Grand Rounds: Tuberculosis & Transplantation - Diagnosis & Management of Donor-Derived Infection

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Tuberculosis & Transplantation – Diagnosis & Management of Donor-Derived Infection
Overview

• Background
  – Epidemiology of TB in Transplantation
  – Donor-Derived TB
• Organ Procurement Process
  – Timing & Challenges
  – Deceased Donor Screening
• Diagnosis in Deceased & Living Donors
• Management
  – Potential Donors
  – Organ Recipients

Background

• *Mycobacterium tuberculosis* infects 1/3 of the world's population
• TB is now one of the most common bacterial causes of solid organ transplant donor-derived infection reported in the U.S.
• Incidence of post-transplant TB
  – 20-74 times higher risk than general population
  – 1% Germany
  – 13.7% India
  – 0.35-6.6% US & Europe
• 33-50% of post-transplant disease is disseminated or extrapulmonary
• 4% of post-transplant TB cases are donor-derived

Morris MI. Amer J Transpl 2012.
Globalization →
Increased TB risk in low incidence countries:
  Immigration
  World Travel
Increased TB risk in high incidence countries:
  Availability of Organ Transplantation

Outcomes in Post-Transplant TB

- Mortality up to 30%
  - May be higher in low incidence countries due to delayed diagnosis
- Morbidity including loss of transplant allograft
- Treatment challenges due to complex drug interactions with immunosuppressive agents
Sources of TB in Transplant Recipients

- Donor-Derived – transmitted through organ allograft
  - Likely more common in lung recipients
- Reactivation in Recipients with untreated or unrecognized latent or active TB
- Post-transplant exposure
  - Likely more common in high TB incidence countries

Donor-Derived TB Cases
**2007 TB Transmission Donor History**

- EtOH abuse, homeless, recent incarceration
- Treated for pneumonia 6 months before death, retreated 1 month before death
- PPD negative at both admissions, no AFB testing done
- Admitted with seizures, altered mental status, and aspiration pneumonia
- Death due to cerebral vasculitis
- CSF grew M. tuberculosis 3 weeks post-transplant
- OPOs & transplant centers notified 6-7 weeks after death
- Donor & Recipient TB sequencing matched

MMWR 2008.

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**Recipient A:** 50 y/o female kidney recipient presented with fever, pancytopenia, sepsis 6 weeks post-transplant → bone marrow AFB + → died 9 weeks post-transplant
Blood, liver, spleen, lung cultures matched donor TB typing.

**Recipient B:** 23 y/o female kidney recipient presented with fever, headache 7 weeks post-transplant → CSF AFB negative, bone marrow granulomas, AFB negative → kidney biopsy AFB negative, AFB grew from blood & urine matched to donor strain → survived.

Liver Recipient: 59 y/o male started on TB treatment 2 months post-transplant. No symptoms. Liver biopsy 7 months post-transplant TB culture negative.
Donor-Derived TB – Presentations & Outcomes

