Physician-initiated courtesy MODS testing for TB and MDR-TB diagnosis and patient management

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S U M M A R Y

SETTING: Laboratorio de Investigación de Enfermedades Infecciosas, Universidad Peruana Cayetano Heredia (UPCH) and government health centres, Lima, Peru.

OBJECTIVE: To evaluate the contribution of unselected (courtesy) microscopic observation drug susceptibility (MODS) testing to the diagnosis and/or drug susceptibility testing (DST) of tuberculosis and their subsequent impact upon patient management.

DESIGN: Retrospective database analysis and case note review of MODS culture-positive cases.

RESULTS: *Mycobacterium tuberculosis* was isolated in 28.9% of 225 samples (209 patients); 22.2% of 63 positive cases were multidrug-resistant. In 58 MODS culture-positive cases with follow-up data available, MODS provided culture confirmation of diagnosis, DST or both in 82.8%, before any standard method. In 41.4%, this result should have prompted a modification in patient management. Delays between laboratory result and initiation or change of treatment, where applicable, took on average 42 and 64 days, respectively, of which a delay of respectively 17 and 48 days occurred after the receipt of results by the health facility.

CONCLUSION: MODS provides important data for clinical management within a meaningful timeframe and should contribute positively to patient outcomes due to earlier initiation of appropriate therapy. Although clinicians may successfully select patients likely to benefit from MODS, ongoing work is required to identify optimal implementation of the assay and to reduce logistical and health system derived delays.

KEY WORDS: tuberculosis; diagnosis; MODS; multidrug resistance (MDR)

DESPITE NOTABLE documented gains in tuberculosis (TB) control over the past decade,[1] over 5000 people die of this curable disease every day, almost all in resource-limited settings. Delay in initiating appropriate treatment is the principal cause of TB mortality. This arises primarily from two scenarios: 1) failure to detect drug-susceptible TB and administer empiric first-line treatment through lack of access to adequate diagnostic testing, or 2) failure to recognise that detected TB is multidrug-resistant (MDR, defined as resistance to both isoniazid and rifampicin), and thus likely to lead to treatment failure, ongoing transmission and death[2] due to the unavailability of drug susceptibility testing (DST).

Delays arise at all stages of the diagnostic process.[3–8] Delays attributable to the health system often exceed those due to patients,[6–8] and are mainly due to the long laboratory processing times.[9] Sensitive, rapid detection of TB and early, accurate identification of MDR-TB followed by prompt initiation of appropriate treatment aims to improve patient outcomes and prevent transmission in the community.

The microscopic observation drug susceptibility assay (MODS) is a culture and direct DST method for safe, rapid, low-cost detection of TB and MDR-TB,[10–12] recently incorporated into the Peruvian National TB Control Programme (NTP) guidelines.* Its sensitivity and specificity have been demonstrated to be respectively 97.8% and 99.6%, exceeding both the automated mycobacterial culture and Löwenstein-Jensen (LJ) methods.[12] The technique was developed, evaluated and refined in the Laboratorio de Enfermedades Infecciosas at Universidad Peruana Cayetano Heredia (UPCH) in Lima, Peru. As a courtesy to collaborators participating in these clinical studies, the laboratory offered physicians the facility of cost-free, off-protocol MODS testing for patients ineligible for clinical trials,

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* http://www.minsa.gob.pe/normaslegales/2006/RM383-2006.pdf

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albeit a limited number per month, on the understanding that (until 2006) MODS was regarded as an investigational test. Physicians selected patients they believed would benefit from MODS testing—often those who were persistently smear-negative or suspected to have MDR-TB. No prerequisites were imposed nor were requests screened for suitability at laboratory level. Outcomes of this testing had not previously been analysed.

We analysed the clinical and laboratory data of a recent cohort of such patients with the aim of evaluating the utility of this physician-initiated MODS testing for diagnosis, DST and subsequent patient management, over and above the contribution of the standard diagnostic facilities available, namely Ziehl-Neelsen (ZN) stain and LJ culture.

