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Correspondence: Marissa A. Valentine-King (Marissa.Valentine-King@bcm.edu).

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Study Need and Importance: Patients with recurrent cystitis have a greater risk of having a UTI caused by an antibiotic-resistant uropathogen, which creates a challenge for choosing the correct empiric therapy. Recurrent cystitis guidelines recommend relying on a local antibiogram or prior urine culture to guide empirical prescribing, yet little data exist to quantify the predictive value of a prior culture. We created a urinary-specific antibiogram and evaluated the utility of a prior urine culture for predicting subsequent antibiotic resistance and susceptibility among patients with uncomplicated, recurrent cystitis in primary care or urology clinics.

What We Found: We included 597 visits from 232 patients with recurrent cystitis, and half of visits lacked a urine culture. Our urinary *Escherichia coli* antibiogram (median isolate number: 100) revealed considerable antibiotic resistance to earlier generation cephalosporins (>52%), trimethoprim-sulfamethoxazole (SXT; 38%), and fluroquinolones (27%-28%), but preserved activity to nitrofurantoin (5.5% resistance). Prior cultures (within 2 years) had good predictive value for detecting future susceptibility to first-line agents nitrofurantoin (85% probability) and SXT (78% probability) and excellent predictive value (≥90% probability) for cefepime, ceftriaxone, cefuroxime, ciprofloxacin, levofloxacin, gentamicin, tobramycin, piperacillin-tazobactam, and imipenem.

Limitations: Our study included patients from 3 clinics in a single academic medical center. The study was retrospective and relied on electronic medical records. As we excluded patients with complicated UTI and had a low number of men in our study, our findings are not necessarily applicable to these populations.

Interpretation for Patient Care: Antibiotic resistance among *E coli* exceeded 20% to several antimicrobials. Providers should consider referring to a prior urine culture for guidance when treating cystitis, as susceptibility on the prior culture had good predictability of future susceptibility for SXT and nitrofurantoin, and excellent predictability for aminoglycosides, cefepime, ceftriaxone, cefuroxime, and fluoroquinolones.

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Predicting Antibiotic Susceptibility Among Patients With Recurrent Urinary Tract Infection Using a Prior Culture

Marissa A. Valentine-King,[1,2] Barbara W. Trautner,[2,3] Roger J. Zoorob,[1] Jason L. Salemi,[4] Kalpana Gupta,[5] and Larissa Grigoryan[1,2]

[1]Department of Family and Community Medicine, Baylor College of Medicine, Houston, Texas
[2]Center for Innovations in Quality, Effectiveness and Safety (IQuESt), Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas
[3]Section of Health Services Research, Department of Medicine, Baylor College of Medicine, Houston, Texas
[4]College of Public Health, University of South Florida, Tampa, Florida
[5]Boston Veterans Affairs Healthcare System and Boston University School of Medicine, Boston, Massachusetts

Purpose: Recurrent cystitis guidelines recommend relying on a local antibiogram or prior urine culture to guide empirical prescribing, yet little data exist to quantify the predictive value of a prior culture. We constructed a urinary antibiogram and evaluated test metrics (sensitivity, specificity, and Bayes' positive and negative predictive values) of a prior gram-negative organism on predicting subsequent resistance or susceptibility among patients with uncomplicated, recurrent cystitis.

Materials and Methods: We performed a retrospective database study of adults with recurrent, uncomplicated cystitis (cystitis occurring 2 times in 6 months or 3 times in 12 months) from urology or primary care clinics between November 1, 2016, and December 31, 2018. We excluded pregnant females, patients with complicated cystitis, or pyelonephritis. Test metrics were calculated between sequential, paired cultures using standard formulas.

Results: We included 597 visits from 232 unique patients wherein 310 (51.2%) visits had a urine culture and 165 had gram-negative uropathogens isolated. Patients with gram-negative uropathogens were mostly females (97%), with a median age of 58.5 years. Our antibiogram found 38.0%, 27.9%, and 5.5% of *Escherichia coli* isolates had resistance to trimethoprim-sulfamethoxazole, ciprofloxacin, and nitrofurantoin, respectively. Prior cultures (within 2 years) had good predictive value for detecting future susceptibility to first-line agents nitrofurantoin (0.85) and trimethoprim-sulfamethoxazole (0.78) and excellent predictive values ($\geq$0.90) for cefepime, ceftriaxone, cefuroxime, ciprofloxacin, levofloxacin, gentamicin, tobramycin, piperacillin-tazobactam, and imipenem.

Conclusions: Considerable antibiotic resistance was detected among *E coli* isolates in patients with recurrent, uncomplicated cystitis. Using a prior culture as a guide can enhance the probability of selecting an effective empirical agent.

Key Words: urinary tract infection, recurrence, antibiogram, outpatient, urology

UTIs accounted for 404.6 million cases globally in 2019.[1] In the United States, UTIs are one of the most common infections treated in ambulatory settings, with a total of 3.6 million and 2.4 million cases seen in either office or emergency department (ED) settings as of 2018.[2,3] Furthermore, UTIs served as the second highest indication for antibiotic prescribing in ambulatory care between 2010 and 2011.[4,5] A substantial number of patients, particularly women, develop recurrent UTI, defined as 2

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Data Availability: The data sets generated during and/or analyzed during the current study are not publicly available due to patient confidentiality, but a de-identified data set is available from the corresponding author on reasonable request.

