Empirical therapy for uncomplicated urinary tract infections in an era of increasing antimicrobial resistance: a decision and cost analysis

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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
The use of a 3-day course of either fluoroquinolones (FQ) or trimethoprim-sulphamethoxazole (TMP-SMZ) in the treatment of uncomplicated urinary tract infections (UTIs).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women aged over 18 years, with uncomplicated UTI caused by Escherichia coli (E. coli).

Setting
The setting was primarily in primary care, although the model incorporated hospital admissions for possible complications. The model was designed at the Division of Infectious Diseases, Harbor-University of California, Los Angeles Medical Center, Torrance, California.

Dates to which data relate
The effectiveness data were obtained mainly from studies published between 1986 and 2000, although one source was published in 1974. The resource use data were derived from protocols and guidelines published between 1986 and 1999. The costs were taken from sources published between 1995 and 2000.

Source of effectiveness data
The effectiveness data were based on a review and synthesis of published studies.

Modelling
A decision tree model was used to estimate the expected treatment costs.

Outcomes assessed in the review
The probabilities of the following were assessed in the review:

FQ resistance;
hospitalisation;  
pyelonephritis;  
yeast infection after 3 and more than 3 days of antibiotic therapy;  
medical visit due to yeast infection;  
changing the therapy (rather than extending the treatment) due to a lack of clinical response to TMP-SMZ or FQ; and  
clinical cure.  
The probabilities of a clinical cure were assessed for:  
a FQ-resistant infection treated with a FQ (ciprofloxacin);  
a TMP-SMZ-resistant infection treated with TMP-SMZ;  
a FQ-susceptible infection treated with a FQ (ciprofloxacin); and  
a TMP-SMZ-susceptible infection treated with TMP-SMZ.

Study designs and other criteria for inclusion in the review  
The estimates of clinical response were derived from prospective clinical trials or investigations.

Sources searched to identify primary studies  
The authors searched MEDLINE from 1966 to June 2000. The manufacturers of three antibiotics were also contacted for additional response data.

Criteria used to ensure the validity of primary studies  
No validity criteria were stated.

Methods used to judge relevance and validity, and for extracting data  
The abstracts of articles were reviewed. Articles were selected for review if the abstracts suggested that they contained clinical cure rates for uncomplicated UTIs based on antimicrobial resistance.

Number of primary studies included  
Twenty-two studies were included in the review.

Methods of combining primary studies  
The mean value of the published estimates was taken as the base rate for the probabilities, with the highest and lowest probabilities forming the bounds for a sensitivity analysis. A range of at least -50% to +200% of the point estimate was used where there was one or no published source for the estimate.

Investigation of differences between primary studies  
Not stated.

Results of the review
The base-case probabilities were as follows, where the values used in the sensitivity analysis are in parenthesis:

- FQ resistance, 0.005 (range: 0 - 0.1);
- hospitalisation, 0.2 (range: 0 - 0.5);
- pyelonephritis, 0.04 (range: 0 - 0.08);
- yeast infection after 3 days of antibiotics, 0.05 (range: 0 - 0.2);
- yeast infection after more than 3 days of antibiotics, 0.066 (range: 0 - 0.2);
- medical visit due to yeast infection, 0.25 (range: 0 - 0.5);
- change in therapy due to lack of response to TMP-SMZ, 0.75 (range: 0 - 1.0);
- change in therapy due to lack of response to FQ, 0.25 (range: 0 - 1.0);
- clinical cure of FQ-resistant infection with FQ (ciprofloxacin), 0.9 (range: 0.6 - 1.0);
- clinical cure of TMP-SMZ-resistant infection with TMP-SMZ, 0.6 (range: 0.4 - 0.8);
- clinical cure of FQ-susceptive infection with FQ (ciprofloxacin), 0.99 (range: 0.9 - 1.0);
- clinical cure of TMP-SMZ-susceptible infection with TMP-SMZ, 0.96 (range: 0.9 - 1.0).

**Measure of benefits used in the economic analysis**
A cost-minimisation analysis was performed, thus there was no summary measure of health benefit.

**Direct costs**
The unit costs were reported. The total quantities were not reported, although they could be inferred from the text. The costs reported were relevant to a health service or a third-party payer. The costs of the following were included:

- the antibiotics, i.e. ciprofloxacin, generic TMP-SMZ and generic miconazole);
- hospitalisation for pyelonephritis;
- outpatient treatment for infection unresponsive to FQ treatment, or for pyelonephritis caused by FQ-resistant E. coli;
- the initial and follow-up physician visits;
- the urine culture; and
- the initial and follow-up urinalysis.

The antibiotic costs were taken from the Red Book of wholesale drug prices, 2 teaching hospitals, 5 retail pharmacies and 2 Internet pharmacies. The costs of hospitalisation and physician visits were taken from published literature and a survey of 2 teaching hospitals. The mean cost from each source was used in the base-case analysis. No distinction was made between the prices and the costs.