METHODS

Retrospective laboratory database and case note analysis

Courtesy samples processed between April 2005 and September 2006 were identified from the computerised laboratory database and demographic patient data were extracted. Dates and results of auramine staining and MODS culture performed at UPCH were recorded for each sample. Further data were obtained on MODS culture-positive cases by review of request form (including indications for testing), hospital/health centre records, and interviews with health care personnel and individual patients where necessary. Data on dates and results of ZN smear, LJ cultures and DST testing performed in other government laboratories were abstracted where available, and the temporal sequence of receipt of MODS result and subsequent treatment initiation or modification noted, where applicable.

Definitions

A MODS result was considered 'significant' if it:

1 provided important diagnostic information by:
   a) confirming the diagnosis of TB in the absence of any other method or before any other method, and/or
   b) providing DST results in the absence of any other method or before any other method, regardless of whether or not the patient had previously commenced anti-tuberculosis treatment, or
2 resulted in initiation or change of treatment due to the following:
   a) a positive result in a patient not previously on anti-tuberculosis treatment,
   b) monodrug resistance or MDR result in a patient on standard treatment,
   c) a non-MDR result in a patient previously started on empirical MDR treatment on the basis of clinical suspicion.

RESULTS

Demographic and laboratory data

A total of 225 samples from 209 subjects (51.2% female) were received during the 18-month period studied. The median age of the subjects was 23.5 years (range 3 months–79 years); 132 samples (59%) were from health centres, 88 (39%) from a hospital, and 2 (1%) from the university (UPCH); in the remaining 3 cases, no site was recorded. The samples processed were sputum ($n = 187$, 83.1%), gastric aspirate (33, 14.7%), urine (3, 1.3%) and cerebrospinal fluid (two from one patient, 0.9%).

Using the MODS assay, *Mycobacterium tuberculosis* was isolated from 28.9% of the samples, which comprised 61 sputum samples and 4 gastric aspirates from 63 patients (one patient contributed 3 samples). Of these, 47 (72.3%) were auramine smear-positive and 60 (93.2%) were also positive on LJ culture. MDR-TB was detected in 14 cases (22.2%). The mean time between specimen processing and positive results in the laboratory was 8.7 days for MODS and 21.7 days for LJ culture.

Population characteristics and indications for MODS testing

Case notes were available for review for 58 of the 63 cases (92%), 34 of whom had been started on TB treatment before sampling took place. In 33 cases, the duration of treatment before MODS test was known, and was a median of 27 days (range 1–165); 36.4% had been on treatment for less than a week, 27.3% for >2 months, and 9.1% for >4 months at the time of testing. Fourteen started treatment during the sample processing period and 10 initiated treatment after the MODS result.

All but one of the patients had symptoms suggestive of TB. In 33 (56.9%), the requesting physician suspected MDR-TB (16 had a previous history of TB treatment, 10 had contact with a MDR-TB case, 1 was an intravenous drug user, and in 6 the reason for suspicion of MDR-TB was unknown). Four of the MDR-TB suspects were persistently smear-negative, one of whom was confirmed as MDR-TB with MODS culture and DST.

Of the remaining requests, 9 (15.5%) had a previous history of TB (2 of which were also smear-negative), a further 7 (10.3%) were persistently smear-negative, and in the remaining 9 cases (15.5%), the reason for MODS testing was not stated, although 6 of these cases were smear-positive and had commenced treatment within 4 days or not at all, suggesting that MODS was performed to exclude MDR-TB.

Diagnosis and patient management outcomes

MODS provided the first culture confirmation of the TB diagnosis in 44 cases (75.9%), and the first DST result in 48 cases (82.8%). The results of MODS are
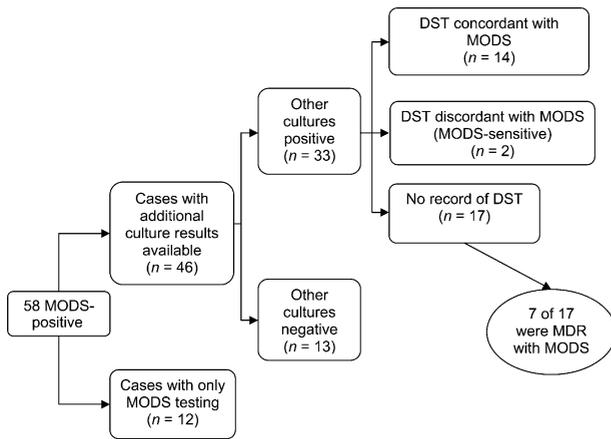
Figure Results of MODS testing in comparison to results obtained for LJ cultures (where these were performed) at other laboratories. MODS = microscopic observation drug susceptibility; LJ = Löwenstein-Jensen; DST = drug susceptibility testing.

