Incidence and risk factors for empiric treatment failure among females with uncomplicated urinary tract infections in an integrated health delivery network

Jeffrey J. Ellis,[1] Anushree Iyengar,[2] Hari Bandi,[2] Michiel J.M. Niesen,[2] Ediz S. Calay,[2] Tyler E. Wagner,[2] Madison T. Preib,[1] Amy G. Edgecomb,[1] Meghan E. Luck[1]

[1]GSK, Collegeville, PA, USA; [2]nference Inc., Cambridge, MA, USA

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The incidence of treatment failure in females treated empirically for uUTI is notable (15%). Consideration should be given to factors associated with greater risk of failure, including older age, recurrent UTI, diabetes, and prior ABX resistance

Introduction

- Treatment failure (TF) in uUTIs can prolong and intensify patient distress, leading to increased clinical and economic burden[1–3]
- Guideline-directed empiric treatment decisions in uUTIs may minimize the occurrence of TF, thus curtailing suboptimal outcomes[4,5]
- There are limited published data on risk factors for empiric TF in uUTI

Aim

- This study aimed to identify the incidence of, and risk factors for, empiric TF in females with uUTI treated within a US Integrated Delivery Network (IDN)

Methods

- Retrospective, observational cohort study using de-identified electronic health record (EHR) data from a US IDN[6] to assess female outpatients with uUTI aged ≥12 years between January 1, 2017–January 31, 2022
- Patients with TF (as defined below: "TF cohort") and without TF ("no-TF cohort") were identified
- Crude and adjusted odds of TF were computed for covariates of interest
  - p-values and 95% CIs for the crude ORs were determined using the Fisher exact method
  - Least Absolute Shrinkage and Selection Operator regression on 1000 bootstrap samples of the study cohort was used to determine adjusted ORs along with empirically determined 95% CIs and p-values
- Study design is presented in **Figure 1** and key eligibility criteria are described in **Table 1**

Treatment failure definition: ≥1 of the following ≤28 days after the index date

- Prescription of a new oral ABX for uUTI, or second prescription of the same empirically prescribed oral ABX for uUTI
- Administration of an IV ABX treatment
- Primary diagnosis of UTI in an acute care setting (excluding index uUTI)

Figure 1: **Study design schematic**

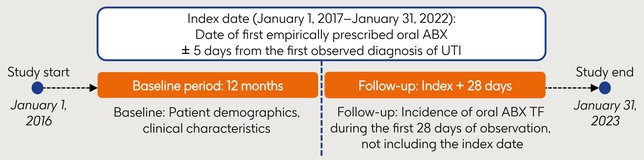


Table 1: **Key eligibility criteria**

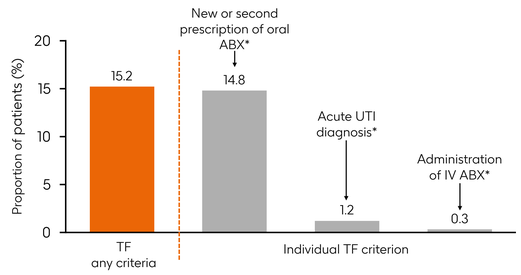
Key inclusion criteria	Key exclusion criteria
• Females aged ≥12 years old on the index date with ≥1 uUTI diagnosis in an outpatient or emergency department (ED) setting after January 1, 2017	• ABX susceptibility test results of the index uUTI diagnosis within 14 days prior to or on the index date
• ≥1 empiric prescription for nitrofurantoin (NTF), trimethoprim-sulfamethoxazole (SXT; separately or in combination), fluoroquinolones, fosfomycin, or β-lactams within ± 5 days of the uUTI diagnosis date	• Evidence of a complicated UTI* ≤12 months prior to or on index date
• ≥12 months of EHR activity before and after the index date	• Hospitalization ≤28 days prior to index date
	• Resident of a nursing home or long-term care facility ≤12 months prior to index date

**Complicated UTI included: pregnancy; diagnosed with urological abnormalities, uncontrolled or complicated diabetes, or severe renal dysfunction; immunosuppressed or treated with immunosuppressive therapy; urological or nephrological procedures (e.g., catheter, surgery) within 28 days prior to or on index date; ureteral stent procedure during the baseline period; IV ABX within 28 days prior to or on index date.*

Results

- Overall, the study population (N=28,460) was predominantly White or Caucasian (95%), with a mean age of 51.6 years (**Table 2**)
- TF occurred in 15.2% (n=4330) of patients, primarily based on the need for additional oral ABX (14.8%; n=4207) (**Figure 2**)
- NTF was the most common empirically prescribed oral index ABX in the TF and no-TF cohorts (**Table 2**)
- β-lactams were the most commonly prescribed new or second oral ABX after TF occurred (**Figure 3**)

