Predictors of Sputum Culture Conversion Among Patients With Tuberculosis in the Era of Tuberculosis Resurgence

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Background: Sputum culture conversion among patients with tuberculosis (TB) is the most important indicator for the effectiveness of treatment and the infectivity of the disease. We sought to investigate predictors for documented sputum culture conversion among TB cases reported in the surveillance system.

Methods: This study included 780 patients with pulmonary TB who were initially sputum culture positive in New Jersey in 1994-1995. These patients were followed up for at least 1 week and up to 1 year. Kaplan-Meier curves and Cox proportional hazards models were performed to analyze the data.

Results: Overall, 469 (60.1%) of the 780 patients had documented sputum culture conversion. The elderly (36%) and non-Hispanic whites (41.3%) were the least likely to have documented sputum conversion. Patients who were initially given 4 or more drugs were 36% more likely to have documented sputum conversion than those who were initially given fewer than 4 drugs, after adjusting for other factors. Patients who were under the care of chest clinics and the model TB center were about 3 times more likely to have documented sputum conversion than those under care of private physicians. Sex, recurrent TB, foreign-born status, homelessness, injecting drug use, human immunodeficiency virus infection and drug-resistant TB were not significantly associated with the documentation of sputum culture conversion.

Conclusions: A substantial proportion of sputum culture-positive TB patients have no documented sputum culture conversion. The type of care provider was the predominant determinant for the documentation of sputum culture conversion.

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EARLY IDENTIFICATION and effective treatment of active tuberculosis (TB) have been the key elements in TB control and prevention.1 Adequate therapy for patients with TB is the single most important strategy for prevention of drug-resistant TB.2,3 Effective treatment of infectious patients can also significantly reduce the number of new transmissions. However, TB must be treated for a relatively long duration (6-24 months) as compared with the treatment of many other infectious diseases. Because of the potential for the emergence of multidrug-resistant TB (MDR TB) and patient nonadherence to prescribed treatment, it is extremely essential to monitor the effectiveness of treatment. Sputum culture conversion of Mycobacterium tuberculosis is the major indicator to monitor the effectiveness of antituberculosis therapy for patients with initially culture-positive pulmonary TB. Pulmonary TB constitutes more than 80% of all TB cases reported in the United States.4 Patients with pulmonary TB are the major source for the spread of TB. Sputum culture conversion, therefore, is also an important indicator for the infectivity of a patient with pulmonary TB. The Centers for Disease Control and Prevention (CDC) has included sputum culture conversion as one of the few follow-up measures for national TB surveillance.5,6

The recent resurgence of TB and the emergence of MDR TB have raised new challenges for TB control and prevention.7-10 New risk factors for TB, such as human immunodeficiency virus (HIV) infection, are challenging problems for TB control agencies worldwide.11,12 Under these new circumstances, documentation of sputum culture conversion becomes more important than ever before. However, few studies have been conducted to evaluate the factors associated with the documentation of sputum culture conversion. The objective of this study was to investigate predictors for the documentation of sputum culture conver-
METHODS

TB PATIENT POPULATION IN NEW JERSEY

Patients with active TB for this study were identified through the routine surveillance system in New Jersey. By law, all persons diagnosed or suspected as having TB in New Jersey are required to be reported to the Tuberculosis Program in the New Jersey Department of Health and Senior Services. These reports are examined and verified by program staff, according to the CDC surveillance criteria. Contact investigations, cross-matching with the acquired immunodeficiency syndrome (AIDS) registry and examinations of death certificates were also conducted to identify new cases. During 1994-1995, 1701 persons with TB were verified and 1337 (78.6%) of them had pulmonary TB. Among the 1337 pulmonary TB patients, 834 (62.4%) were initially sputum culture positive. The analysis was limited to 780 of the 834 patients who were alive at diagnosis and were followed up for at least 1 week after the first positive culture was obtained.

