Factors Related to In-hospital Deaths in Patients With Tuberculosis

Leonard Vernon Sacks, MD; Stella Pendle, MD

**Background:** Deaths from tuberculosis (TB) continue to occur despite the availability of effective antimicrobial agents. Multidrug resistance, human immunodeficiency virus (HIV) infection, and delayed therapy have been implicated.

**Objective:** To examine clinical factors associated with in-hospital death in patients with active TB.

**Methods:** A retrospective case-control study was performed on patients admitted to a government hospital in Johannesburg, South Africa, used as a referral center for patients with TB. Eighty patients admitted with TB who died during hospitalization were matched with 80 similar patients with TB who survived hospitalization. Clinical, demographic, and radiological characteristics of each group were compared.

**Results:** In-hospital fatalities were associated with female sex ($P = .01$), lower admission hemoglobin level ($P < .01$), and weight ($P < .01$), and a trend to more extensive infiltrative patterns on chest radiographs. Multidrug resistance, extrapulmonary disease, and HIV infection were unexpectedly not related to in-hospital mortality. High mortality in the first weeks of admission suggested that late presentation was a major factor for in-hospital death. The HIV-infected participants in the study showed less drug resistance than HIV-negative patients ($P = .07$), equivalent extents of infiltrative patterns on chest radiographs, but much less cavitation and fibrosis ($P < .01$).

**Conclusions:** Clinical predictors of early mortality from TB included anemia, low body weight, and extensive infiltrates, while multidrug resistance and HIV infection were not significant factors. Previous exposure to TB and delayed presentation may have influenced our findings. Since patients present late in their illness, aggressive case finding would be important in controlling TB in this population.

Arch Intern Med. 1998;158:1916-1922

Almost 90 million new cases of tuberculosis (TB) worldwide have been predicted for the decade of 1990 through 1999. This astronomical figure reflects the failure to control the disease despite the availability of effective antimicrobials. The specter of TB has become even more threatening in the face of burgeoning multidrug resistance and large numbers of individuals rendered susceptible to the disease by human immunodeficiency virus (HIV) infection. Increasing evidence is accumulating to support the pivotal role of host immunity and cytokine kinetics in individual responses to the infection. A large percentage of individuals fail to develop the disease at all despite exposure. Others develop extensive and often uncontrolled pulmonary and extrapulmonary spread. This may be because of compromised immunity. However, in a substantial number of seemingly immunocompetent patients, the reasons for dissemination are not clear. Attempts have been made to implicate environmental and hereditary factors. While several predisposing conditions such as HIV disease, steroid treatment, and diabetes have been well characterized, many patients with aggressive disease appear to be otherwise immunologically normal.

In addition to the spectrum of responses to exposure, individual patients manifest a wide variety of presentations once the disease has established itself. These range from healed primary complexes to fibrocavitary disease, interstitial pneumonitis to miliary infiltrates, and isolated pleural effusions to meningitis to name a few. The significance of varying pulmonary radiological types has not been clearly understood, although it is recognized that immunocompromised patients may show more diffuse and unchar-
PATIENTS AND METHODS

The study was conducted at Rietfontein Tropical Disease Hospital, a 500-bed government institution in Johannesburg, South Africa, serving as a referral center for patients with complicated TB. This included patients with extensive disease, those with a checkered treatment history in whom defaulting from therapy was a problem, patients with multidrug-resistant infection, and those judged clinically too ill to be treated as outpatients from the beginning. During the years that this study was conducted, we observed a 6% mortality rate for all admissions to this hospital. Most of these deaths occurred in patients with TB. Most patients at this institution were black and we limited our patient population to adults older than 16 years.

