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Clinical Risk Scores to Predict Nonsusceptibility to Trimethoprim-Sulfamethoxazole, Fluoroquinolone, Nitrofurantoin, and Third-Generation Cephalosporin Among Adult Outpatient Episodes of Complicated Urinary Tract Infection

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Background. Clinical risk scores were developed to estimate the risk of adult outpatients having a complicated urinary tract infection (cUTI) that was nonsusceptible to trimethoprim-sulfamethoxazole (TMP-SMX), fluoroquinolone, nitrofurantoin, or third-generation cephalosporin (3-GC) based on variables available on clinical presentation.

Methods. A retrospective cohort study (1 December 2017–31 December 2020) was performed among adult members of Kaiser Permanente Southern California with an outpatient cUTI. Separate risk scores were developed for TMP-SMX, fluoroquinolone, nitrofurantoin, and 3-GC. The models were translated into risk scores to quantify the likelihood of nonsusceptibility based on the presence of final model covariates in a given cUTI outpatient.

Results. A total of 30 450 cUTIs (26 326 patients) met the study criteria. Rates of nonsusceptibility to TMP-SMX, fluoroquinolone, nitrofurantoin, and 3-GC were 37%, 20%, 27%, and 24%, respectively. Receipt of prior antibiotics was the most important predictor across all models. The risk of nonsusceptibility in the TMP-SMX model exceeded 20% in the absence of any risk factors, suggesting that empiric use of TMP-SMX may not be advisable. For fluoroquinolone, nitrofurantoin, and 3-GC, clinical risk scores of 10, 7, and 11 predicted a ≥20% estimated probability of nonsusceptibility in the models that included cumulative number of prior antibiotics at model entry. This finding suggests that caution should be used when considering these agents empirically in patients who have several risk factors present in a given model at presentation.

Conclusions. We developed high-performing parsimonious risk scores to facilitate empiric treatment selection for adult outpatients with cUTIs in the critical period between infection presentation and availability of susceptibility results.

Keywords. antibiotic resistance; complicated urinary tract infections; risk score.

Complicated urinary tract infections (cUTIs) are among the most common bacterial infections in adult patients [1, 2]. In the United States, an estimated >2.8 million cUTI episodes occur among adults per year, with approximately 80% in the outpatient setting [3]. Oral antibiotics have been a mainstay in the treatment of adult outpatients with cUTIs, but the prevalence of resistance to commonly used agents has increased dramatically over the past decade [4–14]. Adult outpatients with antibiotic-resistant cUTI are at an increased risk for delayed receipt of appropriate antimicrobial therapy [15–22]. This is highly concerning as the adverse outcomes associated with delayed appropriate therapy in this patient population are well documented [15–22]. To facilitate empiric antibiotic selection [23–26], risk prediction models can be used to identify patients at greatest risk for having a resistant infection prior to availability of culture and antibiotic susceptibility results [27, 28]. To date, most risk prediction tools have been developed for inpatient use, and few are available to facilitate antibiotic selection in the outpatient setting [28, 29]. To address this evidence gap, this study sought to develop clinical risk prediction scores using commonly available clinical data to estimate the probabilities of nonsusceptibility to frequently used antibiotics among adult outpatients with cUTIs.

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METHODS

Setting

Kaiser Permanente Southern California (KPSC) is an integrated health care organization with >4.7 million members who are representative of the socioeconomic and racial/ethnic diversity of the geographic area's population [30]. KPSC uses electronic health records to integrate medical information, including diagnoses, medications, procedure codes, and laboratory results from outpatient, emergency department, and hospital settings.

Patient Consent Statement

The study protocol was approved by KPSC's institutional review board, which waived requirement for informed consent.

Study Design and Population

We conducted a retrospective case-cohort study among adult KPSC members (≥18 years) who had a documented cUTI in the outpatient setting between 1 January 2017 and 31 December 2020. An outpatient setting was defined as a health care encounter/visit in any of the following: physician's office (ambulatory), urgent care, emergency department with no subsequent hospital admission on the same day [3], and synchronous virtual care via video or telephone. Patients were considered to have a cUTI if there was

- A positive urine culture result with antibiotic susceptibility
- A diagnosis of a cUTI based on *ICD-10-CM* codes (Supplementary Materials *A*–*D*) [3] ±7 days of urine culture collection date
- ≥1 antibiotic dispense ±3 days of index urine culture collection date: levofloxacin, ciprofloxacin, trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin, amoxicillin, amoxicillin-clavulanate, ampicillin, ampicillin-sulbactam, cephalexin, fosfomycin, cefaclor, cefpodoxime, cefixime, cefdinir, ceftriaxone, ertapenem, cefazolin, cefepime, cefotaxime, or piperacillin-tazobactam [31]

For routine urine cultures, the minimum colony count for a positive result was 10 000 CFU/mL. Susceptibility testing was dependent on organism, Clinical and Laboratory Standards Institute (CLSI) guidelines, colony count, and processes specific to the KPSC laboratory. The index date was defined as the time of the first urine specimen collection for a cUTI episode. Patients were also required to have 12 months of continuous KPSC enrollment prior to the index date (allowing for 45-day enrollment gaps) and KPSC pharmacy benefits at time of the index date. Patients were excluded if they were in the inpatient setting for any cause on the outpatient index date or if they had a cUTI diagnosis within the prior 30 days of an index date in January 2017. Given the recurrent nature of cUTIs, patients could have ≥1 cUTI episode (ie, recurrence) during the study period if the end of treatment for the initial and subsequent cUTIs were >30 days apart [32, 33]. Each episode was included as an independent event, and baseline covariates differed across episodes.