TABLE 2
Clinical presentation, therapy and outcome of tuberculosis (TB) transmitted by solid organ transplantation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Months to onset</th>
<th>Clinical presentation</th>
<th>Weeks until therapy</th>
<th>Therapy</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>10</td>
<td>1</td>
<td>Pulmonary TB</td>
<td>2</td>
<td>INH, Rif and Eth for &gt;3 months</td>
<td>Cure</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>Gastrointestinal TB</td>
<td>NR</td>
<td>INH and Rif for 6 months</td>
<td>Graft failure</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>Miliary TB</td>
<td>NR</td>
<td>INH and Rif for 2 months, then Pyr, Eth and Rif for 2 months</td>
<td>Death</td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>Miliary TB</td>
<td>4</td>
<td>INH, Rif and Eth for &gt;6 months</td>
<td>Graft failure</td>
</tr>
<tr>
<td>18</td>
<td>7</td>
<td>Pulmonary TB</td>
<td>10</td>
<td>NR</td>
<td>Death</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>Miliary TB</td>
<td>NR</td>
<td>&gt;3 agents, including INH</td>
<td>Cure</td>
</tr>
<tr>
<td>14</td>
<td>9</td>
<td>Pulmonary TB</td>
<td>NR</td>
<td>INH, Eth and Pyr</td>
<td>Cure</td>
</tr>
<tr>
<td>16</td>
<td>11</td>
<td>Graft TB abscesses</td>
<td>1</td>
<td>INH, Rif, Eth and Strep for 2 months, then Eth and Rif for 2 months</td>
<td>Death</td>
</tr>
<tr>
<td>15</td>
<td>12</td>
<td>Graft granuloma</td>
<td>NR</td>
<td>“Standard therapy” for 9 months</td>
<td>Graft failure</td>
</tr>
<tr>
<td>17</td>
<td>14</td>
<td>Pulmonary TB</td>
<td>1</td>
<td>INH, Rif, Eth and Pyr tapered to INH and Pyr (total 36 weeks)</td>
<td>Cure</td>
</tr>
<tr>
<td>19</td>
<td>15</td>
<td>Graft granuloma</td>
<td>8</td>
<td>Pyr, Eth and Cipro for 2 months with 2 weeks of Strep, then INH, Eth and Cipro for 9 months</td>
<td>Cure</td>
</tr>
</tbody>
</table>

Cipro, Cipro/floxacin; Eth, Ethambutol; INH, Isoniazid; NR, Not reported; Pyr, Pyrazinamide; Rif, Rifampicin; Rif, Rifabutin; Strep, Streptomycin


Patient | Age/sex | Organ | Donor | TB status of donor | Recipient TB status |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32/M</td>
<td>Kidney</td>
<td>LR</td>
<td>TST positive, CXR normal</td>
<td>TST negative, CXR normal</td>
</tr>
<tr>
<td>2</td>
<td>14/F</td>
<td>Kidney</td>
<td>LR</td>
<td>TST positive</td>
<td>TST negative</td>
</tr>
<tr>
<td>3</td>
<td>34/M</td>
<td>Kidney</td>
<td>C*</td>
<td>TST negative, CXR unknown, Mycobacterium tuberculosis grown 3 weeks postmortem</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>35/M</td>
<td>Kidney</td>
<td>C*</td>
<td>TST negative, CXR unknown, Mycobacterium tuberculosis grown 3 weeks postmortem</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>46/F</td>
<td>Kidney</td>
<td>C1</td>
<td>CXR normal, TST unknown</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>48/M</td>
<td>Kidney</td>
<td>C1</td>
<td>CXR normal, TST unknown</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>23/F</td>
<td>Heart/Lung</td>
<td>C</td>
<td>NR</td>
<td>TST negative</td>
</tr>
<tr>
<td>8</td>
<td>NR/M</td>
<td>Kidney</td>
<td>LR</td>
<td>Post-transplant developed active TB</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>42/F</td>
<td>Lung</td>
<td>C2</td>
<td>CXR normal, but both recipients developed the same strain of TB</td>
<td>NR</td>
</tr>
<tr>
<td>10</td>
<td>63/F</td>
<td>Lung</td>
<td>C3</td>
<td>CXR normal, but both recipients developed the same strain of TB</td>
<td>NR</td>
</tr>
<tr>
<td>11</td>
<td>1/F</td>
<td>Liver</td>
<td>LR</td>
<td>Post-transplant developed active TB</td>
<td>NR</td>
</tr>
<tr>
<td>12</td>
<td>44/M</td>
<td>Kidney</td>
<td>C3</td>
<td>CXR normal, but both recipients developed the same strain of TB</td>
<td>NR</td>
</tr>
<tr>
<td>13</td>
<td>61/F</td>
<td>Liver</td>
<td>C4</td>
<td>CXR normal, but both recipients developed the same strain of TB</td>
<td>NR</td>
</tr>
<tr>
<td>14</td>
<td>49/F</td>
<td>Lung</td>
<td>C4</td>
<td>CXR, Calcifications and apical opacity, from endemic area</td>
<td>NR</td>
</tr>
<tr>
<td>15</td>
<td>43/M</td>
<td>Liver</td>
<td>C5</td>
<td>From endemic area</td>
<td>TST negative, CXR normal</td>
</tr>
</tbody>
</table>
Donor-Derived Disease Transmission

