

Predictive Utility of Prior Positive Urine Cultures

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Background. A patient's prior urine cultures are often considered when choosing empiric antibiotic therapy for a suspected urinary tract infection. We sought to evaluate how well previous urine cultures predict the identity and susceptibility of organisms in a patient's subsequent urine cultures.

Methods. We conducted a multinational, multicenter, retrospective cohort study, including 22 019 pairs of positive urine cultures from 4351 patients across 2 healthcare systems in Toronto, Ontario, and Chicago, Illinois. We examined the probability of the same organism being identified from the same patient's positive urine culture as a function of time elapsed from the previous positive urine specimen; in cases where the same organism was identified we also examined the likelihood of the organism exhibiting the same or better antimicrobial susceptibility profile.

Results. At 4–8 weeks between cultures, the correspondence in isolate identity was 57% (95% confidence interval [CI], 55%–59%), and at >32 weeks it was 49% (95% CI, 48%–50%), still greater than expected by chance ($P < .001$). The susceptibility profile was the same or better in 83% (95% CI, 81%–85%) of isolate pairs at 4–8 weeks, and 75% (95% CI, 73%–77%) at >32 weeks, still greater than expected by chance ($P < .001$). Despite high local rates of ciprofloxacin resistance in urine isolates across all patients (40%; 95% CI, 39.5%–40.5%), ciprofloxacin resistance was <20% among patients with a prior ciprofloxacin sensitive organism and no subsequent fluoroquinolone exposure.

Conclusions. A patient's prior urine culture results are useful in predicting the identity and susceptibility of a current positive urine culture. In areas of high fluoroquinolone resistance, ciprofloxacin can be used empirically when prior urine culture results indicate a ciprofloxacin-susceptible organism and there has been no history of intervening fluoroquinolone use.

Keywords. antimicrobial resistance; nosocomial infection; stewardship.

Urinary tract infections (UTIs) are among the most common bacterial infections. They affect nearly 1 in 3 women and are estimated to account for ≥ 7 million office visits, 1 million emergency room visits, and >100 000 hospitalizations annually in the United States [1]. In 2011, joint guidelines for the treatment of UTIs were published with support from infectious diseases and microbiology societies from the United States, Europe, and Canada [2], which recommended foregoing trimethoprim-sulfamethoxazole as empiric treatment for lower UTIs in many regions of

the world, given that trimethoprim-sulfamethoxazole resistance already exceeded the accepted threshold of 20% [3–5]. However, another common class of antibiotic frequently used for UTIs, the fluoroquinolones, now face resistance rates approaching or exceeding this level in many jurisdictions [4, 5]. Because of this mounting antimicrobial resistance, appropriate and informed selection of antimicrobial therapy for UTIs is becoming ever more challenging.

Appropriate and timely antibiotic coverage can affect morbidity, mortality, and healthcare expenditures [6–8]. Decisions on empiric therapy should be made with the intent of covering expected organisms and resistance patterns based on the clinical scenario, local resistance patterns, and factors predisposing to the acquisition of antibiotic resistance [9–13]. Antibiograms based on aggregate local susceptibility data are frequently used to guide empiric treatment options; however, these are overgeneralizations and do not incorporate potentially valuable information from the patient's personal

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microbiologic history [14]. Preexisting colonization is a well-documented phenomenon for many hospital- and community-acquired infections [9, 15], including UTIs, and provides a motivation to consider previous cultures in treatment decisions.

Despite the seemingly common practice of reviewing results of a patient's prior culture results before prescribing empiric antibiotic therapy, the actual utility of this practice has not been studied. There is evidence suggesting that prior resistance to certain antibiotics predicts subsequent resistance [13], but the overall information gained from review of prior clinical isolate results, as a function of time between isolates, is ill defined. The purpose of this study was to evaluate the usefulness of a patient's prior urine cultures in predicting the identity and susceptibility of subsequent urine culture results.

