Prior antimicrobial drug exposure: a risk factor for trimethoprim–sulfamethoxazole-resistant urinary tract infections

Joshua P. Metlay1,2*, Brian L. Strom2 and David A. Asch1,2

1Center for Health Equity Research and Promotion, Philadelphia Veterans Affairs Medical Center; 2Departments of Medicine and Biostatistics and Epidemiology, the Center for Clinical Epidemiology and Biostatistics, the Center for Education and Research on Therapeutics, and the Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA, USA

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Objectives: Antimicrobial drug use is believed to be an important risk factor for the emerging problem of antimicrobial drug resistance, yet strong evidence for the causal relationship in community settings has been limited. Detailed analysis of this risk factor at the level of the individual patient has been hampered by limited availability of drug exposure data among patients with outpatient infections. We used a novel data system to identify patterns of individual antimicrobial drug exposures associated with trimethoprim–sulfamethoxazole-resistant urinary tract infections (UTIs).

Materials and methods: This was a retrospective case–control study. Subjects were veterans with Gram-negative UTIs seen at the Philadelphia VA Medical Center from 1 July 1996 to 31 December 1999. Subjects were linked to a national VA outpatient pharmacy database. Cases and controls were identified based on the results of trimethoprim–sulfamethoxazole susceptibility testing.

Results: Three hundred and ninety-three veterans with UTIs could be linked to electronic pharmacy records. The overall rate of trimethoprim–sulfamethoxazole drug resistance was 13%, without significant annual variation. Antimicrobial drug exposure within 6 months was strongly associated with the probability of a trimethoprim–sulfamethoxazole-resistant infection (OR = 4.1, 95% CI 2.2–7.5). This association extended to exposure to other antimicrobial drugs in addition to trimethoprim–sulfamethoxazole and the overall association displayed a dose–response relationship in terms of the number of prior drug exposures.

Conclusions: Prior antimicrobial drug exposure is a strong risk factor for infection with trimethoprim–sulfamethoxazole-resistant Gram-negative bacteria among patients with UTIs.

Introduction

Recently, there has been a growing awareness that the individual benefits of antibiotic use are diminished by a societal cost, which is the emergence of antibiotic resistance among bacterial pathogens. Although initially more prevalent in hospital settings, the prevalence of drug resistance in community settings is also rising among bacterial pathogens, particularly Streptococcus pneumoniae1–3 and Escherichia coli.4,5

It seems likely that this rising resistance is due to Darwinian selection resulting from widespread use of antibiotics. However, evidence for this causal relationship in community settings is limited and includes ecological (i.e. population level) studies, comparing community level rates of resistance with rates of antibiotic consumption,6–9 and carriage studies, examining the causal association between antibiotic exposure and carriage of, not infection with, resistant bacteria.10,11 Moreover, if antibiotic exposure is causal, then exposure...
should demonstrate a clear dose–response relationship with the subsequent risk of a drug-resistant infection rising as the number of courses of antibiotics increases.12 There is a growing awareness that not all antimicrobial drugs and patterns of antimicrobial drug use are equivalent in terms of their propensity to select for drug-resistant bacteria.13 However, data on these relationships have been limited by the difficulties in accurately measuring antimicrobial drug exposures through traditional methods of patient self-report or medical record review.

Recently, the Department of Veterans Affairs established a national formulary and began maintaining centralized records of all pharmacy dispensings throughout the Veterans Health Administration. Such a database, if linked to laboratory data capturing drug-resistant and -susceptible infections, could provide valuable details on the risk factors for drug-resistant infections. We chose to study veterans with trimethoprim–sulfamethoxazole-resistant Gram-negative urinary tract infections (UTIs) because these are common infections with a clinically relevant level of resistance to a first-line antimicrobial therapy. The specific aim of this study was to identify patterns of antimicrobial drug exposure associated with infection with trimethoprim–sulfamethoxazole-resistant Gram-negative pathogens in veterans with UTIs.

