Risk Factors for the Development of Non-Response to First-Line Treatment for Tuberculosis in Southern Vietnam

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Background. Acquired resistance to standard chemotherapy for tuberculosis (TB) is an increasing problem worldwide. Vietnam has one of the highest incidences of TB and also has a large population of potential migrants to other countries. Since 1979 the International Organisation for Migration (IOM) has been running a supervised programme of TB treatment for intending migrants from Vietnam where few facilities for bacteriological culture and sensitivity testing exist. This study aimed to assess the most important factors for predicting non-response to first-line treatment as treatment starts and whether any further indicators occur during the course of treatment which may enable more accurate prediction of non-response.

Methods. In all, 130 subjects failing to respond to first-line therapy (cases) between 1990 and 1995 were compared with 673 subjects who responded to therapy (controls) on various demographic and clinical characteristics using logistic regression to create a prognostic index. Variables analysed included the patient history of past TB treatment, weight, age, sex and radiological and bacteriological findings. All subjects also tested negative for HIV status.

Results. The chief markers of successful response were x-ray signs and degree of sputum smear positivity. These markers provided a prognostic index with an optimal cutoff providing about 70% sensitivity and 80% specificity. Incorporating further measures obtained through the first 3 months of treatment improved the sensitivity to 80%.

Conclusion. While this study enabled prediction of the majority of subjects failing to respond to first-line therapy, other factors need to be assessed before recommendations for altering treatment regimens can be made. The prognostic index could be useful in assessing subjects for closer supervision.

Keywords: tuberculosis, chemotherapy, multidrug resistance, migration, diagnostics
Vietnam in 1975, IOM has been responsible for the medical screening of some 1.5 million Vietnamese as part of their migratory processing. The programme in Vietnam is referred to as the Orderly Departure Program and has been fully described elsewhere where the prevalence of TB among prospective migrants was estimated at 641 per 100,000 in 1993. As reliable facilities for sputum culture and sensitivity are not available in Vietnam, the diagnosis and monitoring of the response to TB treatment is based on sputum smears.

The aim of this study is to ascertain, based on the data collected at the commencement of anti-TB therapy, what the most important factors are for predicting non-response to first-line treatment, and whether any further indicators occur during the course of treatment which may enable more accurate prediction of non-response with a view possibly to starting second-line therapy earlier.

SUBJECTS AND METHODS

Treatment
All patients found to be smear-positive for *Mycobacterium tuberculosis* are commenced on treatment. The standard first-line regime being 2HREZ/4HRE (i.e. 6 months of daily isoniazid, rifampicin, ethambutol, with accompanying pyrazinamide for the first 2 months). This protocol is standard for all migrants processed through the Departure Program and is similar to the treatment schedule recommended by the CDC/American Thoracic Society, which however only recommends two drugs in the last 4 months. The treatment is strictly supervised at central locations within Ho Chi Minh City on 6 days per week, with a compliance rate of better than 95% for completion of the 6-month course. Compliance is good because of the incentive of the permission to migrate and because of the use of direct observation of therapy.

Treatment-compliant patients who continue to produce an unequivocally positive smear into the fifth month of treatment are considered ‘resistant’ to standard therapy and are usually commenced on an alternative regimen. The second-line regimen includes at least three of the following four drugs: capreomycin, cycloserine, ethionamide and ofloxacin.

Data Collection
Patients treated for TB in these programmes are included in a computerized database which is frequently updated. The database was developed using the ‘EPI INFO’ computer program. Data have been collected since 1990 for non-responding subjects and since 1992 for all subjects.

An assessment was also made as to whether there was improvement, progression, or no change in comparison to previous x-rays where available.

