

Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: outcomes for patients with *E.coli* UTIs

Christopher C Butler, Sharon Hillier, Zoë Roberts, Frank Dunstan, Anthony Howard and Stephen Palmer

ABSTRACT

Background

Antimicrobial resistance is considered to be one of the major threats to public health. However, the practical implications for patients and workload in primary care are largely unknown.

Aim

To determine outcomes for patients managed in primary care with an antibiotic resistant compared to an antibiotic sensitive *Escherichia coli* (*E. coli*) urinary tract infection (UTI).

Design

Nested case control study with prospective measurement of outcomes.

Setting

Ten general practices in South Wales.

Method

Patients consulting with symptoms suggestive of UTI identified through systematic sampling, and with a laboratory proven *E. coli* infection, were followed up by interview 1 month after their consultations and by searching of their medical records.

Results

Nine hundred and thirty-two patients were interviewed and had their medical records reviewed. The risk of patients reporting 'feeling poorly', 'frequency or pain on urinating' and being 'out of action' for more than 5 days after consulting was significantly increased for patients with resistant compared to sensitive infections. After adjusting for risk factors, there was an increased risk of 'frequency or pain on urinating' and 'being out of action' for those infected with a resistant *E. coli*. The median number of maximum reported days with at least one symptom was 12 days for patients with *E. coli* infections resistant to trimethoprim, 7 days for infections resistant to ampicillin, 7 days for infections resistant to any antibiotic, and 5 days for infections sensitive to all tested antibiotics. Even if treated with an appropriate antibiotic, infections caused by a resistant strain were symptomatic for longer. For those infected with an organism resistant to at least one antibiotic, the odds ratio (OR) for re-visiting their GP within the next 30 days for the UTI was 1.47 (95% confidence interval [CI] = 1.10 to 1.95). The OR was 1.49 (95% CI = 1.11 to 2.00) for ampicillin resistance and 2.48 (95% CI = 1.70 to 3.59) for trimethoprim resistance.

Conclusions

Resistant *E. coli* UTIs are symptomatic for longer and cause increased work load in general practice.

Keywords

anti-bacterial agents; cohort study; drug resistance; bacterial; primary health care; treatment outcomes; urinary tract infections.

INTRODUCTION

Antibiotic resistance increases the length of hospital stay¹ and mortality² in secondary care, but the situation in primary care is far from clear.³ Primary care clinicians are concerned about the issue, but only infrequently report encountering treatment failure associated with antibiotic resistance and may see it as a 'public health or hospital issue', remote from prescribing decisions for their individual patients.⁴

If it could be shown clearly that resistant infections were associated with poorer outcomes for patients managed in primary care, this may concentrate attention on the impact of antibiotic resistance for primary care and further promote the appropriate use of antibiotics. We therefore set out to compare outcomes for patients infected with resistant and sensitive *Escherichia coli* (*E. coli*) urinary tract infections (UTIs).

We chose to study UTI because UTI is one of the commonest bacterial infections managed in general

C Butler, MD, professor of Primary Care Medicine; *S Hillier*, PhD, senior research fellow; *Z Roberts*, PhD, lecturer; *F Dunstan*, DPhil, professor; *S Palmer*, FFPHM, professor of Epidemiology and Public Health, Department of Epidemiology, Statistics and Public Health, Centre for Health Sciences Research, Cardiff University, Heath Park, Cardiff.
A Howard, FRCPath, director, Infection and Communicable Disease Service, National Public Health Service for Wales, ICDS Corporate Office Temple of Peace & Health, Cathays Park, Cardiff.

Address for correspondence

Christopher C Butler, Professor of Primary Care Medicine
Department of General Practice, Cardiff University, Centre for Health Sciences Research, School of Medicine, 3rd Floor, Neuadd Meirionnydd, Heath Park, Cardiff CF14 4XN.
E-mail: butlercc@cf.ac.uk

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practice, accounting for between 1 and 3% of all general practice consultations⁵ and 15% of all community prescriptions for antibiotics.⁶ *E. coli* cause 75–90% of cases.⁷

METHOD

Ten GP practices from the former Bro Taf Health Authority, South East Wales, UK, were selected to be geographically dispersed, yet representative of all practices in Bro Taf in relation to antibiotic prescribing rates, number of registered patients and social deprivation. Participating clinicians were asked to approach sequentially all patients presenting with a clinically suspected UTI to participate in the study during an 89-week period (17 July 2002 to 31 March 2004).

