**Mycobacterium tuberculosis** Infection in Solid-Organ Transplant Recipients: Impact and Implications for Management

Nina Singh and David L. Paterson

Tuberculosis is a serious opportunistic infection in transplant recipients. On the basis of the compilation of published reports in the literature, the incidence of *Mycobacterium tuberculosis* infection in organ transplant recipients worldwide ranged from 0.35% to 15%. Nonrenal transplantation (P = .004), rejection within 6 months before the onset of tuberculosis (P = .02) and type of primary immunosuppressive regimen (P = .007) were predictors of *M. tuberculosis* infection occurring within 12 months after transplantation. Thirty-three percent (155) of 476 transplant patients with tuberculosis had disseminated infection; receipt of OKT3 or anti–T cell antibodies (P = .005) was a significant predictor of disseminated tuberculosis. Overall, the mortality rate among 499 patients was 29%; disseminated infection (P = .0003), prior rejection (P = .006), and receipt of OKT3 or anti–T cell antibodies (P = .0013) were significant predictors of mortality in patients with tuberculosis. Clinically significant hepatotoxicity due to isoniazid occurred in 2.5%, 4.5%, and 41% of renal, heart and lung, and liver transplant recipients, respectively. The diagnosis and effective management of tuberculosis after transplantation warrant recognition of the unique epidemiological and clinical characteristics of tuberculosis in transplant recipients.

Tuberculosis is a significant opportunistic infection in transplant recipients worldwide. Whereas the frequency of *Mycobacterium tuberculosis* infection in most developing countries ranges from 1.2% to 6.4% [1–8], up to 15% of transplant recipients in areas of high-level endemicity may develop tuberculosis [5]. Although tuberculosis is documented less frequently in transplant centers in North America, the incidence of tuberculosis among transplant recipients (even those in the United States) is 36- to 74-fold higher than that among the general population [9–12].

Regardless of the geographic variation in the incidence, tuberculosis remains one of the most serious bacterial infections after transplantation. Tuberculosis in transplant recipients, even in the 1990s, is associated with mortality rates ranging from 25% to 40% [12–15]. Furthermore, it is often not appreciated that allograft loss due to rejection may ensue in up to 33% of transplant patients receiving antituberculosis therapy [13, 16]. *M. tuberculosis* infection after transplantation often defies early recognition and timely diagnosis, since extrapulmonary disease occurs frequently [3, 17–22]. The management of tuberculosis in this setting is equally challenging because of the side effects of antituberculous agents and their potential interactions with immunosuppressive drugs. Opinions on the approach to chemoprophylaxis are based largely on observations from individual cases or series with small sample sizes [5, 14, 23, 24]. Nevertheless, concerns about hepatotoxicity due to isoniazid have rendered prophylaxis a complex and controversial issue for transplant recipients.

The existing literature on *M. tuberculosis* infection after transplantation is largely made up of institutional experiences with a few patients or case reports. Given the small number of transplant recipients with tuberculosis who are encountered at individual institutions, a prospective study addressing aforementioned and other relevant issues appears largely unfeasible. However, an adequate cumulation and synthesis of existing studies could yield valuable data regarding the overall impact and management of tuberculosis in transplant recipients. This review addresses and summarizes the unique epidemiological features of *M. tuberculosis* infection after transplantation; diverse clinical sequelae; identifiable risk factors; diagnosis; efficacy and adverse consequences of chemoprophylaxis; variables influencing outcome; and differences in epidemiology, presentation, risk of isoniazid hepatotoxicity, and outcome for different types of solid organ transplant recipients.

**Methods**

Previously described *M. tuberculosis* infections in transplant recipients from 1967 through 1997 were identified via a MEDLINE search by cross-referencing the keywords *tuberculosis* and *transplantation* or *transplant*. Additional cases were identified by an extensive review of the reference lists of the original articles and textbooks. Cases were excluded if they did not occur in solid organ transplant recipients or occurred before transplantation. Reports where distinction of the cases of *M. tuberculosis* infections from nontuberculous mycobacterium

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infections could not be made or in which the precise criteria for the diagnosis of tuberculosis could not be discerned were not included. Finally, the reports were limited to those published in or translated into English. Cases reported in more than one report from a single institution were considered only once.

A patient was considered to have tuberculosis if *M. tuberculosis* was detected in a culture of any clinical specimen, body fluid, or tissue specimen or if acid-fast bacilli or caseating granulomas were documented along with a clinical response to antituberculous therapy specifically directed against *M. tuberculosis* [13]. Cases of fever of unknown origin or pulmonary infection suspected of being due to tuberculosis but in which a definitive diagnosis of *M. tuberculosis* infection was either not pursued or not documented were not included.

Tuberculosis was considered to be disseminated when cultures of specimens from two or more noncontiguous organ sites were positive for *M. tuberculosis* or if acid-fast bacilli and/or granulomas were detected in specimens from one or more organ sites in a patient for whom culture of a specimen from a noncontiguous site was positive for *M. tuberculosis* [13]. Determination of the time of onset was based on individually detailed case studies; summarized data where only a mean or range for the group of transplant recipients was provided were excluded from this analysis. For the assessment of predictors or risk factors for a particular end point (e.g., mortality, disseminated disease, etc.), only individually detailed cases where the variables to be analyzed were explicitly stated were included. Mortality was considered attributable to tuberculosis if *M. tuberculosis* infection was documented at autopsy or if there was evidence of active tuberculosis at the time of death and no other etiology accounted for death.

