Clinica di Malattie Infettive e Tropicali
Università degli Studi dell'Insubria –
Ospedale di Circolo e Fondazione Macchi, Varese
Direttore: Prof. Paolo Grossi

6th INTERNATIONAL CONGRESS

INFECTIONS & TRANSPLANTATION

Varese, 18-20 Maggio 2017

ATA Hotel

PROGRAMMA SCIENTIFICO PRELIMINARE

Tuberculosis in solid organ transplantation

Daniela Dalla Gasperina

Emerging Issue, but Old Infection


GRAN TEATRO LA FENICE

Per la sera di Domenica 6 Marzo 1853. Recita XLI.

PRIMA RAPPRESENTAZIONE DELL'OPERA NUOVA

LA TRAVIATA

S. BERNARDETTE SOUBIROUS DE LOURDES, SIMON BOLIVAR, LOUIS BRAILLE, GEORGES CANETTI, NAPOLEONE II, MARIA FELICE GARCIA, ANTON GHON, IRVING WASHINGTON, GIACOMO LEOPARDI, POPELIN JEAN-BAPTISTE -MOLIERE, SAINTE THERESE MARTIN DE LISIEUX, JEAN CALVIN….

…..FRANZ KAFKA
SARAH BERNARDT
FREDERICH CHOPIN
ELEONORA DUSE
ALBERT CAMUS
ANTON CHEKHOV
PAUL GAUGUIN
VIVIEN LEIGH
THOMAS MANN
NICCOLÒ PAGANINI
GEORGE ORWELL
ALLAN EDGAR POE
LOUIS STEVENSON
IGOR STRAVINSKI
RICHELIEU….

World Health Organization

TUBERCULOSIS

Global Tuberculosis Report 2016

49 million lives saved between 2000-2015
TB deaths fell by 22% in the same period

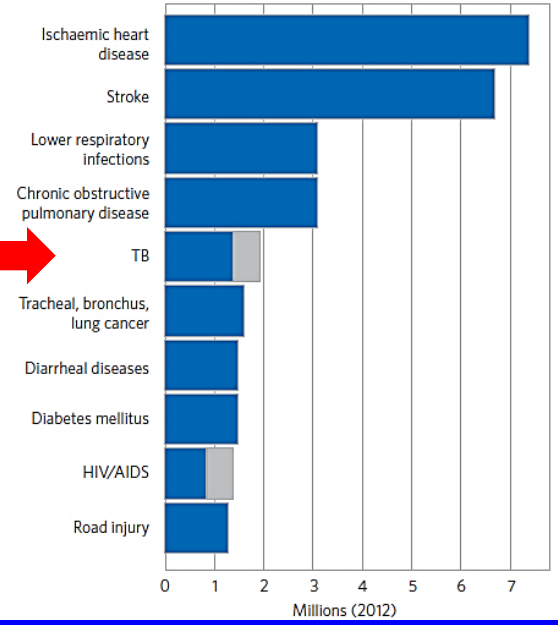
1.8 MILLION TB DEATHS
INCLUDING 0.4 MILLION TB DEATHS AMONG PEOPLE WITH HIV*
TB was one of the top ten causes of death worldwide
TB was responsible for more deaths than HIV and malaria

MDR-TB crisis with gaps in detection and treatment
Only 1 in 5 needing MDR-TB treatment were enrolled on it

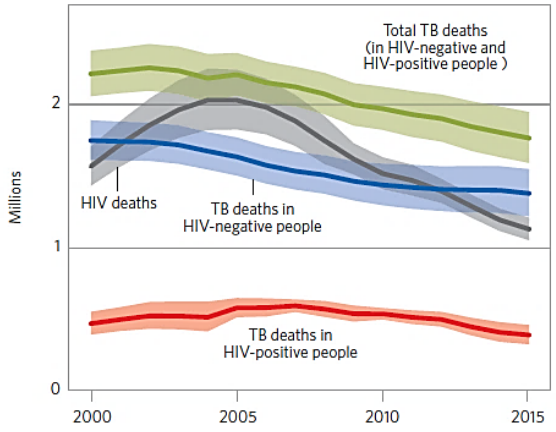
US$ 2 BILLION GAP
Funding shortfall for TB implementation
Gap of over US$1 billion per year for TB research

DESPITE PROGRESS AND MILLIONS OF LIVES SAVED, GLOBAL ACTIONS AND INVESTMENTS FALL FAR SHORT OF THOSE NEEDED.

Top causes of death worldwide in 2012.[a,b,c,d] Deaths from TB among HIV-positive people are shown in grey.[d]



Global trends in the estimated number of deaths caused by TB and HIV (in millions), 2000–2015.[a,b] Shaded areas represent uncertainty intervals.

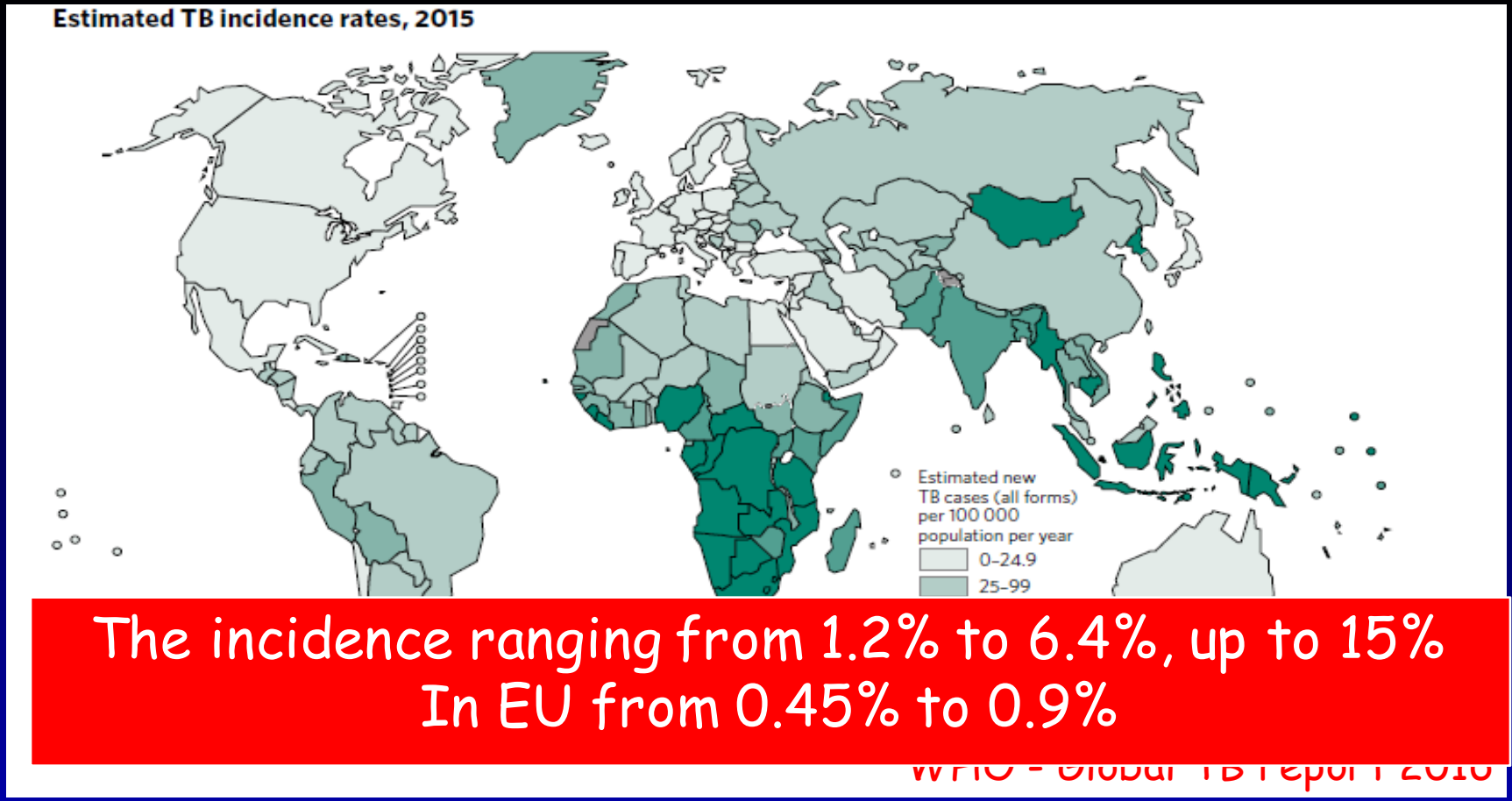


[a] For HIV/AIDS, the latest estimates of the number of deaths in 2015 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2016/HIV_estimates_with_uncertainty_bounds_1990-2015. For TB, the estimates for 2015 are those published in this report.

