UNCOMPLICATED CYSTITIS

Acute, uncomplicated lower urinary tract infections in women are among the most common infections encountered by family physicians. Such infections have also been associated with considerable "over-use" of antibiotics, both in terms of quantity and choice. As a result, limiting antimicrobial use to only 3 days in such cases is one of the targets in UK plans to address the antimicrobial resistance challenge and this has been endorsed by Australian commentators. Concerns have been expressed about the extent to which newer agents such the fluoroquinolones (e.g. ciprofloxacin) are being used as first-line agents in uncomplicated cases. Both duration of therapy and choice have been shown to be amenable to intervention, either by quality assurance means, or by changing reimbursement policies.

Given the prevalence of UTIs in general practice, it is appropriate that family physicians have a pre-prepared personal drug (P-drug) list at hand from which to choose an appropriate agent for a particular patient. Searching the medical literature on this topic can be daunting though – a Medline search with the simple term "urinary tract infection" yields 28 380 citations; restricting that by adding the term "review" only reduces the number to 2983 articles. A simpler starting point might be the primary level Standard Treatment Guidelines, which suggest empirical use of either:

- trimethoprim/sulphamethoxazole (cotrimoxazole) 160/800mg every 12 hours for 5 days, or
- amoxycillin 250mg every 8 hours for 5 days.

Applying the P-drug process, let us see what the available literature says about this choice. The first step is therefore to define the diagnosis carefully - this list should be applicable only to women who fulfill the following criteria:

- community-dwelling
- non-elderly
- presenting with dysuria, frequency or urgency without flank pain or fever; with a history of 7 days or less
- otherwise healthy (e.g. not diabetic
- not pregnant
- have no known abnormalities of the urinary tract.

The next step would be to specify the treatment objectives. Although simple at first glance – eradication of the infecting organism and clinical cure, with avoidance of complications – there have been suggestions that short-course empirical management can be used to screen for complicated or upper tract infections. If that is the case, a higher failure rate at first treatment would be acceptable, as follow-up and microbiological investigation would be planned.

The next step would be to compile an inventory of possible treatments. A desirable agent should have the following characteristics:

- activity against the major pathogens (of which there are few, and where only 2 – E. coli and S saprophyticus – are traditionally considered to account for some 90% of cases)
- low potential for the development of resistance
- high tolerance and acceptability to patients
- high urinary levels for an adequately prolonged period to eliminate organisms rapidly
- removal of periurethral flora without causing perineal fungal colonisation
- inhibiting bacterial adherence
- unaffected by urinary pH or the presence of cations
- little effect on gastrointestinal flora

Table 1: Common antimicrobials for UTIs in South Africa, with illustrative prices

Drug	Quantity in a typical course	Retail cost (Rand)
Cotrimoxazole 80/400mg tablets	20	21.07
Amoxycillin 250mg capsules	15	27.10
Co-amoxiclav 375mg tablets	15	108.63
Nitrofurantoin 100mg capsules	21	162.74
Fosfomyc in granules	3g sachet	181.20
Ciprofloxacin 250mg tablets	10	125.75

- result in a prolonged period between recurrences
- not result in allergic reactions after repeated use.

Although many agents may fit one or more of those criteria, the widely used agents in the South African setting, with illustrative current retail costs, are shown in Table 1 (where possible maximum medical aid prices or generic prices are quoted).

The next step is then consideration of the groups of agents (sulphonamide combinations; beta-lactams with and without beta-lactamase inhibitors, including cephalosporins; quinolones; urinary antiseptics; newer agents), using the following criteria:

- demonstrated efficacy
- safety profiles
- suitability and ease of use
- cost.

Space constraints do not permit an extensive consideration of all the agents in this article against all criteria, but the following pointers can be gleaned from the literature.

Cotrimoxazole resistance is increasing worldwide, but particularly in developing countries. Any selection policy must take into account local resistance patterns. However, most routine laboratory samples are obtained from complicated, non-resolving or hospital-acquired infections and therefore are a poor indication of community resistance. Critically, a prospective community survey in the Cape Town in 1991 showed 47.3% of strains resistant to cotrimoxazole. Retrospective data from the same laboratory showed similar resistance levels, from 40 to 50%, in the preceding 6 years. Resistance to amoxicillin was even higher – 65.1% in the prospective study, and between 60 and 70% for the years from 1985 to 1990. Even though there is an acknowledged mismatch between laboratory susceptibility breakpoints based on serum concentrations and clinical effects resulting from higher levels reached in the urine, if cotrimoxazole resistance is greater than 10-20%, then an alternative regimen should be used.7

Most guidelines point to the use of shorter (3 day) rather than longer (5-7 day) regimens. Beta-lactams as a group (aminopenicillins such as amoxicillin, and cephalosporins) are considered to be less effective than cotrimoxazole or the quinolones. There is insufficient evidence to back the use of the combinations with beta-lactamases (e.g. co-amoxiclav). Despite many years of use, nitrofurantoin remains a useful agent (9.8% resistance in the Cape Town study cited above), but there is no evidence of the efficacy of short courses as yet. There is renewed interest in this group of agents – the nitrofurans. Although the efficacy of single dose fosfomycin has been demonstrated, it has not been tested against the standard 3-day regimens. Irrespective of the antibiotic used, a British study showed that between 12 and 16% of women would return within 28 days for further treatment.

Although single-day regimens of the standard agents (cotrimoxazole, beta-lactams and quinolones) are associated with fewer side effects, they are not as effective as 3-day regimens.9 A meta-analysis that combined 16 studies showed that the odds ratios for cure rates with any single dose antibiotic compared with conventional treatment, as measured 14 days post-treatment, was 0.49 (95% CI 0.36-0.67, $p<0.01$). The reported incidence of side effects ranged from 0-25% in the single-dose arms and from 0-44% in patients given the usual treatment regimens.

Although largely well tolerated, none of the drugs used are without side effects. The risks of Stevens-Johnson syndrome with cotrimoxazole must always be considered. Gastro-intestinal effects with co-amoxiclav are common. However, an added consideration with all antimicrobials is the ecological effect and its implications for society over the longer term. Unfettered use of the well-tolerated and highly effective quinolones must be re-considered in this light.

That brings us to the last criterion – cost. If, as has been shown, there can be criticism of the EDL choice on the basis of efficacy (based on increasing resistance if not clinical evidence of insufficient cure rates), then which of the alternatives could be considered in private practice? Paradoxically, one of the oldest and most effective agents – nitrofurantoin – is also one of the more expensive, partly because of a lack of competition in this sub-market. A shorter course of nitrofurantoin might prove to be an attractive alternative, but data to support that option are currently lacking. Fosfomycin is the most expensive, although the suitability of a single-dose regimen cannot be beaten.

A final practice-oriented note: if empiric management is sufficient, with follow-up and investigation only if initial therapy fails, then other practice options may be feasible. A randomised trial showed that telephonic management was as effective as seeing patients face-to-face. For similar reasons, a British committee recommended in 1999 that repeat treatment of uncomplicated UTIs with agents indicated only for this purpose might be considered for (P) rather than (POM) status – allowing for pharmacist-initiated treatment without a prescription. An earlier American study had however warned that any short-term economic

gains of such a policy might be outweighed by the losses due to earlier resistance to standard regimens.

In conclusion, while the national EDL/STG might be criticised on the basis of available evidence, alternatives are either costly, less convenient to use or increase the possibility of worsening resistance to important classes of antimicrobials. An alternative worth exploring might be shorter course nitrofurantoin. In time, greater use of this agent might improve the chances of generic competition and hence lower prices.

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