Not so simple cystitis: How should prescribers be supported to make informed decisions about the increasing prevalence of infections caused by drug-resistant bacteria?

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SUMMARY

Trimethoprim is a safe, effective, and inexpensive treatment for cystitis. However, at least 25% of bacteria isolated from urine samples in general practice are now resistant to trimethoprim in the laboratory. The relationship between laboratory resistance and clinical outcome is complex. Cephalexin appears to be more active than trimethoprim in the laboratory but has been consistently less effective in clinical trials. There is little point in collecting data about the prevalence of drug resistance in urinary bacteria unless it is linked to evidence about the impact of resistance on clinical outcomes. Pragmatic clinical trials are required to provide practices with clear thresholds for managing their antibiotic policies; for example, 'Change from trimethoprim to drug X when the probability of trimethoprim resistance reaches Y%.' Prescribers should be aware that trimethoprim resistance is most likely to occur in patients who have been exposed to trimethoprim or other antibiotics in the previous six months, and that the risk increases with age. This inform-ation could be used to stratify women according to risk of infection by trimethoprim-resistant bacteria. Health education leaflets are an effective method for reducing the frequency of recurrent cystitis. Symptomatic treatment can control symptoms and allow time for microbiological investigation. Both of these strategies may help to reduce unnecessary prescribing of antibiotics in general and quinolones in particular.

Keywords: *drug-resistant bacteria; cystitis; urinary bacteria.*

Introduction

TRIMETHOPRIM is widely recommended as the firstline therapy for community-acquired urinary infections in many practice formularies. However, resistance has been increasing globally. This is particularly marked in countries in which consumption of trimethoprim and co-trimoxazole is not restricted by prescription.[1,28,32,39] However, even in the United States, where antibiotics are not available over-the-counter, resistance to trimethoprim and trimethoprim-sulfamethoxazole in *Escherichia coli* increased linearly from 9% in 1992 to more than 18% in 1996.[19] This paper reviews international publications and local evidence from Tayside related to this issue, and argues that better information systems are required to allow general practitioners (GPs) to make the most informed choices possible.

Ms Jayne MacKenzie, a 27-year-old accountant, presents with frequency and dysuria for the past 48 hours. She has been prescribed three courses of trimethoprim in the past two years for similar symptoms. Five years ago she was investigated for recurrent urinary tract infection and no structural abnormalities were detected. On this occasion she says that she does not want trimethoprim in case the bacteria have become resistant to this antibiotic. She cites the news reports after the 1998 Standing Medical Advisory Committee Report on antibiotic resistance.[40]

How do GPs respond to the problem of antibiotic resistance?

Concern about resistance may lead doctors to prescribe newer antibiotics, which are generally designed to overcome mechanisms of resistance to older drugs. New antibiotics are accepted more rapidly than any other drug class,[30] but this is only a temporary solution to the problem, as resistance will eventually develop to these new drugs as well.[11,31] Moreover, there are inevitable increases in drug costs, and patients are exposed to drugs with less proven safety. For example, temafloxacin, a quinolone, was withdrawn after fewer than six months of clinical use because of an unexplained, and sometimes fatal, haemolytic uraemic syndrome.[2]

What is the prevalence of trimethoprim resistance among urinary isolates?

Over the past 10 years the prevalence of trimethoprim resistance has risen steadily from less than 10% in the early 1980s to 25% or more in the 1990s. In the past three years, the prevalence of trimethoprim resistance in Tayside has been 27% to 28% in Gram-negative bacteria isolated from urine samples from general practice (Table 1). Of course, what the GP wants to know is, 'Which antibiotic should I use to treat this patient?' Unfortunately, information from a urine sample from this patient is probably 48 hours or more away. Knowing the prevalence of resistance in recent urinary isolates from local practices may be helpful, but only if this information is linked to evidence about the impact of resistance on clinical outcome.

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Table 1. Sensitivity to cephalexin, nitrofurantoin, and trimethoprim of Gram-negative bacteria isolated from urine samples sent by GPs in Tayside.

Year	Bacteria	Number of samples	Sensitivity to		
			Cephalexin (%)	Nitrofurantoin (%)	Trimethoprim
1995	Escherichia coli	3181	94	98	77
	Proteus spp	192	86	0	5
	Other Gram-negative isolates (excluding Pseudomonas spp)	354	60	55	67
	All Gram-negative isolates	3727	91	86	72
1996	Escherichia coli	3710			77
	Proteus spp	297			43
	Other Gram-negatives (excluding Pseudomonas spp)	448			73
	All Gram-negative isolates	4455			73
1997	Escherichia coli	4407			76
	Proteus spp	270			49
	Other Gram-negatives (excluding Pseudomonas spp)	423			75
	All Gram-negative isolates	5100			73

Should GPs always prescribe the antibiotic that most isolates are sensitive to?

