Fluoroquinolone Resistance Among Gram-Negative Urinary Tract Pathogens: Global Smart Program Results, 2009-2010

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Abstract: OBJECTIVES: To determine the rates of fluoroquinolone resistant (FQR) in gram-negative bacilli urinary tract infections (UTIs) in a global population. METHODS: The Study for Monitoring Antimicrobial Resistance Trends (SMART) collected 1,116 FQR gram-negative urinary pathogens from hospitalized patients in 33 countries during 2009-2010. Amikacin, ertapenem, and imipenem were the most active agents tested against FQR UTI pathogens, including extended-spectrum beta-lactamase producers. RESULTS: FQR rates vary widely country to country with a range of 6% to 75%. Regional FQR rates were 23.5% in North America, 29.4% in Europe, 33.2% in Asia, 38.7% in Latin America, and 25.5% in the South Pacific. CONCLUSIONS: These observations suggest that fluoroquinolones may no longer be effective as first-line therapy for gram-negative UTI in hospitalized patients.

Keywords: Ertapenem, Fluoroquinolone resistance, Imipenem, SMART Global Surveillance, Urinary Tract Infection.

INTRODUCTION

Fluoroquinolone resistance in UTI pathogens has been increasing globally [1, 2]. Poor health, urinary catheterization, recent hospitalization, and previous UTI are risk factors associated with increased fluoroquinolone resistance [3-5]. Independent risk factors also include prior exposure to antimicrobial agents including trimethoprim-sulfamethoxazole, metronidazole, cephalosporins, and fluoroquinolones [3-5]. Additionally, the increasing prevalence of beta-lactamases, including the global spread of CTX-M beta-lactamases with frequent cross-resistance with fluoroquinolones has become a major concern [6-9]. The Study for Monitoring Antimicrobial Resistance Trends (SMART) has tracked resistance in gram-negative aerobic pathogens of intra-abdominal infections since 2002, and in 2009 began including isolates from urinary tract infections (UTI). Evidence for increasing fluoroquinolone resistance in UTI is presented.

MATERIAL AND METHODS

A total of 98 investigational sites (Africa 1, Asia 19, Europe 27, Middle East 1, North America 29, Latin America 14, and South Pacific 7) from 33 countries each contributed up to 50 gram-negative UTI isolates from hospitalized patients in 2009 and 2010. The isolates collected were non-duplicate, consecutive isolates from hospitalized patients with UTI. All isolates were gram-negative isolates deemed to be clinically significant ($>10^5$ cfu/ml) by the participating site. Only one isolate per patient was accepted. The only patient-specific data collected was age and gender. Isolates were further classified as hospital-associated (HA) or community-associated (CA) if the specimen was obtained ≥48 hours or <48 hours after admission, respectively. Isolates were identified to the species level at each participating site and submitted to the central reference study center (Laboratories International for Microbiology Studies, a subsidiary of International Health Management Associates, Inc., Schaumburg, IL, USA) for identification confirmation and susceptibility testing. In 2009-2010, 3,845 gram-negative bacilli were submitted of which 1,116 were fluoroquinolone-resistant (FQR; resistant to both levofloxacin and ciprofloxacin).

Minimum inhibitory concentrations (MICs) were determined at the central laboratory using MicroScan® dehydrated microdilution panels (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA). Drug susceptibilities were defined using the Clinical and Laboratory Standards Institute M100-S20-U interpretive criteria breakpoints [10]. Quality control was performed on each day of testing using the CLSI recommended QC strains: *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* ATCC 700603 (positive ESBL control). Isolates were classified as ESBL producers when there was at least an eight fold reduction of the MICs for ceftazidime and/or cefotaxime tested in combination with clavulanic acid compared with the MICs when tested alone [10]. Significance was determined by Fisher's Exact Test, two-tailed.

RESULTS

The 3,845 urinary tract infection (UTI) isolates included 33 species of which the top 12 most frequently encountered

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species (n>20) comprised >98% (3,781) of all isolates collected. The majority of the isolates (59.6%) were collected from North America and Europe. The remaining isolates originated from Asia (17.6%), Latin America (13.8%), South Pacific (7.5%), the Middle East (0.8%), and Africa (0.6%). Overall, females represented 65% of the patients. Almost half the isolates were from elderly patients >65 years of age (1,845, 49%) and <10% (359) were from pediatric patients (0-16 years) with a mean age of 58.1 years for all patients represented. Isolates were evenly distributed between HA and CA UTIs, 38.4% versus 38.7%, respectively (p>0.05, Table **1**). The 1,116 FQR isolates were evenly distributed between HA and CA populations as were the 381 fluoroquinolone-resistant extended-spectrum beta-lactamase producing (ESBL+) isolates (p>0.05).