[b] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

Tuberculosis in solid organ transplantation

- Is TB really a surprise in SOT, or not so much? Epidemiology and mortality
- Risk factors
- Epidemiological exposure
- Some clinical peculiarities ?
- Diagnostic difficulties ?
- Any therapeutic difficulties?
- Prophylaxis: who, what, when, how long?



The incidence ranging from 1.2% to 6.4%, up to 15%
In EU from 0.45% to 0.9%

WHO - Global TB Report 2016

The incidence of TB among SOT recipients seems to be directly associated with the specific incidence in the general population, but the former is usually 20–74 times higher than the latter

Singh N. CID 1998; Aguado JM. GESITRA. Transplantation 1997; Muñoz P. CID 2005; Torres-Cisneros J CID 2009; Canet E Nephrol Dial Transplant 2011;

TB in SOT: Mortality

Study, year	Country	Tx organs	N. of Tx	Mortality Rate
Quinibi, 1990	Saudi Arabia	Kidney	403	14%
Singh N,1998	US	Liver	511	29%
Lattes, 1999	Argentina	Kidney	384	14%
Ergun, 2006	Turkey	Kidney	283	20%
Torre-Cisneros, 2009	Spain	Kidney, pancreas, liver, lung, heart	4388	19%
Clemente WT, 2009	Brazil	Liver	319	0%
Lopez de Castilla, 2010	NY, US	Kidney, liver, lung, heart	4925	15%
Al-Mukhaini, 2017	Saudi Arabia	Kidney, liver, lung, heart	1966	5%

	2003-2007	2008-2011	p
Mortality	21%	10%	*P*= .20

Sun HY et al
Prog Transplant.
2014; 24(1):37

Incidence of TBC in SOT
RESITRA Network (2003-2005)

Type of transplant	Frequency	Incidence/10^5 IC90%	Odds ratio
Heart	1/404 (0.25)	255 (6.5-1421)	13.7 (1.9-97.3)
Kidney	7/2052 (0.34)	358 (144-728)	19.0 (9.0-39.7)
Liver	8/1507 (0.53)	541 (269-1065)	29.5 (14.8-58.9)
Kidney-pancreas	1/122 (0.82)	1204 (30.5-6710)	45.5 (6.5-320.4)
Lung	4/303 (1.32)	2072 (565-5306)	73.3 (27.7-194.1)
Total	21/4388 (0.49)	512 (317-783)	26.6 (17.4-40.8)

Torre-Cisneros J, Doblas A, Aguado JM et al. Clinical Infectious Diseases 2009; 48:1657–65

Risk Factors for TB

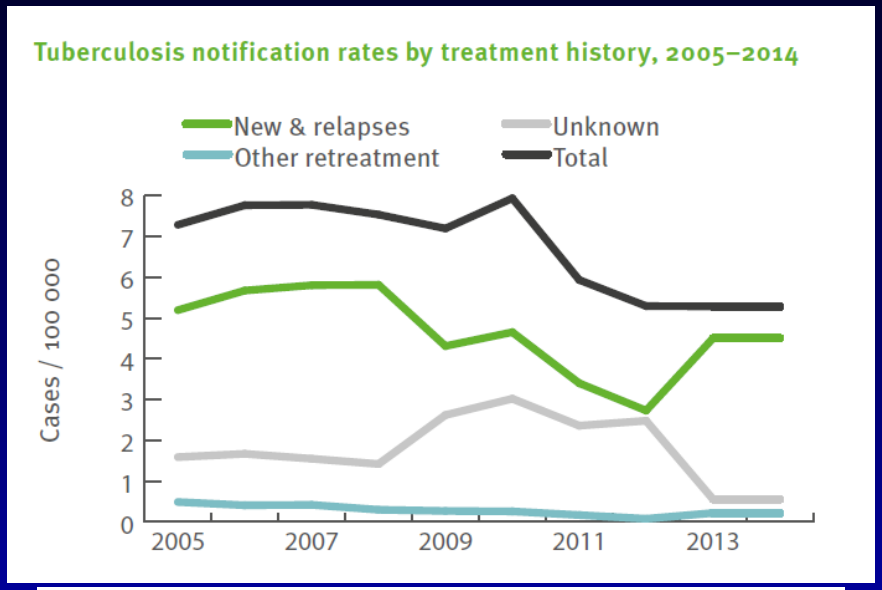
Risk factors
High-risk factors ✓ HIV/AIDS ✓ Close contacts ✓ SOT ✓ Chronic renal failure requiring dialysis ✓ TNF-alpha blockers ✓ Silicosis
Moderate-risk factors ✓ Fibronodular diseases on chest x-ray ✓ Immigrants from high-TB-prevalence countries ✓ Health-care workers ✓ Prisoners, homeless persons, IDUs
Low-risk factors ✓ Diabetes mellitus ✓ Smoking ✓ Use of corticosteroids ✓ Underweight

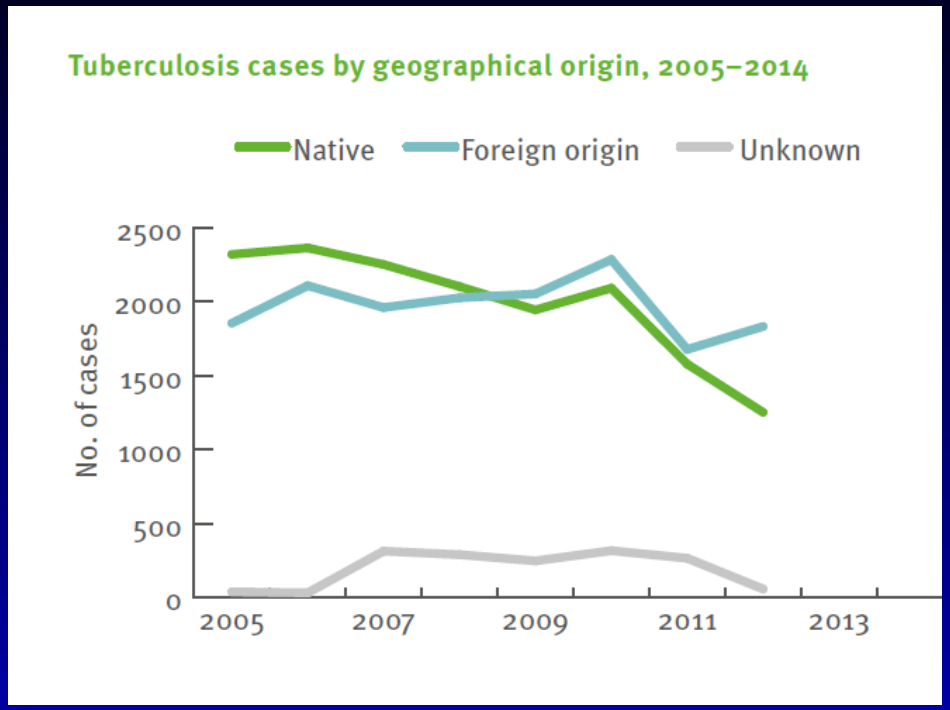
Ai J-W et al. Emerging Microbes and Infections 2016
(from multiple studies)