To maximize the generalizability of the prediction tools, cUTI infections were limited to the following 13 organisms (accounting for 93% of cUTI organisms):

Gram-negative (n = 11): *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter cloacae complex, Enterobacter aerogenes, Citrobacter koseri, Klebsiella oxytoca, Citrobacter freundii, Morganella morganii, and Serratia marcescens*

Gram-positive (n = 2): *Enterococcus faecalis, Enterococcus species*

We defined nonsusceptibility as having resistant or intermediate antimicrobial testing results for the drugs of interest based on CLSI guidance at the time of study. In limited situations when susceptibility results were not available, algorithms based on CLSI guidance documents were developed to define susceptibility [34]. For example, if an organism was ampicillin susceptible and susceptibility data to third-generation cephalosporin (3-GC) were not available, it was considered susceptible to ceftriaxone.

Data Elements

Demographic, clinical, pharmacy, and laboratory data for cUTI episodes were obtained from patients' electronic health records on the index date of urine culture collection. Demographic data included age, sex, and race/ethnicity. Clinical characteristics collected from the electronic health records in the 12 months prior to the index date included

- Chronic medical conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, liver disease, diabetes with or without complications, renal disease, any malignancy (including leukemia and lymphoma, except malignant neoplasm of skin; see Supplementary Table 1 for definitions), and other immune conditions
- Current or prior residence in a long-term care facility (nursing home or skilled nursing facility)
- Prior hospitalizations and emergency department visits
- Number of UTIs

The following information was also documented: cumulative number of prior inpatient and outpatient antibiotics and specific individual agents received in the 90 days prior to the index urine culture collection date, the presence of any urinary tract devices in the 30 days prior to the index date, and pregnancy status within 7 days of the index date.

Statistical Analyses

Clinical risk scores were developed separately for each of the following nonsusceptibility phenotypes: TMP-SMX, fluoroquinolone (ie, nonsusceptibility to ciprofloxacin or levofloxacin), nitrofurantoin, and 3-GC (ie, nonsusceptibility to ceftriaxone). For each nonsusceptibility phenotype of interest, the distribution of covariates between patients with susceptible and nonsusceptible infections was compared with the chi-square or Fisher exact test. To identify potential risk factors for prediction modeling, we performed bivariable logistic regression of covariates and each nonsusceptibility phenotype. All variables associated with nonsusceptibility ($P < .2$) in the bivariable analyses that had clinical relevance were selected as candidates for prediction modeling in multivariable analyses. Two separate logistic regression models were developed for each nonsusceptibility phenotype of interest. One included the cumulative number of antibiotics received prior to the index date, while the second included the individual antibiotics received prior to the index date.

The study population was first randomly split (60:40) into training and validation data sets for development of each risk score. In the training data sets, multivariable logistic regression models were developed via the LASSO logistic regression (least absolute shrinkage and selection operator). As part of model development, variables were assessed for collinearity with the variance inflation factor and correlation prior to inclusion in the multivariable model. Lack of multicollinearity between predictors was defined as a variance inflation factor <2.5 or a correlation coefficient <0.6 [35]. When ≥2 variables were collinear, we selected variables for inclusion based on magnitude of effect and clinical relevance. The final multivariable models were selected to balance predictive performance, parsimoniousness, and clinical feasibility.

Based on the final multivariable models, risk scores were developed according to methods previously described by Sullivan et al [36]. We highlighted clinical risk scores across each model that were associated with a ≥20% likelihood of nonsusceptibility, a critical resistance threshold for empiric use of TMP-SMX for uncomplicated cystitis and pyelonephritis in women [37]. Calibration of the final prediction models was assessed in the training and validation data sets. We assessed the calibration of the point-based risk score system by comparing the risk observed with the risk predicted by the risk score within the validation data set, visualized in plots of observed risk and the average point-based predicted risk by deciles [38]. All analyses were performed with SAS version 9.4 (SAS Institute).

RESULTS

The study included 30 450 cUTIs among 26 326 patients overall (Supplementary Figure 1). The median (IQR) age was 65.0 (47.0–77.0) years, with a similar distribution between those <65 years and ≥65 years. More cUTIs occurred in females (54.4%), and the most common racial/ethnic category was Hispanic (41.6%). The presence of a urinary tract device in the 30 days prior to the index urine culture collection was observed in 12.6% of episodes, and 53.4% of cUTI episodes were preceded by a urinary tract infection (UTI). Prior exposure to health care facilities was commonplace, as documented by the presence of a prior hospitalization (23.6%) or emergency department visit (49.5%).

Among the 30 450 cUTI episodes, 32 230 uropathogens were identified (Supplementary Table 2). Among the 32 230 identified uropathogens, 37.4% of cUTI organisms were nonsusceptible to TMP-SMX, 19.8% to fluroquinolone, 27.0% to nitrofurantoin, and 24.0% to 3-GC. Multidrug resistance was common. Overall, 2.8% of cUTIs were nonsusceptible to all 4 antimicrobials of interest, while 12.8% were nonsusceptible to ≥3, 34.4% to ≥2, and 60.7% to ≥1. Cross-resistance among agents was high, ranging from 34% to 65%. For TMP-SMX–nonsusceptible uropathogens, 34.0%, 35.3%, and 38.0% were nonsusceptible to fluoroquinolone, nitrofurantoin, and 3-GC, respectively (Supplementary Table 3). For fluoroquinolone-nonsusceptible uropathogens, 65.4%, 35.9%, and 45.1% were nonsusceptible to TMP-SMX, nitrofurantoin, and 3-GC. For nitrofurantoin-nonsusceptible uropathogens, 50.0%, 34.8%, and 37.5% were nonsusceptible to TMP-SMX, fluoroquinolone, and 3-GC. For 3-GC–nonsusceptible isolates, 52.7%, 31.6%, and 41.9% were nonsusceptible to TMP-SMX, fluoroquinolone, and nitrofurantoin. Antibiotic dispenses in the ±3 days of the index date are included in Supplementary Table 4.

Covariates associated with nonsusceptibility were largely consistent across the 4 nonsusceptibility phenotypes of interest (Table 1). When compared with patients with susceptible infections, patients with nonsusceptible cUTI organisms were more likely to be aged ≥65 years and male with more comorbid conditions. The nonsusceptibility phenotypes were also more pronounced in patients who had a UTI in the year prior to the index date and had urinary tract devices in the 30 days prior to the index date. Patients with nonsusceptible cUTI organisms had higher numbers of prior antibiotics, more prior hospitalizations and emergency department visits, and more cUTI recurrences and were more likely to have resided in long-term care facility in the year prior to the index date.

