Diploma thesis

Screening and therapy for latent tuberculosis (LTB) before liver, kidney and heart transplantation at the LKH Graz between 2007 and 2012

Prevalence of LTB in transplant candidates at the LKH Graz

by

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Graz am 06.12.2020 *Piet Rosenstock eh*

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List of abbreviations

BCG	*Bacillus Calmette–Guérin*
CFP -10	Culture filtrate protein 10
ESAT-6	Early secretary antigenic target - 6
GESITRA	Group for the Study of Infection in Transplant Recipients
HIV	*Human immunodeficiency virus*
IGRA	Interferon-γ-release-assays
LTB(I)	Latent tuberculosis (infection)
MTB(C)	*Mycobacterium tuberculosis (complex)*
NTM	*Non-tuberculous mycobacteria*
SD	Standard deviation
TB	Tuberculosis
TBnet	Tuberculosis network European trials group
THT	Tuberkulin-Hauttest
TNF-alpha	Tumour necrosis factor alpha
TST	Tuberculin skin test
UKF	University clinic of Freiburg
UKS	University clinic of Saarland
WHO	World Health Organization

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Abstract

Introduction/Background: Recommendations for screening and therapy for latent tuberculosis (asymptomatic, non-active infection) in immunosuppressed patients exist, but they are mostly based on data from high prevalence countries. In Austria there is no general approach yet for managing latent tuberculosis in transplant candidates. Handling of those patients is a matter of experience and judgement. Therefore, we took part in a larger study performed by TBnet. The aim was to retrospectively collect data on latent tuberculosis prevalence in transplant recipients, their respective outcome and confounders.

The incidence of active tuberculosis (symptomatic infection) among transplant recipients is stated to be 20- to 74-fold times higher than the general population.

This is in consistence with the consensus statement of the Spanish Society of Infectious Diseases and Clinical Microbiology (GESITRA) from 2009, in which they estimated an incidence of active tuberculosis among solid organ recipients of 512 cases per 100,000 inhabitants per year.

Because active tuberculosis after transplantation is usually based on pre-existing latent tuberculosis, gathering of data about latent tuberculosis prevalence in transplant candidates is highly important.

Materials and Methods: This was an explorative study. Data were collected retrospectively about transplant patients, their comorbidities and latent tuberculosis incidence, preventive treatment and outcome. We used a questionnaire, provided by TBnet, to collect data from the Styrian electronic communication and information-network MEDOCS, which is used by all hospitals of the Styrian hospital network KAGES. The aim was to include all patients who were transplanted at the Medical University Graz between 2007 and 2012. There were no factors, which excluded patients from this study. In this diploma thesis clinical data from all KAGES associated hospitals was evaluated.

Results: In total, there were 261 renal, 11 renal/pancreas, 90 liver and 27 heart transplantations. Latent tuberculosis screening tests were performed in 15.5% (n=58) of all patients. Most frequently (n=59) interferon-gamma-release-assays

were used, either alone (n=57) or in combination with tuberculin skin test (n=2). A single time (n=1) tuberculin skin test alone was used. Out of the 58 screened patients only 3 had a positive test result and received a chemoprevention with isoniazid. None of the 375 transplanted patients developed active tuberculosis after transplantation. We lost follow-up only of 23 patients.

Discussion: There is a lack of dependable data for latent tuberculosis in transplant recipients in countries with low tuberculosis incidence. In this study, which only evaluated data from patients who were transplanted at the Medical university of Graz, we found that even with a presumed higher tuberculosis risk in solid organ recipients, none of our patients developed active tuberculosis after transplantation. This further raises the question how to handle screening and preventive treatment in transplant candidates in countries with a low tuberculosis prevalence like in Austria.

Zusammenfassung

Einleitung/Hintergrund: Während Empfehlungen für das Screening und die Therapie der latenten Tuberkulose bei TransplantationskandidatInnen existieren, basieren diese hauptsächlich auf Daten aus Ländern mit hoher Tuberkulose-Prävalenz. Der Umgang mit TransplantationskandidatInnen in Regionen mit allgemein niedriger Tuberkulose-Inzidenz ist eine Frage der Erfahrung und Einschätzung des behandelnden Arztes. In Österreich gibt es noch keinen allgemeinen Ansatz für den Umgang mit latenter Tuberkulose bei TransplantationskandidatInnen.

Deshalb haben wir an einer größeren Studie von TBnet teilgenommen. Ziel war es retrospektiv Daten über die Prävalenz von latenter Tuberkulose bei TransplantationskandidatInnen zu sammeln, die an unserem Klinikum transplantiert wurden.

Die Inzidenz von Tuberkulose nach einer Transplantation ist unter Organempfängern laut Literatur zwischen 20-74-mal höher als unter der normalen Bevölkerung.

Dies ist im Einklang mit der 2009 veröffentlichten Konsenserklärung der Spanischen Gesellschaft für Infektionskrankheiten und Klinischen Mikrobiologie (GESITRA), welche die Inzidenz auf 512 Fälle pro 100.000 Einwohner pro Jahr schätzte. Nachdem Tuberkulose bei TransplantationskandidatInnen am häufigsten aus einer latenten Tuberkuloseinfektion hervorgeht ist es wichtig, dass Erkenntnisse über die Prävalenz von LTB bei diesen PatientInnen erlangt werden.

Materialien und Methoden: Zur Bestimmung der Prävalenz der latenten Tuberkulose bei TransplantationskandidatInnen wurde in dieser explorativen Studie retrospektiv Daten von TransplantationskandidatInnen, ihre Komorbiditäten, deren Behandlung und deren Outcome erfasst. Zur Datenerhebung haben wir mit einem Fragebogen von TBnet Daten aus dem steirischen elektronischen Kommunikations- und Informationsnetzwerk MEDOCS erhoben. Vorgabe und Grundlage dieser Studie waren alle TransplantationskandidatInnen am Universitätsklinikum Graz zwischen 2007-2012. Es gab keine Faktoren, welche PatientInnen von dieser Studie

ausschlossen. In dieser Diplomarbeit wurden patientenbezogene Daten aus allen KAGES assoziierten Landeskrankenhäusern erfasst und ausgewertet.

Ergebnisse: Im Zeitraum 2007 - 2012 gab es insgesamt 261 Nieren-, 11 Nieren-/Pankreas-, 90 Leber- und 27 Herztransplantationen. Screening-Tests auf latente Tuberkulose wurden bei 15,5% (n=58) aller PatientInnen durchgeführt. Am häufigsten wurde ein Interferon-Gamma-Release-Assay eingesetzt (n=59), entweder alleine (n=57) oder in Kombination mit dem Tuberkulin-Hauttest (n=2). In einem Fall (n=1) wurde ausschließlich ein Tuberkulin-Hauttest appliziert. In nur drei Fällen fiel der Screening-Test positiv aus. Jeder dieser 3 PatientInnen erhielt eine Chemoprävention mit Isoniazid. Nach der Transplantation wurde bei keinem der 375 TransplantationskandidatInnen eine aktive Tuberkulose beobachtet. Bei 23 PatientInnen konnten keine Daten zur Nachkontrolle eruiert werden.

