Incidence of Tuberculosis in Deceased-Organ Donors and Transmission Risk to Recipients in Spain

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Background. Globalization and migration patterns have increased the number of donors from countries with high incidence rates of tuberculosis (TB) in low incidence countries, with the subsequent increase in risk of TB transmission to the recipients.

Methods. Retrospective cohort study, including all actual deceased donors in Spanish hospitals between January 1998 and June 2011 and all the recipients who had received an organ from donors identified as TB cases.

Results. Six actual donors were identified as TB cases, representing an annual incidence of 30.6 cases/100,000 donors (95% CI, 4–58). Two cases did not become utilized donors, because TB was detected in the organ recovery and were therefore excluded. Annual incidence in utilized donors was 23 cases/100,000 donors (95% CI, 6–59). Annual incidence of the Spanish population in the same period was 17.5 cases/100,000 inhabitants (95% CI, 17–18). Annual incidence in actual donors belonging to the Romanian immigrant community was 2353 cases/100,000 donors (95% CI, 286–8242). Variations in the prophylactic strategy utilized in recipients were observed. TB was transmitted to three recipients (27.3% transmission), two of whom developed active TB.

Conclusions. Incidence of TB in actual donors is greater than that of the general population ($P<0.001$). The risk of immigrant communities should be grouped according to the real incidence in donors. Transmissibility of TB is high; therefore, transplant teams should be immediately informed when TB donor transmission is suspected to prevent TB in the recipient.

keywords: Tuberculosis, Solid-organ transplantation, Donor, Donor-transmitted.

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Annual incidence of tuberculosis (TB) in solid-organ transplant recipients in Spain (512 cases/10^5 transplants) is much higher than that of the general population and especially high in lung transplants (2072 cases/10^5 transplants) (*1*). TB most commonly appears due to reactivation of a latent infection; thus, correct pretransplantation screening of the recipient is fundamental to identify latent TB infection (LTI) and to be able to prescribe prophylactic treatment (*2, 3*). Infection may also be acquired de novo, after transplantation, or transmitted by the donated organ. Finally, it must not be forgotten that the chronic debilitating diseases motivating the transplant may predispose to this infection. Therefore, some candidates could already have TB when they receive the transplant, and it may appear in the immediate posttransplantation period (*4*).

Recent publications have highlighted an increase of donor-transmitted TB, as a result of changes in donor profile, due to globalization, increased travel, and new migratory patterns (*5–9*). It is becoming increasingly more frequent to find donors in countries with low incidence that were born or have lived for a long time in a country with high incidence. These changes precipitated a consensus document on recommendations for management of TB in organ donors (*10, 11*).

In recent years, Spain has not been an exception regarding these changes, with the population of those not born in Spain going from 5% in 1990 to 15% in 2011 (*12*). Incidence of TB in donors or its transmissibility is unknown in the present.

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TABLE 1. Incidence of TB in Spain in the general population and in the actual and utilized donors (1998–2011)

	General population			Actual donors			Utilized donors		
Year	TB cases	Population	Incidence[a] 100,000 inhabitants	TB cases	Actual donors	Incidence 100,000 donors	TB cases	Utilized donors	Incidence 100,000 donors
1998	9008	39,852,651	22.6	0	1241	0.0	0	1118	0.0
1999	8417	40,202,160	20.9	0	1291	0.0	0	1177	0.0
2000	7958	40,499,791	19.6	1	1307	76.5	0	1183	0.0
2001	7334	41,116,842	17.8	0	1335	0,0	0	1200	0.0
2002	7493	41,837,894	17.9	2	1409	141.9	1	1267	78.9
2003	7330	42,717,064	17.2	0	1443	0.0	0	1297	0.0
2004	6760	43,197,684	15.6	1	1495	66.9	1	1330	75.2
2005	6841	44,108,530	15.5	0	1546	0.0	0	1381	0.0
2006	6560	44,708,964	14.7	0	1509	0.0	0	1317	0.0
2007	8056	45,200,737	17.8	0	1550	0.0	0	1363	0.0
2008	8221	46,157,822	17.8	0	1577	0.0	0	1368	0.0
2009	7652	46,745,807	16.4	0	1606	0.0	0	1400	0.0
2010	7162	47,021,031	15.2	0	1502	0.0	0	1292	0.0
2011[a]	NA	NA	NA	2	807	247.8	2	695	287.8
Global	7599.4	43,335,921.3	17.5	0.4	1401.3	30.6	0.3	1242.0	23.0

[a] 2011 data refer to the January–June period. General population data are from National Statistics Institute (*10*), not available for first 2011 semester. NA, not available.