They explained the study to eligible patients, obtained written informed consent, and asked all patients to submit a urine specimen for culture and analysis. Catheterised patients and those who had a laboratory confirmed UTI within the previous 4 weeks (non-incident) were excluded. Copies of the laboratory results for these specimens were sent to the research team at the same time as they were sent to the practices.

Our research nurse contacted patients who had provided consent and who had submitted a urine specimen positive for an *E. coli* infection. The research nurse administered a structured questionnaire with patients during a face-to-face interview or over the telephone. She was blind to the reported sensitivity of the patients' *E. coli* infections. The questionnaire collected information on treatment and symptoms of the incident UTI infection, re-consultation with GP, comorbidity and socioeconomic factors.

The questionnaire asked whether the patient 'felt poorly or generally unwell', had 'pain or discomfort when urinating', had 'back or groin pain', 'urinated more frequently', had a 'high temperature', and the number of days that each of these symptoms were present. In addition, patients were asked about the number of days they had taken off work or school, or, if not working, whether they were able to undertake usual activities. We called this variable 'number of days out of action'. The number of days was calculated from day of consultation as 'day 0'. The nurse aimed to interview patients 4 weeks after their initial consultation.

The research nurse or practice staff reviewed participating patients' medical records and recorded the antibiotic treatment prescribed for the incident UTI and re-consultations for UTI within the next 30 days. Specimens were sent to laboratories using routine transport systems. They were analysed in the local microbiology department

How this fits in

In hospital settings, antimicrobial resistant organisms are associated with increased morbidity, mortality and costs. The effect of antimicrobial resistance on common infections managed in primary care has not previously been well described. General medical practitioners often view their antibiotic prescribing decisions as distant or unconnected with the problem of antimicrobial resistance, consequent poorer outcomes for their patients, and increased workload for themselves. This study is one of the first to show that patients with a resistant compared to a sensitive *E. coli* urinary tract infection are symptomatic and out of action for longer, even if treated with an appropriate antibiotic. Furthermore, patients infected with a resistant *E. coli* are also more likely to re-consult for the same infection in the subsequent month.

(Cardiff PHL [Lab 1]; Royal Glamorgan Hospital, Llantrisant [Lab 2]; and Prince Charles Hospital, Merthyr Tydfil [Lab 3]) for red and white cells, bacterial pathogens and susceptibility for routine diagnostic purposes. A threshold of >105 organisms per ml defined a positive culture.

Mixed infections were included if *E. coli* was reported. Sensitivity to trimethoprim, ampicillin, co-amoxiclav, cephalexin, ciprofloxacin and nitrofurantoin were reported using the British Society of Antimicrobial Chemotherapy methods. Laboratory procedures were subject to careful quality control in cooperation with the Antibiotic Reference Unit. Lab 1 retested a proportion of *E. coli* specimens from all of the labs for reproducibility. Laboratories tested resistance to ampicillin, which we have considered equivalent to amoxicillin.

Questionnaire and clinical record data were double entered and checked. Sensitivity data from the laboratories for all urine specimens during the study period were made available as Excel files. Morbidity was coded according to the International Classification of Diseases.¹⁰ Social class was determined from the patient's job title and work sector. Data were cleaned, coded, merged using Access, and then transferred into SPSS for analysis.

Odds ratios (ORs) with 95% confidence intervals (CIs) were used to investigate the univariate effect of risk factors on three binary clinical outcomes. Logistic regression was used to calculate ORs to measure the effect of resistance on poor clinical outcome after adjusting for significant risk factors. We used 'greater than 5 days after consulting' as the measure of duration of symptoms, since 5 working days represents a common practical limit for self certification for sickness absence in the UK. We summarised the maximum number of days patients reported experiencing any of the symptoms using the median and interquartile range

(IQR). A comparison between patients with sensitive and resistant infections was made using the Mann–Whitney test. A new approximately normally distributed variable, the logarithm of the maximum number of days +1, was used in a multivariate linear regression analysis to adjust this comparison for risk factors. Results of this analysis are reported in terms of the percentage increase in the maximum number of days with any one symptom.