Sputum culture conversion was defined as those patients who had at least 1 documented negative culture following the initial positive sputum culture. The date for the specimen collected on the first consistently negative culture should be at least 1 week after the last positive culture was obtained. There should be no positive cultures after this date. Outreach and/or clinic staff at the local or county level are responsible to ensure that a status report is submitted for each patient, at minimum, every 3 months until termination from the registry. This includes telephone calls to the supervising physician at the hospital or private level. Results of laboratory examinations, if any, were requested and included on the status reports. Thus, “documented” sputum culture conversion includes sputa that were collected and for which the results were submitted on a status report.

STUDY VARIABLES

In response to the increase in TB morbidity and the emergence of MDR TB in the United States, expanded TB surveillance was implemented nationwide in 1993. The details of the expanded surveillance system have been described elsewhere. In addition to the demographic and clinical information collected previously, new epidemiological and clinical variables were added to the surveillance system. Those included HIV infection, injecting drug use, homelessness, residence at time of diagnosis (correctional or long-term care facilities), occupation, initial drug regimen, and initial drug susceptibility testing. Follow-up variables included sputum culture conversion, completion of chemotherapy, and the use of directly observed therapy.

In addition to the elements requested by CDC, other variables, mostly for case management purposes, are also collected in New Jersey. Two such variables, useful to this study, are last care provider (refers to physicians treating a TB patient when the patient information was last updated) and the last date that patient information was updated. Information on last care provider was obtained for all TB patients verified in 1993.

RESULTS

Overall, 469 (60.1%) of the 780 patients had documented sputum culture conversion within 1 year since the first positive culture was identified. Most (88.9%) of the 469 patients who converted had documented conversion within 6 months and 62% had documented conversion within 3 months. The median follow-up time was 8.0 months for patients without documented sputum culture conversion and 2.4 months for patients with documented conversion. Among the 311 of the 780 patients who had no documented sputum culture conversion, 145 (46.6%) completed therapy, 101 (32.5%) died, 50 (16.1%) were lost to follow-up, and 15 (4.8%) moved to other states before they completed therapy. The median follow-up time was 11 months for those who completed therapy, 3.2 months for those who died, and 6.9 months for those who were lost to follow-up. Among the 145 patients who completed therapy, 75.2% had been followed up for more than 8 months.
DEMOGRAPHIC FACTORS AND DOCUMENTED SPUTUM CULTURE CONVERSION

The percentage of documented sputum culture conversion was not different between males and females (Table 1). However, a marked difference was observed among different age and racial/ethnic groups. The elderly (≥65 years old) and non-Hispanic whites were the least likely to have documented sputum culture conversion (36% and 41.3%, respectively). Among the 126 non-Hispanic whites, 49 (38.9%) were the elderly. Other age groups had similar percentages of documented sputum conversion with a range of 62.7% to 64.6%. Hispanics were found to have the highest proportion of documented sputum conversion. Unadjusted results showed that patients younger than 65 years were about 2 times more likely to have documented sputum culture conversion than the elderly. After adjustment for sex, race/ethnicity, initial drug regimens, and type of care providers, however, relative hazards were significantly reduced from approximately 2.0 to 1.3 and the association between age and documented sputum culture conversion was no longer significant. Adjusted results found that Hispanic patients were 70% more likely to have documented sputum conversion than were non-Hispanic whites. The proportions of documented sputum culture conversion in African Americans and Asians were not significantly different from those in non-Hispanic whites after adjusting for other risk factors.

Figure 1. Kaplan-Meier curves for the documentation of sputum culture conversion among patients with active tuberculosis in New Jersey, 1994-1995, by racial/ethnic group (top) and by age group (bottom).
TB RISK FACTORS AND DOCUMENTED SPUTUM CULTURE CONVERSION

As shown in Table 1, none of the TB risk factors, except for excess alcohol use, had a significant relationship to the rate of documented sputum culture conversion after adjusting for age, sex, race/ethnicity, initial drug regimens, and type of care providers. Excess alcohol use was marginally significant and associated with increased proportion of documented sputum culture conversion (relative hazard, 1.29; 95% confidence interval, 1.03-1.63). The proportion of documented sputum culture conversion was almost identical between US-born and foreign-born patients. The proportion in homeless patients was not different from other groups either. Patients with unknown status of injecting drug use, excess alcohol use, and HIV infection had a relatively lower proportion of documented sputum culture conversion than those with known status.

