Optimizing treatment of antimicrobial-resistant Neisseria gonorrhoeae

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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
Four strategies for the diagnosis and treatment of gonorrhoea were examined.

Ciprofloxacin (CIP) plus culture test (CT) plus CIP susceptibility test (ST1): prescribe CIP to symptomatic patients and CT to all patients; test 80% of all positive specimens for CIP resistance; recall and treat asymptomatic gonorrhoea patients and patients with CIP-resistant strains.

CIP plus non-CT (ST2): prescribe CIP to symptomatic patients and use non-CT on all patients; recall and treat positive asymptomatic gonorrhoea patients.

Ceftriaxone (CEF) plus CT plus CEF susceptibility tests (ST3): prescribe CEF to symptomatic patients and CT to all patients; recall and treat asymptomatic gonorrhoea patients; test 20% of positive isolates for resistance to cephalosporin.

CEF plus non-CT (ST4): prescribe CEF to symptomatic patients and use non-CT on all patients; recall and treat asymptomatic gonorrhoea patients.

The doses considered were a single, oral 500-mg dose of CIP and a single 125-mg dose of CEF by intramuscular injection.

Type of intervention
Diagnosis and treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of adult women.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1989 and 2002. The costs and some resource use data were obtained from sources published between 1989 and 2005. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' opinions.
Modelling
A decision tree was constructed to assess the cost-effectiveness of the four diagnosis and treatment strategies in a hypothetical cohort of one million women. The gonorrhoea-related health outcomes included in the evaluation of each strategy were pelvic inflammatory disease (PID) and PID-associated sequelae (chronic pelvic pain, ectopic pregnancy and infertility). The probability and associated costs of female-to-male transmission of gonorrhoea was also considered. It was assumed that if the male partner were infected, either urethritis or epididymitis could develop and the infection could be transmitted to another female partner. The structure of the tree was given in the appendix. The time horizon of the model was not explicitly reported.

Outcomes assessed in the review
The outcomes assessed from the literature were:

the prevalence of disease;
the rates of treatment failure;
the rates of infected and non-infected, and symptomatic and asymptomatic women;
accuracy of the tests;
the rates of concurrent transmission of the human immunodeficiency virus (HIV);
the rates of PID and sequelae;
the rates of urethritis and epididymitis;
the rates of culture-positive samples; and
the rates of gonorrhoea transmission.

Study designs and other criteria for inclusion in the review
The authors stated that a review of the published literature was undertaken to identify the primary studies. However, no information on the design and characteristics of the primary studies was provided.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Thirteen primary studies provided the clinical inputs.

Methods of combining primary studies
A narrative approach was used to combine the primary estimates.
Investigation of differences between primary studies
Not stated.

Results of the review
The prevalence of gonorrhoea in the community among women was 1% (range: 0 - 15).
The prevalence of CIP-resistant Neisseria gonorrhoeae was 0.1% (range: 0 - 20).
The rate of women infected with gonorrhoea and symptomatic was 30% (range: 20 - 50).
The rate of women non-infected but with gonorrhoea symptoms was 20% (range: 10 - 40).
The rate of recalled patients returning to the clinic was 40% (range: 20 - 80).
The sensitivity of non-CT was 95% (range: 85 - 100) and the specificity was 97% (range: 95 - 99).
The sensitivity of CT was 93% (range: 85 - 95) and the specificity was 97% (range: 95 - 97).
The rate of concurrent HIV transmission was 0.066 (range: 0 - 0.5).
The rate of women developing PID and sequelae among untreated gonorrhoea cases was 16% (range: 10 - 40).
The rate of women developing PID only (no sequelae) was 70% (range: 70 - 72).
The probabilities of developing infertility, ectopic pregnancy and chronic pelvic pain were 6% (range: 1 - 6) for infertility, 8% (range: 5 - 9) for ectopic pregnancy and 16% (range: 15 - 20) for chronic pelvic pain.
The rate of urethritis was 50% (range: 36 - 65) and the rate of epididymitis was 2% (range: 1 - 5).
The rate of both female-to-male and male-to-female transmission of gonorrhoea was 50% (range: 30 - 75).

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
The prevalence of CEF-resistant Neisseria gonorrhoeae was 0%.
The rate of treatment failure when the strain is not resistant to antimicrobial agent was 100%.
For ST1, the percentage of culture-positive samples tested for antimicrobial susceptibility was 80%.
For ST3, the percentage of culture-positive samples tested for antimicrobial resistance was 20%.

Measure of benefits used in the economic analysis
The summary benefit measure used was the proportion of women who did not develop PID. This was estimated using a modelling approach. No discounting was applied due to the short time horizon of the analysis.

Direct costs
The analysis of the costs was carried out from the perspective of the health care system. It included all direct costs related to diagnostic testing, antimicrobial therapy for gonorrhoea, and subsequent sequelae of untreated gonorrhoea. The cost categories considered were non-CT, CT, antimicrobial susceptibility test, care associated with PID and
sequelae, outpatient treatment of epididymitis, clinician visits, CEF and CIP, and resources associated with the transmission of gonorrhoea and HIV. The cost of diagnostic tests covered the reagents, kits, equipment, supplies and the laboratory technician's time. The unit costs were presented separately from the quantities of resources used for the majority of items. Most data on resource consumption and costs came from published studies and market prices. Other unit costs came from personal communication from health department laboratories. Discounting was not relevant due to the short timeframe of the analysis and, appropriately, was not applied. All the costs were updated to 2001 values using the Consumer Price Index.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case, but probabilistic distributions (uniform or triangular) were assigned to model inputs in the sensitivity analysis.

