Cost-effectiveness of diagnostic tests for toenail onychomycosis: a repeated-measure, single-blinded, cross-sectional evaluation of 7 diagnostic tests

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 study compared the following diagnostic tests for onychomycosis:

- a potassium hydroxide preparation (KOH) alone, with interpretation by a dermatologist (KOH-CLINIC) and a laboratory technician (KOH-LAB);
- KOH with dimethyl sulfoxide (KOH-DMSO) or chlorazol black E (KOH-CBE);
- culture with dermatophyte test medium (DTM);
- culture with Mycobiotic and Inhibitory Mold Agar (Cx); and
- histopathologic analysis with periodic acid-Schiff staining (PAS).

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised individuals with at least one toenail with 25% or more clinical involvement (defined as symptoms of subungual debris with onycholysis and/or onychauxis). Patients younger than 18 years of age were excluded from the study, as were those with documented psoriasis, lichen planus, or other nail dystrophies. Also excluded were patients on oral antifungal medication for more than 2 months during the 12 months prior to enrolment, and individuals who had used topical ciclopirox nail lacquer within 6 weeks of enrolment.

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

Dates to which data relate
The effectiveness data were collected between March and May 2003. The cost data were derived from sources published in 2003 and from actual data from the same year. The price year was 2003.

Source of effectiveness data
The effectiveness data were derived from a single study.
Link between effectiveness and cost data
It appears that the costing has been carried out prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
The sample size was not determined in the planning phase of the study. In addition, power calculations were not conducted retrospectively. Patients volunteered for inclusion in the study. Of the 294 patients who initially volunteered, 90 were excluded because they refused consent (46) or did not meet the inclusion criteria (44). Thus, overall, 204 patients (95.5% male) were included in the study. The patients had an average age of 69.5 years (standard deviation, SD=11.5), a history of onychomycosis for a maximum of 15 years, and an average of 5 (SD=3.6) toenails with mycosis. It was reported that 83.3% of the patients had all seven tests performed, while 16.7% (34 patients) had at least one test not performed.

Study design
The analysis was based on a repeated-measure, blinded, cross-sectional study that was conducted in a single centre. Researchers who interpreted the test results were blinded to the patient's identification and to the results of further tests. Two independent investigators interpreted the results from the slides (KOH-CLINIC, KOH-CBE and KOH-DMSO). These results were compared using the SAS procedure Proc Compare (Statistical Analysis System, SAS Institute Inc., Cary).

Analysis of effectiveness
The outcome for the analysis was the sensitivity of the different tests. The "gold standard" criterion for the documentation of onychomycosis was assumed to be at least three positive tests. The sensitivity of a test was defined as the number of participants with a positive result for the specific test divided by the number of participants with at least three positive tests. Sensitivity results were compared in pairs and details of the statistical tests performed were reported.

Effectiveness results
The sensitivity was:

98.8% (95% Bonferroni-adjusted confidence interval, CI: 93.2 to 99.9) for PAS;
94.3% (95% Bonferroni-adjusted CI: 86.1 to 97.9) for KOH-CBE;
90.9% (95% Bonferroni-adjusted CI: 82.6, 95.5) for KOH-CLINIC;
87.8% (95% Bonferroni-adjusted CI: 78.9 to 93.3) for KOH-LAB;
79.5% (95% Bonferroni-adjusted CI: 69.4 to 87.0), KOH-DMSO;
79.3% (95% Bonferroni-adjusted CI: 69.3 to 86.7) for Cx; and
57.3% (95% Bonferroni-adjusted CI: 46.5 to 67.5) for DTM.

Between-test comparisons demonstrated that PAS was the most sensitive test (98.8%) and that the difference was generally statistically significant in comparison with all other tests (i.e. all pairwise test statistics >2.99, the Tukey Honest Significant Difference (HSD) 5% significance-level critical value). The only exception was the KOH-CBE test (test statistic = 2.18).

Clinical conclusions
The analysis demonstrated that PAS has a statistically significantly higher sensitivity than most other tests, the
exception being the KOH-CBE test. Culture using DTM was the least sensitive test.