DRUG RESISTANCE AND DOCUMENTED SPUTUM CULTURE CONVERSION

Patients with isolates resistant to 1 or more drugs were slightly more likely to have documented sputum culture conversion than those whose isolates were not resistant to any drugs (Table 1). The difference was not statistically significant between the 2 groups. Patients with isolates resistant to at least isoniazid and rifampin (MDR TB) had a proportion of documented sputum culture conversion of 65.2%. The results showed that the documentation of sputum culture conversion was not significantly different between patients with drug-resistant TB isolates and those whose isolates were not resistant to any drugs. The median time to conversion was 2.6 months for patients who had documented sputum culture conversion and whose isolates were resistant to 1 or more drugs and 3.2 months for MDR TB patients who had documented sputum culture conversion. Kaplan-Meier curves showed no difference in the rate of documented sputum culture conversion between drug-resistant patients and nonresistant patients (data not shown).

INITIAL DRUG REGIMENS AND DOCUMENTED SPUTUM CULTURE CONVERSION

As shown in Table 2, 65.2% of patients who were initially treated with 4 or more drugs and 48.3% of those who were initially treated with fewer than 4 drugs had documented sputum culture conversion within 1 year. After adjusting for age, sex, race/ethnicity, and type of care providers, patients in the former group were 36% more likely to have documented sputum culture conversion than those in the latter group. The difference of documented sputum culture conversion over time between the 2 groups is shown by the Kaplan-Meier curves in Figure 2, top. Patients who were initially treated with 4 or more drugs were not only more likely to have documented sputum culture conversion, but also more likely to have the conversion earlier than those who were treated with fewer than 4 drugs. Three months after the initial positive cultures, approximately 50% of patients who were initially treated with 4 or more drugs had documented sputum culture conversion, as compared with only 30% of patients who were treated with fewer than 4 drugs. The rate of documented sputum culture conversion between the 2 groups was significantly different (P<.001).

Table 2. Relative Hazards for Documented Sputum Culture Conversion Among Active Tuberculosis Patients in New Jersey, 1994-1995, by Initial Drug Regimens and Care Providers*

<table>
<thead>
<tr>
<th>Factors</th>
<th>No. of Sputum Culture–Positive Cases</th>
<th>% Culture Converted</th>
<th>Relative Hazard (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial drug regimen</td>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>&lt;4 Drugs</td>
<td>234</td>
<td>48.3</td>
<td>1.0</td>
</tr>
<tr>
<td>≥4 Drugs</td>
<td>546</td>
<td>65.2</td>
<td>1.59</td>
</tr>
<tr>
<td>Care provider</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private physicians</td>
<td>82</td>
<td>35.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Hospitals</td>
<td>70</td>
<td>30.0</td>
<td>1.16</td>
</tr>
<tr>
<td>Chest clinics</td>
<td>176</td>
<td>75.6</td>
<td>3.33</td>
</tr>
<tr>
<td>Model TB center</td>
<td>77</td>
<td>80.5</td>
<td>4.07</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; TB, tuberculosis.
†Adjusted for sex, age, and race/ethnicity.
Patients with TB were classified into 4 groups according to their care providers: those who were last treated at the hospital and the chest clinic of the New Jersey Medical School, University of Medicine and Dentistry of New Jersey (UMDNJ-MS; 19%), those at other chest clinics (43.5%), those at other hospitals (17.3%), and those at private physicians’ offices (20.2%). The majority of the TB patients were treated at chest clinics. Patients who were last treated at UMDNJ-MS were chosen as the reference group because the federally funded model TB center is located at the medical school. The assumption was that the TB patients treated at the medical school should receive the most appropriate care, possibly better than that given at other institutions, and the subsequent analysis supported this assumption. The proportion of documented sputum culture conversion in patients cared for by UMDNJ-MS (model TB center), chest clinics, hospitals, and private physicians was 80.5%, 75.6%, 30%, and 35.4%, respectively (Table 2). After adjustment for age, sex, race/ethnicity, and initial drug regimens, patients under the care of physicians at the model TB center and other chest clinics were about 3 times more likely to have documented sputum culture conversion than those under the care of private physicians (Table 2). Kaplan-Meier curves by type of care providers were conducted for the documentation of sputum culture conversion over time (Figure 2, bottom). The difference in documented sputum culture conversion between the model TB center and chest clinics, and between hospitals and private physicians was not significant. However, the model TB center and chest clinics had significantly higher rates of documented sputum culture conversion than hospitals and private physicians (P<.001).