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Corresponding Author: Marissa A. Valentine-King, PhD, MPH, RN, Department of Family and Community Medicine, Baylor College of Medicine, 3701 Kirby Dr, Suite 600, Houston, TX 77098 (Marissa.Valentine-King@bcm.edu).

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culture-proven episodes of bacterial cystitis with symptoms within 6 months, or 3 within 12 months.[6-10] Prospective studies in outpatient settings found 24% to 44% of women and 14% of older men develop recurrent UTI.[6-9] Recurrent UTIs exert negative impacts on several aspects of physical, mental, and sexual health, with a subset of patients experiencing extreme symptoms.[11-14]

As recurrent UTIs require repeated courses of antibiotics coupled with prophylactic treatment regimens, this increased exposure places patients at higher risk for developing antimicrobial resistance and treatment failure.[15] Indeed, a Brazilian study conducted among patients seen in the ED or urological office found those with recurrent cystitis or pyelonephritis had significantly higher resistance to 13 antibiotics compared to those with sporadic UTI.[16] A multinational surveillance study in Europe and Brazil also found generally higher levels of antimicrobial resistance among patients with recurrent UTI compared to individuals with sporadic UTI.[17] However, antibiotic resistance among patients with recurrent UTI in the US is not well described.

This risk for resistance creates a challenge when choosing correct empiric therapy for recurrent episodes. The AUA/CUA/SUFU (American Urological Association/Canadian Urological Association/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction) published treatment and management guidelines for uncomplicated, recurrent cystitis in women in 2019.[10] These guidelines recommend relying on a local antibiogram and a prior culture to guide empirical prescribing. However, no data were included regarding the predictive utility of a prior culture on resistance or susceptibility. Among the few international studies examining the predictive utility of a prior culture, most have been limited to inpatients[18,19] or focused on multidrug-resistant UTIs,[20] and the single study conducted among outpatients did not require patients to meet recurrent UTI criteria for inclusion.[21]

Thus, we created a urinary-specific antibiogram and evaluated the utility of a prior urine culture for predicting subsequent antibiotic resistance and susceptibility among patients with uncomplicated, recurrent cystitis in primary care or urology clinics.

MATERIALS AND METHODS

Study Design

We retrospectively extracted data from patients meeting recurrent cystitis criteria from our Epic Clarity database who sought care between November 1, 2016, and December 31, 2018, at family medicine, internal medicine, or urology offices within a large academic medical center in Houston, Texas. Briefly, we included patients who were ≥18 years old that had an International Classification of Diseases Tenth Revision (ICD-10) diagnosis for acute (N30.0) or unspecified cystitis (N30.9), or a UTI (N39.0) from an office, telephone, or refill encounter that occurred twice in 6 months or 3 times in 12 months, at least 6 days apart. We excluded patients who had ICD-10 codes at the qualifying visit or in the prior 12 months that indicated evidence of complicated UTI, defined as any abnormality that impacts the structural or functional ability of the genitourinary tract, chronic kidney disease, signs or symptoms of pyelonephritis (at the qualifying visit only), pregnancy, neoplasms of the bladder or prostate, interstitial cystitis, or being immune compromised.[22] These exclusion criteria were applied via an electronic algorithm to exclude predetermined ICD-10 codes indicating complicated UTI and via 2 manual chart reviews conducted by an internal medicine physician to identify provider level notes revealing evidence of complicated cystitis or pyelonephritis.[22] For patients meeting inclusion criteria for this study, we extracted demographic data, visit-associated ICD-10 codes, and urine culture susceptibility data within 3 days of the qualifying visit. The study was approved by the Baylor College of Medicine Institutional Review Board (protocol number-H-46627) and a waiver of consent was granted for this database study.

Antibiogram Construction

We only extracted susceptibility data when bacterial species had ≥30 isolates.[23] Although traditional antibiograms recommend using antibiotic susceptibility data for the first isolate per patient, per year, we used all isolates for each patient to attain an accurate representation of antibiotic susceptibilities for patients with recurrent cystitis presenting at any 1 time. For the purposes of our antibiogram, isolates with intermediate susceptibility were considered resistant. Urinary cultures were obtained, processed, and analyzed in corporate laboratories that hold Clinical Laboratory Improvement Amendments certification via the College of American Pathologists. The College of American Pathologists ensures clinical laboratories comply and incorporate the Clinical Laboratory Standards Institute guidelines for breakpoint and antimicrobial susceptibility testing.[24] There were no major changes in Clinical Laboratory Standards Institute breakpoints for Enterobacteriaceae during the study period.[25]

Test Metrics

As we aimed to determine the predictiveness of a prior culture on subsequent resistance or susceptibility, we considered the prior culture from a single patient as the "test" and the current culture from that same patient as the "gold standard" (Figure 1, A). We evaluated concordance between paired gram-negative isolates between a single patient. The maximum time between cultures was 2 years. If a patient had a second gram-negative organism from the same visit with a different susceptibility profile than the primary gram-negative organism, distinct comparisons were made between each primary and secondary organism and the prior culture or subsequent paired culture. We calculated sensitivity, specificity, Bayes' positive (PPV) and negative predictive values (NPV) using standard formulas (Figure 1, B).[26] We used Bayes' formula for PPV and NPV, which incorporates the pretest probability or prevalence of resistance in the population, as traditional PPVs and NPVs reflect the resistance level

