The potential liver donor with tuberculosis: A fresh look at international recommendations based on a survey of practice in Indian liver transplant centres

SANJAY GOVIL, SANDEEP SATSANGI, JAYANTH REDDY, SURESH RAGHAVAIAH, SUBRAMANIAN SWAMINATHAN

ABSTRACT

Background. The western recommendations for the use of organs from liver donors with tuberculosis (TB) come from an environment where the burden of disease is low and cadaveric organ donation rates are high—in complete contrast to the Indian scenario, where these recommendations may be too restrictive.

Methods. A questionnaire relating to current practice on the use of organs from liver donors with TB was sent to all liver transplant centres in India.

Results. Responses were obtained from 94% of centres. Two-thirds accepted organs from deceased donors with TB in the elective setting, especially for recipients with a high MELD (Model for end-stage liver disease) score. The proportion rose by 1.5 times in the setting of acute liver failure. Two-thirds advised anti-TB treatment (ATT) for corresponding recipients, and the remaining advised isonicotinic acid hydrazide (INH) prophylaxis. Untreated living donors with TB were not accepted. Half the respondents accepted living donors after completion of ATT, and did not treat recipients postoperatively. The remainder accepted them after 8 weeks of treatment and advised INH prophylaxis or ATT for recipients.

Conclusions. That this practice has not impacted recipient outcomes suggests that the guidelines for management of liver donors and recipients may need to be altered for populations endemic for TB.

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INTRODUCTION

Liver transplant recipients (LTRs) are at increased risk of developing tuberculosis (TB) compared to the general population.[1–5] Although mainly due to reactivation or *de novo* infection,[1,5] it is estimated that 4% of TB in LTR is donor-driven.[3,5] Most patients are diagnosed within 6 months of transplant.[1] The symptoms of post-transplant TB are often atypical, diagnosis is often delayed and the risk of disseminated or extrapulmonary disease is high, resulting in high disease-associated mortality.[1–6] Treatment with anti-TB medication may be prolonged and associated with adverse drug reactions.[7,8]

The approach to the organ donor with TB in western countries is determined in the setting of low disease burden and high cadaveric organ donation rates.[1,5,9–11] Europe, North America and Australia together host approximately 6% of the worlds burden of TB.[12] Organ donation rates in these countries range from 6 to 47 per million population.[13] In this context, the recommendation to decline organs from donors with inadequately treated TB seems appropriate.

In contrast, India hosts 27% of the approximately 10 million individuals in the world with TB.[12] Approximately 3% of these patients have multidrug-resistant TB.[14] The organ donation rate in India is only 0.3 per million population and liver transplant programmes are largely living donor-based.[15] Tuberculin skin tests or interferon gamma release assay to diagnose latent TB infections are of dubious value in this clinical scenario and are not routinely performed on either organ donors or recipients in India.[16] Nor is prophylaxis with isonicotinic acid hydrazide (INH) commonly used for LTR.[16] This scenario may be common to other low infrastructure countries in which liver transplant programmes are likely to develop in the next decade. Are the recommendations from western expert consensus statements applicable, or should they be modified to suit the different environment?

We have attempted to determine the current practice in liver transplant centres in India and compared this to international recommendations.

METHODS

A list of all recognized liver transplant centres in India were obtained from the website of Multi-Organ Harvesting Aid Network Foundation.[17] Centres at which a visiting transplant team from a larger centre performed the liver transplant were excluded from the study, as were centres where the programme had been discontinued. A questionnaire (Tables Ia and b) was sent to the lead surgeon or hepatologist at each active and independent liver transplant centre through email. The answers to the questions were collated and analysed. The following definitions were used:

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TABLE Ia. Questionnaire sent to each liver transplant centre for deceased donor liver transplantation

1. Would you accept an untreated deceased donor for your liver transplant recipient in the following clinical scenario?

TB status	Chronic liver disease	Acute liver failure	Acute-on-chronic liver failure
Pulmonary TB AFB+	Yes/no	Yes/no	Yes/no
Pulmonary TB AFB–	Yes/no	Yes/no	Yes/no
Cervical LN TB	Yes/no	Yes/no	Yes/no
Abdominal TB	Yes/no	Yes/no	Yes/no
Disseminated TB	Yes/no	Yes/no	Yes/no

2. Does the MELD score influence your decision in patients with chronic liver disease? If so, please state the MELD score above which you would accept the donor.

