MAJOR ARTICLE

Mycobacterial Infection: A Difficult and Late Diagnosis in Stem Cell Transplant Recipients

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The Infectious Diseases Working Party of the European Blood and Marrow Transplant Group conducted a survey to obtain information about the frequency, presentation, and treatment of mycobacterial infection (MBI) in stem cell transplant (SCT) recipients. Among 29 centers, MBI was diagnosed in 0.79% of 1513 allogeneic and 0.23% of 3012 autologous SCT recipients during 1994–1998 a median of 160 days after transplantation. The mean interval between first symptoms and diagnosis was 29 days and was still longer for patients with atypical MBI or recipients of corticosteroid therapy. The prevalence of MBI was highest among those who received matched unrelated or mismatched STCs from related donors. Of 31 patients, 20 had tuberculosis, 8 had atypical MBI, and 3 had diagnoses based on histological findings only. Five patients (16%) died, all of whom had received an allogeneic SCT. Because of the increased numbers of unmatched donors and transplantation programs in countries with a high prevalence of tuberculosis, constant vigilance is required to early detect MBI in SCT recipients.

The incidence of mycobacterial infection (MBI), including that due to nontuberculous mycobacteria (NTM), among stem cell transplant (SCT) recipients has been estimated in the past to be 0.6%–9.7% in the United States [1–4] and, until recently, was considered to be a rare complication and received little attention. However, since the onset of the AIDS epidemic and the emergence of multidrug-resistant strains of *Mycobacterium tuberculosis* [5, 6], there has been an increasing number of reports of MBI in SCT recipients [7–18]. This increase has been attributed to a number of factors, including the availability of new molecular biology methods to recover and identify mycobacteria [19], the increasing use of T cell depletion techniques that may impair host defense recovery [4], and the increasing number of transplantations in countries in which the prevalence of tuberculosis is higher than that in the United States [12–15, 18].

However, the exact incidence of MBI associated with different stem cell transplantation procedures is currently unknown. The development of transplantation programs in most European countries where the prevalence of tuberculosis is higher than that in the United States led us to reevaluate the prevalence and clinical presentation of tuberculosis in the current population of SCT recipients. We conducted a retrospective study to determine the incidence, clinical presentation, and management of MBI in member countries of the European Blood and Marrow Transplant Group (EBMT).

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PATIENTS AND METHODS

Patient population. In 1999, we sent an initial questionnaire to all 420 EBMT centers in 37 countries to determine the management policies of MBI before or after transplantation and to propose an epidemiological and case study of MBI after SCT during 1994–1998. Thirty-nine centers responded, including some non-European centers that participated in EBMT surveys. We sent a second questionnaire to these 39 centers to obtain clinical, outcome, and microbiological data for SCT recipients with MBI. Ten centers that answered the first questionnaire on treatment policies did not answer the second questionnaire. Twenty-nine centers answered the second questionnaire and reported 19 cases during 1994–1998. In addition, 10 centers (8 centers that had already reported cases during 1994–1998, as well as 2 additional centers) spontaneously sent descriptions of 12 cases observed in 1999. A total of 31 case descriptions were included in the study.

Definitions. Tuberculosis was defined according to Rieder et al. [20]. In brief, MBI was considered to be microbiologically proven when *M. tuberculosis* or *Mycobacterium bovis* was isolated from any body sample and associated with consistent symptoms. When direct examination of Ziehl-Neelsen or similar stains of a tissue sample showed the presence of acid-fast bacilli and histopathological analysis revealed granulomas or any tissue lesion compatible with the diagnosis of MBI concomitant with negative culture results, MBI was considered to be only histologically proven. NTM infections were defined by the isolation of NTM from culture of tissue, blood, or endobronchial samples obtained from patients with clinical pneumonia and consistently abnormal chest radiograph findings.