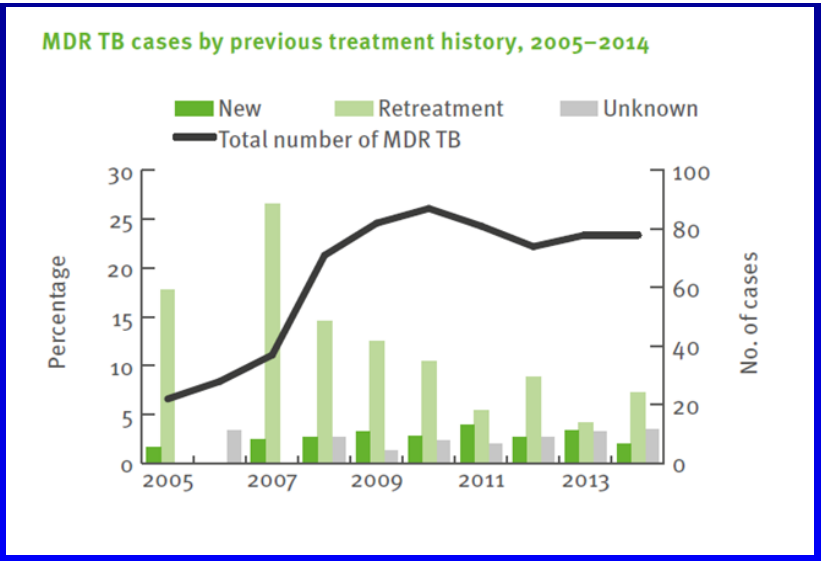
SOT
Previous data of TBC
Underlying disease ✓ Hemodialysis. Longer preTx HD ? (x2) ✓ Diabetes mellitus (x 2-4) ✓ Older age
Coexisting infection: ✓ CMV, PCP, HCV (x 1.6-2.3)
Lung Tx
Higher intensity immunosoppression

Klote MM. Am J Transplant 2004;
John GT. Kidney Int 2001;
Basiri A. Transplant Proc 2005.
Basiri A. Tranpl Infect Dis 2007;
Torres J. Transpl Int. 2008.
Aguado JM. Clin Infect Dis 2009; 48:1657–65
Horne DJ. CID 2013

TB notification in Italy

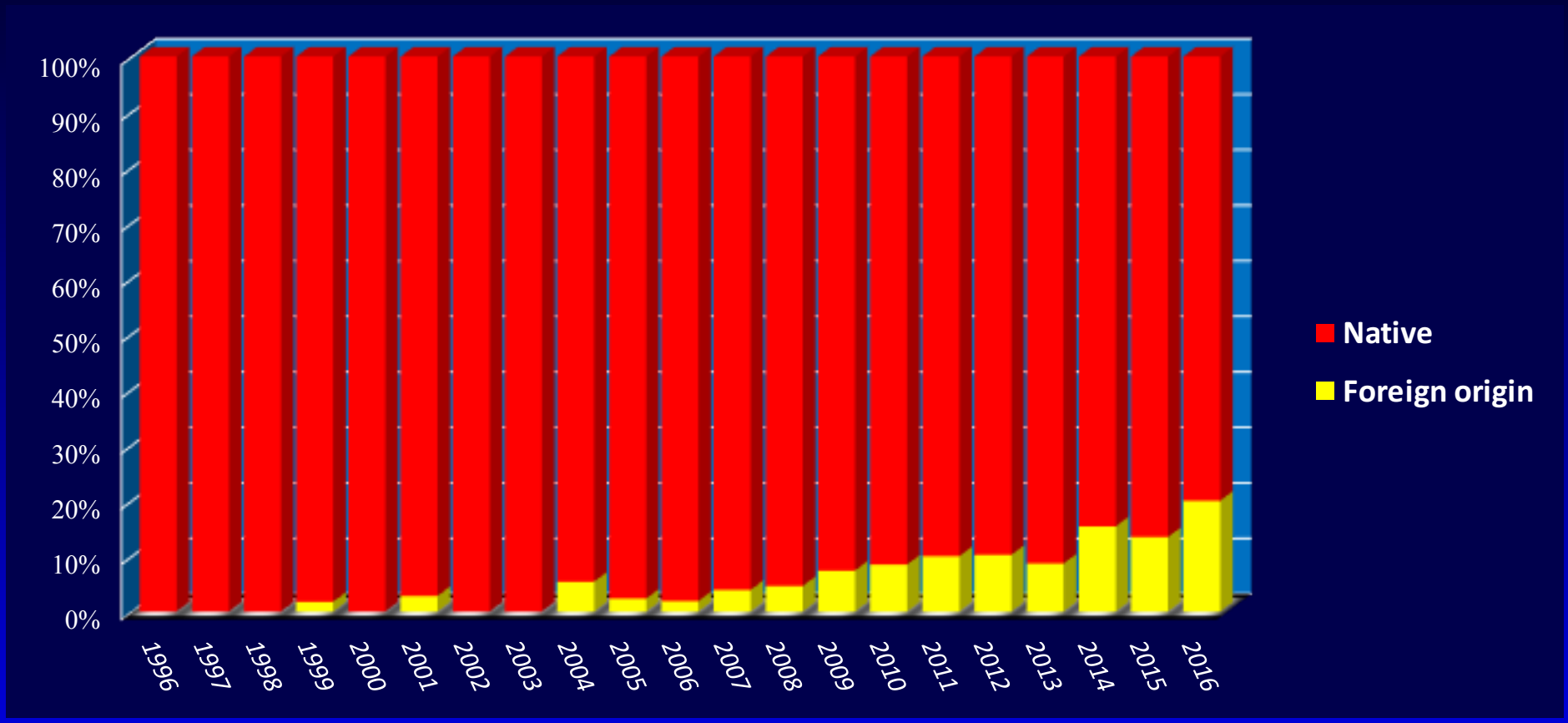






Tuberculosis surveillance and monitoring in Europe 2016.

Kidney and Kidney-Pancreas Transplant Recipients -VA (n.= 856)

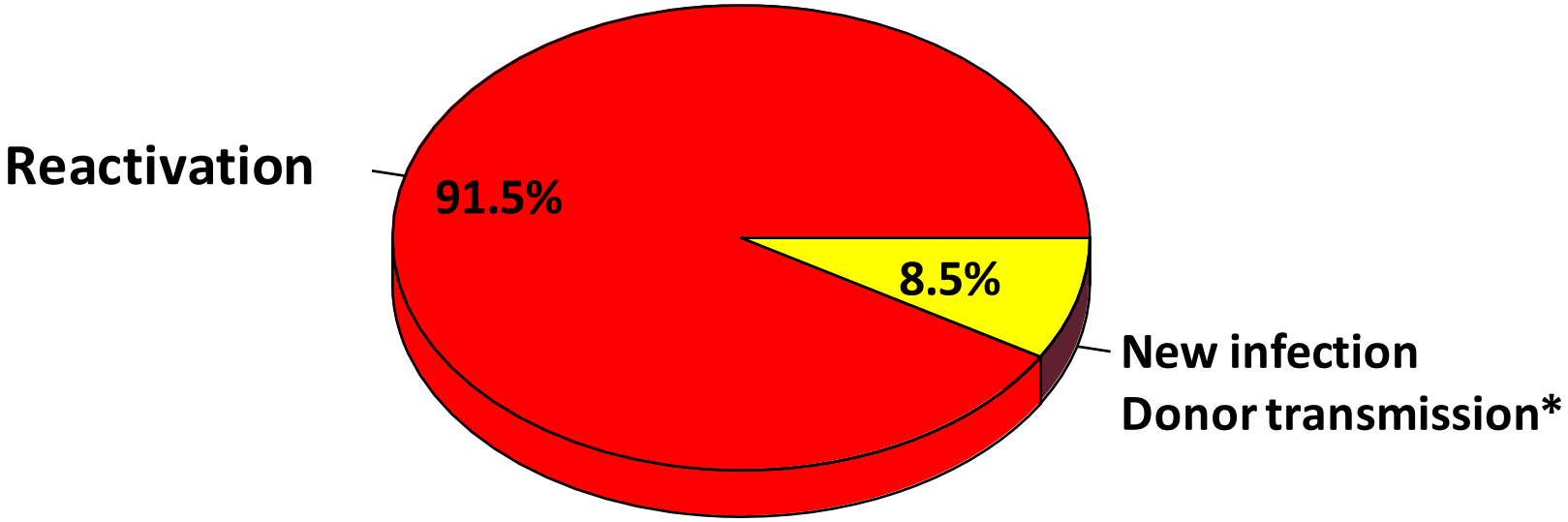


Factors determining the risk of infection in transplant recipients

- The net state of immunosuppression
- Epidemiological exposure
  - Donor-derived infections
  - Recipient-derived infections
    - Latent infections
    - Nosocomial infections
    - Community infections