MATERIALS AND METHODS

Study Design, Setting, and Patients

We conducted a retrospective cohort study of all adult patients receiving care at Sunnybrook Health Sciences Centre (SHSC) and NorthShore University HealthSystem (NUH) between May 2010 and May 2012 with ≥ 2 positive urine cultures. Both outpatient and inpatient specimens were considered. Patients aged ≤ 16 years were excluded. Serving approximately 31 000 inpatients annually, SHSC is one of the largest medical centers in Canada, with 677 beds for acute care beds, 82 for intensive care, and 535 for long-term care. Care is delivered across multiple sites, including the main Sunnybrook acute care campus, the Veterans long-term care center, and the Holland Orthopedic & Arthritic Centre. Located in suburban Chicago, Illinois, the NUH comprises 4 hospitals and >100 outpatient clinics and serves $>300\,000$ patients annually. The SHSC and NUH ethics boards approved this study.

Data Sources

Data were obtained from the Stewardship Program Integrated Resource Information Technology (SPIRIT) database at SHSC. The database, as described elsewhere [16, 17], is automatically populated by health level 7 messages from microbiology, pharmacy, and electronic patient care databases for all admitted and previously admitted patients. The database resides on a secure server and includes anonymized data on pharmacologic treatment, clinical isolates, demographics, and other clinical, administrative, and laboratory variables. Data from NUH were acquired from NorthShore's Enterprise Data Warehouse, a large data repository that gathers information daily from the electronic health record for all patient encounters.

Urine Specimen Collection, Processing, and Reporting

Culture media for urine specimens as well as biochemical testing algorithms were performed in accordance with Clinical and Laboratory Standards Institute guidelines [18]. Routine organism

identification and susceptibility testing at SHSC and NUH were performed using Vitek 2 cards (bioMérieux). Common contaminants were excluded, including nonsaprophytic coagulase-negative staphylococci. In comparisons of susceptibility, organisms without either susceptibility test results or a predictable antibiotic susceptibility profile were also excluded. Most notably, susceptibility testing is not routinely performed for *Enterococcus* spp. isolated from urine specimens at SHSC, so this organism was included in analyses of organism identity correspondence but was excluded from analyses of antimicrobial susceptibility correspondence. Some organism susceptibilities were not routinely reported, but predictable sensitivities to specific antimicrobials (eg, penicillin susceptibility for β -hemolytic streptococci) were used when possible. Polymicrobial isolates or isolates containing fungi were excluded.

Covariates

Variables of interest collected for this study included: patient demographics (age and sex), hospital variables (city/ward/service, outpatient/inpatient status), culture variables (date and time of clinical specimen collection, identities and susceptibilities of isolates, a negative urine culture collected between the paired positive cultures), and treatment variables (antibiotic use between collection of paired positive cultures).

Statistical Analysis

Univariate Analysis

All positive urine cultures with a corresponding subsequent positive urine culture collected from the same patient >1 day from the initial culture were identified. The percentage correspondence of the paired cultures (proportion of corresponding isolates with the same organism identity or antibiotic susceptibility) was plotted as a function of time between specimens. Substratification based on city, receipt of intervening antimicrobial therapy, and organism type was performed. The main analysis included all possible pairs of positive cultures within each unique patient; a sensitivity analysis narrowed this to a single randomly selected pair of cultures for each unique patient.

Calculation of Chance and Observed Agreement of Organism Identity

The chance of identifying a matching organism was determined using sums of squares of species prevalence, which is the equivalent of the Pearson χ^2 test statistic. Species prevalence was calculated based on the number of isolates from a particular species divided by the total number of isolates. The identity correspondence of paired cultures was compared with chance agreement by means of the χ^2 1-sample test.

Calculation of Chance and Observed Agreement of Organism Susceptibility

To calculate the probability of paired specimens having a same or better susceptibility profile by chance (no new acquisition of

resistance to any tested antimicrobial), we used the following approach. First, average susceptibility to each antibiotic for each organism species was computed across the entire sample of isolates during the study period. Intermediate susceptibility results accounted for <5% of total test results and were excluded to simplify interpretation (leaving only the 2 categories of susceptible and resistant for each antimicrobial tested). For each isolate, we then calculated the probability of no new resistance detection, specifically, we calculated the sum of probabilities of all combinations of the resistant states converting to the

susceptible states for each drug in addition to the probability that the susceptibility profile remained exactly the same. These individual chance values for each index isolate were then summed and divided by the total number of isolate pairs to determine the overall probability of chance agreement. Chance agreement estimates were performed separately for each city, based on the city-specific urine isolates and susceptibility patterns. The susceptibility correspondence of paired cultures was compared with chance agreement using the χ^2 1-sample test.

