Prevention and Management of Tuberculosis Among Solid Organ Transplant Recipients

Cybele L. R. Abad, MD
Infectious Diseases
Philippines

Disclosures

- No financial disclosures

OUTLINE

I. Background
II. Prevention of Tuberculosis (TB)
   - Evaluating for TB
   - Management of latent TB infection (LTBI)
III. Active Tuberculosis
   - Identifying TB disease
   - Management of TB
   - Transplant as treatment

- TB can be a significant infection after solid organ transplantation (SOT)

TB Among All SOT Recipients

PARAMETER	Singh & Peterson	Abad & Razonable
Inclusion, yr	1967-1997	1998-2016
# total TB cases	511	2,082
Overall frequency	0.35-15	0.05-13.27
Asia	3.1-15	0.34-13.27
Africa	1.5-8.2	2.85-7.32

Clin Infect Dis 1998;27:1266–77
Clin Transplant. 2018 Jun;32(6):e13259. doi: 10.1111/ctr.13259

TABLE 1.

Frequency of tuberculosis in transplant recipients

	High and intermediate TB burden (≥40 cases × 100 000 population)			Low TB burden (<40 cases × 100 000 population)		
	Prevalence, %	Incidence cases x 100 000 p-years (95% CI)		Prevalence, %	Incidence cases × 100 000 p-years (95% CI)	
SOT (overall)	1.38	—	China[11]	0.48	512 (317-783)	Spain[8]
Pulmonary	—	—		1.32	2072 (565-5306)	Spain[8]
Heart	3.17		Taiwan[12]	0.25	255 (6.5-1421)	Spain[8]
Liver	3.53	—	China[11]	0.47-2.3	541 (269–1065)	Spain[8]
Renal						Spain[8]
		—	Pakistan			
Renal-pancreatic	—	—		0.82	1204 (30.5-6710)	Spain[8]
HSCT (overall)	3.52	688	Taiwan[16]	0.25 (0.14-0.36)	101 (56.5-145)	Spain[15]
Allograft	2	1830 (590-2720)	Korea[17]	0.41 (0.21-0.73)	135.6 (58.9-212)	Spain[15]
Autologous	—	—		0.15 (0.047-0.26)	71.1 (21.8-120)	Spain[15]

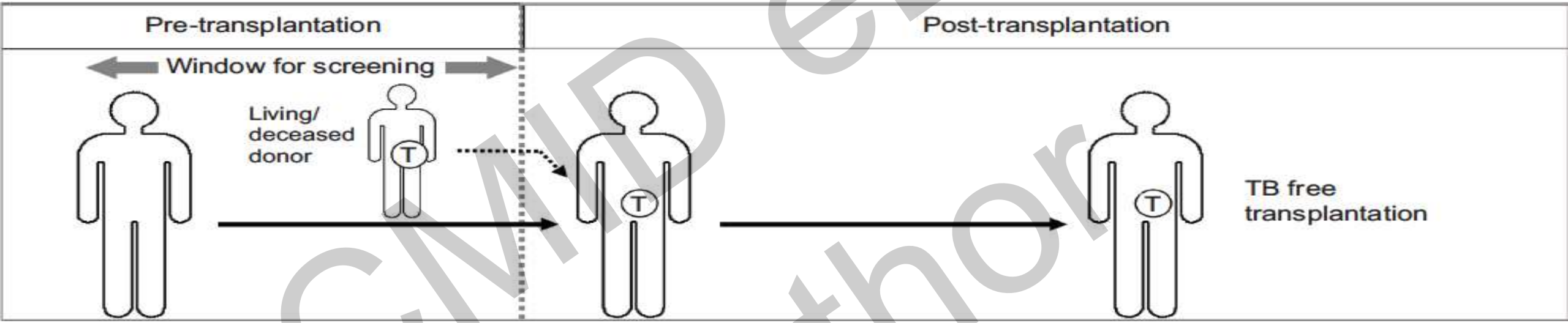
95% CI, 95% confidence interval.

