"Shotgun" versus sequential testing: cost-effectiveness of diagnostic strategies for vaginitis

Carr P L, Rothberg M B, Friedman R H, Felsenstein D, Pliskin J S

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 authors compared diagnostic strategies for the detection of vaginitis as well as different treatment methods. Overall, 28 different diagnostic strategies were compared. These involved vaginal pH, vaginal cultures for Candida and Trichomonas, Gram's stain for bacterial vaginosis (BV), and DNA probes for Neisseria gonorrhoeae and Chlamydia (GC or Chlamydia probes), used either alone or in combination.

The treatment options evaluated were as follows.

Option 1: if the etiology of vaginitis was Candida species, treatment consisted of fluconazole (150 mg orally taken once), and terconazole 0.8% cream as second treatment (nightly for 3 nights).

Option 2: if the etiology of vaginitis was bacterial vaginosis, treatment consisted of metronidazole (500 mg orally twice daily for 7 days or metronidazole (2 g orally taken once).

Option 3: if the etiology of vaginitis was Trichomonas vaginalis, treatment consisted of metronidazole (2 g orally taken once) or metronidazole (500 mg orally twice daily for 7 days).

Option 4: if the etiology of vaginal discharge was cervicitis, treatment comprised ceftriaxone (350 mg intramuscular), doxycycline (100 mg orally twice daily for 7 days) and azithromycin (2 g orally taken once).

Option 5: a treatment option depending on vaginal pH (with single dose of fluconazole for Candida when the pH was less than 4.9 or treatment with 2 g of metronidazole in order to cover Trichomonas and/or BV when the pH was more that 4.9).

Option 6: combined treatment with fluconazole and metronidazole.

Type of intervention
Diagnosis and treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised healthy women with vaginal discharge, pruritus, irritation or odour who could not be diagnosed at the initial office evaluation. This initial office evaluation was conducted using pH, wet mount (KOH and normal saline) preparations for Candida species, Trichomonas vaginalis, mucopurulent discharge and the four criteria used to diagnose bacterial vaginosis (thin homogeneous discharge, pH>4.5, clue cells and positive whiff test). Pregnant women and women using over-the-counter medical treatment for vaginitis were excluded from the study.

Setting
The setting was primary care. The economic study was carried out in the USA.
Dates to which data relate
The effectiveness data were derived from studies published between 1983 and 2004. All costs were derived from official sources reflecting 2003 prices.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of studies. Some estimates of effectiveness were based on expert opinion.

Modelling
The authors constructed a decision tree using Decision Maker 7.06 software (Pratt Medical Group, Boston) to evaluate the cost-effectiveness of the vaginitis treatment options. The model was based on several assumptions:

- Each case of vaginitis had only one etiology;
- All patients who were not cured after two courses of therapy, along with patients still remaining undiagnosed after a complete set of tests, would be referred to an infectious disease or gynaecology specialist.

The specialist would repeat all tests and the patient would subsequently follow adequate therapy.

Outcomes assessed in the review
The following input parameters were used in the model:

- The probability of etiological agents causing vaginitis;
- Treatment options according to each etiological agent;
- The probability of treatment side effects;
- The sensitivity of wet mount in different etiological agents;
- The probability of pH>4.9 in different etiological agents;
- The sensitivity of Candida culture, Gram's stain, Trichomonas vaginalis culture, DNA probe (GC), DNA probe (Chlamydia); and
- The prevalence of several etiological agents after negative wet prep and pH testing.

Study designs and other criteria for inclusion in the review
The authors reported that peer-reviewed articles written in English were included in their review, and that estimates of treatment efficacy and side effects were retrieved from randomised clinical trials. However, no further study designs or inclusion criteria were reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.
Methods used to judge relevance and validity, and for extracting data
The validity of the primary studies does not appear to have been judged.

Number of primary studies included
Overall, 30 primary studies were included in the review.

Methods of combining primary studies
The results of the individual primary studies do not appear to have been combined.