Eleven of the top twelve UTI pathogens demonstrated resistance to the fluoroquinolones in varying degrees; only *Citrobacter koseri* remained 100% (45/45; 95% confidence interval=91%-100%) susceptible to fluoroquinolones. The *in vitro* percents susceptible for all study drugs against FQR isolates are presented in Table **2**. Overall, only amikacin, the carbapenems, and piperacillin-tazobactam inhibited >75% of all FQR isolates.

Only ertapenem and imipenem inhibited >95% of FQR *E. coli* including both ESBL+ and ESBL- strains. The least active agent was ampicillin-sulbactam. Amikacin susceptibility percentages were >90% for *C. freundii* (100%), *Enterobacter aerogenes* (100%), *E. coli*, ESBL- (97%), *Klebsiella oxytoca*, ESBL- (100%), *Morganella morganii* (100%), and *Proteus mirabilis*, (93%). Ertapenem and imipenem were particularly active against FQR ESBL+ and ESBL- *E. coli* with susceptibility percentages ranging from 95% to 100%. None of the study drugs inhibited >79% (imipenem) of FQR *K. pneumoniae*. Only ertapenem demonstrated consistent activity against *P. mirabilis*, inhibiting 100% of all isolates including both ESBL+ and ESBL- strains.

FQR rates varied widely among regions and countries. Regionally, FQR rates were: Latin America (38.7%); Asia (33.2%); Europe (29.4%); South Pacific (25.5%); Africa (25%; one country only); North America (23.5%); and Middle East (20.7%). There was much wider variance among individual countries. FQR rates ranged from a low of 6% in Estonia and the United Kingdom (1 site each) to 75% in India (3 sites) (Fig. **1**). The United States, contributing the most isolates from the largest number of sites (1,026 isolates, 23 sites), had a FQR rate for all UTI isolates of 24%.

DISCUSSION

The SMART program has analyzed trends in antibiotic resistance in gram-negative bacilli isolated from patients with intra-abdominal infections since 2002 and, beginning in 2009, global trends in resistance in gram-negative bacilli in hospitalized patients with urinary tract infections. This study confirms the prevalence of UTIs in females compared to males in a 2:1 ratio previously reported [11] and may reflect the observation that females are more prone to contract UTIs as compared to males.