Among the 780 patients analyzed in this study, 532 (68.2%) completed the prescribed course of therapy. By excluding patients who died (n=137) or moved (n=25) before they completed therapy, 85.9% of the remaining 618 patients completed therapy. Among the 618 patients, 422 (68.3%) had documented sputum culture conversion. On the other hand, the proportion of patients who completed therapy was 92.1% for those with documented sputum culture conversion and 74% for those without documented sputum culture conversion. The difference between the 2 groups was statistically significant (P<.001). The result indicated that the documentation of sputum culture conversion was associated with a high proportion of the completion of therapy.

**Comment**

This study investigated predictors for documented sputum culture conversion among initially culture-positive pulmonary TB patients based on statewide TB surveillance data in New Jersey. The patients were followed up for at least a week and up to 1 year. To our knowledge, this is the first population-based study to evaluate predictors of documented sputum culture conversion since the reemergence of TB and emergence of MDR TB in the United States. This study was not intended to determine actual effectiveness of a specific drug or regimen, but rather to identify factors associated with the documentation of sputum culture conversion on a population basis. Sputum culture conversion is an important indicator for the effectiveness of treatment and the infectivity of a patient with pulmonary TB. Therefore, closely monitoring sputum culture conversion is not only essential in the treatment of TB patients but also important in the control of TB spread.

A substantially high proportion of initially sputum culture–positive TB patients in New Jersey (39.9%) were found to have no documented sputum culture conversion. There are 2 possible explanations for not documenting sputum culture conversion. First, follow-up sputum cultures were obtained, but never reported to the state health department. In New Jersey, clinical laboratories are not required to report negative sputum cultures as they do for positive sputum cultures. However, the results should be reported to physicians. With the implementation of case managers in the statewide TB surveillance system in New Jersey, failure to report sputum culture conversion is not likely to be a major issue. Second, the most likely reason for the low proportion of sputum culture conversion is that sputum was never collected to monitor culture conversion. As described in the “Results” section, among the 311 patients without documented sputum culture conversion, 145 (46.6%) completed therapy and 75.2% of the 145 patients were followed up for more than 8 months. Sputum culture conversion would have been demonstrated for most of these patients if sputum had been collected. Yet, no culture conversion was documented for these patients. Although some patients including the elderly, who were treated successfully, might not be able to produce acceptable sputum in some occasions, the percentage of these patients is not known. However, only 29 (20%) of the 145 patients who completed therapy and had no documented sputum culture conversion were 65 years or older. Therefore, the elderly might only contribute a small part of the overall problem to the low proportion of sputum culture conversion.

Hispanic origin is the only demographic factor that was significantly associated with documented sputum culture conversion after adjusting for other factors. Hispanic patients were 70% more likely to have documented sputum culture conversion than were non-Hispanic whites. The reason for the low proportion of documented sputum culture conversion among non-Hispanic whites is not clear. The elderly, who are less able to produce sputum than others, may be one of the possible explanations, but they only constitute 22.8% of the non-Hispanic whites included in this study. Another possible explanation is that physicians may not treat white patients as intensively as they treat minority patients because TB has the lowest incidence rate in non-Hispanic whites. One of our previous studies conducted...
in New Jersey found that non-Hispanic whites with TB were much more likely to be initially treated with fewer than 4 drugs than were other TB patients.21 The last explanation, but not the least, is that a large proportion of white patients (43.9%) were under the care of private physicians who, as a group, are less likely to follow standard guidelines.22

This study did not find any significant relationship between documentation of sputum culture conversion and TB risk factors, such as country of origin, homelessness, HIV infection, and use of injecting drugs. Patients with TB isolates resistant to antituberculosis drugs had a similar rate of documented sputum culture conversion as patients without any resistance. These results suggest that the characteristics of TB patients are not likely to be a significant determinant of the documentation of sputum culture conversion.

