

Longitudinal Analysis of the Susceptibility of *E. coli* to Empiric Urinary Tract Infection (UTI) Agents; Impact of Introduction of

Generic Ciprofloxacin on Fluoroquinolone Resistance

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REVISED ABSTRACT

Background: Per IDSA guidelines for empiric treatment of uncomplicated UTI commonly caused by *E. coli* (EC), trimethoprim-sulfamethoxazole (SXT) is recommended as first-line. Where SXT resistance (R) is high (>10-20%), IDSA calls for the use of fluoroquinolones (FQ). With the introduction of generic ciprofloxacin (CIP) in 2005, it is unclear whether generalization would lead to increased use and whether there would be a cause and effect relationship of increased use and increased R.

Objective: The activity of CIP and levofloxacin (LVX) against EC was analyzed using surveillance and utilization data during the years 2003-2008 to evaluate the impact of the introduction of generic CIP on FQ-R. In addition FQ susceptibility data from a US surveillance network was evaluated for EC on a national and state (Florida) basis.

Methods: EC isolates (n = 7,860) from TRUST surveillance '03-'08 were centrally tested by broth microdilution (CLSI M7-A7; M100-S18) against ampicillin (AMP), SXT, CIP, LVX, and gentamicin (GEN), the agents commonly associated with multidrug-resistant phenotypes. Utilization data for GU (genitourinary) prescriptions (Rx) for CIP and LVX were obtained from SD/IMS for Jan-Jun of each year, which coincided with the time that surveillance data was obtained for each year from '03-'08. The Surveillance Network (TSN8) database was used for the trending of CIP-R EC nationally and in FL from '02-'08.

Results: R among EC increased for all drugs tested in TRUST over the years from 2003-2008. R in 2008 compared to 2003 was as follows: AMP, 48.2% (+13.6%); SXT, 27% (+10.2%); CIP 25% (+15.9%), LVX, 24.3% (+15.2%); and GEN, 10.3% (+6.3%). Prior to generic CIP (2003-2005) the rates of increase for both CIP and LVX were less than 0.5% per year. Since the introduction of generic CIP, CIP-R increased from 9.8% ('05) to 25% ('08), a rate of increase of ~5% per year. Nearly identical R trends were noted for LVX over the same period ('05 - 9.4%, '08 - 24.3%). These trends coincide with susceptibility data from the Surveillance Network (TSN8) and also with a 50% increase in the rate of CIP GU Rx from 3.4 million (Jan-Jun '04), to 5.1 million (Jan-Jun '08), while levofloxacin GU Rx remained constant (at ~1.7 million) over the same time period. The increased use of CIP starting in '05 paralleled the increased R to FQs while LVX R remained constant during the same time period. The cross-resistance to LVX illustrates the potential consequences of increased use of a generic agent on the activity of other agents within the class.

BACKGROUND

Trimethoprim-sulfamethoxazole is recommended as first-line agent for treatment of uncomplicated urinary tract infections, commonly caused by *Escherichia coli*, per the Infectious Disease Society of America (IDSA) guidelines. However, where resistance is high (>10-20%), the IDSA recommends fluoroquinolones for initial empiric therapy (Warren et al. *CID*, 1999; 29:745-58). With the introduction of multiple generic ciprofloxacin in 2005 and free distribution of generic ciprofloxacin in 2007 in select states (in particular Florida) it was unclear if the availability of generic ciprofloxacin would lead to increased use and whether there would be a cause and effect relationship of increased use of ciprofloxacin and increased resistance to the fluoroquinolone class. Previous studies have indicated similar susceptibility rates for ciprofloxacin and levofloxacin against *E. coli*, however they differ in their initial mechanism by which resistance is induced leading to higher *E. coli* minimum inhibitory concentration values to ciprofloxacin, but not to levofloxacin (Yang, et al. *JAC*, 2003;51:545-56). For example, the more hydrophilic nature and smaller size of the ciprofloxacin molecule (2-ringed core structure) makes it a better substrate for efflux pumps than the more hydrophobic and larger levofloxacin molecule (3-ringed core structure). Selecting for an efflux-over expressed subpopulation of *E. coli* after exposure to ciprofloxacin may have a survival advantage. The selected predominant efflux-overexpressed population allows for a longer bacterial survival time, which may enable the selection of spontaneous resistance mutations, e.g., *gyrA* mutations, leading to isolates in the fluoroquinolone class (Sahm, et al. *Paediatr Med*, 2008; 120(S3):53-59). This study reviewed the impact of the introduction of generic ciprofloxacin on fluoroquinolone resistance based on surveillance and utilization data.