TB occurs 20-74 times higher in the transplant population

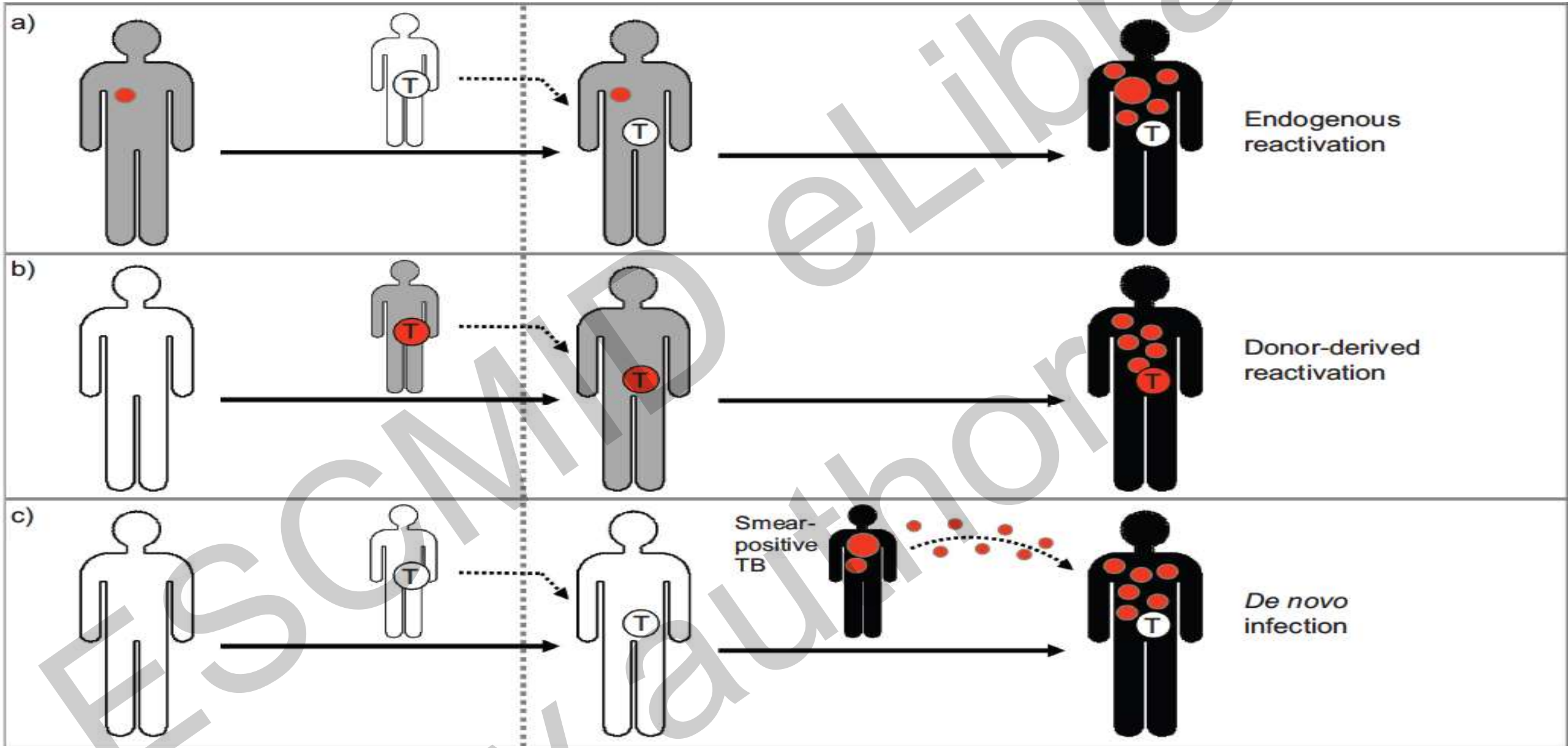
Munoz and Santin: Transplantation 2016;100: 1840–1852

THREE WAYS TO TB

TB Free Transplant



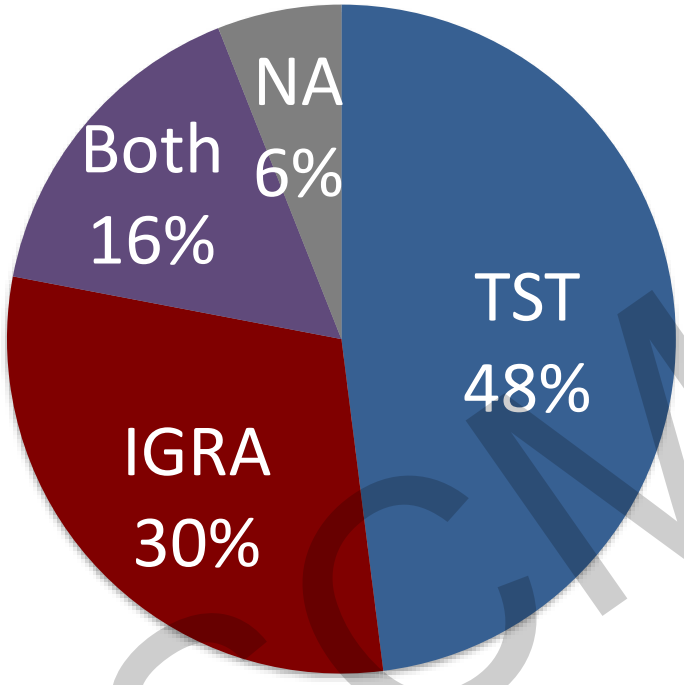
Bumbacea, et al 2012: Eur Respir J 2012; 40: 990–1013