**Statistical analysis.** Patient demographics were entered into the database PROPHET Statistics Version 5.0 (BBN Systems and Technologies, Cambridge, MA). The χ² or Fisher’s exact test was used to compare categorical variables (e.g., presence or absence of an underlying condition). Continuous variables (e.g., time of onset, etc.) were compared by using the t test or the Mann-Whitney *U* test. Multiple comparisons were done by using analysis of variance and the Kruskal-Wallis test. The time of onset of tuberculosis relative to transplantation was examined by using a Kaplan-Meier probability plot; the two Kaplan-Meier curves were compared by using the Mantel-Cox test.

**Results**

A total of 511 cases of tuberculosis in solid organ transplant recipients were identified and reviewed [1–109]. Of these 511 cases, 210 were individually detailed, and 301 were summarized in reports containing from two to 51 cases. Only 13% of the studies reported 10 or more cases.

**Epidemiology and Demographic Characteristics**

Of 511 cases of tuberculosis, 437, 44, 17, and 13 occurred in renal, liver, heart, and lung (heart and lung, 5; double lung, 4; and single lung, 4) transplant recipients, respectively. Of 239 renal transplant recipients, 51% (122) received a cadaveric allograft, 44% (106) received a living-related allograft, and 5% (11) received a living-unrelated allograft. To our knowledge, thus far no cases of tuberculosis have been described in bowel or pancreatic transplant recipients. The incidence of tuberculosis in transplant recipients worldwide ranged from 0.35% to 15%. The incidence among renal transplant recipients was 0.35% to 1.2% in the United States, 0.7% to 5% in Europe, 1.5% to 3.5% in the Middle East, 1.5% to 8.2% in South Africa, 3.1% to 5% in Southeast Asia, and 5% to 15% in India and Pakistan. *M. tuberculosis* infections in nonrenal transplant recipients have been described almost exclusively in Europe and the United States; the frequency of tuberculosis ranged from 1% to 1.4%, 0.9% to 2.3%, and 2% to 6.5% among heart, liver, and lung transplant recipients, respectively [11, 12, 14, 25, 36–38, 64, 65, 67, 70, 93, 97].

The patients’ ages ranged from 10 months to 71 years (mean, 39 years); various types of solid organ transplant recipients did not differ significantly from each other with respect to age. Sixty-six percent of the patients were male. In two (7%) of 29 liver transplant recipients and in six (4%) of 135 renal transplant recipients, tuberculosis occurred after retransplantation; none of the heart or lung transplant patients with tuberculosis underwent retransplantation. Of the 511 transplant recipients, only 0.4% (two) were HIV-positive [13, 14]; these patients included one liver transplant recipient known to have HIV infection before transplantation and one renal transplant recipient in whom HIV infection was inadvertently acquired from the donor [13].

For 410 transplant recipients, the primary immunosuppressive regimen was cyclosporine and azathioprine in 47% (193), azathioprine in 37% (151), cyclosporine in 13% (54), and tacrolimus in 3% (12). Overall, 20 (10%) of 207 patients had received OKT3 or anti–T cell antibodies, including 5 (25%) of 20 liver transplant recipients, 2 (20%) of 10 lung recipients, and 3 (7%) of 177 renal transplant recipients. The mean dose of prednisone for patients for whom this information was stated was 20 mg, 5 mg, and 2.5 mg for the renal, heart, and liver transplant recipients, respectively. Fifty percent (70) of 139 transplant recipients had experienced allograft rejection at any time preceding tuberculosis; rejection episodes had occurred within 6 months of the onset of tuberculosis in 38% (53) of 139 patients.

**Time of Onset**

Tuberculosis occurred a median of 9 months (range, 0.5 to 144 months) after transplantation (table 1). Tuberculosis occurred significantly later in renal transplant recipients than...
Table 1. Timing of the onset of tuberculosis in solid organ transplant recipients.

<table>
<thead>
<tr>
<th>Type of transplant</th>
<th>No. of patients</th>
<th>No. (%) of patients with tuberculosis at indicated time of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>150</td>
<td>&lt;6 mo  53 (35)  6–12 mo  33 (22)  &gt;1–2 y  24 (16)  &gt;2–5 y  28 (19)  &gt;5 y  12 (8)</td>
</tr>
<tr>
<td>Liver</td>
<td>29</td>
<td>18 (62)  6 (21)  1 (9)  3 (10)</td>
</tr>
<tr>
<td>Heart</td>
<td>11</td>
<td>6 (55)  1 (9)  1 (9)  3 (27)</td>
</tr>
<tr>
<td>Lung</td>
<td>10</td>
<td>8 (80)  1 (10)  1 (10)</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>85 (43)  41 (20)  28 (14)  34 (17)  12 (6)</td>
</tr>
</tbody>
</table>

in other organ transplant recipients; the median time to onset after transplantation was 11.5 months, 4 months, 4 months, and 3.5 months for renal, liver, heart, and lung transplant recipients, respectively (P = .004). Overall, 57% (86) of 150 renal transplant recipients, 83% (24) of 29 liver transplant recipients, 64% (7) of 11 heart transplant recipients, and 90% (9) of 10 lung transplant recipients who had tuberculosis developed this infection within 12 months of transplantation. Significant predictors of early onset tuberculosis (occurring ≤12 months after transplantation) were nonrenal transplantation compared with renal transplantation (80% [40 of 50] vs. 57% [86 of 150], respectively; P = .004), allograft rejection occurring <6 months before the onset of tuberculosis compared with that occurring ≥6 months before the onset (80% [40 of 50] vs. 59% [48 of 82], respectively; P = .02), and type of primary immunosuppressive regimen (P = .007). Forty-six percent (11) of 24 patients receiving cyclosporine alone, 53% (34) of 64 patients receiving azathioprine alone, 68% (42) of 62 patients receiving cyclosporine plus azathioprine, and 100% (11) of 11 patients receiving tacrolimus alone developed tuberculosis within 1 year of transplantation (P = .007).

