

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

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ABSTRACT

Background: Uncomplicated urinary tract infection (uUTI) is a common outpatient infection. Rising resistance rates among gram-negative bacteria have made oral antibiotics less effective for uUTI, highlighting the potential risk of adverse outcomes related to initial inappropriate antibiotic therapy (IIAT). The impact of IIAT for uUTI due to susceptible and non-susceptible Enterobacteriaceae has not been clearly established.

Materials/methods: We queried the BD Insights Research Database to evaluate ambulatory antibiotic fill history for patients from 15 U.S. institutions with a positive ambulatory urine culture for an Enterobacteriaceae. Patients who filled a prescription for an oral antibiotic were further categorized into those with a urine culture positive for a susceptible (S) or non-susceptible (NS) pathogen. Outcome was assessed using two surrogate endpoints, specifically, hospital admission, or a follow-up oral antibiotic within 28 days of initial antibiotic fill.

Results: A total of 5,587 ambulatory urine cultures associated with an oral antibiotic fill were identified in 4,792 patients. Of all cultures obtained, 4,058 (73%) had $\geq 100,000$ CFU/mL identified. In 1,234 (22%) of the culture-positive episodes, the organism was NS. 1,250 episodes (22%) had a second antibiotic prescribed within 28 days of the initial antibiotic fill. The overall hospitalization and antimicrobial fill rates within 28 days of the initial antibiotic fill were both significantly higher for NS vs S episodes (12.2% vs 5.6%, $p < 0.001$; and 34% vs 19%, $p < 0.001$, respectively).

Susceptibility	$\geq 100K$ CFU/mL			Any positive culture			Hospitalizations ¹	
	Episodes N	28-Day Fill N	28-Day Fill* (%)	Episodes N	28-Day Fill N	28-Day Fill* (%)	n/N	(%)*
Susceptible	3,129	575	18	4,353	830	19	234/4207	5.6
Not susceptible	929	305	33	1,234	420	34	145/1188	12.2
Overall	4,058	880	22	5,587	1,250	22	379/5395	7.0

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

Conclusions: >20% of patients with a uUTI have resistant pathogens. Prescribing an oral antibiotic to patients with uUTI due to NS pathogens is more likely to result in a second antibiotic prescription and/or hospitalization compared with episodes due to susceptible strains. These findings highlight the need for novel oral antimicrobial options with activity against non-susceptible Enterobacteriaceae.

INTRODUCTION

- Acute cystitis remains one of the most common indications for prescribing antimicrobials to otherwise healthy women, resulting in as many as 13.5 million office or emergency room visits and 21 million prescriptions in the United States annually.
- Escherichia coli* is the primary cause of urinary tract infections, and the increased resistance to multiple antibiotics has led to severely limited oral treatment options for this infection, resulting in reliance on older and less commonly used antibiotics such as nitrofurantoin and fosfomycin.
 - Quinolone resistance and resistance to trimethoprim-sulphamethoxazole amongst *E. coli* is >20% in the United States (CDC summary data)
- Sulopenem is a thiopenem antibiotic being developed for the treatment of infections caused by multi-drug resistant bacteria
 - Inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins
 - 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. morgani*
- Initial fill with an oral antibiotic was identified as a fill for any of the following oral antibiotics on the day before, day of or day after urine culture collection date and further categorized as susceptible vs. non-susceptible:
 - Quinolones, trimethoprim-sulfamethoxazole, nitrofurantoin, fosfomycin, amoxicillin-clavulanate, amoxicillin, and oral cephalosporins
 - Cases were classified as susceptible (S) or non-susceptible (intermediate or resistant) to the initial oral antibiotic filled.
- 28-day outcomes evaluated:
 - Re-prescription rate with any additional antimicrobial fill after initial antibiotic fill
 - Hospital admission, hospital admission receiving IV/PO antimicrobial therapy/appropriate antimicrobial therapy for cUTI pathogens

RESULTS

Table 1: Demographics and Characteristics of Outpatients with UTI

Characteristic	Results N=4,792 [§]
Mean Age (years, \pm SD)	57.0 \pm 22.0
Median Age (years)	60.1
Gender, n (%)	
Female	4,092 (85.4)
Male	700 (14.6)
Key Pathogens, n/N (%)	
<i>E. coli</i>	4,216/5,587 (75.5)
<i>Klebsiella</i> spp.*	815/5,587 (14.6)
<i>P. mirabilis</i>	293/5,587 (5.2)
Baseline Pathogen Susceptibility to Prescribed Antibiotic, n/N (%)	
Susceptible	4353/5587 (77.9)
Non-Susceptible	1234/5587 (22.1)