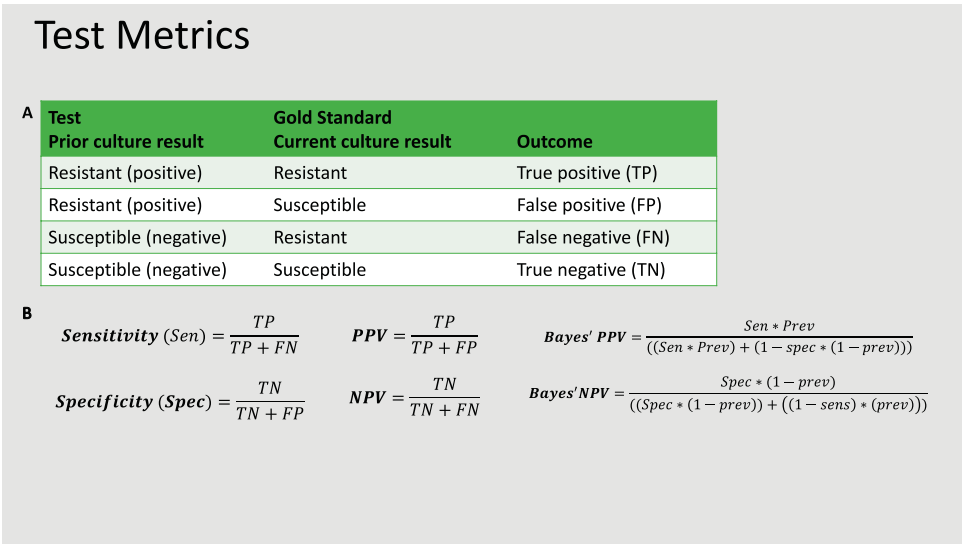

Figure 1. Test metric derivation (A) and formulas (B) used to calculate sensitivity (Sen), specificity (Spec), traditional positive predictive value (PPV), negative predictive value (NPV), and Bayes' PPV and NPV. Prev indicates prevalence.

in a sample, which would only be our subsample that had paired cultures. As the PPV varies directly with disease prevalence (resistance) and the NPV has an inverse relationship with prevalence, we used the antibiotic resistance prevalence from our entire sample population that had a gram-negative organism (vs only those with paired cultures) to more accurately represent how the test performed given the antibiotic resistance in our entire sample.[26]

RESULTS

After applying exclusion criteria, our study population consisted of 232 patients accounting for 597 recurrent cystitis visits (Figure 2). As previously reported, almost half of visits (N = 287) lacked a urine culture.[22] Among the remaining 310 visits with a culture, 165 (27.6%) had at least 1 gram-negative uropathogen isolated, 73 (12.2%) had no or low growth ($<10^4$ CFU/mL), 48 (8.0%) were contaminated (containing either coagulase-negative *Staphylococcus*, nonspeciated diphtheroids, or "mixed urogenital flora"), and 24 (4.0%) contained only gram-positive organisms. Of the 165 visits containing a gram-negative organism, the median (quartiles) number of paired gram-negative organisms with antibiotic susceptibility across the 15 antimicrobials evaluated was 42 (31-56). Antibiotic susceptibility panels varied by organism and laboratory, which accounts for the differing number of paired cultures by antibiotic. Among the 189 recurrent cystitis visits with a uropathogen-positive culture, 196 uropathogens were isolated (Figure 3). The predominant isolate was *Escherichia coli* (N = 130, 66.3%), followed by *Klebsiella pneumoniae* (N = 19, 10.0%), while *Proteus mirabilis* and *Enterococcus* spp. accounted for 12 isolates (6.0%) each.

Table 1 displays the patient demographics, health, and visit characteristics among the 116 patients who accounted for 165 visits with a gram-negative organism and of the overall population that had recurrent, uncomplicated cystitis (N = 232 patients with 597 visits). Overall, the patients with a gram-negative organism isolated were mostly female (97%), middle-aged (median age 58.5 years), and had few comorbidities (median Elixhauser score 0). These patients had a median (quartiles) of 3 (2-3) visits throughout the study period with a median (quartiles) of 81 (25-149) days separating visits. The majority of the 165 visits (81.2%) transpired in an office setting and approximately 60% took place in primary care, while the remainder occurred at urology practices. Most patient and visit characteristics of patients with a gram-negative organism did not differ substantially from the overall sample of patients with uncomplicated, recurrent UTI criteria. However, the overall uncomplicated recurrent cystitis population had a shorter number of days between visits (median 56 days vs 81 days), fewer visits occurred in an office setting (66.5% vs 81.2%), and there was a more equal balance between practice type (52.9% primary care vs 47.1% urology) than patients with a gram-negative organism (61.2% primary care vs 38.8% urology).

