

Microscopic-observation drug-susceptibility assay was more sensitive than standard tests for diagnosing tuberculosis

Moore DA, Evans CA, Gilman RH, et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. *N Engl J Med*. 2006;355:1539-50.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Hospitalists ★★★★★☆☆ Infectious Disease ★★★★★☆☆ Pulmonology ★★★★★☆☆

QUESTION

How accurate is the microscopic-observation drug-susceptibility (MODS) assay for diagnosing tuberculosis and multidrug-resistant tuberculosis in sputum samples?

METHODS

Design: Blinded comparison of the MODS assay with automated mycobacterial culture and Löwenstein-Jensen culture.

Setting: 2 hospitals and 15 government clinics in Lima, Peru.

Patients: 1980 patients ≥ 18 years of age (median 32 y, 58% women) from 3 target groups: 1570 unselected patients with suspected tuberculosis, 253 patients at high risk for tuberculosis or multidrug-resistant tuberculosis, and 157 patients hospitalized for HIV infection. Most patients provided 2 sputum samples.

Description of tests: MODS assay: Decontaminated sputum samples were cultured in broth for ≤ 40 days in 12 tissue-culture wells, 4 wells with no drug and 2 wells for each of 4 drugs at 2 doses. Cultures were examined periodically by inverted light microscope, with positive cultures identified by characteristic cord formation. Löwenstein-Jensen culture: Inoculated slants were incubated for ≤ 60 days. Automated mycobacterial culture: Inoculated MBBaCT bottles were cultured for ≤ 42 days.

Diagnostic standards: Tuberculosis diagnosis: A positive reference result was defined as a positive culture according to ≥ 1 of the 3 methods; a negative reference result was defined as a negative result by all 3 methods. Drug resistance: The concordant result from automated mycobacterial culture and the proportion method with Löwenstein-Jensen cultures (if discordant, results from 2 microplate Alamar blue assays were used).

Outcomes: Sensitivity, specificity, and likelihood ratios.

MAIN RESULTS

401 of 3760 sputum samples (10.7%) were positive for tuberculosis. Diagnostic test characteristics were calculated per sample (Table). The MODS assay detected 89% of cases of tuberculosis with the first sample and an additional 8.2% of cases with the second sample. 349 positive samples were available for drug-resistance testing. The kappa value between the MODS result and the reference

result was 1.0 for rifampin (resistance prevalence 10.7%), 0.89 for isoniazid (19.5%), 0.93 for the combination of rifampin and isoniazid (10.4%), 0.72 for streptomycin (21.4%), and 0.71 for ethambutol (10.1%). Median time for drug-susceptibility testing was 7 days for MODS, 22 days for automated mycobacterial culture, and 68 days for Löwenstein-Jensen culture with proportion-method testing.

CONCLUSIONS

The microscopic-observation drug-susceptibility (MODS) assay was faster and more sensitive than currently used tests for diagnosing tuberculosis in sputum samples. The MODS assay was faster and had good agreement with the other tests for identification of drug-resistant tuberculosis.

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Microscopic-observation drug-susceptibility (MODS) assay compared with 2 standard tests for diagnosis of tuberculosis in sputum samples*

Tests	Sensitivity (95% CI)	Specificity (CI)	+LR	-LR	Days to positive test†
MODS assay	97.8 (97.3 to 98.2)	99.6 (99.5 to 99.8)	245	0.02	7 (6 to 8)
Automated mycobacterial culture	89 (88 to 90)	99.9 (99.8 to 100)	890	0.11	13 (10 to 16)
Löwenstein-Jensen culture	84 (83 to 85)	100 (99.9 to 100)	∞	0.16	26 (21 to 33)

*Diagnostic terms defined in Glossary; LRs and CI calculated from data in article.

†Median (interquartile range).

COMMENTARY

Tuberculosis kills 1.7 million people every year. Sputum microscopy is the primary method for diagnosing tuberculosis in resource-limited countries where 95% of tuberculosis cases occur (1), but it can only detect, at best, 50% of the cases. Sputum processing and fluorescence microscopy are more sensitive than conventional direct microscopy (2, 3).

Inadequate case detection and increasing multidrug resistance have resulted in tuberculosis reemerging as a major public health concern. The MODS assay is a promising candidate for reducing transmission because it addresses both these issues. As shown in the study by Moore and colleagues, the MODS assay can diagnose tuberculosis with greater sensitivity than direct microscopy and with greater speed than other culture methods.

Despite these advantages, a few concerns about the MODS assay need to be addressed. In an editorial accompanying the article, Iseman and Heifets stressed the need for "a well-organized tuberculosis laboratory using mandatory implementation of biosafety level 3 standards" to safely perform MODS culture (4); however, such labs are relatively sparse in resource-limited settings and costly to establish. With the MODS assay, the detection of typical cord formation is done microscopically. Because

potential exposure time for the health care worker is greater than with other culture techniques that use either direct visual or automated methods, measures must be taken to ensure containment of the cultures during examination. However, infection control and discarding of biohazardous waste are still rudimentary in developing countries.

In most resource-limited settings, physicians do not rely on laboratory diagnosis but rather treat patients empirically. The study population of Moore and colleagues was not exposed to empirical treatment; further evaluation of the MODS assay for populations in which empirical treatment is widespread is warranted.

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References

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