By means of a Kaplan-Meier probability plot (figure 1), patients with a history of exposure to Mycobacterium tuberculosis (i.e., those with a positive tuberculin skin test or radiographic evidence of old active tuberculosis) developed tuberculosis earlier than those without a history of exposure, although this difference was not statistically significant (P = .08; Mantel-Cox test). Seventy-nine percent (15) of 19 evaluable patients who had received OKT3 or anti–T cell antibodies developed tuberculosis within 12 months of transplantation compared with 64% (63) of 99 who had not received OKT3 or anti–T cell antibodies (P = .19). Age, rejection occurring >6 months before the onset of tuberculosis, and country of origin were not significant predictors of early- vs. late-onset tuberculosis.

Mode of Acquisition and Source

Reactivation of old dormant tuberculosis and, rarely, nosocomial acquisition or donor transmission were considered to be the most frequent modes of acquisition of tuberculosis. Pretransplant chest radiographs of 12% (25) of 207 patients revealed evidence of old active tuberculosis; the proportion of patients whose chest roentgenograms demonstrated abnormalities did not differ significantly between the various types of organ transplant recipients. An additional 5% (10) of 208 patients had a history of tuberculosis before transplantation [7, 13, 16, 31, 32, 41, 87].

Donor transmission was the proposed source of tuberculosis in 4% (nine) of 243 patients. Tuberculosis involving the renal allograft was documented 35 and 39 days after renal transplantation; the median time to onset after transplantation was 11.5 months, 4 months, 4 months, and 3.5 months for renal, liver, heart, and lung transplant recipients, respectively; P = .004). Overall, 57% (86) of 150 renal transplant recipients, 83% (24) of 29 liver transplant recipients, 64% (7) of 11 heart transplant recipients, and 90% (9) of 10 lung transplant recipients who had tuberculosis developed this infection within 12 months of transplantation. Significant predictors of early onset tuberculosis (occurring ≤12 months after transplantation) were nonrenal transplantation compared with renal transplantation (80% [40 of 50] vs. 57% [86 of 150], respectively; P = .004), allograft rejection occurring <6 months before the onset of tuberculosis compared with that occurring ≥6 months before the onset (80% [40 of 50] vs. 59% [48 of 82], respectively; P = .02), and type of primary immunosuppressive regimen (P = .007). Forty-six percent (11) of 24 patients receiving cyclosporine alone, 53% (34) of 64 patients receiving azathioprine alone, 68% (42) of 62 patients receiving cyclosporine plus azathioprine, and 100% (11) of 11 patients receiving tacrolimus alone developed tuberculosis within 1 year of transplantation (P = .007).

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Figure 1. Kaplan-Meier probability plot depicting that tuberculosis developed signficantly earlier in solid organ transplant recipients with prior exposure to Mycobacterium tuberculosis (i.e., those with a positive tuberculin skin test or radiographic evidence of old quiescent tuberculosis [wide line]) than in those without a history of exposure (thin line) (P = .08; Mantel-Cox test).
ary to antituberculosis therapy necessitated allograft nephrectomy) [30]. The same *M. tuberculosis* isolates were recovered from two recipients of a single-lung transplant from a common donor; restriction fragment length polymorphism analysis demonstrated that the isolates were the same [84]. Disseminated tuberculosis was also found in two recipients of kidney allografts from the same donor [42]. Neither of the two recipients had a history of active tuberculosis or tuberculosis reactivity before transplantation [42].

Donor transmission was considered highly probable for a pediatric recipient of a living-related segmental hepatic transplant; the sole site of *M. tuberculosis* infection in this patient was a tuberculous abscess in the hepatic allograft [35]. Pulmonary (right upper lobe) tuberculosis was detected concomitantly in this patient’s mother who had donated the segmental hepatic allograft [35]. For two renal transplant recipients, donor transmission was considered likely in light of positive tuberculin skin tests documented for both donors of living-related renal allografts and negative tuberculin skin tests without prior evidence of tuberculosis for the recipients [9, 56]. Donor transmission was also implicated for two bilateral-lung transplant recipients in whom *M. tuberculosis* infection was found only in the allografts [11].

Data on tuberculin skin testing were considered evaluable if the administration of the tuberculin skin test (whether performed) and the results were explicitly documented in the report; data for 209 patients were evaluable in this analysis. Before transplantation, only 47% (98) of 209 transplant recipients underwent tuberculin skin testing. Of these 98 patients, 22% (22) were PPD-positive, and the remaining 76 (78%) were PPD-negative or anergic. PPD positivity was documented for 73% (8) of 11 liver transplant recipients, 15% (8) of 52 renal transplant recipients, and none of three heart or two lung transplant recipients who underwent tuberculin skin testing. Of 30 solid organ transplant recipients, 20% (six) were PPD-positive [13].

A nosocomial outbreak of tuberculosis that involved 10 renal transplant patients was documented from one institution; eight of the 10 cases were clustered within a 5-month period [52]. The source case occurred in a renal transplant recipient who was exposed to tuberculosis at another hospital. Tuberculosis was not suspected in the source patient at the time of admission, thus delaying isolation precautions. Restriction fragment length polymorphism analysis documented transmission of the donor *M. tuberculosis* strain to five renal transplant recipients. It is notable that the median incubation period for tuberculosis in this outbreak was only 7.5 weeks, and death occurred in five of 10 patients a median of 8 weeks after diagnosis.