Table 1. Demographic and Clinical Variables in Patients With 2 Positive Urine Isolates (Matching Organism) or 2 Positive Urine Isolates With the Same Organism (Same or Better Susceptibility)

Variable	Paired Positive Cultures for Assessment of Organism Correspondence ^a	Paired Cultures of the Same Organism for Assessment of Susceptibility Correspondence ^a
Pairs of isolates, No.	22 019	9590
Unique patients, No.	4351	2430
Age, mean (IQR), y	72 (52–92)	72 (51–93)
Sex of patient		
Male	4787 (22)	1959 (20)
Female	17 232 (78)	7631 (80)
City		
Toronto	3914 (20)	1681 (18)
Chicago	18 105 (80)	7909 (82)
Interval between isolates, mean (IQR), d	184 (47–284)	172 (42–263)
ICU admission ^b	559 (3)	296 (3)
Surgical admission ^b	1372 (6)	523 (5)
Outpatient culture ^b	15 633 (71)	7211 (75)
Negative intervening culture	10 449 (47)	4184 (44)
Antibiotics between cultures	18 948 (86)	7897 (82)
Cultures during same admission	2133 (10)	877 (9)
Gram-positive organism	3687 (17)	298 (3)
Most common organisms, No. (%) of isolates ^d		
<i>Escherichia coli</i>	23 318 (53)	14 468 (75)
<i>Enterococcus</i>	5455 (12)	. . . ^c
<i>Klebsiella</i>	6184 (14)	2296 (12)
<i>Pseudomonas</i>	. . .	878 (5)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

^a Unless otherwise specified, data represent No. (%) of isolate pairs.

^b At collection of the second positive culture.

^c *Enterococcus* was excluded from this analysis, because susceptibility profiles were not routinely tested for this organism at both centers.

^d The values for specific organisms represent individual isolates (not pairs).

Calculation of Likelihood of Susceptibility to Ciprofloxacin

Using a candidate antibiotic commonly used for UTI, ciprofloxacin, we sought to illustrate the utility of a previous sensitive urine culture in predicting ciprofloxacin sensitivity for a subsequent positive urine culture. To do this, we identified index urine cultures with organisms susceptible to ciprofloxacin and then determined what proportion of subsequent isolates were susceptible to ciprofloxacin (regardless of whether the organism identity was the same as the initial isolate). We excluded cultures without noted susceptibilities. Cultures with intermediate results were assumed to be resistant, giving the most conservative estimate of susceptibility rates. These results were stratified by documented exposure to any fluoroquinolones in the interim between the paired cultures. Only data from NUH could be included with this analysis, as class specific antibiotic exposure was less accessible from the SHSC database, and ciprofloxacin susceptibility testing is not routinely performed for *Enterococcus* spp. at SHSC (cultures of *Enterococcus* spp. were included in this analysis).

Multivariate Analysis

Multivariable logistic regression was performed using response variables of concordance of species identity and concordance of antibiotic susceptibility profile that were the same or better. Predictor variables included the patient, hospital, culture, and treatment covariates listed above. Generalized estimating equations were used to account for clustering within patients. Statistical analysis was performed using SAS software (version 9.3; SAS Institute).

RESULTS

Population Characteristics

A total of 22 019 pairs of urine culture isolates from 4351 unique patients were included for evaluation of organism correspondence, including 3914 isolate pairs (20%) from SHSC and 18 105 (80%) from NUH. *Escherichia coli* was the most common bacteria, present in 23 318 (53%) of individual cultures analyzed, followed by *Klebsiella* spp. in 6184 (14%), and *Enterococcus* spp. in 5455 (12%). The cultures included 17 232 pairs from female and 4787 from male patients. Patients had a mean age of 72 years (interquartile range, 62–82 years), and the mean

Table 2. Multivariate Analysis to Identify Predictors of Organism Correspondence in Patients With ≥ 2 Positive Urine Cultures^a

Variable	Odds Ratio	P Value
Male sex	1.06	<.001
Age (in years)	0.99	<.001
City of Toronto ^b	1.00	.89
Antibiotics between cultures	0.90	<.001
Time between cultures (in months)	0.99	<.001
Negative culture between positive cultures	0.91	<.001
Cultures obtained during same admission	1.10	<.001
Outpatient setting ^c	1.04	.02
ICU admission ^c	1.00	.94
Surgical admission ^c	0.99	.73
<i>Escherichia coli</i> ^d	1.39	<.001

Abbreviation: ICU, intensive care unit.