Statistical Analysis
Logistic regression analysis was used to examine the separate and combined effects of these variables on the odds of being a ‘case’ (i.e., resistant to first-line therapy). The odds ratios (OR) presented here are not intended to be estimates of the relative risk or the...
incidence rate ratio as in the more usual case-control study but are used to estimate the probability of being a 'case' as in a standard discriminant analysis. Variables were included in the regression models in a stepwise fashion, first demographic variables and then medical variables. Any variable found not to be significant at \( P < 0.10 \) was excluded. The OR for all variables were calculated alone and subsequently adjusted for all other variables included. Two-way interactions of all variables were also included in the same way, in particular the radiological and bacteriological variables with each other and with previous treatment (any or none). It was also necessary to adjust for year of treatment in case of possible confounding or interaction with other variables. Year of treatment was significant of itself because of the design of the study, however this was of no interest or importance for assessment of effects on non-response unless confounding or interaction was also present.

The final logistic model was then used to develop a prognostic index for predicting cases. If \( p \) is the probability of developing non-response, the estimated logistic models were represented in the following way:

\[
\log(p/1-p) = a + \sum b_i x_i,
\]

so that, \( p/1-p = \exp(a + \sum b_i x_i) \)

and \( p = \exp(a + \sum b_i x_i)/(1+\exp(a + \sum b_i x_i)) \)

Where \( a \) is the constant, and \( b_i \) the regression coefficients for variables \( x_i \). The probability of developing non-response was then estimated for each subject and used as a prognostic index. Results from this were described by a receiver operating characteristic (ROC) curve by plotting the sensitivity (proportion of all who developed non-response who were identified by the index) against (1-specificity) (proportion of all who did not develop non-response but who were predicted to do so) for the prognostic index at different cutoff points of the value of the probability \( p \). A plot of (sensitivity + specificity) against the prognostic score was also made to illustrate where the test performed best (provided sensitivity and specificity are equally important).

Two separate prognostic indicators were developed, the first based solely on data available at the time of treatment start, and the second including data that may have changed as treatment developed over the first 3 months.

### RESULTS

Differences between cases and controls in the measured variables are shown in Table 1. Cases were lighter, had worse radiological signs and had greater numbers of acid-fast bacilli on their sputum smears than controls. The cases were also significantly older but this difference disappeared once differences in proportions with previous treatment were controlled (Table 2). No sex differences were found and once the effects of the other x-ray signs were included there was no additional effect of lesion size on outcome. The effect of each category increase in smear count was uniform: about 60–70% increase each (+) when fitted separately at each time point.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Cases Mean (SD)</th>
<th>Controls Mean (SD)</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>45 (9)</td>
<td>48 (8)</td>
<td>0.95</td>
<td>0.93–0.98</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>17.9 (3.1)</td>
<td>18.9 (2.6)</td>
<td>0.86</td>
<td>0.79–0.93</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43 (17)</td>
<td>48 (18)</td>
<td>1.02</td>
<td>1.01–1.03</td>
</tr>
<tr>
<td>Female</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39 (30)</td>
<td>216 (32)</td>
<td>0.91</td>
<td>0.6–1.4</td>
</tr>
<tr>
<td>Any previous treatment</td>
<td>74 (57)</td>
<td>163 (24)</td>
<td>4.1</td>
<td>2.8–6.1</td>
</tr>
<tr>
<td>X-rays</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive lesions</td>
<td>101 (78)</td>
<td>227 (34)</td>
<td>6.8</td>
<td>4.4–10.7</td>
</tr>
<tr>
<td>Large lesion size</td>
<td>78 (60)</td>
<td>167 (25)</td>
<td>4.5</td>
<td>3.1–6.7</td>
</tr>
<tr>
<td>Cavities</td>
<td>57 (44)</td>
<td>95 (14)</td>
<td>4.8</td>
<td>3.2–7.2</td>
</tr>
<tr>
<td>Mediastinal shift</td>
<td>50 (39)</td>
<td>49 (7)</td>
<td>8.0</td>
<td>5.0–12.6</td>
</tr>
<tr>
<td>Sputum smears</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average score at entry</td>
<td>1.9 (1.3)</td>
<td>0.6 (0.9)</td>
<td>1.7</td>
<td>1.4–2.0</td>
</tr>
<tr>
<td>Worst score</td>
<td>2.3 (1.5)</td>
<td>0.9 (1.3)</td>
<td>1.7</td>
<td>1.5–2.0</td>
</tr>
</tbody>
</table>
period. Therefore the smear variables were fitted as a continuous 0–4 variable (based on the worst smear in each month or the average smear score in each month of treatment). The effect of weight implied that the risk of non-response declined by 5% per kg increase in weight (Table 1) or by 2% after adjustment for other variables (Table 2). No further significant effects were found including all possible two-way interactions (for example whether the effect of bodyweight was different in subjects with previous anti-TB treatment compared with those without). There were also no apparent confounding or interaction effects of calendar time of treatment commencement. Average monthly smear score was a slightly better predictor than maximum monthly smear score which was expected since the average score should have been less prone to the effects of observer error than the maximum score.