Investigation of differences between primary studies
Differences between the primary studies do not appear to have been investigated.

Results of the review
There were too many results to report in this abstract.

Methods used to derive estimates of effectiveness
Some estimates of effectiveness were based on authors’ and experts’ assumptions.

Estimates of effectiveness and key assumptions
The estimates of effectiveness based on experts’ assumptions were:

- sensitivity of wet mount in “other” etiological agents, 0 (range: 0), and
- probability of pH>4.9 in Neisseria gonorrhoeae, 0.67 (range: 0.60 to 0.74).

It was also assumed in the model that pH test results would be ready during the initial visit or further results of tests besides the initial evaluations would necessitate two days. This assumption was most probably based on the authors' clinical experience. In addition, it was assumed that all treatment side effects would persist for two days and their severity would be comparable to that of vaginitis symptoms. These assumptions were made with reference to the literature.

Measure of benefits used in the economic analysis
The authors used the number of symptom days as the measure of benefit in the economic analysis. This measure was derived from the model.

Direct costs
The health care costs included in the analysis were for wet mount preparation, Gram stain, vaginal culture (Candida species), Trichomonas vaginalis culture, Neisseria gonorrhoeae DNA probe, Chlamydia DNA probe, herpes DNA amplification probe, human papillomavirus testing, physician office visit, specialist consultation and drugs used for treatment. The costs and the quantities were reported separately for the drugs, and all unit costs were reported in full. The drug costs were based on average wholesale prices for the year 2003. All other costs were derived from official published sources and were reported for the price year 2003. Discounting was not relevant as the costs were incurred during a short time.

Statistical analysis of costs
The costs were treated deterministically.
Indirect Costs
Productivity losses due to the patients visiting physicians were also included. The costs and the quantities were reported separately, and the costs were derived from official published sources (US Bureau of Labour Statistics). All costs were reported for the price year 2003. Discounting was not relevant as the costs incurred during a short time.

Currency
US dollars ($).

Sensitivity analysis
The authors conducted a one-way sensitivity analysis to investigate the robustness of the cost-effectiveness results to variability in the data. All quantitative parameters were investigated in sensitivity analyses, using ranges derived from the literature. A probabilistic analysis was also carried out, varying all input parameters of the model simultaneously in order to estimate confidence intervals (CIs) for all cost-effectiveness results. One thousand Monte Carlo simulations were carried out and, each time, random values from within each parameter’s 95% CIs were selected using logit distributions.

Estimated benefits used in the economic analysis
The estimated benefits for each of the 28 diagnostic strategies compared were fully reported. The most effective diagnostic strategy, which resulted in 7.3 symptom days, was initial pH testing, yeast cultures and DNA probes for gonorrhoeae and Chlamydia for all patients, followed by Gram's stain and Trichomonas culture only in patients with pH>4.9. The least effective strategy, which resulted in 8.58 symptom days, was testing for sexually transmitted diseases including probes for Neisseria gonorrhoeae and Chlamydia along with vaginal pH testing. When treatment was taken into consideration, it was reported that diagnostic testing in combination with treatment based on the vaginal pH test results while awaiting further test results decreased symptom days from 0.6 to 1.3, depending on the diagnostic strategy used.

Cost results
The average costs per diagnostic strategy were reported. These ranged from $330 (initial pH testing, yeast cultures and DNA probe for gonorrhoeae and Chlamydia for all patients, followed by Gram's stain and Trichomonas culture only in patients with pH>4.9) to $441 (testing for sexually transmitted diseases including probes for Neisseria gonorrhoeae and Chlamydia along with vaginal pH testing).

Depending on the diagnostic strategy used, when treatment was also taken into consideration, it was reported that using empirical treatment while awaiting further test results could result in cost-savings ranging from $8 to $62 (mean savings $39).

Synthesis of costs and benefits
An incremental cost-effectiveness analysis was performed. This demonstrated that all strategies were dominated by the strategy of initial pH testing, yeast cultures and DNA probes for gonorrhoeae, followed by Gram's stain and Trichomonas cultures only in patients with documented pH>4.9 (comprehensive testing).