Materials and methods

Subjects

We conducted a retrospective case–control study using linked local laboratory and national pharmaceutical electronic records within the VA Healthcare System. The study was based at the ambulatory care clinics within the VA Medical Center, Philadelphia, PA from 1 July 1996 to 31 December 1999. The specific locations included were any of the outpatient primary care clinic sites (including separate geriatric and women’s health clinics), the emergency department and the outpatient urology clinic. We identified the location of potential subjects based on the coded source of submission for all urine cultures submitted to the hospital laboratory during the study period.

Potential study subjects were all subjects with growth from a urine specimen of ≥5 × 10^4 cfu/mL of either a single Gram-negative bacterium or a dominant bacterium (i.e. ≥5 × 10^4 cfu/mL of one pathogen and ≤10^3 cfu/mL of a second pathogen). The cutpoint for significant growth was chosen because this was the lowest density of growth that consistently underwent susceptibility testing during the study period. Others have demonstrated that as low as 10^5 cfu/mL of a single uropathogen is a sensitive and specific indicator of UTIs in men.14,15

Urine cultures

All data for this study were obtained through existing electronic databases within the VA Healthcare System. Laboratory data are housed at local VA facilities in a decentralized data structure called Veterans Information Systems Technology Architecture (VISTA).16 We captured all positive urine cultures for the study period, including date of infection, hospital location for test submission and results of urine culture, including all susceptibility testing.

All potentially eligible urine cultures were analysed during the period 1 July 1996 to 31 December 1999. For those subjects with more than one positive culture during the study period, we included only the initial positive culture during the 3.5 year study window. Susceptibility results were collected based on the clinical laboratory report of the results of in vitro trimethoprim–sulfamethoxazole susceptibility testing. Susceptibility testing was carried out with an automated rapid susceptibility testing instrument, VITEK (bioMérieux), with resistance to trimethoprim–sulfamethoxazole defined at ≥24 mg/L trimethoprim and ≥76 mg/L sulfamethoxazole.

Antibiotic exposure

Drug exposure data were extracted from the Pharmacy Benefits Management (PBM) database, maintained by the PBM Strategic Health Care Group at Hines Hospital, IL, USA. Since 1999, this national pharmacy database has excluded outpatient and inpatient drug dispensing data from each VA medical facility. We were able to expand the local Philadelphia PBM data back to 1 January 1996 using archived electronic pharmacy dispensing data at the local facility, thus providing at least 6 months of pharmacy data preceding the most recent infections in our study.

For the initial Gram-negative UTI for each patient identified within the 3.5 year laboratory database, we linked to the PBM data for the 6 months preceding the date of culture. Antimicrobial drug exposures preceding the UTI were identified based on the VA pharmacy codes of the dispensed drugs. The VA drug class code is a five-digit code that captures the category and class of drug dispensed. We captured all outpatient dispensings in order to categorize antimicrobial drugs as well as other drugs that might be indicators of chronic conditions. We excluded antimicrobial drugs prescribed within 14 days of the index urine culture in order to avoid the potential for misclassification of a treatment as a preceding exposure. For patients who received antimicrobial drugs during the 6 month window preceding infection, we recorded the drug class and cumulative number of separate prescriptions for antimicrobial drugs.

The pharmacy database provided a limited opportunity to examine the potential role of other factors as determinants of trimethoprim–sulfamethoxazole-resistant UTIs. We selected factors based on their prior identification as potential risk factors as well as the accuracy of the pharmacy database to identify these conditions.17 The two factors included in this study were the presence of pharmacologically treated diabetes mellitus (VA pharmacy codes for insulin or oral hypo-
glycaemic agents) and the chronic use of an indwelling catheter (VA pharmacy codes for Foley catheters or urine collection devices).

