

Impact of Initial Inappropriate Antibiotic Therapy on Outcome for Uncomplicated Urinary Tract Infection Due to Fluoroquinolone Non-susceptible Enterobacteriaceae

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ABSTRACT

Background: Urinary tract infection (UTI) is the most common outpatient bacterial infection. Rising resistance rates among gram-negative bacteria have made common oral antibiotics less effective for uncomplicated UTI (uUTI), highlighting the risk of adverse outcome related to initial inappropriate antibiotic therapy (IIAT). There's limited published data quantifying the impact of IIAT in patients with UTI treated in the outpatient setting due to susceptible and non-susceptible Enterobacteriaceae.

Materials/methods: The BD Insights Research Database was queried to evaluate ambulatory antibiotic fill history for patients from 15 U.S. institutions with a positive ambulatory urine culture for an uropathogen. Patients who initially filled a prescription for a fluoroquinolone were further categorized into those with a urine culture positive for a fluoroquinolone-susceptible (QS) versus fluoroquinolone-non-susceptible (QNS) pathogen. Outcome was assessed using two surrogate endpoints: hospital admission and re-prescription within 28 days of initial fluoroquinolone fill.

Results: A total of 2,184 ambulatory urine culture episodes with a fluoroquinolone fill were identified in 1,999 patients. Hospitalization data was available for 2,035 of these episodes. 1,576 (72%) had $\geq 100,000$ CFU/mL and 608 (28%) had $< 100,000$ CFU/mL of an uropathogen identified. The re-prescription rate and rate of all-cause hospitalization within 28 days of the initial fill were significantly higher in the subset of patients with UTI caused by a QNS pathogen, as shown in the Table below.

Quinolone Susceptibility	28-day fill Rate						Hospital Admission Rate		
	Urine $\geq 100K$ CFU/mL			Overall			Overall		
	N	28-day fill n (%)	P value	N	28-day fill n (%)	P value	N	Admissions n (%)	P value
Susceptible	1,216	184 (15.1)	<0.001	1,712	272 (15.9)	<0.001	1,595	136 (8.5)	<0.001
Not susceptible	360	133 (36.9)		472	177 (37.5)		440	71 (16.1)	
Overall	1,576	317 (20.1)		2,184	449 (20.6)		2,035	207 (10.2)	

*P value <0.001; ¹192 patients excluded as the prescription data was unavailable

Conclusions: A considerable proportion of outpatient UTI episodes are due to QNS pathogens. Prescribing IIAT to patients with outpatient UTI due to QNS pathogens is more often associated with a second antibiotic prescription and hospitalization compared with episodes caused by QS strains. These findings highlight the need for novel oral antimicrobial options with activity against QNS uropathogens.