3. If the answer to any part of question 1 is yes, please choose which of the following treatments you would use for the recipient postoperatively.

TB status	Modified ATT	INH prophylaxis	Observation
Pulmonary TB AFB+	Yes/no	Yes/no	Yes/no
Pulmonary TB AFB–	Yes/no	Yes/no	Yes/no
Cervical LN TB	Yes/no	Yes/no	Yes/no
Abdominal TB	Yes/no	Yes/no	Yes/no
Disseminated TB	Yes/no	Yes/no	Yes/no

4. If your answer to Question 3 is 'Modified ATT', when would you initiate treatment?

a. Once postoperative transaminases normalized
b. Immediately postoperatively
c. Other

TB tuberculosis AFB acid-fast bacillus LN lymph node MELD model for end-stage liver disease ATT antituberculosis therapy INH isonicotinic acid hydrazide

TABLE Ib. Questionnaire sent to each liver transplant centre for living donor liver transplantation

1. If no alternative donor was available, would you accept an untreated living donor for your liver transplant recipient in the following clinical scenario?

TB status	Chronic liver disease	Acute liver failure	Acute-on-chronic liver failure
Pulmonary TB AFB+	Yes/no	Yes/no	Yes/no
Pulmonary TB AFB–	Yes/no	Yes/no	Yes/no
Cervical LN TB	Yes/no	Yes/no	Yes/no
Abdominal TB	Yes/no	Yes/no	Yes/no
Disseminated TB	Yes/no	Yes/no	Yes/no

2. Does the MELD score influence your decision in patients with chronic liver disease? If so, please state the MELD score above which you would accept the donor.

3. If the recipient condition permits, what is the minimum condition you would accept before proceeding with donor hepatectomy?

a. Completion of the intensive phase of ATT
b. After obtaining AFB culture/sensitivity report
c. Completion of full course of ATT

4. If the answer to any part of question 1 is yes, please choose which of the following treatments you would use for the recipient postoperatively.

TB status	Modified ATT	INH prophylaxis	Observation
Pulmonary TB AFB+	Yes/no	Yes/no	Yes/no
Pulmonary TB AFB–	Yes/no	Yes/no	Yes/no
Cervical LN TB	Yes/no	Yes/no	Yes/no
Abdominal TB	Yes/no	Yes/no	Yes/no
Disseminated TB	Yes/no	Yes/no	Yes/no

5. If your answer to question 4 is 'modified ATT', when would you initiate treatment?

a. Once postoperative transaminases normalized
b. Immediately postoperatively
c. Other

TB tuberculosis AFB acid-fast bacillus LN lymph node MELD model for end-stage liver disease ATT antituberculosis therapy INH isonicotinic acid hydrazide

Sputum-positive pulmonary TB. Acid-fast bacilli seen on either a tracheal aspirate or broncho-alveolar lavage specimen.

Sputum-negative pulmonary TB. Radiological abnormality on chest X-ray or computed tomography scan highly suspicious for TB but acid-fast bacilli not seen on tracheal aspirate or bronchoalveolar lavage specimen.

Lymph node TB. Cervical lymph node or cold abscess confirmed to be TB on the evaluation of aspirated pus or on biopsy.

Abdominal TB. Ileocaecal, ileal or peritoneal TB confirmed on histology.

Disseminated TB. Tuberculous infection diagnosed by radiology and/or microbiology and pathology at two or more non-contiguous sites.

RESULTS

Of the 113 centres across India certified to perform liver transplantation, 52 had active, independent liver transplant programmes. Responses were obtained from 49 (94%) of these centres. Sixteen (30%) centres performed more than 50 liver transplants annually. The three non-responders were low-volume centres.