Patients admitted to the hospital with TB between August 1994 and March 1997 and who died while in the hospital were selected for chart review and analysis of their presenting chest x-ray films. Each case patient who died was matched with a patient admitted with TB during the same week who survived hospitalization (control patient). From a sequential list of admissions, each control patient was selected as the patient admitted closest in time to the admission time of the corresponding case patient, who satisfied the criteria for the diagnosis of TB as detailed herein, and who survived hospitalization and was discharged. The maximum interval between admission times of each case patient and control was 1 week. Controls were only matched for admission time and clinical diagnosis of TB, since all other demographic and clinical parameters were to be investigated for their impact on mortality.

A retrospective collection of data from clinical records covered reported duration of symptoms, admission hemoglobin level, white blood cell count, and weight, time from admission to death among the case patients, sputum smear results, and sensitivity of the infecting isolate if available. Isolates resistant to at least isoniazid and rifampicin were recorded as multidrug resistant. Susceptibility tests were performed by a single reference laboratory. Resistance to first-line agents was determined using critical concentrations in liquid media and resistance to second-line drugs was determined similarly on Lownstein Jansen slants.

Treatment histories were intricate and often unclear; hence, we simplified the issue into those who had received any courses of treatment (remote or recent, single or multiple, completed or otherwise) prior to the current admission and those who had not. On admission, patients presenting with drug-sensitive isolates were treated with a standard regimen of daily isoniazid, rifampicin, pyrazinamide, and ethambutol for 8 weeks followed by 16 weeks of daily isoniazid and rifampicin. Patients with multidrug-resistant isolates who did not die before drug sensitivity results were available were treated with a median of 4 drugs to which the organism was sensitive. The HIV-infected patients with CD4 lymphocyte counts below $0.20 \times 10^9/L$ (200 cells/µL) were given a combination product of trimethoprim and sulfamethoxazole prophylaxis for *Pneumocystis carinii* pneumonia. Antiretroviral therapy was not available for any of the patients.

The HIV antibody status and, when positive, admission CD4 lymphocyte count were recorded. Other underlying illnesses, including diabetes, liver disease, or cardiac failure, were gathered from the clinical notes. The proximate cause of death was recorded where available. Complications of TB such as respiratory failure, cor pulmonale, thromboembolic disease, and hemoptysis were systematically recorded. Sites of extrapulmonary TB were listed from the relevant charts.

The diagnosis of TB was accepted based on the clinical assessment of the supervising medical officer, a compatible chest radiograph, and a suggestive medical history. Wherever possible the diagnosis was supported by a positive sputum smear and culture or characteristic biopsy findings showing typical granulomas. We elected to include patients with negative smear results and a suggestive clinical profile to incorporate patients who died before bacteriologic confirmation could be obtained and also to include the small number of patients anticipated to present with negative smear findings resulting from insensitivity of the assay.

Admission posteroanterior chest radiographs were scored for the percentage of visible lung that was predominantly affected by cavitation, fibrosis, and infiltrate. A transparent grid of squares, $3 \times 3$ cm, was placed over each film. The total number of squares each showing more than 50% visible lung tissue was used to estimate the total area of visible lung on each chest radiograph. Squares showing more than 50% cavitation were enumerated and expressed as a percentage of total visible lung to represent the percentage of visible lung showing predominant cavitation. Similarly, squares were enumerated showing more than 50% fibrosis (typified by dense linear shadows not following the bronchovascular anatomy) and expressed as a percentage of total visible lung to represent the percentage of visible lung showing predominant fibrosis. Squares showing predominant infiltrate included alveolar, reticulonodular, and miliary patterns and were treated in the same way to estimate the percentage of visible lung showing predominant infiltrate. Radiographs showing pleural effusions were not included in this analysis. All films were scored by 2 blinded medical officers experienced in the management of TB, and the mean of their readings was taken as the final score.

Statistical calculations for the comparison of case patients and controls were performed using Epi Info Version 6. Odds ratios for patients who died compared with those who survived were reported for each categorical variable with 95% confidence intervals, and $P$ values from $\chi^2$ tests were determined. Comparison of odds for small cells was made using the Fisher exact test. Continuous variables for case patients and controls were compared using Student $t$ tests. Tests of significance were 2-tailed and $P < .05$ was regarded as significant.

