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A patient-specific clinical predictive model to anticipate the risk of treatment failure in uncomplicated urinary tract infections

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ABSTRACT

Background: Over twenty million prescriptions are written in the United States every year for treatment of outpatient urinary tract infections. Treatment failures place a burden on both the patient and the healthcare system. A tool based on an individual's medical history which could help identify those at greatest risk for treatment failure which may help refine initial treatment and improve patient outcomes.

Methods: We analyzed patients in the BD Insights Research Database (Franklin Lakes, NJ USA) from 15 U.S. institutions that had an ambulatory antibiotic fill history, demographic information and an ambulatory urine culture for an Enterobacteriaceae. Using a linear probability model of treatment failure (a second prescription or hospital admission within 28 days), we identified several variables that significantly modify the risk of failure.

Results: The baseline risk of quinolone treatment failure for urinary Enterobacteriaceae in a 60-year-old woman with normal creatinine, no DM, and no history of resistant Enterobacteriaceae was 17%. This risk is additively modified by the variables in the table below.

Variable	Marginal percentage-point effect	p value
Age, per decade, over 60 years	2%	<0.01
Male sex	5%	<0.01
Diabetes mellitus	4%	0.02
Elevated creatinine (>2 mg/dL)	13%	0.05
Index treatment (vs quinolone)		
Amoxicillin	21%	<0.01
Augmentin	7%	<0.01
Nitrofurantoin	6%	<0.01
Trimethoprim Sulfamethoxazole	8%	<0.01
Cephalexin	4.5%	0.03
Index treatment with AND previous resistance to the same class[1]		
Quinolone	22%	<0.01
Trimethoprim Sulfamethoxazole	26%	<0.01
Nitrofurantoin	36%	<0.01

N = 5,329; [1]No statistical difference in outcome observed between classes when mismatched therapy was prescribed.

A 70-year-old woman with Diabetes, elevated creatinine and a prior history of a quinolone-resistant organism treated with a quinolone has a predicted failure rate of 58% (41% over the baseline risk).

Conclusions: The most significant risk for treatment failure is treatment of the index infection with an antibiotic to which the organism in a prior infection was resistant. Given the empiric nature of treatment of uUTI, new antibiotics are needed to optimize management of this disease.

INTRODUCTION

- Acute cystitis remains one of the most common indications for prescribing antimicrobials to otherwise healthy women
  - 15 million office or emergency room visits annually
  - 21 million prescriptions in the United States annually
- In the hospital, *Escherichia coli*, the most common cause of urinary tract infections (UTI), are becoming progressively more likely to demonstrate resistance *in vitro*:
  - β-lactams >13%; Trimethoprim-sulfamethoxazole > 20%
  - Quinolones > 33%; Multi-drug resistance (resistance to ≥3 classes) > 7%
- If similar rates of resistance are seen in the community, empiric oral antibiotic therapy may be more likely to result in treatment failure when the pathogen is resistant to the chosen antibiotic
- This study is a retrospective database analysis that describes the difference in 28-day outcomes for patients with an uncomplicated urinary tract infection whose pathogens were susceptible or non-susceptible to empiric therapy.

METHODS

- We analyzed patients in the BD Insights Research Database (Becton Dickinson and Company, Franklin Lakes, NJ USA) from 15 U.S. institutions.
- All selected patients had a positive ambulatory antibiotic fill history, demographic information and an ambulatory urine culture with Enterobacteriaceae and susceptibility information.
- The initial antibiotic selection was categorized as appropriate or inappropriate if the patient's corresponding organism was susceptible or non-susceptible to the antimicrobial class
- Susceptibility testing was performed at the local institution.
- A represcription was defined as a subsequent antibiotic fill within 28-days of the initial fill, excluding any prescription within one day of the availability of antimicrobial susceptibility test results
- Using a linear probability model of treatment failure (a second prescription or hospital admission within 28 days), we identified several variables that significantly modify the risk of failure.

RESULTS

Table 1. Baseline Demographics

Characteristic	Results (N=4,792)
Mean Age (years, ± SD)	57.0 ± 22.0
Median Age (years), Range (25th, 75th percentile)	60.1 (38, 76)
Gender, n (%)	4,092 (85.4)
Female	
Male	700 (14.6)
% Serum creatinine >2.0 mg/dL(N=1232)	1.8
% WBC > 10^5 /μL (N=1159)	9.3
Hyperglycuria, n/N (%)	399/3801 (10.5)
Diabetes Mellitus, n (%)	1214 (22.5)
Hospitalized patients, n (%)	527 (11.0)
Median Age (years)	69
Serum creatinine >2.0 mg/dl (N=221)	3.4
% WBC > 10^5 /μL (N=221)	13.3
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	4,353/5587 (77.9)
Non-Susceptible	1,234/5587 (22.1)

Table 2. 28-day represcription and hospitalization rate by degree of antibiotic class resistance