Deceased donors

Many responders would accept organs from deceased donors with untreated TB. This ranged from 7 (14.3%) for donors with disseminated TB to 31 (63.3%) for those with cervical lymphadenopathy/cold abscess for recipients with decompensated chronic liver disease. Fifty-five per cent respondents accepted such donors only for recipients with MELD (model for end-stage liver disease) scores above 25. The proportion increased by a factor of 1.25 (range 1.15–1.35) for recipients with acute-on-chronic liver failure and 1.5 (range 1.3–1.7) for those with acute liver failure.

Two-thirds of respondents treated recipients of organs from deceased donors with untreated TB with antitubercular therapy (ATT). Most started ATT after postoperative transaminases had normalized. Three respondents started treatment with ethambutol and levofloxacin immediately postoperatively and added other drugs after transaminases returned to normal. Nearly all the remaining one-third responders gave recipients of these organs INH prophylaxis. A small minority (3%–5%) preferred to observe recipients and start ATT once the disease became clinically apparent (Fig. 1a-c).

Living donors

Very few centres would accept organs from untreated living donors with TB irrespective of the recipients' condition. Cervical lymph node TB was an exception with 7 (14.3%) and 12 (24.5%) respondents willing to accept them in the elective and acute liver failure scenario, respectively. There were varying opinions regarding how best to treat LTR from living donors with untreated TB, with the consensus being approximately two-thirds to one-third in favour of ATT as against INH prophylaxis.

Respondents were approximately equally divided between those who would accept living donors upon completion of the intensive phase of ATT versus a full course of ATT. Among the former, 25%, 33% and 42% advised INH prophylaxis, ATT and observation for recipients from these donors, respectively. No treatment was advised by any of the respondents for recipients of organs from donors who had completed a full course of ATT (Fig. 2a-c).

DISCUSSION

Strict restrictions are put on the use of potential organ donors with TB in western countries where the burden of TB is low and the cadaveric organ donation rate high[1,5,9–13] translating to a low incidence of donor-derived TB.[5] In contrast, TB is highly prevalent in India[12] while cadaveric organ donation rates remain