Characteristic patterns than the typical upper lobe fibrocavitary features in immunocompetent adults. Furthermore, TB still carries an appreciable mortality despite treatment. Why some patients die of the disease is also not clear. Multidrug resistance has accounted for some of the mortality. Where isolates are sensitive, immunocompromised patients may also play a role in mortality, although HIV-infected patients are thought to respond well to antimicrobial therapy.

With these features in mind we investigated the clinical factors that were most strongly associated with mortality in patients with active TB. A retrospective case-
control study was undertaken comparing patients with TB who died while in the hospital and patients with TB who survived and were discharged. A variety of clinical and radiological parameters were investigated to determine the pattern of presentation in relation to the prognosis.

RESULTS

Eighty case patients who died in the hospital and 80 controls who survived hospitalization were analyzed. Of 160 patients in the cohort, 111 were men and 49 women. Despite this uneven distribution of case patients, there was an unequal distribution of case patients (40% vs 21%; P = .008). The mean age of the case patients was 42.1 years and the controls, 36.6 years (range, 19-80 years) (Table 1). The mean hemoglobin level for case patients was 10.3 g/L compared with 11.5 g/L in controls (P < .01).

Drug sensitivities of isolates were often not available either because patients were too sick on admission to provide adequate sputum specimens or because initial sensitivities were not requested. Among the 43 sensitivity reports of case patients, 15 (35%) were multidrug resistant. This was not significantly different from controls in which 15 (25%) of 61 tested isolates were multidrug resistant (P = .25). Patterns ranged from 2-drug resistance to 6-drug resistance, with resistance to 4 drugs being the most common.

Besides 14 pleural effusions (7 in each group), extrapulmonary disease was recorded in 26 patients. These included 6 case patients with tuberculous meningitis (5 in case patients and 1 in a control), 5 case patients with miliary TB identified in bone marrow or liver biopsy material (1 in a case patient and 4 in controls), and 2 case patients with tuberculous adenitis and isolated cases affecting other organs. Extrapulmonary disease was not significantly more common among the case patients than the controls (P = .47).

Despite the chronic nature of the illness, patients often presented with advanced disease resulting in high death rates during the first week of hospitalization. While the mean time to death for all the case patients was 75 days, half the patients died within the first 19 days of admission. Thirty-two percent of the case patients died within the first week of hospitalization (Figure). Controls were hospitalized for a mean of 139 days (range, 6-474 days).

Significantly lower hemoglobin levels were seen in case patients on admission compared with controls (Table 1). The mean hemoglobin level for case patients was 10.3 g/L compared with 11.5 g/L in controls (P < .01).

*HIV indicates human immunodeficiency virus; OR, odds ratio; CI, confidence interval; and ellipses, not applicable.
admission white blood cell count was $9.1 \times 10^9/L$ in case patients compared with $7.9 \times 10^9/L$ in controls ($P = .16$). The mean weight of patients who died was also significantly lower than that of survivors. The mean weight on admission was 47 kg in case patients compared with 53 kg in controls ($P < .01$).

Unexpected trends in the radiological presentations for case patients and controls suggested a difference in the disease profile between these groups. Fibrosis and cavitation were equivalent in controls and in case patients but infiltrative patterns were more extensive in case patients than in controls (Table 1). We were concerned that this may have reflected either misdiagnosis or superinfections particularly in patients dying too soon before a bacteriologic diagnosis. We looked at the more stringent subset of patients with positive smear results on admission and we were able to detect the same trend (Table 2). Finally, to exclude the possibility that advanced HIV infection might have predisposed patients to infiltrative patterns on chest radiographs perhaps due to concurrent undiagnosed Pneumocystis carinii infections, for example, we performed the same analysis on the subset of HIV-negative patients. We confirmed yet again the trend to more extensive infiltrates in those who died than in survivors.

