Prevention and Management of Tuberculosis in Solid Organ Transplant Recipients

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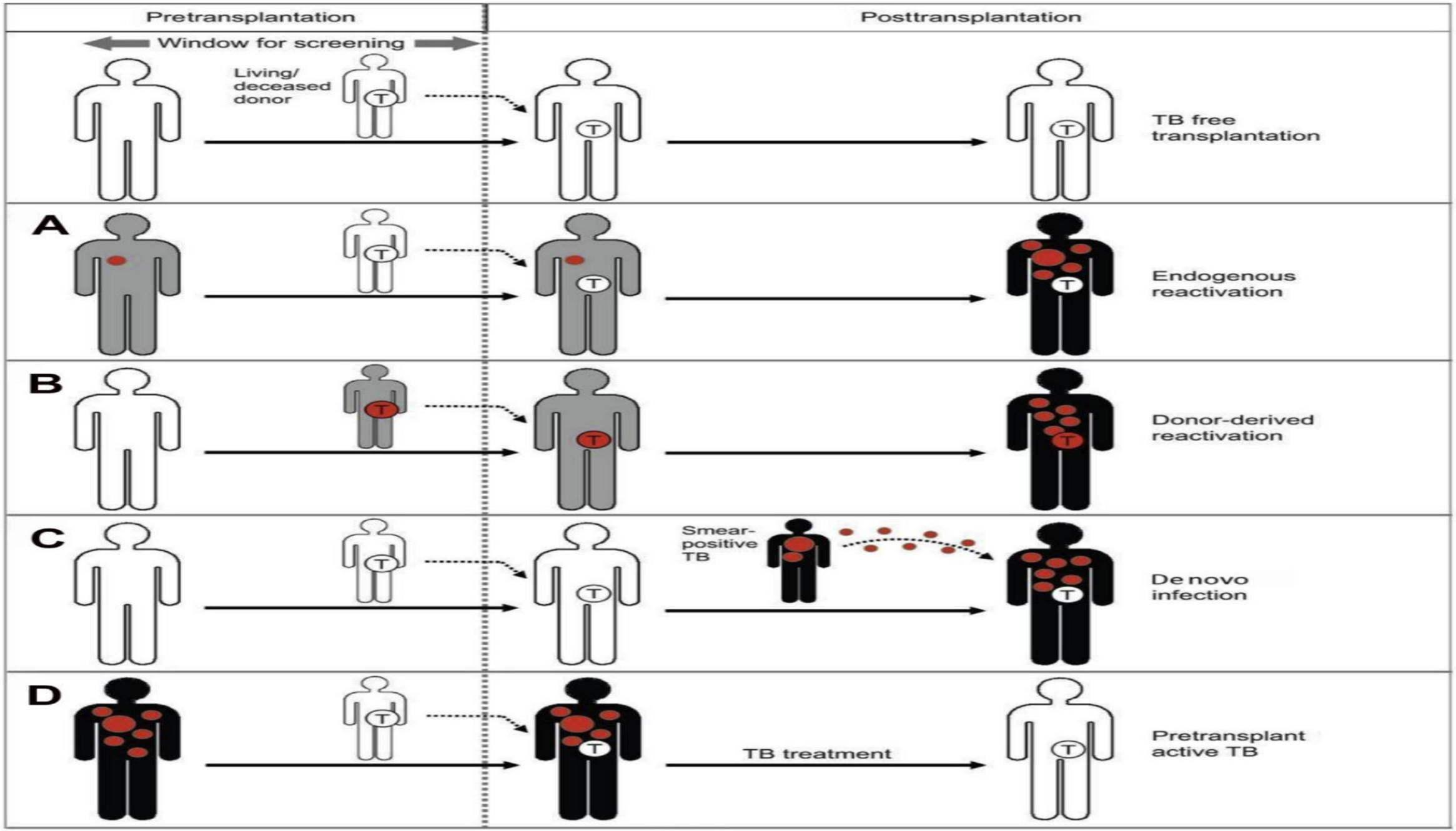