[§]A total of 4,792 patients had 5,587 UTI episodes in the study period

* *K. pneumoniae*, *K. oxytoca*

RESULTS

Table 2: Microbiologic Etiology and 28-Day Antibiotic Fill

Organism	Initial Baseline Outpatient Urine Culture (Enterobacteriaceae)				
	% Causing Outpatient UTI N=5571*	$\geq 100K$ CFU/mL N=4045		<100K CFU/mL N=1526	
		28-Day Fill (%)	N	28-Day Fill (%)	N
<i>Escherichia coli</i>	75.7	20.7	3,118	22.1	1,098
<i>Klebsiella pneumoniae</i>	13.7	27.7	546	29.2	216
<i>Proteus mirabilis</i>	5.2	23.1	173	26.7	120
<i>Enterobacter cloacae</i>	1.2	29.2	48	45.0	20
<i>Enterobacter aerogenes</i>	1.2	23.5	51	26.3	19
<i>Citrobacter freundii</i>	1.3	14.0	50	13.0	23
<i>Klebsiella oxytoca</i>	0.9	14.3	35	61.1	18
<i>Morganella morgani</i>	0.3	30.0	10	37.5	8
<i>Serratia marcescens</i>	0.3	21.4	14	25.0	4

*excludes 16 *S. saprophyticus* isolates

Table 3: 28-Day Fill Rate by Initial Antibiotic

Drug	Episodes n (%)	28-Day Fill n	28-Day Fill %
Quinolones			
Ciprofloxacin	1,773 (31.4)	346	19.5
Levofloxacin	169 (3.0)	47	27.8
Beta-lactams			
Amoxicillin	54 (0.9)	19	35.2
Amoxicillin-clavulanate	334 (5.9)	82	24.6
Cephalexin	851 (15.1)	196	23.0
Cefdinir	88 (1.5)	22	25.0
Cefpodoxime	20 (0.3)	4	20.0
Cefixime	4 (0.1)	1	25.0
Other			
Nitrofurantoin	1,272 (22.5)	293	23.0
Trimethoprim-sulfamethoxazole	1,083 (19.2)	252	23.3
Fosfomycin	1(0.0)	0	0.0
Overall*	5,649	1,262	22.3

*62 patients received multiple drugs as initial dispense

Table 4: Impact of Mismatched Antibiotic Therapy on Outcomes within 28 Days

Parameter	Susceptible N=4353	Non-Susceptible N=1234
Antibiotic re-prescription rate*, n (%)	830 (19.1)	420 (34.0)
Hospitalization*, n/N (%)		
All-cause	339/4207 (8.1)	176/1188 (14.8)
With IV/PO antibiotics	247/4207 (5.9)	147/1188 (12.4)
With IV/PO antibiotics appropriate for cUTI pathogens	234/4207 (5.6)	145/1188 (12.2)

*5587 UTI episodes had prescription data available; 5395 UTI episodes had hospitalization data available; includes all UTI episodes regardless of colony count of baseline pathogen; *P value <0.001

CONCLUSIONS

- Greater than 20% of patients with an outpatient UTI receive an antibiotic to which their pathogen is resistant
- The 28-day antibiotic refill rate did not differ significantly by baseline pathogen or initial antibiotic prescribed
 - Refill rate did not differ by colony forming units at baseline pathogen ($>10^5$ /mL or $< 10^5$ /mL)
 - 28-day refill rates were similar for all oral antibiotics
- Compared with episodes due to susceptible strains, prescribing an oral antibiotic to patients with outpatient UTI to which their pathogen is resistant is more likely to result:
 - in a second antibiotic prescription within 28 days
 - and, almost twice as likely to result in a hospitalization
- Further regression analyses will help define subsets of patients who are most vulnerable to inappropriate and mismatched initial therapy
- These findings highlight the need for novel oral antimicrobial options with activity against non-susceptible Enterobacteriaceae
 - especially for the most vulnerable populations