Of 243 patients for whom a history of exposure to tuberculosis was sought, 3% (eight) had had contact with a family member with tuberculosis either before or after transplantation [4, 13, 28, 65, 67, 91]. None of these patients received chemoprophylaxis for tuberculosis.

**Clinical Manifestations**

Of 476 patients, 51% (244) had pulmonary tuberculosis, 16% (77) had extrapulmonary tuberculosis, and 33% (155) had disseminated tuberculosis. Disseminated tuberculosis occurred in 48% (14) of 29 liver transplant recipients, 38% (5) of 13 lung transplant recipients, 40% (61) of 152 renal transplant recipients, 36% (4) of 11 heart transplant recipients, and 25% (13) of 51 solid organ transplant recipients in a mixed group; the difference in the frequency of disseminated disease between various organ transplant recipients was not statistically significant (table 2). Disseminated infection was documented in 49% (27) of 55 transplant recipients from the United States, 50% (34) of 68 transplant recipients from Europe, and 28% (20) of 71 transplant recipients from all other regions of the world (*P* = .01). This finding is likely due to the fact that nonrenal solid organ transplant recipients with tuberculosis in this report (in whom cumulative immunosuppression may be greater) were almost exclusively from the United States and Europe. Patients with disseminated infection were also more likely to have received OKT3 (*P* < .005) than were patients without disseminated tuberculosis (table 2). Age, type of organ transplant, type of primary immunosuppressive regimen, rejection, and history of exposure to tuberculosis were not significant predictors of disseminated tuberculosis (table 2). Fifteen cases were diagnosed only at autopsy.

Fever was a common occurrence in organ transplant recipients with tuberculosis. Fever was significantly more likely to occur in patients with disseminated infection than in those with localized tuberculosis (91% [70 of 77] vs. 64% [62 of 97], respectively; *P* = .0001). Overall, 91% (70) of 77 patients with disseminated tuberculosis, 66% (42) of 64 patients with pulmonary tuberculosis, and 63% (20) of 32 patients with extrapulmonary tuberculosis had fever (*P* = .0001). Constitutional symptoms (e.g., night sweats and weight loss) were also frequently observed. The leukocyte count was documented for 26 patients; only 35% (nine) of these 26 patients had leukopenia.

**Pulmonary tuberculosis.** The lung was the most frequently involved site of tuberculosis (71% [336] of 476 patients). Fifty-one percent (244) of 476 patients had pulmonary involvement only, whereas 19% (92) of 476 patients had pulmonary involvement as part of disseminated tuberculosis.

The radiographic appearance of the pulmonary infiltrate(s) in 226 patients was a focal infiltrate in 40% (90), a miliary pattern in 22% (49), nodules in 15% (35), pleural effusions in 13% (30), diffuse interstitial infiltrates in 5% (12), and cavitary lung disease in 4% (8). Forty-six percent (13) of 28 nonrenal transplant recipients compared with 14% (22) of 156 renal transplant recipients had nodular infiltrates due to tuberculosis. The frequency of other radiographic patterns of tuberculosis did not differ between various organ transplant recipients.

**Gastrointestinal tuberculosis.** Gastrointestinal tract involvement was documented in 32 cases. Although the gastrointestinal...
Isolated pancreatic tuberculosis was found in two patients; one was suspected of having a pancreatic malignancy, and the other (for whom a culture of an aspirate yielded *M. tuberculosis*) had a pancreatic pseudocyst [15, 96]. Tuberculous peritonitis was observed in eight cases (as part of disseminated tuberculosis in seven and as localized gastrointestinal disease in one) [3, 6, 7, 12, 18, 42, 50, 92].

Hepatic involvement was documented in 48% (13) of 27 liver transplant recipients [12, 22, 28, 35, 36, 65, 71, 86, 87, 93]; liver biopsies demonstrated granulomas with or without acid-fast bacilli in all cases. By comparison, of 29 other solid organ transplant recipients whose liver tissue samples (obtained at biopsy or autopsy) were histopathologically studied, 55% (16) also had hepatic tuberculosis, including 14 of 25 renal transplant recipients and two of four heart or lung transplant recipients [3, 10, 17–19, 21, 33, 38–40, 42, 46, 48, 49, 66, 68, 78, 80, 81, 83].

**Skin, muscle, and osteoarticular tuberculosis.** In 23 cases, tuberculosis of the skin, muscle, and/or osteoarticular sites was documented. These cases occurred in 5 patients with long-bone osteomyelitis and septic arthritis of the peripheral joints (wrist, knee, and elbow), 4 with thoracic vertebral osteomyelitis, 3 with pyomyositis, 1 with tenosynovitis, and 7 with cutaneous ulcers or abscesses [3, 4, 7, 10, 19, 26, 28, 38–40, 50, 51, 54, 62, 63, 75, 77]. The precise site was unspecified in 3 cases. Whereas 87% (13) of the 15 patients with septic arthritis, cutaneous abscesses, and pyomyositis had disseminated disease, 80% (four) of the five patients with vertebral osteomyelitis and tenosynovitis had localized *M. tuberculosis* infection.

**CNS tuberculosis.** Tuberculous meningitis was reported in 13 cases; in 12 of these patients, meningitis was part of disseminated infection [2, 3, 6, 16, 18, 23, 28, 38, 48, 60, 61, 63, 70, 83, 108]. Five patients had brain abscesses due to *M. tuberculosis*; for two of these patients, the brain was the only documented site of infection, whereas the other three had disseminated tuberculosis [2, 3, 28, 70, 87]. Caseous material containing acid-fast bacilli was found in the cerebral vessels of a patient with culture-proven disseminated *M. tuberculosis* infection [94].