Pathogenesis

47 TB in Kidney Tx



(*) Donor with history or TBC or + PPD with a negative Recipient

Lichtenstein IH *Rev Infect Dis* 1983;5:216

American Journal of Transplantation 2013; 13: 9–21
Wiley Periodicals Inc.

doi: 10.1111/ajt.12094

Special Article

Screening of Donor and Recipient in Solid Organ Transplantation

S. A. Fischer[a,*], K. Lu[b] and the
Diseases Community of Practic

REVIEW 10.1111/1469-0691.12557

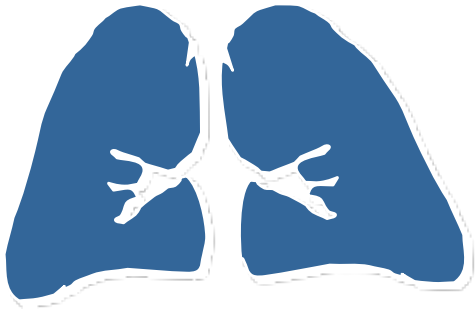
Recommendations for screening of donor and recipient prior to solid organ transplantation and to minimize transmission of donor–derived infections

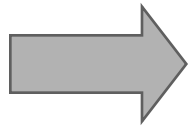
O. Len[1,*], C. Garzoni[2,3,*], C. Lumbreras[4], I. Molina[1], Y. Meije[1], A. Pahissa[1], P. Grossi[5] on behalf of the ESCMID Study Group of Infection in Compromised Hosts (ESGICH)

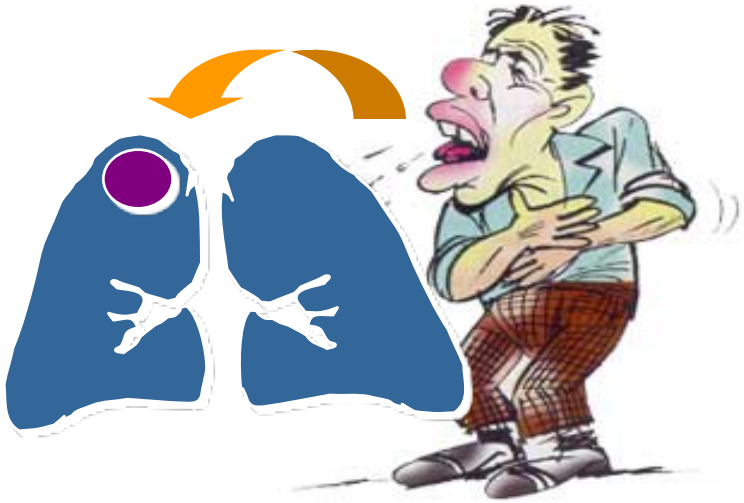
- Pretransplant screening of potential organ donors and recipients is ESSENTIAL to the success of SOT
- The goals of pre-Tx infectious disease screening are to identify conditions which may disqualify either donor or recipient; identify and treat active infection pre-Tx; recognize and (if possible) define the risk of infection and develop strategies for preventing and mitigating post-tx infection; and implement preventative measures, including immunizations.

DONOR

RECIPIENT







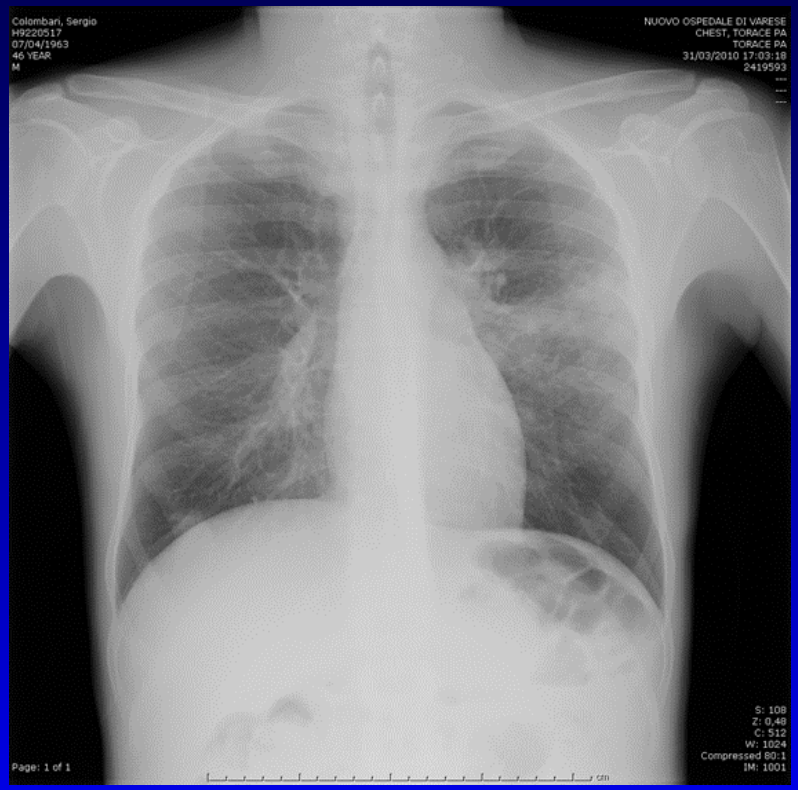
New infection

Transplant Proc. 2011

Pulmonary Tuberculosis in an HIV- and Hepatitis C Virus–Coinfected Kidney-Pancreas Transplant Recipient: A Case Report

D. Dalla Gasperina, M. Tozzi, N. Astuti, M.L. Balsamo, D. Donati, A. Rossi, R. Dionigi, and P.A. Grossi

- 47 yrs, man, HIV and HCV pos
- Pre-tx screening: PPD neg, chest X-ray no abnormalites; no known TB exposures.
- Kidney-pancreas Tx (April, 2007)
- Tacrolimus, MMF (prednisolone only first 1 month post-tx)
- HAART: 3TC+ABC+FPV/r
- 35 months after-Tx: fatigue, fever, and night sweating
- HIV-RNA undetectable, CD4 cells count 307/mm3



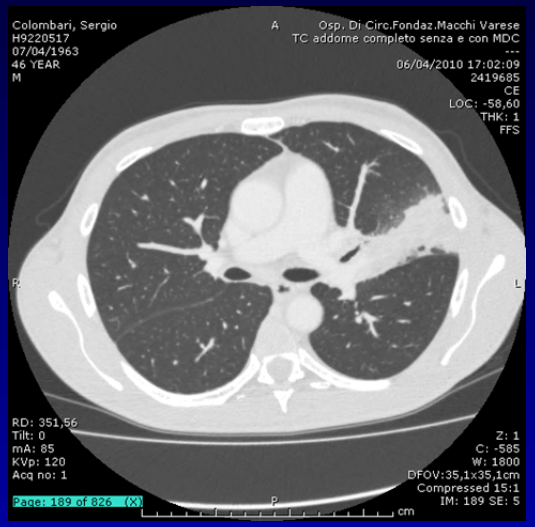
ELSEVIER

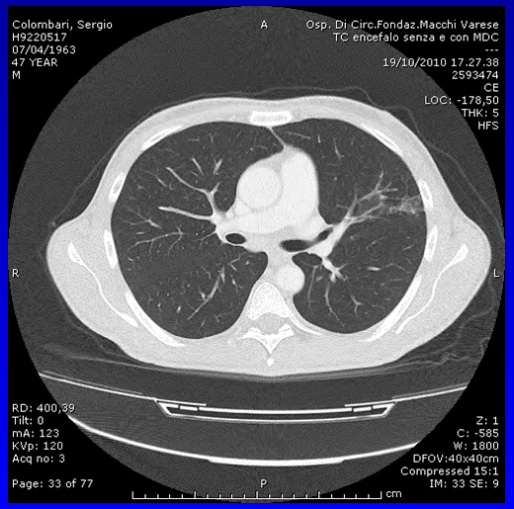
Transplant Proc. 2011

Pulmonary Tuberculosis in an HIV- and Hepatitis C Virus–Coinfected Kidney-Pancreas Transplant Recipient: A Case Report