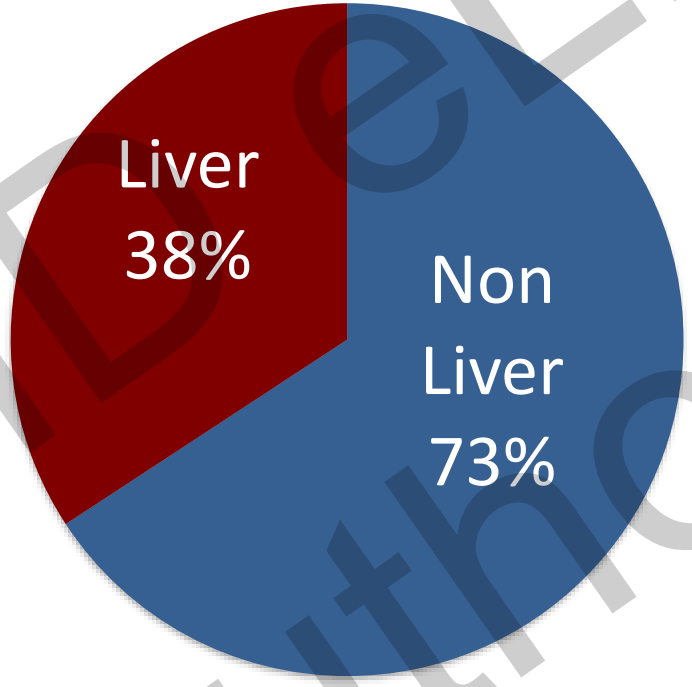
- “There are three principles for optimal management of TB in transplantation: prevention, rapid diagnosis and adequate treatment.”

Doblas and Cisneros, AJT 2011:1769-70

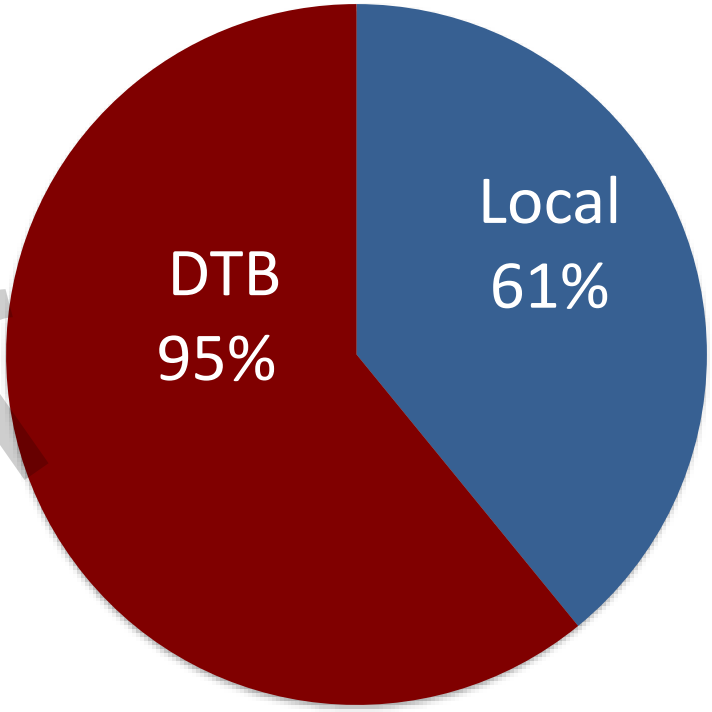
DIAGNOSTICS



LTBI TREATMENT



TREATMENT w/ RIF



IGRA: Interferon Gamma Release Assay
TST – Tuberculin Skin test

Blanco et al Transplant International 26 (2013) e69–e70

PREVENTION OF TB

- Early detection of tuberculosis through screening of patients at increased risk for TB may provide a window of opportunity for interventions such as treatment to prevent the development of active TB.

Hasan T, et al. BMJ Open 2018;**8**:e022445.

Issues:

- The diagnosis of TB is difficult in transplant candidates/recipients:
  - Most are asymptomatic
  - Chest radiographs are normal in almost half
  - PPD tests are often negative

- Emergent/urgent transplantations are often performed before cultures are available

Torre Cisneros, et al. Transplantation 2004: (77) 9: 1376-80

Solution:

- An aggressive screening protocol is required to detect tuberculosis in all transplant candidates

RISK ASSESSMENT

Visit or travel to an endemic country

Household contact of active TB

Exposure to healthcare

Homelessness

Living in an endemic country

Yehia and Blumberg. Liver Transplantation 2010: 16:1129-1135

Pre-transplant Screening

- Diagnostic tests
  - Interferon Gamma Release Assay (IGRA), tuberculin skin test (TST) or both?
  - CXR, Chest CT scan or both ?
  - TB studies

IGRA or TST?

GUIDELINE/STATEMENT	Screening for LTBI
TBNET, 2012, International	TST or IGRA or BOTH
GESITRA, 2009 (Spain)	High incidence countries
ESGICH, 2014 (Europe)	Any risk factors for TB
Subramanian and Morris 2019 (US)	

- IGRAs are replacing TST as the diagnostic modality of choice for assessment of LTBI

Manuel et al. Am J Transplant 2007;7:2797–2801.