Discounting was irrelevant as the timeframe of the model was less than 1 year. The study reported the marginal costs.

The cost data were published between 1995 and 2000. No adjustment for inflation was reported. The cost results were not reported for any particular price year.
Statistical analysis of costs
No statistical analysis of costs was reported.

Indirect Costs
The indirect costs were not included in this study.

Currency
US dollars ($).

Sensitivity analysis
A two-way sensitivity analysis was conducted on all the cost and probability parameters, and on the proportion of TMP-SMZ resistant E. coli. The highest and lowest costs obtained by the survey were used as ranges for the cost estimates. The possibility of no initial office visit was also incorporated. The ranges for the probability estimates were derived from those obtained in the review. Where there was one or no published source for the estimate, a range of at least -50% to +200% was used.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The mean cost of treatment with FQ at the "current level of FQ resistance" (probability of 0.005) was $107.

The mean cost of treatment with TMP-SMZ was $92 when the TMP-SMZ resistance level was 0%. The mean cost was $99 at 10% resistance, $106 at 20% resistance, $113 at 30% resistance, and $120 at 40% resistance.

Thus, the point at which the mean cost of the two treatment strategies was equal (break-even rate) was at a TMP-SMZ resistance rate of 22%.

The results were sensitive to the cost of ciprofloxacin and the cost of a follow-up medical visit. They were also sensitive to the proportions of FQ-susceptible, TMP-SMZ susceptible and TMP-SMZ resistant E. coli in the population. All other parameters in the model had a negligible effect on the break-even rate.

Synthesis of costs and benefits
Not applicable.

Authors' conclusions
A 3-day course of trimethoprim-sulphamethoxazole (TMP-SMZ) was less expensive than fluoroquinolone (FQ) therapy for uncomplicated urinary tract infections (UTIs), when the TMP-SMZ resistance was less than 22%.

CRD COMMENTARY - Selection of comparators
The comparator for the study was chosen in order to examine the current guidelines from the Infectious Diseases Society of America.

Validity of estimate of measure of effectiveness
The authors stated that a systematic review of the literature had been undertaken, although it is unclear whether the review was conducted systematically to identify the relevant research and to minimise bias. For example, despite
limiting the review to only prospective trials, the exclusion criteria for the studies were not stated. Also, it was not stated how the effectiveness data provided by the drug manufacturers were assessed for quality. The estimates of effectiveness were combined by calculating a mean value, and using the upper and lower estimates as bounds for the sensitivity analysis. By taking a raw mean value, which applies equal weight to all studies, factors such as the study sample size were not taken into account. However, the use of the upper and lower bounds in the sensitivity analysis reduced the possibility of bias.

Validité de l'estimation de la mesure de bénéfice

The analysis of benefits was based on the therapeutic equivalence of treatment alternatives. Therefore, the economic analysis only included the costs.

Validité de l'estimation des coûts

All categories of cost relevant to a health care payer were included in the analysis. The unit costs were reported individually, but there was no summary table of the resource quantities. No distinction appears to have been made between the prices and the costs, even though some data were derived from retail sources while others came from wholesale or hospital sources.

A sensitivity analysis of the quantities was not undertaken, which may limit the interpretation of the study's findings.

A sensitivity analysis of the unit costs was performed, using the highest and lowest costs quoted from their sources as the extremities of the ranges. The costs were taken from sources published between 1995 and 2000, but there appears to have been no conversion to quote the prices in a consistent price year. This may affect the study's results. You should check whether the relative prices appear appropriate to your own setting.

Autres questions

The authors could not make any comparisons of their results with other studies as, to their knowledge, their study was the first to look at the relationship between antibiotic resistance and clinical decision-making using a formal decision analysis. The issue of generalisability to other settings was not addressed, although the model was presented in a very transparent manner and should be simple to reproduce. The authors did not present their results selectively, and their conclusions reflected the scope of the analysis. They acknowledged that the analysis was, by definition, a simplification of reality, and that there were excluded costs. They therefore adjusted their recommendation accordingly (see next section below).

The authors reported a number of further limitations to their study. These included the exclusion of antibiotic allergies, and uncommon adverse events such as pseudo-membranous colitis. They did state, however, that the cost of pyelonephritis, the adverse event that was included, had a minimal impact on the results. The authors also acknowledged that their study was limited to E. coli infections, which was justified as E. coli causes 70 to 95% of UTIs. The study focused on treatment with ciprofloxacin since there was a lack of data on treatment with any other FQ.

Implications of the study

The current policy in the authors' setting is to use FQ when TMP-SMZ resistance exceeds 10 to 20%. The authors recommend that this be increased to at least 22%. In addition, due to the limited perspective of the study, a rate of 30% may be more appropriate to address concerns over inducing greater FQ resistance. The authors recommend that further research should be conducted, to obtain better estimates of the cure rates of TMP-SMZ against infections resistant and susceptible to this drug.

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