^a Unless otherwise noted, all categorical variables default to yes as the baseline value.

^b Chicago is the referent city.

^c At the time of the second isolate collection.

^d Species of index isolate.

interval between cultures was 184 days (interquartile range, 66–303 days; Table 1).

The subset of 9590 pairs of cultures with the same organism identified in both cultures, from 2430 unique patients, were included in an evaluation of antimicrobial susceptibilities. Of these, 1681 (18%) of isolates were from SHSC and 7909 (82%) were from NUH. *Escherichia coli* was the most common bacteria present in 14 468 individual cultures (75%), followed by *Klebsiella* spp. in 2296 (12%), and *Pseudomonas* spp. in 878 (5%; Table 2).

Univariate Analysis

Correspondence of Organism Identity

The correspondence of organism identity as a function of time between positive urine cultures is shown in Figure 1. Overall, organism correspondence declined as a function of time. At 4–8 weeks, the correspondence of organism identity was 57% (95% confidence interval [CI], 55%–59%), and at >32 weeks it was 49% (95% CI, 48%–50%). However, even at prolonged intervals between cultures, the correspondence was substantially greater than chance agreement, which was calculated as 21% and 36% for SHSC and NUH, respectively (both $P < .001$), respectively.

Correspondence of Organism Susceptibility

The correspondence of organism susceptibility (no new resistance development) as a function of time is shown in Figure 2A–D. Overall, susceptibility correspondence declined very gradually with increasing time between isolates. The

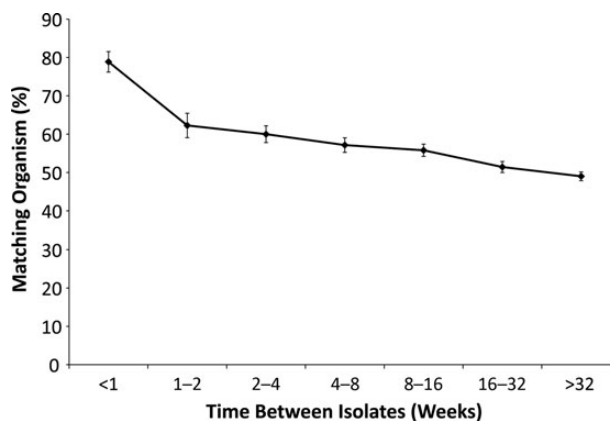


Figure 1. Observed correspondence of organism identity in paired positive urine isolates.

susceptibility profile was the same or better in 83% (95% CI, 81%–85%) of isolate pairs at 4–8 weeks and in 75% (95% CI, 73%–77%) at >32 weeks. Even at prolonged intervals between cultures, correspondence was substantially greater than chance agreement, which was calculated as 26% and 33% for SHSC and NUH respectively (both $P < .001$). When stratified by antibiotic exposure (Figure 2C), the likelihood that the susceptibility profile was the same or better was higher in patients without intervening antibiotic use. For those without documented antibiotic exposure, this likelihood was 87% (95% CI, 83%–91%) at 4–8 weeks and 80% (95% CI, 75%–85%) at >32 weeks. It was lower in patients with *E. coli* growing in the initial culture (Figure 2D): 80% (95% CI, 77%–83%) at 4–8 weeks and 73% (95% CI, 71%–75%) at >32 weeks.