TST
PROS
Cheap
CONS
Affected by prior BCG
Anergy
Requires multiple visits
Subject to reader variability

IGRA
PROS
Lower rate of false positives
Higher specificity
Less subjective results
CONS
Expensive
Indeterminate rates

(%) Prevalence of LTBI among Transplants

TEST	KIDNEY	LIVER	HCT
TST	21 (16-27)	24 (14-33)	14 (9-19)
IGRA	31 (25-37)	25 (17-33)	13 (10-16)

- The concordance between TST/IGRA is about 75-83% among SOT recipients

Rahimifard, et al. Microbial Pathogenesis 125: 2018 ; 401-410
Kim et a l, Transplant Proc 2013 (45) 2899e2902
Ahmadinejad, TID 2013: 15: 90–95

CAUTION:

- Several series have reported culture-proven TB presenting with negative IGRA test results

- Indeterminate IGRA occurs depending on the population

Munoz and Santin. Transplantation 2016: 1840–1852

IGRA Indeterminate results

STUDY, YR	N	INDT rate	MELD SCORE (INDT vs DT)
Manuel, 2007	153	7.8	17.8 vs 14.3
Jafri, 2011	119	12.6	20.7 vs 14.9
Theodoropolous, 2016	310	40.6	20.3 vs 14.3
Roth, 2015	246	21	NR
Hand 2017	148	27	NR

Am J Transplant 2007 (12): 2797-801
Liver Tr2011: 17(3):306-14
TID. 2012;14(1):1-8
TID 2016: (18)1:14-21
TID 2018;20(2):e12845.

Imaging

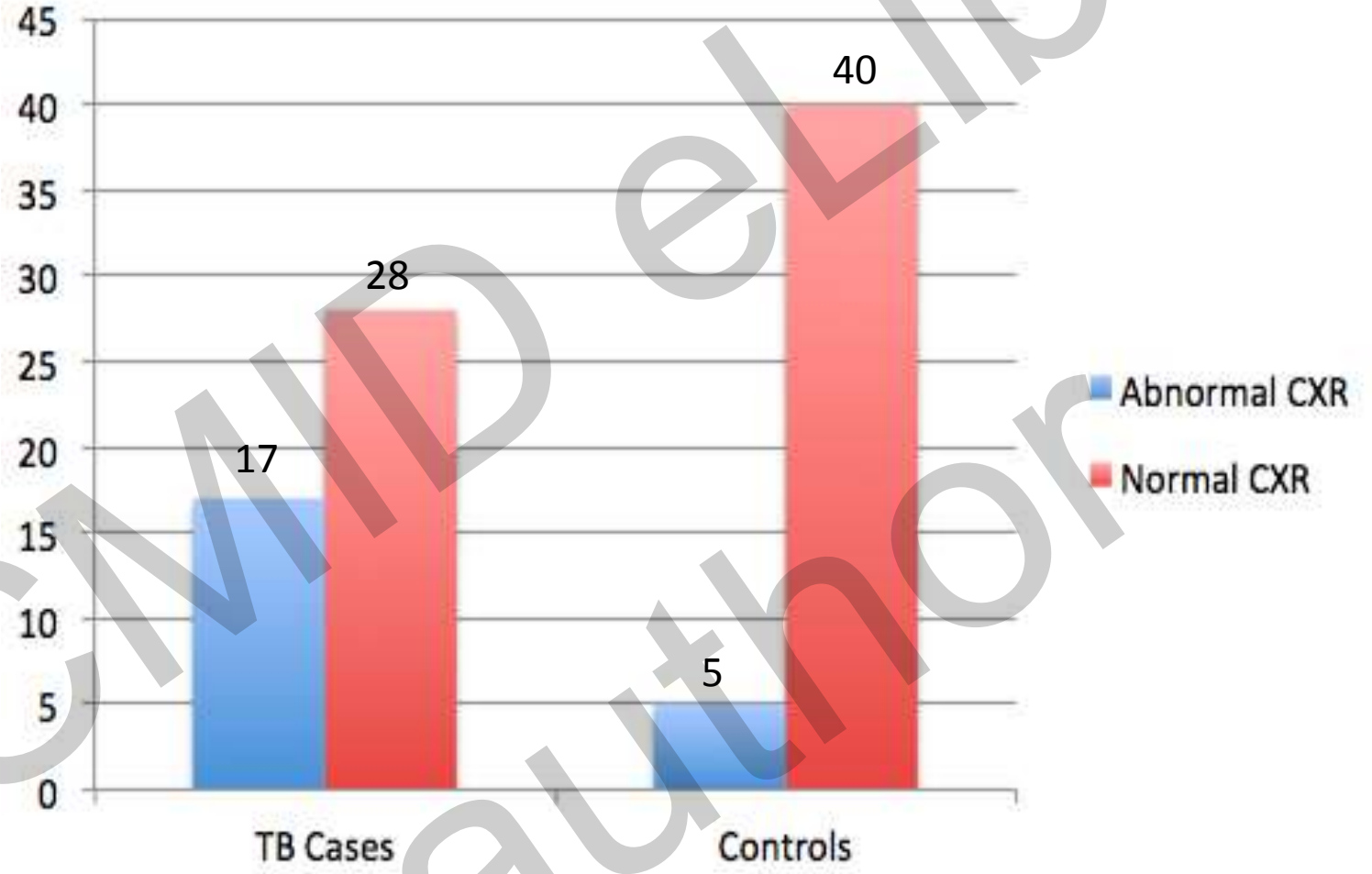
- Chest x-ray is usually routinely performed for patients during the pre-transplant evaluation

- Incidentally discovered pulmonary parenchymal abnormalities on prior imaging should similarly prompt evaluation to rule out active disease as appropriate.