Analysis

Descriptive statistics were used to present the distributions of Gram-negative bacterial pathogens, susceptibility results and antimicrobial drug exposures among study subjects. Bivariate associations between the presence of antimicrobial drug exposures or other potential risk factors and the subsequent antimicrobial susceptibility of the uropathogen were analysed using χ² or Fisher’s exact statistics as appropriate.\(^\text{18}\) The impact of number of courses of antimicrobial exposure on susceptibility was tested with the Mantel–Haenszel χ² test for trend,\(^\text{19}\) excluding those subjects without prior antimicrobial drug exposure since they do not contribute information to the dose–response analysis. Stratified analyses were conducted to examine the impact of site care on the relationship between antimicrobial drug exposure and the probability of a trimethoprim–sulfamethoxazole-resistant infection. The Breslow–Day test statistic was used to assess the homogeneity of odds ratios across the site strata.\(^\text{20}\) Multivariable logistic regression was used to assess the independent association between prior antimicrobial drug exposure and the probability of a trimethoprim–sulfamethoxazole-resistant infection, controlling for patient age, site of care, Foley catheter use and the presence of treated diabetes mellitus. A separate logistic regression was used to assess the independent association between each class of antimicrobial drug exposure and the probability of a trimethoprim–sulfamethoxazole-resistant infection, simultaneously controlling for all other classes of antimicrobial drug exposure. All analyses were conducted with SAS for Unix (Release 6.12; SAS Institute, Cary, NC, USA).

Results

During the 3.5 year study period, 1033 urine cultures were positive for any bacterial growth; 756 (73%) of these urine cultures were considered clinically significant based on the growth of a single or dominant Gram-negative pathogen at ≥5 × 10^4 cfu/mL. These cultures represented 559 unique patients seen in urgent care settings at the VA; 393 (70%) of these patients could be linked to VA pharmacy records and represent the study population for this analysis. Of these patients, 32% were seen in primary care, 25% were seen in the emergency room, 6% were seen in the women’s health clinic, 4% were seen in the urology clinic and 33% were seen in other outpatient specialty clinics.

Table 1 reports the characteristics of these patients and their infections; 53% of the study subjects were ≥65 years at the time of their UTI. Based on pharmacy dispensing records, 25% of subjects had diabetes mellitus and 9% of subjects required intermittent or chronic bladder catheterization; 33% of the subjects had received at least one antimicrobial drug in the 6 month window of time preceding the UTI, and this rate of exposure did not vary significantly over the study years. The most commonly prescribed antimicrobial drugs for this study population included trimethoprim–sulfamethoxazole (40% of all antimicrobial drugs prescribed), quinolones (32%) and penicillins (23%). The proportion of antimicrobial drug prescriptions accounted for by trimethoprim–sulfamethoxazole declined over the study period from a high of 70% to a low of 23% (P = 0.007 for trend), whereas the other major drug classes remained relatively constant.

The most frequently identified Gram-negative bacterial pathogen was E. coli (62%), followed by Klebsiella species (15%) and Proteus species (7%). This distribution was relatively stable over time. The overall prevalence of trimethoprim–sulfamethoxazole resistance among the sample of uropathogens was 13%. There were no significant trends in the overall prevalence of resistance to trimethoprim–sulfamethoxazole over the study period.

Table 2 compares the antibiotic exposure frequencies of patients with trimethoprim–sulfamethoxazole-susceptible and -resistant UTIs. Prior exposure to any antimicrobial drug was found among 61% of patients with trimethoprim–sulfamethoxazole-resistant UTIs compared with 27% of those with trimethoprim–sulfamethoxazole-susceptible UTIs (OR = 4.1, 95% CI 2.2–7.5). Patient age, presence of treated diabetes mellitus and chronic use of Foley catheters were not significantly associated with the probability of a trimethoprim–sulfamethoxazole-resistant infection. In analyses stratified by the site of care, the relationship between prior antimicrobial drug exposure and infection with a trimethoprim–sulfamethoxazole-resistant uropathogen demonstrated significant heterogeneity (P = 0.03 by Breslow–Day test), but when the urology site of care was excluded from the analysis, the relationship between prior antimicrobial drug exposure and infection with a trimethoprim–sulfamethoxazole-resistant uropathogen was homogeneous across the remaining site of care strata (P = 0.17). In multivariable logistic regression analysis, the association between prior antimicrobial drug exposure and infection with a trimethoprim–sulfamethoxazole-resistant uropathogen remained essentially unchanged after adjusting for age, site of care, treated diabetes mellitus and Foley catheter use (OR = 4.4, 95% CI 2.3–8.5 with urology sites included; OR = 5.3, 95% CI 2.7–10.5 with urology sites excluded).