- Any disease present in the donor that is transmitted to at least one of the organ recipients
- Complicates <1% all transplants
- Multiple regulating agencies
- UNOS – United Network for Organ Sharing
- OPTN – Organ Procurement & Transplantation Network
- DTAC – Disease Transmission Advisory Committee

OPTN Policy 4.5 (11/9/10)

POST-TRANSPLANT REPORTING OF POTENTIAL TRANSMISSION OF DISEASE OR MEDICAL CONDITIONS, INCLUDING MALIGNANCIES. In order to promote prompt notification of potential risk of disease transmission through organ transplantation, all events involving unexpected potential or proven transmission of a medical condition, including infections and malignancies, discovered after procurement of a donor organ must be reported to the OPTN Patient Safety System™.

When an organ recipient is suspected to have, is confirmed positive for, or has died from a potential transmissible disease or medical condition for which there is substantial concern that it could be from donor origin, then the transplant program must notify the Host OPO by phone and provide available documentation to the Host OPO as soon as possible, and not to exceed 24 hours of this knowledge/concern. The transplant center that suspects potential transmission should not wait for all medical documentation that may eventually be available, but must inform the Host OPO and/or the OPTN Patient Safety System to transfer knowledge/concern as soon as possible to all other centers that received organs from the same donor.

When a Host OPO learns of new information regarding a donor (i.e. final culture results, information from autopsy report, etc.) as part of its donor follow-up (See Policy 2.2.5) that indicates risk of potential transmission of disease or malignancy, the Host OPO must report the donor through the OPTN Patient Safety System™.
DTAC Classification System

• Expected or Unexpected
• Probability of Donor-Derived Nature
  – Proven: Pathogen in donor and at least one recipient
  – Probable: Pathogen in one or more recipients with suggestive data about the donor
  – Possible: Evidence to suggest but not prove transmission (includes potential cases prior to 2008)
  – Potential: No transmission occurred - typically because appropriate organ wasn’t used or prophylaxis was used

<table>
<thead>
<tr>
<th>Table 7: Definition of donor-derived TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven transmission</td>
</tr>
<tr>
<td>Requires confirmed evidence of transmission including all of the following:</td>
</tr>
<tr>
<td>- Suspected transmission through transplantation.</td>
</tr>
<tr>
<td>- Laboratory evidence of M. tuberculosis infection in the donor.</td>
</tr>
<tr>
<td>- Laboratory evidence of M. tuberculosis infection in one or more recipients of the same donor.</td>
</tr>
<tr>
<td>- If possible, demonstration of clonality or molecularly identical isolates both in the donor and at least one recipient.</td>
</tr>
<tr>
<td>- Pretransplant testing, if performed, must indicate that the recipient had no evidence of M. tuberculosis infection prior to transplantation.</td>
</tr>
</tbody>
</table>

Morris MI. Amer J Transpl 2012.
Donor-Derived Infectious Disease Transmission
Importance of TB

<table>
<thead>
<tr>
<th>Disease</th>
<th># of donor reports</th>
<th># of recipients with confirmed transmission</th>
<th># of DDD-attributable recipient deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus²</td>
<td>86</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Bacteria³</td>
<td>30</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>Fungus³</td>
<td>30</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>Mycobacteria⁷</td>
<td>26</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Parasitic⁴</td>
<td>21</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Total infections</td>
<td>201</td>
<td>106</td>
<td>29</td>
</tr>
</tbody>
</table>

¹Each report reflects a single donor but may involve multiple recipients.
²Number of recipients with a confirmed infectious disease transmission classified by DTAC as either proven, probable or possible.