compared with the results obtained for LJ cultures and DST at other laboratories, where performed, in the Figure. Of 33 cases where MDR-TB was suspected by the requesting physician, 11 were confirmed to be MDR, nine of whom (81.8%) had been receiving first-line or no treatment. Of the remaining 22 who did not have MDR-TB on MODS testing, four (18.2%) were on empiric MDR treatment. In the 25 cases where there was no suspicion of MDR-TB, two (8%) were identified as MDR on MODS testing.

In 24 cases (41.4%) the MODS result should have had an impact on patient management by prompting initiation of or change in treatment, although this only occurred in 16 cases. For example, of the 13 smear-negative patients who underwent MODS testing, four should have commenced treatment and two should have changed treatment based on the result. The im-

Table Effect of positive MODS results (*n* = 58) upon patient management

Potential impact of MODS result on clinical management	Actual outcome
24 should provoke management change	8 initiated appropriate treatment
	8 changed to appropriate treatment
	1 initiated treatment based on other results
	3 indeterminate*
	4 no change
34 should not provoke any management change†	2 changed treatment based on other results
	32 no change

* Two patients initiated treatment and one changed treatment after results of both MODS and alternative culture, making it unclear which results prompted action.
† Where MODS should not have resulted in initiation or change in treatment, the utility was realised as confirmation of diagnosis or DST, or both, in 24 patients already started on appropriate empirical treatment. In the remaining 10 cases, additional information provided by MODS was non-contributory.
MODS = microscopic observation drug susceptibility; DST = drug susceptibility testing.

pact of positive MODS results on patient management, in terms of initiation or change in treatment, is illustrated in the Table.

In 26 cases (41.3%), there was documentation that the patient had been informed of the MODS result.

Time to appropriate action

It took an average of 42.4 days to initiate TB treatment, from the date of a diagnostic positive MODS result, where the patient had not previously commenced treatment (*n* = 8), 17 days of which post-dated the arrival of the result at the health care facility. Results that would have been expected to trigger a change in previously initiated treatment (*n* = 8) arrived at the health care facilities within a mean of 16 days, but a further 48.4 days passed before treatment was changed, partly reflecting the previously lengthy procedures for effecting therapeutic change in the TB programme.

Three illustrative case studies

Case 1: A 19-year-old female presented to her community physician with a 3-week history of symptoms suggestive of TB but had no known contacts. A sputum smear obtained on the day of consultation was negative for acid-fast bacilli (AFB) and no treatment was initiated. The next day a sputum sample was provided for MODS testing. This was processed within 3 days, and within 10 days growth of fully sensitive *M. tuberculosis* was identified in the MODS assay (confirmed by positive LJ culture 18 days later), the results of which were made available to the health care facility within a further 10 days. The patient was subsequently started on standard TB treatment with first-line drugs.

Case 2: A 21-year-old male was diagnosed with TB in November 2005 based on suggestive symptoms, a known household contact (his brother, an intravenous drug user with unknown DST and human immunodeficiency virus status) and a positive sputum smear result. No culture or DST results were available at the time of initial diagnosis. After 3 months of standard first-line treatment, he was reviewed by his physician, who felt that his clinical improvement was unsatisfactory and was concerned about the possibility of MDR-TB. A sputum sample was provided for MODS analysis, and drug-susceptible *M. tuberculosis* was isolated within 1 week. His original treatment was continued and his progress reviewed regularly until clinical recovery and completion of treatment.