Statistical analysis. Differences in incidence of MBI between recipients of autologous or allogeneic SCTs, among recipients of allogeneic SCTs (i.e., those who received SCTs from genetically identical vs. unrelated vs. related mismatched donors), and among autologous SCT recipients (i.e., those who received CD34 cell–selected vs. unselected SCTs) were tested using 2-tailed Pearson's χ^2 tests (or Fisher's exact test, when appropriate). The differences between continuous variables were analyzed using the Mann-Whitney *U* test. Only data from the 29 centers that answered questions about their incidence of MBIs and who agreed to report their cases were used to calculate the overall frequency of MBI during 1994–1998, because all the participating centers did not provide data for 1999.

RESULTS

Management policies. Thirty-nine centers in 14 countries (Austria, Australia, Belgium, France, Germany, Hungary, Italy, Portugal, Slovenia, Spain, Sweden, The Netherlands, Turkey, and the United Kingdom) completed the first questionnaire about treatment and management policies. The responses are summarized in table 1.

Frequency of MBI. Of the 4525 transplantations performed in 29 centers in 13 countries (all of the countries mentioned above except the United Kingdom), 19 cases of MBI were identified during 1994–1998 (table 2). MBI was significantly higher in recipients of allogeneic SCTs, compared with recipients of autologous SCTs ($P = .01$), and, among the former, the frequency was significantly higher among those who received mismatched SCTs from related donors ($P = .04$). Among recipients of autologous SCTs, there was no difference

Table 1. Responses by 39 centers in 13 European countries and Australia to a questionnaire on current practices for management of mycobacterial infections in stem cell transplant recipients.

Question, response	No. (%) of centers
Do you have a program of vaccination against tuberculosis in your country?	
Yes	20 (51)[a]
No	19 (49)
Do you systematically screen your patients before transplantation by PPD skin test?	
Systematically	4 (10)
Only in case of suspicion	20 (51)
Never	14 (36)
No response	1 (3)
Do you systematically question your patient before transplantation about familial exposure?	
Yes	22 (56)
No	16 (41)
No response	1 (3)
In case of proven mycobacterial infection before transplantation in the recipient, do you provide any prophylaxis?	
Yes	31 (79)
No	2 (5)
No response	6 (15)
In case of suspicion (but no microbiological proof) of tuberculosis before transplantation, do you provide any prophylaxis to the recipient?	
Yes	27 (69)
No	9 (23)
No response	3 (8)
If yes, which drug?	
Isoniazid alone	17 (63)[b]
Isoniazid and another drug	8 (30)[b]
No response	2 (7)[b]

NOTE. PPD, purified protein derivative.

[a] Data represent 7 of 14 countries.

[b] Data represent 27 centers who responded "Yes" to the previous question in the list.

Table 2. Frequency of mycobacterial infections (MBIs) at 29 stem cell transplantation (SCT) centers, 1994–1998.

Type SCT	No. of MBIs	No. of SCTs	Frequency of MBI, %
Allogeneic, by donor type			
Genetically identical sibling	5	1026	0.49
Unrelated	4	386	1.04
Related mismatched	3	101	2.97
Total	12	1513	0.79
Autologous			
Unselected	6	2552	0.24
CD34 cell selected	1	460	0.22
Total	7	3012	0.23
Overall	19	4525	0.42

between recipients of CD34 cell–selected SCTs and recipients of nonselected SCTs. Because of the low numbers of *M. tuberculosis* and NTM infection, the incidence is presented for all the MBIs together (i.e., those due to *M. tuberculosis* and NTM).

Patients. Thirty-one cases of MBI, including the 19 cases used to calculate frequency and 12 additional cases reported in 1999, were reported from 15 centers in 13 countries (Germany and Spain reported 5 cases each; Brazil reported 4; France reported 3; Australia, Hungary, Sweden, The Netherlands, and Turkey reported 2 each; and the Czech Republic, Italy, Slovenia, and Switzerland reported 1 each). The main characteristics of patients with MBI are summarized in table 3. Five of the patients were <15 years old. Among the 8 autologous SCT recipients, 2 were in a program involving sequential transplantations, and MBIs in both were diagnosed after the second procedure. Of the 3 patients with T cell–depleted grafts, 1 patient with autoimmune disorder received an autologous STC, and 2 received an allogeneic STC.