Diskussion: Belastbare epidemiologische Daten zur Prävalenz der latenten Tuberkulose bei TransplantationskandidatInnen in Regionen niedriger Tuberkulose-Inzidenz sind rar.
In dieser Studie, welche sich nur auf Patientendaten von in Graz transplantierten PatientInnen fokussiert, konnte trotz dem theoretisch erhöhtem Tuberkulose-Risiko bei TransplantationskandidatInnen in der Steiermark in keinem Fall nach der Transplantation eine aktive Tuberkulose beobachtet werden.
Es stellt sich somit die Frage, mit welchem Ansatz das Screening auf latente Tuberkulose und deren Behandlung bei TransplantationskandidatInnen in der Steiermark, beziehungsweise in Österreich, gerechtfertigt ist.

1 Introduction

1.1 Tuberculosis

1.1.1 Epidemiology

There are estimated 1.7 billion people infected with *Mycobacterium from the Mycobacterium tuberculosis complex (MTBC)* worldwide (1). Around 5-10% of these people fall sick with active (symptomatic) TB in their lifetime (1,2). It is one of the top 10 causes of death in the world and the most frequent infection from a single infectious agent. Around 10 million people worldwide fell sick with TB in 2017. The majority (90%) of these people were older than 15 years of age (1).

However, in most high income countries TB is a rare infectious disease with only an estimated incidence of <10 new cases per 100,000 people (1). In detail, there have been 8.2 new cases per 100,000 in Austria in 2016. In Austria there were only 71 reported deaths from TB with 634 incident cases in 2016 (3).

1.1.2 Pathogenic agent

In general, Mycobacteria can be divided in three groups: the *Mycobacterium tuberculosis complex*, the *Mycobacterium leprae* and *nontuberculous mycobacteria* (4).

The pathogenic agent of tuberculosis is in 95% *MTB*. Other pathogenic agents of the *MTBC* are *Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti, Mycobacterium canettii, Mycobacterium pinnipedii, Mycobacterium mungi* (2).

MTB is an obligatory aerobic, acid-resistant pathogenic bacterium. Due to the mycolic-acids and mycosides present in their cell wall it is especially resistant against external factors (5).

Three components contained in the cell wall make mycobacteria so special:

“Cord-factor” or trehalose-6,6′-dimycolate is the most prevalent lipid (6). It is the cause of the plait-like or garlandlike growth of *MTB* in cultures (5,7).

Lipoarabinomannan is a lipopolysaccharide which interferes with the activation of macrophages through interferon-γ and additionally causes them to produce TNF-alpha (7).

Muramyl-dipeptide is a peptide also contained in the cell-wall with complex immunomodulatory functions (7).

1.1.3 Infection

Infection with *MTB* typically occurs through contact with patients suffering from open lung TB. The pathogens are transmitted by droplets produced by speaking, coughing or sneezing. An infection through functional skin or mucous membrane is presumed not to be possible (8). Long-term intensive contact with highly infectious patients in poorly ventilated rooms is one of the highest risks of infection with pathogens. While the risk of becoming infected with pathogens depends mainly on exogenous factors, the risk of developing TB depends mainly on endogenous factors (9).

The complement system and macrophages play a major role in the defence and containment of *MTB*. *MTB* binds complement receptor CR3 and thereby stimulates phagocytosis. Lysosomes cannot eradicate the bacteria due to mycobacterial components, so that the bacteria can survive inside of the cell (7).

Immunocompetent people form epithelioid-cell granuloma through direct cytotoxic effect and component of the mycobacterial cell wall (7). Granuloma are usually able to seal *MTB* off from the host. Inside, the mycobacterium “switches to a non-replicating but energy-generating life style” (10).

Although unclear exactly how, in 10% of cases this latent infection can reactivate even after decades and thus cause post-primary TB (11).

1.1.4 Stages of tuberculosis

1.1.4.1 Latent tuberculosis infection

When *MTB* bacilli persist within the host, without causing symptoms it is called latent tuberculosis infection (LTBI). Usually this happens after an immunocompetent host get infected but cannot eradicate the bacilli (12).

If the patient does not show any clinical symptoms or even no radiographic signs but will respond positive to either interferon-γ-release-assays (IGRA) or tuberculin skin test (TST) we can assume that the patient is in a latent state of infection.[1] The state of immunocompetence in a healthy person can be compromised, for example through HIV, immunosuppressive drugs or malnutrition, which increases the risk of reactivating the infection and developing TB (2,12).

1.1.4.2 Primary tuberculosis

Primary TB describes the initial infection with *MTB* and the development of TB symptoms or signs in a previously healthy patient shortly after the infection. Most of the time the primary infection remains asymptomatic, while pleuritic symptoms can occur in some patients. In primary pulmonary TB coughing, shortness of breath and chest pain are typical symptoms (13). Typical radiological features are middle lobe infiltrates and hilar lymphadenopathy. However, other presentations like miliary TB or any kind of extrapulmonary manifestation are possible (2).

1.1.4.3 Postprimary tuberculosis

Immunocompetent adults are most susceptible to this disease. After a person has fended off the first infection with *MTB* and developed immunity, reactivation of previously dormant and in granuloma locked-in mycobacteria can lead to the development of a late onset symptomatic TB, the so-called postprimary TB. Postprimary TB can develop months or even decades after initial infection (14).

In contrast to the primary TB, usually the upper lobes of the lung are affected without involving lymph nodes or other organs (15). In pulmonary cavities the bacilli can

[1] Presumed other factors (e.g. immunosuppression or vaccination with BCG), which could compromise the sensitivity and specificity, are not at play.

proliferate and are the cause of almost 100% of the transmission of *MTB* between people (14).