D. Dalla Gasperina, M. Tozzi, N. Astuti, M.L. Balsamo, D. Donati, A. Rossi, R. Dionigi, and P.A. Grossi

- Empirically treated pip/taz and levofloxacin in another center, without clinical improvement.
- The patient was transferred to our hospital
- Close contact in last months
- PPD test and QuantiFERON-TB: positive
- Sputum smear: negative
- BAL: positive
- Ethambutol, isoniazid, moxifloxacin, and pyrazinamide (latter stopped after 2 months) for 18 months





Clinical Characteristics

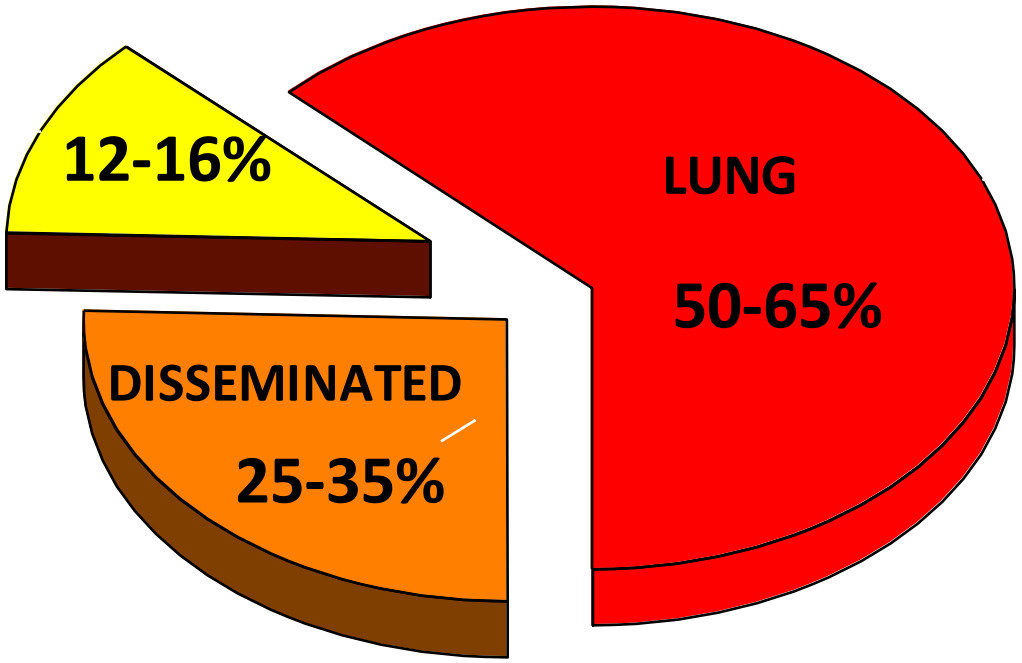
(RESITRA Cohort, 2002-2005)

	Early TB (< 3 mo.)	Late TB (> 3 mo.)
Time of onset	20 days (5-50 days)	12 months (3-30 m)
Frequency	10%	90%
Source Risk factors	TB in transplant candidate. Donor transmission. Latent TB (Chest XR, PPD).	Reactivation. Nosocomial. Primary infection.
Clinical manifestations	Pulmonary , extra-pulmonary, disseminated, FUO.	Pulmonary
Crude mortality	40%	15-20%
Related mortality	2-3%	1%

Sites of infection

EXTRAPULMONARY

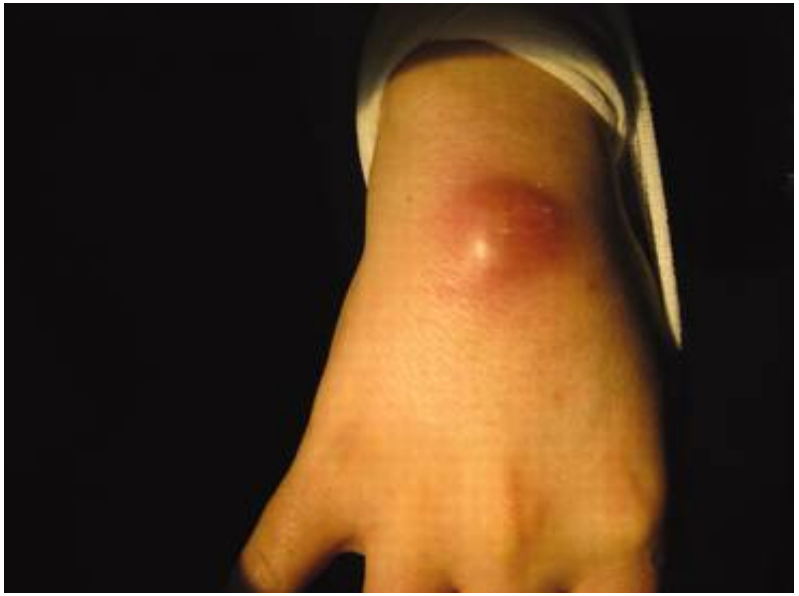
- ✓ Skin and soft tissues 4%,
- ✓ Osteoarticular 1%
- ✓ Genitourinary 0.6%
- ✓ Liver, pancreas, larynx, adrenal glands, thyroid, eye



Singh N. Clin.Microb.Rev. 2005; Aguado JM. GESITRA. Transplantation. 1997, John 2001

Think about TB!!

- 38 year old woman.
- Pain in right hand 6 years after KT
- TST -
- Normal chest X-ray
- Wrist lesion



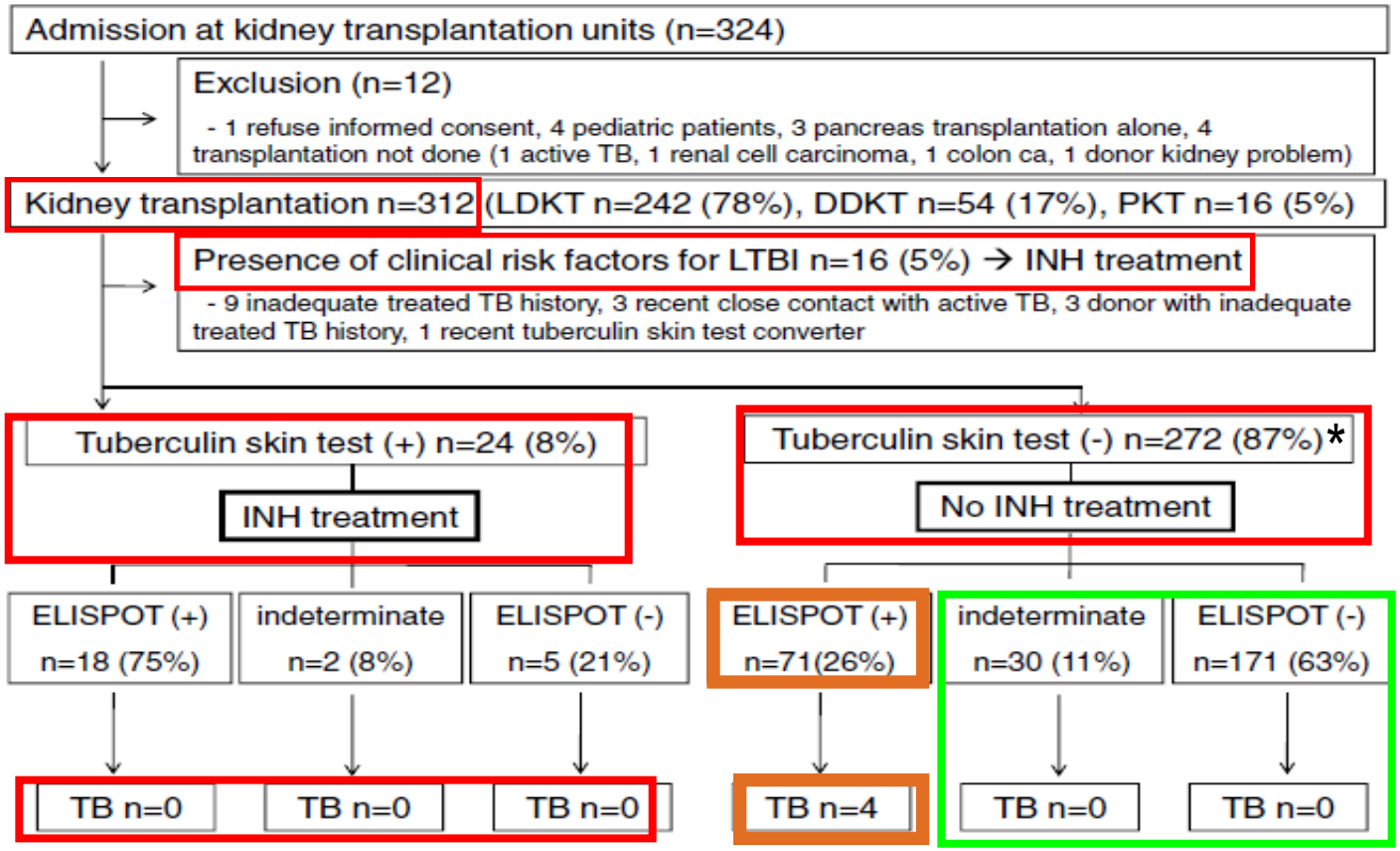
- **Consider TB in any transplant recipient with FUO or infection of unclear origin**
- **Take samples for MTB even if other microorganisms are isolated**

