Prolonged hospitalisation for immigrants and high risk patients with positive smear pulmonary tuberculosis

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ABSTRACT: Prolonged hospitalisation for immigrants and high risk patients with positive smear pulmonary tuberculosis. R. Luzzati, M. Confalonieri, A. Cazzadori, P. Della Loggia, R. Cifaldi, C. Fabris, M. Biolo, M. Borelli, C. Longo, E. Concia.

Background and objective. Tuberculosis (TB) occurring in immigrants and resistance to drugs are major problems for TB control in Western countries. Directly observed therapy (DOT) reduces disease transmission, but this approach may have poor results among illegal immigrants. Our aim was to evaluate a prolonged hospitalisation programme to improve early outcome of TB treatment in high risk patients.

Methods. All the consecutive adult patients with sputum smear-positive pulmonary TB admitted to 2 Italian referral TB Centres were evaluated. Hospital-based DOT was provided to high risk patients up-to smear conversion. Demographic, microbiological and clinical conditions, as potential factors associated with confirmed smear conversion at 60 and 90 days of anti-tuberculous therapy were evaluated.

Results. 122 patients were studied, 45.9% of them were immigrants (20% illegal) from high-prevalence TB countries. HIV testing was negative in all cases. Twelve patients had M. tuberculosis resistant to ≥1 first-line anti-TB drugs. The rate of defaulting from TB treatment was 7.3%. Sputum smear became negative in 84.4% cases after 60 days and 93.3% cases after 90 days. At such time, smear conversion rates were similar among different high risk subgroups such as illegal immigrants (95.9%), legal foreign-born (92.5%) and Italian persons (94.8%). Persistent sputum smear positivity was independently correlated with the extent of pulmonary lesions at 60 (p<0.0001) and 90 days (p=0.038) of hospital-based DOT.

Conclusions. These findings suggest that prolonged hospitalisation for illegal immigrants and high risk TB patients, may positively influence the early outcome of TB treatment despite of drug resistance and legal status. Monaldi Arch Chest Dis 2011; 75: 2, 141-145.

Keywords: Pulmonary tuberculosis, Mycobacterium tuberculosis, Drug-resistant tuberculosis, Sputum smear conversion, hospitalization, Directly observed therapy, Illegal immigrants.

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Introduction

Increased proportion of tuberculosis (TB) occurring among immigrants and resistance to drugs are major problems for TB control in Western countries including Europe and United States [1, 2]. A high rate of defaulting from treatment among high risk patients is a major task to optimise TB control in low incidence countries [3]. Early detection and treatment by directly observed therapy (DOT) reduces disease transmission [4], but active therapy obtained a low completion rate among illegal immigrants according to a previous study [5]. Sputum smear conversion at the second month of treatment is a key result to determine TB control [6], but this early outcome depends on a strict adherence to treatment. The need for efficient care delivery led us to establish the strategy of long hospital stay in order to manage the high risk of positive smear pulmonary TB patients because of their social status and/or drug resistance. The aim of this 4- year duration study was to evaluate the effectiveness of our hospital-based strategy to achieve sputum smear conversion after 60 and 90 days from the initiation of hospital-based DOT.