Case 3: A 24-year-old male was diagnosed with TB in January 2005, when he presented with characteristic symptoms and a positive sputum smear. He reported contact with a known MDR-TB patient. A single sputum sample was sent for LJ culture after 1 month of first-line TB treatment and was culture-negative, and thus no DST results were available. A follow-up smear 4 months into treatment was positive

for AFB, prompting the sending of a sputum sample for MODS testing. MDR-TB was isolated within 10 days and his treatment was altered accordingly.

DISCUSSION

These data clearly demonstrate the potential benefit to patients and physicians of the availability of MODS for TB and MDR-TB testing in this setting. Positive cultures were obtained in 29% of submitted samples, and MDR-TB was detected in 25% of positive cultures. This compares with 8.7% positives and 10.5% MDR in unselected TB suspects recruited at the same sites in a recent study.[12] The mean time for a positive MODS result in these patients, many of whom were receiving TB treatment, was 8.7 days, which is consistent with published results for this rapid diagnostic test.

This cohort of highly selected patients were generally chosen by their attending physicians for MODS testing because of suspicion of MDR-TB (due to significant contact or history of prior treatment) or because of strong clinical suspicion of active TB in the face of negative sputum smear microscopy, as seen in 13 cases (22.4%). Although these results are not representative of the wider population of TB suspects attending for diagnosis, they nevertheless demonstrate the important utility of MODS in a setting where a significant prevalence of MDR-TB poses a particular threat to patient management and infection control, and show the ability of clinicians to identify patients warranting further investigation.

Although therapeutic changes directly attributable to the use of MODS were only indicated in 24 of 58 cases (41.4%), there was considerable additional value in the confirmation of culture positivity and MDR or non-MDR status in a further 24 cases where MODS results supported ongoing empiric management in the absence of any other culture or DST results. This important benefit arising from the rapid availability of DST results is illustrated by Case 2, as the information averted a change to treatment with toxic, less effective and expensive second-line drugs based upon an erroneous clinical suspicion of MDR-TB. As shown in the study cohort, if the suspicion of MDR-TB led to empiric treatment change before DST results were available, this would have led to unnecessary patient risk and potential development of drug resistance in two thirds of cases.

Conversely, a delay in initiating MDR-TB treatment where appropriate has even more serious consequences. Until recently, management algorithms in the Peru NTP required subjects to fail first-line treatment before the sputum culture and DST were performed. This resulted in delays commonly lasting up to 6 months before the diagnosis of MDR-TB and initiation of appropriate treatment. During this time, when patients are attending the health facility every day to receive ineffective treatment, transmission of MDR-TB to household contacts, other patients and health care personnel continues.

The above-average prevalence of MDR cases detected in this cohort, particularly in the subgroup tested due to suspicion of MDR-TB (33% prevalence), demonstrates that physicians are selecting appropriate patients for rapid DST even in the early stages of treatment. However, we observed that in the 24 cases where the MODS result had management implications, appropriate action took place only in 16 (66.7%). In addition, although the MODS assay provided reliable positive results within a mean of 1 week, delays were observed both in the time to inform the requesting physician of the MODS results, and in the time then taken for appropriate action to be initiated. Inappropriate management, in conjunction with health system delays (on average 40 days to initiate and 64 days to modify treatment, which are consistent with previous observations)[9] also contribute to ongoing transmission of TB and MDR-TB in the community.

An important weakness of this study is that we only investigated the effect of the availability of positive results upon patient management and thereby failed to consider the important advantage that a negative culture result can often convey, particularly when it is available within 3 weeks. Despite thorough case note review and, where possible, substantiating interviews, our retrospective data collection is liable to recall bias and clinicians do not necessarily accurately recall their reasons for management decisions taken some months earlier.

Further work involved with educating physicians in risk factors for MDR-TB and disseminating information on the validity of the MODS assay, along with guidance for its implementation, may promote earlier identification of MDR cases, increase awareness and understanding of this relatively new technique and further reduce delays to appropriate treatment.

