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Journal Title: Emerging Infectious Disease
Volume: Volume 7, Number 1
Publisher: Centers for Disease Control and Prevention | 2001-01-01, Pages 123-127
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.3201/eid0701.010117
Permanent URL: https://pid.emory.edu/ark:/25593/s7txg

Final published version: http://dx.doi.org/10.3201/eid0701.010117

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Accessed December 29, 2018 8:25 PM EST
Research

Hospital Control and Multidrug-Resistant Pulmonary Tuberculosis in Female Patients, Lima, Peru

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We examined the prevalence of tuberculosis (TB), rate of multidrug-resistant (MDR) TB, and characteristics of TB on a female general medicine ward in Peru. Of 250 patients, 40 (16%) were positive by sputum culture and 27 (11%) by smear, and 8 (3%) had MDRTB. Thirteen (33%) of 40 culture-positive patients had not been suspected of having TB on admission. Six (46%) of 13 patients whose TB was unsuspected on admission had MDRTB, compared with 2 (7%) of 27 suspected cases (p=0.009). Five (63%) of 8 MDRTB patients were smear positive and therefore highly infective. In developing countries, hospital control, a simple method of reducing the spread of MDRTB, is neglected.

From 1990 to 2000, tuberculosis (TB) caused an estimated 88 million new infections and 30 million deaths worldwide (1). In Peru, tuberculosis is highly endemic; a shantytown in Lima had an annual incidence of pulmonary tuberculosis of 364 per 100,000 population (2). Despite the implementation of community-based treatment and control programs in Peru (3), management of the disease has been complicated by high rates of multidrug-resistant (MDR) TB. In one study in Peru, 4.5% of all reported cases were resistant to isoniazid and rifampin (4). Nosocomial spread of MDRTB has been reported in both industrialized and developing countries and has been linked to inadequate hospital infection control practices (5-7).

We investigated the potential for nosocomial spread of MDRTB in one city hospital in Lima. We assessed the prevalence of TB among hospitalized patients on a general medicine ward, the rate of MDRTB and the extent to which active pulmonary TB had been suspected in patients at the time of admission.

Methods

Study Population and Design

The study was conducted from January to December 1997 in the Arzobispo Loayza Hospital, an urban public hospital in Lima, Peru. This hospital was founded as a women’s hospital in the eighteenth century and continues to serve...
a largely female patient population. We solicited
the participation of all patients admitted to one of
the hospital’s eight female internal medicine
wards (an open room with 30 beds) during the
study period. The most common admission
diagnoses over the year of study were
pneumonia, bronchiectasis, cardiac insufficiency,
TB, cellulitis, diabetes mellitus and chronic renal
failure. The study protocol was approved by the
institutional review boards of the Johns Hopkins
University and Loayza Hospital. All study
participants gave informed consent.

Patients who agreed to participate in the
study answered a brief questionnaire and
underwent physical examination. The medical
records were reviewed. A tuberculin skin test
(TST) (5 tuberculin units, Connaught, Swiftwater,
PA) was administered and was read after 48 to 72
hours. The TST was considered positive if the
area of induration measured \( >10 \) mm both
vertically and horizontally. At least one sputum
specimen \( >1 \) mL in volume was obtained;
whenever possible, additional sputum specimens
were obtained on consecutive days.

Laboratory Testing for TB

Acid-fast Bacilli Smear Microscopy

All samples were digested and concentra-
ted by the standard N-acetyl-L-cysteine NaOH-
Na citrate method for processing mycobacterial
cultures (8). Ziehl-Neelsen and Auramine
staining were performed by standard tech-
niques (8).