This study aimed to evaluate the incidence and characteristics of TB in deceased donors in Spain and its possible transmission to solid-organ recipients. The results obtained should provide information on the effectiveness of current recommendations on screening for TB in the donation process and may help to evaluate the need to implement additional measures.

RESULTS

Incidence and Characteristics of TB in Actual Donors

During the study period, 19,618 actual donors were registered, allowing transplantations for 45,373 recipients. Five donors fulfilled the previously described criteria of a TB case. Another TB donor case was included because criteria for donor-transmitted TB were met: it was an 11-month old donor with Dandy Walker syndrome, who died of cerebral infarction. TB was not suspected during the donation process and autopsy was not performed. A pediatric liver recipient without history or background of TB developed liver TB (*Mycobacterium tuberculosis* isolated in gastric fluid). A tuberculin skin test (TST)–negative recipient of a double kidney transplant from the same donor developed an LTI (TST positive after transplantation). These two facts, together with the fact that donor's parents belonged to the Romanian community (community with high incidence of TB), was consistent with a donor-transmitted TB (probable transmission according to Disease Transmission Advisory Committee criteria), which led us to consider this as a donor TB case. Therefore, six TB cases, in total, were considered for the calculation of incidence.

Table 1 shows the global and annual accumulated incidence in the Spanish general population and in actual and utilized donors. In actual donors, the annual incidence was 30.6 cases/10^5 donors (95% CI, 4–58). However, only four of the six donors were utilized, because two were excluded before performing any transplantation. Thus, the annual incidence in utilized donors was 23 cases/10^5 donors (95% CI, 6–59). Incidence for the Spanish population in the same period was 17.5 cases/10^5 population (95% CI, 17–18), significantly lower than incidence in donors ($P<0.001$ in both cases).

Table 2 shows the characteristics of the six actual donors with TB.

Case 1 was a 3-month-old girl who died as a result of hydrocephalia. Although hydrocephalia was diagnosed as secondary to a congenital malformation, the autopsy showed it was actually secondary to tuberculous meningitis, for which she had never received treatment.

Case 2 was a 44-year-old diabetic male who died due to cerebral anoxia secondary to cardiac arrest. The autopsy showed pulmonary miliary TB that had been overlooked in the chest X-ray. Unfortunately, it was not possible to obtain a radiograph for confirmation.

Donors 3 and 4 came from Romanian immigrant communities (2 of 6 [33.3%] of donor TB cases). Case 3 was a Romanian male who died from a stroke and for whom no autopsy was performed. He had been diagnosed with TB 10 years earlier. His family stated he had received adequate treatment and was asymptomatic. His chest X-ray was normal. Among different organs, his lungs were donated for a bipulmonary transplant. The polymerase chain reaction (PCR) of apical lung lesions of the donor was positive for *M. tuberculosis* (negative microscopy). Case 4 was an 11-month-old boy born in Spain of Rumanian parents, included because criteria for donor-transmitted TB were met. During the study period, there were 85 actual donors from the Romanian community. Thus, the annual incidence of TB in

TABLE 2. Characteristics of actual donors who had TB or who were considered index cases of TB transmitted by utilized donors in Spain (1998–2011)

Donor ID	Donor utilization	Cause of death	Age	Gender	Social risk factor	Background	Days ICU	Chest X-ray	TB in donor	
									Diagnosis	Type
1	Yes	Tuberculous meningitis	3 m	M	No	Hydrocephalus	9	Normal	Autopsy (histology)	Extrapulmonary (meningeal)
2	Yes	Cerebral anoxia	44 y	H	No	Diabetes	0	Without available information	Autopsy (histology)	Pulmonary (miliary)
3	Yes	Stroke	40 y	H	Immigrant from high TB incidence country	TB smoker	1	Normal	PCR pulmonary graft (microbiology)	Pulmonary
4	Yes	Stroke	11 m	H	Parents from high TB incidence country	Dandy Walker syndrome	14	Normal	Donor transmission criteria	Not proven
5	No	Stroke	64 y	M	No	Diabetes	1	Normal	Liver biopsy in recovery (histology)	Extrapulmonary (hepatic)
6	No	Stroke	48 y	M	No	Down's syndrome, hypothyroidism	2	Alveolar lobar consolidation	Biopsy—intestinal and of perinephritic lymph nodes (histology)	Disseminated

Case 4 was classified as TB case because probable TB donor transmission criteria were met: suspicion of TB transmission, diagnosis of active TB in one recipient, LTI in other previously negative recipient and being a donor belonging to a social risk group (Romanian immigrants). ICU, intensive care unit; m, months; y, years.

actual donors from this community was 2353 cases/10^5 actual donors, although a great variation was observed among the years studied, ranging from 0 to 25,000 (95% CI, 286–8242).