Supplementary Table 5 and Table 2 show the final adjusted covariate risk estimates and points for the nonsusceptibility risk scores for TMP-SMX, fluroquinolone, nitrofurantoin, and 3-GC in models that included cumulative number of prior antibiotics at model entry. In the models that included the cumulative number of prior antibiotics, the number of antibiotics received in the 90 days prior to the index date conferred the greatest point counts for TMP-SMX, fluroquinolone, and 3-GC clinical risk scores (Table 2). For the nitrofurantoin model, the most important predictors were male sex (5 points),

Table 1. Characteristics of Study Cohort by Resistance to TMP-SMX, Fluoroquinolone, Nitrofurantoin, and 3-GC

		TMP-SMX		Fluroquinolone		Nitrofurantoin		3-GC	
Covariates[a]	Total[b] (N = 30 450)	NS (n = 11 289)	Susceptible (n = 19 159)	NS (n = 5808)	Susceptible (n = 22 985)	NS (n = 8114)	Susceptible (n = 22 316)	NS (n = 7180)	Susceptible (n = 23 265)
Age at index date, y									
<65	15 061 (49.5)	5057 (44.8)	10 003 (52.2)	2358 (40.6)	12 255 (53.3)	2730 (33.6)	12 320 (55.2)	2398 (33.4)	12 661 (54.4)
≥65	15 389 (50.5)	6232 (55.2)	9156 (47.8)	3450 (59.4)	10 730 (46.7)	5384 (66.4)	9996 (44.8)	4782 (66.6)	10 604 (45.6)
Male	13 897 (45.6)	5757 (51.0)	8139 (42.5)	3099 (53.4)	9551 (41.6)	5073 (62.5)	8819 (39.5)	4561 (63.5)	9333 (40.1)
Race/ethnicity									
White	12 453 (40.9)	4526 (40.1)	7927 (41.4)	2177 (37.5)	9367 (40.8)	3809 (46.9)	8635 (38.7)	3266 (45.5)	9186 (39.5)
Black	2525 (8.3)	865 (7.7)	1659 (8.7)	497 (8.6)	1887 (8.2)	801 (9.9)	1722 (7.7)	591 (8.2)	1933 (8.3)
Hispanic	12 682 (41.6)	4892 (43.3)	7789 (40.7)	2637 (45.4)	9608 (41.8)	2878 (35.5)	9797 (43.9)	2713 (37.8)	9966 (42.8)
Other/unknown	2790 (9.2)	1006 (8.9)	1784 (9.3)	497 (8.6)	2123 (9.2)	626 (7.7)	2162 (9.7)	610 (8.5)	2180 (9.4)
Chronic comorbidities in the 12 mo prior to the index date									
Myocardial infarction	2219 (7.3)	986 (8.7)	1233 (6.4)	573 (9.9)	1451 (6.3)	902 (11.1)	1317 (5.9)	821 (11.4)	1398 (6.0)
Congestive heart failure	3389 (11.1)	1503 (13.3)	1886 (9.8)	893 (15.4)	2212 (9.6)	1417 (17.5)	1971 (8.8)	1322 (18.4)	2065 (8.9)
Peripheral vascular disease	10 888 (35.8)	4646 (41.2)	6241 (32.6)	2636 (45.4)	7376 (32.1)	4088 (50.4)	6794 (30.4)	3687 (51.4)	7198 (30.9)
Cerebrovascular disease	2698 (8.9)	1242 (11.0)	1455 (7.6)	720 (12.4)	1775 (7.7)	1163 (14.3)	1533 (6.9)	1027 (14.3)	1671 (7.2)
Dementia	2145 (7.0)	1065 (9.4)	1079 (5.6)	642 (11.1)	1327 (5.8)	1051 (13.0)	1093 (4.9)	946 (13.2)	1199 (5.2)
Chronic pulmonary disease	6467 (21.2)	2572 (22.8)	3895 (20.3)	1460 (25.1)	4604 (20.0)	2047 (25.2)	4415 (19.8)	1872 (26.1)	4595 (19.8)
Liver disease (mild, moderate, and severe)	2502 (8.2)	1062 (9.4)	1439 (7.5)	580 (10.0)	1753 (7.6)	746 (9.2)	1755 (7.9)	735 (10.2)	1767 (7.6)
Diabetes with or without complications	9891 (32.5)	4010 (35.5)	5881 (30.7)	2426 (41.8)	6840 (29.8)	3277 (40.4)	6610 (29.6)	2864 (39.9)	7025 (30.2)
Renal disease	7520 (24.7)	3180 (28.2)	4339 (22.6)	1808 (31.1)	5145 (22.4)	2842 (35.0)	4670 (20.9)	2575 (35.9)	4942 (21.2)
Any malignancy, including leukemia and lymphoma, except malignant neoplasm of skin	2228 (7.3)	953 (8.4)	1275 (6.7)	493 (8.5)	1524 (6.6)	803 (9.9)	1422 (6.4)	756 (10.5)	1472 (6.3)
Other immune conditions	2828 (9.3)	1287 (11.4)	1541 (8.0)	737 (12.7)	1885 (8.2)	1073 (13.2)	1752 (7.9)	1033 (14.4)	1794 (7.7)
Pregnancy ±7 d from index date	133 (0.4)	38 (0.3)	94 (0.5)	9 (0.2)	122 (0.5)	15 (0.2)	118 (0.5)	10 (0.1)	123 (0.5)
Urinary tract instruments/devices 30 d prior to index date	3837 (12.6)	1967 (17.4)	1870 (9.8)	905 (15.6)	2525 (11.0)	1813 (22.3)	2016 (9.0)	1776 (24.7)	2059 (8.9)
Cumulative number of prior antibiotics ≤90 d prior to index date									
0	16 288 (53.49)	4662 (41.3)	11 626 (60.7)	1984 (34.2)	13 669 (59.5)	3142 (38.7)	13 144 (58.9)	2197 (30.6)	14 089 (60.6)
1	5702 (18.73)	2244 (19.9)	3456 (18.0)	1100 (18.9)	4301 (18.7)	1655 (20.4)	4042 (18.1)	1345 (18.7)	4356 (18.7)
2 or 3	4965 (16.31)	2312 (20.5)	2653 (13.8)	1384 (23.8)	3219 (14.0)	1783 (21.97)	3179 (14.3)	1758 (24.5)	3205 (13.8)
≥4	3495 (11.48)	2071 (18.3)	1424 (7.4)	1340 (23.1)	1796 (7.8)	1534 (18.9)	1951 (8.7)	1880 (26.2)	1615 (6.9)
Prior receipt ≤90 d prior to index date									
TMP-SMX	2391 (7.85)	1397 (12.37)	993 (5.18)	749 (12.9)	1453 (6.32)	842 (10.38)	1546 (6.93)	909 (12.66)	1481 (6.37)
Fluoroquinolone	4636 (15.22)	2450 (21.7)	2185 (11.4)	1973 (33.97)	2199 (9.57)	1662 (20.48)	2968 (13.3)	2090 (29.11)	2544 (10.93)
Nitrofurantoin	2040 (6.7)	1020 (9.04)	1020 (5.32)	650 (11.19)	1220 (5.31)	621 (7.65)	1416 (6.35)	766 (10.67)	1274 (5.48)
3G-C	5276 (17.33)	2779 (24.62)	2497 (13.03)	1497 (25.77)	3247 (14.13)	2208 (27.21)	3057 (13.7)	2497 (34.78)	2778 (11.94)
Other antibiotics	9666 (31.74)	4527 (40.1)	5139 (26.82)	2517 (43.34)	6492 (28.24)	3508 (43.23)	6143 (27.53)	3449 (48.04)	6215 (26.71)