Antibiogram Results

Our *E coli* antibiogram showed the highest levels of resistance were to beta-lactams without beta-lactamase inhibitors (ampicillin [57.0%, 95% CI: 48.0%-65.7%] and piperacillin [47.2%, 95% CI: 33.3%-61.4%]) and to first-generation cephalosporins, cefazolin (57.4%, 95% CI: 44.1%-70.0%) and cephalothin (52.0%, 95% CI: 37.4%-66.3%; Figure 4). Second- and

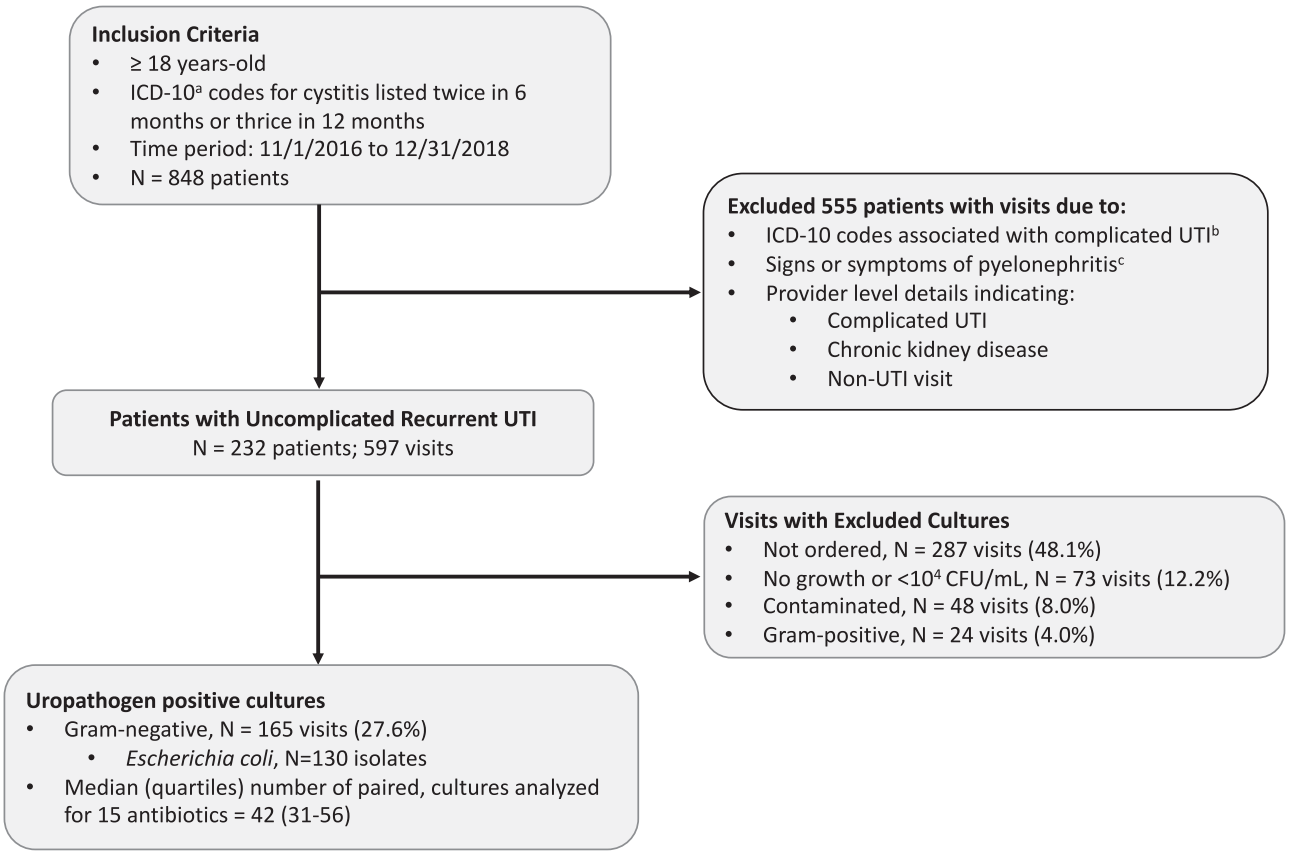

Figure 2. Flow chart depicting patient and visit inclusion and exclusion criteria, overview of urine culture results, and breakdown of urine cultures eligible for antibiogram and paired culture analysis among antibiotics evaluated. [a]International Classification of Diseases (ICD-10) codes N30.0, N30.9, and N39.0. [b]ICD-10 codes T86, Q53, Q54, Q64.0, N13.7, T83, N31, N32, Z99.2, Z93.3, N30.10, N30.11, N76.0, D89.9, Z33.1, Z33.3 C61, C67, N13, N18, N20, N35, N40, N41, and R33. [c]Includes costovertebral angle tenderness, flank pain, fever, nausea and vomiting. CFU indicates colony forming units.