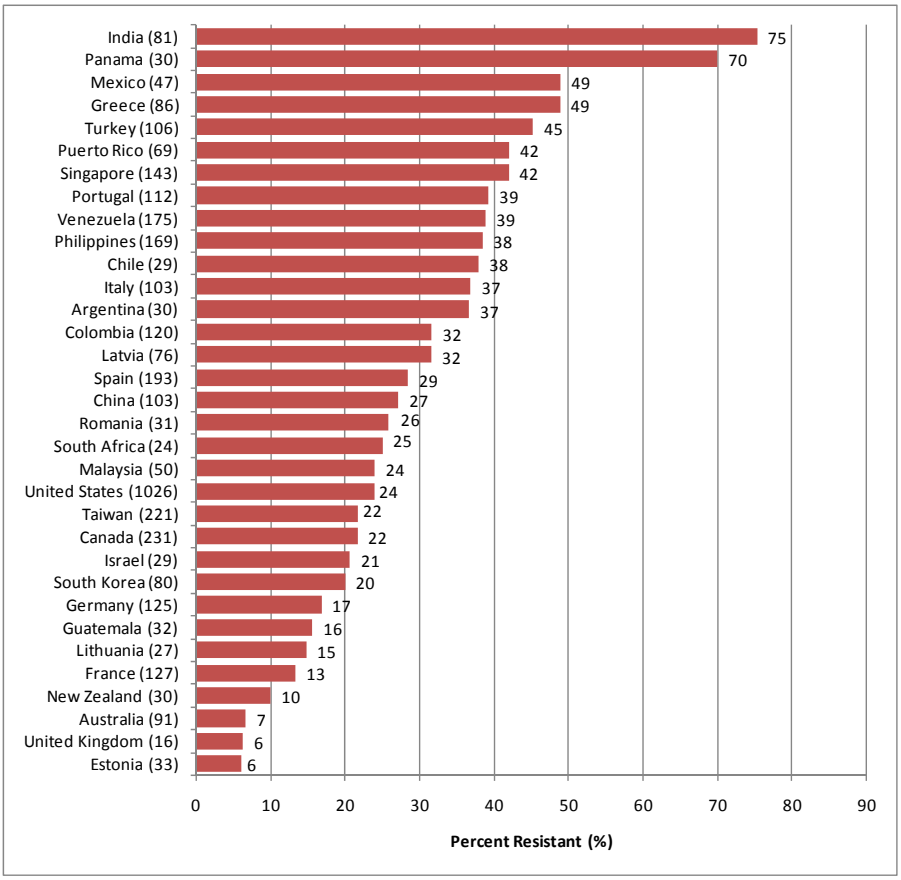

Fig. (1). Percent fluoroquinolone resistance* in 3,845 UTIs by country (n).

A distinction was made in the collection time of the UTI specimen to categorize the infection as HA (specimen collection ≥48 after admission) or CA (specimen collection <48 hrs after admission). Although there was a statistically significant difference in the percentage of ESBL+ isolates between HA (47.8%) and CA (33.8%) UTIs ($p<0.001$), there were no significant differences in the percentages of fluoroquinolone-resistant ESBL+ UTIs for HA (44.6%) and CA (36.8%) ($p>0.05$). This may reflect the growing numbers of community-acquired ESBLs containing the CTX-M-15 ESBL genotype that is strongly associated with multi-drug resistant phenotypes including fluoroquinolone resistance [12, 13].

The *in vitro* activity of the drugs in this study suggests that there are relatively few therapy alternatives for treatment of fluoroquinolones-resistant gram-negative UTI pathogens. Low susceptibility rates were seen for ampicillin-sulbactam, cefotaxime, cefoxitin, ceftazidime, and ceftriaxone against the majority of isolates. Only ertapenem and imipenem demonstrated consistent activity against ESBL+ isolates, with both equally active against ESBL+ *E. coli*, imipenem more active against ESBL+ *K. oxytoca*, and ertapenem more active against ESBL+ *P. mirabilis*. None of the study drugs were more than 88% active (imipenem) against all *K. pneumoniae*. Overall, amikacin and piperacillin-tazobactam had similar *in vitro* activity to ertapenem and imipenem against all FQR isolates combined.

Fluoroquinolone resistance varied from country to country and less so, but significantly nevertheless, from region to region. The highest regional FQR rate was seen in Latin America at 38.7%, but resistance was as high as 70% in one hospital in Panama and above 40% from three sites in Puerto Rico and Mexico. The highest fluoroquinolone resistance rates in this study were seen in India where 75% of all UTIs were non-susceptible to the fluoroquinolones. The average for the Asian countries was 33.2%. Fluoroquinolone resistance rates for Canada and the United States were 22% and 24%, respectively, and were more than double the rate reported as recently as 2006 by Karlowsky *et al*., in 1,858 *E. coli* [14]. Notably, the current rate of 49% resistance seen in Turkey is also almost double the 25% rate reported for that region during the same 2005-2006 time frame but that report was limited to *E. coli* only [1]. The lowest rates reported in this study were seen in Estonia and the United Kingdom (6%), however, the significance of this is diminished due to the low n's and the fact that the isolates were collected from a single lab in each country.

This study is limited by four factors: (1) inconsistency in the sites reporting from 2009 and 2010 with only about half of the sites participating in both years; (2) the number of sites per county is limited, averaging 3 per country, and 13 countries having a single investigative site; (3) the lack of molecular characterization of resistance mechanisms limits the depth, but not necessarily the overall breadth of a surveillance of this type; and (4) the exclusion of useful UTI antimicrobials such as colistin, the tetracyclines, and trimethoprim-sulfamethoxazole in the evaluation. On the other hand, since all patients in this study were hospitalized patients, it is likely the majority of the UTIs were complicated, not uncomplicated, and the use of oral agents in such cases would have limited utility.