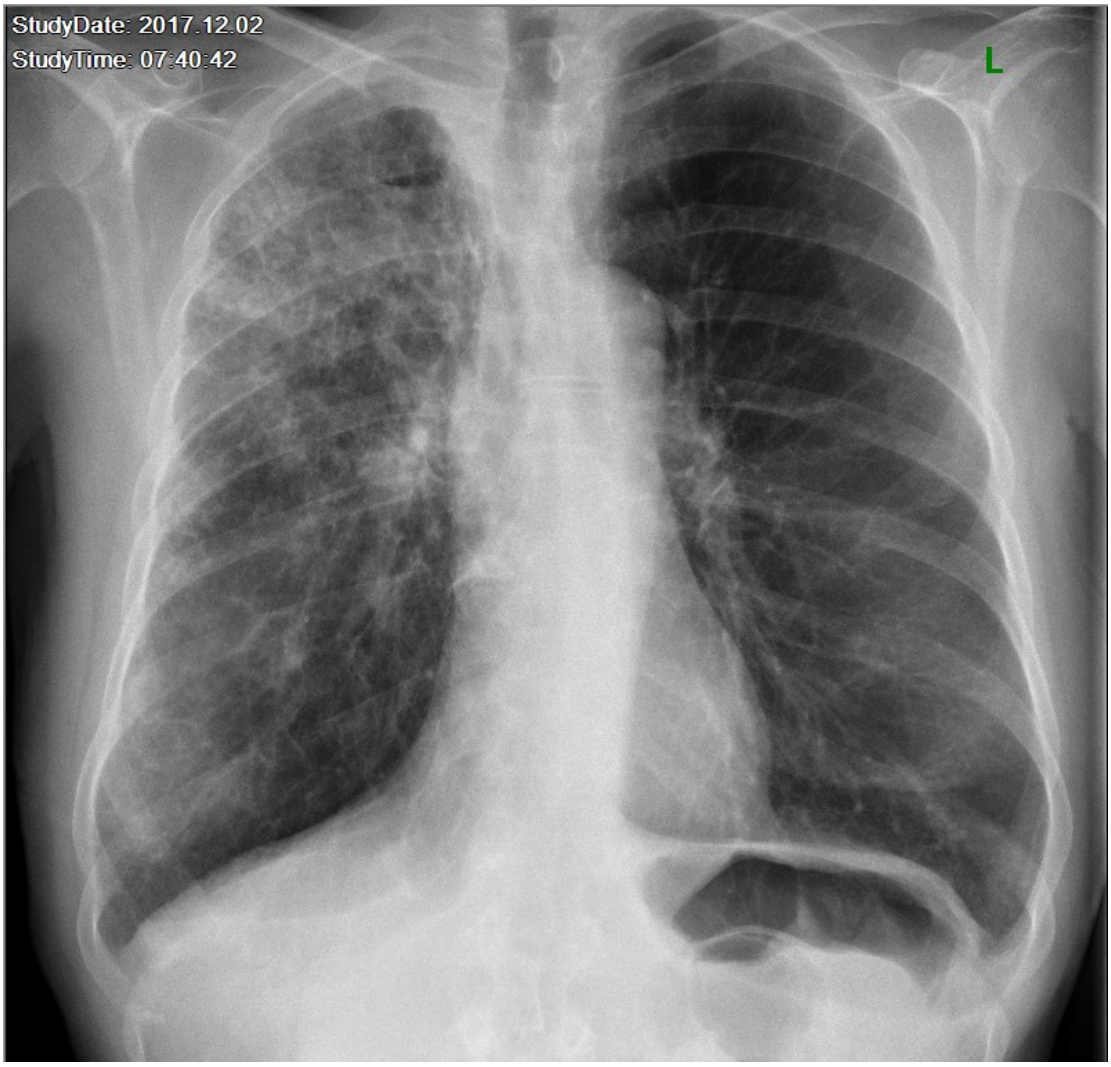

Figure 1: Upper lobe pulmonary infiltrates and small cavity in postprimary tuberculosis

1.1.5 Diagnosis

There are two main tests performed to assess if an individual has LTBI. Both have advantages and disadvantages for the diagnosis of TB, and both rely on our immune system response.

The lack of a gold standard has made it difficult to determine the sensitivity and specificity of both of these tests. As a recent review and meta-analysis has shown, prospective studies for comparison of these two tests are rare and should be evaluated with caution (16).

TST, also known as Mendel-Mantoux test, uses the delayed hypersensitivity reaction of T-cells (5,9). Usually the WHO – approved tuberculin PPD RT23 is used to be injected intracutaneous into the forearm of the patients. About 48-72h after injection the induration at the injected spot will be assessed. Reference is according to WHO >5mm, in patients who are immunosuppressed or had intensive contact with an infectious individual (9).
A review from 2008 shows that TST seems to lack specificity for people, which have been vaccinated with BCG (17).

IGRA, short for interferon-gamma release assays, are in-vitro immune tests. They rely on the production of IFN-γ by lymphocytes, which will then be measured by ELISA. If there is a latent *MTB* infection present, lymphocyte will produce IFN-γ, when stimulated by ESAT-6 and/or CFP-10. The amount of IFN-γ can be measured and used to determine, whether an individual is positive for LTBI. Indeterminate tests are also possible, when there's a low immune response to the injected peptides. This could be caused by "insufficient lymphocytes, reduced lymphocyte activity due to prolonged specimen transport or improper specimen handling, including filling/mixing of blood tubes, or the inability of the patient's lymphocytes to generate IFN-γ" (2,18).
IGRA seems to have the advantage that it is unaffected by BCG vaccination and should therefore be the preferred test in vaccinated patients (17). The test is also less affected by immunosuppression and thus has advantages in the detection of LTBI in already immunocompromised patients (19).

Both tests should be administered before transplantation and associated immunosuppressive therapy, to ensure the maximum specificity and sensitivity (20). Furthermore IGRAs performed in patients receiving immunosuppressive treatment should be evaluated with care, because of a higher number of indeterminate results (21).

1.1.6 Prevention

The TBnet consensus-statement from 2012 suggests preventive treatment for all TST/IGRA positive transplant candidates. Furthermore, treatment should be

considered for all patients with “high-risk pre-transplant exposure history (even with negative TST or IGRA), residence in an endemic TB region during the early post-transplant period, specific *Mycobacteria tuberculosis* exposure post-transplant, or with a donor history of untreated or incompletely treated LTBI or TB” (20).

Drugs such as isoniazid, rifampicin and fluoroquinolones are recommended either alone or in combination. The decision should be made on availability, regional anti-TB drug resistances, as well as drug interactions. Isoniazid (often in combination with pyridoxine) for 9 months or rifampicin for 4 months are frequently used treatments (20).

The following treatments were recommended by the WHO in 2015: Isoniazid for 6 or 9 months, 3 months regimen of weekly rifapentine plus isoniazid, or 3 - 4 months isoniazid plus rifampicin, or 3 - 4 months rifampicin alone (22).

1.1.7 Risk of tuberculosis in transplant recipients

TB incidence among transplant recipients is suggested to be 20- to 74-fold times higher, than in the general population (23).
A review published in 2016 compared main guidelines and consensus statements and concluded that the prevalence of active TB in solid organ transplant recipients in a low-incidence region (Spain) is 0.48% (24).
A 2018 published review of 2082 TB cases suggests that the overall mean incidence rate of active TB among transplant candidates in cohort studies is 2.37%. For Europe they calculated a TB incidence of 2.57%. Highest incidence among solid organ transplant candidates had kidney transplant recipients at 1.69% (range, 0.027-13.27) (25).
The consensus statement of GESITRA from 2009 concluded, that risk factors for the development of active TB after transplantation include: e.g. type of immunosuppressive therapy (e.g. anti-T lymphocyte antibodies, rejection therapy), history of exposure to *MTB,* positive TST, Diabetes mellitus, Hepatitis C, chronic liver disease, or other coexisting infections (26).

While there is community-acquired or donor transmitted TB in transplant recipients, the most common form of active TB after solid organ transplantation is the reactivation of LTBI (23,25–27).

Risk of developing active TB after transplantation is high, but there is a lack of data for the incidence of LTBI before transplantation for low (<40/100000) or very low (<10/100000) regions.
Data from high-prevalence countries suggests screening all individuals undergoing transplant surgery, but whether this is the best approach for regions with low prevalence of TB is uncertain (24).

1.2 Eurotransplant

Eurotransplant, founded in 1967, is a non-profit international service organization, responsible for the allocation and distribution of organs between the 8 countries which are participating (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands, Slovenia). The aim of Eurotransplant is the optimal use of available organs. Apart from mediation of transplant organs, collection of follow-up data and medical research are top priorities (28).