Cultures

Mycobacterial growth indicator tubes (Becton
Dickinson, Sparks, MD) containing both 10% OADC
(oleic acid, albumin, dextrose, and
catalase) (Becton Dickinson, Sparks, MD), and
100 \( \mu \)L of PANTA Antimicrobial Supplement
(Polymyxin B, Amphoterin B, Nalidixic acid,
Trimethoprime, and Azlocillin) (Becton Dickinson)
were injected with 500 \( \mu \)L of decontaminated
sputum sample according to the manufacturer’s
specifications. Löwenstein-Jensen slants (Difco,
Detroit, MI) and Middlebrook 7H11 medium
plates (Difco, Detroit, MI) were injected with
250 \( \mu \)L of decontaminated sample. Tubes were
incubated at 37°C and examined for mycobacte-
rial growth at least weekly for up to 6 weeks with
a 365-nm UV transilluminator. Löwenstein-
Jensen slants and micro-agar 7H11 plates were
incubated at 37°C with and without 5% CO\(_2\) and
examined by light microscopy for mycobacterial
growth at least weekly for 2 to 8 weeks after
injection (8). Criteria for positive mycobacterial
growth have been previously described by the
Centers for Disease Control (9).

Sensitivity Testing

The microplate alamar blue assay was used
to determine mycobacterial drug resistance (10).
Bacterial suspensions were prepared from
colonies grown on Middlebrook 7H11 agar.
Samples of the bacterial suspension (20 \( \mu \)L) were
grown in 96-well plates containing serial
dilutions of anti-TB drugs (isoniazid, rifampin,
ethambutol, streptomycin, capreomycin,
ciprofloxacin) until control wells tested positive
for mycobacterial growth, usually in 5 to 6 days.
Alamar blue reagent was then added to each well,
and mycobacterial growth was identified by a
change in media color from blue to pink. MIC was
defined as the lowest drug concentration at which
no blue-to-pink color change was observed. MICs
for the panel of six anti-TB drugs were
determined for each isolate.

Data Analysis

Patients were included in the study if they
completed the questionnaire, had a physical
examination, and provided one adequate sputum
specimen. A patient was considered to have
MDRTB if the sputum exhibited growth in media
containing both isoniazid and rifampin. HIV tests
were not performed as part of this study, but HIV
test results were available for some patients.

All data were entered twice, and the two
databases were compared to eliminate data entry
errors. Data were analyzed with SPSS version
7.5 (SPSS Inc., Chicago, IL) and Epi Info version
6.0 (CDC, Atlanta, GA). The chi-square and
Fisher’s exact tests were used to measure
strengths of association for categorical variables.
The Wilcoxon 2-sample test was used to compare
continuous variables.

Results

From January to December 1997, 250 (78%)
of 319 patients admitted to the ward had a
completed questionnaire and physical examina-
tion and at least one adequate sputum specimen.
Forty patients (16%) had sputum cultures
positive for Mycobacterium tuberculosis, and 26
of these had positive sputum smears. One patient
had a positive smear but a negative culture. Only three patients had a diagnosis of HIV infection; none of the three had a positive sputum specimen. Of the 69 ward patients who declined to participate or were unable to provide an adequate sputum specimen, 4 (6%) had been admitted with a diagnosis of suspected TB. If we assume all excluded patients to be negative for TB, the minimum estimated TB prevalence on the ward was 13%.

Patients with a cough of any duration, a cough that lasted >2 weeks, reported weight loss, hemoptysis, or a family history of TB were more likely to have sputum cultures positive for TB (Table 1). Anorexia was associated with a lower likelihood of TB. Because of logistic constraints, we were able to place and read a TST at 48 to 72 hours only on a subset of patients. Of the 67 patients with TST results, a positive reading was observed in 11 (55%) of 20 culture-positive patients compared with 10 (21%) of 47 patients without TB (p=0.007). Among culture-positive patients, those with a positive TST response were younger than those with a negative reading (median 23 years of age [range 19-66] vs. 47 years [range 25-88], p=0.02 by Wilcoxon 2-sample test). The socioeconomic status of patients with and without TB was similar.

