Factors associated with trimethoprim-resistant bacteria isolated from urine samples

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Urine samples with trimethoprim-resistant or trimethoprim-sensitive Gram-negative bacteria and samples with no bacterial growth (NG) were identified. Age–sex matched community controls were generated with each trimethoprim-resistant case. These four groups were evaluated for exposure. Prior trimethoprim use was significantly more common in the trimethoprim-resistant group when compared with the trimethoprim-sensitive or the NG group. Prior hospitalization was significantly less common in the trimethoprim-resistant than the trimethoprim-sensitive group, but not with the NG group. Prior oestrogen exposure was associated with trimethoprim resistance. There were no associations found for diabetes or prior corticosteroid exposure. Community controls were found to be inappropriate controls for the study of trimethoprim-resistant bacteria in urine samples.

Materials and methods

Study population

The study population comprised community patients who had submitted a midstream urine sample to their GP to test for culture and sensitivity. The results of the culture and sensitivity analyses were recorded on a database in the Medical Microbiology Laboratory at Ninewells Hospital. Catheter samples were excluded. Data for the month of July 1994 were available for analysis.

Study design

The study used a case–control design. Cases were defined as subjects for whom trimethoprim-resistant Gram-negative bacteria were isolated from urine in July 1994. Three sets of controls were collected for comparison. One set of controls were subjects with trimethoprim-sensitive Gram-negative bacteria isolated from urine in July 1994. The second set consisted of samples that had no bacterial growth (NG). The third set of controls consisted of community subjects selected from the MEMO database with no urine sample submitted to test for their appropriateness as controls. Two community controls were randomly selected from the general population and age–sex matched to each case. The
index date of analysis for the community controls was the date of sample for the matched case.

Exposure to trimethoprim and any antibiotic in the previous 6 months was determined using the MEMO record-linkage database. Prior hospitalization, corticosteroid use, oral contraceptive and oestrogen replacement therapy in the 6 months prior to the index date were also evaluated. Patients with diabetes mellitus were identified using a record-linked diabetes database.

Statistical analysis

The number of subjects in the trimethoprim-resistant group exposed and unexposed to each risk factor was determined and compared with the control groups (trimethoprim-sensitive, NG and community controls). Odds ratios (OR) and 95% CI were calculated using Epi Info 5.01a (Centers for Disease Control, Epidemiology Program Office; Atlanta, GA, 1991). Too few data were collected to assess the relationships using multivariate analyses.

Results

The results from 828 community subjects were identified in the study period. Trimethoprim-resistant Gram-negative bacteria were isolated from 52 samples, trimethoprim-sensitive Gram-negative bacteria were isolated from 213 samples and 563 samples had no bacterial growth.

Figure 1 shows the relative risks for each factor between trimethoprim-resistant and each of the control groups (trimethoprim-sensitive and NG). Prior trimethoprim use was significantly more common in the trimethoprim-resistant group when compared with the trimethoprim-sensitive group (31% vs 15%, OR 2.51; 95% CI 1.18–5.34) or the NG group (31% vs 16%, OR 2.40; 95% CI 1.22–4.70). The trimethoprim-resistant group had similar exposure to any antibiotic when compared with the other groups.

Prior hospitalization for any ICD-9 code was significantly less common in the trimethoprim-resistant group compared with the trimethoprim-sensitive group (4% vs 16%, OR 0.21; 95% CI 0.03–0.94), but not significantly so with the NG group (4% vs 14%, OR 0.24; 95% CI 0.04–1.04). Prior oestrogen exposure was also associated with trimethoprim resistance (trimethoprim-resistant vs trimethoprim-sensitive, OR 4.29; 95% CI 1.37–9.52), (trimethoprim-resistant vs NG, OR 2.61; 95% CI 1.02–6.47). There were no associations found for diabetes or prior corticosteroid exposure.