Advantages of Imaging

- Abnormal CXR or CT scans can be predictive of TB occurrence
- CT scans may be more sensitive

Lyu et al. Liver Transpl 17:963-968, 2011
Liu et al. BMC Infectious Diseases 2014, 14:387



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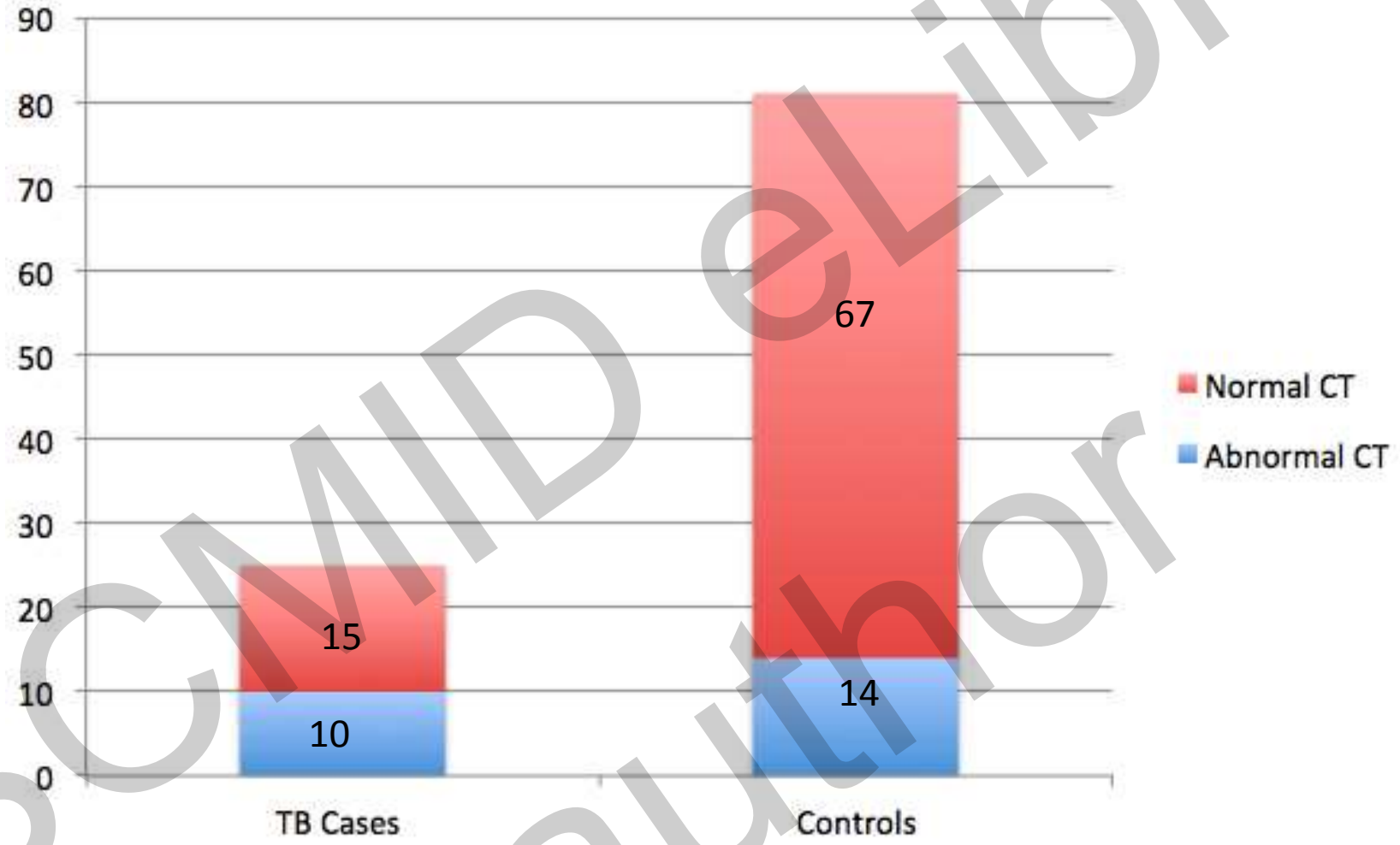
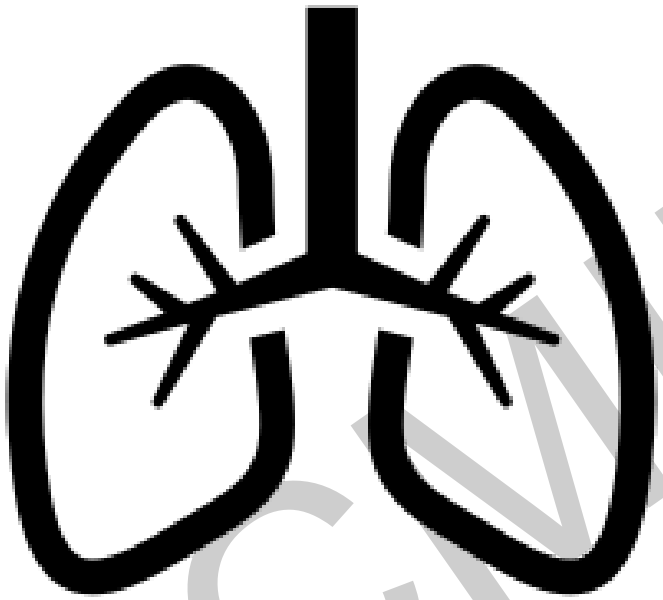