**Renal and genitourinary disease.** *M. tuberculosis* infection of the kidneys was histopathologically documented for 9% (18) of 200 patients, including 16 of 149 renal transplant recipients, 1 of 12 lung transplant recipients, 1 of 11 heart transplant recipients, and none 28 liver transplant recipients [3, 10, 15, 16, 19, 30, 41, 44, 58, 66, 68, 77, 78, 81, 87, 95]. Four renal transplant recipients had epididymo-orchitis, and three heart transplant recipients and one liver transplant recipient had involvement of an unspecified genitourinary site [3, 28, 59, 70]. An additional 8% (16) of 200 organ transplant recipients had *M. tuberculosis* bacteremia, including 9% (13) of 149 renal transplant recipients, 9% (1) of 11 heart transplant recipients, 7% (2) of 28 liver transplant recipients, and none of 12 lung transplant recipients.

### Table 2. Risk factors for disseminated tuberculosis in solid organ transplant recipients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Disseminated tuberculosis</th>
<th>Localized tuberculosis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>39.9</td>
<td>37.9</td>
<td>NS</td>
</tr>
<tr>
<td>Type of transplant</td>
<td>Renal (152)*</td>
<td>Liver (29)</td>
<td>Heart (11)</td>
</tr>
<tr>
<td>Time of onset</td>
<td>≤12 mo (124)</td>
<td>&gt;12 mo (75)</td>
<td></td>
</tr>
<tr>
<td>Primary immunosuppressive regimen</td>
<td>Cyclosporine (24)</td>
<td>Azathioprine (68)</td>
<td>Cyclosporine plus azathioprine (66)</td>
</tr>
<tr>
<td>Prior rejection</td>
<td>Yes (85)</td>
<td>No (25)</td>
<td></td>
</tr>
<tr>
<td>Rejection within 6 mo before tuberculosis</td>
<td>Yes (53)</td>
<td>No (84)</td>
<td></td>
</tr>
<tr>
<td>Receipt of OKT3 or anti-T cell antibodies</td>
<td>Yes (20)</td>
<td>No (102)</td>
<td></td>
</tr>
<tr>
<td>Place of origin</td>
<td>United States (55)</td>
<td>Europe (68)</td>
<td>Other regions (71)</td>
</tr>
</tbody>
</table>

NOTE: NS = not significant (P > .05). Unless stated otherwise, data are no. (%) of patients.

* No. of patients for whom data were available.

† Radiographic evidence of old active tuberculosis and/or a positive tuberculin skin test.

tract was the most frequent extrapulmonary site of tuberculosis in transplant recipients, these findings should be interpreted with caution in light of possible reporting bias. Fever of unknown origin and gastrointestinal bleeding (which may occasionally be exsanguinating) or abdominal pain were the most common presenting features of gastrointestinal tuberculosis [15, 18, 20–22, 96, 108]. In 20 individually detailed cases of gastrointestinal tuberculosis, the ileocecal area was the most common site involved (35% [seven] of the cases) [5, 15, 20, 28, 32, 81, 108]. In five of seven cases, the ileum was the only site of *M. tuberculosis* infection. Colonic tuberculosis presenting as a perforated abscess or mimicking a tumor was reported in two cases [22, 49]. The diagnosis was not suspected until laparotomy or colonoscopy in any of the cases [5, 15, 20, 32, 94, 108].
To determine the frequency with which renal allograft involvement could be conclusively documented for renal transplant recipients, data on all renal tissue samples (16 allograft biopsy specimens, 12 allograft nephrectomy specimens, and 11 autopsy specimens) for which histopathologic findings were detailed were compiled [2, 3, 9, 10, 16, 17, 19, 21, 26, 28, 30, 33, 39, 41, 44, 48, 58, 60, 62, 73, 77, 80, 81, 94]. Overall, tuberculous involvement (granulomas with or without acid-fast bacilli) was shown in 41% (16) of the 39 histopathologically studied renal tissue samples (9 allograft biopsy specimens, 2 allograft nephrectomy specimens, and 5 autopsy specimens). In all but one of these 16 cases, renal involvement was part of disseminated tuberculosis. M. tuberculosis infection was shown in 72% (13) of the 18 renal biopsy samples obtained before antituberculous therapy, whereas allograft rejection was demonstrated only in 6% (one) of the 18 samples (P = .00008). On the contrary, rejection was shown in 43% (nine) of the 21 histopathologic samples obtained 6 weeks to 26 months after antituberculous therapy, and tuberculosis was found only in 10% (two) of these 21 histopathologic samples (P = .03).

Lymphadenitis. Tuberculous lymphadenitis was described in 18 patients [5, 7, 17, 23, 28, 32, 54, 60, 65, 79, 82, 90, 93]. The sites involved included the mediastinum in 5 patients, the cervical area in 5 (one of whom also had abdominal lymphadenopathy), the submandibular area in 1, the axillary area in 1, and an unspecified area in 6. In one case of fever of unknown origin, tuberculosis was serendipitously diagnosed when examination of a lymph node removed during parathyroidectomy revealed M. tuberculosis [17]. In all but three cases (two in mediastinal areas and one in an unspecified site), lymphadenitis was part of disseminated tuberculosis.