Few data were available on the donors' histories and the risk of tuberculosis exposure. None of the 23 donors had a history of MBI, 1 had a negative purified protein derivative (PPD) test result, and 7 had received bacille Calmette-Guérin (BCG) vaccine during childhood. Of the 2 allogeneic recipients considered to be at risk for MBI before transplantation, 1 had previous documented lung tuberculosis 2 years before transplantation, and the other, a child with Griscelli syndrome, had been vaccinated with BCG before the transplantation. Both received antituberculosis drugs before and during transplantation.

The mean interval between the first symptoms attributable to MBI and diagnosis was 29 days and was significantly longer for the 12 patients receiving corticosteroids than for the 19 patients who were not (mean duration, 37 and 19 days, respectively). Of the 23 patients (74%) who were febrile, 11 were febrile despite the administration of corticosteroids. CD4 cell counts were available for only 5 patients (mean CD4 cell count, 160 cells/mm^3; range, 120–410 cells/mm^3). Of 15 patients in whom IgG levels were measured, only 3 had levels <3 g/L, all of whom were in the group of patients with tuberculosis. The mean serum IgG level was 7.7 g/L. Three of the 6 patients with extensive chronic graft-versus-host disease (GVHD) had bronchiolitis obliterans. Three patients had concomitant cytomegalovirus infection, 1 had concomitant cytomegalovirus and *Toxoplasma* infections, and 6 had concomitant bacterial infection and positive results of blood or lung specimen cultures. The clinical features, organ involvement, and outcome of the 31 patients are presented in table 4.

The lung was the organ most often involved, with cough present in 15 patients (48%), dyspnea in 10 (32%), and hypoxemia in 9 (29%). Chest radiography revealed a diffuse interstitial pattern in 8 patients, diffuse alveolar or alveolar-interstitial in 6, and focal lesions in 3. Of 13 patients with normal chest radiograph findings, culture of a bronchoalveolar lavage specimen obtained from 1 was positive for *M. tuberculosis.*

Patients who died from MBI received this diagnosis significantly earlier than did patients who survived MBI (148 ± 132 vs. 312 ± 300 days after transplantation; $P < .001$). This was mainly the result of more acute clinical patterns associated with the cases that were diagnosed earlier rather than later. MBI was diagnosed in 2 of these patients on the day of death, so they did not receive specific treatment. The other 3 patients died within 2, 6, and 11 days after the diagnosis of MBI, and only 2 received a specific treatment between diagnosis and death. None of the 8 recipients of autologous SCTs died of MBI. Three of these patients died of septic shock, with no pathogen documented other than mycobacteria 8–16 weeks after transplantation. Two of them had GVHD.

Tuberculosis cases. Twenty (64%) of the 31 patients developed tuberculosis. Among these, cases in 4 patients have been reported elsewhere (2 cases in [14] and 1 case each in [15] and [12]). Two cases were proven on the basis of open lung biopsy after endoscopic procedures failed. A 2-year-old girl with Griscelli syndrome and myelodysplastic syndrome received BCG vaccine and developed many disseminated cutaneous lesions over her entire body. PCR analysis of the lesions was positive for mycobacteria. She died from adenovirus infection 40 days after receiving a T cell–depleted SCT from a mismatched related donor. Two patients had cystitis presenting with hematuria and were shown to have tuberculosis in the urinary tract, with positive results of culture of bladder biopsy specimens and urine for one patient and a positive urine culture for the other. One patient, who had received an autologous SCT for T cell acute lymphoblastic leukemia with mediastinal involvement 19 months earlier, developed fever and enlarged mediastinal lymph nodes mimicking the initial tumor. She was considered to be in relapse and received corticosteroids for

Table 3. Main demographic and clinical characteristics of 31 patients with mycobacterial infections (MBIs) after undergoing stem cell transplantation (SCT).