Urgent scale-up of the DOTS-Plus strategy to tackle MDR-TB,[13] which involves making low-cost second-line drug therapies through the Green Light Committee more widely available, offers the opportunity for effective MDR treatment and control.[14–17] A key component to its success, however, is the capacity to effectively diagnose MDR-TB, particularly in resource-poor settings. Appropriately targeted MODS could be one key to unlocking this proven potential.

CONCLUSION

This study demonstrates that the MODS assay has important potential to contribute significantly to patient management outcomes. However, to maximise its impact ongoing work is required to identify optimal strategies of implementation and usage of MODS, complemented by efforts to overcome the health system obstacles to swift action when a significant result arises.

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RÉSUMÉ

CONTEXTE : Laboratoire de Recherche sur les Maladies Infectieuses, Université Péruvienne Cayetano Heredia (UPCH) et les centres de santé du gouvernement à Lima, Pérou.

OBJECTIF : Evaluer la contribution d'un test MODS non sélectif (à titre gracieux) pour le diagnostic et/ou les tests de sensibilité aux médicaments (DST) de la tuberculose et leur impact ultérieur sur la prise en charge du patient.

SCHÉMA : Analyse rétrospective d'une base de données et revue des dossiers des cas MODS à culture positive.

RÉSULTATS : Sur 225 échantillons correspondant à 209 patients, on a pu isoler *Mycobacterium tuberculosis* chez 28,9%. Sur les 63 cas positifs, 22,2% étaient multi-résistants. Sur 58 cas à culture MODS positive où les données de suivi étaient disponibles, le MODS a assuré une confirmation du diagnostic par culture, le DST ou les deux chez 82,8% avant toute autre méthode standard. Dans 41,4%, ce résultat aurait dû entraîner une modification de la prise en charge du patient. Le délai entre le résultat du laboratoire et la mise en route ou la modification du traitement quand ils étaient d'application a représenté respectivement en moyenne 42 et 64 jours, desquels 17 et 48 jours de délai sont survenus après réception du résultat dans le service de santé.

CONCLUSION : Le MODS fournit des données importantes pour la prise en charge clinique dans un délai tout à fait valable, et devrait contribuer de manière positive aux résultats chez le patient grâce à une mise en route plus précoce d'un traitement approprié. Bien que les cliniciens puissent sélectionner avec succès les patients susceptibles de bénéficier du MODS, un travail en cours s'impose pour identifier la mise en œuvre optimale de la technique et pour réduire les délais logistiques et ceux liés au système de santé qui précèdent une action appropriée.

RESUMEN

MARCO DE REFERENCIA : Laboratorio de Investigación de Enfermedades Infecciosas, Universidad Peruana Cayetano Heredia (UPCH) y centros de salud del gobierno, Lima, Perú.

OBJETIVO : Evaluar la contribución de las pruebas MODS no seleccionadas (cortesía) para el diagnostico y/o susceptibilidad a medicamentos contra la tuberculosis (DST), y su subsiguiente impacto en el manejo de pacientes.

DISEÑO : Estudio analítico retrospectivo y revisión de datos de los casos de MODS con cultivo positivo.

RESULTADOS : *Mycobacterium tuberculosis* fue aislado en 28,9% de 225 muestras (209 pacientes). De 63

positivos, 22,2% correspondieron a muestras multidrogo-resistentes. Mediante MODS se obtuvo confirmación diagnóstica, DST o ambos en el 82,8% de los 58 casos de MODS positivos en los que contaba con información del seguimiento antes que otro método estándar. En el 41,4% este resultado debió producir una alteración en el manejo de los pacientes. La demora en los resultados de laboratorio para el inicio o cambio de terapia tomó un promedio de 42 y 64 días, respectivamente, de los cuales 17 y 48 días de retraso ocurrieron después de recibir los resultados en el centro de salud.

CONCLUSIÓN : MODS proporciona datos importantes para del manejo clínico de los pacientes precozmente, contribuyendo significativamente a iniciar la terapia apropiada. Aunque los clínicos tengan éxito al seleccionar pacientes que se beneficiarían de la utilización de MODS, se requiere de un trabajo continuo para identificar la óptima implementación de la prueba y reducir los retrasos derivados de la logística y del sistema de salud con el fin de tomar acciones apropiadas.