Among individual drug classes, exposure to trimethoprim–sulfamethoxazole was identified for 27% of patients with trimethoprim–sulfamethoxazole-resistant infections and 11% of patients with susceptible infections (P = 0.003). Other drug classes significantly associated with trimethoprim–sulfamethoxazole resistance included tetracyclines and quino-
### Table 1. Characteristics of study subjects with Gram-negative UTIs and their antimicrobial drug exposures, 1996–1999

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1996 (%)</th>
<th>1997 (%)</th>
<th>1998 (%)</th>
<th>1999 (%)</th>
<th>Overall (%)</th>
<th>P value for trend&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>18–45</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>12</td>
<td>11</td>
<td>0.37</td>
</tr>
<tr>
<td>46–64</td>
<td>46</td>
<td>33</td>
<td>36</td>
<td>33</td>
<td>36</td>
<td></td>
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<tr>
<td>65+</td>
<td>42</td>
<td>55</td>
<td>54</td>
<td>55</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Presence of diabetes mellitus</td>
<td>25</td>
<td>28</td>
<td>25</td>
<td>21</td>
<td>25</td>
<td>0.34</td>
</tr>
<tr>
<td>Use of indwelling bladder catheter</td>
<td>10</td>
<td>12</td>
<td>5</td>
<td>10</td>
<td>9</td>
<td>0.51</td>
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<tr>
<td>Prior courses of antimicrobial drugs&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>62</td>
<td>60</td>
<td>70</td>
<td>74</td>
<td>67</td>
<td>0.05</td>
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<td>1</td>
<td>19</td>
<td>24</td>
<td>17</td>
<td>14</td>
<td>18</td>
<td></td>
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<td>2</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>4</td>
<td>7</td>
<td></td>
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<tr>
<td>≥3</td>
<td>10</td>
<td>11</td>
<td>3</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Antimicrobial drug classes prescribed&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SXT</td>
<td>70</td>
<td>36</td>
<td>39</td>
<td>23</td>
<td>40</td>
<td>0.007</td>
</tr>
<tr>
<td>Quinolones</td>
<td>25</td>
<td>22</td>
<td>42</td>
<td>38</td>
<td>32</td>
<td>0.09</td>
</tr>
<tr>
<td>Penicillins</td>
<td>10</td>
<td>40</td>
<td>21</td>
<td>8</td>
<td>23</td>
<td>0.18</td>
</tr>
<tr>
<td>Others&lt;sup&gt;e&lt;/sup&gt;</td>
<td>15</td>
<td>27</td>
<td>16</td>
<td>35</td>
<td>23</td>
<td>0.32</td>
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<tr>
<td>Pathogen isolated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>63</td>
<td>61</td>
<td>60</td>
<td>65</td>
<td>62</td>
<td>0.75</td>
</tr>
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<td><em>Citrobacter</em> species</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>0.75</td>
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<tr>
<td><em>Enterobacter</em> species</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>0.28</td>
</tr>
<tr>
<td><em>Klebsiella</em> species</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>0.87</td>
</tr>
<tr>
<td><em>Proteus</em> species</td>
<td>13</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>0.13</td>
</tr>
<tr>
<td><em>Pseudomonas</em> species</td>
<td>2</td>
<td>8</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>0.79</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0.61</td>
</tr>
<tr>
<td>Pathogen resistance to SXT</td>
<td>12</td>
<td>15</td>
<td>15</td>
<td>11</td>
<td>13</td>
<td>0.75</td>
</tr>
</tbody>
</table>

<sup>a</sup>Represents the second half of 1996, all other years are full years.

<sup>b</sup>Mantel–Haenszel test for trend across study years.

<sup>c</sup>Drugs dispensed during the time window starting 6 months before infection and ending 14 days before infection.

<sup>d</sup>Proportion of each drug class prescribed among all antimicrobials prescribed for study subjects.

<sup>e</sup>Includes cephalosporins, macrolides and tetracyclines.

SXT, trimethoprim–sulfamethoxazole.