Ison MG, Nalesnik MA. Amer J Transpl 2011.

U.S. Donor-Derived TB Cases

- 30 cases of possible/probable/proven donor-derived TB in solid organ transplant recipients described in literature or confirmed by DTAC (9/2012)
- 4 of these cases were from living kidney donors
- 17% recipients died
- Diagnosis often delayed
- Extrapulmonary disease common

Organ Donation & Donor Screening

Solid Organ Transplant Facts

- More than 115,000 people in the U.S. are currently on the organ transplant waiting list (117,317 as of 2/28/13).
- Another name is added to the national transplant waiting list every 12 minutes.
- On average, 18 people die every day from the lack of available organs for transplant.
- 7% of people on the waiting list, > 6,500 each year, die before they are able to receive a transplant.
- 1 deceased donor can save up to 8 lives through organ donation and can save/enhance > 100 lives through tissue donation.

Potential Organ Donor Screening – Deceased Donor

- Local OPO (Organ Procurement Organization) representative evaluates prospective donor & obtains consent
- Detailed history & physical obtained by OPO
- Contraindications to donation ruled out
- Potential donor testing including infection screening
- Donor maintenance in ICU setting
- Recipient identification based on size, ABO matching & immunologic factors, UNOS (United Network for Organ Sharing) criteria

Donor Medical History – ID Aspects

- Previous infections
- Vaccinations
- Occupational exposures
- Travel history
- Transfusions with blood/blood products
- Contacts with HIV, HBV, HCV
- Tattooing, Piercing
- Illicit drug use
- Sexual behavior
- Incarceration
- Animal/insect contact – bats, stray dogs, rodents
The Complex Nature of Donor Screening

- Deceased Donors – History obtained from relatives, sometimes distant or uninformed, often inaccurate
- Living Donors – Often relatives, close friends; may not wish to disclose risk behaviors
  - Incarceration
  - Substance Abuse

Donor Management

- Brain death
- Eval
- Consent
- 6-48 hours
- Aortic cross-clamp
- Referral Pt. on Ventilator
- Meds, Stabilize, Labs, Echo, Bronch Place organs
- Surgical Organ Recovery

Slide provided by Susan Ganz, M.D.
Donor Risk Factors for Tuberculosis

Country of Origin | Incidence > 100/100,000
---|---
Social Risk Factors | Homeless
Incarceration
Alcoholism
Known TB contact
Medical Risk Factors | History of Untreated TB
Radiographic evidence of prior TB
BMI < 18.5
Diabetes Mellitus
Cigarette Smoking
Organ Transplanted | Lung


RISK FACTORS FOR TB IN INDIVIDUALS FROM LOW RISK REGIONS (INCLUDING THE U.S.)

- Close contacts of persons with infectious TB
- Those who spend significant time in areas of the world with high rates of TB (green shaded area on Table 1, and all but the lightest shaded area of Figure 1)
  - >3 months
  - Relief work in a country with high TB risk
- History of injection drug use
- Persons who reside (or ever resided) or worked in institutional settings which resulted in increased risk of exposure to TB (hospitals, nursing homes, correctional facilities, other health care settings, homeless shelters)
- National Health and Nutrition Examination Survey (NHANES) data indicate other higher risk groups among U.S. born persons to include:
  - Non-Hispanic black/African American (5.7%)
  - Older age (4.8% >65 years old)
  - Mexican/Mexican American (2.5%)
  - Low income/poverty (2.8%)

A Moving Target: Tuberculosis Risk by Country of Origin

<table>
<thead>
<tr>
<th>Country</th>
<th>3/4 to 10/000</th>
<th>100-299/10000</th>
<th>50-99/10000</th>
<th>25-49/10000</th>
<th>&lt;25/10000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa with exceptions</td>
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<tr>
<td>Angola</td>
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<tr>
<td>Cambodia</td>
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<td>Cameroon</td>
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<td>Ethiopia</td>
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<td>Gabon</td>
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<td>Ghana</td>
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<td>Kenya</td>
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<td>Madagascar</td>
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<td>Malawi</td>
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<td>Mozambique</td>
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<td>Senegal</td>
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<td>South Africa</td>
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<td>Sudan</td>
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<td>Tanzania</td>
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<td>Uganda</td>
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<tr>
<td>Zambia</td>
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</tbody>
</table>


Most Important Risk Factor for TB in U.S.