Table 1. Continued

Covariates[a]	Total[b] (N = 30 450)	TMP-SMX		Fluroquinolone		Nitrofurantoin		3-GC	
		NS (n = 11 289)	Susceptible (n = 19 159)	NS (n = 5808)	Susceptible (n = 22 985)	NS (n = 8114)	Susceptible (n = 22 316)	NS (n = 7180)	Susceptible (n = 23 265)
In the 12 mo prior to index date									
Prior UTI event	16 256 (53.4)	7010 (62.1)	9244 (48.2)	4322 (74.4)	10 913 (47.5)	5360 (66.1)	10 880 (48.8)	5102 (71.1)	11 151 (47.9)
Health care utilization									
Hospitalization	7184 (23.6)	3415 (30.3)	3768 (19.7)	1975 (34.0)	4635 (20.2)	2944 (36.3)	4227 (18.9)	2875 (40.0)	4308 (18.5)
ED visit	15 072 (49.5)	6373 (56.5)	8698 (45.4)	3557 (61.2)	10 451 (45.5)	5204 (64.1)	9852 (44.1)	4839 (67.4)	10 231 (44.0)
Recurrence cUTI	4334 (14.2)	2023 (17.9)	2309 (12.1)	1506 (25.9)	2574 (11.2)	1688 (20.8)	2640 (11.8)	1619 (22.5)	2714 (11.7)
Long-term care (nursing home or SNF) in the 12 mo prior to index date	1695 (5.6)	916 (8.1)	779 (4.1)	639 (11.0)	944 (4.1)	923 (11.4)	772 (3.5)	834 (11.6)	860 (3.7)

Data are presented as No. (%).

Abbreviations: 3-GC, third-generation cephalosporin; cUTI, chronic urinary tract infection; ED, emergency department; NS, nonsusceptible; SNF, skilled nursing facility; UTI, urinary tract infection; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Chi-square or Fisher exact test ($P < .05$).

[b]Totals for treatment categories may not add to 30 450 due to small numbers of missing susceptibility results.

receipt of ≥2 prior antibiotics (4 points), and the presence of a urinary tract device in the 30 days prior to the index date (4 points). The risk scores associated with a ≥20% predicted likelihood of nonsusceptibility to TMP-SMX, fluoroquinolone, nitrofurantoin, and 3-GC were 0, 10, 7, and 11, respectively (Figure 1*A* and Table 2). Supplementary Table 6 shows the distribution of pathogens (total and nonsusceptible number) when the predicted probability of nonsusceptibility is <20% vs ≥20%. Relative to cUTI episodes with risk scores associated with a <20% predicted probability of nonsusceptibility for each antibiotic, there was a higher proportion of nonsusceptible *E coli* and a greater frequency of non–*E coli* uropathogens for risk scores associated with a ≥20% predicted probability of nonsusceptibility. In the validation data set, the predicted risk for the 4 nonsusceptibility phenotypes of interest was closely aligned with observed risk (Figure 2*A*). Final models restricted to unique patients demonstrated similar point values as those conducted at the episode level (Supplementary Table 7).

Similar covariates were retained in the final models that included prior receipt of individual antibiotics vs cumulative number of prior antibiotics (Supplementary Table 8 and Table 3). Prior receipt of individual antibiotics (TMP-SMX, fluoroquinolone, nitrofurantoin, 3-GC, and other) was a significant covariate in all final models with few exceptions. The strongest predictor of nonsusceptibility to TMP-SMX or fluoroquinolone was prior receipt of that antibiotic (eg, prior receipt of fluoroquinolone had the highest assigned points in the fluoroquinolone nonsusceptibility model), while prior receipt of a 3-GC was the second-most important predictor in the 3-GC nonsusceptibility model. Models for individual antibiotics were nearly identical to the models for cumulative number of prior antibiotics—specifically, the risk scores associated with a ≥20% predicted likelihood of nonsusceptibility to TMP-SMX, fluoroquinolone, nitrofurantoin, and 3-GC were 0, 9, 7, and 11, respectively (Figure 1*B* and Table 3). The predicted risk for the 4 nonsusceptibility phenotypes of interest was closely aligned with the observed risk in the training validation data sets through the ninth decile of risk (Figure 2*B*).