When used as a diagnostic test to measure non-response, the model used for Table 2 (Model 1) performed reasonably well (Figure 1). The best cutoff gave about 70% sensitivity and 80% specificity (Figure 2), that is about 30% of future non-responders would be missed and about 20% of responders would be included. Using the model from Table 3 (Model 2), that is with variables measured into the first 3 months of treatment, the optimal cutoff probability increased sensitivity to 80% at the same specificity, due to the increased sensitivity of smear scores in the third month. Once the latest smear score was available, earlier smear scores had no additional predictive value either alone or as interactions with the current score.

Failure to respond to treatment could be due to infection with other mycobacteria than M. tuberculosis, so the rate of occurrence of the most common other mycobacterial infection, M. avium, was estimated where possible. Although none of the subjects in this study had recorded culture results, a recent series of tests examining cultures with a hybridization protection assay in a DNA probe format identified 3% as being M. avium complex, and among 320 sputum specimens examined at the CDC in Atlanta and the Central Chest Laboratory in Bangkok (a CDC approved government facility), six of the 200 that grew out an organism were identified as M. avium.

**DISCUSSION**

The major predictors of successful response: x-ray signs and degree of sputum smear positivity, are similar

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Effects of baseline variables on risk of non-response, each variable adjusted for all others, only significant (P &lt; 0.10) variables considered in order of stepwise inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Mediastinal shift</td>
<td>2.1</td>
</tr>
<tr>
<td>Average smear score</td>
<td>1.5</td>
</tr>
<tr>
<td>Extensive lesions</td>
<td>3.6</td>
</tr>
<tr>
<td>Any previous treatment</td>
<td>2.3</td>
</tr>
<tr>
<td>Cavities</td>
<td>1.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

**Figure 1** Receiver operating characteristic (ROC) curves indicating difference in diagnostic performance of test for prediction of treatment failure based on variables known at start of treatment only (Model 1–Table 2), and during treatment (Model 2–Table 3)
to some described before.\textsuperscript{13} We are however unaware of any other studies that have looked for predictors of treatment failure in compliant subjects. Previous work appears to have examined either predictors for initial drug resistance\textsuperscript{14} or predictors for failing to complete the chemotherapy course.\textsuperscript{15}

After adjustment for other risk factors, the effect of previous anti-tuberculous treatment was reduced, but still appeared important. This is probably because many of the clinical signs of TB are manifestations of long-standing disease which would be more likely to be associated with past treatment. People with previous treatment are much more likely to have acquired resistance. It is likely however that there is greater relative inaccuracy in reporting of past treatments than there is in any of the clinical variables, so that the effect of past treatment is likely to be underestimated.