Pretransplantation
Posttransplantation
Window for screening
Living/
deceased
donor
T
TB free
transplantation
A
Endogenous
reactivation
B
Donor-derived
reactivation
C
Smear-
positive
TB
De novo
infection
D
TB treatment
Pretransplant
active TB
Latent infection with M tuberculosis
Active TB
T Transplanted graft

TIME OF ONSET

- **About 45-60% of TB occurs in the first year after transplantation.**
- **The median time for onset at nine months post transplantation.**
- **Median onset to be 26 months for those who received azathioprine and prednisolone as immunosuppression and 11 months for those who received cyclosporine along with other immunosuppressive agents.**

- **An earlier occurrence was noted with non-renal solid organ transplantation:**

- **Cyclosporine.**
- **Anti CD3 therapy**
- **Malnutrition**
- **Secondary to prolonged dialysis**
- **Exposure to the organism in hospital setting.**
- **Immunosuppression with tacrolimus or mycophenolate**

RISK FACTORS FOR POST TRANSPLANT TUBERCULOSIS

- **Chronic liver disease (2 times)**
- **Coexisting infections, particularly deep mycoses, Pneumocystis pneumonia and Nocardia (1.6 times)**
- **OKT3 (1.8 times)**
- **CMV infections (2.25 times).**
- **Cyclosporine use**

CLINICAL MANIFESTATIONS

- **Pulmonary tuberculosis**
- **Extra-pulmonary tuberculosis**
- **Allograft tuberculosis**

TREATMENT OF ACTIVE TB

- **First-line therapy for transplant patients with active TB disease is the same as for immunocompetent and other hosts (strong, high)**
- **Daily dosing of active TB therapy is recommended as opposed to twice- or thrice-weekly dosing (strong, moderate)**
- **Treatment duration for uncomplicated pulmonary TB is at least 6 months, but longer for cavitary disease or disease with persistent sputum culture-positive status after 2 months of therapy**

TREATMENT OF ACTIVE TB

- **Treatment duration for bone and joint disease (6-9 months) (strong, high)**
- **central nervous system disease (9-12 months) (strong).**
- **Severe disseminated disease (6-9 months) (strong, moderate)**

TREATMENT OF ACTIVE TB

- **Longer treatment courses are recommended if second-line drugs are used or if there is resistance to rifampin ± other drugs (weak, moderate).**

- **Treatment durations of TB after SOT reported in the literature range between 7.3 and 18 months.**

- **Rifamycin is strongly recommended in the initial drug regimen, but rifabutin is typically substituted for rifampin (strong, high).**

TREATMENT OF ACTIVE TB

- **Rifampin is a potent inducer of the microsomal enzymes (P450-3A4) that metabolize calcineurin inhibitors and mTOR inhibitors and may also interfere with corticosteroid metabolism.**

- **Successful use of rifampin has been reported in transplant recipients, but doses of cyclosporine, tacrolimus, and sirolimus will have to be increased at least two- to fivefold**

TREATMENT OF ACTIVE TB

- **Second-line therapy for TB has not been systematically studied in transplant recipients although case reports are available where moxifloxacin, cycloserine, and capreomycin have been successfully used.**
- **Clofazamine has been used in transplant patients with leprosy or atypical mycobacterial infections, but there are no data for treatment of TB in transplant patients**
- **Multi-drug and extremely drug-resistant TB remains rare in the transplant population to date**

Drug	Daily dose (adult)
Amikacin Kanamycin IM/IV	15 mg/kg (max 1 g) daily vs 25 mg/kg three times weekly
Capreomycin IM/IV	15 mg/kg (max 1 g) daily vs 25 mg/kg three times weekly
Para-amino salicylic acid PO/IV[d]	8-12 g (usually 4 g 2-3 times daily)
Levofloxacin PO/IV	500 mg-1000 mg
Moxifloxacin PO/IV	400 mg
Other drugs	
Linezolid PO/IV	600 mg
Clofazimine PO[e]	100-200 mg
Bedaquiline PO	400 mg daily for 2 wk, followed by 200 mg three times weekly; only studies for max duration of 24 wk
Delamanid PO	100 mg twice a day with food (max duration of studies is 26 wk)
Imipenem-cilastatin IV	1 g every 12 h (must be given with clavulanate 125 mg every 8-12 h)