Ciprofloxacin Susceptibility With Previously Susceptible Positive Cultures

The likelihood of susceptibility of a positive urine culture to ciprofloxacin, in patients with a prior urine culture susceptible to this antibiotic, is shown in Figure 3. For patients with a prior ciprofloxacin susceptible isolate, who did not receive subsequent fluoroquinolones (3819 of 9082 isolate pairs; 42%), the likelihood of a subsequent positive urine culture yielding a ciprofloxacin-susceptible organism was consistently greater than the 80% threshold endorsed by international UTI treatment guidelines, and was still as high as 85% (95% CI, 83%–87%) when the interval between isolates was >32 weeks.

Multivariate Analysis

Multivariable logistic regression analyses, using generalized estimating equations, were performed to examine predictors of concordant results for the organisms' identity (Table 2) or the same or better susceptibility profile (Table 3). Factors that predicted decreased organism or susceptibility correspondence

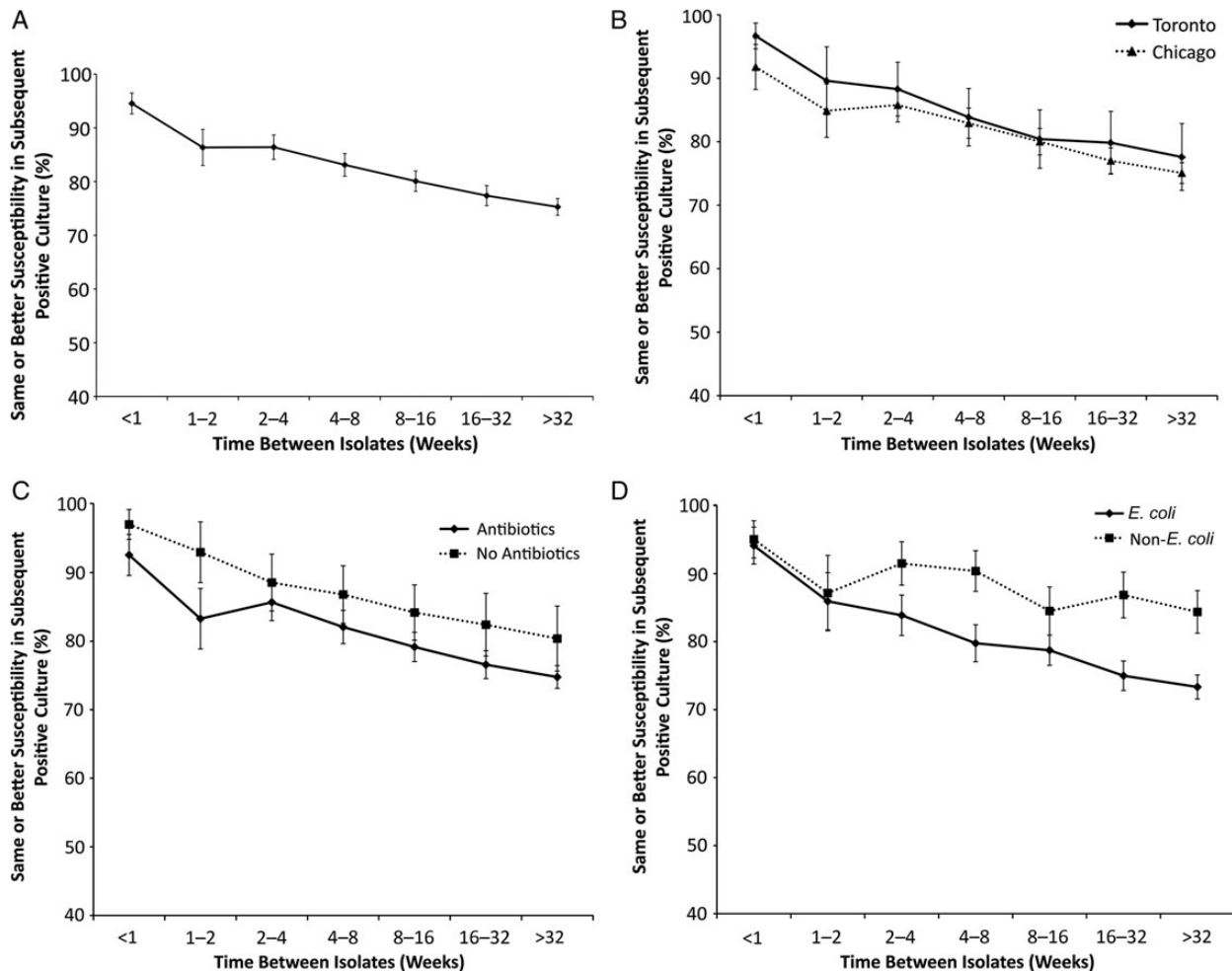


Figure 2. Observed susceptibility (same or better pattern) of subsequent positive urine isolates compared with previous positive urine isolates from the same patient with an organism of the same species in entire cohort (A), subgroups stratified by city (B), subgroups by antibiotic exposure (C), and subgroups by organism type (D). Abbreviation: *E. coli*, *Escherichia coli*.

were increasing age, antibiotic exposure between isolates, time between isolates, or negative urine cultures obtained in the interim between positive cultures. Variables that predicted increased likelihood of organism correspondence were outpatient status at collection of the subsequent culture, cultures collected during the same admission, and male sex.

DISCUSSION

In this multicenter retrospective cohort study, we examined the value of the common practice of reviewing a patient's prior microbiologic culture history to guide current treatment decisions. We found that patients' prior urine culture results are predictive of the organism identity and susceptibility of subsequent urine isolates detected even weeks to months later. Key factors