The most significant determinant of the documentation of sputum culture conversion identified in this study was the type of care providers. Patients who were under the care of physicians at the model TB center and other chest clinics were about 3 times more likely to have documented sputum culture conversion than those who were under the care of private physicians. In the mid-1980s, a policy was made in New Jersey that private physicians could not send their patients to public clinics for medications, unless they turned the patients over to the clinic. Prior to the change in policy, the clinics collected specimens as a condition for providing the medication. This policy needs to be reevaluated.

There are 2 potential biases in assessing the relationship between the type of care provider and the documentation of sputum culture conversion. First, the patients’ extent of disease and ability to produce sputum might be different for various types of care providers. For example, patients under care of private physicians included more elderly (34.1% of the patients ≥65 years old vs 9.1% of those cared for by physicians at the model TB center) and, therefore, might be less likely to produce sputum. However, the multivariate analysis used in this study had adjusted the differences in age, HIV status, and other TB risk factors among various types of care providers. Furthermore, the method of survival analysis (Cox proportional hazards model) used in this study accounted for the unequal lengths of time that patients were observed for the documentation of sputum culture conversion. This method allowed us to include patients who died or were lost to follow-up as long as they were followed up for more than 1 week. In fact, the proportion of patients who died was almost identical between patients cared for by private physicians (14.6%) and by physicians at the model TB center (15.6%). The results from the analysis of data by excluding patients who died were essentially the same as the results reported in Tables 1 and 2. Second, it should be noted that the last care provider of each TB patient was used in this analysis. The last care provider was not necessarily the provider who documented the sputum culture conversion. The majority of patients, however, rarely made any changes in their outpatient care providers after being discharged from hospitals. Misclassification of care providers might have occurred for a few patients, but it is not likely to differentiate among types of care providers. Therefore, bias due to misclassification may cause underestimation of the association between documented sputum culture conversion and type of care provider. In other words, the association would be stronger if there was no misclassification of care providers.

Another significant predictor of documented sputum culture conversion identified in this study was the number of drugs included in the initial drug regimens. Patients who were initially treated with 4 or more drugs had faster documented sputum culture conversion than those who were initially treated with fewer than 4 drugs. There are 2 possible explanations for this finding. First, care providers who follow the 4-drug regimen recommendation are also more likely to follow the recommendation on collecting sputum to document conversion. Second, the initial 4-drug regimen may indeed cause faster sputum culture conversion. This explanation is consistent with findings of previous studies.23 An initial 4-drug regimen for the treatment of TB in areas with high prevalence of isoniazid resistance (≥4%) was recommended by the American Thoracic Society and CDC.24,25 In this study, 30% of the 780 sputum culture–positive patients were not initially treated with 4 or more drugs. The proportion of TB patients who were resistant to isoniazid was about 10% in New Jersey during the same period.26 In one of our previous studies,21 98% of TB patients in New Jersey were found to be reported from counties with an isoniazid-resistant proportion of 4% or more. According to the American Thoracic Society and CDC recommendation, an initial 4-drug regimen should be prescribed for all TB patients in New Jersey. The combination of the initial 4-drug regimen and the completion of full-course therapy is a safety factor in avoiding drug resistance. The fact that this is not occurring could be a harbinger of MDR TB in the future and suggests the possibility of such provider noncompliance in other states with a less high profile TB program.

In summary, this study indicated that the characteristics of TB patients had little effect on documented sputum culture conversion rates. The type of care provider was the predominant determinant for documented sputum culture conversion. To increase sputum culture conversion rates, efforts should be directed at educating physicians, especially private practitioners, on the importance of collecting sputum from their patients on a periodic basis, so as to monitor the effectiveness of prescribed therapy and prevent new TB transmissions.

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