How strong is the evidence that antibiotic use is a risk factor for antibiotic-resistant, community-acquired urinary tract infection?

Sharon L. Hillier1, John T. Magee2, Anthony J. Howard2 and Stephen R. Palmer1*

1Department of Epidemiology, Statistics and Public Health, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XW; 2PHLS in Wales, University of Wales Hospital, Cardiff, UK

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The prevalence of antibiotic resistance in community-acquired infections is rising but in contrast to popular perception there has been little published work on its epidemiology. This systematic review evaluates the published evidence on the relationship between antibiotic prescribing and antibiotic resistance of organisms causing community-acquired urinary tract infection. Fourteen papers met the inclusion criteria and these reported on five ecological studies and ten studies of individuals. Only one ecological study provided good evidence of a link with prescribing rates. The remaining studies had no control for population differences in demographics and/or no comparison population. Studies at the individual level lacked clear case definitions and statistical power. Until the epidemiology of antibiotic resistance is better defined the design of effective interventions will not be possible.

Introduction

The prevalence of antibiotic resistance in community-acquired infections is rising,1–5 but in contrast to hospital-acquired infections, and contrary to popular perception, there has been little published work on its epidemiology. This review evaluates the published evidence on the relationship between antibiotic prescribing and antibiotic resistance of organisms causing community-acquired urinary tract infection (UTI).

Materials and methods

Embase was searched from 1980 to 2000 using the following subject headings and key words:

1. Antibiotic resistance—subject heading
2. Resistance—key word
3. Urinary tract infection—subject heading
4. Cystitis—subject heading
5. Pyelonephritis—subject heading
6. Bacteriuria—subject heading
7. (1 or 2) and (3 or 4 or 5 or 6)

1721 papers were identified and all English abstracts were evaluated. Papers were excluded if: they had studied patients with hospital-acquired infections; they discussed only pharmacology/treatment issues; they did not present new data; and less than five subjects were studied. Twelve papers were identified. The reference lists of these publications were reviewed and two additional studies were identified. The Cochrane database of systematic reviews was searched using the terms ‘urinary tract infection’ and ‘antibiotic resistance’. Eight reviews were identified but only three of these had been completed. All of the reviews discussed treatment only and were excluded. The abstracts of the included studies identified in the reviews were reviewed to check for completeness of the Embase search. No further studies were identified.

Results

Ecological studies (Table 1)

Skold and colleagues6 reported that outpatient prescriptions for trimethoprim in the population of the county of Jamtland, Sweden increased substantially in women after 1975. Women received twice as many trimethoprim prescriptions as men and prescribing rates were higher in older people. One hundred and fifty-three trimethoprim-resistant strains were collected in a bacteriological laboratory over eight months. These...
Table 1. Ecological studies on antibiotic use and resistance rates in UTI isolates