RESULTS

A total of 13 805 urine samples were submitted from the participating practices during the study period: 2124 identified an *E. coli* infection; 10 737 had no growth identified; and 944 samples showed an infection other than *E. coli*. Of the 2124 *E. coli* samples, 496 were duplicate samples and 120 patients were excluded by the health professional for the following reasons: catheterised ($n = 18$); lab confirmed UTI in previous 4 weeks ($n = 3$); patient unable to give consent (too ill/confused) ($n = 59$); patient not registered at practice ($n = 19$); unable to speak English ($n = 2$); died ($n = 4$); not suitable to contact ($n = 8$); and unknown ($n = 7$). Questionnaires were completed for 932 patients, 62% of the 1508 eligible cases. The median number of days to interview was 32 (IQR = 20–48).

Of those interviewed, 420/922 (45.1%) were infected with an *E. coli* resistant to at least one tested antibiotic: 10 samples were not tested for resistance to any antibiotics. Resistance to specific antibiotics were: ampicillin 40.0%; trimethoprim 17.4%; Augmentin® (GlaxoSmithKline) 13.2%; and cephalosporin 8.1%. The medical records of 903 interviewed patients (97%) were reviewed: 26 of the remaining 29 patients had left the practice and the records were missing for three. In total, interview and medical record validation data were complete for 60% of 1508 eligible cases.

Demographic characteristics of those who provided informed consent were compared to those who did not to see if they were similar in terms of age, sex and practice. There were no significant differences except that patients from two practices had a higher rate of providing informed consent than patients from other practices. There were 39 patients who consented to participate but were lost to follow up. Of these, 38/39 (97%) were female compared to 843/932 (90%) in those interviewed. The median age of those who consented but were not interviewed was 28.3 years (IQR = 33.3–68.7) in comparison to 51.5 years (IQR = 46.1–76.7) in those who were interviewed.

Quality assurance of laboratory data showed that sensitivity results to ampicillin, trimethoprim and

ciprofloxacin were consistent for samples tested at Labs 2 and 3 and then re-tested at Lab 1 (347 samples).

The risk of patients reporting 'feeling poorly' for more than 5 days after consulting was significantly increased for patients with resistant compared to sensitive *E. coli* infections (Table 1). This was found for resistance to at least one antibiotic, resistance to ampicillin, and resistance to trimethoprim. Identified confounders were comorbidity, previous bladder operation and previous catheterisation. After adjusting for these factors, the relationship between resistance and time 'feeling poorly' remained significant for those patients with infections resistant to the prescribed antibiotic (Table 2).

The risk of 'frequency or pain on urinating' for more than 5 days was significantly increased for patients with an antibiotic resistant compared to sensitive *E. coli* infections (Table 1). This was found for resistance to at least one antibiotic, resistance to ampicillin, and resistance to trimethoprim. Identified confounders were older age, comorbidity, previous bladder operation, and previous catheterisation. After adjusting for these factors, patients with a trimethoprim-resistant UTI were still at increased risk of 'frequency or pain on urinating' for more than 5 days, although statistical significance was lost for ampicillin resistance and for resistance to at least one antibiotic where the patient was prescribed an antibiotic to which their infection was sensitive (Table 2).

The risk of being more than 5 days 'out of action' was significantly increased for patients infected with an *E. coli* resistance to at least one antibiotic, resistance to ampicillin, and resistance to trimethoprim, compared to sensitive to all (Table 1). Identified confounders were being prescribed an antibiotic to which the organism was resistant, male sex, comorbidity, previous bladder operation and previous catheterisation. After adjusting for these factors, the risk of being 'out of action' for more than 5 days remained significant for all categories. Although the size of the effect was reduced (Table 2), the ORs exceeded 3 for patients with infections resistant to the prescribed antibiotic and, in the case of trimethoprim resistance, the OR was 3 for patients with infections sensitive to the prescribed antibiotic.

There was no significant association found between social class and any of the three clinical outcomes presented in Table 1. This was also the case for age, with the exception of those in the 65–84 year age group who had a significantly increased odds (OR = 1.82, 95% CI = 1.23 to 2.69) of having pain or frequency for greater than 5 days compared to the 25–44 year age group.

Table 1. Results of univariate analyses to investigate risk factors for three different clinical outcomes.