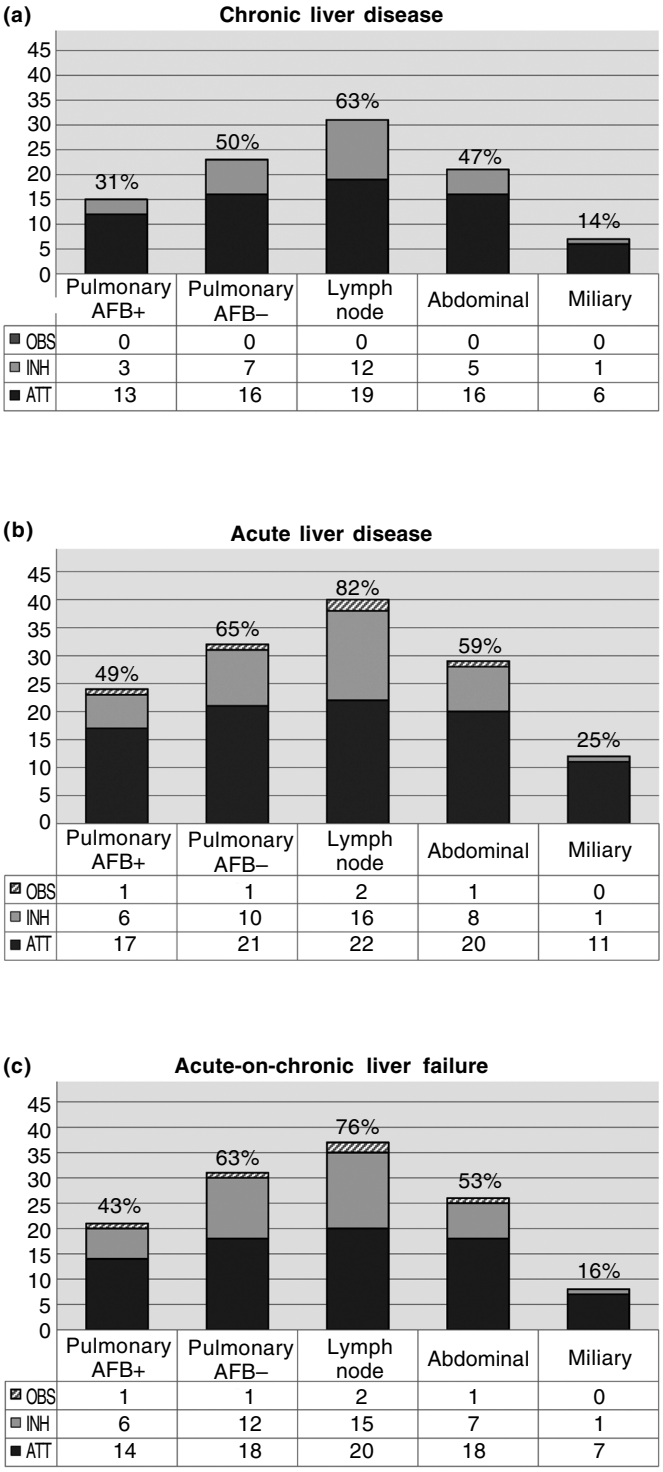
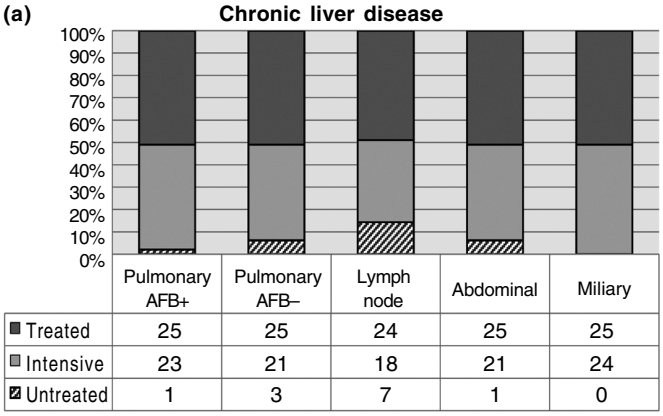
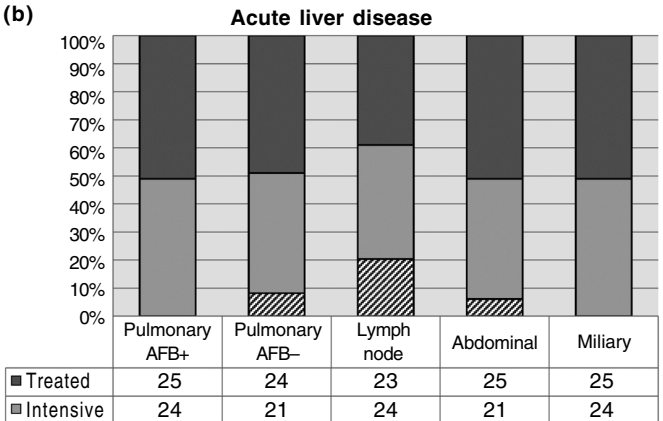


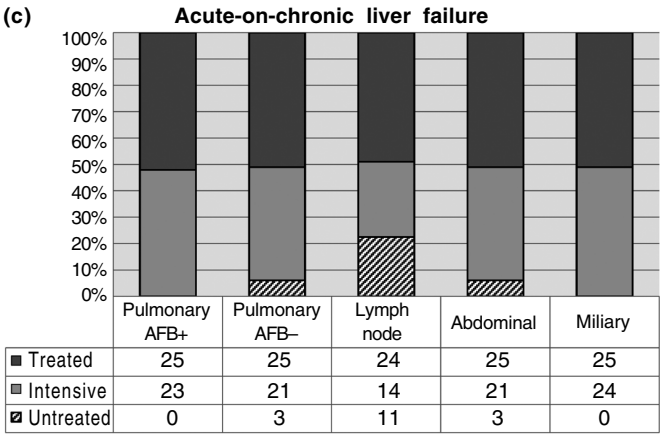
FIG 1. Liver transplant centre acceptance for deceased donors with tuberculosis (TB): (a) recipient with decompensated chronic liver disease; (b) recipient with acute liver failure; (c) recipient with acute-on-chronic liver failure. Horizontal axis (left to right): Deceased donors with sputum +ve pulmonary TB, sputum –ve pulmonary TB, lymph node TB, abdominal TB and miliary TB. Vertical axis: Number of transplant centre respondents (total=49). Bar height: Number and percentage acceptance by transplant centre respondents for deceased donors with TB. Bar colour: Proportion of transplant centres recommending observation (OBS), INH prophylaxis (INH) or anti-TB treatment for recipients following deceased donor liver transplantation from donors with TB