Characteristic	MBI confirmed by *Mycobacterium* isolation		MBI proven by histological findings (n = 3)	Total (n = 31)
	M. tuberculosis or *M. bovis* (n = 20)	Nontuberculous mycobacteria (n = 8)		
Age, median years (range)	31 (2–54)	36 (10–50)	32 (22–38)	32 (2–54)
Sex, M/F	11/9	1/7	3/0	15/16
Type of transplant				
Autologous	4	4	0	8 (26)
Allogeneic	16	4	3	23 (74)
HLA-identical sibling	14	2	0	16
Related mismatched donor	1	0	0	1
Unrelated donor	1	2	3	6
Origin of transplant				
Marrow	12	4	3	19[a]
Autologous	1	1	0	2
Allogeneic	11	3	3	17
PBMCs	8	4	0	12[b]
Autologous	5	1	0	6
Allogeneic	3	3	0	6
Underlying disease				
Acute myeloid leukemia or myelodysplastic syndrome	4	0	2	6
Acute lymphoid leukemia	4	0	1	5
Chronic myeloid leukemia	8	3	0	11
Lymphoma	2	2	0	4
Myeloma	0	1	0	1
Aplastic anemia	1	0	0	1
Solid tumor	1	0	0	1
Immune deficiency	1	0	0	1
Autoimmune disorder	0	1	0	1
Conditioning regimen with total body irradiation	10	3	1	14
Considered at risk for MBI at pre-SCT visit	2	0	0	2
Time between SCT and diagnosis of MBI, mean days ± SD (median)	326 ± 327 (181)	154 ± 99 (131)	368 ± 282 (207)	284 ± 284 (160)
Time between onset of symptoms and MBI diagnosis, mean days (range)[c]	6 (0–14)	43 (4–210)	6 (0–14)	29 (0–210)
Mycobacterium species isolated				
M. tuberculosis	19	…	…	19
M. bovis	1	…	…	1
Atypical (nontuberculous)	…	8	…	8
M. avium intracellulare	…	2	…	2
M. chelonae	…	2	…	2
M. haemophilum	…	2	…	2
M. xenopi	…	1	…	1
M. szulgai	…	1	…	1
Neutropenia at MBI diagnosis[d]	3	0	…	0

(continued)

Table 3. ***(Continued.)***

Characteristic	MBI confirmed by *Mycobacterium* isolation		MBI proven by histological findings (n = 3)	Total (n = 31)
	M. tuberculosis or *M. bovis* (n = 20)	Nontuberculous mycobacteria (n = 8)		
Graft-versus-host-disease at MBI diagnosis				
Acute (grade ⩾1)	2	0	0	2
Chronic	8	1	2	11
Limited	2	0	2	4
Extensive	5	1	0	6
Not graded	1	0	0	1
Onset of MBI in recipients of allogeneic transplants, days after SCT				
⩽100	3	4	3	10
>100	15	3	3	21

NOTE. Data are no. or no. (%) of patients, unless otherwise indicated.

[a] Sixty-one percent of the SCTs included in the study.
[b] Thirty-nine percent of the SCTs included in the study.
[c] Onset of symptoms was determined retrospectively.
[d] Polymorphonuclear neutrophil count <500 cells/mm^3.

several days until a pulmonary infiltrate appeared, which led to the diagnosis of tuberculosis on the basis of fibroscopic examination and analysis of bronchoalveolar lavage specimens. The patient was treated, and the mediastinal lymph nodes disappeared completely. At the time of writing, 10 years later, she is healthy.

Three patients, all of whom received allogeneic SCTs, died with or due to tuberculosis. One patient died from cerebral tuberculosis confirmed by analysis of brain biopsy specimens on day 79 after receipt of an HLA-identical allogeneic SCT. One recipient of an HLA-matched SCT from an unrelated donor died on day 59 from septic shock. *M. tuberculosis* was found in cultures of sputum, bronchoalveolar lavage, and blood specimens. One recipient of an allogeneic HLA-identical SCT from a sibling died from septic shock and multiorgan failure on day 118. Culture of bronchoalveolar lavage specimens and bronchial aspirates obtained after death yielded *M. tuberculosis*.