<table>
<thead>
<tr>
<th>Study</th>
<th>Time period</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Number in study</th>
<th>Antibiotic</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skold⁶</td>
<td>8 month period in 1979</td>
<td>Jamtland, Sweden ((n = 17,600))</td>
<td>trimethoprim-resistant urinary pathogen isolated infected urine specimen</td>
<td>153 isolates</td>
<td>trimethoprim, trimethoprim–sulphonamide</td>
<td>(E. coli, Klebsiella) sp., (Proteus) sp., (Pseudomonas) sp.</td>
</tr>
<tr>
<td>Towner⁷</td>
<td>3 years (1980–1982)</td>
<td>Nottingham Health District ((n = 650,000))</td>
<td>all urinary cultures submitted to laboratories</td>
<td>5930 isolates</td>
<td>trimethoprim, trimethoprim–sulphonamide</td>
<td>(E. coli, Klebsiella) sp., (Proteus) sp.</td>
</tr>
<tr>
<td>Raz⁸</td>
<td>2 years (1/1/86–31/12/87)</td>
<td>Served by two microbiology labs in Israel ((n = 888,700))</td>
<td></td>
<td>50,699 isolates</td>
<td>ampicillin, co-trimoxazole, cefalexin, nitrofurantoin, nalidixic acid</td>
<td>Enterobacter, enterococci, (E. coli, Klebsiella pneumoniae, Proteus) sp., staphylococci</td>
</tr>
<tr>
<td>Magee⁹</td>
<td>2 years (1/3/96–30/4/98)</td>
<td>Registered with GPs in selected centres in Wales, UK ((n = 1,200,000))</td>
<td>all routine urine specimens for diagnosis of UTI</td>
<td>30,000 isolates</td>
<td>amoxicillin, co-amoxiclav, cephalosporin, trimethoprim, quinolone</td>
<td>coliform organisms</td>
</tr>
<tr>
<td>Olafsson¹⁰</td>
<td>4 years (1/1/92–31/12/95)</td>
<td>Akureyri, Iceland ((n = 6614))</td>
<td>symptomatic, uncomplicated lower UTI in women 10–69 years of age</td>
<td>516 episodes</td>
<td>penicillins, ampicillin, mecillinam, cephalosporins, cefalothin, trimethoprim/co-trimoxazole, sulfafurazol, macrolides, tetracyclines, nitrofurantoin</td>
<td>(\beta)-haemolytic streptococci, enterococci, (E. coli, Klebsiella) sp., (Proteus) sp., (Pseudomonas) sp., staphylococci</td>
</tr>
</tbody>
</table>
tended to be obtained from specimens from older age groups. The report did not present trend data for antibiotic resistance or data on the percentage of resistant organisms from different age groups. Correlations could merely reflect prevalence of UTI investigations by age or the varying pathologies in underlying UTIs in different age groups. It is noteworthy that resistant strains were obtained from an equal number of men and women despite the prescribing difference between the men and women. However, without any denominator data, it is not possible to interpret this finding.

Towner et al. investigated the correlation between trimethoprim resistance and changes in prescription behaviour in the Nottingham area from 1978 to 1985. In the first 6 months of each year they recorded the sensitivity data on all infected urine specimens received by the Public Health Laboratory from the community of the Nottingham Health District (population c. 650 000). Estimates of usage of trimethoprim were recorded for years 1980 to 1982 and this was found to reduce by c. 20% over the three years. However, trimethoprim resistance levels rose steadily until 1984 (Escherichia coli 0.3% resistant in 1978 to 11.3% in 1984) with a slight decrease in 1985 (E. coli 9.3% resistant).

Raz et al. in Israel found that Haifa had higher resistance rates than Jezreel for ampicillin, co-trimoxazole and cefalexin, and higher overall antibiotic usage. There was a marked correlation between ampicillin usage and resistance. However, prescribing rates for co-trimoxazole and cefalexin were similar despite substantial differences in resistance rates. The authors reported that differences existed in the two areas with respect to the age profile of the population and in the use of antibiotics in veterinary and agricultural practice.

Magee et al. showed for the first time that antibiotic prescribing at the general practice level was related to resistance in community urinary coliforms isolated from patients in these practices. In data from seven laboratories and 200 general practices in Wales over a two year period there were large variations in antibiotic prescribing between practices (400–1700 prescriptions per thousand population per annum). High rates of resistance correlated with high levels of prescribing, and associations were demonstrated between resistance and age, locality and social deprivation. However, the strength of association was not strong (trimethoprim r = 0.153; ampicillin r = 0.319). Potential sampling biases were evaluated and no evidence was found that practices with high resistance rates were more selective in submitting urine samples to the laboratory.

Olafsson et al. in the Adureyri District of Northern Iceland noted high resistance rates in E. coli (35% for ampicillin) in episodes of symptomatic but otherwise uncomplicated lower UTI in women aged 10–69 years presenting to primary care. The defined daily dose of antibiotics was estimated and was also said to be high. The authors noted that the results did not necessarily imply an association but claimed that the data supported other studies which indicate this relationship. However, no trend data were supplied and no control population was available to assess a putative link.