This study has found that the majority of non-responding TB cases can be predicted from the clinical characteristics at the time of presentation and that the accuracy of this prediction can be significantly improved as treatment progresses. An argument could be made for introducing second-line therapy for those performing badly on the prognostic score either initially or at 3 months. However, before alterations would be made to any treatment regimen, several factors have to be considered. First, the prediction model needs to be ratified on further data; these kinds of discriminant analyses invariably perform better on the so-called ‘training’ dataset than on further testing. Second, a more precise estimate of the failure rate is required. The success rate on this Program has been estimated from one year of data at 86\% with 5\% of patients progressing to second-line therapy\textsuperscript{10} and is similar to that found in other populations.\textsuperscript{16} The estimated sensitivity, specificity and positive predictive value can then be applied to these figures. Thus, assuming that the prognostic index would have similar sensitivity and specificity in future patients, for every 100 patients treated, one patient would be missed ($0.2 \times 0.05 \times 100$) and 19 patients ($0.2 \times 0.95 \times 100$) would be placed on second-line therapy unnecessarily. Third, there needs to be evidence on how well second-line therapy performs in comparison with initial therapy, especially if it is to be introduced without the initial treatment.

\begin{table}
\centering
\caption{Effects of variables recorded in the first 3 months of treatment on the risk of developing non-response, only significant ($P < 0.10$) variables considered}
\begin{tabular}{lcc}
\hline
 & Odds ratio & 95\% CI \\
\hline
Extensive lesions & 3.0 & 1.8–5.2 \\
Mediastinal shift & 2.4 & 1.3–4.5 \\
Average smear score & 3.5 & 2.7–4.5 \\
third month & & \\
Weight (kg) & 0.97 & 0.94–1.00 \\
Progressive x-ray & 2.1 & 0.9–5.0 \\
Any previous treatment & 1.8 & 1.1–3.1 \\
\hline
\end{tabular}
\end{table}
regime. Further work using this database is being undertaken to determine the natural history and success of second-line therapy in these subjects. Only then can the best decision be made in terms of patient time, illness and side effects, costs for the supervising system for staff time, supervision procedures and drug costs, as well as the societal cost of additional contribution to the ‘pool’ of resistant strains of \textit{M. tuberculosis}.

Non-response to treatment for these subjects can be for two reasons, either the initial infection was by a multi-drug resistant (MDR) strain of \textit{M. tuberculosis}, or the resistance was acquired after initiation of therapy. It is not possible to distinguish the two reasons. With adequate laboratory services, a diagnosis of MDR TB is based on \textit{in vitro} microbiological testing. This is why we have used the term TB that is non-responsive to first-line treatment, or non-response, which is the combination of what has been defined before as primary, initial, and acquired resistance, together with failure or relapse.\textsuperscript{17} It is not possible to say what proportion of non-responders had initial resistance, but the comparatively small effect of previous treatment implies that the proportion is likely to be small. It must also be remembered that initial drug resistance does not automatically lead to treatment failure,\textsuperscript{18} and that other factors are involved.\textsuperscript{19} However, it is certain that the greater proportion of drugs for which there is initial resistance, the greater the rate of failure.\textsuperscript{17,18} It is often assumed that treatment failure is due largely to poor compliance, however this is unlikely in the situation reported here because of the great incentive of permission to migrate and the directly observed administration of medication.\textsuperscript{20}

Although it was not possible to examine directly the effect of infection with \textit{M. avium}, it is unlikely that the estimated 3% prevalence has much bearing on overall treatment results. The additional possibility of re-infection after cure\textsuperscript{21} is only likely to be a problem in HIV related cases, which none of these were, or in areas with a much higher prevalence of disease.

The results from this study relate to the practical effectiveness of anti-tuberculous treatment. They cannot however contribute to the debate on the relative rates of primary, initial and acquired resistance,\textsuperscript{22} unless laboratory testing procedures are introduced, given that these can now be carried out fairly cheaply.\textsuperscript{23}

REFERENCES
\textsuperscript{7} Meropol S B. Health status of pediatric refugees in Buffalo, NY. \textit{Arch Ped Adolesc Med} 1995; 149: 887–92.

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