Nontuberculous cases. Eight patients developed microbiologically proven NTM. All cases were consistent with definite (6 cases) or probable (2 cases) NTM, as defined by Gaviria et al. [3]. The mean and median times to onset of MBIs after receipt of SCTs were shorter for patients from whom NTM was isolated, but this was not statistically significant. Lung and skin were the most frequent organs infected. Two patients from the same center had central venous catheter tunnel infections due to *Mycobacterium haemophilum,* one after receipt of an autologous SCT and the other after receipt of an allogeneic SCT. One developed skin inflammation and lymphadenopathy, followed by ulcerated lesions along the track of a previously placed catheter; *M. haemophilum* was isolated from 2 adjacent lymph nodes. The second patient developed ulcerated and purulent lesions at the insertion site of a previous catheter that had been in place for only a few hours. *M. haemophilum* was isolated from purulent discharge obtained from the tunnel. Details of these 2 cases have been reported elsewhere [16].

Two of these 8 patients, both of whom received an allogeneic SCT, died with or due to NTM. One recipient of an HLA-mismatched SCT from an unrelated donor died due to septic shock on day 122 after transplantation; simultaneous blood cultures were negative, but culture of bronchoalveolar lavage specimens was positive for *M. avium.* One allogeneic PBMC SCT recipient with extensive chronic GVHD died 13 months after transplantation due to septic shock, with simultaneous identification of *Serratia marcescens* and *Mycobacterium chelonae* in blood specimens.

Histologically confirmed MBIs. The diagnoses were confirmed by histological analysis of lymph node, bone, and liver specimens. Smears were positive for acid-fast bacilli, and results of histological analysis showed granulomas, which, in addition to other signs and symptoms, were suggestive of tuberculosis. Two patients presented with febrile pancytopenia. Both were successfully treated with antituberculosis therapy.

Susceptibility testing. Susceptibility test results were retrospectively available in 12 cases. None of the 9 strains of *M. tuberculosis* for which the susceptibility test results were available was resistant to any of the antituberculosis drugs tested. Among the 8 cases of NTM, susceptibility test results were available for 3, all of which showed that the strains were sus-

Table 4. Clinical features at presentation and outcome for 31 patients with mycobacterial infections (MBIs) occurring after stem cell transplantation.

Characteristic	MBI confirmed by *Mycobacterium* isolation		MBI proven by histological findings (n = 3)	Total (n = 31)
	M. tuberculosis or *M. bovis* (n = 20)	Nontuberculous mycobacteria (n = 8)		
Infection site				
Lung	12	5	…	17 (55)
Pleura	1	…	…	1 (3)
Liver	…	…	1	1 (3)
Skin	1	3[a]	…	4 (13)
Brain and/or meninges	2	…	…	2 (6.5)
Bone and/or bone marrow	2	…	2	4 (13)
Lymph nodes	1	…	1	2 (6.5)
Bladder	2	…	…	2 (6.5)
Clinical feature				
Fever	17	4	2	23 (74)
Bacteremia	2	1	…	3 (9.6)
Septic shock	2	2	…	4 (13)
Death concomitant with or due to MBI	3	2	…	5 (16)

NOTE. Data are no. or no. (%) of patients.

[a] Two were catheter related.

ceptible to most of the tested drugs, including ethambutol and clarithromycin.

DISCUSSION

Until recently, most of the reports of MBI after SCT have come from American centers, with incidences varying from 0.6% [17] to 1% [1]. A higher incidence rate of 3% among recipients of allogeneic SCTs was reported in the United States by Kurzrock et al. [2]. However, the cohort of patients was small (n = 90), and this higher incidence could be partly explained by a higher prevalence of tuberculosis in Texas, compared with other parts of the United States. Teams from other countries in which the prevalence of tuberculosis in the normal population is higher than it is in the United States have reported incidences varying from 1.6% in Spain [15] and Turkey [14] to 5% in Hong Kong and Taiwan [13, 18]. More recently, 2 series of NTM have been reported, 20 cases of which were observed during 1977–1997 in Seattle [3] and 50 cases of which were observed during 1993–2001 in New York City [4]. The large difference in the incidences at these 2 centers (0.67% in Seattle vs. 8.7% in New York) suggests that environmental factors may play a role in the risk of MBI after SCT, which is also suggested by reports involving other immunocompromised patients from the New York area [21, 22]. However, MBIs are still considered to be rare complications of SCTs.