Studies of individuals (Table 2)

In the same study as discussed above Skold et al. described a series of 20 patients from whom trimethoprim-resistant bacteria had been isolated. Thirteen had previously been prescribed trimethoprim. No comparison group was available to assess the significance of this finding.

Pedersen et al. in Denmark reported a case series of community-acquired bacteraemia (a quarter of whom had UTI) and their antibiotic therapy in the 6 months before hospital admission. They found that a history of antibiotic prescriptions was associated with up to a four-fold increase in the risk of E. coli infections resistant to ampicillin, sulphonamides and trimethoprim, after adjustments for age, sex and focus of infection. The strength of association decreased as the period between prescription and admission increased. However, only 14% of patients had been prescribed antibiotics during the 30 days before admission and 37% in the previous 6 months, and similar trends were not observed for Staphylococcus aureus or Enterobacteriaceae other than E. coli. It does not appear that recurrent infections were excluded from the case series.

Steinke et al. in Scotland compared community cases of trimethoprim-resistant Gram-negative UTI with three control groups: trimethoprim sensitive, no bacteria identified and community controls. Trimethoprim prescription in the previous 6 months was 2.5 times more common in the trimethoprim-resistant group (95% CI 1.18–5.34), although only 31% patients in this group had received the drug. Sixty per cent had received an antibiotic of some sort during this period. No adjustment was made for age/sex differences in sensitive and resistant groups, and recurrent cases seem to have been included.

Allen et al. in Canada carried out a case–control study of children attending a tertiary referral centre from 1992 to 1994. Cases and controls were defined by presence of an isolate in urine and therefore included colonized as well as truly infected individuals. Patients who received any of eight antibiotics for >4 weeks in the previous 6 months were c. 23 times (95% CI 12.0–47.6) more likely to have isolates resistant for trimethoprim–sulfamethoxazole. Other risk factors were genitourinary tract abnormalities (OR 2.4, 95% CI 1.2–4.5) and previous hospital admission (OR 2.3, 95% CI 1.4–7.5).

Wright et al. studied factors associated with trimethoprim–sulfamethoxazole resistance in urinary coliform isolates from emergency department patients with evidence from medical records of UTI. Multivariate analysis revealed current use of any antibiotic and current use, or use within the previous 3 months, of trimethoprim–sulfamethoxazole were
Table 2. Studies of individuals on previous antibiotic use and resistance