INTRODUCTION

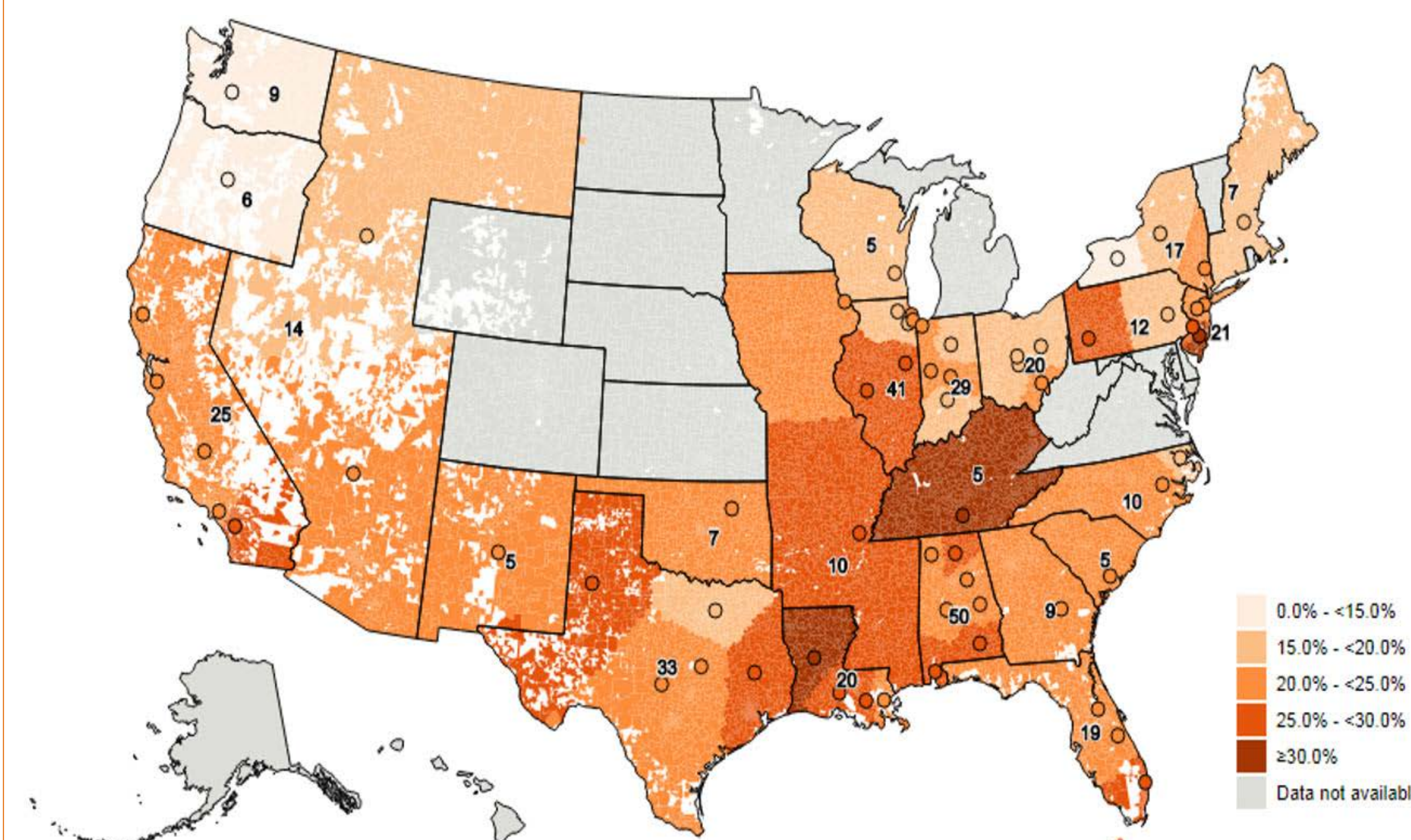
- Acute cystitis remains one of the most common indications for prescribing antimicrobials to otherwise healthy women, resulting in:
 - 13.5 million office or emergency room visits
 - 21 million prescriptions in the United States annually
- Escherichia coli* is the most common cause of urinary tract infections (UTI)
- Fluoroquinolone resistance amongst *E. coli* in hospitalized patients is about 34% in the United States (CDC summary data)
- Clinical outcomes for patients with UTI caused by quinolone non-susceptible (QNS) pathogens and treated with oral quinolones in the outpatient setting are not clearly described
 - Yet quinolones remain the most commonly prescribed class of antibiotics for outpatient uncomplicated UTI (uUTI)
- We conducted a retrospective database analysis to describe 28-day outcomes for outpatients with presumed UTI caused by QNS pathogens and treated with oral quinolones
- Sulopenem is a thiopenem antibiotic being developed for the treatment of infections caused by multi-drug resistant bacteria
 - Has potent activity against Enterobacteriaceae
 - Including those with ESBLs or AmpC-type β -lactamases
 - Has an intravenous and oral formulation

METHODS

- All patients with a positive ambulatory urine culture for the Enterobacteriaceae listed below, and an oral antibiotic fill were identified from 15 institutions (BD Insights Research Database, Franklin Lakes, NJ USA) from 2015-2017
 - E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. aerogenes*, *E. cloacae*, *S. marcescens*, *C. freundii*, *P. mirabilis*, and *M. morganii*
- Initial fill with an oral fluoroquinolone antibiotic was identified as a fill on the day before, day of or day after urine culture collection date and further categorized as susceptible vs. non-susceptible:
 - Cases were classified as susceptible (S) or non-susceptible (intermediate or resistant) to fluoroquinolones.
 - Based on susceptibility testing performed at the local institution
- 28-day outcomes evaluated:
 - Re-prescription rate with any additional antimicrobial fill (as recommended by the IDSA uUTI guidelines) after initial antibiotic fill with the following exception:
 - We excluded antimicrobial fills on the day of or the day after susceptibility results became available so as to not capture antimicrobial changes due to availability of culture results.
 - Hospital admission, hospital admission receiving IV/PO antimicrobial therapy/appropriate antimicrobial therapy for isolated pathogens

RESULTS

Figure 1: Quinolone Non-Susceptibility Among Outpatient Urinary Isolates of *E. coli*, *Klebsiella* spp. and *P. mirabilis* in Q2 2017 from 379 Facilities