	>5 days poorly		>5 days pain or frequency		>5 days 'out of action'	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Sensitive to all	151/476 (31.7)	Ref	132/457 (28.9)	Ref	70/493 (14.2)	Ref
Resistance to at least one antibiotic	154/389 (39.6)	1.41 (1.07 to 1.87)	146/378 (38.6)	1.55 (1.16 to 2.07)	98/410 (23.9)	1.90 (1.35 to 2.67)
Resistance to ampicillin	137/341 (40.2)	1.45 (1.08 to 1.93)	127/332 (38.3)	1.53 (1.13 to 2.06)	85/360 (23.6)	1.87 (1.32 to 2.65)
Resistance to trimethoprim	74/147 (50.3)	2.18 (1.50 to 3.18)	80/141 (56.7)	3.23 (2.19 to 4.77)	51/154 (33.1)	2.99 (1.97 to 4.56)
Treated with antibiotic resistant to						
No	234/728 (32.1))	Ref	212/703 (30.2)	Ref	126/754 (16.7))	Ref
Yes	55/95 (57.9)	2.9 (1.88 to 4.49)	52/94 (55.3)	2.87 (1.85 to 4.44)	34/98 (34.7)	2.65 (1.68 to 4.19)
Sex						
Male	36/84 (42.9)	Ref	28/74 (37.8)	Ref	29/86 (33.7)	Ref
Female	272/790 (34.4)	0.7 (0.44 to 1.11)	253/769 (32.9)	0.81 (0.49 to 1.32)	141/827 (17.0)	0.4 (0.25 to 0.65)
Any comorbidity						
No	85/296 (28.7)	Ref	83/288 (28.8)	Ref	45/307 (14.7)	Ref
Yes	223/578 (38.6)	1.56 (1.15 to 2.11)	198/555 (35.7)	1.37 (1.01 to 1.87)	125/606 (20.6)	1.51 (1.04 to 2.20)
Bladder operation						
No	260/784 (33.2)	Ref	239/758 (31.5)	Ref	146/817 (17.9)	Ref
Yes	47/80 (58.8)	2.87 (1.80 to 4.59)	39/76 (51.3)	2.29 (1.42 to 3.68)	23/85 (27.1)	11.71 (1.02 to 2.84)
Catheter						
No	216/668 (32.3)	Ref	197/654 (30.1)	Ref	115/702 (16.4)	Ref
Yes	88/188 (46.8)	1.84 (1.33 to 2.56)	77/171 (45.0)	1.90 (1.35 to 2.68)	52/191 (27.2)	1.91 (1.31 to 2.78)
Diabetes						
No	287/414 (35.3)	Ref	258/787 (32.8)	Ref	157/850 (18.5)	Ref
Yes	20/56 (35.7)	1.02 (0.58 to 1.80)	21/53 (39.6)	1.35 (0.76 to 2.38)	12/59 (20.3)	1.13 (0.58 to 2.17)

OR = odds ratio.

The maximum number of days on which patients reported experiencing at least one of the symptoms recorded was significantly greater for resistant infections compared to sensitive infections. The median number of maximum reported days with at least one symptom was 5 days (IQR = 3–12) for those with infections sensitive to all tested antibiotics. In comparison, for those with infections resistant to trimethoprim, the median was 12 days (IQR = 5–23, $P < 0.001$), 7 days for those resistant to ampicillin (IQR = 3–17, $P = 0.029$) and 7 days for those resistant to any antibiotic (IQR = 3–17, $P = 0.12$).

To investigate this further, we subdivided patients into those who were infected with an organism resistant to the prescribed antibiotic and those who were infected with an organism sensitive to the prescribed antibiotic (Table 3), and adjusted for the confounders comorbidity, sex, previous catheterisation and previous bladder surgery. We found that patients with an *E. coli* resistant to at least one antibiotic ($n = 420$) and who were prescribed an antibiotic to which the organism was resistant, had a significantly increased number of days with at least one symptom compared to those sensitive to all antibiotics; an increase of 60% (95% CI = 30 to 97).

Similar results were found for those resistant to ampicillin ($n = 369$) and those resistant to trimethoprim ($n = 161$). Indeed, for those infected with a trimethoprim-resistant organism and who were prescribed an antibiotic to which the organism was sensitive, there was still a significant increase in the number of days with at least one symptom. Women without comorbidity, and never

Table 2. Results of multivariate logistic regression model to measure the effect of resistance on poor clinical outcomes after adjusting for significant risk factors.