Diagnosis

- Delayed diagnosis > mortality
  - ✓ association with other infections
  - ✓ aggressive diagnostic techniques: FB, BX...
- TST testing
  - ✓ Low efficacy (only 20-25% of patients are PPD+)
- IGRAs: Quantiferon-TB Gold, T-SPOT.*TB*
  - ✓ IFN-g from sensitized Lymphocytes

A Prospective Longitudinal Study Evaluating the Usefulness of a T-Cell-Based Assay for Latent Tuberculosis Infection in Kidney Transplant Recipients

Kim S-H et al. Am J Transplant 2011;11:1927



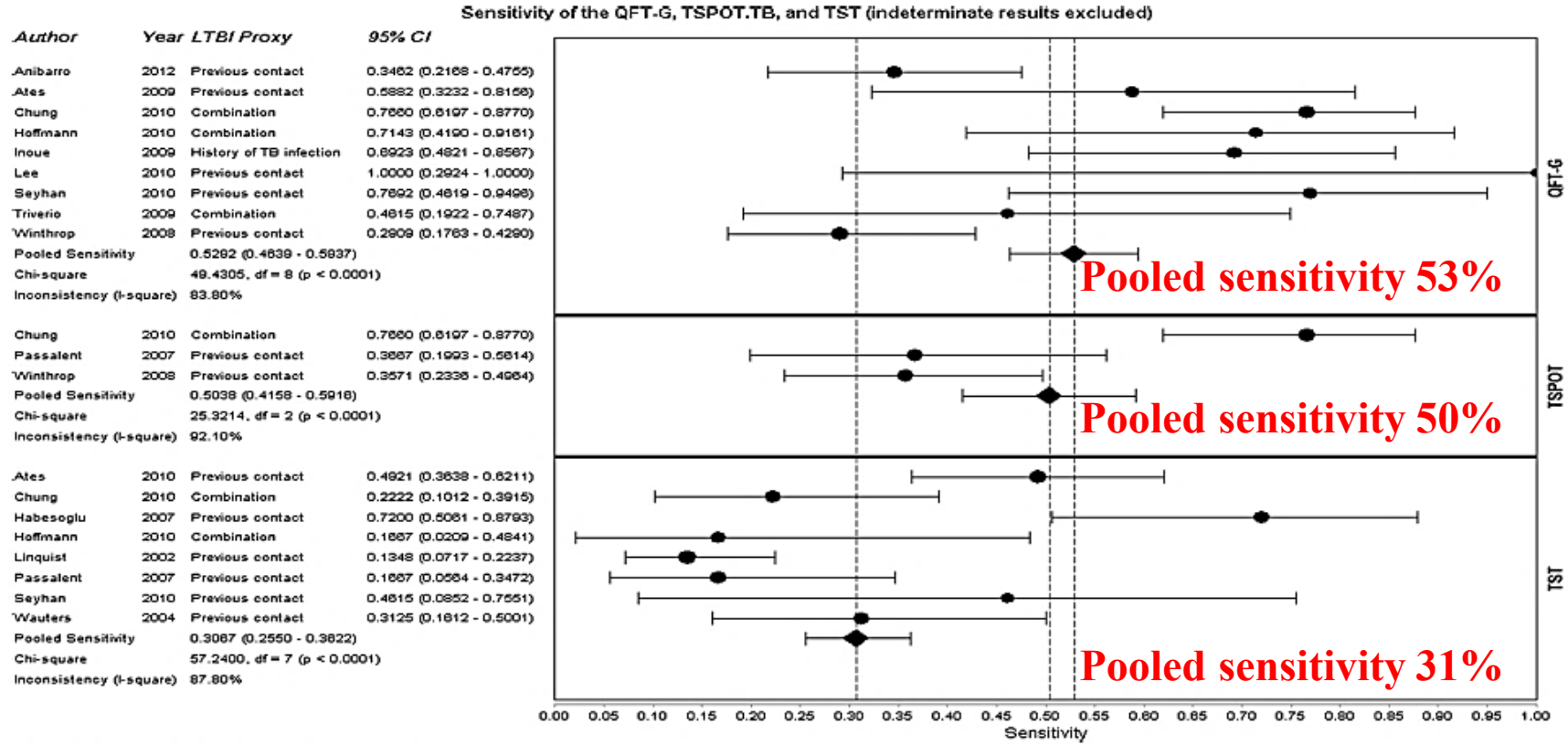
* TST (>10 mm) was performed immediately before or after of surgery . No booster.

Original Clinical Science

Transplantation 2015;99: 1084

The Diagnostic Accuracy of Tests for Latent Tuberculosis Infection in Hemodialysis Patients: A Systematic Review and Meta-Analysis

Thomas W. Ferguson,[1,2] Navdeep Tangri,[1,2,3] Kerry Macdonald,[2,4] Brett Hiebert,[1] Claudio Rigatto,[2,3] Manish M. Sood,[5] Souradet Shaw,[1] Blake Lerner,[2] Yang Xu,[2] Salaheddin Mahmud,[1] and Paul Komenda[2,3]



Clinical Infectious Diseases

IDSA GUIDELINE

Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Clin Infect Dis. 2016;63:853-67

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Payam Nahid,[1] Susan E. Dorman,[2] Narges Alipanah,[1] Pennan M. Barry,[3] Jan L. Brozek,[4] Adithya Cattamanchi,[1] Lelia H. Chaisson,[1] Richard E. Chaisson,[2] Charles L. Daley,[5] Malgosia Grzemska,[6] Julie M. Higashi,[7] Christine S. Ho,[8] Philip C. Hopewell,[1] Salmaan A. Keshavjee,[9] Christian Lienhardt,[6] Richard Menzies,[10] Cynthia Merrifield,[1] Masahiro Narita,[12] Rick O'Brien,[13] Charles A. Peloquin,[14] Ann Raftery,[1] Jussi Saukkonen,[15] H. Simon Schaaf,[16] Giovanni Sotgiu,[17] Jeffrey R. Starke,[18] Giovanni Battista Migliori,[11] and Andrew Vernon[8]