Our results suggested a profile of patients dying in the hospital characterized by female sex, lower body weights, lower hemoglobin levels, and a tendency to infiltrative patterns in response to infection. To test the predictive value of these parameters on our database we selected all patients from the cohort who had an admission hemoglobin level of more than 11 g/L, a body weight of more than 50 kg, and a percentage of visible lung showing an infiltrative pattern of less than 36%. Of the 16 patients fulfilling all these criteria, only 1 patient died compared with a 1/2 chance of in-hospital death for the cohort as a whole.

While a proportion of deaths in the study were attributed to acquired immunodeficiency syndrome, HIV disease was not found to be significantly more prevalent in patients who died compared with those who survived. Human immunodeficiency virus was slightly more prevalent among women in the cohort.

Twenty-seven (60%) of 45 tested women and 46 (48%) of 92 tested men were positive for HIV ($P = .25$). Mean CD4 lymphocyte counts on admission were $0.148 \times 10^9/L$ in HIV-positive women and $0.209 \times 10^9/L$ in HIV-positive men ($P = .70$). The HIV positivity had an impressive impact on the radiological presentation of all patients (Table 3). Cavitation and fibrosis were both significantly less extensive in HIV-positive subjects compared with HIV-negative counterparts ($P < .01$), while the extent of infiltrative patterns was no different in HIV-positive and HIV-negative patients. Extrapulmonary disease was more common in HIV-positive men ($P = .11$). Mean body weight was unexpectedly higher in HIV-positive patients than HIV-negative patients, although this was not statistically significant ($P = .60$). Admission hemoglobin levels were lower in HIV-infected patients than in HIV-negative patients ($P < .01$). Sputum smear positivity on admission was less common in HIV-positive than HIV-negative subjects ($53/66$ vs $56/62$ smear positive, respectively; $P = .11$). Multi-drug resistance was less common in HIV-positive than HIV-negative subjects ($8/43$ vs $18/51$; $P = .07$). In the composite picture of risk factors that we examined associated with in-hospital deaths, HIV infection was
related to several, including female sex, extrapulmonary disease, and lower admission hemoglobin level.

There was no indication as to why women were underrepresented in the cohort as a whole. When we addressed the question as to why women were more likely to die than men, HIV infection appeared not to be an important factor. Among the patients who died, 18 (62%) of 29 tested women and 23 (56%) of 41 tested men were HIV positive (P = .60). Radiological presentations in women were not significantly more extensive than in men (data not shown). Proximate causes of death were diverse and in many instances, accurate clinical details immediately preceding death were not available.

### Causes of Death

<table>
<thead>
<tr>
<th>Causes of Death</th>
<th>No. (%) of Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired immunodeficiency syndrome</td>
<td>20 (25)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>11 (14)</td>
</tr>
<tr>
<td>TB</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5 (6)</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (16)</td>
</tr>
</tbody>
</table>

* Values are corrected to the nearest whole number.

Death from acquired immunodeficiency syndrome was recorded in 20 patients and from uncomplicated TB in 10. Respiratory failure was implicated in 11 deaths. Hemoptysis was documented in 6 deaths and hypoglycemia in 2 more deaths.

### COMMENT

Mortality from TB remains a major threat despite the availability of effective antimicrobials. With an estimated 2.5 million deaths worldwide in 1990 and a projected 30 million deaths for this decade, it is clear that interventional strategies must address other factors contributing to the global failure of TB control. A number of recent studies have examined the outcome of cohorts infected with TB. In several prospective studies with follow-up periods ranging between 6 months and 3.5 years, HIV was identified as a dominant factor affecting the survival of patients with TB. Late treatment, advanced age, and drug resistance were important contributors to mortality from TB. This study of factors influencing the in-hospital mortality of patients with TB brought to light several new findings. Our population also appeared unique in incorporating patients with advanced disease and a high proportion of complicated infections requiring hospitalization.