Other sites of M. tuberculosis infection included the pericardium, spleen, larynx, tonsil, and ocular choroid [3, 5, 15, 17, 18, 32, 33, 46, 49, 58, 67, 79, 94]. Of these 83% (120) of 145 patients received isoniazid plus rifampin as part of antituberculous therapy for at least 6 months. European centers (41 [79%] of 52) were less likely to employ a rifampin-containing regimen than were those in the United States (35 [92%] of 38) or other regions (42 [91%] of 46; P = .10). The effect of antituberculous regimens on outcome was evaluated in 145 individually detailed cases; cases with no treatment or those diagnosed only at autopsy were excluded in this analysis. Mortality rates did not differ among patients who received a regimen containing isoniazid plus rifampin (25 [21%] of 120) and those who received an isoniazid-containing regimen without rifampin (six [24%] of 25; P > .05).

Hepatotoxicity. Hepatotoxicity (any elevation in amino-transferase levels) was documented for 9% (18) of 198 renal transplant recipients who received isoniazid as part of antituberculous therapy. Therapy with isoniazid (along with rifampin) was discontinued for 12 of these 18 patients but was resumed without any adverse events for seven of the 12 patients [7, 13, 19, 48]. Thus, discontinuation of isoniazid therapy was required for 2.5% (five) of 198 renal transplant recipients. Hepatotoxicity occurred between 7 days and 6 weeks in cases where timing was specified.

Since the issues of hepatotoxicity are particularly relevant in the context of liver transplantation, we undertook a detailed analysis of cases where antituberculous regimen and clinical, laboratory, and liver biopsy findings were individually detailed [28, 35, 36, 65, 69, 71, 85, 93]. Liver biopsies performed a median of 30 days (range, 7–12 days) after antituberculous therapy revealed acute or chronic rejection plus granulomas in 40% (six) of 15 patients; two of 15 biopsies (done 4 days and 7 weeks after therapy, respectively) showed only granulomas [28, 35, 36, 65, 71, 85]. Acute rejection with hepatitis was documented for three patients, and hepatitis alone was found in four patients. Isoniazid therapy was discontinued for the seven patients with hepatitis, a patient with elevated liver enzyme levels (who did not undergo biopsy), and three of 12 liver transplant recipients described in a group report [13, 14]. Thus, hepatotoxicity requiring discontinuation of isoniazid therapy occurred in 41% (11) of 27 liver transplant recipients.

Hepatotoxicity was documented for one (10%) of 10 heart transplant recipients [38] who received therapy with isoniazid, rifampin, and pyrazinamide; none of 12 lung transplant recipients had hepatotoxicity.

Chemoprophylaxis. Although the efficacy of isoniazid prophylaxis has not been demonstrated in a controlled trial to our knowledge, case series and reports suggest that chemoprophylaxis is effective for high-risk transplant recipients. A double-blind, randomized, controlled trial of primary isoniazid prophylaxis for dialysis and renal transplant recipients demonstrated a trend toward a lower incidence of tuberculosis in isoniazid recipients [54]. The study, however, lacked sufficient power; nearly one-half of the study patients had underlying hepatitis B virus infection, and administration of isoniazid and placebo was discontinued because of hepatitis in over one-third of the patients in both treatment groups.

Of 278 patients who received isoniazid prophylaxis in seven other reports, none developed tuberculosis [2, 27, 28, 33, 34, 55, 85]. There were no cases of tuberculosis in 12 high-risk patients who received prophylaxis, but of 27 patients who did not receive prophylaxis, 22% (six) developed tuberculosis [28].

In a study of liver transplant recipients, hepatotoxicity was significantly more likely to occur if isoniazid was administered as treatment of tuberculosis in a multidrug regimen than if it was administered as single-agent chemoprophylaxis [85]. All five patients who received isoniazid in a multidrug regimen
that included rifampin developed hepatotoxicity. In contrast, none of eight patients who received isoniazid alone (or in combination with ethambutol in two cases) as chemoprophylaxis developed hepatotoxicity [85].

Only two studies of renal transplant recipients rigorously evaluated the toxicity associated with isoniazid chemoprophylaxis [27, 34]. Of 119 renal transplant recipients who received azathioprine as primary immunosuppressive therapy, 2.5% (three) developed clinically significant hepatotoxicity [34]. None of 83 cyclosporine-treated renal transplant recipients who received isoniazid therapy for a mean of 344 days developed hepatotoxicity [27].

Mortality

Overall, the mortality rate among organ transplant recipients with tuberculosis was 29% (146 of 499). The mortality rate was 30% (120 of 397), 21% (6 of 28), 18% (2 of 11), and 17% (2 of 12) among renal, liver, heart, and lung transplant recipients, respectively, and 31% (16 of 51) among a mixed group [13] of solid organ transplant recipients. In 57% (68) of 119 renal transplant recipients, 83% (five) of six liver transplant recipients, and all heart and lung transplant recipients with tuberculosis who died, mortality was attributable to M. tuberculosis infection.

Risk factors for mortality could be analyzed in 202 individually detailed cases. Age, time of onset after transplantation, primary immunosuppressive regimen, history of exposure, hepatotoxicity, rejection after antituberculous therapy, and place of origin were not significant predictors of outcome (table 3). The mortality rate was 38% among patients from the United States, 28% among those from Europe, and 27% among those from other parts of the world. Disseminated tuberculosis compared with localized tuberculosis (44% [36 of 82] vs. 20% [24 of 120], respectively; \( P = .0003 \), prior rejection compared with no prior rejection (39% [26 of 67] vs. 18% [12 of 68], respectively; \( P = .006 \), and receipt of OKT3 or anti-T cell antibodies compared with no receipt of OKT3 or anti-T cell antibodies (60% [12 of 20] vs. 24% [24 of 100], respectively; \( P = .0013 \)) were significant predictors of mortality in transplant recipients with tuberculosis (table 3).