Methods

This study included all consecutive adult patients (aged > 18 years) admitted to two referral TB Centres (University Hospital of Trieste and Verona, Italy) for high risk positive smear culture-confirmed pulmonary TB between January 2004 and December 2008. Both TB centres are located in 2 metropolitan areas in northern east Italy (Trieste and Verona), with a population of nearly 250,000 and 700,000 respectively. The decision to admit to hospital a sputum smear positive pulmonary TB patient for a hospital-based DOT treatment was taken according to at least one of the following criteria: a) resistance to one or more anti-TB drugs, b) foreign-born person, c) illegal immigrant, d) previous treat-
ment, e) being an injecting drug user, f) HIV infec-
tion, g) social and/or familiar condition not assuring
good adherence to treatment (living alone, residents
of confined institutions, comprehension difficulties
on modalities of treatment). Decision on patient
hospital discharge was taken when the patient
achieved into clinical improvement and confirmed
sputum conversion following hospital-based DOT.
The sputum was collected on a 15-day period basis
until the smear became negative for 3 consecutive
samples (confirmed smear conversion), which were
collected on different days. The laboratories per-
formed culture and drug sensitivity test including
second-line drugs, and were validated according to
the World Health Organization External Quality As-
essment WHO EQA) proficiency scheme, being
part of the Multicenter Italian Study on Resistance
to Antituberculosis Drugs (SMIRA) network [7].
Multidrug-resistant (MDR) TB is defined as a spe-
cific form of drug-resistant TB due to TB bacteria
resistant to at least isoniazid and rifampicin. Cases
with follow-up shorter than 60 days were excluded.
Analyses focused on potential factors associated
with confirmed smear conversion at 60 and 90 days
of anti-tuberculous therapy. Candidate variables
were: age, sex, country of origin (Italy or other
countries), illegal immigrant condition, underlying
diseases (chronic obstructive pulmonary disease,
cancer, diabetes mellitus, alcohol abuse, and HIV
infection), previous history of tuberculosis, semi-
quantitative evaluation of organisms on sputum
smear (≤ or > 1/10 fields) [8], resistance to any first-
line antituberculous drug, presenting pulmonary X-
ray pattern (cavitary or not cavitary disease) and
disease extent. Pulmonary disease extent on the ini-
tial chest radiography was based on the number of
lung zones involved; each lung was considered to
have 3 zones (upper, middle, and lower). Involv-
ment of 1-2 zones was considered to be localized
disease, 3-4 zones as moderate disease, and 5-6
zones as extensive disease [9]. A rough comparison
of the results of this study with estimates of the
costs of prolonged hospitalisation and drop-out rate
of historically patients was finally made.

Statistical analysis

Normally distributed data was tested by Kol-
smogorov-Smirnov, and was summarised by mean
(median) and standard deviation (quartiles). Statis-
tical inference in the former case was approached by
F test and subsequently by Student-Welch t test,
wheras in the latter by Wilcoxon test. Survival
analysis was applied to determine the difference in
time to event data. Generalised linear models with
binomial error distribution and logistical linking
were used to assess covariate predictors involved in
smear negativity. A logistic model was performed to
check for independent risk factor(s). In all in-
stances, alpha error = 5%. To assess covariate asso-
ciated to smear conversion, a multivariate additive
generalized linear model with binomial (positive
vs. negative) response was analysed. A significant
minimal adequate models fitting the data were
found by backward elimination process. Statistical
analysis was performed by open source statistical
package R version 2.6.2 (R Development Core Team: R: A language and environment for statisti-
cal computing. R Foundation for Statistical Com-

Results

Among a total of 228 patients admitted to our
hospitals for pulmonary TB during the study period,
122 patients, 76 (62.3%) males and 46 females, had
sputum smear-positive culture-confirmed TB filling
one or more criteria for high risk smear positive TB.
A total of 7, 13, and 18 patients were discharged from
hospital during the follow-up respectively within 15-
day, 60-day, and 90-day periods after the initiation
of anti-tuberculous therapy. The reasons for discharge
varied (family, job, personal decision, etc.), but only
15 patients were lost at follow-up. The rate of de-
faulting from TB treatment was 7.3% (9 patients),
and 1 of them did not have confirmed smear conver-
sion. Underlying diseases were present in 36% of
cases, and included chronic obstructive pulmonary
disease (16 cases), cancer (15 cases) and diabetes (13
cases). Twelve patients (9.8%) had M. tuberculosis
bacilli resistant to ≥1 first-line anti-tuberculous
agents. No second-line drug resistance was detected.
Of the latter patients, one had a multidrug-resistant
isolate (MDR). Fifty-six patients (45.9%) were im-
migrants and refugees from high-prevalence coun-
tries. Twenty-four patients (20%) were illegal immi-
grants. Twenty patients (16.4%) had a medical histo-
ry of alcohol abuse with wide range of liver and neu-
rologic involvement. Human Immunodeficiency
Virus (HIV) testing was negative in all cases, and 3
patients were injecting drug user. Adherence to treat-
ment was 96% among patients who completed the 60
and 90 days hospital-based DOT period. The treat-
ment completion rate was 93.4% including the pa-
tients lost at follow-up. Hospital discharge follow-
ing confirmation of sputum smear conversion was ob-
tained after a mean of 85 ± 12 days. At that time, all
patients started to receive the current outpatient DOT
programme. Sputum examination of the smear be-
came negative in 25 (21.8%) cases after 15 day of
treatment, 60 (53.1%) cases after 30 days, 92 (84.4%)
cases after 60 days and 97 (93.3%) cases after 90
days. Culture of sputum for M. tuberculosis
became negative in 9 (7.8%), 32 (27.8%), 59 (54.1%),
73 (70.2%) cases respectively after 15, 30, 60, 90 days
of treatment. Smear conversion rates after 90 days
were similar among high risk subgroups: illegal immi-
grants (95.9%), legal immigrants (92.5%) and Italian
persons (94.8%), with no statistical difference.
Factors potentially associated with smear conver-
sion at 60 and 90 days of treatment are detailed in
Table 1. By univariate analysis, cavitary pulmonary
disease, moderate or extensive X-ray pulmonary le-
sions, and resistance to any antituberculous drug re-
sulted to be significantly associated with persistent
smear positivity. To assess covariate associated to
smear conversion, an additive generalised linear
model with binomial (positive vs. negative) response
was analysed. Two significant minimal adequate
models fitting the data were found by backward elimi-
ination process, as follows: at 60 days, moderate or extensive pulmonary lesions ($p<0.0001$); at 90 days, antibiotic resistance to any first-line anti-tuberculous drug ($p=0.007$) and moderate or extensive pulmonary lesions ($p=0.038$). Log-rank testing showed high significant difference ($p<0.001$) between time to smear conversion only to curves belonging to patients with moderate or extensive pulmonary lesions on one hand, and localised lesions on the other (figure 1).