	Adjusted OR ^a (95% CI)		
	>5 days versus 0–5 days		
	Poorly	Pain or frequency	'Out of action'
Resistance to at least one antibiotic			
Resistant to antibiotic prescribed	2.9 (1.8 to 4.7)	3.4 (2.1 to 5.5)	3.4 (2.0 to 5.8)
Sensitive to antibiotic prescribed	1.0 (0.7 to 1.4)	1.1 (0.8 to 1.6)	1.6 (1.0 to 2.3)
Resistance to ampicillin ^b			
Resistant to antibiotic prescribed	3.4 (2.0 to 5.7)	3.8 (2.3 to 6.4)	3.6 (2.0 to 6.3)
Sensitive to antibiotic prescribed	1.1 (0.8 to 1.5)	1.1 (0.8 to 1.6)	1.5 (1.0 to 2.3)
Resistance to trimethoprim ^b			
Resistant to antibiotic prescribed	2.8 (1.7 to 4.7)	4.0 (2.4 to 6.9)	3.6 (2.0 to 6.4)
Sensitive to antibiotic prescribed	1.3 (0.7 to 2.4)	2.7 (1.5 to 5.1)	3.0 (1.6 to 5.8)

^aAdjusted for age, sex, comorbidity, previous bladder operation and previous catheterisation.^bStrains resistant to both trimethoprim and ampicillin were included in both analyses.

Table 3. Results of multivariate linear regression model to measure the effect of resistance on number of days with any one symptom after adjusting for significant risk factors.

	% increase in number of days with any one symptom ^a compared to those sensitive to all antibiotics			
	Resistant to antibiotic prescribed		Sensitive to antibiotic prescribed	
	<i>P</i> -value	Increase (95% CI)	<i>P</i> -value	Increase (95% CI)
Resistant to trimethoprim ^b	<0.001	56 (25 to 94)	<0.001	70 (30 to 123)
Resistant to ampicillin ^b	<0.001	72 (39 to 114)	0.669	-3 (-16 to 12)
Resistant to at least one antibiotic	0.001	60 (30 to 97)	0.943	1 (-13 to 16)

^aAdjusted for sex, comorbidity, previous bladder operation and previous catheterisation.

^bStrains resistant to both trimethoprim and ampicillin were included in both analyses.

catheterised, and who had not had bladder surgery who are infected with an *E. coli* that is sensitive to all tested antibiotics would have a mean maximum duration of symptoms of 5.1 days (95%CI = 4.3 to 5.9) after consulting. This compares to a mean of 8.7 days (95%CI = 7.0 to 10.8) for an infection that is resistant to the antibiotic initially prescribed. As these CIs do not overlap, this difference of 3.6 days is highly significant.

However, there were differences in the antibiotic initially prescribed between these groups. Of the 478 patients with *E. coli* sensitive to all antibiotics, 375 (78.4%) were initially prescribed trimethoprim. The 63 patients with an infection resistant to trimethoprim but sensitive to the prescribed antibiotic were mostly prescribed cephalexin ($n = 24$) and nitrofurantoin ($n = 22$). Among the 87 patients with infections resistant to trimethoprim and resistant to the prescribed antibiotic, 76 were initially prescribed trimethoprim.

We also investigated how antibiotic resistance affected workload and found that 30% of our patients revisited the GP within 30 days of the UTI and that 25% had at least one additional course of antibiotics prescribed. Patients infected with a resistant *E. coli* UTI compared to a sensitive *E. coli* UTI were at increased risk of revisiting the GP within the next 30 days for the UTI. For those infected with an organism resistant to at least one antibiotic, the OR was 1.47 (95% CI = 1.10 to 1.95). For ampicillin resistance, the OR was 1.49 (95% CI = 1.11 to 2.00) and for trimethoprim resistance the OR was 2.48 (95% CI = 1.70 to 3.59). In addition, the patients were at increased risk of having to change their antibiotic with an OR of 2.3 (95% CI = 1.69 to 3.13) for those resistant to at least one antibiotic; OR = 2.2 (95% CI 1.60 to 3.00) for those resistant to ampicillin; and OR = 7.1 (95% CI = 4.70 to 10.60) for those resistant to trimethoprim.