Figure 2: **Incidence of TF to empirically prescribed oral ABX among female outpatients with uUTI**



**Not mutually exclusive. A patient could have experienced >1 criterion.*

Figure 3: **ABX selection when new or second oral ABX prescribed after TF occurred (n=4207)**

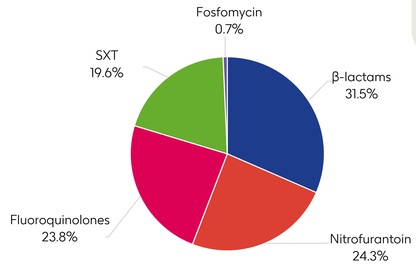
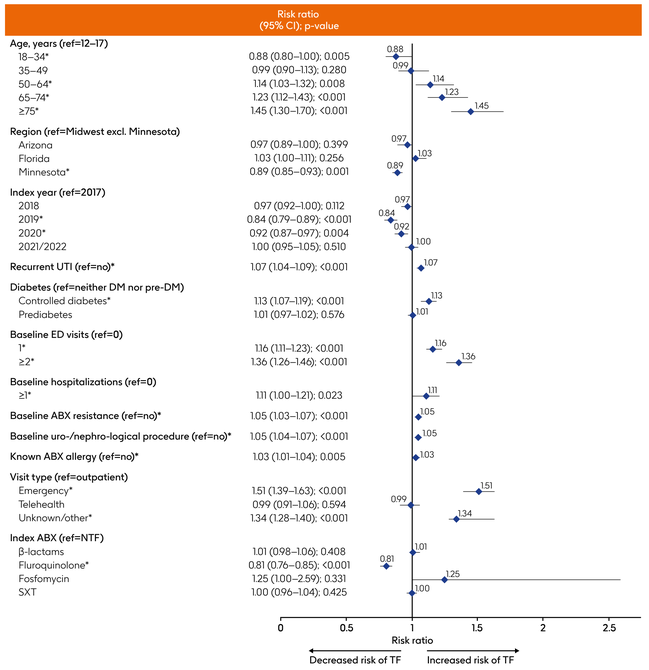


Table 2: **Baseline patient characteristics**

	TF cohort (n=4330)	No-TF cohort (n=24,130)	p-value
Age at index, years, mean (SD)	54.4 (21.2)	49.3 (20.8)	**<0.001**
Elixhauser index, mean (SD)	1.83 (5.90)	0.93 (4.71)	**<0.001**
Race, n (%)			0.138
White/Caucasian	4130 (95.4)	22,885 (94.8)	
Asian	59 (1.4)	397 (1.6)	
Black/African American	59 (1.4)	369 (1.5)	
Other/unknown	35 (0.8)	272 (1.1)	
Native American/Pacific Islander	23 (0.5)	104 (0.4)	
Not disclosed	24 (0.6)	103 (0.4)	
Index year, n (%)			**<0.001**
2017	1602 (37.0)	8256 (34.2)	
2018	959 (22.1)	5274 (21.9)	
2019	665 (15.4)	4311 (17.9)	
2020	596 (13.8)	3586 (14.9)	
2021/2022	508 (11.7)	2703 (11.2)	
Region, n (%)			**<0.001**
Arizona	298 (6.9)	1415 (5.9)	
Florida	300 (6.9)	1367 (5.7)	
Minnesota	1277 (29.5)	7856 (32.6)	
Midwest excl. Minnesota	2455 (56.7)	13,492 (55.9)	
Index ABX, n (%)			**<0.001**
NTF	2292 (52.9)	13,411 (55.7)	
SXT	822 (19.0)	4544 (18.8)	
β-lactams	708 (16.4)	3195 (13.2)	
Fluoroquinolones	480 (11.1)	2910 (12.1)	
Fosfomycin	28 (0.6)	40 (0.2)	
Recurrent UTI, n (%)	590 (13.6)	2036 (8.4)	**<0.001**
Diabetes, n (%)			**<0.001**
Neither diabetic nor prediabetic	3331 (76.9)	19,914 (82.5)	
Controlled diabetes	121 (2.8)	454 (1.9)	
Diabetes, control unknown	703 (16.2)	2914 (12.1)	
Prediabetes	175 (4.0)	848 (3.5)	
Baseline uro-/nephro-logical procedure, n (%)	199 (4.6)	504 (2.1)	**<0.001**
Known prior ABX resistance, n (%)	386 (8.9)	1237 (5.1)	**<0.001**

Bold font in p-values represents statistical significance (p<0.05).