	28-Day Represcription				28-Day Admission			
	Total (%)	Failures		p value	Total (%)	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
Resistance								
1 class	1,937 (35)	514	26.5	< .0001	1,752 (32)	163	9.3	.0797
2 class	637 (11)	202	31.7	< .0001	588 (11)	87	14.8	< .0001
3 class	149 (3)	44	29.5	< .0001	142 (3)	34	23.9	< .0001
4 class	48 (1)	11	22.9	0.2153	42 (1)	17	40.5	< .0001
**3 and 4 class	197 (4)	55	27.9	< .0001	184 (3)	51	27.7	< .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-sulfamethoxazole and β-lactams; 4-class also includes resistance to nitrofurantoin; the grouping of classes above are mutually exclusive

RESULTS

Table 3: 28-day represcription and hospitalization rates by pathogen and by antibiotic received

			28-day Represcription n/N (%)		Hospitalizations n/N (%)	
Antibiotic class /Pathogen	Frequency (%)	Resistance to class % (n)	Susceptible	Non-susceptible	Susceptible	Non-susceptible
Quinolone	**100.0**	**22.8 (1,232)**	**237/1,483 (16.0)**	**140/390 (35.9)**	**130/1,483 (8.8)**	**65/390 (16.7)**
Escherichia coli (n=4,081)	70.7	27.2 (1,111)	126/979 (12.9)	128/345 (37.1)	59/979 (6.0)	53/345 (15.4)
β-lactam (ESBL)	**100.0**	**6.6 (356)**	**224/980 (22.9)**	**91/329 (27.7)**	**81/980 (8.3)**	**48/329 (14.6)**
Escherichia coli (n=4,081)	76.1	7.4 (303)	152/737 (20.6)	71/259 (27.4)	46/737 (6.2)	28/259 (10.8)
Trimethoprim-sulfamethoxazole	**100.0**	**27.6 (1,491)**	**134/753 (17.8)**	**106/288 (36.8)**	**71/753 (9.4)**	**45/288 (15.6)**
Escherichia coli (n=4,081)	76.9	32.6 (1,330)	87/536 (16.2)	98/265 (37.0)	47/536 (8.8)	39/265 (14.7)
Nitrofurantoin	**100.0**	**15.9 (857)**	**214/1,055 (20.3)**	**64/173 (37.0)**	**73/1,055 (6.9)**	**23/173 (13.3)**
Escherichia coli (n=4,081)	81.7	3.4 (138)	197/971 (20.3)	9/32 (28.1)	66/971 (6.8)	5/32 (15.6)
Fosfomycin	**N/A**	**N/A**	**0/1 (0.0)**	**-**	**0/1 (0.0)**	**-**
Grand Total		**N=5,395**	**802/4,237 (18.9)**	**401/1,178 (34.0)**	**351/4,237 (8.3)**	**179/1,178 (15.2)**

Table 4. Represcription rate by pathogen and colony forming units per liter (CFU/mL)

Organism	Total N=5,571*	≥10^5 CFU/mL N=4,045		<10^5 CFU/mL N=1,526	
	N (%)	28-day represcription		28-day represcription	
		N	(%)	N	(%)
Escherichia coli	4,216 (75.7)	3,118	20.7	1,098	22.1
Klebsiella pneumoniae	762 (13.7)	546	27.7	216	29.2
Klebsiella oxytoca	53 (0.9)	35	14.3	18	61.1
Proteus mirabilis	293 (5.2)	173	23.1	120	26.7
Enterobacter cloacae	68 (1.2)	48	29.2	20	45.0
Enterobacter aerogenes	70 (1.2)	51	23.5	19	26.3
Citrobacter freundii	73 (1.3)	50	14.0	23	13.0
Morganella morganii	18 (0.3)	10	30.0	8	37.5
Serratia 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

Table 5. Linear probability model (LPM) estimates of partial effects on treatment failure

Variable	Marginal percentage-point effect	p value
Age, per decade, over 60 years	2%	<0.01
Male sex	6%	<0.01
Diabetes mellitus	6%	0.02
Elevated creatinine (>2 mg/dL)	11%	NS (p=0.1)
Index treatment with AND previous resistance to the same class		
Quinolone	22%	<0.01
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Trimethoprim Sulfamethoxazole	8%	<0.01
Cephalexin	5%	0.03
Constant (60 year old female, empiric quinolone, no h/o resistant pathogen)	17%	< 0.001

CONCLUSIONS

- Treatment failure and hospitalization rates double with mismatched empiric antibiotic therapy
  - The more class resistance the higher likelihood of treatment failure
- While nitrofurantoin resistance rates for *E. coli* are low, overall treatment failure remains high
- A threshold of 10^5 CFU/mL did not distinguish between rates of treatment failure
- Age, gender, Diabetes mellitus and prior resistance to antibiotics increased the likelihood of treatment failure
  - A 70-year-old woman with Diabetes and a prior history of UTI with a quinolone-resistant organism who gets treated with a quinolone has a predicted failure rate of 47% (30% over the baseline risk)
- The most significant risk for treatment failure is treatment of the index infection with an antibiotic to which the organism in a prior infection was resistant
- Given that treatment of uUTI is empiric, new antibiotics are needed to manage this disease, especially in vulnerable patients

29th European Congress of Clinical Microbiology and Infectious Diseases; April 13–16, 2019; Amsterdam, Netherlands

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