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Time period</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Number in study</th>
<th>Antibiotic</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skold⁶</td>
<td>case series</td>
<td>8 month period in 1979</td>
<td>Jamtland, Sweden (n = 17 600)</td>
<td>trimethoprim-resistant urinary pathogen isolated confirmed community-acquired bacteraemia who were hospitalized</td>
<td>20 patients</td>
<td>trimethoprim, trimethoprim–sulphonamide penicillin G, ampicillin, amoxicillin, isoxazolyl penicillins, pimemecillin, sulphamides, trimethoprim, fluoroquinolones, tetracyclines, macrolides</td>
<td>not defined</td>
</tr>
<tr>
<td>Pederson¹¹</td>
<td>case series</td>
<td>5 years (1/1/92–12/96)</td>
<td>Northern Jutland, Denmark (n = 490 000)</td>
<td>cases: trimethoprim-resistant Gram-negative bacteria. Controls: 1, trimethoprim sensitive; 2, no bacteria; 3, no urine sample</td>
<td>1717 patients</td>
<td>ampicillin, trimethoprim–sulfamethoxazole, gentamicin, cefazolin, cefotaxime, nitrofurantoin, norfloxacin, ticarcillin</td>
<td>Enterobacteriaceae, E. coli, S. aureus, Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Steinke¹²</td>
<td>case–control</td>
<td>1 month (July 1994)</td>
<td>patients presenting to their GP</td>
<td>cases: trimethoprim-resistant Gram-negative bacteria. Controls: 1, trimethoprim sensitive; 2, no bacteria; 3, no urine sample</td>
<td>52 cases, 213 control 1, 563 control 2, 100 control 3</td>
<td>ampicillin, trimethoprim–sulfamethoxazole, gentamicin, cefazolin, cefotaxime, nitrofurantoin, norfloxacin, ticarcillin</td>
<td>Gram-negative bacteria</td>
</tr>
<tr>
<td>Wright¹⁴</td>
<td>case–control</td>
<td>3 years (1995–1997)</td>
<td>participants (&gt;14 years) presenting to the emergency department of a hospital in Nashville, USA</td>
<td>UTI symptoms with urine cultures for uropathogenic organism with multiple resistance</td>
<td>67 cases, 381 controls</td>
<td>ampicillin, trimethoprim–sulfamethoxazole, nitrofurantoin, co-amoxiclav, ofloxacin, gentamicin</td>
<td>Citrobacter freundii, Enterobacter sp., E. coli, K. pneumoniae, Morganella morgani, Proteus mirabilis, Providencia sp.</td>
</tr>
<tr>
<td>Wright¹⁵</td>
<td>case series</td>
<td>2 years 3 months (1995–3/97)</td>
<td>participants (≥16 years) presenting to the emergency department of a hospital in Nashville, USA</td>
<td>UTI symptoms with positive urine culture</td>
<td>435 patients with 466 isolates</td>
<td>ampicillin, trimethoprim–sulfamethoxazole, nitrofurantoin, co-amoxiclav, ofloxacin, gentamicin</td>
<td>Citrobacter freundii, Enterobacter sp., K. pneumoniae, P. mirabilis, Pseudomonas aeruginosa, Staphylococcus sp., streptococci</td>
</tr>
<tr>
<td>Iravani¹⁶</td>
<td>double blind randomized trial</td>
<td>not stated</td>
<td>college women who presented to the Kidney Clinic of the University of Florida, USA</td>
<td>UTI symptoms and positive urine culture</td>
<td>49 patients treated with co-amoxiclav and 49 patients treated with cefaclor</td>
<td>co-amoxiclav and cefaclor</td>
<td>Enterobacteriaceae, E. coli</td>
</tr>
<tr>
<td>Iravani¹⁷</td>
<td>clinical trial</td>
<td>not stated</td>
<td>college women who presented to the University of Florida outpatient clinic</td>
<td>UTI symptoms and positive urine culture</td>
<td>71 treated with nalidixic acid and 64 with trimethoprim–sulfamethoxazole</td>
<td>nalidixic acid and trimethoprim–sulfamethoxazole</td>
<td>Enterobacteriaceae</td>
</tr>
</tbody>
</table>
Antibiotic use and antibiotic resistance in UTI

independent predictors of resistance. Forty-three per cent of patients fell into the latter category. Wright et al. also published a study of multiple antibiotic resistance and found three independent risk factors: antibiotic use, urinary catheter use and age 65 years or older. Fifty-nine per cent of resistant cases had antibiotics in the previous 3 months. Recurrent infections were not excluded in either study.

Iravani et al. reported a clinical trial of treatment of UTI in college women in the USA. In the cefaclor treatment group there was no change in resistance rates. In the co-amoxiclav treatment group the prevalence of resistant pathogens increased in recurrent infections, although the numbers were small. This was in contrast to two earlier studies from the same authors of nalidixic acid and trimethoprim–sulfamethoxazole and co-amoxiclav, which did not show any emergence of resistant pathogens causing the recurrent UTI.

Preiksaitis et al. investigated the efficacy of nalidixic acid and cefalexin in 81 adult women with recurrent UTI presenting to the infectious disease outpatient clinic of the University of Manitoba, Canada. There was no evidence that the small number of re-infections were more likely to be caused by resistant organisms.