DISCUSSION

Treatment of adult outpatients with cUTIs is complicated by an increased prevalence of resistance to the most widely used oral antibiotics [4–14], leading to delays in receipt of active antibiotic therapy in many outpatients [15–22] and poorer outcomes [15, 17–22, 39–41]. It is well established that certain factors and conditions predispose patients to having an antibiotic-resistant cUTI [12, 42–46]. However, few studies have assessed the likelihood that an adult outpatient cUTI is resistant to commonly used oral antibiotics when these risk factors are simultaneously present [28, 29]. As a measure to ensure that adult outpatients have a higher likelihood of receiving early appropriate therapy, we developed a set of clinical risk scores using information routinely available at patient presentation. To date, most published clinical prediction tools have focused on 1 pathogen or antibiotic-resistant phenotype [28, 29, 47, 48]. Although helpful in the antibiotic selection process, the risk factors for various antibiotic-resistant cUTI phenotypes are largely overlapping. Thus, we developed clinical risk scores that estimate the probabilities of having a cUTI that was nonsusceptible to TMP-SMX, fluoroquinolone, nitrofurantoin, or 3-GC. We selected these antibiotic-nonsusceptible phenotypes as they are the most used oral cUTI agents [3] and nonsusceptibility to

Table 2. Baseline Clinical Covariates and Associated Point Values and Predicted Probability of Nonsusceptibility in the 4 Clinical Risk Scores for Models That Included Cumulative Number of Prior Antibiotics at Model Entry

Baseline Clinical Covariates	Associated Point Values for Covariates in the 4 Clinical Risk Scores			
	TMP-SMX NS	FQ NS	NIT NS	3-GC NS
Age ≥65 y	…	…	1	1
Male sex	2	2	5	6
Chronic comorbidities in the 12 mo prior to index date				
Peripheral vascular disease	…	…	1	…
Dementia	…	…	4	4
Diabetes	…	2	1	…
Renal disease	…	…	1	…
Chronic pulmonary disease	…	…	…	1
Urinary tract device in the 30 d prior to index date	1	…	4	4
Cumulative number of antibiotics in the 90 d prior to index date				
1	4	3	3	5
2 or 3	6	6	4	7
≥4	9	10	4	12
In the 12 mo prior to index date				
UTI event	1	6	2	2
Hospitalization	1	…	2	2
ED visit	1	…	2	2
Recurrence cUTI	…	4	2	1
Long-term care (nursing home or SNF) in the 12 mo prior to index date	…	4	4	2

Score	Predicted Probability of Nonsusceptibility Based on Score, %			
0	25	8	12	8
1	27	9	13	9
2	29	10	14	9
3	32	11	15	10
4	34	13	17	11
5	36	14	18	13
6	39	15	20	14
7	42	17	22	15
8	44	18	24	17
9	47	20	26	18
10	50	22	28	20
11	53	24	30	22
12	55	26	33	24
13	58	28	35	26
14	61	30	38	28
15	63	33	40	30
16	66	35	43	33
17	68	37	46	35
18	71	40	49	38
19	73	43	51	40
20	75	45	54	43
21	77	48	57	46
22	79	51	60	48
23	81	54	62	51
24	82	56	65	54
25	84	59	67	57
26	…	62	70	59
27	…	64	72	62
28	…	67	74	64
29	…	69	76	67
30	…	71	78	69
31	…	74	80	72
32	…	76	82	74
33	…	78	83	76
34	…	80	85	78
35	…	81	86	80
36	…	83	87	81
37	…	84	88	83
38	…	…	90	85
39	…	…	91	86
40	…	…	91	87
41	…	…	…	88
42	…	…	…	89
43	…	…	…	90
44	…	…	…	91
45	…	…	…	92
46	…	…	…	93
47	…	…	…	94
48	…	…	…	94
49	…	…	…	95

Abbreviations: 3-GC, third-generation cephalosporin; cUTI, complicated urinary tract infection; ED, emergency department; FQ, fluoroquinolone; NIT, nitrofurantoin; NS, nonsusceptible; SNF, skilled nursing facility; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

them is becoming increasingly common across most areas of the United States [4, 5, 7–14].

Consistent with previous reports, we identified multiple covariates that are readily identifiable and available at clinical presentation to be significantly associated with each nonsusceptibility phenotype [12, 28, 29, 42–45, 47]. The most important independent risk factor for all 4 nonsusceptibility phenotypes in both sets of models was receipt of prior antibiotics. This finding is biologically plausible given that receipt of antibiotics disturbs the natural endogenous genitourinary tract flora and predisposes patients to recurrent UTI and colonization by resistant uropathogens over time [48–50]. One of the most predictive factors of nonsusceptibility to TMP-SMX, fluoroquinolone, nitrofurantoin, or 3-GC was prior receipt of the individual antibiotic. The results also indicate that cumulative antibiotic exposure history is a critical determinant in the assessment of a patient's likelihood of having a nonsusceptible cUTI. Prior UTI events, the presence of urinary tract devices, male sex, advanced age, recent exposure to a health care facility, and comorbid conditions were additional significant risk factors for most nonsusceptibility phenotypes. These factors