DISCUSSION

Summary of main findings

To our knowledge, this is the first report of a pragmatic study of outcomes for systematically sampled patients managed in primary care with an antibiotic-resistant compared to antibiotic-sensitive common infection that has been able to adjust for a range of potential confounding factors.

We have shown that an *E. coli* UTI, managed in general practice, which is resistant to at least one antibiotic is significantly associated with patients reporting 'feeling poorly', 'experiencing pain and frequency' and being 'out of action' for more than 5 days after consulting. Similar results were found for those infections resistant specifically to ampicillin and those resistant to trimethoprim. After adjusting for a range of risk factors, resistance to trimethoprim remained strongly associated with pain or frequency of urinating for more than 5 days, when the infection was resistant and also when sensitive to the antibiotic prescribed.

After similar adjustment, resistance to at least one antibiotic, resistance to ampicillin and resistance to trimethoprim remained significant risk factors for patients being out of action for more than 5 days. This suggests that even if a resistant infecting organism is treated with an antibiotic to which it is sensitive, and taking into account a range of demographic factors and comorbidity, patients are likely to have symptoms for longer than if they had been infected with a sensitive organism.

We found that the median number of days with at least one symptom was 5 for patients with an *E. coli* sensitive to all antibiotics compared to a median of 7 days for patients infected with an organism resistant to any antibiotic or resistant to ampicillin, and 12 days for those infected with an *E. coli* resistant to trimethoprim, more than twice the value for *E. coli* sensitive to all antibiotics. These differences remained significant, even when adjusted for important confounding factors.

In addition to increasing symptom duration, we have also shown that antibiotic resistance affects workload in primary care as it increases the chance that the patient will re-consult for the UTI, and is associated with an increased risk of the patient being prescribed a second antibiotic. These factors have an obvious impact on an already busy general practice.

Strengths and limitations of the study

Strengths of our study include a systematic approach to sampling, face-to-face interviews (only 6% were conducted over the telephone) with a large number of patients to determine outcomes, validation of interview data with data derived from

medical records, and validation of laboratory sensitivities. Basic demographic characteristics were similar to those that consented to participate and those that did not, suggesting a low risk of selection bias. We successfully followed up 97% of those who provided consent to participate. Those who provided consent to participate but who were not interviewed were younger and almost all female, but the small number of these patients suggests a low level of risk of attrition bias affecting our results.

We found a relatively low level of samples positive for *E. coli* (15%). However, there was no selection regarding our denominator and it included duplicate samples, and samples sent for pregnant women. We included data on the most common forms of resistance and most frequently used antibiotics for treating UTI in general practice. Duration of symptoms was determined at interview, about a month after consulting, so recall bias is possible for this outcome.

An important aspect of our study design was that health professionals were asked to request specimens for all clinically suspected UTI. The extent to which this happened was not easily validated, as practices were not able to keep a log of all patients presenting with UTI symptoms. However, we identified an overall increase in total urine specimens submitted from all study practices from an average of 6505 per year previous to the study to an average of 8059 per year during the study period (24% increase).

Comparison with existing literature

Outcomes associated with treating a UTI with an antibiotic to which the infecting organism is resistant have previously been assessed using secondary analyses of randomised controlled trial data. Most treatment trials exclude patients with infections resistant to the antibiotic being evaluated, and most of these studies focus on microbiological outcomes rather than clinical cure.⁷

Comparisons of outcomes for resistant compared to sensitive UTIs derived from trial data have included small numbers and not controlled for comorbidity, age and sex when comparing outcomes for those with a resistant compared to a sensitive infection.⁸⁻¹²

In an observational study, Raz and colleagues followed 618 women presenting to outpatient clinics with dysuria, frequency, urgency and a positive urine culture treated with trimethoprim/sulphamethoxazole for 5 days. After 1 week, 293/333 of those infected with a sensitive organism were cured compared to 81/151 infected with a resistant organism.¹³ These authors did not attempt to adjust for age, social class, past medical history and comorbidity.

Implications for future research and clinical practice

It is not clear why infections caused by *E. coli* resistant to trimethoprim should last longer even if treated with an appropriate antibiotic. Trimethoprim resistance may make *E. coli* generally more resilient *in vivo* by an, as yet, unknown mechanism. We have shown that those with *E. coli* resistant to trimethoprim but sensitive to the prescribed antibiotic were initially prescribed different antibiotics to those with a resistant *E. coli* infection that was resistant to the initial antibiotic.

