Poster # 4561

Failure of Empiric Treatment of Uncomplicated Urinary Tract Infection (UTI) Associated with Resistant Pathogens

Michael W. Dunne[1], Kenneth Snow[2], Rajesh Mehta[2]
[1]Iterum Therapeutics, Old Saybrook, CT; [2]Healthagen LLC, a division of Aetna, New York, NY

ABSTRACT

BACKGROUND: Given increasing rates of antibiotic resistance among pathogens associated with urinary tract infection, we performed a retrospective analysis of a large claims database to evaluate the presence of treatment failure for patients whose UTI pathogen was resistant to the initial empiric choice of antibiotic.

METHODS: Aetna insured members between 18 and 64 years old and Medicare Advantage members who received therapy for a UTI between January 1, 2014 and July 31, 2017 were included. Patients were classified based on the empiric antibiotic regimen and susceptibility of the UTI organism as having a resistant or non-resistant pathogen at baseline. Treatment failure was defined as either a second prescription for the same UTI within 30 days, including a repeat prescription within the same antibiotic class, or a UTI-related hospitalization.

RESULTS: 500,318 episodes of urinary tract infection (outpatients, emergency room or inpatient setting) occurred among 387,028 patients, for an average of 1.3 episodes per patients over the observation period. 89% of patients were female, the average age was 54.5 years and 17.2% of patients had diabetes mellitus. Demographics, treatment setting, pathogen susceptibility results and treatment outcome data from patients treated specifically in the outpatient setting were available for 43,659 (8.7%) episodes.

Resistance to First Antibiotic	Treatment Success		
	Non-Diabetic	Diabetic	Total
No	22,205 / 31,493 (70.5%)	3,782 / 5,766 (65.6%)	25,987 / 37,259 (69.7%)
Yes	2,064 / 5,005 (41.2%)	558 / 1,395 (40.0%)	2,622 / 6,400 (41.0%)
Total	24,269 / 36,498 (66.5%)	4,340 / 7,161 (60.6%)	28,609 / 43,659 (65.5%)

15% of patients had an organism resistant to the antibiotic prescribed at baseline and clinical success rates in this population were significantly lower (resistant vs non-resistant: 41.0% vs 69.7%, respectively; p< 0.001). Patients with diabetes mellitus, relative to non-diabetics, were more likely to fail treatment [success rate: 60.6% vs 66.5%, respectively; p<0.001] and have a baseline organism resistant to the first prescribed antibiotic [19.5% vs 13.7%; p<0.001]; treatment success was again less likely than those with susceptible pathogens [39.9% vs 65.6%; p < 0.001].

CONCLUSION: 15% of patients with an episode of uncomplicated urinary tract infection receive empiric treatment with an antibiotic for which the offending organism is resistant, resulting in a substantially higher rate of treatment failure. Diabetics are more likely to receive the wrong empiric antibiotic and fail therapy.

INTRODUCTION

- Urinary tract infection is a common reason for prescribing antimicrobials to otherwise healthy women
  - 15 million office or emergency room visits annually
  - 21 million prescriptions in the United States annually
- *Escherichia coli*, the most common cause of urinary tract infections (UTI), frequently demonstrates in vitro resistant to common antimicrobials.
  - β-lactams >13%; Trimethoprim-sulfamethoxazole > 20%
  - Quinolones > 33%; Multi-drug resistance (resistance to ≥3 classes) > 7%
- Empiric oral antibiotic therapy delivered in the community 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 outcome at 30-days for patients with an uncomplicated urinary tract infection, comparing patients whose pathogens were susceptible at baseline to those which were non-susceptible to the selected empiric therapy.

METHODS

- Retrospective assessment of patients with a UTI along with their treatment and outcomes from a medical claims database.
- Patients included in analysis:
  - Fully Insured Commercial 18 – 64 years and Medicare Advantage members
  - Index Event between January 1st, 2014 and 31st July, 2017
  - Treated for a UTI
  - Had demographics, medical and pharmacy utilization data, costs and clinical outcomes
- Initial treatment antibiotic was determined then:
  - Urine culture and resistance data identified within claim
  - Patients classified based on antibiotic resistance
- Treatment failure defined as:
  - Switch of antibiotic, or second prescription of same class of antibiotic, within 30 days of initial prescription fill, and/or
  - Hospitalization, or observation stays, with a primary or secondary diagnosis of UTI
- Cost of treatment includes those related to the antibiotic, primary care provider, specialist, and clinic or emergency department
- Multivariable model created to identify factors correlated with treatment failure based on UTI episodes with urine cultures available