Discussion

The rates of antibiotic resistance in community-acquired UTI are being measured in the ECO SENS project, which is the first international survey to investigate the prevalence and susceptibility of pathogens causing community-acquired, uncomplicated UTI in women. The interim results from 1960 specimens showed rates of resistance among E. coli strains of 30% for ampicillin and sulfamethoxazole, 15% for trimethoprim alone or with sulfamethoxazole, 6% for nalidixic acid, 3% for ciprofloxacin and 2% or less for co-amoxiclav, mecillinam, cefadroxil, nitrofurantoin and fosfomycin.

However, the evidence base relating this resistance to the prescribing of antibiotics in the community is very weak. Our review supports the view of the Standing Medical Advisory Committee, who recognized that there is a lack of pharmacoepidemiological studies to elucidate the dynamics of bacterial resistance and thereby design effective interventions. Only one ecological study provided good evidence of a link with prescribing rates and even then only c. 10% of the variance between rates of antibiotic resistance could be explained by variations in prescribing rates. The remaining studies were incapable of providing useful evidence since there was no control for population differences in demographics and/or no comparison population. Ecological studies have to be interpreted cautiously as they tell us nothing about the relationship between antibiotic and antibiotic-resistant infections for the individual. Harbarth et al. found in a hospital-based study that analysis of the same data on antibiotic exposure and

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Strains</th>
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<tbody>
<tr>
<td>amoxicillin-potassium clavulanate</td>
<td>nalidixic acid and cefalexin</td>
</tr>
<tr>
<td>116 patients</td>
<td>61 patients, 68 episodes treated with nalidixic acid and 63 treated with cefalexin</td>
</tr>
<tr>
<td>UTI symptoms and positive urine culture of recurrent UTI</td>
<td>bacteriauria and history of recurrent UTI</td>
</tr>
<tr>
<td>college women who presented to the University of Florida student health service</td>
<td>adult women who presented to the outpatient clinic, University of Manitoba, Canada</td>
</tr>
<tr>
<td>randomized, single-blind clinical trial</td>
<td>not stated</td>
</tr>
<tr>
<td>Preiksaitis</td>
<td>not stated</td>
</tr>
</tbody>
</table>

- Citrobacter sp., E. coli, Enterobacter aerogenes, K. pneumoniae, p. mirabilis, Staphylococcus saprophyticus, aerobic, Gram-negative organisms
resistance at a group level and individual level produced divergent results. Studies at the individual level are few in number and suffer from lack of specificity in case definition and statistical power. Without clear case definitions, studies could be detecting risk factors for colonization or for recurrent infection rather than for new infections, and the risk factors for these may differ. Even in those studies where a correlation between the prevalence of resistance and prescribing was noted, less than half the patients with resistant organisms had a recent past history of antibiotic prescriptions, and therefore other factors must be considered in the aetiology of resistant infections. The studies identified did not discuss the heterogeneity of the populations studied and indeed several excluded groups such as pregnant women who are at increased risk of serious morbidity. All three of the case–control studies satisfied the criteria proposed by Harris et al.\(^{21}\)

Many studies have shown that patients on antibiotics may develop resistant organisms and consequently become treatment failures. It has also been shown that during treatment of UTIs and other infections, faecal coliforms develop resistance.\(^{22}\) However, based on published studies, the evidence that recent antibiotic use increases the risk of infection with resistant UTI pathogens is inconclusive. Important issues that would have a major bearing on designing effective intervention strategies are: relating resistance to the reasons and appropriateness for the previous use of antibiotics; the relative influence of type of antibiotic on development and transmission of resistance; number of previous antibiotic courses; antibiotic use in household contacts; and existence of co-morbidities. Furthermore, Austin & Anderson\(^{23}\) have highlighted the need for additional information on risk factors to be able to build up realistic mathematical models of antibiotic resistance. Models to date have assumed a homogeneous population, an assumption that needs to be tested. Until the epidemiology of antibiotic resistance is better defined, with a better understanding of the roles of individual antibiotic use, transmission of resistant organisms within the community and consequences of veterinary prescribing, the design of effective interventions\(^{24}\) will not be possible.

References

1. Standing Medical Advisory Committee, Sub-Group on Anti-


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