

Recurrent Tuberculosis: Why Do Patients Develop Disease Again? A United States Public Health Service Cooperative Survey

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Abstract: In October 1983, a retrospective survey was initiated to determine if patients reported to the Centers for Disease Control as having recurrent tuberculosis truly had recurrent disease and, if so, why they had developed tuberculosis again. Twenty-three health jurisdictions provided information on 800 patients diagnosed as having recurrent tuberculosis during 1981 and 1982. We found that 199 (25 per cent) of the cases did not meet the criteria for recurrent disease. Of the remaining 601 recurrent cases, 20 per cent had no chemotherapy prescribed for their previous episodes of tuberculosis, 20 per cent were prescribed inadequate or inappropriate therapy, and

33 per cent were not compliant with their prescribed therapy regimens.

Patients who, during their original episode of tuberculosis, received the major portion of their medical care from physicians in private practice were more compliant than those treated by other health care providers. However, those same patients were more likely to have received inappropriate therapy than patients treated by other providers. Better patient and physician education, closer monitoring, and greater use of preventive therapy and directly observed therapy are necessary to resolve these problems. (*Am J Public Health* 1988; 78:30-33.)

Introduction

Tuberculosis is considered a curable disease. After completing an adequate course of therapy with appropriate drugs, very few patients will develop the disease again. Therefore, continued follow-up of these patients is not recommended.¹ Nevertheless, in 1981 and 1982, a total of 2,955 tuberculosis cases reported to the Centers for Disease Control (CDC) were recurrent cases, i.e., persons who had had tuberculosis disease sometime in the past and later developed the disease again.^{2,3}

We wanted to learn more about these recurrent cases, in order to suggest strategies for preventing such cases in the future. Therefore, we elicited the cooperation of the State Health Departments and large city health departments in providing information about a sample of cases reported as recurrent in 1981 and 1982.

Methods

CDC guidelines for reporting tuberculosis morbidity define recurrent cases as persons who had verified tuberculosis in the past, were discharged from or lost to supervision for more than 12 months, and who have verified disease again.⁴

When this survey was initiated in October 1983, the most recent and complete information available about recurrent tuberculosis was for the year 1982. That year, 48 states and the District of Columbia reported 1,477 recurrent cases, just one less than the 1,478 recurrent cases reported in 1981. Thirty-six areas (35 States plus the District of Columbia) had reported a total of 10 or more recurrent cases during the years 1981 and 1982 and were invited to participate in the survey. These 36 areas accounted for 2,890 of the 2,955 reported recurrent cases during the two-year period. Ultimately, 23 health jurisdictions, which had reported a total of 1,235 recurrent tuberculosis cases during 1981 and 1982, agreed to participate and submitted detailed information on 800 of these patients. The information was entered on forms developed by the Division of Tuberculosis Control (DTBC), Centers for Disease Control, to ensure standardized data collection. Detailed instructions for completing the forms were likewise

prepared by the DTBC (available on request to authors). The 800 patients represented 27 per cent of all recurrent cases reported to CDC during the years 1981 and 1982.

Eleven of the participating health jurisdictions provided information on all 447 recurrent cases which they reported during the two-year period; the remaining 12 areas provided information on approximately 45 per cent (N = 353) of the 788 recurrent cases they reported during the same period—a representative sample selected by CDC using a computer-generated randomization scheme.

The recurrent cases were grouped into six categories:

1. Patients who did not meet the criteria for a recurrent case;
2. Patients who received no chemotherapy for their original episode of tuberculosis;
3. Patients who failed to comply with their treatment regimen;
4. Patients who were compliant but who were prescribed inadequate or inappropriate chemotherapy for their original episode of disease;
5. Patients who completed an appropriately prescribed therapy regimen; and
6. Patients for whom there was insufficient information available to place them in any of the other five categories.

Determinations of the adequacy and/or appropriateness of prescribed regimens were made in light of current knowledge regarding the chemotherapy of tuberculosis.⁵ Patients were considered to be noncompliant if their medical records so indicated, or if they took less than 80 per cent of their prescribed medication.