In two cases (cases 5 and 6), no organ was finally transplanted (nonutilized donors) because the biopsy of suspicious lesions (adenopathies) observed during organ recovery showed histology compatible with TB and stopped the donation process.

TB Transmitted by Utilized Donors

In this study, 11 different patients received an organ from donors classified as TB cases (Table 3). Two patients developed TB (pulmonary and hepatic) and one patient developed LTI (conversion of TST negative to TST positive); thus, the transmission rate in these recipients was 27.3% (3 of 11). Because only two cases developed active infection, the frequency of active TB transmitted by donors was 18.2% (2 of 11). Considering the three cases observed, the annual incidence of donor transmitted TB among the 45,373 transplants carried out in this period was 6.6/10^5, and it was 4.4/10^5 when only active infection was considered.

The two TB cases responded to the treatment prescribed. The liver transplanted patient developed hepatotoxicity, which was controlled after discontinuation of isoniazid and pyrazinamide. The LTI patient received isoniazid for 9 months and did not develop active TB.

In accordance with the recommendations established to avoid donor-transmitted infections, the centers were notified as soon as the donor TB was known. In donors 1 and 2, autopsy results were notified to transplant teams 2 and 4 days after transplantation respectively. In donor 3, the positive PCR result for *M. tuberculosis* was available on the sixth day after transplantation. In the last case, TB in the liver recipient was notified to the Organización Nacional de Trasplantes of Spain 2 months after transplantation, which led to the other transplant team affected (with a double kidney recipient) being informed immediately.

Six patients received only isoniazid, and in one case, the patient received treatment with three drugs. All treatments were prescribed immediately after the transplant team was informed of the donor TB, except one that was initiated when LTI in the recipient was diagnosed. Two patients did not undergo any treatment: one kidney recipient with a previous positive TST and one liver recipient without previous TST. None of these nine recipients developed active TB.

DISCUSSION

This is the first study on the incidence of TB in donors and its transmissibility in Spain. Following the guidelines of the Spanish Consensus Document (*13*), the annual incidence of TB in actual donors was approximately twice that observed in the general population (30.6 vs. 17.5 cases/10^5 donors). The higher incidence might be explained by the depth of the medical screening techniques performed in donors; much more thorough than in general population, detecting latent cases otherwise undetected. This study shows that monitoring for TB should continue in organ recovery by means of biopsy of any unusual lesion observed (especially adenopathies). These biopsies enabled us to reduce the annual incidence of TB in utilized donors, that is, in those from whom an organ

TABLE 3. TB transmitted by utilized donors in Spain (1998–2011): characteristics and clinical management of the organ recipients from case-index donors

Donor ID	Graft	Age	Previous TST	Prophylaxis/treatment drug (start after Tx, duration)	TB/LTI (time Tx- diagnosis)	Time follow-up (months)	Patient status	Graft status
1	Double kidney	54	Not performed	H (2 d-6 m)	No	114	Alive	Functioning
	Liver	2	Not performed	No	No	115	Alive	Functioning
2	Right kidney	42	Not performed	H (3 d-3 m)	No	89	Alive	Explant +3 d (not related with TB); retransplant 4 y+3.5 y functioning
	Left Kidney	56	Not performed	H-E-Le (1 d-9 m)	No	82	Alive	Explant +18 m (not related with TB; retransplant 4 y+1 y functioning
3	Right kidney	46	Positive	No	No	15	Alive	Functioning
	Pancreas/left kidney	36	Negative	H (7 d-3 m)	No	3	Exitus (abdominal sepsis)	Not applicable
	Liver	62	Negative	H (7 d-2 m[a])	No	14	Alive	Functioning
	Heart	46	Not performed	H (7 d-12 m)	No	12	Alive	Functioning
	Double lung	59	Negative	H-E-M-Z (7 d-18 m)	Pulmonary TB (6 d)	14	Alive	Functioning
4	Double kidney	49	Negative	H (7 m-9 m)	LTI (TST positive) (3 m)	12	Alive	Functioning
	Liver	4	Not performed	H-E-Z-Le (2 m-1 m), E-Le-Li (3 m-14 m)	Liver TB (2 m)	17	Alive	Functioning

[a] Withdrawal due to suspicion of neurotoxicity then clinical follow-up afterwards.

d, days; E; ethambutol; H; isoniazid; Le; levofloxacin; Li; linezolid, m, months; M; moxifloxacin; T, time; Z; pyrazinamide.

was implanted (23 cases/10^5 donors); therefore, we deduce the usefulness of this screening procedure.