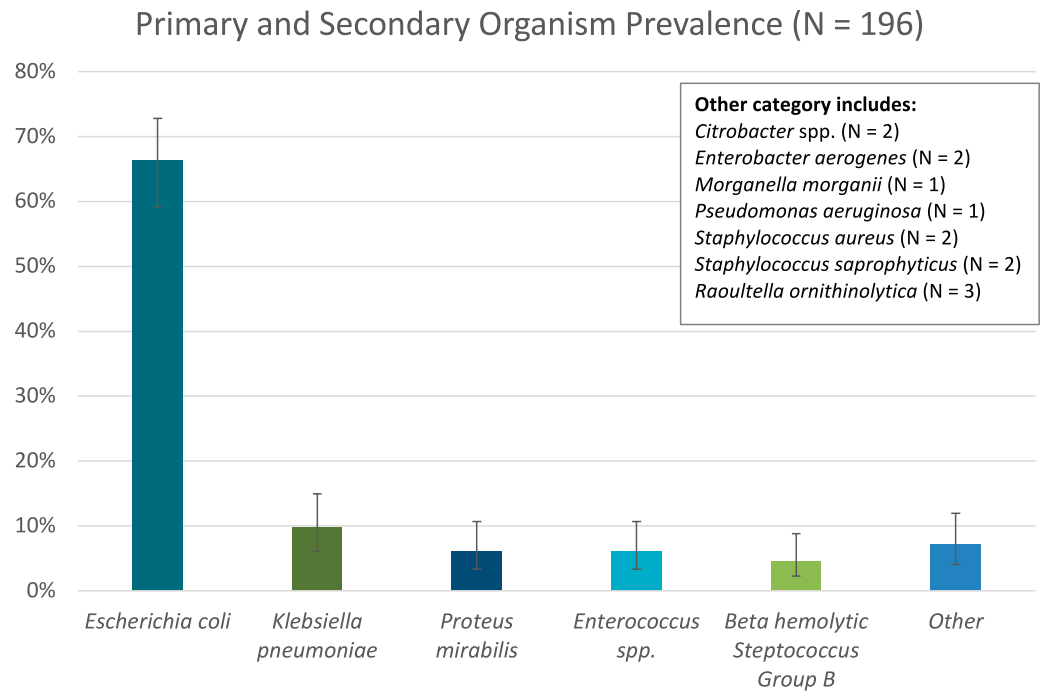

Figure 3. Urinary organism prevalence among 196 organisms from 189 recurrent UTI visits with an uncontaminated urine culture. Error bars represent 95% confidence intervals.

Table 1. *Patient and Visit Characteristics Among Patient Encounters Yielding a Gram-Negative Uropathogen and Among the Overall Population With Recurrent, Uncomplicated UTI*

	Patients with a GN organism		All patients with uncomplicated, recurrent UTI	
Patient characteristics	(N = 116)		(N = 232)	
Age, median (quartiles), y	58.5	(40-69)	58	(41-68)
Elixhauser score, median (quartiles)	0	(0-0)	0	(0-0)
Sex and pregnancy status, No. (%)				
Male	4	(3.4)	18	(7.8)
Female	112	(96.6)	214	(92.2)
Race and ethnicity, No. (%)				
White	73	(62.9)	146	(62.9)
Black or African American	15	(12.9)	30	(12.9)
Asian/Pacific Islander	9	(7.8)	10	(4.3)
Hispanic	8	(6.9)	19	(8.2)
Other/unknown	11	(9.5)	27[a]	(11.6)
Visits per patient, median (quartiles)	3	(2-3)	3	(2-3)
Visit characteristics	(N = 165)		(N = 597)	
Practice type, No. (%)				
Family medicine	95	(57.6)	275	(46.1)
Internal medicine	6	(3.6)	41	(6.9)
Urology	64	(38.8)	281	(47.1)
Encounter type, No. (%)				
Office	134	(81.2)	397	(66.5)
Telephone or refill	31	(18.8)	199	(33.3)
Interval between visits, median (quartiles), d	81	(25.3-149.3)	56	(21.0-119.8)

Abbreviations: GN, gram-negative.
[a] Other includes non-Hispanic American Indian (N = 2).

third-generation cephalosporins (cefuroxime and ceftriaxone) had decreased resistance at 20.4% (95% CI: 13.4%-29.0%) and 18.6% (95% CI: 12.3%-26.4%), respectively, and cefepime, the sole fourth-generation cephalosporin evaluated, had the lowest resistance among cephalosporins (7.9%, 95% CI: 3.2%-15.5%). Concerning levels of resistance were present among *E coli* to trimethoprim-sulfamethoxazole (SXT; 38.0%, 95% CI: 29.6%-46.9%), ciprofloxacin (27.9%, 95% CI: 20.4%-36.5%), and levofloxacin (27.1%, 95% CI: 19.7%-35.7%). However, low resistance was detected to nitrofurantoin at 5.5% (95% CI: 2.2%-10.9%), which is a first-line agent for uncomplicated cystitis.[27] *E coli* resistance to gentamicin and tobramycin hovered around 15%. No resistance was detected to ertapenem (95% CI: 0%-4.7%) or imipenem (95% CI: 0%-3.9%).

Prior Culture Predictability Among Enterobacterales

We reported test metric data for 15 UTI-relevant antimicrobial agents (Table 2). Among the 15 antimicrobial agents, there was a median of 98 days, or approximately 3.3 months, between paired cultures. We did not report test metric data to cephalothin or piperacillin as these agents only had 18 paired cultures. We also did not report test metric data for ertapenem, as zero culture pairs met classification criteria for being "true positives," "false positives," or "false negatives."