There were 100 age–sex matched controls found from the general population. For two cases, no matching community controls were found. These cases were excluded from the analysis. Cases were more likely than community controls to be exposed to antibiotics (60% vs 39%, OR 2.35; 95% CI 1.17–4.70) and trimethoprim (36% vs 7%, OR 7.47; 95% CI 2.86–19.54) in the 6 months before submitting a urine sample. There were no significant differences in the exposure to corticosteroids, diabetes mellitus, oestrogen, hormone replacement therapy or prior hospitalization.

Discussion

This study demonstrates an association between bacterial antibiotic resistance and prior antibiotic use. The association was strengthened when trimethoprim exposure alone was studied in association with bacterial trimethoprim

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**Figure.** Relative risk (95% CI) of the variables for trimethoprim-resistant cultures vs sensitive cultures (▲) and trimethoprim resistant cultures vs NG samples (●).
Trimeprprim-resistant bacteria from urine

resistance. To our knowledge, this is the first patient-specific study that illustrates this association.

The results from this study compare well with the results found in a community-based study of bacterial resistance in urinary isolates in two regions in Israel. Consistently higher rates of resistance were found in one region compared with the other. Further investigation revealed that the number of defined daily doses (DDD) of antibiotic given to the subjects in the health centres was also consistently higher in the region with high rates of resistance. Moreover, in both regions there was a strong correlation between resistance rates for each individual drug and the number of DDDs per 1000 inhabitants.

Antimicrobial usage is not the sole factor responsible for resistance patterns in a population. Most studies have concluded that prior antibiotic treatment is a predisposing factor, but few studies have demonstrated a causal relationship of antibiotic use to bacterial resistance. The risk factors for bacterial resistance seem to be multifactorial and complex in nature, implying that other factors affect the resistance patterns in a population. Prior hospitalization has been reported to increase infection or gut colonization with resistant bacteria, with or without antibiotic treatment. Patients in hospital are sicker and require elaborate treatment including invasive procedures and they receive multiple broad-spectrum antibiotics that facilitate colonization and infection with drug-resistant organisms. Our results show that hospitalization was less common in the trimethoprim-resistant group than in the trimethoprim-sensitive group. We hypothesize that the trimethoprim-sensitive group may have received antibiotics other than trimethoprim in hospital thus decreasing the likelihood of developing bacterial resistance to trimethoprim. The trimethoprim-resistant group may have been more likely to receive trimethoprim from their GP as an antibiotic of choice. A larger sample size and more information on the subjects would aid in determining the extent of this effect. Intrafamilial transmission of resistant bacteria is a method of transference of resistant bacteria. A study by Rydberg et al. found trimethoprim-resistant Escherichia coli in >30% of family members studied as compared with 2% in the control group, indicating that this form of transmission is not unusual.

Community controls were found to be inappropriate for the evaluation of antibiotic use when compared with the trimethoprim-resistant group. Controls should be selected to represent a population of individuals who would have been identified and included as cases had they also developed the disease. Bacteria resistant to trimethoprim may be present in the general population, but at a level where symptoms of infection are not seen. Hence, these people are less likely to submit a urine sample to be identified as trimethoprim-resistant. The OR that we found when comparing the trimethoprim-resistant group with community controls is therefore less likely to represent a true estimate of increased risk of antibiotic use and trimethoprim resistance.

Results from this study provide strong support for the hypothesis that urinary infection with trimethoprim-resistant Gram-negative bacteria is more common in subjects with prior trimethoprim exposure. This may suggest that initial treatment was unsuccessful or a recurrence of infection, but this is unclear with the limited size and study period of this study. Nevertheless, 48% of subjects with trimethoprim-resistant bacteria had no exposure to any antibiotic in the 6 months before sample submission either in hospital or community suggesting that there may be other factors involved in the transmission of bacterial resistance. Further studies with a larger sample are required to identify factors that contribute to risk of UTI with trimethoprim-resistant bacteria.

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References


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