Results

One hundred ninety-nine (25 per cent) of the 800 cases reported to CDC as recurrent tuberculosis did not meet the criteria for a recurrent case. Sixty-one of the 199 patients had no previous diagnosis of tuberculosis; less than 12 months had elapsed between disease episodes for 22 patients; 10 had their 1981 or 1982 diagnosis rescinded; and 104 had insufficient information to document a previous episode of disease. Two additional cases were excluded from analysis because they were reported as recurrent prior to 1981.

Of the 601 recurrent tuberculosis patients for whom there was sufficient information to document a previous

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episode of tuberculosis, 92 per cent experienced only one previous episode; the other 8 per cent had between two and four prior episodes. Thirty per cent of the 601 patients developed disease again within five years of their original diagnosis of tuberculosis. An additional 22 per cent developed disease again within six to 10 years; the remaining 48 per cent experienced their second episode 11 to 62 years after the original diagnosis.

The median age of the recurrent patients at the time of their first episode of tuberculosis was 40 years (range: one to 86 years). At the time of their latest diagnosis, the median age was 60 years (range: 5 to 95 years).

Seventy-one per cent of the patients were males. Non-Hispanic Whites constituted 49 per cent of the patients while Blacks and Native Americans contributed 36 per cent and 7 per cent, respectively. Asians and Hispanics combined contributed less than 8 per cent of the patients.

Only 9 per cent of the cases were foreign-born. Among these, Asians accounted for 54 per cent, and 4 per cent were from Mexico. Forty-three per cent of the foreign-born cases experienced their original episode of tuberculosis before they entered the United States.

When originally diagnosed, 87 per cent of the patients had pulmonary tuberculosis, 9 per cent had extrapulmonary disease, and 4 per cent had both forms. At the time of their latest diagnosis, 84 per cent had pulmonary tuberculosis, 12 per cent extrapulmonary, and 4 per cent had both forms of disease.

Analysis of the diagnostic test results of the recurrent cases at the time of their original and latest diagnoses revealed that the percentages of positive and negative tuberculin skin tests and abnormal and normal chest x-rays were similar for both episodes. The percentage of patients for whom no skin test was done at the time of the latest episode of disease (30 per cent) was five times greater than that at the first episode (6 per cent). Eighty-seven per cent of the recurrent cases had either a positive smear or culture, or both, at the time of their latest episode, as compared to 66 per cent during their original episode. Much of this difference could be due to the fact that, at the time of their original episode, no bacteriologic test results were available for 20 per cent of the patients, whereas at the latest episode, only 1 per cent of the patients had no results available.

Seventy-nine per cent (N = 477) of the 601 recurrent tuberculosis patients had chemotherapy prescribed for their original episode of disease, and 20 per cent (N = 120) did not. No determination could be made as to whether therapy was prescribed for the remaining 1 per cent. Of the 120 patients not prescribed chemotherapy, 64 were diagnosed before 1947 (i.e., in the prechemotherapy era), and an additional 33 were diagnosed between 1947 and 1951. Thus, 81 per cent of the 120 patients were diagnosed prior to the time isoniazid (INH) was available. Another 17 per cent were diagnosed between 1952 and 1962.

Table 1 lists the major source of supervision and compliance status of the 477 recurrent cases prescribed chemotherapy for their original episode of tuberculosis. Of the 424 cases for whom compliance status was known, 226 were compliant and 198 were not. Compliance was highest among patients of private physicians (34/53 or 64 per cent) and lowest among those supervised by hospitals and other institutions (61/125 or 49 per cent).