Unlike previous studies, we were surprised to find a similar prevalence of HIV disease in both patients who died and those who survived hospitalization. Comparing our results with those of a New York City study on mortality from TB highlighted these differences. Why were 79% of their fatalities associated with HIV positivity compared with 59% of ours despite equal HIV prevalence in the cohorts (50% in theirs and 53% in ours)? Why was multidrug resistance associated with a relative risk of death of 5.8 in New York City yet multidrug resistance was equally prevalent in our patients who died and those who survived? The answer seems to come from the fact that we were dealing with a specific population of hospitalized patients with much more advanced TB, often where death was imminent. The median time to death was 6.3 months in New York City patients compared with only 19 days in ours. Delayed and inadequate therapy presumably results in substantial fatalities from TB, long before the toll from HIV and multidrug resistance can be observed. Nunn et al noted no difference between HIV-positive and HIV-negative patients in the early (1-month) mortality from TB. Undoubtedly, long-term follow-up of our survivors would eventually demonstrate many more deaths related to HIV positivity and multidrug resistance. The follow-up of New York City patients was 3.5 years compared with the period of hospitalization in our patients. Our study on in-hospital mortality has revealed a different spectrum of clinical issues influencing early deaths from TB before the data are affected by the impact of HIV on mortality.

We found that patients who died were statistically more likely to be female. The preponderance of female deaths might be due to late presentation and poor access to women's health care, perhaps prejudiced by not being part of the labor force. Females in our study were perhaps less likely to present to the hospital because of the obligations of child care. We could not substantiate this since at least on entry parameters, women and men were equally matched for severity of disease. More women in our study were HIV positive than men, with lower mean CD4 lymphocyte counts on admission; hence, HIV disease may have contributed to excess female mortality. Whether there may be a biological reason for a higher short-term mortality in women requires further investigation, particularly with regard to the duration of illness before presentation.

We obtained fewer positive sputum smears in patients who died than in survivors. This was partly a function of early deaths in sick patients, which militated against obtaining good sputum samples. Extrapulmonary disease and HIV infection were other factors among the dying patients that may have reduced the yield on sputum smears. Control sputum smears were not censored beyond the interval from admission until death in corresponding cases. Hence, we could not infer a meaningful correlation between reduced sputum positivity and in-hospital death.

Unexpectedly, multidrug resistance was not significantly more common for those who died than for those who survived hospitalization. While this finding must be viewed in perspective and the long-term prognosis in multidrug-resistant infections may indeed be worse than in patients with sensitive organisms, it differs nevertheless from several published reports suggesting a rapidly fatal course in patients harboring this infection. Median survival of multidrug-resistant patients in certain series has been as short as 2.1 months in HIV-positive subjects. Accumulating evidence suggests a different behavior of drug-resistant TB in South Africa. Unlike the experience in the United States, multidrug resistance appears to be less common in HIV-positive vs HIV-negative patients according to our findings, and no more
common in HIV-positive than HIV-negative patients according to others.20

It was also noted that a history of treatment that had failed either because of poor compliance, drug resistance, or breakdown of healed TB appeared to have no different impact on in-hospital mortality than did a history of first-time treatment. While probably affecting the long-term prognosis, the in-hospital outcome appeared favorable once treatment was carefully supervised.

Extrapulmonary TB was prevalent in our cohort but no more likely to be present in patients who died than in survivors. There was a slight difference in age between survivors and patients who died, in contrast to the substantial mortality in aged patients in industrialized countries.17

The mean admission body weight of patients who died was significantly lower than survivors. Human immunodeficiency virus disease did not appear to influence this, since HIV-positive patients in the study had a higher mean body weight than HIV-negative patients. The preponderance of females in the group of patients who died may have partially influenced this finding. Lower admission hemoglobin levels were also significantly associated with the patients who died (although in this instance HIV was significantly associated with anemia). The combination of low body weight and low hemoglobin levels suggests either long-standing illness, or more extensive illness and this question requires further research.