To evaluate if the screening procedure can be improved, it is essential to analyze the cases that went undetected. In this study, two thirds of the cases were Spanish native donors with TB, who were incorrectly diagnosed, in spite of the recommended screening procedures and were finally utilized. This shows the difficulties found in the diagnosis of this infection, especially in cases of disseminated TB, meningoencephalitis, or pulmonary miliary TB. This problem has already been ascertained by other authors (*5, 6, 8*), when cultures taken from the donors only turned positive, after transplantation had already been performed. This should alert countries with low incidence rates to increase their level of suspicion for high-risk donors (immigrants from high incidence zones, impoverished persons, prisoners, diabetics, alcoholics, etc.).

Notably in this study, one third of the cases of TB in actual donors (50% in the utilized donors) were from the Romanian immigrant community; hence, they might be considered high-risk donors. The percentage of Romanians in donors is lower than their percentage in global Spanish population (0.43 vs. 0.77 on average over the time period); therefore, this does not explain the higher TB incidence in donors. In the Morris Consensus Report, Romania was already considered a country having a high incidence of TB (*10*). In our study, the annual incidence of TB in actual donors of this community was 2353 cases/10^5. However, we have not found this problem in donors from other larger immigrant communities from countries with high TB incidence rates, such as those from Latin America. We cannot rule out the existence of a relationship with the level of integration and living conditions of each community. Countries having middle/low incidence should group the risk of their donors, according to the real incidence data for each immigrant community, individualizing screening procedures, based on the potential risk of these groups.

Recent introduction of the interferon-γ release assays (IGRA) for diagnosis of LTI should make us raise the question of its usefulness in the donation process to reduce the risk of donor transmission (*14*). Nevertheless, IGRA testing has not yet been validated in deceased donors and has not been tested in this setting. It is extremely likely that IGRA results will be confounded by many false-positives and false-negatives in this population (*14–16*). The utility of IGRA testing, as well as PCR techniques, for high-risk donors is an area for further investigation (*17*).

When a donor has TB, the possibility of transmitting the infection is high (27.2%). In our study, 25.0% of the utilized donors with TB (1 of 4) had a history of having suffered the disease in the past. The current recommendation is to offer treatment (triple therapy) to all recipients when donor transmitted TB is suspected (*10*). Nevertheless, only 3 of the 11 recipients in this study received triple therapy (two were TB confirmed recipients). Six recipients received only isoniazid and the two remaining received no treatment/prophylaxis, although all had been informed of the risk of transmission. This could open the discussion on which is the most adequate option to prevent TB in the recipient, because TB treatment is not free of adverse reactions and/or interactions with immunosuppressive drugs used in recipients.

The need to perform TST in all transplant candidates must be emphasized, with prophylaxis in TST-positive lung recipients being strongly recommended (*2*). However, in this series, only 45.4% of the recipients had a TST, confirming previous results observed in Spain (*1, 18*). We cannot consider that excellence consists only in implementing new diagnostic tools, when we do not perform to perfection in daily practice (TST).

In conclusion, the annual incidence of TB in actual donors is high in spite of existing screening; however, it can be reduced if any macroscopic lesion compatible with TB observed in the donor during recovery is biopsied. The risk of donors should be grouped according to the incidence of each immigrant community in addition to that of their country of origin. Transmission to the recipient is frequent (27.2% in our study) when there is a donor with TB. Thus, any suspicion should be reported immediately to the recipient medical team to prevent TB transmission. The variation of treatment observed reflects both an opportunity to study the optimal prophylactic strategy (and even the question of whether prophylaxis was warranted in the first place) and the need to better educate the community.

MATERIALS AND METHODS

Design

This was a retrospective cohort study that included all the actual donors (donors from whom at least one organ was recovered) in the Spanish hospitals between January 1998 and June 2011 inclusive and all the recipients who had received an organ from donors identified as cases of TB.

