The prevalence of Enterobacteriaceae resistant to all major classes of oral antibiotics from outpatient urine cultures in the United States and effect on clinical outcomes

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ABSTRACT

Background: Over 99% of all outpatient urinary tract infections (UTI) in the United States are treated with either a quinolone, β-lactam, trimethoprim-sulfamethoxazole (T/S) or nitrofurantoin (NFH). Resistance to all classes of antibiotics is now reported in the US, making the selection of empiric oral therapy increasingly unlikely to cover the offending uropathogen.

Methods: We queried the BD Insights Research Database (Franklin Lakes, NJ) to evaluate ambulatory antibiotic fill history for patients from 15 U.S. institutions with an ambulatory urine culture positive for ≥10^3 CFU/mL of an ENT. Patients who filled a prescription for an oral antibiotic were further categorized into those with a urine culture positive for a susceptible or non-susceptible (NS) pathogen. ESBL positivity was presumed if the isolate was NS to extended spectrum cephalosporins. Outcome was assessed using two surrogate endpoints: hospital admission, or a follow-up oral antibiotic within 28 days of initial antibiotic fill. Urine 30 day non-duplicate ambulatory three drug resistance rates in Q2 2017 were determined by zip code for 379 facilities.

Results: 48/5,587 (0.9%) episodes of UTI with an outpatient urine culture had an Enterobacteriaceae that was resistant to quinolones, T/S, and NFH, and was ESBL-positive. Of those with at least three-drug class resistance, the hospital admission rate was 28%.

	28-day Prescription Fill				28-Day Admission			
	N (%)	Failures	Fail %	P value	N (%)	Failures	Fail %	P value
Overall	5,587	1250	22		5,395	379	7	
Pan-Susceptible	1,771 (32)	287	16	0.0001	1,627 (30)	124	8	0.0001
3-4 class resistance*	197 (4)	55	28		184 (3)	51	28	

*all resistant to quinolones, T/S, and β-lactams; 4-class also includes resistance to NFH

Figure. Geographic prevalence of three drug class resistance (quinolones, β-lactam, T/S) among Enterobacteriaceae causing UTI in the outpatient setting

Conclusions: Multiclass resistance to existing oral antibiotics is prevalent throughout the United States in patients for whom an outpatient urine culture is available, with 1% of organisms resistant to all commonly available oral classes. Multidrug resistance in patients with an outpatient urine culture is associated with a significantly increased risk of treatment failure and subsequent hospitalization.

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)
- Multidrug resistance (non-susceptible to at least 1 drug from at least three classes of antibiotics) among *E. coli* has been rising in the United States – from 6.4% in 2011 to 8% in 2014 (CDC summary data: https://gis.cdc.gov/grasp/PSA/MapView.html)
  - However, the prevalence of carbapenem resistance has decreased among *E.coli* from 1% in 2011 to 0.6% in 2014
- Clinical outcomes for patients with UTI caused by pathogens non-susceptible (NS) to the drugs prescribed in the outpatient setting are not clearly described
- We conducted a retrospective database analysis to describe 28-day outcomes for outpatients with presumed UTI caused by pathogens non-susceptible to the oral antibiotics prescribed
- 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, or quinolone non-susceptible
  - 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 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 the antibiotics prescribed.
  - Based on susceptibility testing performed at the local institution
- 28-day outcomes evaluated:
  - Re-prescription rate with any additional antimicrobial fill 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
    - Receiving IV/PO antimicrobial therapy
    - Receiving appropriate antimicrobial therapy for isolated pathogens

RESULTS

Table 1: Demographics and Characteristics of Outpatients with UTI treated with Oral Antibiotics

Characteristic	Results N=4,792§
All patients, Baseline	
Mean Age (years, ± SD)	57.0 ± 22.0
Median Age (years), Range (25th, 75th percentile)	60.1 (36, 76)
Female, n (%)	4,092 (85.4)
% Serum creatinine >2.0 mg/dL, (N=1,159)	1.1
% Leukocytosis	9.3
Diabetes Mellitus§, n (%)	1214 (22.5)
Among subset of patients hospitalized	
Hospitalized patients, n (%)	527 (11.0)
Median Age (years)	69
% Serum creatinine >2.0 mg/dL, (N=221)	3.4
% Leukocytosis (N=221)	13.3
Diabetes Mellitus (N=160)	30.4
Key Pathogens, n/N (%)	
E.coli	4,216/5,587 (75.5)
Klebsiella spp.	815/5,587 (14.6)
P. mirabilis	293/5,587 (5.2)
*Other**	263/5,587 (4.7)
Baseline Pathogen Susceptibility to Prescribed Antibiotic n/N (%)	
Susceptible	4,353/5,587 (77.9)
Non-Susceptible	1234/5,587 (22.1)

§A total of 4,792 patients had 5,587 UTI episodes in the study period; § A patient is considered to have a diagnosis of diabetes if the patient had either a hemoglobin A1C (HbA1C) > 7% or prescription filled for a diabetic medication in the last six months* *Includes E. cloacae, E. aerogenes, C. freundii, S. marcescens, M. morganii*

RESULTS

Table 2: Impact of Mismatched Antibiotic Therapy on 28-Day Outcomes

	28-day Prescription Fill				28-Day Admission			
	N (%)	Failures	Fail %	P value	N (%)	Failures	Fail %	P value
Overall	5,587	1,250	22.4		5,395	379	7.0	
Matched	4,353 (78)	830	19.1	0.0001	4,207 (78)	234	5.6	0.0001
Mis-matched	1234 (22)	420	34.0		1,188 (22)	145	12.2	

Matched implies that pathogen was susceptible to prescribed antibiotic; Re-prescription rates were 40%, 33%, 31% and 16%, and admission rates were 10%, 18%, 27% and 40% for one-, two-, three- and four-class resistance, respectively.