Discussion

This review illustrates the characteristics and problems unique to transplant recipients with tuberculosis; to our knowledge, it represents the only exhaustive and systematic analysis of tuberculosis in a large number of transplant recipients. Tuberculosis occurred in 0.35% to 15% of the transplant recipients worldwide; this incidence was eightfold to 100-fold higher than that among the general population in the respective countries [3, 7, 9–11, 13, 22, 38]. The median time to onset was 9 months after transplantation; 63% of the cases occurred within 12 months of transplantation. The time between transplantation and the onset of tuberculosis was significantly longer for renal transplant recipients than for other organ transplant recipients. Renal transplant recipients are generally less immunosuppressed than liver, heart, or lung transplant recipients, which could have accounted for the later occurrence of tuberculosis in renal transplant recipients. On the other hand, renal transplantation has been in existence longer than other organ transplantations. Thus, later occurrence of tuberculosis in renal transplant recipients may merely be reflective of longer follow-up of these patients.

Tuberculosis in organ transplant recipients may develop after reactivation of old quiescent disease, nosocomial expo-

Table 3. Risk factors for mortality in solid organ transplant recipients with tuberculosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death</th>
<th>Survival</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>38.7</td>
<td>39.1</td>
<td>NS</td>
</tr>
<tr>
<td>Median time of onset (mo)</td>
<td>9</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Type of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated (82)*</td>
<td>36 (44)</td>
<td>46 (56)</td>
<td>.0003*</td>
</tr>
<tr>
<td>Localized (120)</td>
<td>24 (20)</td>
<td>96 (80)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary only (84)</td>
<td>16 (19)</td>
<td>68 (81)</td>
<td>.001†</td>
</tr>
<tr>
<td>Extrapulmonary only (36)</td>
<td>7 (20)</td>
<td>27 (79)</td>
<td></td>
</tr>
<tr>
<td>Prior rejection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (67)</td>
<td>26 (39)</td>
<td>41 (61)</td>
<td>.006</td>
</tr>
<tr>
<td>No (68)</td>
<td>12 (18)</td>
<td>56 (82)</td>
<td></td>
</tr>
</tbody>
</table>
| Rejection within 6 mo before tuber-
|culosis                          |       |          |              |
| Yes (52)                         | 20 (38) | 32 (62) | .025         |
| No (82)                          | 17 (21) | 65 (69) |              |
| Receipt of OKT3 or anti-T cell
| antibodies                       |       |          |              |
| Yes (20)                         | 12 (60) | 8 (40)  | .0013        |
| No (100)                         | 24 (24) | 76 (76) |              |
| Primary immunosuppressive
| regimen                          |       |          |              |
| Cyclosporine (23)                | 7 (30)  | 16 (70)  | NS           |
| Azathioprine (66)                | 25 (38) | 41 (62)  |              |
| Cyclosporine plus
| azathioprine (51)                | 11 (22) | 40 (78)  |              |
| Tacrolimus (12)                  | 4 (30)  | 8 (67)   |              |
| History of exposure†             |       |          |              |
| Yes (81)                         | 17 (21) | 64 (79)  | NS           |
| No (23)                          | 7 (30)  | 16 (70)  |              |
| Place of origin                  |       |          |              |
| United States (53)               | 20 (38) | 33 (62)  | NS           |
| Europe (65)                      | 18 (28) | 47 (72)  |              |
| Other regions (70)               | 19 (27) | 51 (73)  |              |

NOTE. NS = not significant \( (P > .05) \). Unless stated otherwise, data are no. (%) of patients.
* No. of patients for whom data were available.
† Comparison of disseminated tuberculosis and localized tuberculosis.
‡ Comparison of disseminated tuberculosis and only pulmonary or extrapulmonary tuberculosis.
§ Radiographic evidence of old active tuberculosis and/or a positive tuberculin skin test.
tuberculosis. Indeed, the number of patients with disseminated disease was distinctly unusual in organ transplant recipients with tuberculosis.

Twenty-nine percent of 499 patients who developed tuberculosis died. Disseminated tuberculosis, prior rejection, and receipt of OKT3 or anti-T cell antibodies for rejection were significant predictors of death in transplant recipients with tuberculosis. Perhaps equally worrisome was the significant morbidity associated with tuberculosis in the patients who survived. Accelerated metabolism of immunosuppressive drugs and corticosteroids by rifampin may trigger allograft rejection [112]. A reduction in corticosteroid levels, albeit to a lesser degree, can also occur with isoniazid therapy [3]. Graft loss was observed in 27% (41) of 150 renal transplant recipients with tuberculosis and was attributable to chronic rejection in most of these patients. Although simultaneous use of cyclosporine and rifampin has been accomplished by increasing the cyclosporine dose three- to fivefold (with the frequency of administration increased from twice to thrice daily) and by doubling the dose of corticosteroids [47], other investigators have found it virtually impossible to continue administration of the combination of cyclosporine and rifampin [38, 67].

In one study, patients developing acute rejection as a consequence of drug interactions were significantly more likely to die than were those who did not develop acute rejection [13]. Thus, use of rifampin must be undertaken with extreme caution and with frequent monitoring of immunosuppressive drug levels. Employment of isoniazid-containing regimens, without inclusion of rifampin, is a valid alternative since the use of such regimens was associated with outcomes comparable with those associated with regimens that included rifampin. Regimens not including rifampin should, however, be continued for 12–18 months.