Fluoroquinolone resistance is increasing in UTI gram-negative pathogens both locally and regionally [1, 2, 5, 11]. The SMART program plays a significant role in monitoring the evolution of resistance and emergence of specific resistance mechanisms and phenotypes. Close monitoring of resistance patterns may prove useful in directed empiric therapy not just in the treatment of UTI but other infections as well. Although *in vitro* data do not always equate to clinical outcomes, especially in UTIs where the fluoroquinolones often achieve high concentrations, this study suggests that alternatives to fluoroquinolone therapy may deserve consideration in environments of increasing fluoroquinolone resistance.

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Table 1. Distribution of Isolates between Hospital and Community Associated Urinary Tract Infections Traparancy delavation

Specimen Collection*	All UTI Isolates		Fluoroquinolone Resistant UTI Isolates		All UTI ESBL+		Fluoroquinolone Resistant UTI ESBL+	
	N	% of Total	N	% of Total	N	% of Total	N	% of Total
≥48 hrs (HA)	1476	38.4%	454	40.7%	255	47.8%	170	44.6%
<48 hrs (CA)	1488	38.7%	413	37.0%	180	33.8%	140	36.8%
None Given	881	22.9%	249	22.3%	98	18.4%	71	18.6%
Total	3845		1116		533		381	
p-Value †	>0.05		>0.05		<0.001		>0.05	

* HA, hospital-associated; CA, community-associated.

† >0.05, not statistically significant; <0.001, statistically significant (Fisher's Exact Test, two-tailed).

Table 2. Percents Susceptible (%) of FQR Urinary Tract Pathogens (n=1,100)

Organism* (FQR N/Total N Tested)	AK	A/S	CPE	CTF	CFX	CAZ	CAX	ETP	IMP	P/T
A. baumannii (30/57)	37	23	7	3	na	7	7	na	43	10
C. freundii (5/50)	100	20	80	40	0	40	40	80	80	60
E. aerogenes (2/58)	100	0	50	0	50	0	0	50	100	50
E. cloacae (23/140)	83	0	57	4	4	17	4	35	100	26
E. coli (763/2163)	93	14	65	55	76	56	56	96	99	86
ESBL+ (300/367)	88	7	12	0	74	0	0	95	100	81
ESBL− (463/1796)	97	19	99	91	77	92	92	97	99	89
K. oxytoca (8/86)	87	0	38	25	87	25	25	87	100	38
ESBL+ (6/13)	83	0	17	0	83	0	0	83	100	17
ESBL− (2/73)	100	0	100	100	100	100	100	100	100	100
K. pneumoniae (96/582)	74	4	26	18	48	21	17	57	79	34
ESBL+ (65/135)	78	0	8	0	51	0	0	55	88	25
ESBL− (31/447)	65	13	65	55	42	65	52	61	61	52
M. morganii (8/49)	100	0	38	38	50	50	38	100	50	100
P. mirabilis (38/209)	84	37	81	55	73	60	55	100	27	90
ESBL+ (10/18)	60	30	40	0	80	0	0	100	20	100
ESBL− (28/191)	93	39	96	75	71	82	75	100	29	86
P. aeruginosa (124/295)	62	na	31	7	na	49	8	na	54	73
S. marcescens (3/47)	67	0	67	0	0	67	33	67	67	33
All FQR Isolates Combined (1100/3781)	86	13	56	44	61	57	44	78	88	76

* *C. koseri* (n=45) not included as all were fluoroquinolone-susceptible.
AK, Amikacin; **A/S**, Ampicillin-Sulbactam; **CPE**, Cefepime; **CTF**, Cefotaxime; **CFX**, Cefoxitin; **CAZ**, Ceftazidime; **CAX**, Ceftriaxone; **ETP**, Ertapenem; **IMP**, Imipenem; **P/T**, Piperacillin-Tazobactam. na, CLSI breakpoints not available for this species/drug combination (na's were calculated as resistant for purposes of Grand Total percentages).

CONFLICT OF INTEREST

S. Bouchillon, D. Hoban, S. Hawser, and R. Badal served as scientific advisors or consultants to Merck, and received research support from Merck to conduct this study.

TRANSPARENCY DECLARATION

The authors are responsible for the work described in this paper. All authors were involved in at least one of the following: conception, design, acquisition, general analysis, statistical analysis, interpretation of data, and drafting the manuscript and/or revising the manuscript for important intellectual content. All authors provided final approval of the version to be published.

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