This suggests that these groups of patients may have been different in clinically important, but as yet unidentified, ways. Thus, we may not have taken into account possible additional, important confounders. Our findings need replication and further exploration.

Our findings clearly indicate to clinicians and patients that being infected with a resistant organism does have important implications for patients managed in primary care, and that the problem of antimicrobial resistance is not confined to more dramatic but less frequent cases managed largely in hospitals. Since consumption of antibiotics is the most important risk factor for infection with a resistant *E. coli* compared to an *E. coli* sensitive to all tested antibiotics,^{14,15} our findings should concentrate attention on improving the appropriate use of antibiotics in primary care.

There is a danger that clinicians respond by increasing their use of newer, broad spectrum antibiotics as empirical therapy. This may contribute to a vicious cycle of driving resistance levels up further and encouraging the use of even more powerful antibiotics. Instead, these results, taken together with evidence that recent antibiotic prescribing is a major risk factor for being infected with a resistant organism, should encourage a more cautious use of any antibiotic. There is an urgent need for rapid point-of-care tests that not only identify or rule out significant bacterial urinary tract infections, but also identify whether or not significant infections are caused by resistant organisms.

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Ethics Committee

Ethics approval was granted by the South East Wales LREC (01/4329 [17 Jan 2002])

Competing interests

The authors have stated that there are none

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REFERENCES

1. Einarsson S, Kristjansson M, Kristinsson *et al*. Pneumonia caused by penicillin-non-susceptible and penicillin-susceptible pneumococci in adults: a case-control study. *Scand J Infect Dis* 1998; **30**(3): 253–256.
2. Feikin DR, Schuchat A, Kolczak M, *et al*. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995–1999. *Am J Public Health* 2000; **90**(2): 223–229.
3. Gupta K, Stamm WE. Outcomes associated with trimethoprim/sulphamethoxazole (TMP/SMX) therapy in TMP/SMX resistant community-acquired UTI. *Int J Antimicrob Agents* 2002; **19**(6): 554–556.
4. Butler CC, Rollnick S, Maggs-Rapport F, *et al*. Understanding the culture of prescribing: A qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *BMJ* 1998; **317**: 637–642.
5. MeRec. Urinary tract infection. *MeRec Bulletin* 1995; **6**(8): 29–32.
6. Mazzulli T. Resistance trends in urinary tract pathogens and impact on management. *J Urol* 2002; **168**(4 Pt 2): 1720–1722.
7. Gupta K, Hooton TM, Stamm WE. Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections. *Ann Intern Med* 2001; **135**(1): 41–50.
8. McCarty JM, Richard G, Huck W, *et al*. A randomized trial of short-course of ciprofloxacin, ofloxacin, or trimethoprim/sulfamethoxazole for the treatment of acute urinary tract infection in women. Ciprofloxacin Urinary Tract Infection Group. *Am J Med* 1999; **106**(3): 292–299.
9. Talan DA, Stamm WE, Hooton TM, *et al*. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. *JAMA* 2000; **283**(12): 1583–1590.
10. Hooton TM, Scholes D, Gupta K, *et al*. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. *JAMA* 2005; **293**(8): 949–955.
11. Masterton RG, Bochsler JA. High-dosage co-amoxiclav in a single dose versus 7 days of co-trimoxazole as treatment of uncomplicated lower urinary tract infection in women. *J Antimicrob Chemother* 1995; **35**(1): 129–137.
12. Nicolle LE, Hoepelman AI, *et al*. Comparison of three days' therapy with cefcanel or amoxicillin for the treatment of acute uncomplicated urinary tract infection. *Scand J Infect Dis* 1993; **25**(5): 631–637.
13. Raz R, Chazan B, Kennes Y, *et al*. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. *Clin Infect Dis* 2002; **34**(9): 1165–1169.
14. Steinke DT, Seaton RA, Phillips G, MacDonald TM, *et al*. Factors associated with trimethoprim-resistant bacteria isolated from urine samples. *J Antimicrob Chemother* 1999; **43**(6): 841–843.
15. Wright SW, Wrenn KD, Haynes ML. Trimethoprim-sulfamethoxazole resistance among urinary coliform isolates. *J Gen Intern Med* 1999; **14**(10): 606–609.