Analysis of the radiological patterns in those who died compared with those who survived demonstrated a trend to more extensive infiltrative patterns in fatalities. Subgroup analyses both of patients admitted with positive sputum smears and of HIV-negative patients again demonstrated a trend to more extensive infiltrative patterns on chest radiographs of fatalities. Cavitation and fibrosis were equally extensive in survivors and fatalities. Our findings suggested that host responses to TB are variable and seem to be related to in-hospital survival. Fibrovascular reactions to TB with limitation of pulmonary infiltration are features of patients surviving admission. Histological21 and radiological22 containment of TB have been found to be impaired in immunocompromised patients, and perhaps the same deficit in HIV-negative patients may play a role in early mortality as our radiological findings suggest. In a study23 of similar design performed on patients from Vojvodina, Yugoslavia, hospital deaths were also shown to be related to radiological extent of disease, although cavitation and infiltration were not separately analyzed and the influence of HIV infection was not determined. A major contributor to TB-related mortality in our cohort was inferred from the time from hospitalization to death, namely, late presentation. Despite the chronic nature of the illness, almost a third of in-hospital deaths occurred within the first week of hospitalization. Others in eastern Europe have reported death rates from TB as high as 74% in the first 4 days of hospitalization.23 Progression of disease is insidious and patients may deteriorate over months or more before seeking attention, often at a point where therapy may no longer succeed. In many instances the time at which patients are first infected is impossible to ascertain and extensive life-threatening disease may already be present by the time patients develop symptoms. Furthermore, in communities of low socioeconomic status, access to health care facilities may be a problem resulting in life-threatening delays in presentation. Delays in therapy, at least from the time that microbiological confirmation of TB is obtained, have been shown to have an impact on survival.12

Our findings serve to support the recommendations of the World Health Assembly24 emphasizing the importance of case detection. We presume that apart from jeopardizing their own survival, patients presenting with advanced disease have spread the infection in their communities over months, vilifying the efforts of TB control programs.

In a minority of our patients a potentially preventable or treatable preterminal event was identified. Hypoglycemia, sepsis, and pulmonary embolus accounted for these instances. Respiratory failure or massive hemoptysis were the exception rather than the rule suggesting that other parameters play an important role in predicting a fatal outcome. When we tested the predictive value of an admission hemoglobin higher than 11 g/l, a weight of more than 50 kg, and a percentage of visible lung affected by infiltrative changes of less than 36%, the chances of a patient dying were reduced from 1 in 2 in the cohort to 1 in 16. Recognition of these clinical prognosticators may motivate for more aggressive and vigilant clinical management in selected patients if survival rates from TB are to improve.

Although 25% of the deaths in our study were acquired immunodeficiency syndrome rather than TB, this distinction may not be possible when both HIV infection and TB are concurrently identified. Autopsy series from Africa show that active TB at the time of death is common in HIV-infected patients,25 emphasizing that TB may account significantly for deaths from acquired immunodeficiency syndrome.

Our conclusions were that the mortality from TB in our hospitalized patients was strongly related to late presentation, stressing the importance of public health programs to facilitate case finding. We were able to identify several simple predictors of short-term mortality that may ultimately allow for more intensive therapy in such patients. The chronic and insidious nature of the condition results in a long period of infectivity and high mortality rates. Even such simple measures as screening communities by body weight and following up of patients with abnormally low readings may pave the way to reducing the morbidity and mortality from TB.

Accepted for publication February 5, 1998.

We thank Leif Thonell, MD, Marie Andre, MD, Dragan Orlovic, MD, Liesl Pageship, MD, and Maria Botha, MD, for their assistance with data collection, and Rand Merchant Bank, Johannesburg, South Africa, for donating our computer equipment.

Corresponding author: Stella Pendle, MD, Rietfontein Tropical Diseases Hospital, Private Bag X2, Sandringham 2131, Johannesburg, South Africa (e-mail: tropdis@global.co.za).
REFERENCES