The one-way sensitivity analyses demonstrated that the results were fairly robust. The only uncertainties were regarding the performance of Neisseria gonorrhoeae (GC) and Chlamydia probes during the initial visit. When the sensitivities of initial diagnostic testing for yeast, BV or Trichomonas were low (0.20, 0.60 and 0.20, respectively), the performance of GC and Chlamydia testing was least cost-effective. Similarly, if the cost of an office visit was low ($29), the performance of GC and Chlamydia probes at the initial office visit became less cost-effective. In addition, if the sensitivity of pH testing for Trichomonas is less than 85%, pH testing should not be performed on account of the great delay in Trichomonas diagnosis caused by false negatives.
The Monte Carlo probabilistic analysis demonstrated that only two of the 28 diagnostic strategies were cost-effective. Testing for yeast, BV and Trichomonas without GC/Chlamydia probes was the least costly strategy 42% of the time, while comprehensive testing including GC/Chlamydia probes was the most effective strategy in all simulations and the least costly strategy in 52% of the simulations.

Authors’ conclusions
A comprehensive pH-guided testing strategy performed at the initial office visit was the most cost-effective strategy.

CRD COMMENTARY - Selection of comparators
A justification was provided for the comparators used. The authors chose basic diagnostic tests with reference to related literature and clinical practice in their setting. You should decide if this represents a widely used technology in your own setting.

Validity of estimate of measure of effectiveness
A systematic review of the literature was not undertaken. Although this is common practice with models, it does not always ensure that the best data available are used in the model. No methods were used to combine data from the available studies, as the authors appear to have used the data selectively. There was little comment on the quality of the retrieved studies, probably due to the size of the model, making it difficult to comment on the quality of the estimates used in the model. In addition, the impact of differences between the studies identified was not investigated. However, the authors conducted a number of sensitivity analyses relating to the parameters used in model. Some estimates of effectiveness were based on experts’ assumptions. While some assumptions were justified with reference to the medical literature, there were some estimates for which no justification for the choice of assumptions was provided. However, all of the estimates were investigated in sensitivity analyses.

Validity of estimate of measure of benefit
The authors used the number of symptom days, which were derived directly from the model. This outcome may be convenient but it may not reflect the entire health benefit to the patients.

Validity of estimate of costs
The analysis of the costs was performed from a societal perspective. Some relevant costs seem to have been omitted from the analysis. In particular, the costs of side effects due to treatment were not included. However, it is not possible to know whether their omission has affected the authors’ conclusions. The costs and the quantities were reported separately, thus enhancing the reproducibility of the study in other settings. In addition, sensitivity analyses were conducted to assess the robustness of the estimates used, but the ranges used and their source were not reported. All of the costs were derived from official, published sources and the price year was reported, which will aid any future reflation exercises.

Other issues
The authors did not compare their findings with those from other studies, so it is not known how far their results agree with other published results. The issue of generalisability of the results to other settings was directly addressed. The authors presented only a limited number of the results obtained. The results for all other treatment options except empirical treatment were not reported, but no justification for these omissions was provided. The study enrolled healthy women with symptoms of vaginitis undiagnosed after initial evaluation and this was reflected in the authors’ conclusions.

The authors reported a number of limitations to their study. First, the prevalence of disease in patients with negative initial office results is an unknown parameter and, along with the sensitivity of the initial office visit tests, was based on data from the authors’ setting which may not be generalisable to other settings. The sensitivity of the tests may also vary with physician expertise. Second, the model was also limited by the lack of available data on women who remain
undiagnosed by simple tests conducted in office practices. Third, the authors’ assumption that each case of vaginitis has a single etiologic agent does not apply in practice since coexistence of multiple etiologic agents is often observed.

**Implications of the study**
The authors did not make any specific recommendations for changes in policy or practice. However, they called for further research to establish the etiology and prognosis of women who remain undiagnosed by simple tests conducted in primary care settings.

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