affecting the correspondence of organism and susceptibility between 2 positive cultures include the time between cultures, antibiotic use between cultures, and negative intervening cultures.

Correspondence of Organism Type

The correspondence of organism identity declines slowly over time but still remains greater than chance even at >32 weeks. Although UTIs can emerge from diverse intestinal flora [19], we see a strong colonization effect that highlights the predictive value of reviewing a patient's previous culture results. Intervening antibiotic exposure makes knowledge of the previously identified organism less helpful, potentially through elimination of the implicated microbial reservoir. Similarly, negative intervening cultures are probably indicative of clearance of colonization and thus a reduced likelihood of recurrent infection relating

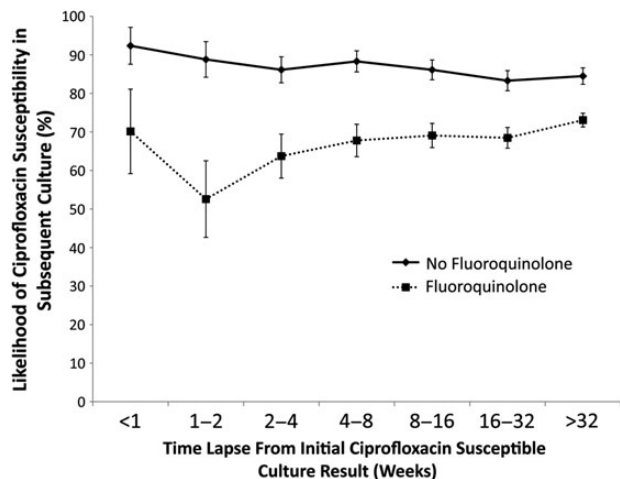


Figure 3. Likelihood of ciprofloxacin susceptibility of a positive urine culture after a previous positive urine culture yielded a ciprofloxacin susceptible organism, as a function of time between cultures, and stratified for intervening fluoroquinolone exposure.

to relapse from the same organism. Multivariate results confirm the univariate findings and also suggest that outpatient status at the time of the second isolate, or isolates from the same admission, are predictors of organism correspondence. The former may be due to less antimicrobial exposure compared with an inpatient setting, whereas the latter may be due to increased use of catheters or recalcitrant infection. Having an index isolate of

Table 3. Multivariate Analysis to Identify Predictors of Same or Better Susceptibility Patterns in Patients With the Same Organism Growing in ≥ 2 Positive Urine Cultures^a

Variable	Odds Ratio	P Value
Male sex	1.01	.70
Age (in years)	1.00	.32
City of Toronto ^b	1.02	.37
Antibiotics between cultures	0.96	.01
Time between cultures (in months)	0.99	<.001
Negative culture between positive cultures	0.97	.02
Cultures obtained during same admission	1.04	.11
Outpatient setting ^c	1.00	.80
ICU admission ^c	1.00	.89
Surgical admission ^c	0.99	.80
<i>Escherichia coli</i> ^d	0.90	<.001

Abbreviation: ICU, intensive care unit.