2 Materials and methods

2.1 Study Objectives

The objectives of this study were:

- What percentage of transplant candidates underwent LTB screening?
- Which tests were used for LTB screening?
- What is the prevalence of LTB in Graz before transplantation and how many LTB positive transplant candidates were treated for LTB?
- Which treatment was used?
- How many transplanted patients developed active TB after transplantation?

2.2 Study Design

The study we participate in, was designed by Prof. Dr. Martina Sester (UKS) and Dr. Berit Lange (UKF) as a retrospective descriptive European multicentre cohort-study. The ethics-commission at the Albert-Ludwigs-university in Freiburg granted permission for this study in June of 2017 (EK296/17).
As part of this larger study the Medical University of Graz joined in collecting data. Without definition of a primary endpoint, this was an exploratory study performed by us. After gathering the data, the complete dataset was sent to the principal investigators, to be included in the study “Influence of screening for tuberculosis on tuberculosis incidence after organ transplantation in regions of tuberculosis incidence of <40/100000”.

The ethics-commission at the medical university of Graz granted permission to us to perform the study in December 2017 (EK30-053 ex17/18). The collection of data was performed from December 2017 to February 2018. All extracted patient-data was evaluated anonymously.
All solid organ-transplant patients at the Medical University of Graz, who received either a heart, liver, kidney or kidney/pancreas transplantation between 2007-2012 were included. There were no factors which excluded candidates from the study.
This diploma thesis evaluates only data from patients who were transplanted in Graz and which are important for our study goals.

2.3 Data Collection and analysis

To collect the data, the Styrian electronic communication and information-network MEDOCS was used. The data were collected using the study-protocol, a questionnaire, given to us by the principal investigators.
The Department of Transplantation Surgery of the Medical University Graz helped us to identify all transplant patients in the given time period.
General patient data were collected. This included date of birth, gender, ethnicity, transplant date, type of transplant and country of birth. We also collected data on comorbidities such as diabetes, alcoholism, smoking and their immigrant status, respectively.
All types of diabetes were included. Alcohol abuse was also included in the study, but according to current guidelines active alcohol abuse is a contraindication for transplantation, so only stopped alcohol abuse was included. Likewise, patients who smoke or have smoked were included in the study as smokers, even if they were occasional smokers.

Most important we gathered data about history of TB (year of onset & if a treatment was performed), history of exposure, about screening tests performed before transplant surgery, whether a chemoprevention was offered and accepted by the patient, if active TB developed after surgery and their respective outcome (alive, dead or loss-of-follow-up).

Screening for LTBI was identified by searching through all laboratory test results the patients received, in addition to doctors' entries.
Collection of data was carried out by means of a questionnaire in the form of a PDF (inserted in the Annex). After finishing, the data was then extracted by the principal investigators and sent back to us in form of an excel sheet. We used Microsoft Excel (Version 16.20, for Mac OS) and IBM SPSS 25 to evaluate the data. Descriptive statistic was used to present results.

In the following, a "renal/pancreas" surgery refers to a simultaneous transplantation of a kidney and a pancreas. Median and mean age results in figures were rounded to whole numbers for a better overview.

3 Results

3.1 Demographic Data

3.1.1 Type of transplant

We evaluated all renal, renal/pancreas, liver and heart transplant recipients. A total of 375 patients underwent surgery and 389 transplantations were performed at the LKH Graz during the period (2007-2012) investigated by us.

Of all performed transplantations, 261 (67.1%) were kidney transplantations, 11 (2.8%) patients received a combined kidney-pancreas transplantation. Altogether 90 (23.1%) patients received a liver transplantation and 27 (6.9%) people underwent heart transplant surgery.

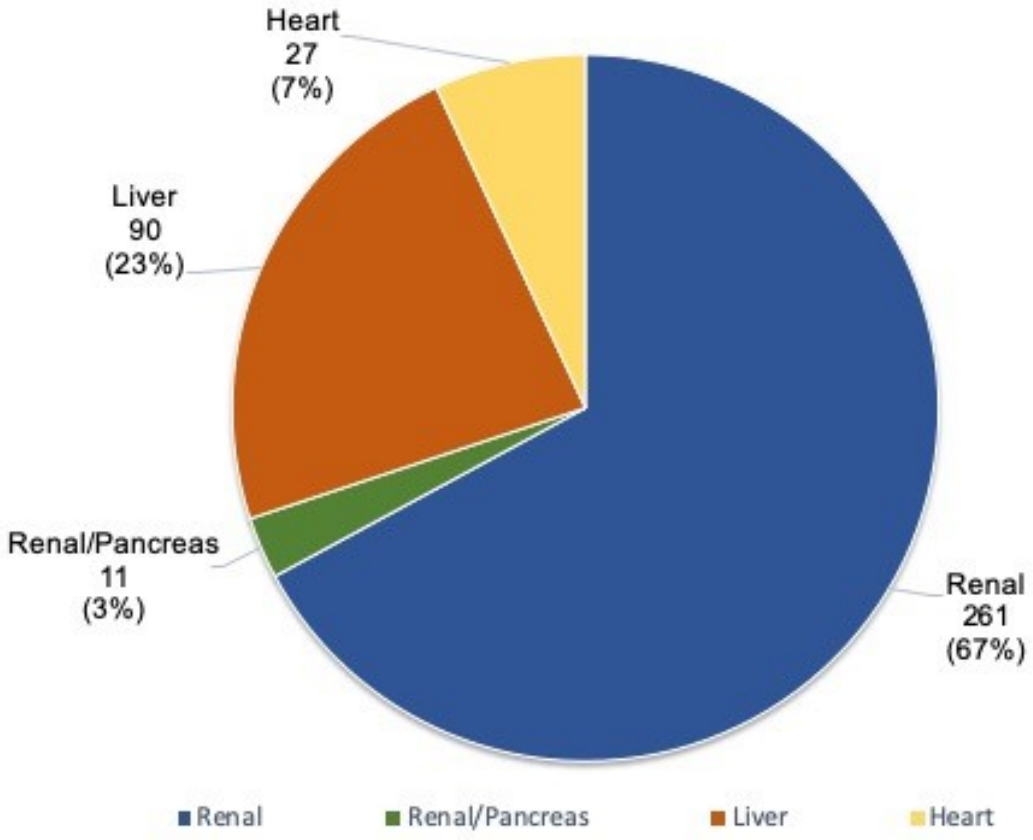

Figure 2: Type of transplant (n=389) during 2007-2012

3.1.2 Median age at date of transplantation

After review of our data, we found that the overall median age for transplantation recipients between 2007 and 2012 was 53.2.

Patients who received a liver transplantation had the highest overall median age at 58.7, followed by heart transplant recipients with a median age of 58.6.

Renal transplant patients had a median age of 50.4 years, while patients who received a combined kidney and pancreas transplantation had a median age of 48.6.