NPVs and Specificity

Our data revealed that relying on a prior susceptible culture had very good predictability of future

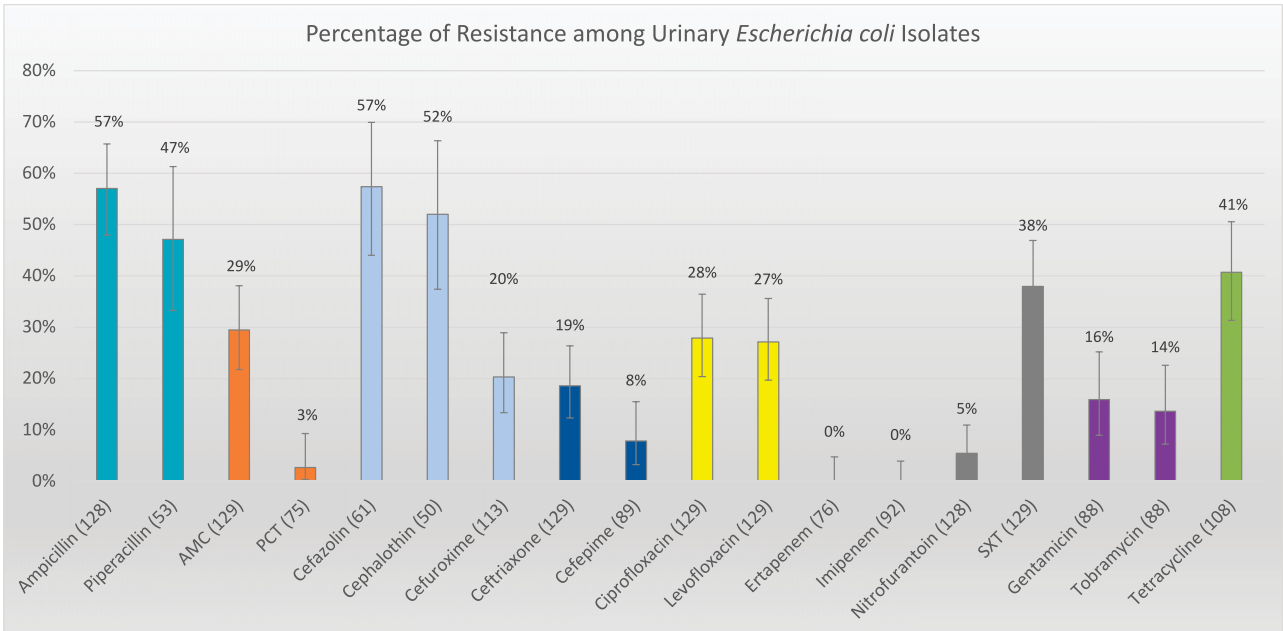

Figure 4. *Escherichia coli* antibiogram. Error bars represent 95% confidence intervals. Numbers in parentheses next to each antibiotic represent the number of isolates evaluated. Antibiotics are grouped and their bars are colored according to antibiotic category: beta-lactams without beta-lactamase inhibitors in teal, beta-lactams with beta-lactamase inhibitors in orange, early-generation cephalosporins in light blue, extended-spectrum cephalosporins in dark blue, fluoroquinolones in yellow, first-line agents for uncomplicated cystitis in gray, aminoglycosides in purple, and tetracyclines in green. AMC indicates amoxicillin-clavulanic acid; PCT, piperacillin-tazobactam; SXT, trimethoprim-sulfamethoxazole.

Table 2. *Test Metric Results From Comparing Paired, Gram-Negative Organisms by Antibiotic*

Antibiotic (No. of paired isolates)	Resistance, %[a]	Median d (quartiles) between cultures	Sensitivity (95% CI)[b]	Bayes' PPV (95% CI)[c]	Specificity (95% CI)[d]	Bayes' NPV (95% CI)[e]
AMC (n = 58)	25.4	99 (30-183)	0.53 (0.28-0.77)	0.48 (0.30-0.67)	0.80 (0.65-0.91)	0.83 (0.75-0.89)
Ampicillin (n = 56)	61.4	99 (31-178)	0.85 (0.71-0.94)	0.84 (0.69-0.92)	0.73 (0.45-0.92)	0.76 (0.59-0.88)
Cefazolin (n = 31)	48.4	100 (29-214)	0.88 (0.62-0.98)	0.67 (0.52-0.80)	0.60 (0.32-0.84)	0.84 (0.57-0.95)
Cefepime (n = 33)	6.9	91 (31-150)	0.33 (0.04-0.78)	0.25 (0.05-0.66)	0.93 (0.76-0.99)	0.95 (0.91-0.97)
Ceftriaxone (n = 55)	16.4	98 (26-177)	0.92 (0.64-1.00)	0.72 (0.46-0.88)	0.93 (0.81-0.99)	0.98 (0.90-1.00)
Cefuroxime (n = 42)	18.2	110 (33-254)	0.71 (0.29-0.96)	0.58 (0.33-0.80)	0.89 (0.73-0.97)	0.93 (0.81-0.98)
Ciprofloxacin (n = 55)	24.9	91 (26-172)	0.93 (0.66-1.00)	0.76 (0.55-0.89)	0.90 (0.77-0.97)	0.97 (0.85-1.00)
Gentamicin (n = 34)	13.3	90 (33-145)	0.78 (0.40-0.97)	1.00 (0.59-1.00)	1.00 (0.86-1.00)	0.97 (0.90-0.99)
Levofloxacin (n = 57)	24.4	98 (22-175)	0.87 (0.60-0.98)	0.70 (0.50-0.85)	0.88 (0.74-0.96)	0.95 (0.85-0.99)
Nitrofurantoin (n = 57)	18.5	98 (29-175)	0.36 (0.11-0.69)	0.32 (0.15-0.56)	0.83 (0.69-0.92)	0.85 (0.78-0.90)
Tetracycline (n = 41)	40.5	112 (37-258)	0.71 (0.42-0.92)	0.69 (0.50-0.83)	0.78 (0.58-0.91)	0.80 (0.63-0.90)
SXT (n = 54)	32.2	95 (30-172)	0.55 (0.32-0.77)	0.53 (0.35-0.70)	0.76 (0.59-0.89)	0.78 (0.68-0.86)
Imipenem (n = 31)	0.9	79 (34-115)	[f]	[f]	0.97 (0.83-1.00)	0.99 (0.99-0.99)
PCT (n = 29)	4.8	88 (22-175)	[f]	[f]	0.89 (0.71-0.98)	0.95 (0.94-0.95)
Tobramycin (n = 32)	10.5	84 (22-175)	0.75 (0.35-0.97)	1.00 (0.54-1.00)	1.00 (0.86-1.00)	0.97 (0.91-0.99)
Median No. (quartiles) of paired isolates (n = 42, 31-56)	21.7	98 (30-175)[g]	0.75 (0.40-0.96)[g]	0.69 (0.50-0.83)[g]	0.89 (0.73-0.97)[g]	0.95 (0.85-0.97)[g]