OBJECTIVE

The activity of ciprofloxacin and levofloxacin against *E. coli* was analyzed using TRUST surveillance data, fluoroquinolone utilization data (IMS), and The Surveillance Network (TSN8) data during the years 2003-2008 to evaluate the impact of the introduction of generic ciprofloxacin on fluoroquinolone resistance.

METHODS

E. coli isolates (n = 7,860) from TRUST (Tracking Resistance in the US Today) surveillance 2003-2008 were centrally tested by broth microdilution (CLSI M7-A7; M100-S18) against ampicillin, trimethoprim-sulfamethoxazole, ciprofloxacin, levofloxacin, and gentamicin, the agents commonly associated with multidrug-resistant phenotypes. Utilization data for GU (genitourinary) prescriptions (Rx) for ciprofloxacin and levofloxacin were obtained from SD/IMS for Jan-Jun of each year, which coincided with the time that TRUST surveillance data was obtained for each year from 2003-2008. The Surveillance Network (TSN8) is an electronic database of strain specific, qualitative and quantitative antimicrobial susceptibility test data reported by >150 clinical laboratories in the United States. TSN8 data were analyzed nationally and by the state of Florida (2002-2008).

Figure 1. Ciprofloxacin and levofloxacin genitourinary scripts; national data 2003-2007

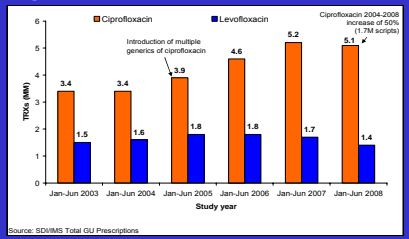


Figure 3. National vs Florida ciprofloxacin utilization data

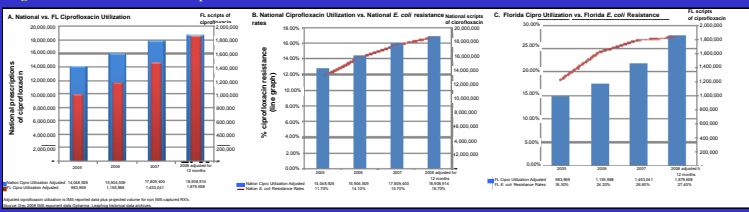


Table 1. National 5 year *E. coli* percent resistance trend: TRUST 2003-2008

Antimicrobial agent	2003 N=915	2004 N=790	2005 N=1303	2006 N=1435	2007 N=1724	2008 N=1723	5-year % increase
Ampicillin	34.8	39.7	41.0	46.7	48.3	49.2	13.6
Trimethoprim-sulfamethoxazole	16.8	19.3	19.5	20.4	26.3	27.0	10.2
Ciprofloxacin	9.1	9.5	9.8	14.8	19.6	25.0	15.9
Levofloxacin	9.1	9.5	9.4	14.0	18.9	24.5	15.2
Gentamicin	4.0	4.9	4.9	6.8	7.9	10.3	6.3

Figure 2. Ciprofloxacin percent resistance among *E. coli*: Florida and national trends 2002-2008 TSN

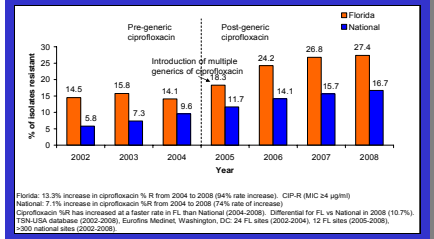
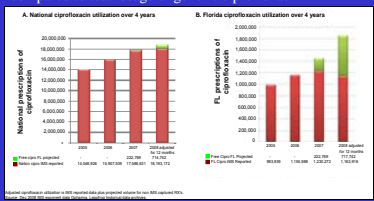


Figure 4. Proportion of free ciprofloxacin volume compared to total usage of generic ciprofloxacin