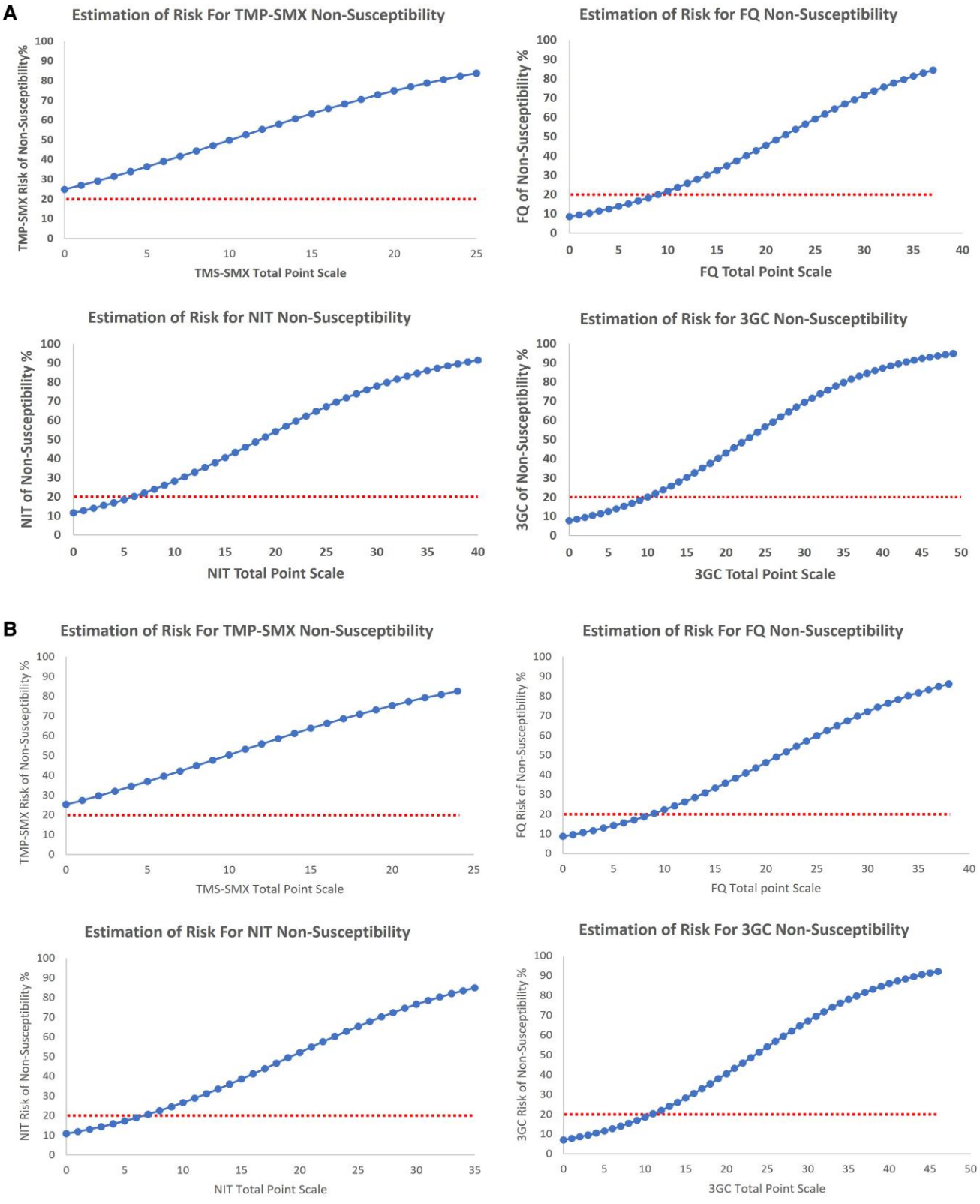

Figure 1. Predicted risk of nonsusceptibility to trimethoprim-sulfamethoxazole, fluoroquinolone, nitrofurantoin, or third-generation cephalosporin by cumulative point score for models that included (*A*) cumulative number of prior antibiotics at model entry and (*B*) prior receipt of individual antibiotics at model entry. 3GC, third-generation cephalosporin; FQ, fluoroquinolone; NIT, nitrofurantoin; TMP-SMX, trimethoprim-sulfamethoxazole.