Despite limited data on isoniazid hepatotoxicity in transplant recipients, it is widely perceived that these patients are at increased risk of isoniazid-associated hepatotoxicity. Temporarily elevated liver enzyme levels have been described in 9%–18% of patients in the general population who receive isoniazid therapy [113–115], with a rate of clinically significant hepatotoxicity of 6.8% [115]. Clinically significant hepatotoxicity developed in 2.5% (three) of 119 renal transplant recipients receiving azathioprine therapy [34]. It should be noted that isoniazid in this study was employed for all renal transplant recipients (irrespective of the results of tuberculin skin testing or other risk factors) for an indefinite period after transplantation; 15% of the patients had hepatitis B infection, and the patients’ status of antibody to hepatitis C virus was unknown. Although preexistent chronic active hepatitis B infection does not appear to increase the risk of hepatotoxicity, it may render determination of the etiology of hepatic dysfunction in transplant recipients problematic.

In a study of primary isoniazid prophylaxis in an area where tuberculosis was endemic and 50% of the patients had hepatis
Table 4. Indications for isoniazid prophylaxis for solid organ transplant recipients.

| I. | Tuberculin reactivity of $\geq 5$ mm before transplantation |
| II. | Patients with the following characteristics, regardless of tuberculin reactivity |
| 1. | Radiographic evidence of old active tuberculosis and no prior prophylaxis |
| 2. | History of inadequately treated tuberculosis |
| 3. | Close contact with an infectious patient |
| 4. | Receipt of an allograft from a donor with a history of untreated tuberculosis or tuberculin reactivity without adequate prophylaxis |
| III. | Newly infected persons (recent conversion of tuberculin skin test to positive) |

B infection, 36% of the placebo-treated patients and 35% of the isoniazid-treated patients required discontinuation of the respective therapy because of clinically diagnosed hepatitis [54]. More recently, in a study of 83 renal transplant recipients receiving cyclosporine therapy, isoniazid chemoprophylaxis was employed for a mean of 344 days after transplantation [27]. None of the patients developed clinical hepatotoxicity or required discontinuation of isoniazid therapy. Ten percent of the patients had mildly elevated transaminase levels before isoniazid therapy was started. During chemoprophylaxis, 3% of the patients had mild self-limited elevations in transaminase levels, usually within 10 days of initiation of therapy, that decreased without the need for discontinuation of isoniazid therapy.

Our data show that clinically significant hepatotoxicity requiring discontinuation of isoniazid therapy occurred in 2.5%, 4.5%, and 41% of renal, heart, and lung, and liver transplant recipients, respectively. Although liver transplant recipients appeared to be more vulnerable to isoniazid-associated hepatotoxicity, it should be noted that liver biopsies of liver transplant recipients receiving antituberculous therapy were as likely to show rejection and/or hepatic tuberculosis as isoniazid hepatotoxicity. Indeed, eight of 15 liver biopsies demonstrated acute or chronic rejection plus granulomas (six) or only granulomas (two) in patients receiving isoniazid-containing regimens. Therefore, these data suggest that a presumptive diagnosis of isoniazid hepatotoxicity may not be accurate for liver transplant recipients. Liver biopsy should be considered for the evaluation of elevated liver enzyme levels, since multiple etiologies could account for the occurrence of abnormal liver enzyme levels in these patients.

On the basis of this review, the following recommendations concerning chemoprophylaxis for tuberculosis in transplant recipients are offered. All transplant recipients should undergo a tuberculin skin test before transplantation. Although up to 70% of such patients may be anergic, tuberculin reactivity (22% of 98 patients in this review) identifies a subgroup at risk for reactivation of tuberculosis after transplantation. Isoniazid prophylaxis should be considered for transplant recipients with the characteristics outlined in table 4.

Although few investigators would argue the need for chemoprophylaxis for patients in categories II and III of table 4, tuberculin reactivity (category I) per se is a controversial indication for prophylaxis for transplant recipients. Risk of hepatotoxicity, relative rarity of tuberculosis in areas of nonendemicity, and manageable disease once tuberculosis develops are the frequently cited arguments against routine prophylaxis for tuberculin-reactive patients [14, 23, 24, 28, 88]. Our data show that nearly one-third of transplant recipients with tuberculosis die, and in an equal number of patients, allograft rejection or graft loss may ensue. The potential for transmission of undiagnosed tuberculosis, particularly in the nosocomial setting, may lead to life-threatening sequelae and costly investigations. Although tuberculosis is treatable when promptly diagnosed, unusual manifestations often defy timely recognition, and many cases are diagnosed only at autopsy. Furthermore, the risk of isoniazid hepatotoxicity, particularly in nonliver transplant recipients, does not appear to be higher for transplant recipients than for the general population. Thus, chemoprophylaxis for all identifiable high-risk patients is recommended (table 4).

Recipients of OKT3 who belong to any of the above-mentioned high-risk categories (including those who have only tuberculin reactivity) must receive prophylaxis, since these patients are at significant risk not only for disseminated disease but also for death if tuberculosis develops. Currently, however, routine use of isoniazid prophylaxis cannot be recommended for anergic transplant recipients who do not belong to the aforementioned high-risk categories.

Although limited by bias inherent to any retrospective study, this review summarizes the overall impact of M. tuberculosis infection in solid organ transplant recipients and highlights key features—many of which were previously poorly defined or perhaps even unappreciated—that are based on case series only. Most M. tuberculosis infections, particularly in nonrenal transplant recipients, occur within the first 12 months of transplantation, and definable variables (portending poor outcome and risk of dissemination) exist. Chemoprophylaxis for identifiable high-risk patients is desirable and feasible.

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References