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RESULTS

- Resistance among *E. coli* increased for all drugs tested over the years, 2003-2008. Resistance in 2008 compared to 2003 from national TRUST surveillance data was as follows (Table 1):
 - Ampicillin: 13.6% increase from 34.6% (2003) to 48.2% (2008)
 - Trimethoprim-sulfamethoxazole: 10.2% increase from 16.8% (2003) to 27% (2008)
 - Ciprofloxacin: 15.9% increase from 9.1% (2003) to 25% (2008)
 - Levofloxacin: 15.2% increase from 9.1% (2003) to 24.3% (2008)
 - Gentamicin: 6.3% increase from 4% (2003) to 10.3% (2008)
- Prior to generic ciprofloxacin (2003-2005) the rates of increase in resistance from national TRUST data for both ciprofloxacin and levofloxacin were less than 0.5% per year (Table 1).
- Since the introduction of generic ciprofloxacin, ciprofloxacin-resistance increased from 9.8% ('05) to 25% ('08), an increase of 15.2% (~5% per year) which was nearly identical for levofloxacin over the same period (2005 - 9.4% R, 2008 - 24.3% R (Table 1)).
- The resistance increase in the TRUST surveillance data coincided with a 50% increase in the rate of ciprofloxacin utilization for GU scripts from pre-generic 3.4 million scripts (Jan-Jun 2004), to post-generic 5.1 million scripts (Jan-Jun 2008), while levofloxacin GU Rx remained constant (at ~1.7 million) over the same time period (Figure 1).
- Based on TSN8 data, resistance to ciprofloxacin among *E. coli* was higher in Florida than that observed nationally (Figure 2).
- In Florida, ciprofloxacin-resistance (R) increased by 13.3% from pre-generic ciprofloxacin in 2004 (14.1%-R) to post-generic ciprofloxacin in 2008 (27.4%-R). The % increase in ciprofloxacin-resistance represented a 94% rate of increase in resistance over a 4-year period. In Florida, prior to the introduction of generic ciprofloxacin, the percent ciprofloxacin-resistance was stable at 14.5-14.1% R (2002-2004 [TSN8] database, Figure 2).
- Nationally, ciprofloxacin-resistance (R) increased by 7.1% from 2004 (9.6%-R) to 2008 (16.7%-R), representing a 74% rate of increase in resistance over 4 years (TSN8] database, Figure 2).
- From 2004 to 2008, the rate of ciprofloxacin-resistance increased faster in Florida than nationally, resulting in a change in the differential percent resistance from 4.5% higher in Florida in 2004 to 10.7% higher in FL in 2008 (Figure 2).
- From 2005 to 2008, the percent increase in ciprofloxacin utilization was higher in Florida with an 80% increase in scripts (IM to 1.8M) than observed nationally with a 31% increase in scripts (14M to 18.3M [IMS database, Figure 3A]). Both in Florida and nationally, the percent ciprofloxacin-resistance trend paralleled the utilization trend (Figures 3B, 3C).
- The current projection of free ciprofloxacin volume compared to total usage of generic ciprofloxacin is increasing and shows a greater increase in Florida than nationally (Figure 4A, 4B).

CONCLUSIONS

- Resistance among *E. coli* to urinary tract infection agents increased from 2003-2008.
- The increased use of generic ciprofloxacin GU scripts starting in 2005 paralleled the increased resistance to fluoroquinolones (2006-2008), while levofloxacin GU scripts remained constant during the same time period.
- Since the introduction of generic ciprofloxacin, the resistance rates have grown both nationally and in the state of Florida; however the increase in fluoroquinolone resistance rates in Florida occurred at a faster rate than the increase in resistance nationally (2004-2008).
- The association of increased ciprofloxacin utilization and increased rates of resistance is compelling, since percent increase in utilization of generic ciprofloxacin in Florida was more than 2.5-fold higher than national (2005-2008), and during the same time period the rate of resistance increased at a faster rate in Florida than nationally.
- The ciprofloxacin cross-resistance to levofloxacin illustrates the potential consequences of increased use of one agent on the activity of other agents within the class.
- The offering of free generic agents such as ciprofloxacin may increase the rate of utilization, and in turn accelerate the rate of resistance to the fluoroquinolone class.