	Pulmonary AFB+	Pulmonary AFB–	Lymph node	Abdominal	Miliary
Treated	25	25	24	25	25
Intensive	23	21	18	21	24
Untreated	1	3	7	1	0



	Pulmonary AFB+	Pulmonary AFB–	Lymph node	Abdominal	Miliary
Treated	25	24	23	25	25
Intensive	24	21	24	21	24
Untreated	0	4	12	3	0



	Pulmonary AFB+	Pulmonary AFB–	Lymph node	Abdominal	Miliary
Treated	25	25	24	25	25
Intensive	23	21	14	21	24
Untreated	0	3	11	3	0

FIG 2. Liver transplant centre acceptance for living donors with tuberculosis (TB): (a) recipient with decompensated chronic liver disease; (b) recipient with acute liver failure; (c) recipient with acute-on-chronic liver failure. Horizontal axis (left to right): Deceased donors with sputum +ve pulmonary TB, sputum –ve pulmonary TB, lymph node TB, abdominal TB and miliary TB. Bar colour: Proportion of transplant centres accepting only fully treated living donors, living donors on completion of the 2-month intensive phase of treatment (Intensive) or untreated donors (Untreated)

low.[13] Adoption of western recommendations may limit availability of organs further. The Indian liver transplant community has responded by relaxing selection criteria for potential organ donors with TB. This survey shows that up to 80% of liver transplant centres would accept deceased donors, and surprisingly 15% would accept living donors with TB in selected LTR.

It is unclear whether this policy is acceptable. Three Indian reports suggest the incidence of new-onset TB after liver transplant between 0.5% and 2.3%[6,18] (Subramanaian S, personal communication; Table II). About 30%–80% of these patients presented with disseminated or extrapulmonary TB and 40% died from TB-related complications.[6,18] These results are similar to the western reports with respect to incidence, disease presentation and mortality, despite the different approach to donor selection. Varghese *et al*.[19] report an incidence of TB of 9% among 67 LTRs but include patients diagnosed during transplant evaluation. Earlier reports in Indian live donor kidney transplant recipients placed the risk of TB at 13%.[20] This has not been noted in LTRs perhaps because of the lower doses of immunosuppression used. Only Bhangui *et al*. report the incidence of TB in potential living donors[18] (Table II).

Consensus conference reports and national guidelines from the West strongly advise against accepting organs from donors with untreated or partially treated TB except in dire circumstances[1,5,9–11] (Table III). One could argue that patients with high MELD scores or acute liver failure might constitute 'dire circumstances' in an Indian environment. However, they also recommend that should such an organ be accepted, the recipient receive ATT postoperatively.[1,5,9–11] Two-thirds of centres in India recommend ATT as per these international guidelines. Most of the remaining third advised INH prophylaxis to avoid the 19%–23% risk of acute rejection reported with rifampicin/rifabutin.[7] The risk of hepatotoxicity does not differ significantly between modified ATT (7%–8%) and INH prophylaxis (6%),[7] and the use of this agent in the background of increasing multidrug-resistant TB in India is questionable. There is ample literature showing the safety of ATT, as well as its efficacy in treating TB in LTRs undergoing LT for ATT-induced liver injury.[8] Although the risk of transmission of TB is likely to be prohibitively high in donors with abdominal or miliary TB, transmission from isolated pulmonary or cervical lymph node TB, remote from the liver may not be. INH prophylaxis may be unnecessary in the latter situation, if biopsy of the graft and hilar lymph nodes do not show granulomas.