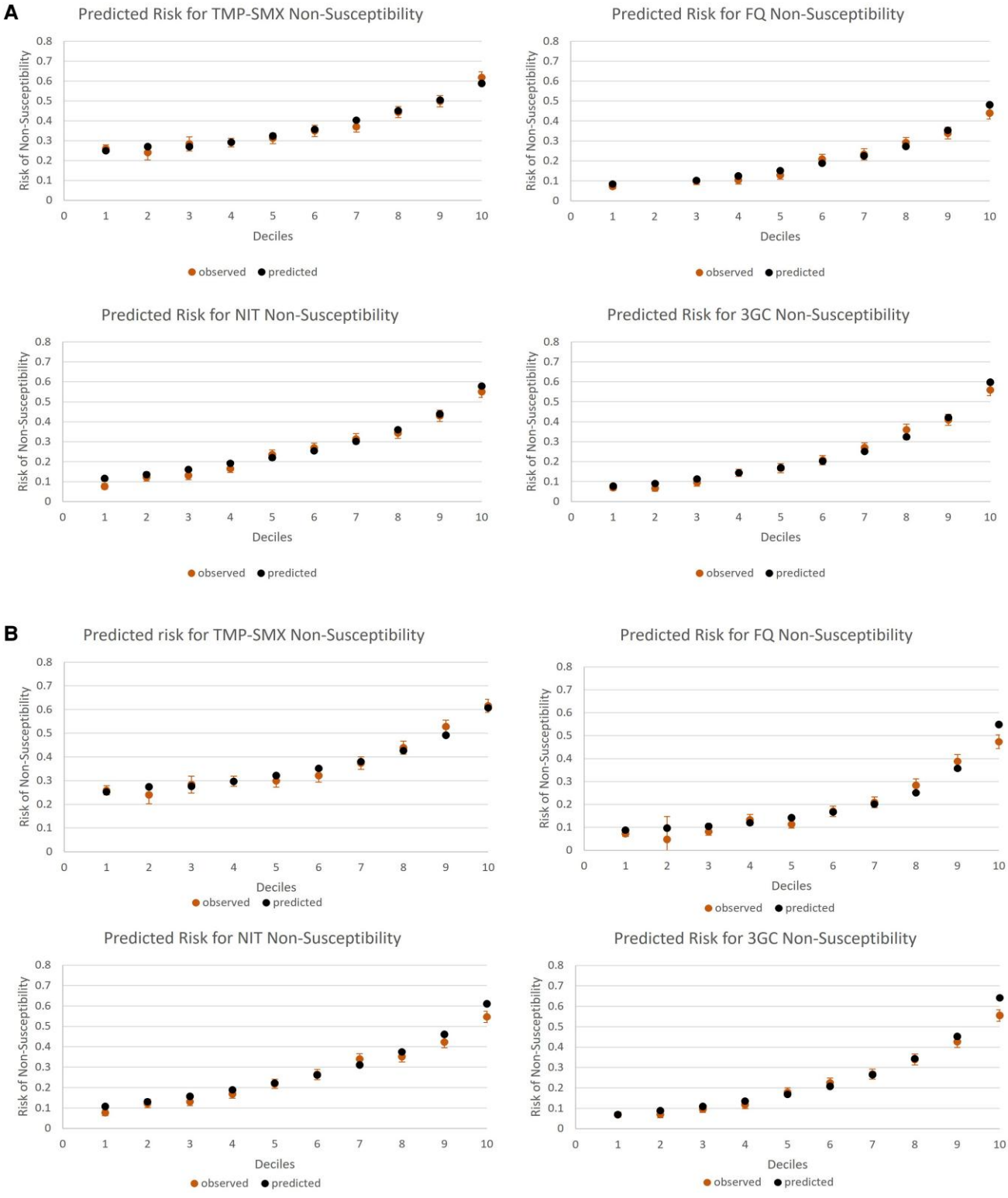

Figure 2. Comparison of observed and point-based predicted risk by deciles according to model-based predicted risk in validation data set for models that included (*A*) cumulative number of prior antibiotics at model entry and (*B*) prior receipt of individual antibiotics at model entry. Error bars indicate the 95% confidence interval for the mean point–based predicted probability and observed outcome. 3GC, third-generation cephalosporin; FQ, fluoroquinolone; NIT, nitrofurantoin; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 3. Baseline Clinical Covariates and Associated Point Values and Predicted Probability of Nonsusceptibility in the 4 Clinical Risk Scores for Models That Included Prior Receipt of Individual Antibiotics at Model Entry

Baseline Clinical Covariates	Associated Point Values for Covariates in the 4 Clinical Risk Scores			
	TMP-SMX NS	FQ NS	NIT NS	3-GC NS
Age ≥65 y	…	…	2	3
Male sex	2	2	5	6
Chronic comorbidities in the 12 mo prior to index date				
Peripheral vascular disease	…	…	1	…
Dementia	…	…	3	4
Diabetes	…	3	1	…
Renal disease	…	…	1	…
Chronic pulmonary disease	…	…	…	1
Urinary tract device in the 30 d prior to index date	2	…	4	4
Receipt ≤90 d prior to index date				
TMP-SMX	6	3	…	1
Fluoroquinolone	3	11	−1	5
Nitrofurantoin	3	3	1	3
3G-C	2	0	2	5
Other antibiotics	2	1	3	3
In the 12 mo prior to index date				
UTI event	1	5	3	3
Hospitalization	2	…	2	3
ED visit	1	…	2	2
Recurrence cUTI	…	4	2	1
Long-term care (nursing home or SNF) in the 12 mo prior to index date	…	6	4	2

Score	Predicted Probability of Nonsusceptibility Based on Score, %			
−1	…	…	10	…
0	25	9	11	7
1	27	10	12	8
2	30	11	13	9
3	32	12	14	10
4	35	13	16	11
5	37	14	17	12
6	40	16	19	13
7	42	17	21	14
8	45	19	23	15
9	48	20	25	17
10	50	22	27	19
11	53	24	29	20
12	56	26	31	22
13	59	29	34	24
14	61	31	36	26
15	64	33	39	28
16	66	36	41	31
17	69	38	44	33
18	71	41	47	35
19	73	44	49	38
20	75	46	52	41
21	77	49	55	43
22	79	52	58	46

Table 3. Continued

Score	Predicted Probability of Nonsusceptibility Based on Score, %			
23	81	55	60	49
24	83	57	63	51
25	…	60	65	54
26	…	63	68	57
27	…	65	70	60
28	…	68	72	62
29	…	70	75	65
30	…	72	77	67
31	…	74	79	70
32	…	76	80	72
33	…	78	82	74
34	…	80	84	76
35	…	82	85	78
36	…	83	…	80
37	…	85	…	82
38	…	86	…	83
39	…	…	…	85
40	…	…	…	86
41	…	…	…	87
42	…	…	…	88
43	…	…	…	90
44	…	…	…	91
45	…	…	…	91
46	…	…	…	92

Abbreviations: 3-GC, third-generation cephalosporin; cUTI, complicated urinary tract infection; ED, emergency department; FQ, fluoroquinolone; NIT, nitrofurantoin; NS, nonsusceptible; SNF, skilled nursing facility; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

were previously identified as risk factors for antibiotic resistance [46, 47, 51–57], especially in patients who recently received antibiotics [49].

While there are several ways of converting results of regression models into clinical prediction tools, we selected a risk score approach to account for all the potential combinations of variables present in each final model when estimating the predicted probabilities of each nonsusceptible phenotype. Risk scores in each cUTI outpatient can be calculated by tallying the patient's total "points" based on the number of model covariates present in that individual. The cumulative risk score for a patient corresponds to one's probability of having a cUTI that is nonsusceptible to TMP-SMX, fluoroquinolone, nitrofurantoin, or 3-GC. Currently, no threshold resistance values exist for cUTI to guide empiric antibiotic use. However, we highlight a ≥20% likelihood of nonsusceptibility, as this has been identified as the resistance threshold for empiric use of TMP-SMX for uncomplicated cystitis and pyelonephritis in women [37]. By using this proposed antibiotic resistance percentage as a provisional threshold to guide empiric antibiotic selection for outpatients with cUTIs, the risk of nonsusceptibility in the