Lyu et al. Liver Transpl 17:963-968, 2011



CXR OR CT IMAGING FINDINGS SUGGESTIVE OF TB
Fibrotic linear opacities
Calcified nodules
Irregular lines
Uncalcified nodules
Fibrotic consolidation

Lyu et al. Liver Transpl 17:963-968, 2011

FINDING	KIDNEY		LUNG		LIVER	TOTAL
	CXR	CT	CXR	CT	CT	N
Ground glass/Consolidation	0	9	1	9	1	20
Cavitation/ Tree in bud	5	29	24	11	47	116
Mediastinal lymph node	6	8	0	4	10	18
Miliary pattern	1	22	0	2	12	37
Pleural effusion	11	5	2	0	0	18
TOTAL	23	73	27	26	70	219

Giacomelli, et al 2018: J Bras Pneumol: 44(2):161-166

Other Imaging Modalities

- FGD-PET may be able to predict inactive vs. active tuberculoma, but this has not yet been validated in the transplant population.

Kim, Eur J Nucl Imaging 2008 35: 808

TB Studies – Rule Out Active Disease

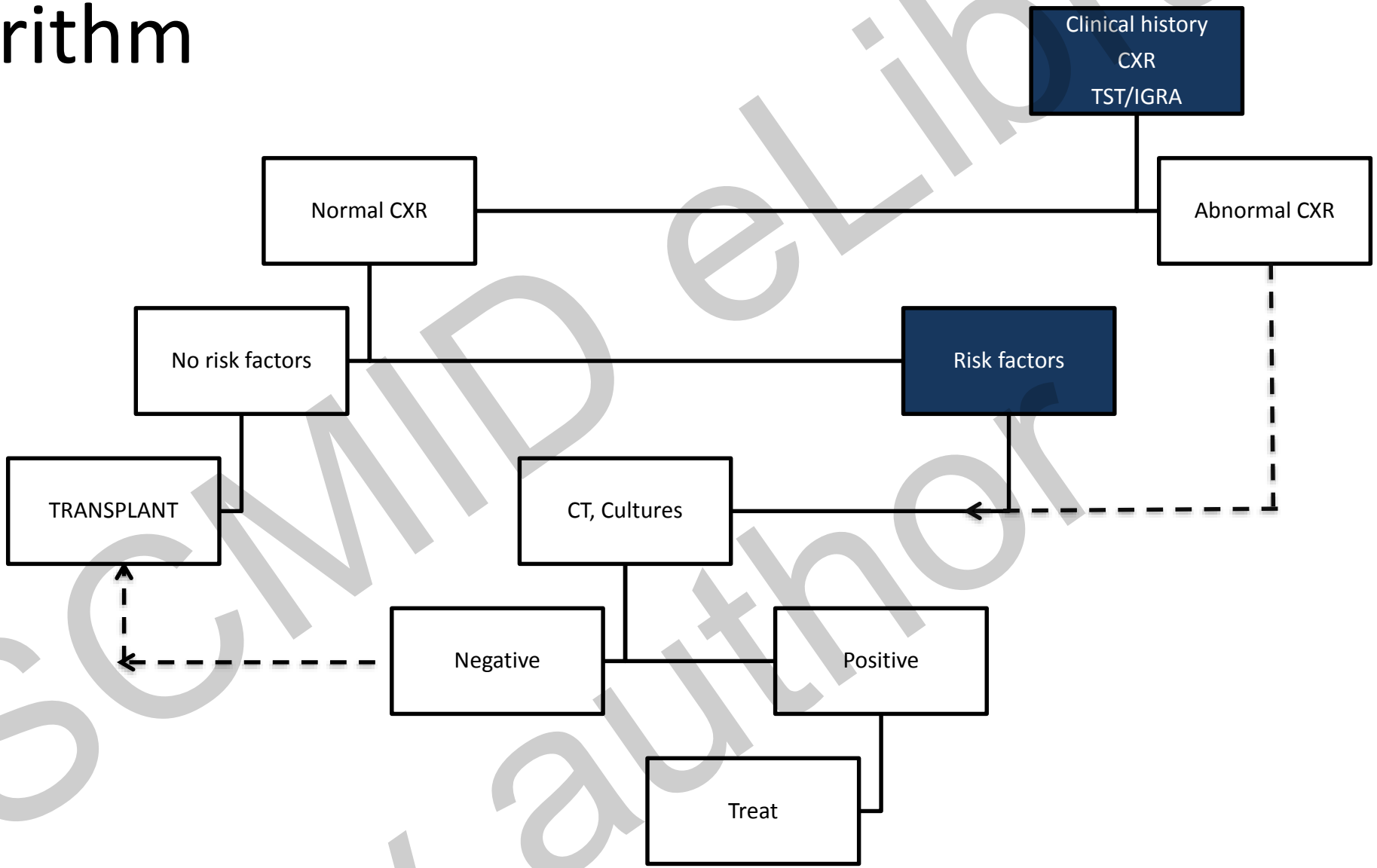
- Culture still the gold standard for diagnosis BUT results may not be available if transplant is urgent

- Novel generations of automated nucleic acid amplification tests, e.g. the Xpert MTB/RIF test (Cepheid, Sunnyvale, CA, USA), could improve the rapid diagnosis of TB in transplant. However, value of this method still needs to be established.