The use of living donors with untreated or partially treated TB is controversial, and is not recommended in any consensus statement,[1,5,9–11] and should be actively discouraged (Table III). Although very few centres stated that they would accept such donors, approximately half accepted them after completion of the intensive phase of ATT. Concerns with this strategy, although unproven, include the potential risk to the donor from restarting ATT on a regenerating liver, the consequences of interruption of ATT during the immediate postoperative period in partially treated donors,[21] and the possibility of transmitting multidrug-resistant TB which constitutes 3% of all cases in India.[14] Living donors and their recipients ought not to be subjected to these risks.

Nunn *et al*.[22] in a review of 15 trials of short-course chemotherapy for TB in Africa and Asia determined that 78% of 574 relapses occurred within 6 months and 91% within 12 months of completion of treatment, respectively, usually at the

TABLE II. Indian data on tuberculosis in liver transplant recipients and donors

Author	Study population	Time of diagnosis of TB		
		Pre-operative (%)	Intra-operative (%)	Post-operative (%)
Bhangui *et al.* (2011)[18]	682 LDLT recipients	18 (2.6)	5 (0.7)	4 (0.6)
	682 living donors*	4	1	na
Olithselvan *et al.* (2014)[6]	141 LDLT recipients	ns	ns	3 (2.1)
	73 DDLT recipients			2 (2.7)
Subramanian *et al.* (2013)[11]	1200 recipients (LDLT+DDLT)	28 (2.3)	8 (0.66)	6 (0.5)

*An additional 6 donors gave a history of treatment for TB in the past na not applicable ns not stated TB tuberculosis
LDLT living donor liver transplantation DDLT deceased donor liver transplantation

TABLE III. Summary of international recommendations for the use of organs from potential donors with tuberculosis and our suggestions based on the survey results

Donor	Treatment for recipient	
	International	Suggested
Deceased donor liver transplantation		
Full treatment for TB >2 years distant	Accept; no treatment	Accept; no treatment
Full treatment for TB <2 years distant	Accept	Accept
Remote organ	INH prophylaxis	No treatment
Same organ	INH prophylaxis	No treatment
Untreated/incomplete TB	Reject	Accept
Remote organ	ATT	ATT
Same organ/DISS/GRANUL	ATT	ATT
Living donor liver transplantation		
Full treatment >2 years distant	Accept; no treatment	Accept; no treatment
Full treatment <2 years distant	Accept	Accept
Remote organ	INH prophylaxis	No treatment
Same organ	INH prophylaxis	No treatment
Partial treatment	Reject	Reject; accept in exceptional circumstances only
Remote organ	ATT	ATT
Same organ	ATT	ATT
Untreated	Reject	Reject

INH isoniazid TB tuberculosis ATT anti-TB therapy

site of the initial infection. Their report[22] forms the basis of international recommendations that recipients of organs from donors completing ATT within the past 2 years receive INH prophylaxis. However, whether liver transplantation constitutes a significant risk for donor-derived TB when the initial TB infection occurred in a remote organ is unclear. No Indian centre recommended INH prophylaxis in LTRs from donors who had completed 6 months of ATT.

This study has a number of deficiencies. The impact of this relaxed policy for donor selection cannot be determined without clear knowledge of the number of potential donors with active TB and the number of recipients with donor-derived TB. One centre stated that they had not been faced with the clinical situations outlined in the questionnaire. They felt it was not possible to adequately assess the deceased donor for TB prior to harvest. The risk of transmission of TB to medical personnel when donors with open pulmonary TB are accepted for organ harvest exists and is unknown. Finally, this is an assessment of current practice rather than correct practice and highlights the need for the Indian transplant community to evaluate outcomes in light of the policy in use at their centre.

In conclusion, this survey shows that most transplant centres in India would accept untreated deceased donors with TB, nearly half would accept living donors with TB after completion of the intensive phase of ATT for high-risk LTRs in the absence of an alternative. Post-transplant treatment for recipients of organs from such donors is often inadequate according to the international recommendations. However, this strategy does not appear to negatively impact LTR according to the available Indian literature. We have suggested alternative recommendations for an Indian scenario (Table III).

Conflicts of interest. None declared

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I, Dr PEUSH SAHNI, hereby declare that the particulars given abovc are true to the best of my knowledge and belief

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Signature of publisher