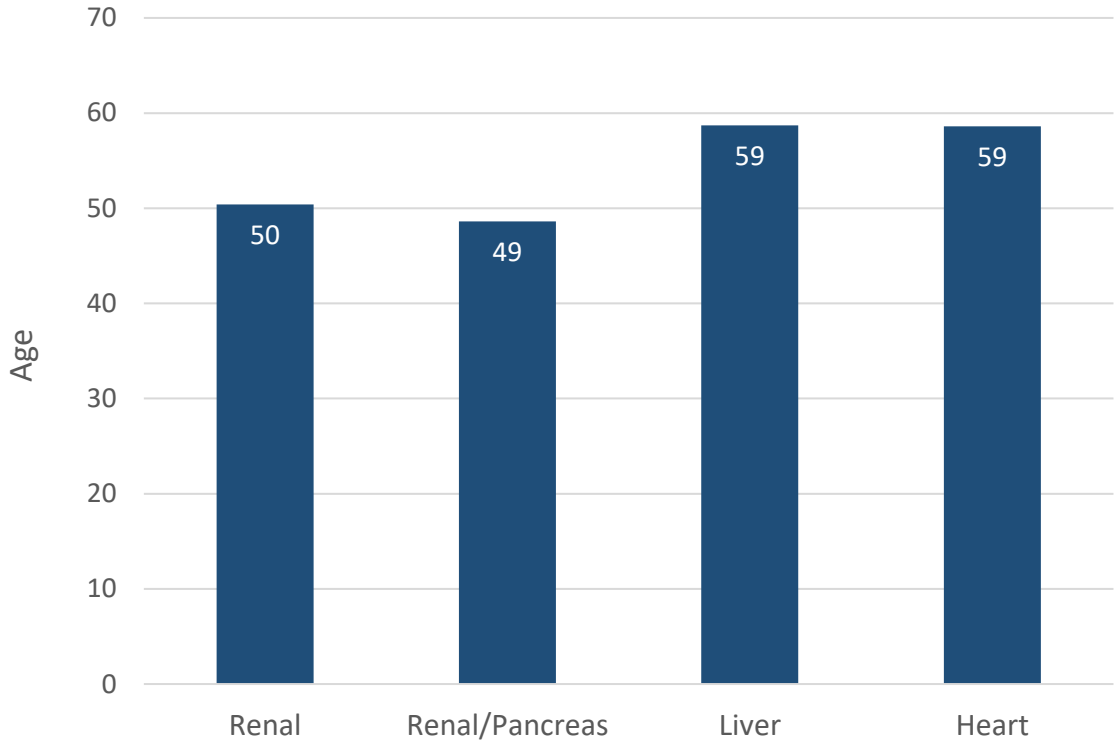

Figure 3: Median age at transplant date

3.1.3 Mean age at transplant date

The mean age of all patients at transplant date was 50.31 years, with a standard deviation of +/-15.91.

The highest mean age had patients who received a liver transplantation at 56.83 (SD +/- 9.32), second highest was those of heart transplant recipients at an average age of 49.47 (SD+/-18.37).

Lowest mean age was those of renal or combined renal/pancreas transplant patients with 48.25 (SD +/- 17.04) and 47.95 (SD +/- 8.36), respectively.

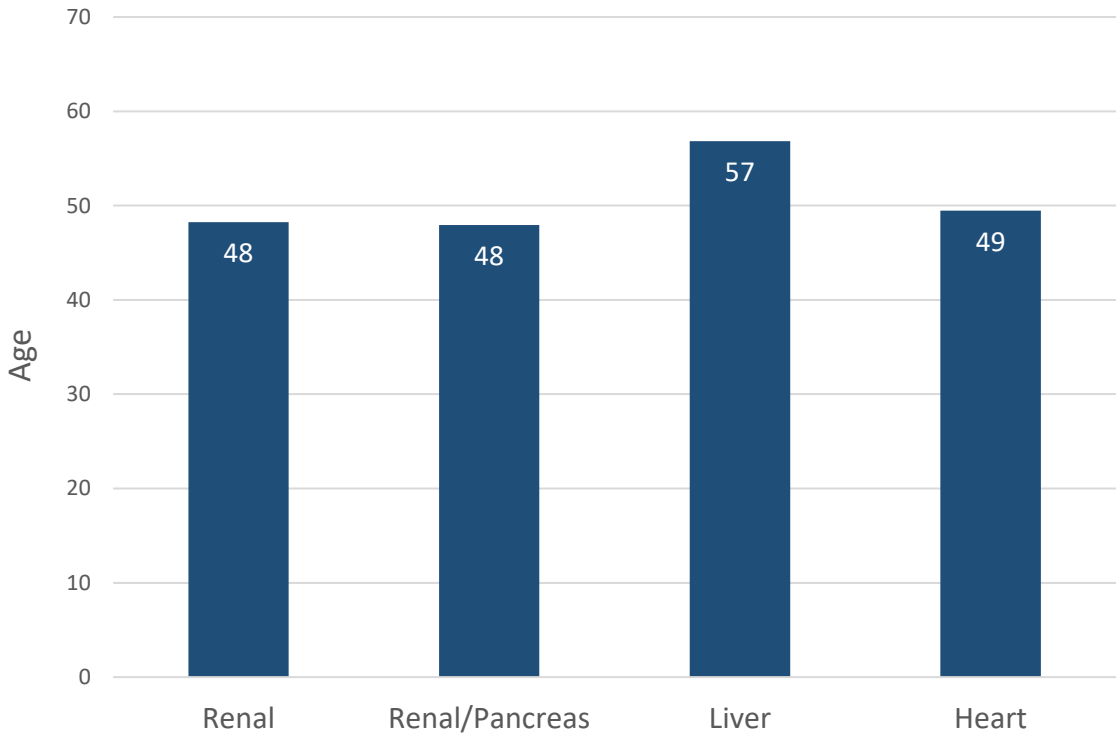

Figure 4: Mean age at transplant date

3.1.4 Comorbidities

We evaluated three main comorbidities. Those were diabetes, smoking and alcoholism. We found that, overall 121 patients suffered from diabetes, while 133 were smokers and 50 patients had a record of stopped alcohol abuse. Overall 161 patients had no comorbidities.

As shown in table 1, all of the patients who received a combined renal/pancreas transplantation were suffering from diabetes. Cases of stopped alcohol abuse were mostly found in patients receiving a liver transplant. No cases of active alcohol abuse were found. All of the comorbidities were more present in male patients.

	Renal (n=257)	**Renal/Pancreas (n=11)**	**Liver (n=81)**	**Heart (n=26)**	Total (n=375)
Diabetes (%)	79 (30.7)	11 (100)	23 (28.4)	8 (30.8)	**121 (32.3)**
Male	59	8	19	7	93
Female	20	3	4	1	28
Smoking (%)	76 (29.5)	6 (54.5)	40 (49.4)	11 (42.3)	**133 (35.5)**
Male	60	5	33	8	106
Female	16	1	7	3	27
Alcoholism (%)	8 (3.1)	0 (0)	40 (50.6)	2 (7.7)	**50 (13.3)**
Male	8	0	31	2	41
Female	0	0	9	0	9

Table 1: Comorbidities: Diabetes, Smoking & Alcoholism

3.1.5 Gender

Of all 389 transplantations 287 were performed in male and 102 in female patients.

There was a total of 273 male and 102 female transplant recipients.

It is apparent that male patients occur more frequently than female patients.