Bumbacea, et al. Eur Respir J 2012; 40: 990–1013

PUTTING IT TOGETHER

Algorithm



TREATMENT OF LTBI

PROPHYLAXIS

- Indications for prophylaxis are not that much different from the none transplant population.

Indication for Prophylaxis

If either positive (TST or IGRA)

Close and prolonged contact with an active TB case

Old untreated or inadequately treated TB

Being born in a country with TB incidence >100/ 100 000 population

Receiving a lung transplant from a donor w/ LTBI

What is the Evidence?

- LTBI treatment (>6 months) is associated with a reduction in developing active MTB

Holty, et al. *Liver Transpl 15:894-906, 2009*
Adamu, et al. 2014
Moon et al. Ann Transplant, 2017; 22: 338-345

Does LTBI treatment Work?

STUDY, Year	Organ	INH	No INH	RR
Adamu, 2014	Kidney	13/250	49/308	0.35
Holty, 2009	Liver	0/61	7/143	0
Moon, 2017	Liver	0/19	7/258	0
Al-Mukhaini, 2017	Multiple	0/177	3/155	0

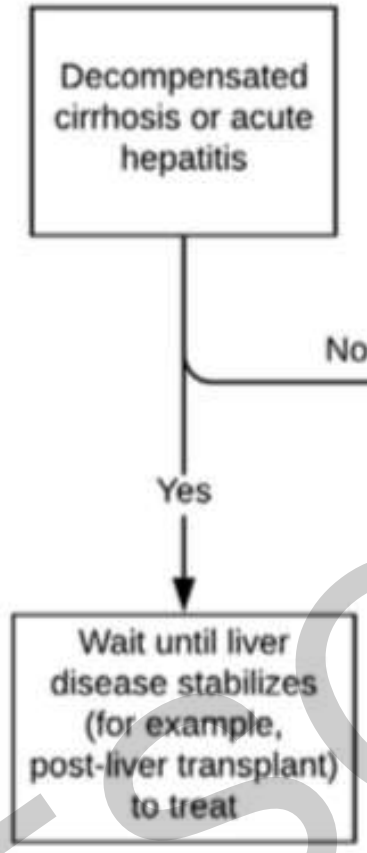
Adamu, et al. *Cochrane Database of Systematic Reviews* 2014, Issue 3
Holty, et al. *Liver Transpl 15:894-906, 2009*
Moon, et al. Ann Transplant, 2017; 22: 338-345
Al Mukhaini, et al. Ann Saudi Med 2017; 37(2): 138-143

BUT ….

- Compliance w/ prophylaxis remains poor
- Liver transplant candidates with LTBI constitute a unique group whom clinicians have sometimes avoided treating given concern for drug-induced liver injury

- Risk of hepatotoxicity w/ INH among liver transplant recipients appears low at 6%

Holty, et al. *Liver Transpl 15:894-906, 2009*



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

Epstein and Subramanian, Infect Dis Clin N Am 32 (2018) 703–718

FIRST LINE	ALTERNATIVE
9H (INH 9 months) 4R (RIF 4 months) 3HP (weekly INH/RPT 12 doses via DOTS)	6H (INH 6 months) RFB 4 mo 3HR (INH/RIF 3 months) 4HR (INH/RIF 4 months) FQ

Epstein and Subramanian, Infect Dis Clin N Am 32 (2018) 703–718

FQ as Alternative Prophylaxis

Characteristic	Torre-Cisneros, et al	Tien, et al
Type of study	RCT	Retrospective
(N)	33H/31 FQ	44 (25 FQ/10H/9R)
Reason for prophylaxis	PPD (+)	IGRA (+)
Completion rates , %	55.6 / 54.5	64/60/67
Hepatotoxicity , %	38.9 / 6	0/40/22
Tenosynovitis, %	0 / 18.2	16/0/0
Permanent withdrawal, %	38.9 / 33.3	8/40/33

Torre Cisneros, et al. CID 2015;60(11):1642–9
Tien et al. CID 2015: 61, 1631

TB DISEASE

Identifying Active TB: Key Features

- Reactivation TB is RARE in the first 3 months, and usually presents AFTER the first year of transplant

  Median, mos 17.5 (CR) -22.5 (Co)

- There are certain caveats:
  - Donor derived TB (usually within 3 months)
  - None- KT transplants < 1 yr

Abad and Razonable. Clin Transplant. 2018 Jun;32(6):e13259.

