethoxazole	≤0.5	>1	78.9[b]	-
Indole-positive *Proteae* (109)				
Amoxicillin/clavulanate	>16	>16	41.3	-
Ampicillin	>16	>16	21.1	-
Cefepime	≤0.12	0.5	95.4	94.5
Ceftazidime	≤1	16	89.9	83.5
Ceftriaxone	≤0.25	4	94.5	79.8
Cefuroxime	>16	>16	32.1	32.1
Ciprofloxacin	≤0.25	>2	78.9	75.2
Gentamicin	>8	>8	82.6	78.9
Imipenem	≤0.25	4	99.1	87.2
Nitrofurantoin	>32	>32	5.5	-
Piperacillin/tazobactam	≤0.5	4	99.1	-
Tetracycline	>8	>8	22.0	-
Trimethoprim/sulfamethoxazole	≤0.5	>1	60.6[b]	-

a. - = no EUCAST breakpoint available.
b. Based only on 1999 and 2003 Europe data.
c. HL = high-level.
d. US-FDA tigecycline breakpoint.

Table 3. ESBL phenotype rates of UTI pathogens by year in Europe from the SENTRY Program (1997-2000, 2003).

Organism (no. tested)	ESBL phenotype[a] rates in Europe by year: All years	1997	1998	1999	2000	2003
E. coli (2,175)	6.3	4.2	7.1	5.9	7.5	6.6
Klebsiella spp. (445)	28.3	26.5	20.0	28.0	34.8	32.0
P. mirabilis (265)	9.0	3.8	17.1	0.0	12.5	3.6

a. Percentage based on ceftazidime or ceftriaxone or aztreonam MIC results ≥2 mg/L (CLSI, 2007).

CONCLUSIONS

- Pathogen occurrence rates for UTI have shown only minor variation over the 7 years monitored with *E. coli* remaining as the dominant pathogen at nearly 50%.
- Commonly used first-line UTI agents such as ampicillin, trimethoprim/sulfamethoxazole, and fluoroquinolones are increasingly becoming compromised by escalating resistance rates.
- Strategies need to be developed and updated to preserve commonly prescribed (and cost effective) UTI agents, limiting the need for more potent parenteral broad-spectrum agents.
- Surveillance programs that provide reliable susceptibility data at the local and regional levels are critical for use in clinical guideline development and formulary decisions regarding optimal use and preservation of available therapeutics, especially without local guidance due to minimal processing by clinical microbiology laboratories.

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