A literal interpretation of resistance data (Table 1) would be that cephalexin should be the most effective of these treatments for cystitis. However, this assumes an absolute correlation between *in vitro* resistance and clinical outcome, whereas there is substantial evidence to show that this is not the case.

There are six published randomised controlled trials (RCTs) comparing cephalexin (or cefadroxil, a very similar drug) to either trimethoprim alone[9,27] or co-trimoxazole alone,[6,18,24] or to both trimethoprim and co-trimoxazole.[7] All of these trials consistently show that recurrence of cystitis is more likely to occur after cephalosporin treatment (Table 2). Pooled results give response rates of 86% (392/457) in the trimethoprim/co-trimoxazole arm compared with 68% (251/367) in the cephalexin/cefadroxil arm: an odds ratio (OR) of 2.8 (95% CI = 2.0–3.9) in favour of trimethoprim/co-trimoxazole.

All of these trials report higher rates of adverse effects after treatment with cephalosporins versus trimethoprim or co-trimoxazole. Much of this difference is accounted for by vaginitis, which, in the most recent trial, was shown to be a result of superinfection by *Candida spp* following cefadroxil treatment.[24] Taking both recurrence of cystitis and candida vaginitis as adverse outcomes, the probability of clinical success in this trial was 67% for co-trimoxazole, 42% for nitrofurantoin, and 28% for cefadroxil.

Observational data from Tayside are consistent with the results of these clinical trials. The probability of clinical success after prescription of co-trimoxazole for urinary tract infection (UTI) was 85%, compared with 64% for cephalexin.[29] In a separate study it was found that the risk of prescription of antifungal drugs was significantly increased after prescription of antibacterial drugs, with an OR of 5.5 (95% CI = 3.9–7.9), and that the attributable risk was highest among those who were taking cephalosporins (OR = 12.8, 95% CI = 9.1–16.5).[4]

How should GPs respond to reports of increasing resistance?

It is clear from these data that sensitivity to cephalexin measured by currently available *in vitro* techniques is a poor predictor of clinical outcome. There are relatively few data about the relationship between *in vitro* resistance to trimethoprim, or co-trimoxazole, and clinical outcome because most of the trials were completed when resistance to these drugs was rare. Moreover, most trials of new drugs exclude patients with infections caused by bacteria that are resistant to any of the drugs in the trial. A recent systematic review identified 21 good quality RCTs in simple cystitis that compared quinolones with co-trimoxazole.[5] However, only six of these trials included women with co-trimoxazole bacteria, and only five provided information about clinical response for patients with resistant or sensitive bacteria.[17,22-24,33] Despite the small numbers, resistance was associated with a markedly reduced probability of successful treatment with co-trimoxazole: 42% for 12 women with co-trimoxazole resistant bacteria versus 95% for 211 women with co-trimoxazole sensitive bacteria; OR = 0.04 (95% CI = 0.01–0.13).

Recurrent cystitis is a common problem, but rates of infection vary widely. For example, in one study of 51 'infection-prone women' over a median of nine years, rates of infection varied from 0.3 to 7.6 episodes per year.[36] Rates of recurrence can be reduced by long-term antibiotic prophylaxis.[36] However, as with treatment, the effectiveness of prophylaxis is being compromised by the increasing prevalence of drug-resistant strains.[36] An alternative strategy is to provide patients with information about prevention and management of cystitis.[3] In this controlled study, 70 women with cystitis were divided into two groups. One group was given an educational leaflet[21] while the other group received normal treatment alone. In the 40 weeks after the first consultation, 29% of women in the intervention group reconsulted with cystitis compared with 66% of women in the control group.

How should prescribers be supported to make better decisions?

Some of the confusion could be resolved with better clinical data. For example, in a randomised trial comparing amoxycillin and co-amoxiclav treatment of cystitis in the elderly, bacterial beta-lactamase production was a strong predictor of clinical failure with amoxycillin treatment.[16] In contrast, Brauner *et al* found that beta-lactamase production did not predict the clinical outcome of cephalexin treatment of cystitis.[6]

Observational studies linking *in vitro* bacterial susceptibility to clinical outcome may be confounded if the risk of infection by drug-resistant bacteria is influenced by co-morbidities which themselves determine outcome.[34] Randomised trials are the best way to deal with this threat to validity. RCTs would be ethical in cystitis because many policies recommend that specimens for antibiotic susceptibility testing should only be taken from patients who fail to respond to empirical treatment.[8] RCTs should assess the cost-effectiveness of other antibiotics in com-

Table 2. Odds ratios for successful clinical outcome of cystitis treated by co-trimoxazole or trimethoprim versus cefadroxil or cephalexin.