Our series show that, in Europe, tuberculosis is more frequent than NTM infection after receipt of an SCT. Although the incidence of and mortality due to MBI were low in our survey (0.42% and 16%, respectively), and although tuberculosis and NTM infection raise different problems because they have different reservoirs, clinical manifestations, and drug susceptibility, some important features were common to both infections and deserve attention. First, diagnosis was difficult, as illustrated by the long mean delay between appearance of the first symptoms and the diagnosis (29 days), especially in the case of NTM infection. Although administration of corticosteroid therapy did not appear to affect fever in most cases, the mean delay between onset of the first symptoms and the diagnosis was especially long (37 days) in the group of patients receiving corticosteroids, which may have masked the symptoms of the disease. Second, our series illustrates that, contrary to other infections that are associated with specific times after transplantation, MBI may occur at any time. Although the mean time to onset of MBI after transplantation was 284 days, in 2 patients, MBI occurred as early as day 56. This interval indicates that MBIs are not associate with neutropenia but rather with the conditions in which various factors lead to the loss of T cell surveillance [4]. Our finding that patients with poor immune reconstitution and early occurrence of MBI have a poor prognosis has also been suggested by others [13].

Sixty-one percent of our patients had tuberculosis, with most

patients presenting with common features of febrile pneumonia. However, several cases illustrate the polymorphism and atypical features of the clinical presentation of tuberculosis in immunocompromised patients. These included 1 case of skin tuberculosis after BCG vaccination, 2 cases of CNS infection, and 2 cases with bone or bone marrow involvement presenting with febrile pancytopenia. In the absence of analysis of marrow biopsy samples, these last 2 patients would have been considered to have experienced graft failure and treated with immunosuppressive regimens. In our 3 patients with septic shock and no documented pathogens other than mycobacteria, one had blood cultures positive for *M. tuberculosis.* Although extremely rare, such an event has been previously reported as a fulminant form of disseminated tuberculosis that is often associated with multiorgan failure, and it should be recognized and treated early with specific therapy to have some impact on the prognosis [23, 24]. The 2 cases of mycobacterial cystitis suggest that MBI should be searched in case of cystitis after transplantation, at least in countries where urinary tuberculosis is not uncommon.

Among our 8 patients with NTM, 2 had rapidly growing strains of *M. chelonae,* and 6 had slowly growing strains. Five of these patients had lung involvement, 3 had skin lesions (which, in 2 patients, were due to tunnel infection at the site of catheterization), and 2 presented with septic shock. In most cases, the clinician was unable to anticipate the diagnosis.

A major problem after transplantation is the lack of criteria to predict MBI. Except for 2 patients who received prophylaxis because they were considered to be at risk before transplantation because of a history of tuberculosis or recent known exposure, it was not possible to predict or assess the risk before transplantation in our series. One explanation may be the lack of routine questioning about exposure. Additionally, even in patients with proven MBI before transplantation, only 21% of the centers provide prophylaxis during transplantation. The reluctance to provide prophylaxis is most likely due to the potential toxicity of antituberculosis drugs, especially on the liver, and the risk of drug interaction with cyclosporine. Also, skin tests are unreliable for screening in such occasions [7]. However, several factors should be considered. First, until recently, one-half of the European children were vaccinated with BCG during infancy, and countries like Taiwan use BCG for mass vaccination [13]. If a positive test result led to specific prophylaxis against tuberculosis, more than one-half of the transplantation candidates would likely receive prophylaxis. This would be unnecessary in view of the rarity of the disease. Second, it is known that some individuals, especially those with impaired T cell functions, may not develop a significant skin reaction [25]; therefore, a negative test result cannot rule out recent MBI in an immunocompromised patient. The use of in vitro methods to assess protective mycobacterial immunity in such patients deserves attention [26].