^a Unless otherwise noted, all binary variables default to yes as the baseline value.

^b Chicago is the referent city.

^c At the time of the second isolate collection.

^d Species of the isolate.

E. coli was associated with an increased likelihood of organism correspondence (greater than chance), and this association may be due to mechanisms unique to the organism, including the ability to form intracellular bacterial communities, that allow more effective persistence in the genitourinary tract [20]. Persistence of genetic clones of *E. coli* has been described in UTIs and supports these observations [21]. However, the high prevalence of *E. coli* as the causative agent in UTIs also contributes to a higher likelihood of identity correspondence by chance alone.

Correspondence of Combined Susceptibility

The likelihood of the same or better susceptibility in the second isolate declined as a function of time lapse from the first isolate, but at >32 weeks it was still greater than would be expected by chance alone. There is high predictive value of prior isolates, 87% (95% CI, 83%–91%) at 2 months in patients not having received antibiotics and decreasing only to 80% (95% CI, 75%–85%) after as long as ≥ 32 weeks. The lower correspondence of susceptibility in *E. coli* could have a number of causes, including less diversity in baseline resistance, the ability to persist intracellularly and accumulate resistant clones in treated patients, or more tested antibiotic susceptibilities.

Ciprofloxacin Susceptibility With Previously Susceptible Positive Cultures

When a patient has a previous urine culture with an organism susceptible to ciprofloxacin, subsequent isolates will be susceptible >80% of the time even when >32 weeks has elapsed between isolates. In the context of empiric treatment of lower UTIs, one can accept a higher rate of resistance compared with upper UTIs. For example, based on mathematical analyses and given the low likelihood of progression to upper tract or invasive disease, the Infectious Diseases Society of America guidelines for lower UTI suggest that up to a 20% risk of resistance can be accepted when considering treatment with trimethoprim-sulfamethoxazole. By extrapolation of this threshold, our data suggest that a prior organism susceptible to ciprofloxacin, without interim fluoroquinolone exposure, would portend an acceptable likelihood of susceptibility to ciprofloxacin even when local resistance rates are high (overall ciprofloxacin resistance rates, 40%; 95% CI, 39.5%–40.5%). Conversely, documented exposure to a fluoroquinolone was associated with unacceptably high rates of resistance, even >32 weeks after the previous susceptible culture. These extrapolations assume that treatment failure would be similar for fluoroquinolone treatment of fluoroquinolone-resistant organisms and trimethoprim-sulfamethoxazole treatment of trimethoprim-sulfamethoxazole-resistant organisms.

Limitations and Strengths

Because of the retrospective study design, we cannot definitively confirm the presence of clinical infection at the time of specimen collection. However, all specimens were collected in the

process of clinical care (rather than for surveillance), so we can infer that infection was at least suspected and that culture results were intended to guide antibiotic therapy. Our data set includes patients with multiple pairs of isolates, and observations are not all independent; however, the use of generalized estimating equations in the multivariate model accounts for clustering of data within subjects. Sensitivity analysis of univariate data was performed with random pairs and also confirmed our findings. We also excluded *Enterococcus* isolates from our antibiotic susceptibility comparisons, owing to the lack of sensitivities available at SHSC. This is unlikely to markedly affect the usefulness of our results, because these results are expressed relative to susceptibility results from prior isolates and many laboratories do not routinely perform susceptibility testing for *Enterococcus* from nonsterile specimens sites, such as urine. The strengths of this study include a large sample size (>22 000 paired isolates) from 2 countries, with significant representation of both inpatient and outpatient populations from a wide variety of care settings.

Conclusions

A patient's prior urine culture results are predictive of subsequent urine culture identity and susceptibility. In most cases, intervening treatment with antibiotics and documentation of negative cultures are predictive of decreased organism or susceptibility correspondence. Even when prevailing ciprofloxacin resistance rates in a region are high among urinary tract pathogens, empiric ciprofloxacin can still be used safely for a patient with cystitis, if review of prior positive urine culture results identify an organism sensitive to this agent and no intervening fluoroquinolone exposure was documented.

Notes

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