- FEVER is the most common symptom (and maybe the only one)
- Compared to the general population, extrapulmonary (EPTB) and disseminated TB (DTB) occur often
- Imaging findings may be NORMAL, are variable, and cannot be relied upon

	OVERALL					
Time of onset, median (mos)						
Early <12 mos	417 (41.16)	255 (37.67)	43 (72.88)	14 (63.64)	15 (75)	0
Late >12 mos	596 (58.84)	422 (62.33)	16 (27.12)	8 (36.36)	5 (25)	2 (100)
Type of TB, n	1642	1257	63	22	19	2
PTB	890 (54.2)	678 (53.94)	23 (36.51)	12 (54.55)	15 (78.95)	1 (50)
EPTB	490 (29.84)	403 (32.06)	23 (36.51)	4 (18.18)	2 (10.53)	0
Disseminated	262 (15.96)	176 (14)	17 (26.98)	6 (27.27)	2 (10.53)	1 (50)
Fever	513/597 (86)	370/533 (69.42)	39/57 (68.42)	13/22 (60)	9/18 (50)	1 (50)

Abad and Razonable. Clin Transplant. 2018 Jun;32(6):e13259.

Treatment of Active Disease

- Treatment of TB should generally adhere to recently published guidelines for the general population, with certain caveats:

Issues

- Potential drug interactions once transplant occurs

- For liver transplant candidates/recipients, the main problem is related to the risk of hepatotoxicity in an already damaged liver

Drug- Drug Interactions

Table 1: Antiinfective drug interactions

Antimicrobial	Immunosuppressant[1]	Severity of interaction[2]	Interaction
Antibacterials			
Fluoroquinolones			
Ofloxacin	CSA, TAC	++	↑ Imm levels
Ciprofloxacin	CSA, TAC	+/–	May ↑ Imm levels
Levofloxacin	CSA	+/–	May ↑CsA
Moxifloxacin	CSA, TAC, SRL, EVR	–	None
Macrolides			
Erythromycin	CSA, TAC, **SRL**, EVR	+++	↑ Imm levels
Clarithromycin	CSA, TAC, **SRL, EVR**	+++	↑ Imm levels
Telithromycin	CSA, TAC, **SRL, EVR**	+++	↑ Imm levels
Azithromycin[4]	CSA, TAC, SRL, EVR	+/–	↑ Imm levels
Rifamycins			
Rifabutin	CSA TAC, **SRL, EVR**	++	↓ Imm levels
Rifapentine[5]	CSA, TAC, SRL, EVR, Prednisone	++	↓ Imm levels
Rifampin	CSA, TAC, **SRL**, EVR, MMF, ECMS	+++	↓ Imm levels

Trofe Clark et al. AJT 2013; 13: 318–326

Solutions: Treatment Regimens

- Standard (HRZE) TB regimen with close monitoring
- Eliminate PZA
- Choose Rifabutin or Rifapentine instead of Rifampin
- Extend therapy for pulmonary disease from 6 to 9 months
- Exclusive use of non-hepatotoxic drugs (e.g. AG, capreomycin, EMB, cycloserine, and FQ), until the patient's liver disease stabilizes.

Nahid, et al. Clin Infect Dis 2016;63(7):e147–95.

Other recommendations

- Daily anti TB therapy (ATT) rather than intermittent therapy
- Pyridoxine for all candidates / recipients
- At least monthly in person by the treating provider; more frequent follow-up may be needed.
- Frequent laboratory monitoring

Monitoring

- AST/ALT and TB concentrations every 1–4 weeks for at least the first 2–3 months of treatment.
- The INR may also be periodically followed for patients with severe hepatic impairment
- For cirrhotics or those with hepatic encephalopathy, weekly or twice-weekly ALT monitoring, interrupting treatment for only a 3-fold elevation of ALT, even if asymptomatic

TRANSPLANT AS TREATMENT?

Is Transplant w/ Active TB Plausible?

- Select cases in a critical situation could undergo transplantation and anti- TB treatment continued after transplantation

- Intraoperative diagnosis of tuberculosis does not necessarily contraindicate transplantation, especially if it results in the loss of the donated organ.

ALF from ATT : Outcomes after LT

N = 26
14/26 Males
Median Age 38 yrs, IQR 25-50

Outcome	RIF+INH N=2 (%)	INH+ETB+FQ N=5 (%)	FQ+ETB+Aminglycosides N=9 (%)	FQ+ETB+CS N=7 (%)	FQ+ETB+RIF N=3 (%)	FQ+ETB+LZD N=2 (%)
Mortality	1 (50)	0 (0)	0 (0)	0 (0)	2 (66)	0 (0)
Rejection	2 (100)	0 (0)	1 (11)	0 (0)	3 (100)	0 (0)
Liver toxicity	0 (0)	0 (0)	1[a] (11)	0 (0)	0 (0)	0 (0)

Bartoletti, et al 2017: Transpl Infect Dis;19:e12658.

Summary: Key Points

- TB is prevalent among transplant recipients
- A thorough evaluation for TB during the pre-transplant phase is critical
- Use of IGRA based tests and CT imaging are optimal

- INH prophylaxis is recommended among high risk patients and reduces the risk of post-transplant reactivation TB

- TB treatment is plausible in the pre-transplant phase, but certain precautions must be taken.

- Transplantation during active TB disease is discouraged, but may be acceptable in certain scenarios

Future Direction

- More sensitive and specific tests for the diagnosis of LTBI and active TB disease are urgently needed
  - Imaging modalities
  - Cell mediated immunity
  - Metagenomics
- Explore other options for treatment
  - New drugs

THANK YOU