Our series also shows, as expected, that the risk is higher among recipients of allogeneic SCTs than among recipients of autologous SCTs, and that, among the former, it is significantly higher for recipients of SCTs from mismatched donors. In recipients of allogeneic SCTs and, especially, recipients of STCs from unrelated or related, mismatched donors, impaired immune function may diminish the containment of previous infection and the formation of granuloma, increasing the risks of primary and reactivation of infection and making the diagnosis of cases difficult when no mycobacteria are isolated. The modified host response may also explain some atypical clinical presentations and the occurrence of acute disseminated life-threatening forms. However, unlike other series [13], one-half of our patients who developed MBI had no GVHD. This suggests that the diagnosis should be considered in both patients with and patients without GVHD, but we did not have sufficient data to analyze the effect of GVHD on the incidence of MBI. Whether IFN-γ receptor deficiency, reported in its genetic form [27, 28], is a predisposing factor to MBI in the SCT population is unknown. It has been shown that non–T cell-depleted allogeneic bone marrow transplantation allows the transfer of PPD-reactive T cells from the donor to the recipient [29], but this transfer may fail [30]. Little is known, in fact, about the immune reconstitution to MBI after transplantation. However, one may assume that the reconstitution is not limited to the recovery of normal T cell functions, but involves more complex mechanisms, especially in cells from the monocytic lineage.

Transplantation centers should maintain a high level of suspicion for MBI during the first 4 months after transplantation, when mortality due to MBIs is at its peak. We also suggest that increased vigilance for SCT patients is warranted, because of the increasing number of patients receiving mismatched SCTs and the fact that many patients, including autologous SCT recipients, are already immunosuppressed before transplantation. Given the increase in stem cell transplantation programs in developing countries, we expect more cases to be reported in the next few years. Special attention should be paid to known previous MBI or exposure of the recipient to an infected person. Whether patients with previous successfully treated MBI should receive prophylaxis during and after transplantation, and for how long, cannot be determined from our data. We suggest that these patients should be closely monitored to identify early reactivation.