TMP-SMX model exceeded 20% in the absence of any risk factors across both sets of models, suggesting that empiric use of TMP-SMX may not be advisable (Figure 1). In the models with a cumulative number of prior antibiotics, clinical risk scores of 10, 7, and 11 were associated with a ≥20% estimated probability of nonsusceptibility to fluoroquinolone, nitrofurantoin, and 3-GC, respectively (Figure 1*A*). Nearly identical clinical scores were associated with a ≥20% estimated probability of each antibiotic nonsusceptibility phenotype in the models that included prior receipt of individual antibiotics at model entry (Figure 1*B*). The findings across the 2 sets of models indicate that clinicians should use caution when considering fluoroquinolone, nitrofurantoin, or 3-GC empirically in patients who have several risk factors present in a given model at baseline. Although we propose a 20% nonsusceptibility threshold for guiding empiric therapy selection, other threshold values may be warranted, and further study is needed to define the most appropriate antibiotic resistance percentage for empiric antibiotic selection for outpatients with cUTIs [58]. This tool was simply designed as a straightforward way for clinicians to estimate an outpatient's risk of having a cUTI that is nonsusceptible to TMP-SMX, fluoroquinolone, nitrofurantoin, or 3-GC (Tables 2 and 3 and Figure 1). More important, the flexible application of this tool can support clinicians to make more informed empiric antibiotic selection decisions and minimize potential delays in the receipt of appropriate therapy, which has been shown to be one of the major drivers of adverse outcomes in adult outpatients with cUTIs [15, 17–22, 39–41].

Several things should be noted when interpreting the findings. We omitted risk factors that are not readily available at presentation, and we may have missed factors that are predictive of nonsusceptibility phenotypes. We did not consider prior colonization or prior infections with a resistant pathogen in the model, as we anticipated that these data would not be universally available to clinicians at the initial outpatient medical encounter. Prior UTIs and recurrent cUTI events were considered at model entry, and both improved the predictive performance of the models. Physical examination findings, physician notes, and urinalysis results were not available, and diagnoses of cUTIs were based on diagnostic and procedure codes, the presence of a positive urine culture result, and receipt of antibiotics in response to urine culture. Since there are no specific codes for a cUTI, a composite case definition was utilized [3, 59]. While it is possible that some patients with uncomplicated UTIs or asymptomatic bacteriuria were misclassified as having cUTIs, the codes used to identify adult outpatients with cUTIs have been validated and shown to have high positive predictive values [60–64]. Finally, all patients were required to receive antibiotic treatment for inclusion in the study, further indicating that patients likely had a cUTI.

Our clinical risk scores were limited to the presence of nonsusceptibility to TMP-SMX, fluoroquinolone, nitrofurantoin, or 3-GC. It is important to note that use of nitrofurantoin is limited to cUTIs that involve only the lower genitourinary tract and may not be an appropriate agent in all outpatients with cUTIs [5, 65]. Other oral antibiotics (ie, amoxicillin-clavulanate and fosfomycin) were not included in this study given their limited use relative to the agents assessed [3]. We opted to examine each nonsusceptibility phenotype vs the percentage of patients resistant to 0, 1, 2, 3, or ≥4 antibiotic classes. Like other studies [4, 6, 66, 67], cross-nonsusceptibility rates (eg, TMP-SMX–nonsusceptible cUTIs that were also nonsusceptible to fluoroquinolone, nitrofurantoin, or 3-GC) were commonplace (Supplementary Table 3), and a similar set of risk factors was identified for each nonsusceptibility phenotype. These findings limit the ability to generate clinically meaningful risk scores to estimate the probability of having a cUTI that was nonsusceptible to 1 specific antibiotic but susceptible to other agents. Although we did not develop models to predict the probability of having resistance to >1 antibiotic, the risk scores identified patient populations in which it may be preferred to use one agent relative to another based on the likelihood of having a cUTI that is nonsusceptible to one antibiotic vs another.

Other prediction methods (eg, neural networks, random forest, machine learning) may have improved the prediction modeling observed in this study [68–70]. However, the observed vs predicted plots in the training and validation data sets indicate that the clinical risk scores accurately described the data and reflected the risk of having a nonsusceptible cUTI. We did not calculate the C statistic or area under the receiver operating characteristic curves to evaluate model performance as part of this study. The C statistic is a measure of discrimination and is of most interest when the goal is classification into groups with or without the outcome, as in diagnostic testing [71]. Since the goal of the study was to estimate the probability that a patient has a cUTI with a nonsusceptible organism based on the number of model covariates present in that individual at clinical presentation, we relied on calibration (ie, a measure of how well predicted probabilities agree with actual observed risk) to assess the accuracy of the models [38]. Given the predictive performance of the models in the training and validation data sets, we believe that our clinical risk scores are of high clinical value as they include data elements that are typically available at the time of empiric antibiotic selection. However, it is possible that different geographic locations and populations may have different distributions of nonsusceptibility and that patterns of nonsusceptibility may change over time. As such, while the models performed extremely well in the validation data sets, an important next step will be to externally validate the risk scores in other geographic settings and other health care systems. Finally, future validation studies should assess not only the ability of the clinical prediction tools to alter initial antibiotic prescribing for adult outpatients with cUTIs but also the

patient outcomes associated with the use of these clinical prediction tools.

In conclusion, we developed parsimonious clinical risk scores to estimate adult outpatient risk of having a cUTI that is nonsusceptible to TMP-SMX, fluoroquinolone, nitrofurantoin, or 3-GC. Our risk scoring systems can help clinicians make more informed empiric antibiotic selection decisions that may minimize delays in the receipt of appropriate therapy and reduce adverse outcomes in adult outpatients with cUTIs [15, 17–22, 39–41]. Conversely, use of these clinical risk scores may help reduce overuse of broad-spectrum oral or intravenous antibiotics among adult outpatients with cUTIs by identifying patients who are likely to have a susceptible cUTI. As with all clinical tools of this nature, caution and appropriate clinical judgment should be exercised with application of the risk scores at other institutions prior to validation of the models.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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