Timing of LTBI therapy

- **Renal transplant candidates awaiting deceased donor transplantation should be treated before transplantation, as they may face long waiting times and renal failure is itself a risk factor for active TB disease.**
- **Treatment should be considered before lung transplantation in TST- or IGRA-positive individuals, because active TB may be difficult to diagnose in the presence of chronic lung disease.**
- **While LTBI treatment is safe in many liver transplant candidates,in unstable liver transplant candidates, it may be preferable to delay the administration of isoniazid until after transplantation, when liver function is relatively stable**

LTBI therapy

- **If Isoniazid is started pre-transplant, it can be held peri-transplant and resumed when the patient is in stable condition and able to take oral medications (strong, moderate).**

LTBI therapy

- **liver transplant recipients who are taking isoniazid, rises in serum transaminase levels should not be automatically ascribed to isoniazid**
- **Transplant recipients receiving isoniazid should routinely be monitored for hepatotoxicity.**
- **A suggested approach is to monitor at 2-week intervals for 6 weeks and then monthly.**
- **A single blood test (ALT) should suffice.**

LTBI therapy

- **Low-grade elevations of hepatic transaminases to 1.5-3 times normal are relatively common during the first months of isoniazid use and may not require immediate discontinuation but should prompt more frequent laboratory monitoring.**

- **LTBI treatment should be discontinued with a threefold increase in hepatic transaminases and signs and symptoms of hepatotoxicity, or fivefold elevation without symptoms**

LTBI therapy

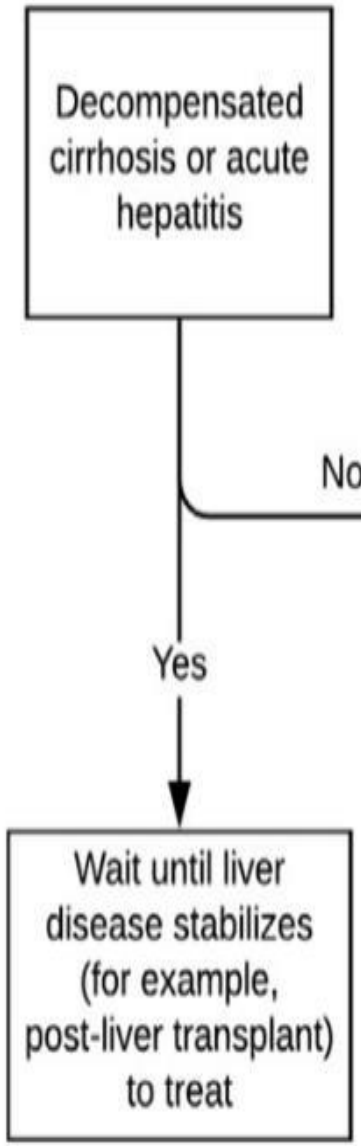
TABLE 2 Regimens used for treatment of LTBI[74,76,77]

First-line regimens:

- 9H (INH × 9 mo)[76]
- 4R (RIF × 4 mo)[76]
- 3HP (weekly INH/RPT × 12 doses)[76]

Alternative regimens with disadvantages relative to first-line regimens:

- 6H (INH × 6 mo)[76]
- RFB × 4 mo[76]
- 3HR (INH/RIF × 3 mo)[74,77]
- 4HR (INH/RIF × 4 mo)[77]



Select regimen based on transplant timing, drug interactions, liver disease, and risk of hepatotoxicity		**Possible transplant within 6 mo (or) rifamycin drug interactions**	
		No	Yes
Liver disease or increased risk of hepatotoxicity[a]	No	9H, 4R, or 3HP	9H
	Yes	4R	9H with close monitoring (or) RFB x 4 mo

Thank You!