Abbreviations: AMC, amoxicillin-clavulanic acid; NPV, negative predictive value; PCT, piperacillin-tazobactam; PPV, positive predictive value; SXT, sulfamethoxazole-trimethoprim.
[a] Resistance levels among all gram-negative organisms.
[b] Sensitivity: ability of a prior culture to detect all those with future resistance (see formulas in Figure 1).
[c] PPV: probability of a prior resistant culture to accurately predict future resistance.
[d] Specificity: ability of a prior culture to detect all those with future susceptibility.
[e] NPV: probability of a prior susceptible culture to accurately predict future susceptibility.
[f] Calculation results not presented as zeros were present in one part of the sensitivity or PPV formula (eg, imipenem and PCT had zero true positives).
[g] Calculated the median of the median number of days between cultures for each antibiotic and the median of the first and third quartiles for each antibiotic.

susceptibility (Bayes' NPV ≥80%) for 13 antimicrobial agents spanning 8 antimicrobial categories (penicillins with beta-lactamase inhibitors, second-generation and extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, tetracyclines, and nitrofurans; Table 2). The median value of Bayes' NPV for all antimicrobial agents was 0.95, with a median lower/upper 95% CI ranging from 0.85 to 0.97. Bayes' NPV was especially high (≥0.90), with a 95% CI not lower than 0.81 to the following agents: cefepime (0.95, 95% CI: 0.91-0.97), ceftriaxone (0.98, 95% CI: 0.90-1.00), cefuroxime (0.93, 95% CI: 0.81-0.98), ciprofloxacin (0.97, 95% CI: 0.85-1.00), levofloxacin (0.95, 95% CI: 0.85-0.99), gentamicin (0.97, 95% CI: 0.90-0.99), tobramycin (0.97, 95% CI: 0.91-0.99), piperacillin-tazobactam (0.95, 95% CI: 0.94-0.95), and imipenem (0.99, 95% CI: 0.99-0.99). The specificity, or the ability of a prior susceptible culture to detect all susceptible isolates, was similarly high, with a median specificity of 0.89 across all 15 antimicrobial agents tested, and a median lower/upper 95% CI of 0.73 and 0.97, respectively.

PPVs and Sensitivity

Bayes' median PPV and sensitivity were 0.69 and 0.75 across the 13 antimicrobials eligible for evaluation, respectively (Table 2). The probability of a prior resistant culture predicting future resistance (Bayes' PPV) was highest for the following agents: ampicillin (0.84, 95% CI: 0.69-0.92), ciprofloxacin (0.76, 95% CI: 0.55-0.89), gentamicin (1.00, 95% CI: 0.59-1.00), and tobramycin (1.00, 95% CI: 0.54-1.00). Meanwhile, relying on a prior resistant culture identified future resistance among urine cultures that had future resistance (sensitivity) in ≥75% of cases for 7 antimicrobials, which included ampicillin, cefazolin, ceftriaxone, ciprofloxacin, gentamicin, levofloxacin, and tobramycin.

DISCUSSION

Our antibiogram from patients with uncomplicated, recurrent cystitis displayed concerning levels of antibiotic resistance to first-line agents for uncomplicated, recurrent cystitis (SXT) and pyelonephritis (ciprofloxacin) at 38% and 28%, respectively,[10,27] and to other UTI-relevant drug classes including extended-spectrum cephalosporins (range: 8%-19%) and aminoglycosides (range: 14%-16%). However, we detected preserved activity to nitrofurantoin (5% resistance) and piperacillin-tazobactam (3%), and no resistance to carbapenems. Outside of nitrofurantoin and these last-resort antimicrobials, these higher levels of resistance to common UTI agents indicate empirical prescribing could often result in organism-drug discordance.