Author and year	Comparison	OR	95% CI
Hooton et al (1995)	Co-trimoxazole and cefadroxil	2.4	0.8–7.2
Cheung et al (1988)	Co-trimoxazole and cephalexin	6.8	1.7–27.1
Kasanen et al (1981)	Trimethoprim and cephalexin	2.2	1.2–4.0
Brauner et al (1978)	Co-trimoxazole and cephalexin	1.52	0.5–5.1
Gower et al (1976)	Co-trimoxazole and cephalexin	19.4	4.2–89.3
Brumfitt et al (1972)	Co-trimoxazole and cephalexin	2.2	1.1–4.6
Brumfitt et al (1972)	Trimethoprim and cephalexin	2.2	1.1–4.7
Pooled results		2.8	2.0–3.9

parison with trimethoprim. There is very little objective evidence about the cost of resistance.[10] Analyses of management strategies in cystitis have been conducted from the perspective of third-party payers for health care and have concentrated solely on health care costs.[13] No previous trial has documented the consequences for the patient, and there is a serious risk that management strategies that appear cost-effective from the health service perspective are, in reality, only transferring costs from the health service to the patient.[35] Not all patients with adverse outcomes will consult GPs, particularly now that antifungal drugs for vaginal candidiasis are available over-the-counter. A more comprehensive economic analysis is required to model the consequences of increasing bacterial resistance to trimethoprim and to assess the potential cost-effectiveness of alternative treatments.

Recently we have shown that the risk of trimethoprim resistance is markedly higher in women who have been exposed to trimethoprim or to other antibiotics in the past six months.[37] However, in a multivariate analysis, increasing age, deprivation category, and exposure to the oral contraceptive pill or hormone replacement therapy were also significantly associated with increased risk of trimethoprim resistance. These data could be used to distinguish markedly different risks of infection with trimethoprim-resistant bacteria. For example, a 20-year-old woman who had not been exposed to any antibiotic in the past six months, and was not taking the oral contraceptive pill, had a 4% risk of trimethoprim resistance compared with nearly 40% for an 80-year-old woman who had received trimethoprim and hormone replacement therapy in the past six months.

In women at high risk of infection with trimethoprim-resistant bacteria, a case could be made for giving second-line treatment empirically. However, cephalexin and nitrofurantoin are markedly less effective against trimethoprim-sensitive bacteria,[24] and resistance to co-amoxyclav is increasing in urinary isolates from the community.[15] A recent systematic review concluded that quinolones were at least as effective as co-trimoxazole for infections caused by co-trimoxazole sensitive bacteria and had significantly fewer adverse effects.[5] However, increasing use of quinolones in the community increases the risk of selection of quinolone resistance among *E. coli*, which is already a major problem in some countries.[14,38] Recent studies from Asia report rates of ciprofloxacin resistance in urinary isolates of 26%[25] and 53%.[26] In order to minimise unnecessary prescribing of quinolones, it may be preferable to restrict prescription to patients with microbiologically-confirmed infection caused by trimethoprim-resistant bacteria. This is a practical strategy, provided that it is supported with effective management of the symptoms of cystitis while waiting for culture results.[20] Once again it is important to emphasise the role of symptomatic relief as an alternative or supplement to antibiotic therapy.[20,21]

Why are these questions important?

Observational data from the Medicines Monitoring Unit (MEMO) suggest a prevalence of new presentation with acute cystitis (no episode within the previous 28 days) of 90 women per 1000 population per year.[29] We have conducted an economic analysis applying United Kingdom health care costs[12] to the data from a recent survey.[24] Assuming that trimethoprim would have similar clinical outcome to co-trimoxazole, the expected total health care cost per patient treated with trimethoprim would be £6 compared with £12 for nitrofurantoin and £15 for cefadroxil. These expected costs include the costs of management of patients with recurrent cystitis and vaginal candidiasis. These data suggest that wholesale switching from trimethoprim to nitrofurantoin or cephalexin for firstline treatment of UTI would result in unnecessary health care costs of £500 and £800 per 1000 population per year respectively, or between £2.5 million to £4 million per year for Scotland as a whole. A heavy price to pay for inferior treatment outcome.

In the absence of hard evidence to support the continuing use of trimethoprim, prescribers will inevitably turn to other drugs as firstline agents for patients such as Ms MacKenzie, which will increase the cost of treatment and may well result in poorer outcome. Prescribers urgently require better quality information about the clinical consequences of bacterial resistance in this common, but far from simple, infection.

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