Furthermore, all patients who received multiple organs were male patients.

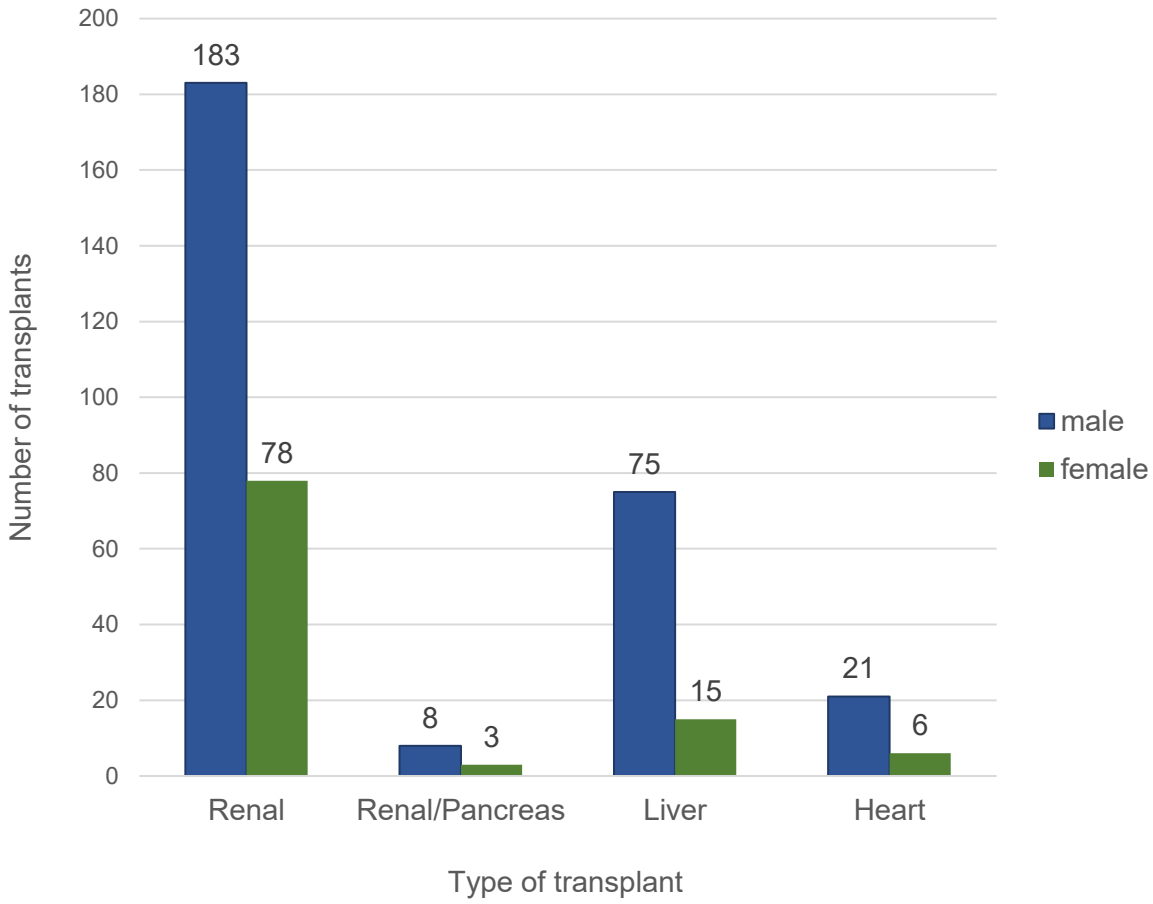

Figure 5: Gender of all transplant recipients between 2007-2012

3.1.6 Country of birth

The majority of organs transplanted were received by Austrian citizens (n=350). Second highest were people from Slovenia with 5 transplantations, while people from all remaining countries had 2 or less transplantations.

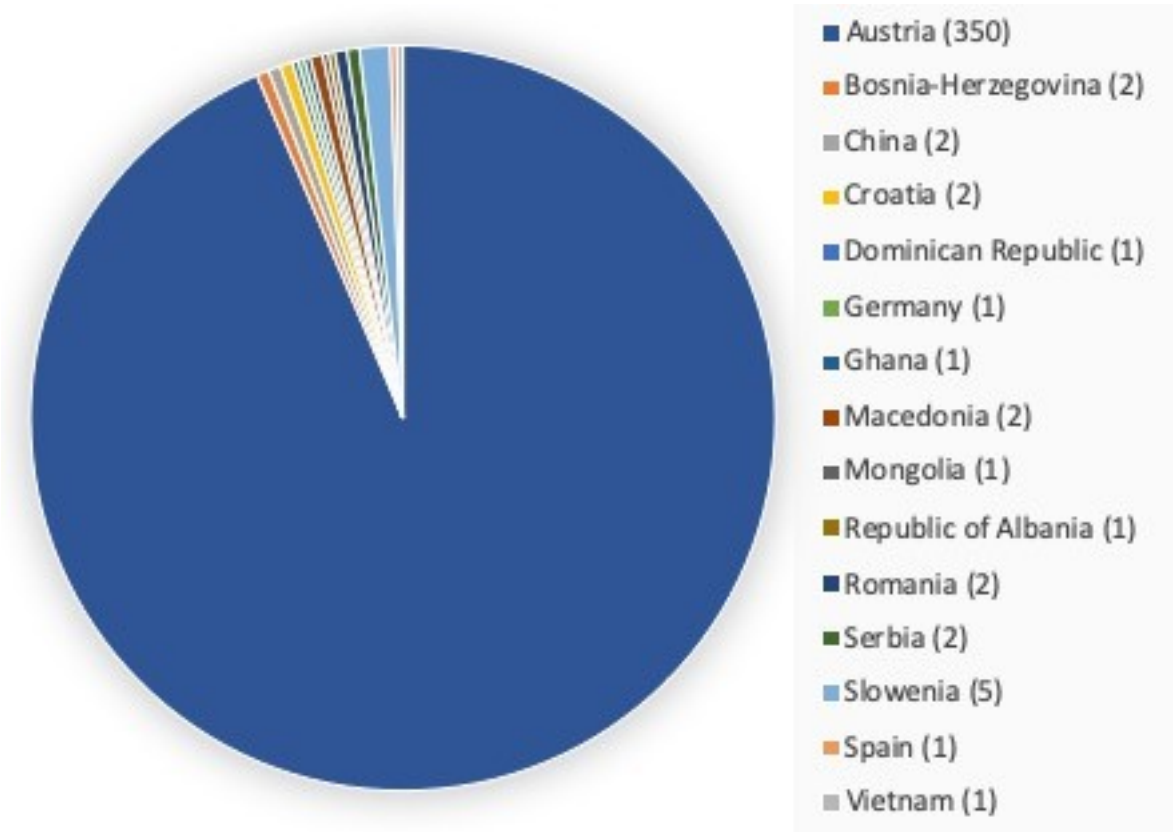

Figure 6: Country of birth

3.2 What percentage of transplant candidates underwent LTB screening?

The majority of screened patients, in total 49, were kidney transplant patients. 2 Renal/Pancreas, 8 liver and 1 heart transplant patient were screened for LTB, respectively.

