Randomized comparative trial and cost analysis of 3-day antimicrobial regimens for treatment of acute cystitis in women

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Three-day oral antimicrobial drug therapies for acute uncomplicated cystitis in women: trimethoprim-sulfamethoxazole (160mg/800mg twice daily) or macrocrystalline nitrofurantoin (100mg four times daily) or cefadroxil (500mg twice daily) or amoxicillin (500mg three times daily).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Women at least 18 years old with symptoms of acute cystitis presenting to a student health centre.

Setting
Primary care setting. The economic study was carried out in Seattle, United States.

Dates to which data relate
The dates of collection for the effectiveness and resource data were not reported. The year to which prices refer was not specified.

Source of effectiveness data
Single study.

Link between effectiveness and cost data
The costing study was undertaken prospectively on the same patient sample as that used in the effectiveness study.

Study sample
The authors estimated that a sample size of 180 patients would allow for: (i) a 90% probability of detecting differences in cure rates between trimethoprim-sulfamethoxazole and the other regimes at the 5% significance level and (ii) 10% of the women enrolled being ineligible for randomization or lost to follow-up. Of the 180 women enrolled into the study, 158 women were randomized and returned for at least one follow-up visit. Twenty-two women (12%) were excluded from the initial sample because either they had no bacteriuria at enrolment or no symptoms. Of the 158 women, 40 were allocated to trimethoprim sulfamethoxazole, 38 were allocated to nitrofurantoin, 37 were allocated to cefadroxil, and 43 were allocated to amoxicillin. Details of the randomization method were not given.
Study design
Randomized controlled trial in a single centre. Women were randomly allocated to one of the four treatment regimes. Patients were followed up at 4-6 days, 12-16 days and 4-6 weeks. Nine patients (6% of those randomized and returning for at least one follow-up visit) were excluded from the final comparison of outcomes (3% of the trimethoprim sulfamethoxazole patients, 3% of the nitrofurantoin patients, 11% of the cefadroxil patients and 2% of the amoxicillin patients). This was because either they were not present at the last visit, they were incompletely assessed on the last visit, or they received non-study antibiotics.

Analysis of effectiveness
The analysis was based on treatment completers only. The primary outcome was the cure rate, defined as the resolution of symptoms and eradication of significant bacteriuria at the last visit in patients who had no post-treatment significant bacteriuria before the visit. Other outcomes compared were recurrence rates, treatment failures and adverse outcomes such as nausea, vomiting, abdominal pain, headaches and diarrhoea. Treatment failures were defined as having persistent significant bacteriuria with initially infecting species at early follow-up visit. Comparability of groups was shown in terms of age, colour, marital status, use of intrauterine device, and history of cystitis but was not tested for significance.

Effectiveness results
(1) 32 out of 39 in the trimethoprim-sulfamethoxazole group were cured at the last follow up visit compared to
(2) 22 out of 36 in the nitrofurantoin group (21% difference, 95% CI: 1 to 41, p=0.04),
(3) 21 out of 32 in the cefadroxil group (16% difference, 95% CI = -4 to 37, p=0.11),
(4) 28 out of 42 in the amoxicillin group (15% difference, 95% CI = -3 to 34, p=0.11).

The recurrence rate (early or late) for the trimethoprim-sulfamethoxazole group was 6/40 compared to 8/38 in the nitrofurantoin group, 11/37 in the cefadroxil group, and 8/43 in the amoxicillin group.

The rate of treatment failures was 1/40 for the trimethoprim-sulfamethoxazole group, 6/38 for the nitrofurantoin group, 0/37 for the cefadroxil group, and 6/43 for the amoxicillin group.

Adverse events were reported by 16/46 of the trimethoprim-sulfamethoxazole group, 18/42 of the nitrofurantoin group, 12/40 of the cefadroxil group, and 13/52 of the amoxicillin group.

Clinical conclusions
The authors conclude that as a 3-day treatment regimen for acute uncomplicated cystitis in women, trimethoprim-sulfamethoxazole is more effective than nitrofurantoin, cefadroxil, and amoxicillin and should be considered a first-line agent.

Measure of benefits used in the economic analysis
The primary outcome was the cure rate, defined as the resolution of symptoms and eradication of significant bacteriuria at the last visit in patients who had no post-treatment significant bacteriuria before the visit. Other outcomes compared were recurrence rates, treatment failures and adverse outcomes such as nausea, vomiting, abdominal pain, headaches and diarrhoea. Treatment failures were defined as having persistent significant bacteriuria with initially infecting species at early follow-up visit.

Direct costs
Costs were considered from the provider's point of view. The costs measured were those of follow-up visit and type of
intervention at follow-up. The number of follow-up visits was observed and assumptions were made about likely interventions at these visits. Drug costs were taken from manufacturers’ wholesale prices plus a mark-up for pharmacy fees. Follow-up test and treatment costs were taken from the charges in one medical centre in Seattle. The date of prices is not specified. Costs did not need to be discounted.

**Currency**
US dollars ($).

**Sensitivity analysis**
A sensitivity analysis was not carried out.

**Estimated benefits used in the economic analysis**
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(2) 22 out of 36 in the nitrofurantoin group (21% difference, 95% CI: 1 to 41, p=0.04),

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The rate of treatment failures was 1/40 for the trimethoprim-sulfamethoxazole group, 6/38 for the nitrofurantoin group, 0.37 for the cefadroxil group and 6/43 for the amoxicillin group.

Adverse events were reported by 16/46 of the trimethoprim-sulfamethoxazole group, 18/42 of the nitrofurantoin group, 12/40 of the cefadroxil group and 13/52 of the amoxicillin group. Benefits up to six weeks after initial clinic visit are considered (ie length of follow-up in the clinical study).

**Cost results**
The cost per patient was $114 for trimethoprim-sulfamethoxazole patients, $155 for nitrofurantoin patients, $155 for cefadroxil patients and $131 for amoxicillin patients. The authors also estimated a cost per patient of $115 for a previous study population receiving ofloxacin.

**Synthesis of costs and benefits**
Benefits and costs were not synthesised.

**Authors’ conclusions**
As a 3-day treatment regimen for acute and uncomplicated cystitis in women, trimethoprim-sulfamethoxazole was more effective and less costly than nitrofurantoin, cefadroxil, and amoxicillin. This was likely to be because of its increased efficacy against E coli in the rectum, urethra and vagina.

**CRD Commentary**
The authors did not mention any method of blinding in the trial. Importantly, they did not comment on the lack of statistical difference in cure rates between trimethoprim-sulfamethoxazole and cefadroxil or amoxicillin. Thus their clinical conclusions may be misleading. The economic study would have been improved if it had related costs to the outcomes measured in the clinical study (cure rates and non-recurrence). The authors made assumptions about the likely treatment patterns for recurrent cases but no justification was given for these assumptions nor for the mark-up of...
pharmacy prices. The authors acknowledged that charges vary between institutions and therefore they should have assessed the effect of varying prices on their results in a sensitivity analysis.

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Other publications of related interest

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