Of the 181 patients who reported past BCG immunization, 178 (98%) had a scar. No vaccine scars were observed among the 68 persons who reported no history of BCG immunization. However, having a BCG scar was not associated with any apparent protective effect (Table 1). The presence of a BCG scar was not associated with a positive TST, even when TB culture positive patients were excluded (p=0.7).

Of 40 patients with at least one positive sputum culture, 23 (58%) had strains resistant to at least isoniazid, 8 (20%) to rifampin, 4 (10%) to ethambutol, and 1 (3%) to streptomycin. None were resistant to ciprofloxacin or capreomycin. Eight patients (20%) had TB resistant to both isoniazid and rifampin and were classified as having MDRTB. All 8 patients with resistance to rifampin also had resistance to isoniazid, and 15 patients had strains resistant to isoniazid but not to rifampin. Of the eight strains resistant to both isoniazid and rifampin, one was also resistant to ethambutol, one to streptomycin, and one to both ethambutol and streptomycin. Of 8 patients with MDRTB, 3 had a previous history of TB treatment.

Culture-positive patients for whom TB was the admitting diagnosis differed from those in whom TB was not suspected at the time of admission (Table 2). Patients whose TB had not been suspected were older and less likely to have the classic findings of cough, hemoptysis, weight loss, and prior personal or family history of TB. Patients whose TB had not been suspected at the time of admission were less likely to have a positive sputum smear, but this difference did not reach statistical significance (p=0.16 by Fisher’s exact test). However, patients whose TB had not been suspected were significantly more likely to have MDRTB. Six (75%) of 8 patients with MDRTB were not suspected to have TB on admission; 3 (50%) of these six were also smear positive. Admitting diagnoses among culture-positive patients whose TB had not been suspected on admission included two patients with diabetes mellitus, one with systemic lupus erythematosus, and one with a lung lesion thought to be a hydatid cyst.

### Table 1. Female patients admitted to a general medicine ward of a hospital, Lima, Peru

<table>
<thead>
<tr>
<th>Mycobacterium tuberculosis culture results</th>
<th>Positive</th>
<th>Negative^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=40, n (%)</td>
<td>N=209, n (%)</td>
<td></td>
</tr>
<tr>
<td>Median age (range)</td>
<td>43 (18-96)</td>
<td>46 (14-92)</td>
</tr>
<tr>
<td>Cough</td>
<td>35 (88)^b</td>
<td>125 (60)^b</td>
</tr>
<tr>
<td>Cough for ≥ 2 weeks</td>
<td>25 (63)^b</td>
<td>64 (31)^b</td>
</tr>
<tr>
<td>Weight loss</td>
<td>33 (83)^b</td>
<td>122 (58)^b</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>12 (30)^c</td>
<td>29 (14)^c</td>
</tr>
<tr>
<td>Anorexia</td>
<td>22 (55)^c</td>
<td>149 (71)^c</td>
</tr>
<tr>
<td>Fever</td>
<td>24 (60)</td>
<td>108 (51)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22 (55)</td>
<td>107 (51)</td>
</tr>
<tr>
<td>TST positive^d</td>
<td>11 (55)^c</td>
<td>10 (21)^c</td>
</tr>
<tr>
<td>BCG scar</td>
<td>28 (70)</td>
<td>150 (71)</td>
</tr>
<tr>
<td>History of BCG vaccination</td>
<td>29 (73)</td>
<td>152 (72)</td>
</tr>
</tbody>
</table>

^aOne patient who was smear positive but culture negative was excluded from the analysis.

^bP value < 0.01 by Mantel-Haenzsel chi-square test.

^cP value < 0.05 by Mantel-Haenzsel chi-square test.