RESULTS

Table 1. Baseline Demographics

Variable	
Count of unique patients	387,028
Female, n (%)	343,394 (89)
Average age (years)	54.5
Newly diagnosed UTI cases, N	500,318
Average UTI episode duration (days)	6.1
UTI cases with culture and susceptibility data, n (%)	44,143 (9)
Comorbidities (%)	
Diabetes	17.2
Benign Prostatic Hypertrophy	4.2
Chronic Renal Failure	6.0
Kidney Stones	2.3
Clinical Setting (%)	
Outpatient	80.5
Emergency Room	14.7
Inpatient	4.7
Unknown	0.1
Index UTI Claim Specialty (%)	
Family Practice	32.9
Internal Medicine	16.5
Acute Short-Term Hospital	12.2
Emergency Physician	10.1
Nurse Practitioner	7.7
Urology	7.2

RESULTS

Table 2. Susceptibility to oral antibiotics

Oral Antibiotic	N	% Resistance
Cephalosporin	5,477	12.4%
Nitrofurantoin	2,650	6.0%
Penicillin	20,527	46.5%
Quinolones	6,421	14.5%
Trimethoprim-sulfamethoxazole	8,305	18.8%
Tetracyclines	1,138	2.6%

Table 3. Treatment Failure in Patients with Outpatient UTI

In vitro susceptibility	Treatment Outcome, n (%)		P value*	Total n (%)
	Success	Failure		
Susceptible	25,987 (70)	11,272 (30)	P< 0.001	37,259 (85)
Resistant	2,622 (41)	3,778 (59)		6,400 (15)
Total	28,609	15,050		43,659

*Chi-square p value for success rate in patients with pathogens susceptible vs resistant

Table 4. Treatment Failure in Patients with Outpatient UTI and Diabetes Mellitus

In vitro susceptibility	Treatment Outcome, n (%)		P value*	Total n (%)
	Success	Failure		
Susceptible	3,845 (65)	2,046 (35)	P< 0.001	5,891(80)
Resistant	577 (40)	870 (60)		1,447 (20)
Total	4,422	2,916		7,338

*Chi-square p value for success rate in patients with pathogens susceptible vs resistant

Table 5. Treatment Failure by Characteristic and Multivariate Adjusted Odds Ratio

Characteristic	Unadjusted % of treatment failure	Adjusted ORs* (95% CI)
Gender		
Male	40.0	Reference
Female	34.2	1.06(0.98-1.15)
Diagnosis of antibiotic resistance		
No		Reference
Yes		
Prior UTI		
No	32.7	Reference
Yes	40.4	1.09 (1.04-1.14)
Comorbidities		
No Diabetes Mellitus	33.7	Reference
Diabetes Mellitus	39.7	1.00(0.94-1.06)
Age (years)		
18-45	28.9	Reference
46-55	32.8	1.14 (1.06-1.22)
56-65	35.6	1.13 (1.06-1.22)
65-75	38.3	1.05 (0.92-1.21)
75-85	42.7	1.07 (0.93-1.23)
>85	42.9	0.96(0.82-1.12)

*Adjusted for demographic variables, geography, antibiotic resistance, payor, and characteristics of UTI

Table 6. Treatment Failure based on initial antibiotic therapy received and susceptibility

Resistance Information	Unadjusted % of treatment failure	Adjusted ORs* (95% CI)
No Cephalosporin Resistance	33.59	Reference
Cephalosporin Resistance	42.49	1.04 (0.97-1.11)
No Nitrofurantoin Resistance	34.17	Reference
Nitrofurantoin Resistance	42.79	1.29 (1.18-1.41)
No Penicillin Resistance	30.79	Reference
Penicillin Resistance	39.18	1.14 (1.09-1.21)
No Quinolone Resistance	31.99	Reference
Quinolone Resistance	50.57	1.55 (1.46-1.64)
No SulfaTrim Resistance	32.63	Reference
SulfaTrim Resistance	43.59	1.24 (1.16-1.31)

Table 7. Cost of Treatment of UTI based on Susceptibility and Clinical Outcome

	All	Susceptible Isolate		Resistant Isolate	
		Success	Failure	Success	Failure
UTI episodes, N	44,143	26, 155	11, 452	2, 675	3, 861
Duration, mean (days)	6.9	3.9	11.9	6.3	12.7
Cost, mean ($)	255	174	382	236	442

CONCLUSIONS

- 15% of patients with an episode of uncomplicated urinary tract infection receive empiric treatment with an antibiotic for which the offending organism is resistant
  - Diabetics are more likely to receive the wrong empiric antibiotic
  - Associated with all oral antibiotics
- Overall, treatment failure costs $200 more per episode, twice that of treatment success
- Empiric selection of initial antibiotic to which the uropathogen is not susceptible results in substantially higher rate of treatment failure.
  - Two-fold increase risk of treatment failure
- The cost of treatment of a patient with a resistant isolate is $60 more than that of a patient with a susceptible isolate
  - Treatment failure with a resistant isolate costs 2.5x that of successful treatment of a susceptible isolate

American Society of Microbiology and Infectious Diseases; June 20-24, 2019; San Francisco, CA

ITERUM therapeutics