**Indirect Costs**
The indirect costs were not included in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
Univariate and multivariate sensitivity analyses were carried out to assess the robustness of the model results to variations in clinical and economic data. The ranges of the values used were derived from the literature or were set by the authors. A Monte Carlo simulation was also carried out by using probability distributions (uniform or triangular) for all model inputs.

**Estimated benefits used in the economic analysis**
The proportion of women who did not develop PID was greater than 99% for all strategies, regardless of disease prevalence. Therefore, the four strategies were considered equivalent and a cost-minimisation analysis was carried out.

**Cost results**
Given that the four strategies were equivalent in terms of effectiveness, the less costly strategy (cost per individual treated) was also considered to be the optimal strategy.

The results were presented for different rates of gonorrhoea prevalence and CIP resistance.

The most striking results were as follows.

With prevalence of gonorrhoea between 0 and 1% and with prevalence of CIP-resistance between 0 and 20%, the optimal strategy (lowest cost per patient treated) was ST1.

With prevalence of gonorrhoea between 2 and 3% and with prevalence of CIP-resistance between 0 and 5%, the optimal strategy was ST1.

With prevalence of gonorrhoea between 2 and 3% and with prevalence of CIP-resistance greater than 5%, the optimal strategy was ST3.

With prevalence of gonorrhoea between 3 and 10% and with prevalence of CIP-resistance between 0 and 20%, the optimal strategy was ST3.

With prevalence of gonorrhoea between 10 and 13% and with prevalence of CIP-resistance between 0 and 3%, the optimal strategy was ST2.
With prevalence of gonorrhoea between 10 and 13% and with prevalence of CIP-resistance greater than 3%, the optimal strategy was ST3.

With prevalence of gonorrhoea between 13 and 15% and with prevalence of CIP-resistance between 0 and 3%, the optimal strategy was ST2.

With prevalence of gonorrhoea between 13 and 15% and with prevalence of CIP-resistance greater than 3%, the optimal strategy was ST4.

Given the equivalence in terms of effectiveness among the strategies, the optimal strategy was not only the cheapest but also the one that yielded the lowest cost per case successfully treated.

The sensitivity analysis showed that the model outputs were sensitive to some parameters. For example, if the ratio of the costs of CIP to CEF were changed from 1:5 (as in the base-case) to 1:2, and the costs of the tests became equal, ST2 and ST4 were optimal for greater combinations of gonorrhoea prevalence and CIP-resistance prevalence than in the base-case.

However, if the ratio of the costs of CT to non-CT was changed from 1:1 to 1:3, then ST1 and ST3 became optimal for all combinations of gonorrhoea prevalence and CIP-resistance prevalence.

The Monte Carlo simulation showed that ST1 had the lowest mean cost per patient treated. Only when gonorrhoea prevalence was 2% and CIP-resistance prevalence was 10% did ST3 have a lower mean cost per patient treated. The probabilistic sensitivity analysis also showed that there was considerable overlap in costs across the two antimicrobial options.

**Synthesis of costs and benefits**
A synthesis of the costs and benefits was not relevant as a cost-minimisation analysis was carried out. Cost-effectiveness ratios were calculated in the appendix, but they were not used in the current analysis as the alternative strategies were similar in effectiveness.

**Authors' conclusions**
The choice of the optimal strategy for the diagnosis and treatment of gonorrhoea in US women depended on several factors, including the prevalence of gonorrhoea and the prevalence of ciprofloxacin (CIP)-resistant gonococcal strains. In general, switching from CIP to ceftriaxone (CEF) was optimal when the prevalence of gonorrhoea was greater than 3% and the prevalence of CIP-resistance was greater than 5%. Similarly, culture test (CT) and susceptibility surveillance were optimal strategies when the prevalence of gonorrhoea was less than 13%, while non-CT was optimal when gonorrhoea prevalence was at least 13%.

**CRD COMMENTARY - Selection of comparators**
The authors justified their choice of the comparators, which were appropriate. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence was estimated from published studies. The authors stated that a review of the literature was undertaken to identify the primary studies, but no information on the methods and conduct of the review was provided. Details of the studies used to estimate the clinical inputs were not provided. Similarly, the methods used to extract and then combine the primary estimates were not described. Some assumptions were also made. The issue of uncertainty in the data was addressed in the sensitivity analysis.

**Validity of estimate of measure of benefit**
No summary benefit measure was used in the analysis because a cost-minimisation analysis was conducted. Please refer
to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

**Validity of estimate of costs**

The perspective adopted in the study was explicitly stated, and the cost categories included in the analysis were consistent with this perspective. A breakdown of the costs was provided for some items, but other costs were presented as macro-categories, which limits the possibility of replicating the results of the analysis in other settings. The unit costs were presented for some items. No statistical analyses of the costs were carried out in the base-case, but the impact of alternative cost estimates was investigated in the sensitivity analysis and probabilistic distributions were assigned to costs in the Monte Carlo simulation. The sources of the economic data were reported for each group of costs. The price year was reported, which will simplify reflation exercises in other settings.

**Other issues**

The authors did not compare their findings with those from other studies. With respect to the generalisability of the study results to other settings, the authors noted that, owing to the large variability in key variables across geographic locations and clinical settings, it is quite unlikely that the same single strategy would be the most cost-effective strategy across all these settings. The results of the study were presented selectively but extensive information was provided in the appendices. The authors stated that the selection of the optimal diagnostic test might be driven by priorities of testing for chlamydia rather than gonorrhoea testing alone. The costs and benefits associated with the diagnosis and treatment of chlamydia were not modelled.

**Implications of the study**

The study results suggest that the collection of data on prevalence is warranted to allow the optimal strategy to be defined.

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None stated.

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**Other publications of related interest**


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