**Measure of benefits used in the economic analysis**
The measure of benefit was the test sensitivity. This was derived from the effectiveness study. The cost-effectiveness ratio was defined as the cost of a test divided by the test sensitivity.

**Direct costs**
Only the costs of tests were included in the analysis. The cost data were derived from an official published source (Medicare Reimbursement) and also actual data (average reimbursement by two large practices in the authors’ area - Minneapolis, USA). Discounting was not relevant as the costs were incurred as lump-sums. Although the price year was not explicitly reported, the costs appear to have been reported for the price year 2003.

**Statistical analysis of costs**
Cost-differences were compared in pairs using pairwise test statistics. Statistical significance at the 5% level (alpha=0.05) was determined if the absolute value of the test statistic was greater than the Tukey HSD critical value (i.e. larger than the standard critical value of 1.96).

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

**Currency**
US dollars ($).

**Sensitivity analysis**
The authors conducted a one-way sensitivity analysis to investigate changes in sensitivities of a diagnostic test by using a looser "gold standard" definition of positive results from two tests (as opposed to three positive tests in the baseline analysis).

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

**Cost results**
The reimbursement costs in private practice were $35 for KOH examination with or without counterstains, $35.5 for Cx and $101.5 for PAS.

The Medicare reimbursement costs were $22.97 for KOH with or without counterstains, $43.74 for Cx and $86.00 for PAS.

**Synthesis of costs and benefits**
Using Medicare reimbursement costs, the cost of the test per test sensitivity was:

- 0.2436 for KOH-CBE,
- 0.2527 for KOH-CLINIC,
- 0.2616 for KOH-LAB,
0.2889 for KOH-DMSO,
0.5516 for Cx,
0.7634 for DTM, and
0.8704 for PAS.

Using private practice reimbursement, the cost of the test per test sensitivity was:

0.3712 for KOH-CBE,
0.3850 for KOH-CLINIC,
0.3986 for KOH-LAB,
0.4403 for KOH-DMSO,
0.4477 for Cx,
0.6195 for DTM, and
1.0273 for PAS.

It was reported that the results were robust to variations in the "gold standard", but details of the sensitivity analysis were not provided.

Authors' conclusions
"KOH-CBE (potassium hydroxide with chlorazol black E) should be the test of choice for practitioners confident in interpreting KOH preparations because of its combination of high sensitivity and cost-effectiveness."

CRD COMMENTARY - Selection of comparators
The analysis compared all commonly used diagnostic tests for toenail onychomycosis in the authors' setting. You should decide if this represents a widely used technology in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a single-centred, cross-sectional study. This appears to have been appropriate given the fact that all health technologies performed were administered to all patients. The study sample was representative of the study population, although power calculations were not conducted to determine the sample size. It is therefore not known if the study was adequately powered to detect statistically significant results. Blinding of the assessors was performed, which will have minimised possible reporting bias.

Validity of estimate of measure of benefit
Test sensitivity, which was derived from the effectiveness study, was used as the measure of benefit in the economic analysis. This is an appropriate benefit measure for the technology being evaluated, although it does not permit comparisons with other types of health care programme.

Validity of estimate of costs
The perspective adopted in the economic analysis was not reported. Only the costs of the tests were included, although this may reflect the scope of the analysis required for this particular technology. No sensitivity analysis was conducted to assess the robustness of the estimates used. This may limit the interpretation of the authors' results and their
Other issues
The authors compared their findings with those from other studies and found them generally to be in agreement. The issue of the generalisability of the results to other settings was directly addressed as the authors pointed out the difficulties and related restrictions. The study enrolled individuals with subungual debris with onycholysis and/or onychauxis and this was reflected in the authors’ conclusions.

The authors reported a number of limitations to their study. First, the "gold standard" definition against which test sensitivities were compared was rather conservative. Second, clinical disease characteristics were not accounted for when estimating test sensitivities. Finally, test specificities were not included in the analysis and their inclusion might have affected the authors’ conclusions.

Implications of the study
The authors made no explicit recommendations for changes in policy or the need for further research, but their discussion highlighted areas where more research-based information is necessary.

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