No association was found between sputum conversion at 60-90 days from hospital-based DOT initiation and the condition of illegal immigrant and/or legal immigrant, age, gender, presence of cavitory lesions, co-morbidities, sputum hypersecretion ($>20$ mL/day), drug-resistance (intercept z value = -2.160).

**Estimate of the costs of prolonged hospitalization and previous failure/drop-out rate among illegal immigrants**

The average cost of hospitalisation at our Infectious Diseases Departments is presumed by our Administration to average €440.00 per day. The mean previous duration of hospital stay for active TB was $20 \pm 9$ days. The prolonged hospitalisation programme for high risk patients with sputum smear positive TB resulted in a duration of hospital stay longer than before ($98 \pm 18$ days), so the extra hospital stay is $78 \pm 9$ days. The extra hospitalisation costs of such a prolonged hospitalisation may be roughly estimated in €34320.00 ± €3960.00. On the other hand, the revision of the historical data (2000-2003) from our registry showed that the rate of drop-out of TB treatment among Italian high risk TB patients was higher (20-25%), and among illegal immigrants was even much higher (40-45%) before the program of prolonged hospitalization than after to implement it.

**Discussion**

In our series, a prolonged hospitalisation programme allowed to achieve efficient care delivery in high risk smear positive pulmonary TB patients, including illegal immigrants. In fact, sputum smear conversion was very high (up to 94%) after 90 days of DOT among these TB patients usually known to be at high risk for treatment failure (drug resistance, socially marginalised groups, illegal immigrants) [10, 11]. This finding can be due to various factors including the absence of HIV-infected patients and the quite low rate of defaulting from treatment (7.3%) in our patient population. The aim of tuberculosis treatment is to obtain a high cure rate and a low default rate. This is mainly a matter of management of the patients. It has been demonstrated long time ago that it is quite possible to reach this target on an ambulatory base, but this can be very difficult to obtain for illegal immigrants and other high risk