^dA total of 67 patients, 20 M. tuberculosis culture-positive and 47 M. tuberculosis culture-negative, had tuberculin skin tests (TST).
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Table 2. Mycobacterium tuberculosis culture-positive patients, by admission diagnosis, Lima, Peru

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Suspected TB</th>
<th>No suspected TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=27, n (%)</td>
<td>N=13, n (%)</td>
<td></td>
</tr>
<tr>
<td>Median age (range)</td>
<td>27 (18-87)</td>
<td>58 (22-96)</td>
</tr>
<tr>
<td>Cough</td>
<td>27 (100)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Cough for ≥ 2 weeks</td>
<td>20 (74)</td>
<td>5 (39)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>25 (93)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>10 (37)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Fever</td>
<td>16 (59)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13 (48)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17 (63)</td>
<td>5 (39)</td>
</tr>
<tr>
<td>Prior history of TB</td>
<td>8 (30)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Smear positive</td>
<td>20 (74)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>MDRTB</td>
<td>2 (7)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>MDRTB and smear positive</td>
<td>2 (7)</td>
<td>3 (23)</td>
</tr>
</tbody>
</table>

*p value < 0.05 by Wilcoxon 2-sample test.

Conclusions

The overall prevalence of TB among our study patients was high: at least 13% of all patients admitted to this general medicine ward had active TB. Two-thirds of TB patients were smear positive and therefore highly infectious, one-fifth had multidrug-resistant strains, and 75% of the patients with MDRTB had not been suspected of having TB when they entered the hospital. As in most Latin American hospitals, no masks or other respiratory devices were used to prevent spread in this hospital, even when the patient was known to be smear positive and highly infectious.

Nosocomial outbreaks of MDRTB in the United States in the 1980s and early 1990s heightened enforcement of stringent hospital control measures (11), leading to measurable decreases in TST conversion rates among hospital staff (12). Although the rate of TB in Peru is approximately 20 times higher than that of New York City (13), no concerted effort has been made to improve TB control measures in Peruvian hospitals.

The spread of MDRTB threatens control efforts (14). The fact that the majority of our patients with MDRTB had no history of past treatment of TB implies that person-to-person transmission of multidrug resistant strains occurs in Peru. Our data suggest that hospital wards may be one of the sites of transmission.

In developing countries where resources are limited, TB control programs focus on identification and treatment of infectious cases (15). Although treatment is clearly an important component of control, person-to-person spread of resistant strains makes isolation a high priority for preventing transmission. TST testing was not useful in identifying the group in need of screening. Anergy, which was common among culture-positive TB cases, was associated statistically with older median age and was perhaps related to concurrent systemic illness and poor nutritional status among hospitalized patients.

Although Peru has implemented an effective community-based TB control program, hospital control has not been a focus. Control measures such as isolation and respiratory precautions, stringently enforced in the past, were relaxed worldwide after the advent of inexpensive, effective anti-TB medications. After 50 years of selective drug pressure, the outbreak of MDRTB in New York City (5) dramatically highlighted the consequences of lapses in infection control.

Our data show that in countries or locales with a known high prevalence of TB, hospitals should screen all patients with respiratory symptoms by sputum smear within 12 hours of admission to hospital. Those found to be smear-positive should be placed in respiratory isolation, apart from TB-negative patients, until the smear becomes negative. Hospital personnel should observe respiratory precautions in caring for these patients. A system of rapid culture diagnosis and susceptibility testing should be implemented, allowing the presumptive diagnosis of MDRTB within 2 weeks (16). In combination, admission screening for TB, reimplementation of effective hospital respiratory control, and rapid TB diagnosis can substantially decrease the transmission of TB, especially MDRTB, in countries like Peru.

Acknowledgments

We thank R. Black, D. Berg, and K. Laserson for helpful comments and J.B. Phu and D. Sara for their assistance.

This study was supported in part by NIH grant number U01-AI35894-03, World AIDS Federation grant number 94.093, Fogarty, FIRCA TW00611 and ITREID and the anonymous RG-ER fund.
Mr. Willingham, a fourth-year medical student at the University of Maryland, performed this study after he completed his Masters in Public Health at the Johns Hopkins School of Public Health. His research interests focus on tuberculosis, infectious diseases, and public health.

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