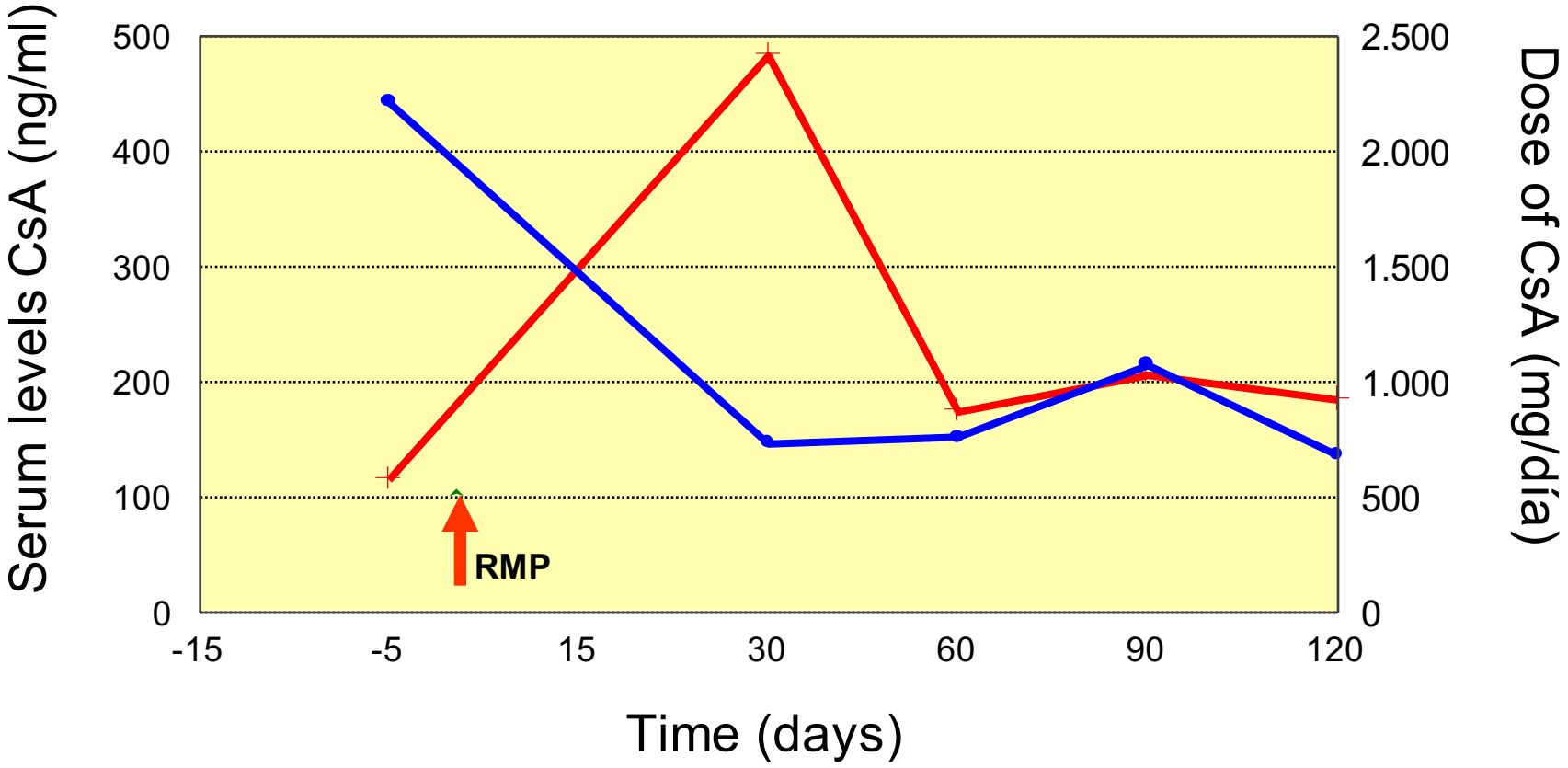
No data and recommendations on TB in SOT recipients

Interactions with Antituberculous drugs

	CyA	FK	MMF	SRL
Isoniazid	-	-	-	-
Rifampin	↓↓	↓↓	↓	↓↓
Rifabutin	↓	↓	↓	↓
Pirazinamide	↓	-	-	-
Etambutol	-	-	-	-
Moxifloxacin	-	-	-	-
Cicloserin	*	-	-	-

* Increase the levels of antituberculous drugs

Interaction between CsA and RFM



Impact of rifampin based anti-tuberculosis regimens on outcomes in SOT recipients

- 63 SOT recipients with TB: RIF 26, non-RIF 37
- Rejection rate and death at 1 year were similar in both groups.
- Immune Reconstitution Syndrome (IRS) more frequent in RIF than in non-RIF (27% vs 5,4%, p=.04)
- Mortality at 1 y: 33% with IRS, 14% without IRS (p =0.15)

Sun HY et al. *Prog Transplant*. 2014 Mar;24:37-43.

Mycobacterium Tuberculosis—Associated Immune Reconstitution Syndrome in Solid-Organ Transplant Recipients

Hsin-Yun Sun,[1,10] Patricia Munoz,[2] Julian Torre-Cisneros,[3] Jose M. Aguado,[4] Roberta Lattes,[5] Miguel Montejo,[6] Ana Garcia-Reyne,[4] Emilio Bouza,[2] Maricela Valerio,[2] Rosario Lara,[3] George T. John,[7] Didier Bruno,[8] and Nina Singh[9]

SRI in 14%; median 47 days after TX; mortality at 1 year: 33,3% with SRI and 17,2% without SIR

TABLE 3. Multivariate analysis of factors associated with immune reconstitution syndrome (Model 1)

Factor	Reference Group	Adjusted OR (95% CI)	*P*
Liver transplantation	No liver transplantation	6.11 (1.08–34.86)	0.04
Rifampin use	No rifampin use	4.56 (0.74–27.95)	0.10
CMV infection	No CMV infection	5.65 (0.93–34.47)	0.06
Risk prediction of IRS			
One of the above factors present	None of the above factors present	11.26 (0.11–14.95)	0.85
More than one of the above factors present	None of the above factors present	19.00 (1.89–190.92)	0.01

Diagnostic accuracy and estimates of probability of IRS using liver transplantation, rifampin use, and CMV infection in the model

Cut point	Sensitivity	Specificity	Positive predictive value	Negative predictive value
≥1 (one or more factor present)	88.89	34.55	18.18	95
≥2 (two or more factors present)	66.67	89.09	50	94.23
>3 (three or more factors present)	22.22	100	100	88.71

Transplantation. 2013;95:1173-81

REVIEW 10.1111/1469-0691.12641

Mycobacterial infections in solid organ transplant recipients

Y. Meije[1], C. Piersimoni[2], J. Torre-Cisneros[3], A. G. Dilektasli[4] and J. M. Aguado[5], on behalf of the ESCMID Study Group of Infection in Compromised Hosts (ESGICH)

1) Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain, 2) Regional Reference Mycobacteria Laboratory, Azienda Ospedaliera Universitaria Ospedali Riuniti, Ancona, Italy, 3) Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Hospital Universitario Reina Sofía, Universidad de Córdoba, Cordoba, Spain, 4) Department of Pulmonary Diseases, Uludag University School of Medicine, Bursa, Turkey and 5) Infectious Diseases Department, Hospital Universitario 12 de Octubre, Madrid, Spain

Clin Microbiol Infect. 2014 Sep;20 Suppl 7:89-101

- ✓ For localized, non-severe forms of TB and periods with high rejection rates, it may be advisable to avoid the use of rifamycins (B-II). INH and EMB (or PZA) for 12–18 months (CIII).
- ✓ For severe forms or disseminated TB, the use of a TB regimen that includes RIF or rifabutin should be considered (B-II). INH and RIF or rifabutin for at least 9 months (BIII).

Reduce immunosuppression?

- ✓ Controversial. Consider in severe cases in kidney Tx

WHO guidelines on LTBI

Recommend regimens

- 6-mo. isoniazid
- 9-mo. isoniazid
- 3-mo. rifapentine + isoniazid once per week
- 3–4 mo. isoniazid plus rifampicin
- 3–4 mo. rifampicin alone

WHO, 2015. http://apps.who.int/iris/bitstream/10665/136471/ 1/9789241548908_eng.pdf (accessed Nov 4, 2014).