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<table>
<thead>
<tr>
<th>Variables</th>
<th>After 60 days hospital-based DOT</th>
<th>After 90 days hospital-based DOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 1&lt;sup&gt;st&lt;/sup&gt; quartile</td>
<td>Smear-negative cases</td>
<td>Smear-positive cases</td>
</tr>
<tr>
<td>Median age</td>
<td>27.50</td>
<td>34.25</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; quartile</td>
<td>68.50</td>
<td>72.00</td>
</tr>
<tr>
<td>Age: male</td>
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<td>13</td>
</tr>
<tr>
<td>Female</td>
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<td>5</td>
</tr>
<tr>
<td>Nationality: Italian</td>
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<td>11</td>
</tr>
<tr>
<td>Foreign-born</td>
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<td>7</td>
</tr>
<tr>
<td>Underlying diseases: yes</td>
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<td>4</td>
</tr>
<tr>
<td>no</td>
<td>53</td>
<td>14</td>
</tr>
<tr>
<td>New TB case</td>
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<td>14</td>
</tr>
<tr>
<td>Relapsing TB case</td>
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<td>4</td>
</tr>
<tr>
<td>Sputum quantification: &lt;1/10 fields</td>
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<td>4</td>
</tr>
<tr>
<td>$\geq$1/10 fields</td>
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<td>12</td>
</tr>
<tr>
<td>Cavitary disease: yes</td>
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<td>14</td>
</tr>
<tr>
<td>no</td>
<td>42</td>
<td>4</td>
</tr>
<tr>
<td>X-ray lesion extent: localised</td>
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<td>2</td>
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<tr>
<td>moderate-extensive</td>
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<td>16</td>
</tr>
<tr>
<td>Resistance to any drug: yes</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>no</td>
<td>82</td>
<td>15</td>
</tr>
</tbody>
</table>
TB patients. Sputum smear conversion at the second month of anti-tuberculous therapy has been considered a predictor of treatment success for pulmonary TB [6], and non-compliance with therapy is associated with poor treatment outcome, acquired drug resistance and increased risk of relapse [10, 11]. The European case-definition of TB is based on culture, and culture conversion is considered as informative as the sputum smear conversion [12]. The encouraging results of our prolonged hospital-based DOT approach were confirmed even in illegal immigrants, which represent a particularly difficult population to achieve compliance to treatment for any TB program in Italy [5, 13]. Almost a half of our study population was foreign-born people, illegal immigrants being more than half of them. Adherence to treatment was high among hospitalised illegal immigrants with a quite high smear conversion rate after 90 days (95%) considering their difficulty to comply with the treatment. Also the results of culture conversion were very similar to smear conversion, this is important because of the risks in the community of sputum conversion only [14]. Our findings might encourage to carry out novel health policies towards such difficult to care TB patients, whose burden on TB control is increasing in low prevalence Countries. The prolonged hospitalisation due to respiratory isolation of these patients may contribute to hasten the spreading of TB resistance and positive smear contacts among general population. Limited data is available to predict the length of time required for a patient to achieve sputum conversion after starting therapy for pulmonary tuberculosis. Although data suggests that once a patient receives effective treatment, infectiousness rapidly ceases [15], the Centers for Disease Control and Prevention (CDC) still recommend the suspension of respiratory isolation only when patients are receiving effective chemotherapy, their clinical conditions are improving, and when 3 consecutive sputum samples, collected on different days, are AFB-smear-negative [17]. Nevertheless, the closure of sanatorium hospitals in low prevalence Countries made hospitalization less frequent and hospital stay shorter than in the past. A major cause of the resurgence of TB in Western Countries is the increased proportion of immigrants from countries where TB is endemic [17]. Furthermore, the condition of illegal immigrant is associated with severe socioeconomic outcasting, uncertain working and living conditions, high mobility and, perhaps, the perception of TB therapy as much less essential than more immediate needs together with fear of deportation. DOT for illegal immigrants with TB requires more human and financial resources than for other patients. Previous Italian surveys already reported a significant correlation between compliance with treatment and legal citizenship status [18]. Even if DOT is expected to increase the rates of completion of treatment [19, 20], the pooled results of randomised controlled trials provide no assurance that current DOT has any quantitatively important effect on cure or treatment completion in people receiving treatment for TB, a recent Cochrane review stated [21]. Providing an hospital-based optimal adherence to treatment, we find that to be a foreign-born people and/or an illegal immigrant does not represent an independent risk factor for smear conversion failure. In our study population, the only variable independently associated with persistence of smear positivity during such period of treatment was the extent of pulmonary lesions. Several factors including numerous AFB on the initial smear and cavitary pulmonary disease

![Image of a tree diagram](image-url)
were reported to be associated with sputum smear conversion at nearly 30-90 days of anti-tuberculous therapy [23-26]. We have found that cavitory disease was associated with persistently smear positive for AFB at 60 days of treatment in bivariate analysis. It became apparent on an additive statistical analysis, however, that cavitory disease was not and independent predictor in our series of high risk patients on prolonged hospital-based DOT. Although costs of prolonged hospitalisation are quite high, the overall costs of defaulting might be higher [22], but this issue was not an end-point of our study. We estimated an extra-cost of hospitalisation of more than € 30,000.00 per patient. Nevertheless, the rate of drop-out and failure of TB treatment resulted much lower after the implementation of a prolonged hospitalisation programme than before. Finally, it must be clearly stated that the present study has several limitations: the study design is retrospective, a control group is lacking, a calculation of the costs of such a prolonged hospitalisation was not provided.

In conclusion, our findings suggest that a prolonged hospital-based DOT programme can obtain quite favourable early outcome in high risk patients including foreign-born and illegal immigrants. If this accounts for a better TB control with compatible cost in the general population of low incidence countries remain to be shown. Further prospective studies are needed to determine the cost-effectiveness of this therapeutic approach.

References