Of the 226 patients who were compliant with drug regimens prescribed for their first episode of disease, 121 (54 per cent) had been prescribed inadequate or inappropriate

TABLE 1—477 Recurrent Tuberculosis Cases Prescribed Chemotherapy for Their Original Episode of Disease by Major Source of Supervision and Compliance Status

Major Source of Supervision	Compliant	Non-compliant	Compliance Unknown	Total
Health Departments	131	115	11	257
Hospitals and Others	61	64	27	152
Private Physicians	34	19	7	60
Unknown	0	0	8	8
Total	226	198	53	477

regimens, whereas 96 (42 per cent) appeared to have been appropriately treated. The adequacy of treatment for the remaining nine patients could not be determined because the dosages of the drugs prescribed were unknown. Table 2 shows the major source of supervision of these patients. Compliant patients supervised by health departments were more likely to have been prescribed adequate therapy (53 per cent) than those supervised by physicians in private practice (29 per cent).

The 121 patients given inadequate or inappropriate therapy included 15 who were prescribed a single drug, 68 who were prescribed drugs for less than the optimal time period (e.g., INH and ethambutol [EMB] for 12 months), 13 who were prescribed less than adequate dosages of drugs, and 20 who were placed on regimens judged to be inadequate with regard to both dosage and duration. The remaining five patients included two who were prescribed inadequate drug combinations (e.g., pyrazinamide [PZA] and EMB), two who were given drugs to which their organisms were resistant, and one whose physician interrupted her treatment for six months because she was pregnant. Three-fourths of these 121 patients were diagnosed between 1963 and 1980, a period in which the state of the art regarding adequate therapy was advanced.

Of the 96 patients who were compliant with appropriately prescribed drug regimens, five took all of their medication but did so over a slightly longer period of time than recommended, e.g., nine months of INH and rifampin (RIF) were taken over an 11-month period of time. No conclusive reason for developing tuberculosis again could be identified for the remaining 91 patients. One had a history of reexposure to an infectious tuberculosis patient and 27 had associated medical conditions at the time of their latest diagnosis of tuberculosis. These conditions included alcoholism (20), diabetes mellitus (3), and one case each of cancer, drug abuse, chronic renal failure, and corticosteroid therapy (for

TABLE 2—Major Source of Supervision of Compliant Recurrent Cases Who Were Prescribed Chemotherapy for Their Original Episode of Tuberculosis

Major Source of Supervision	Inadequate Regimen Prescribed		Adequate Regimen Prescribed		Total Cases
	Number	Percent*	Number	Percent*	
Health Departments	61	47	68	53	129
Hospitals and Others	36	67	18	33	54
Private Physicians	24	71	10	29	34
Total	121		96		217

*Percentages are based on the total number of cases in each major source of supervision.

TABLE 3—Classification of 800 Reported Recurrent Tuberculosis Cases, Based upon Information about their Original Episode of Disease

Survey Results	800 Reported Recurrent Cases		601 True Recurrent Cases	
	Number	Percent	Number	Percent
Did Not Meet Criteria for Recurrent Cases	199	25	—	—
Not Compliant with Prescribed Regimen	198	25	198	33
Inadequate Chemotherapy Regimen Prescribed	121	15	121	20
No Chemotherapy Prescribed	120	15	120	20
Compliant with an Appropriate Regimen	91	11	91	15
Insufficient Information to Classify	71	9	71	12
Total	800	100	601	100

an unidentified condition). Thirteen different treatment regimens (four two-drug regimens and nine regimens of three or more drugs) had been prescribed for these 91 patients. All of the regimens contained INH. The two-drug regimens, and the number of patients assigned to each, were as follows: INH-EMB (23); INH-RIF (14); INH-PAS (13); and INH-Streptomycin [SM] (1).

Drug susceptibility test results were available for 413 patients at the time of their latest diagnosis, 75 of whom had no history of receiving chemotherapy for an earlier episode of tuberculosis. Of the 338 who had received prior therapy, 28 per cent (N = 95) had drug resistant organisms, including 12 per cent (N = 41) who were resistant to multiple drugs. In comparison, 13 per cent of recurrent TB patients who had not received chemotherapy in the past had drug resistant organisms, including 4 per cent who were resistant to multiple drugs. Resistance to isoniazid, rifampin, and ethambutol, among patients who had received prior chemotherapy, was three, four, and five times greater, respectively, than among those who had not received prior therapy.

Table 3 summarizes the results of this survey by classifying the 800 patients according to the information obtained regarding their original episode of tuberculosis.