### Table 2. Proportion of patients with trimethoprim–sulfamethoxazole-resistant and -susceptible UTIs exposed to antimicrobial drugs during the 6 months preceding infection

<table>
<thead>
<tr>
<th>Class of antibiotic prescribed during the preceding 6 months</th>
<th>Number (%) of patients with SXT-susceptible isolates (n = 331)</th>
<th>Number (%) of patients with SXT-resistant isolates (n = 51)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>SXT</td>
<td>36 (11)</td>
<td>14 (27)</td>
<td>0.003</td>
</tr>
<tr>
<td>Quinolone</td>
<td>25 (8)</td>
<td>11 (22)</td>
<td>0.004</td>
</tr>
<tr>
<td>Penicillin</td>
<td>23 (7)</td>
<td>6 (12)</td>
<td>0.25</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>11 (3)</td>
<td>2 (4)</td>
<td>0.69</td>
</tr>
<tr>
<td>Macrolide</td>
<td>7 (2)</td>
<td>3 (6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>2 (1)</td>
<td>5 (10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any antimicrobial drug</td>
<td>91 (27)</td>
<td>31 (61)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Fisher’s exact test (two-sided).

SXT, trimethoprim–sulfamethoxazole.
Drug-resistant UTIs

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setting of multidrug resistance, particularly with the multi-
drug-resistant plasmids that are present in enterobacteria. 
Alternatively, as predicted by mathematical models, any anti-
microbial drugs that reduce the risk of colonization with 
susceptible bacteria may increase the probability that a host 
will be subsequently colonized by specific drug-resistant 
pathogens as the proportion of specific drug-resistant patho-
gens in the environment increases.30

An alternative interpretation of our results is that prior anti-
microbial drug prescriptions are a marker of prior resistant 
UTIs rather than a cause of subsequent resistant UTIs. To the 
extent that providers do not always send cultures before 
treating infections, some prior UTIs may have been missed 
due to our reliance on the laboratory database to identify all 
infections. However, we specifically excluded antimicrobial 
drug prescriptions within 14 days of the positive urine culture 
in order to minimize this misclassification and analysed only 
the first culture documented UTI for each subject.

Several limitations of this study should be noted. First, data 
on antimicrobial drug exposure were limited to information 
included within the outpatient pharmacy dispensing files of 
the VA. Thus, antimicrobial drugs dispensed by non-VA 
pharmacies would not be measured in our study. In a separate 
study, we have shown that 17% of a random sample of 
veterans self-report antimicrobial drug prescriptions from 
non-VA providers over a 6 month period (J. P. Metlay, unpub-
lished observations). Assuming that this under-measurement 
of exposure was non-differential with respect to the sus-
ceptibility of the infection, this bias should have reduced the 
magnitude of the association measured. Moreover, 30% of 
the eligible subjects identified in the microbiology laboratory 
database could not be linked to the pharmacy database, 
reflecting errors in the coding of patient identifiers as well as 
the fact that some patients seen at the VA did not have 
dispensed medications during the 6 month period preceding 
the time of their infection.

Secondly, we had limited information on other risk factors 
beyond prior antimicrobial drug exposure. In particular, we 
focused on UTIs identified in ambulatory care sites but we did 
not have information on prior hospitalizations. Thus, some of 
the pathogens may have been hospital acquired. Moreover, 
the heterogeneous nature of the patient population probably 
resulted in differential thresholds for submitting urine 
cultures in the face of a suspected UTI, which may have 
confounded the relationship between prior drug exposure and 
subsequent risk of a resistant UTI. Indeed, our analysis 
revealed that the observed relationship between prior drug 
usage only to a single agent, trimethoprim–sulfamethoxazole. 
We did not observe sufficient numbers of Gram-positive 
UTIs to include in this analysis, and rates of resistance to other 
agents, particularly fluoroquinolones, were too low for ana-
lysis. Whereas the patterns of association observed in this 
study may be generalizable to other pathogens and other resistance patterns, future studies examining each of these 
conditions will need to consider the potential uniqueness of 
these associations.

In conclusion, prior antimicrobial drug exposure is a strong 
risk factor for infection with a drug-resistant Gram-negative 
uropathogen. The association demonstrates a steep dose– 
response relationship in terms of the number of prior courses 
of antimicrobial drugs. Understanding the complex relation-
ship between patterns of drug exposure and emerging drug 
resistance should inform future guidelines for antimicrobial 
drug therapy. Future studies must establish whether these pat-
terns of association will be consistent across diverse clinical 
settings and different patterns of drug resistance.

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Drug-resistant UTIs

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References