- Data has been aggregated into geographic clusters of five or more hospitals from two or more IDNs. Each cluster's geographic centroid is represented with shaded circles
- Each zip code tabulation area (ZCTA) has been attributed a rate based on that ZCTA's proximity to the nearest cluster's geographic centroid, which are represented with shaded circles.
- Within each state, the number of hospitals in each cluster is distributed equally, and the total number of hospitals at the state level is labeled on the map.
- Data for contiguous states that each contain less than five hospitals has been aggregated (AZ, MT, NV, ID, UT - AR, MS, MO, IA - ME, NH MA, CT - KY, TN)

RESULTS

Table 1: Demographics and Characteristics of Outpatients with UTI treated with oral quinolones

Characteristic	Results N=1,999 [§]
Mean Age (years, \pm SD)	62.4 \pm 20.1
Median Age (years)	66.8
Gender, n (%)	
Female	1,594 (79.7)
Male	405 (20.3)
Key Pathogens, n/N (%)	
<i>E. coli</i>	1,556/2,184 (71.2)
<i>Klebsiella</i> spp.*	366/2,184 (16.8)
<i>P. mirabilis</i>	118/2,184 (5.4)
Baseline Pathogen Susceptibility to Fluoroquinolone, n/N (%)	
Susceptible	1,712/2,184 (78.4)
Non-Susceptible	472/2,184 (21.6)

[§]A total of 1,999 patients had 2,184 UTI episodes in the study period; includes 5 patients with *S. saprophyticus*
 * *K. pneumoniae*, *K. oxytoca*

Table 2: Impact of Quinolones for uncomplicated UTI on Outcomes

Parameter	Susceptible N=1,712	Non-Susceptible N=472
Antibiotic re-prescription rate*, n (%)	272 (15.9)	177 (37.5)
	P value <0.001	
Hospitalization*, n/N (%)		
All-cause	136/1,595 (8.5)	71/440 (16.1)
	P value <0.001	
With IV/PO antibiotics	108/1,595 (6.8)	59/440 (13.4)
	P value <0.001	
With IV/PO antibiotics appropriate for cUTI pathogens	95/1,595 (6.0)	55/440 (12.5)
	P value <0.001	

^{*}2,184 UTI episodes had prescription data available; 2,035 UTI episodes had hospitalization data available; includes all UTI episodes regardless of colony count of baseline pathogen : *within 28 Days

Table 3: 28-Day Quinolone Outcomes by Susceptibility for Enterobacteriaceae, by Individual Pathogens

Pathogen	Frequency (%)	28-day Refill n/N (%)		Hospitalizations n/N (%)	
		Susceptible	Non-susceptible	Susceptible	Non-susceptible
<i>E. coli</i>	71.2	152/1,141 (13.3)	157/415 (37.8)	65/1,068 (6.1)	55/384 (14.3)
<i>K. pneumoniae</i>	15.6	72/317 (22.7)	8/24 (33.3)	41/298 (13.8)	4/23 (17.4)
<i>P. mirabilis</i>	5.4	13/96 (13.5)	8/22 (36.4)	11/87 (12.6)	7/22 (31.8)
Other	7.8	34/153 (22.2)	4/11 (36.3)	19/137 (13.9)	5/11 (45.4)
<i>E. cloacae</i>		14/44 (31.8)	3/5 (60.0)	5/40 (12.5)	2/5 (40.0)
<i>E. aerogenes</i>		5/30 (16.7)	0	5/24 (20.8)	0
<i>C. freundii</i>		4/36 (11.1)	0/3 (0.0)	5/33 (15.2)	1/3 (33.3)
<i>K. oxytoca</i>		7/24 (29.2)	1/1 (100)	3/21 (14.3)	1/1 (100)
<i>S. marcescens</i>		1/10 (10.0)	0/1 (0.0)	1/10 (10.0)	0/1 (0.0)
<i>M. morganii</i>		3/9 (33.3)	0/1 (0.0)	0/9 (0.0)	1/1 (100)
Overall*	100.0	271/1,707 (15.9)	177/472 (37.5)	136/1,595 (8.5)	71/440 (16.1)

*p value on 28-day prescription rate and hospitalizations for susceptible vs non-susceptible < 0.0001

CONCLUSIONS

- Quinolone non-susceptibility is seen in over 20% of isolates from the urinary tract in the US
 - Driven primarily by *E. coli* and *P. mirabilis*
- Over the subsequent 28 days, patients with a quinolone resistant pathogen who received a quinolone for uUTI were significantly more likely:
 - To require another antibiotic prescription and/or
 - Be hospitalized and receive antibiotics
- Further research is needed to understand if these findings can be extrapolated to uUTI patients treated without urine cultures
- Oral antibiotics with activity against quinolone non-susceptible urinary pathogens are needed to facilitate outpatient treatment of uUTI