Definition of Cases of TB and Donor-Transmitted TB

Grupo de Estudio Infecciones en Trasplantados/Red Española de Investigación en Patología Infecciosas consensus-based definitions were used to define cases of TB (*2*). It was considered that a donor/recipient suffered TB when *M. tuberculosis* was isolated from a culture or the DNA of *M. tuberculosis* was isolated through PCR in a representative clinical sample, organ fluid, or tissue. Cases with microscopic or histopathology demonstration were also accepted. TB was classified as pulmonary (involvement of pulmonary parenchyma), extrapulmonary (involvement of other organs), or disseminated (involvement of at least two noncontiguous organs). Cases diagnosed by clinical or radiologic suspicion—in which the corresponding physician prescribed a specific treatment—were not accepted in the present research.

The criteria used to define donor-transmitted TB followed the general criteria of definition of diseases transmitted by transplanted organs established by the Organ Procurement and Transmission Network ad hoc Disease Transmission Advisory Committee (*6, 10*). A case of donor-transmitted TB was defined as when the infection had been demonstrated in the donor and in more than one recipient with a negative TST (proven transmission). If TB infection is evidenced in a single recipient, to consider transmission, there must be suspicion of transmission through transplantation and at least one previous negative TST, or demonstration of infection in the donor, or the existence of other data that strongly suggest but do not prove, that a transmission has occurred (probable or possible transmission).

Identification of the Cases of TB

Donors with suspicion of TB were identified from the information contained in the donation and transplantation activity registry of the Spanish National Organ Procurement Organization (Organización Nacional de Trasplantes). All notifications from transplant teams when donor TB transmission was suspected were also reviewed.

The clinical history and microbiological and pathology studies of the donors identified as possible cases were reviewed, with the collaboration of the transplant coordinators of each center. Donors were considered cases

when TB case definition was met and also in those cases of donor-transmitted TB (proven, probable, or possible), even if TB case definition was not fulfilled.

Similarly, all patients who had received an organ from a donor confirmed as case were reviewed. Recipients also had to meet the criteria of TB case to be considered as such.

Procedure for TB Screening in Donors and Recommendations for Prevention of Donor-Transmitted TB in Recipients

TB screening procedure in organ donors is described on the consensus national document of general recommendations for screening criteria of the organ donor, regarding transmission of infections (*13*), which includes specific recommendations for TB. The recommendations include a detailed clinical history of the donor (TST results in the past, previous exposure to TB, background of active TB, and prophylaxis or treatment received), physical examination, review of the microbiological studies available, and chest X-ray. It is also recommended to consider performing autopsy of the donor to rule out hidden infections that could be treated in the recipient. This consensus document considers the following contraindications for organ donation related to TB: (a) death due to disseminated TB or tuberculous meningitis; (b) active pulmonary TB discards lung donation, but other organs may be evaluated when there is evidence of at least 3 months of adequate TB treatment; and (c) use of lungs when there is evidence of residual pulmonary lesions.

The transplant team is immediately notified of any information regarding TB in the donor as part of the donation process. This permits transplant programs to evaluate the suitability of the donor and allows them to carry out the appropriate preventive measures.

Variables Analyzed

The following variables were gathered from donors: cause of death, age, gender, nationality of origin, social risk factors (indigent, previous or current imprisonment, and alcoholism), smoking habit, diabetes mellitus, days of stay in intensive care unit, comorbidities, previous TB exposure, method of diagnosis of TB (histology and microbiology), and type of TB (pulmonary, extrapulmonary, and disseminated). In recipients, the following were collected: organ transplanted, age, pretransplantation TST, studies performed to rule out TB, treatment or prophylaxis used, follow-up time, and status of the patient (alive/dead) and of the graft (functioning/nonfunctioning) at the time of data collection.

Statistical Analysis

A descriptive analysis was made of the cases. Annual accumulated incidence was calculated in the actual donors and in the utilized donors (those in whom at least one organ had been transplanted). To do so, the average of the annual cases of TB in actual/utilized donors was divided by the average of the actual and utilized donors, respectively, in the analyzed years (1998–2011), expressed in cases/10^5. These calculated incidences were compared with that of the Spanish general population using the comparison test for proportions. Data for Spanish general population were obtained from the Instituto Nacional de Estadística (National Institute of Statistics) (*12*), giving preference to the use of data provided by the Centro Nacional de Epidemiología (National Center of Epidemiology), when available, for the cases of TB (*19*). Incidence of TB transmitted by donors to organ recipients was calculated with the same method: average of annual cases of recipients with transmitted TB divided by the annual average of transplants performed during the study period.

Institutional Review Board

This study was approved by the Research Ethics Committee of Córdoba, University Hospital Reina Sofía (Register CEI 2069).

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