	Renal	Renal/Pancreas	Liver	Heart	Total
Yes (%)	**49** (19.1)	**2** (18.2)	**6** (7.4)	**1** (3.8)	**58** (15.5)
No (%)	**208** (80.9)	**9** (81.8)	**75** (92.6)	**25** (96.2)	**317** (84.5)
Total	257	11	81	26	375

Table 2: Percentages of patients screened before transplantation

3.3 Which tests were used for LTB screening?

The majority of tests (n=55) used were interferon-γ-release-assays. One time only tuberculin-skin-test was used, while in 2 cases both tests were applied.

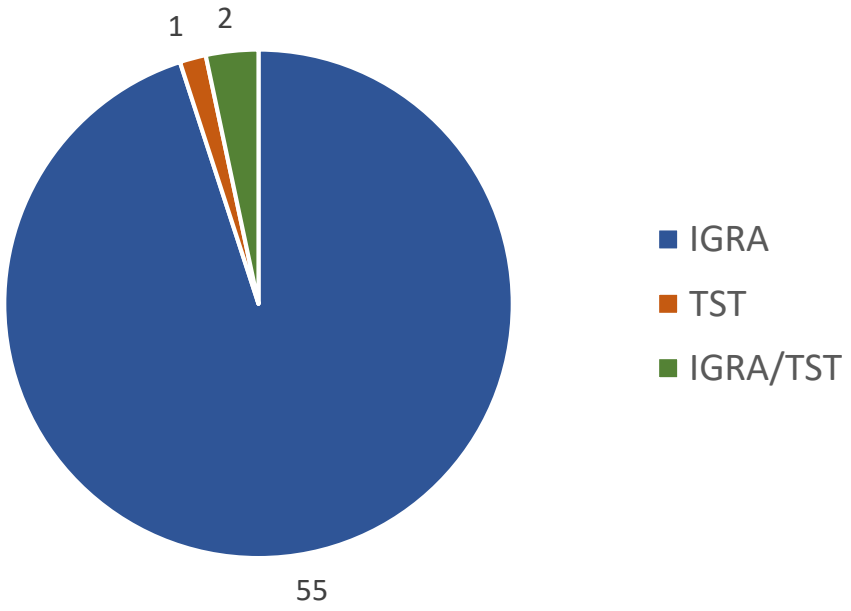

Figure 7: Type of test used to screen for LTB

3.4 What is the prevalence of LTB in Graz before transplantation and how many LTB positive transplant candidates were treated for LTB?

Most of the patients tested for LTB with IGRA, had negative test results.
All 3 patients, which were positively tested with IGRA were also treated with isoniazid. The prevalence of LTB in patients at the Medical university of Graz before transplantation was 0.8%.

In two cases, where TST and IGRA was applied, TST was positive, while IGRA showed a negative result and no chemoprevention was performed.

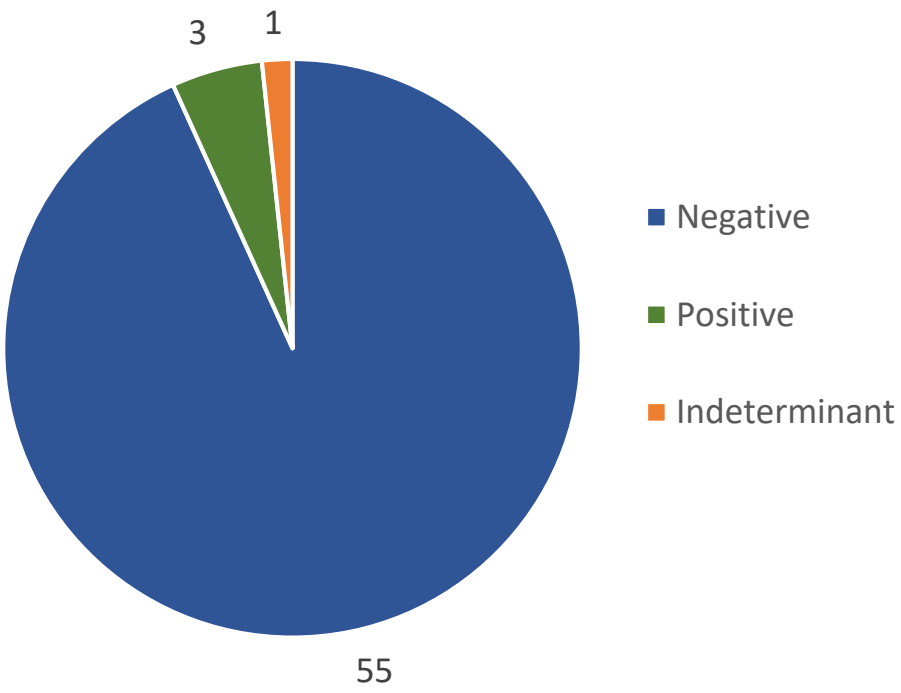

Figure 8: Results of IGRA. Prevalence of LTB before transplantation

3.5 Which treatment was used?

In 3 cases with positive IGRA test result chemoprevention with isoniazid was used. In patients positively tested for LTB (n=3) a 3-months, 6-months or 9-months treatment regimen was followed, respectively.

3.6 How many transplanted patients developed active tuberculosis after transplantation?

After review of all cases after a minimum follow up of 2 years after transplantation and a median follow up time of 6.4 years, we found that none of all patients developed an active TB. We lost follow-up of 23 cases.

Active tuberculosis after transplantation	
Yes (%)	0 (0)
No (%)	352 (93.9)
Loss of follow-up (%)	23 (6.1)
Total	375

Table 3: Development of active tuberculosis after transplantation

4 Discussion

In 2012 the Tuberculosis Network European Trialsgroup (TBnet) provided a consensus statement for screening and handling of LTB in transplant candidates, which mainly based on data from high- or medium incidence countries. However, lack of data from low-incidence countries (<40/100,000) or even very-low incidence countries (<10/100,000) has made it difficult to recommend meaningful LTB management strategies for solid organ transplant candidates in countries like Austria (8.2 new cases per 100,000 in 2016).

To provide more representative data about the prevalence of LTB in transplant candidates from low incidence countries, LTB screening and treatment strategies in European transplant centres as well the frequency of active TB after transplantation in Europe, TBnet initiated a large retrospective multicentre study in 2017. In Austria, only our study group from the Medical University of Graz participated in this TBnet study and provided data on patients transplanted at the Medical University of Graz. These data were analysed and presented in this diploma thesis.

After review of our data we found that from 375 between 2007-2012 in Graz transplanted patients only 15.5% of all transplant recipients in the given time period (2007-2012) were screened for LTB. The low screening rate is based on the lack of national or European LTB screening recommendations before 2012 and also the in general low TB incidence in Austria. Of those transplant recipients screened before transplantation in Graz, only 5% (3/58) revealed a positive test result and chemoprevention with isoniazid was performed.

None of all 375 transplant recipients developed active TB during their posttransplant follow-up time.

Due to the limited number of patients transplanted in Graz in the given time period, we should be careful to draw general conclusions. However, we observed that even with guidelines and recommendations missing during 2007-2012 and LTB screening performed in less than 20% of our cohort, not one of the in Graz transplanted patients developed active TB after transplantation.