Table 3: 28-Day Outcomes by Degree of Antibiotic Class Resistance

	28-day Prescription Fill				28-Day Admission			
	N (%)	Failures		P value	N (%)	Failures		P value
		N	%			N	%	
Overall*	5,587	1,250	22.4	-	5,395	379	7.0	-
Pan-Susceptible	1,771 (32)	287	16.2	Index	1,627 (30)	124	7.6	Index
Resistant								
1 class	1,937 (35)	514	26.5	<0.0001	1,752 (32)	163	9.3	0.0797
2 class	637 (11)	202	31.7	<0.0001	588 (11)	87	14.8	<0.0001
3 class	149 (3)	44	29.5	<0.0001	142 (3)	34	23.9	<0.0001
4 class	48 (1)	11	22.9	0.2153	42 (1)	17	40.5	<0.0001
≥3 class resistance**	197 (4)	55	27.9	<0.0001	184 (3)	51	27.7	<0.0001

*5,587 UTI episodes in 4,792 patients had prescription data available; 5,395 UTI episodes had hospitalization data available; includes all UTI episodes regardless of colony count of baseline pathogen; **all resistant to quinolones, trimethoprim-sulphamethoxazole and β-lactams; 4-class also includes resistance to nitrofurantoin; the grouping of classes above are mutually exclusive

Table 4: 28-Day Re-prescription Rate by Pathogen and Colony Forming Units per Milli-liter (CFU/mL)

Organism	Total N=5,571	≥100K CFU/mL N=4,045		<100K CFU/mL N=1,526	
	N (%)	28 day Prescription Fill		28 day Prescription Fill	
		N	%	N	%
E. coli	4,216 (75.7)	3,118	20.7	1,098	22.1
K. pneumoniae	762 (13.7)	546	27.7	216	29.2
K. oxytoca	53 (0.9)	35	14.3	18	61.1
P. mirabilis	293 (5.2)	173	23.1	120	26.7
E. cloacae	68 (1.2)	48	29.2	20	45.0
E. aerogenes	70 (1.2)	51	23.5	19	26.3
C. freundii	73 (1.3)	50	14.0	23	13.0
M. morganii	18 (0.3)	10	30.0	8	37.5
S. marcescens	18 (0.3)	14	21.4	4	25.0

*5,571 of 5,587 cultures were semi-quantitative cultures with CFU/mL data available

Figure 1: Geographic prevalence of **3-drug class** resistance among Enterobacteriaceae causing UTI in the outpatient setting

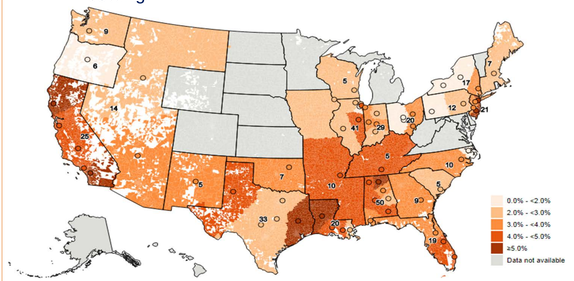
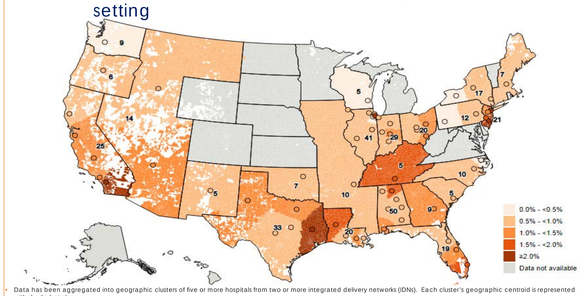


Figure 2: Geographic prevalence of **4-drug class** resistance among Enterobacteriaceae causing UTI in the outpatient setting



- Data has been aggregated into geographic clusters of five or more hospitals from two or more integrated delivery networks (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

CONCLUSIONS

- Multiclass resistance to existing oral antibiotics is prevalent throughout the United States
  - ~150,000 (0.7%) uUTI episodes in the US may not be treatable with existing oral antibiotics
- Mismatched antibiotic therapy led to more re-prescriptions and hospitalizations
  - Regardless of individual pathogen or its quantity observed on culture
- Oral antibiotics with activity against multi-drug resistant urinary pathogens are urgently needed to enable appropriate outpatient treatment of uUTI