Short-Course Isoniazid Plus Rifapentine Directly Observed Therapy for Latent Tuberculosis in Solid-Organ Transplant Candidates

- **INH/RPT for LTBI during 12 weeks (DOT)**
- **13/17 SOT (76%) successfully completed therapy**
- **No patient ↑ ALAT/ASAT x2 basal or x4 normal upper limit**
- **None developed clinical hepatotoxicity.**
- **No cases of TB during 20.4 months after transplant**

Lopez de Castilla D et al. Transplantation 2014;97: 206Y211

Twelve-Week Rifapentine Plus Isoniazid Versus 9-Month Isoniazid for the Treatment of Latent Tuberculosis in Renal Transplant Candidates

Jacques Simkins, MD,[1] Lilian Margarita Abbo, MD,[1] Jose Fernando Camargo, MD,[1] Rossana Rosa, MD,[1] and Michele Ileana Morris, MD[1]

- **Retrospective study of RTC with LTBI**
- **153 patients: 43 on 12-week RPT/INH and 110 on 9-month INH.**
- **Treatment completion higher in the 12-week RPT/INH group (93% vs 47%, P < 0.001).**
- **Transaminase elevations not observed in the RPT/INH group, but occurred in 6 (5%) of the INH group.**
- **There were no differences in adverse reactions leading to discontinuation of LTBI treatment.**

Transplantation. 2016 Jul 12. [Epub ahead of print]

Infection
pp 1–5

Three months of weekly rifapentine plus isoniazid for latent tuberculosis treatment in solid organ transplant candidates

Authors | Authors and affiliations

B. M. Knoll, R. Nog, Y. Wu, A. Dhand

Original Paper

First Online: 08 M

DOI: 10.1007/s15

Methods

Twelve consecutive SOT candidates who underwent DOT with 3HP for LTBI at Westchester Medical Center, Valhalla, New York, USA, between January 2013 and August 2016 were prospectively evaluated for tolerability and safety of 3HP. The diagnosis of LTBI was made in a person with a positive interferon-gamma release test, without a history of previously treated active or latent tuberculosis infection, and without signs, symptoms, or radiographic evidence of active tuberculosis. Patients were followed up 1 month after treatment completion and at routine follow-up visits with their transplant providers.

Results

Eleven patients were men, and the median age was 60 years (range 44–72). Eight patients were liver, and four kidney transplant candidates. The median Model for End-Stage Liver Disease (MELD score) was 17 (range 10–31). All patients completed treatment. Only a single patient developed transaminitis greater than twice the baseline value. Three patients underwent liver transplantation. None of them developed tuberculosis at 9, 22, or 40 months following transplantation.

MAJOR ARTICLE

Clin Infect Dis. 2015;60

Tuberculosis Prophylaxis With Levofloxacin in Liver Transplant Patients Is Associated With a High Incidence of Tenosynovitis: Safety Analysis of a Multicenter Randomized Trial

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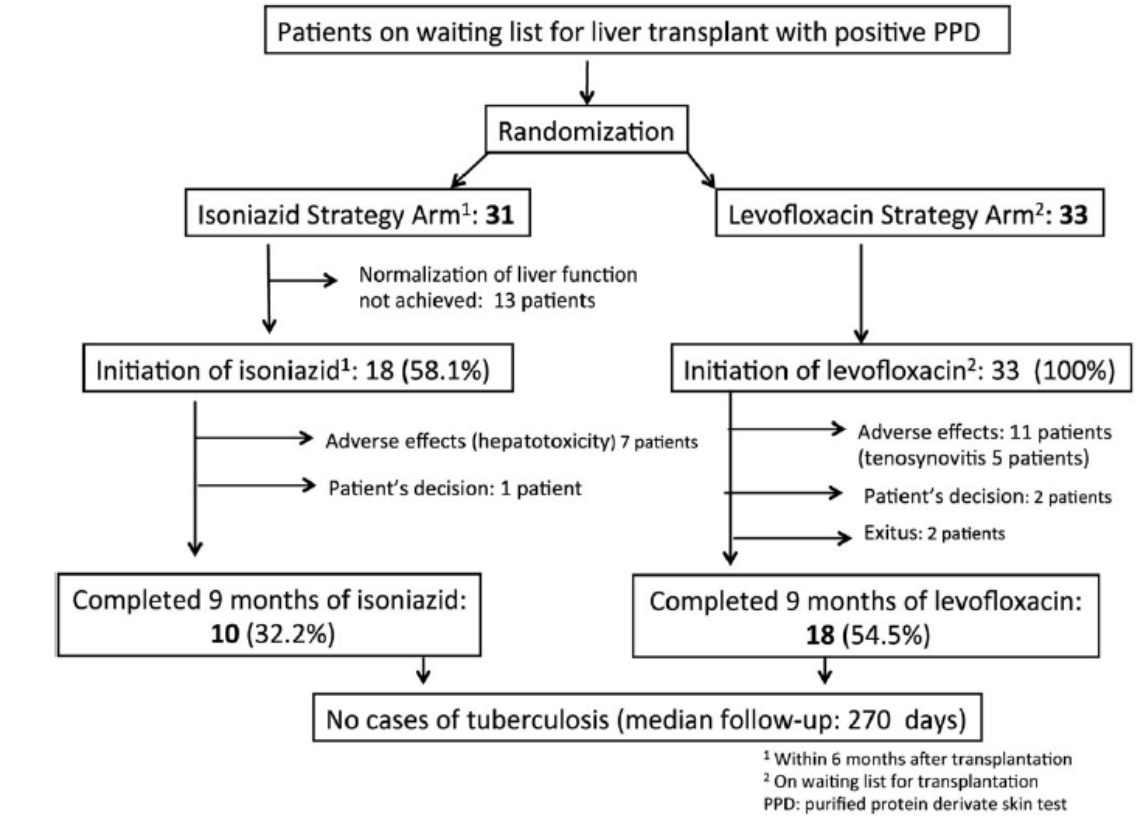


Limitations for the Control of TBC RESITRA Network

Transplant type	PPD performed/total patients[a] (%)	PPD positive/PPD performed[b] (%)	Prophylaxis/PPD positive[c] (%)
Heart	266/404 (65.8)	40/266 (15.0)	30/40 (75.0)
Kidney	625/2052 (30.5)	85/625 (13.6)	45/85 (52.9)
Liver	695/1507 (46.1)	162/695 (23.3)	48/162 (29.6)
Kidney-pancreas	17/122 (13.9)	4/17 (23.5)	2/4 (50.0)
Lung	172/303 (56.8)	47/172 (27.3)	22/47 (46.8)
All	1775/4388 (40.5)	338/1775 (19.0)	147/338 (43.5)

Clinical Infectious Diseases 2009; 48:1657–65

European Survey TB (ESGICH)

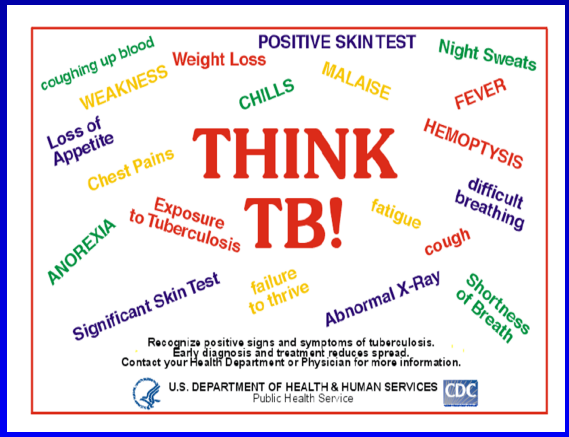
(16 European countries, 50 transplant programs)

- **Screening of TB in SOT candidates**
  - systematically 61%
  - only in patients with risk factors 30%
  - no screening 9%
- **Treatment of latent TB (Prophylaxis)**
  - prior to liver TX 38%
  - no treatment LTB 5%-18% (depending on the organ)
  - considered a temporary contraindication for TX 32%

Boillat-Blanco N, Aguado JM, Manuel O et al. *Transpl Int*. 2013;26:e69-70.

Conclusions

- ✓ *Incidence > general population*
- ✓ *Mortality of SOT recipients with TB has improve in the current era*
- ✓ *Diagnosis of active TB is challenging because of unusual manifestations*
- ✓ *Treatment requires control of interactions*
- ✓ *Prophylaxis reduces the risk of developing TB, but is complicated because of:*
  - *Difficulty in identifying pts at risk*
  - *Toxicity of therapy*



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