Figure 4: **Forest plot of the risk factors of TF and adjusted risk ratios**



*Race, Ethnicity, Obesity, and Prior Oral ABX covariates were included in the model but did not contain any groups with statistically significant (p<0.05) odds ratios, and therefore are not included in the figure. * Denotes statistical significance (p<0.05). DM, diabetes mellitus.*

Table 3: **Crude (unadjusted) risk of TF**

	Crude odds ratio	95% CI	p-value
Age, years (ref=12–17 years)			
18–34	1.04	0.86–1.25	0.740
35–49	1.17	0.97–1.42	0.104
50–64	1.44	1.19–1.73	**<0.001**
65–74	1.59	1.31–1.92	**<0.001**
≥75	2.15	1.78–2.60	**<0.001**
Race: White/Caucasian (ref=other/unknown)	0.89	0.76–1.04	0.143
Ethnicity: Hispanic/Latino (ref=not Hispanic/Latino, or unknown)	1.06	0.88–1.27	0.583
Region (ref=Midwest excl. Minnesota)			
Arizona	1.16	1.01–1.32	**0.033**
Florida	1.21	1.06–1.38	**0.006**
Minnesota	0.89	0.83–0.96	**0.003**
Index year (ref=2017)			
2018	0.94	0.86–1.02	0.144
2019	0.79	0.72–0.88	**<0.001**
2020	0.86	0.77–0.95	**0.003**
2021/2022	0.97	0.87–1.08	0.581
Recurrent UTI	1.71	1.55–1.89	**<0.001**
Prior oral ABX ≥2 (ref=0–1)	1.59	1.45–1.75	**<0.001**
Diabetes (ref=neither diabetic nor prediabetic)			
Controlled diabetes	1.46	1.34–1.59	**<0.001**
Prediabetes	1.23	1.04–1.46	**0.016**
Obesity	1.14	1.06–1.22	**<0.001**
Baseline ED visits (ref=0)			
1	1.32	1.21–1.45	**<0.001**
≥2	1.69	1.51–1.89	**<0.001**
Baseline hospitalizations ≥1 (ref=0)	1.87	1.65–2.11	**<0.001**
Baseline ABX resistance (ref=no)	1.81	1.61–2.04	**<0.001**
Baseline uro-/nephro-logical procedure (ref=no)	2.26	1.91–2.67	**<0.001**
Known ABX allergy	1.33	1.22–1.46	**<0.001**
Visit type (ref=outpatient)			
Emergency	1.70	1.49–1.94	**<0.001**
Telehealth	0.81	0.69–0.94	**0.005**
Unknown/other	1.35	1.26–1.45	**<0.001**
Index ABX (ref=NTF)			
β-lactams	1.30	1.18–1.43	**<0.001**
Fluoroquinolone	0.97	0.87–1.08	0.554
Fosfomycin	4.11	2.53–6.67	**<0.001**
SXT	1.06	0.97–1.16	0.181

Bold font in p-values represents statistical significance (p<0.05).

Conclusions

- Several patient, visit-related, and clinical characteristics were found to increase the odds for TF to empirically prescribed oral ABX for uUTI
- Clinicians should consider risk factors among females with uUTI to identify patients at increased risk of TF when selecting empiric treatment

- The crude (**Table 3**) and adjusted (**Figure 4**) odds of TF were significantly greater for patients who were ≥50 years old or had recurrent UTI, controlled diabetes, prior hospitalization, prior ABX resistance, prior uro-/nephro-logical procedures, or ABX allergy
- ED utilization, both for the index uUTI visit and any prior utilization, was associated with an increased risk of TF (**Table 3, Figure 4**)
- Prior oral ABX history and obesity exhibited statistically significant crude OR (**Table 3**) but were not statistically significant when adjusted for other covariates

Abbreviations

ABX, antibiotic; CI, confidence interval; DM, diabetes mellitus; ED, emergency department; EHR, electronic health record; IDN, Integrated Delivery Network; IV, intravenous; NTF, nitrofurantoin; OR, odds ratio; SD, standard deviation; SXT, trimethoprim-sulfamethoxazole; TF, treatment failure; US, United States; UTI, urinary tract infection; uUTI, uncomplicated urinary tract infection.

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Presenting author: Jeffrey J. Ellis, jeffrey.x.ellis@gsk.com