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References

1. Navari R, Sullivan K, Springmeyer S, et al. Mycobacterial infections in marrow transplant patients. Transplantation **1983**; 36:509–13.
2. Kurzrock R, Zander A, Vellekoop L, Kanojia M, Luna M, Dicke K. Mycobacterial pulmonary infections after allogeneic bone marrow transplantation. Am J Med **1984**; 77:35–40.
3. Gaviria JM, Garcia PJ, Garrido SM, et al. Nontuberculous mycobacterial infections in hematopoietic stem cell transplant recipients: characteristics of respiratory and catheter-related infections. Biol Blood Marrow Transplant **2000**; 6:361–9.
4. Weinstock DM, Feinstein MB, Sepkowitz KA, Jakubowski A. High rates of infection and colonization by nontuberculous mycobacteria after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant **2003**; 31:1015–21.
5. Agerton T, Valway S, Blinkhorn R, et al. Spread of strain W, a highly drug-resistant strain of *Mycobacterium tuberculosis,* across the United States. Clin Infect Dis **1999**; 29:85–92.
6. Salomon N, Perlman D. Editorial response: multidrug-resistant tuberculosis—globally with us for the long haul. Clin Infect Dis **1999**; 29:93–5.
7. Young L. Mycobacterial diseases and the compromised host. Clin Infect Dis **1993**; 17:S436–41.
8. Singh N, Paterson D. *Mycobacterium tuberculosis* infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis **1998**; 27:1266–77.
9. Toren A, Ackerstein A, Gazit D, et al. Oral tuberculosis following autologous bone marrow transplantation for Hodgkin's disease with interleukin-2 and alpha-interferon immunotherapy. Bone Marrow Transplant **1996**; 18:209–10.
10. Roy V, Weisdorf D. Typical and atypical *Mycobacterium.* In: Bowden R, Ljungman P, Paya C, eds. Transplant infections. Philadelphia: Lippincott-Raven, **1998**:195–201.
11. Keung Y, Nugent K, Jumper C, Cobos E. *Mycobacterium tuberculosis* infection masquerading as diffuse alveolar hemorrhage after autologous stem cell transplant. Bone Marrow Transplant **1999**; 23:737–8.
12. De La Camara R, Martino R, Granados E, et al. Tuberculosis after hematopoietic stem cell transplantation: incidence, clinical characteristics and outcome. Bone Marrow Transplant **2000**; 26:291–8.
13. Ku SC, Tang JL, Hsueh PR, Luh KT, Yu CJ, Yang PC. Pulmonary tuberculosis in allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant **2001**; 27:1293–7.
14. Arslan O, Gürman G, Dilek I, et al. Incidence of tuberculosis after bone marrow transplantation in as single centre from Turkey. Haematologia **1998**; 29:59–62.
15. Martino R, Martinez C, Brunet S, Sureda A, Lopez R, Domingo-Albos A. Tuberculosis in bone marrow transplant recipients: report of two cases and review of the literature. Bone Marrow Transplant **1996**; 18: 809–12.
16. Ward M, Lam K, Cannell P, Herrmann R. Mycobacterial central venous catheter tunnel infection: a difficult problem. Bone Marrow Transplant **1999**; 24:325–9.
17. Roy V, Weisdorf D. Mycobacterial infections following bone marrow transplantation: a 20 year retrospective review. Bone Marrow Transplant **1997**; 19:467–70.
18. Ip M, Yen K, Chiu E, Chan J, Lam W, Chan T. Pulmonary infections in bone marrow transplantation: the Hong Kong experience. Respiration **1995**; 62:80–3.
19. Hale YM, Pfyller GE, Salfinger M. Laboratory diagnosis of mycobacterial infections: new tools and lessons learned. Clin Infect Dis **2001**; 33:834–46.
20. Rieder HL, Watson JM, Raviglione MC, et al. Surveillance of tuberculosis in Europe. Working Group of the World Health Organization and the European Region of the International Union Against Tuberculosis and Lung Disease (IUATLD) for uniform reporting on tuberculosis cases. Eur Respir J **1996**; 9:1097–104.
21. Levendoglu-Tugal O, Munoz J, Brudnicki A, Fevzi Ozkaynak M, Sandoval C, Jayabose S. Infections due to nontuberculous mycobacteria in children with leukemia. Clin Infect Dis **1998**; 27:1227–30.
22. Straus W, Ostroff S, Jernigan D, et al. Clinical and epidemiological characteristics of *Mycobacterium haemophilum,* an emerging pathogen in immunocompromised patients. Ann Intern Med **1994**; 120:118–25.
23. Jacobson K, Teira R, Libshitz H, et al. *Mycobacterium kansasii* infections in patients with cancer. Clin Infect Dis **2000**; 30:965–9.
24. Lim K, Chong K. Multiple organ failure and septic shock in disseminated tuberculosis. Singapore Med J **1999**; 40:176–8.
25. Garyfallou GT. Mycobacterial sepsis following intravesical instillation of bacillus Calmette-Guérin [review]. Acad Emerg Med **1996**; 3:157–60.
26. Worku S, Hoft D. In vitro measurement of protective mycobacterial immunity: antigen-specific expansion of T cells capable of inhibiting intracellular growth of bacille Calmette-Guérin. Clin Infect Dis **2000**; 30(Suppl 3):S257–61.
27. Jouanguy E, Altare F, Lamhamedi S, et al. Interferon-γ–receptor deficiency in an infant with fatal bacille Calmette-Guérin infection. N Engl J Med **1996**; 335:1956–61.
28. Jouanguy E, Lamhamedi-Cherradi S, Lammas D, et al. A human IFNGR1 small deletion hotspot associated with dominant susceptibility to mycobacterial infection. Nat Genet **1999**; 21:370–8.
29. Rouleau M, Senik A, Leroy E, Vernant J. Long-term persistence of transferred PPD-reactive T cells after allogeneic bone marrow transplantation. Transplantation **1993**; 55:72–6.
30. Heyderman R, Morgan G, Levinski R, Strobel S. Successful bone marrow transplantation and treatment of BCG infection in two patients with severe combined immunodeficiency. Eur J Pediatr **1991**; 150: 477–80.