Discussion

The finding that 25 per cent of the cases reported as being recurrent could not be verified as such is an indication that criteria—such as positive bacteriology, abnormal radiographic findings, and/or a documented history of treatment—are not being properly applied by many health care providers in determining whether a patient has had tuberculosis in the past. As currently defined, recurrent cases are not strictly synonymous with “reactivation” cases. Reactivation implies a period of inactivity of the disease between the original and subsequent episodes. The definition of recurrent disease requires only that a patient be discharged from, or lost to, supervision for 12 months. Thus some recurrent cases might never have achieved a state of inactivity and could be suffering from an original episode of disease rather than a reactivation. We believe that the definition of a recurrent case and a reactivation case should be synonymous and that patients should be counted as having recurrent tuberculosis only if, following a previous episode of disease, they achieved a state of inactivity and were discharged from supervision.

Of the 601 cases considered truly recurrent, nearly half had experienced their original episode of disease prior to 1971. Although a patient's risk of recurrent disease is greatest shortly after completing therapy, and decreases with time,^{6,7} tuberculosis rates in general have been declining over the

past three decades. Therefore, patients with recurrent disease will increasingly be those who had their original diagnosis a long time ago. To the extent that adequate treatment and supervision are applied to today's patients, this trend will be accelerated.

Demographic factors, such as age, sex and race/ethnicity, could not be assessed as risk factors for recurrent disease in this survey because it was not possible to obtain a comparison group of nonrecurrent cases diagnosed during the same years as the original diagnoses of the recurrent cases.

It is surprising that 19 per cent of the 120 recurrent tuberculosis patients who received no chemotherapy for their original episode of tuberculosis were diagnosed after 1951 when both INH and SM were available. Furthermore, there was no indication that these 120 patients had subsequently received INH preventive therapy despite the fact that preventive therapy for such persons has been recommended for over 20 years.⁸

Noncompliance has been called the most serious remaining problem in tuberculosis control today,⁹ and a variety of means have been proposed to solve it.¹⁰ Better patient education, closer monitoring of patients, and a greater use of directly observed therapy (currently the most reliable and feasible approach to dealing with noncompliant patients) are necessary to address this problem. In this survey, patients managed by the “public sector” were more likely to be noncompliant than those managed by the private sector. This might reflect differences in the patient populations served as well as in the acceptability of services in the two sectors.

Physician noncompliance with the treatment recommendations of expert committees was also found to be a common cause of recurrent disease. Prescribing errors were made less often by health departments than by hospitals or private physicians. Byrd, *et al.*,¹¹ have previously documented the frequency of prescribing errors among military physicians. It is important to assure that physicians caring for patients with tuberculosis are aware of, and follow, current treatment guidelines to reduce the likelihood that inappropriate therapy is prescribed.

Two points must be made concerning the 96 patients who were prescribed, and took, an adequate course of therapy. First, 21 per cent of them had a concomitant diagnosis of alcoholism. This diagnosis suggests the possibility of non-compliance even though their medical records did not contain any evidence of it. Second, the most common regimen prescribed for these 96 patients was INH-EMB. This regimen is less effective than INH-RIF and requires a longer duration of treatment. We urge all providers to use regimens containing INH and RIF for initial treatment whenever possible.

Such treatment not only reduces the risk of treatment failure and relapse, but also makes therapy easier to supervise and rarely leads to acquired drug resistance.¹²

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New Monthly Newsletter to Report on Poverty and Hunger in America

A new publication—*Hunger Action Forum*—was launched by The Hunger Project in September 1987. The new monthly newsletter will report on poverty and hunger in America and on the individuals, actions, and ideas contributing to their resolution. The primary aims of *Hunger Action Forum* are:

- in the words of its editor, to “report briefly, concisely and clearly on poverty and hunger in the United States in the conviction that an awareness of pertinent facts, trends and opinions is the beginning of wisdom and useful action” and,
- to make known the wide array of creative, innovative and effective actions individuals are taking in addressing domestic poverty and hunger.

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