This may suggest, that even with a 20-74 fold higher risk of developing active TB under immunosuppressive therapy, there might no need for a general approach in

screening all transplant patients in a very low incidence country like Austria (23). Such an approach would be in contrast to the review published in 2016, which summarized that all but 2 current guidelines suggest strict LTB screening all transplant candidates (24).

Cost/benefit ratio of screening all patients should be further carefully evaluated. LTB screening of all patients in a low prevalence setting will result in relevant number of false-positive test results and overtreatment of patients.

This raises the risk of unnecessary drug related complications as isoniazid and rifampicin can cause many side effects. For liver transplant candidates drug induced hepatic toxicity is of special concern. Further, especially for rifampicin drug-drug interactions have to be considered.

But LTB treatment is also a matter of cost. These are less related to the direct cost of the used medication as isoniazid and rifampicin are quite affordable. The costs of LTB treatment are much more associated with regularly blood tests (in case of isoniazid LTB treatment every 4 weeks over a period of 9 month) and additional medical and organisational efforts to ensure a safe LTB treatment.

Based on our results, for a very low TB prevalence country like Austria we would suggest a more individualized LTB screening and treatment approach with view on individual LTB risk factors. However, for such an individualized LTB screening and treatment approach, predictors and risk factors (such as past exposure to open lung TB, origin from a high TB endemic country, incompletely treated TB, positive IGRA or TST or conspicuous radiological findings) for the development of posttransplant TB has to be better defined and prospectively evaluated in a very low TB prevalence country like Austria (29).

Since reactivation of LTBI is the most common form TB among solid organ recipients, it is of great importance that dependable data on prevalence of LTB in transplant candidates in low-prevalence countries is acquired (23,25–27). Moreover, in Austria the rate of transplant associated active TB cases should be registered, which is actually not the case.

The retrospective nature of our study holds some limitations. We must assume that all of the data collected in the Styrian communications system MEDOCS are

accurate and complete. Data collected from patients' memory is susceptible to recall bias, which can lead to inaccurate doctors' entries, which then may lead to inaccurate conclusions. This effects especially the history of and exposure to TB.

To further scrutinise LTB and development of TB among solid organ transplant patients we would recommend carrying out a prospective study with an even higher number of patients in the future.

To better determine the presumed rate of LTB in transplant candidates (by positive pretransplant IGRA test results), an additional study with the same study concept should evaluate patients from the Medical University of Graz transplanted between 2012 – 2017. Following the European TBnet recommendations from 2012, since 2012 most solid organ transplant patients from the Medical University of Graz were screened for LTB before transplantation. The screening rate will be nearly 90% and a reliable conclusion about the real LTB rate could be accomplished. In this further study also Styrian lung transplant patients should be involved. Lung transplantation for these patients is generally performed in Vienna, but LTB screening and posttransplant follow up is usually done from Styrian departments of pulmonary diseases or in cooperation with the Medical University of Vienna. Therefore, data will be available also for lung transplant patients.

In conclusion, active TB after solid organ transplantation is a rare event in the low TB prevalence setting of Styria. Further studies are needed to define the best LTB screening and treatment strategies for patients transplanted in Austria.

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5.1 Annex - Questionnaire

Submit by Email | Print Form

Tuberculosis Network European Trialsgroup

TBnet study #52: Management of tuberculosis in transplant recipients

Dear Investigators,

Please complete the form and submit it by Email using the buttons on the top. Please note that at least Adobe Acrobat version 7.0 is required to process these sort of forms. Items numbered in **red** should all be completed, requirement for completion of items numbered in **blue** depends on the previous question.

Center characteristics

This information is only required once per center.

Center ID[1]

Solid organ transplants performed during 2007-2012 (number)

Country of transplant center

Type of screening for tuberculosis generally performed in the center; treatment refers to preventive treatment

If "Other" please describe:

Patient characteristics

1 Investigator (Name, Surname)

2 Patient ID[2]

3 Date of birth

4 Patient gender

5 Ethnicity

6 Transplant date

7 Type of transplant

8 Country of birth

9 if retransplant year of previous transplant

1 for example Initials of investigator and Country code, i.e. Martina Sester, Germany = MSD

2 for example Center ID and consecutive number, i.e.
Patient 1 enclosed by Martina Sester, Germany = MSD-1
Patient 2 enclosed by Martina Sester, Germany = MSD-2

Patient characteristics

10 History of TB: no

if no/unknown, continue with 13

11 *If yes, year of earlier TB (year 4 digits)*: faw

12 *If yes, history TB treatment*:

13 *If yes, year of TB treatment (year 4 digits)*:

14 History exposure:

15 *If yes, year of exposure (year 4 digits)*: afaw

16 Immigrant:

17 *If yes, year of immigration (year 4 digits)*:

18 Diabetes:

19 Alcoholabuse (past/present):

20 Smoker (past/present smoker):

21 Immunosuppressive treatment
(within the last 6 months before transplantation):

22 Initial immunosuppressive drug regimen
tick serveral items by holding the "shift" key if applicable

- Steroids
- Calcineurin inhibito
- MMF
- Azathioprine
- mTOR inhibitor
- IL-2 R Antibody
- Depleting Antibody
- Other
- Unknown

If "Other" please describe:

see "instructions" file for details on drugs

23 Rejection treatment
tick serveral items by holding the "shift" key if applicable

- Depleting antibody
- Steroid pulses
- No
- Other
- Unknown

If "Other" please describe:

see "instructions" file for details on drugs

LTBI screening and treatment

24 LTBI screening before transplantation performed
if no/unknown, continue with 36

25 If yes, type of test for screening
tick serveral items by holding the "shift" key if applicable

- TST
- ELISPOT
- ELISA
- Other (i.e. FACS
- Test unknown

Please insert test results of the screening test that was performed

26 Skin test date

27 Skin test result

28 ELISPOT date

29 ELISPOT result

30 ELISA date

31 ELISA result

32 Other date

33 Other result

34 If test unknown

35 Screening test result

36 Chemoprevention offered
if no/unknown, continue with 41

37 If yes, chemoprevention accepted/performed

38 If accepted/performed, anticipated type of treatment

39 If "Other" please describe:

40 If actual treatment is different from anticipated regimen, state regimen and duration

Outcome

41 Patient outcome (loss of follow-up, alive or dead)

42 If dead, date (month, year/unknown) unknown

43 Date of last known patient assessment
i.e. last visit/document in patient chart

44 Active tuberculosis after transplantation
if no/unknown, continue with 51

45 If yes, date of diagnosis unknown

46 If yes, means of diagnosis confirmation
tick serveral if applicable

- AFB staining
- PCR confirmed
- Culture confirme
- Response to trea
- Other
- Unknown

If "Other" please describe:

47 If yes, date of treatment initiation (month, year) unknown

48 If yes (pulmonary/extrapulmonary/both/unknown)

49 If yes, outcome of tuberculosis treatment

50 If "Other" please describe:

51 Actual date of assessment date of completion of the pdf form

Definitions and reporting framework for *tuberculosis - 2013 revision., WHO 2013, Geneva*