Little data exist describing antibiotic resistance among patients with uncomplicated, recurrent cystitis. A Brazilian study that extracted susceptibility data from urine cultures among patients with uncomplicated, recurrent cystitis seen in the urological ED or office between 2007 and 2012 found similar resistance among *E coli* isolates with a few exceptions.[16] There were similarities (resistance within 5%) to fluoroquinolones, nitrofurantoin, cefepime, and piperacillin-tazobactam. Higher levels of resistance were found in our study to amoxicillin-clavulanic acid (29% vs 9%), cephalothin (52% vs

28%), and gentamicin (16% vs 8%), while lower levels of resistance were detected in our study to ampicillin (57% vs 65%) and SXT (38% vs 47%). Thus, regional variability and the study period may influence and account for differences in antibiogram patterns among patients with recurrent cystitis, as they do among patients with nonrecurrent cystitis.[28]

With resistance in *E coli* exceeding 20% to several important antimicrobials, referring to a prior culture can help optimize empirical prescribing. For example, relying on a prior susceptible culture predicted future susceptibility in ≥90% of scenarios for 9 antimicrobials, including all second-generation or older cephalosporins, fluoroquinolones, aminoglycosides, piperacillin-tazobactam, and imipenem. In contrast, our study did not find previous resistance was as good of a predictor of future resistance, as only cultures with prior resistance to ampicillin, ceftriaxone, aminoglycosides, and fluoroquinolones studied were able to predict future resistance with a probability ≥0.70. From a resistance standpoint, however, this may be a positive indication, as it suggests resistance may have been dissipating in this population during the study period (eg, more false positives [prior resistant cultures with future susceptibility]). A prior culture had better sensitivity, however, as 8 antimicrobials had a sensitivity ≥0.70, indicating fewer false negatives, or a lower likelihood of a sensitive culture turning resistant. This finding may suggest rising resistance is not as common in this population as expected. Taken together, relying on a prior susceptible culture may help predict future susceptibility in over 80% of scenarios (excluding ampicillin and SXT), and resistance may not emerge or may dissipate in this population more quickly than expected.

An outpatient study with a similar design extracted susceptibility data for 5 antibiotics between paired positive urine cultures ($\geq 10^5$ CFU/mL) originating from inpatients and outpatients between 2004 to 2008 in Ireland.[21] Vellinga and colleagues found higher NPVs to nitrofurantoin (0.98, 0.98) for reinfections occurring in the early (3-month) and late (9-12−month) periods compared to our NPV (0.85) and a higher NPV for SXT for the early reinfection period of 0.91 vs our overall NPV of 0.78.[21] We had comparable NPVs (within 5%) for amoxicillin-clavulanic acid and ciprofloxacin, and a similar NPV for SXT when comparing to their late reinfection period.[21]

Limitations

In terms of extrapolating test metric data from a prior culture to gauge future susceptibility or resistance, our study may have generalizability to females with uncomplicated, recurrent cystitis caused by a gram-negative organism, with a lower burden of comorbidities and similar antibiotic resistance levels seen at family medicine, internal medicine, or urology clinics. Importantly, clinicians should note that as PPV and NPV varies based on the prevalence of resistance, results may only generalize to populations with similar levels of antibiotic resistance, and our findings should be confirmed in future studies and evaluated in other populations such as patients with complicated UTI, patients with a gram-positive organism, in male patients, and residents of nursing homes. Our study also is limited as it was retrospective and used data from electronic medical records, which could result in selection bias or incomplete documentation. For example, as only half of patients had a urine culture ordered during the study period, this may not fully capture the antibiogram of all patients with recurrent UTI in these clinics. However, in a prior analysis we did not find that prior resistance was associated with urine culture ordering in this population, so we do not believe this would bias our results towards higher resistance.[22] Incomplete documentation of a patient's health history could potentially allow patients meeting exclusion criteria (eg, complicated UTI) to be included in our study. We minimized this bias by not only applying an electronic algorithm to exclude predetermined ICD-10 codes for complicated UTI, but also manually searching clinician documentation for each encounter to find any evidence of complicated UTI. Our study is also somewhat limited in the smaller numbers of paired cultures we were able to extract out of the 597 initial visits, as only half of clinicians ordered a urine culture, despite it being a recommended practice endorsed by the AUA/CUA/SUFU recurrent UTI guidelines.[10] Regardless, our 95% CIs for NPVs did not fall below 0.80 for data stemming from 9 antimicrobials.

CONCLUSIONS

Our retrospective study of patients with uncomplicated, recurrent cystitis revealed considerable antibiotic resistance to earlier generation cephalosporins, SXT, and fluroquinolones but preserved activity to nitrofurantoin. These findings underscore the need to order urine cultures in patients with recurrent UTI. Further, using results from a prior culture can help optimize empirical prescribing for this patient population for several UTI-relevant agents, although prior cultures were better at predicting susceptibility than resistance. Future directions could include a streamlined approach for extracting this information, validating this relationship in another recurrent cystitis population, and measuring its impact on drug-organism concordance and health outcomes.

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