- Country of origin
- Latent TB U.S. population
  - Latent TB U.S. born 1.8% US residents
  - Latent TB Foreign born 18.7%

Challenges of Optimizing Testing

- Deceased Donor on Life Support
  - Family willingness to tolerate delays for testing
  - Organ procurement delays awaiting test results
- Availability of Testing at Remote Centers
  - Geography delays testing → delays in organ procurement → poor allograft function
  - Inaccurate results → organ loss
Donor-Derived Disease Testing

- OPTN Policy 4.6 (Screening of Donors)
  - Donor testing must use a FDA licensed, approved or cleared screening test unless such tests cannot be performed prior to transplant
  - In the event that such screening tests cannot be performed prior to transplant, then a FDA approved diagnostic test is permissible to assess the donor
  - The Host OPO shall obtain a history to determine if the donor is "high risk"
  - Known conditions that may be transmitted by the donor organ must be communicated to the transplant centers

- Exceptions
  - Organs from donors with a positive screening test or confirmed medical conditions that may be transmittable, with the exception of HIV, may be transplanted at the discretion of the transplanting program with the informed consent of the recipient


Table 1: Known conditions that may be transmitted by the donor organ that must be communicated to the transplant center prior to transplantation (13)

- Unknown infection of central nervous system (encephalitis, meningitis)
- Suspected encephalitis
- Hepatitis C
- Herpes simplex encephalitis or other encephalitis
- History of JC virus infection (caused progressive multifocal leukoencephalopathy)
- West Nile virus infection
- Cryptococcal infection of any site
- Rabies
- Creutzfeldt-Jacob disease
- Other fungal or viral encephalitis
- Bacterial meningitis
- Infection with HIV (serologic or molecular)
- Active varicella zoster, acute EBV (mononucleosis)
- Serologic (with molecular confirmation) evidence of HTLV-I
- Active hepatitis A or B
- Infection by Trypanosoma cruzi, Leishmania, Strongyloides, Toxoplasmosis
- Active Tuberculosis
- SARS
- Pneumonia
- Bacterial or fungal sepsis (e.g. candidemia)
- Syphilis
- Multisystem organ failure due to overwhelming sepsis, such as gangrenous bowel
- Malignancies other active malignancies (e.g., melanoma, Merkel cell, Kaposi's sarcoma)
- Hodgkin's disease and non-Hodgkin's lymphoma
- Multiple myeloma
- Leukemia
- Acute B cell or T cell agranulocytosis
- Miscellaneous carcinosarcomas
- Any new conditions identified by the CDC as being a potentially communicable disease

Ison MG et al. Amer J Transpl 2009
What Donor Testing is Appropriate?

• Epidemiology
  – Incidence sufficient to justify testing
  – Prevalence high enough in donors to make PPV of test reasonable
• Transmissible by organ transplant – all organs?
• Disease \( \rightarrow \) significant morbidity/mortality
  – Prophylaxis available?
  – Treatable?
• Testing platform exists for screening

How Safe is Safe Enough?

Organ Availability Patient Safety
Compromise Goal: Risk Stratification

- Data for risk focuses on active infection
  - Ideally not using donors with active infection who will clearly be high risk donors
  - Risk for latently infected donors unknown
- Rough guideline for who may pose greatest risk for transmission of TB
- Application likely to vary country to country and even region to region
- May just be a tool to help determine how aggressively to pursue TB diagnosis in febrile patients post-transplant
TB Diagnosis in the Transplant Donor

TB Diagnosis in Potential Donors

- History & Physical Exam
  - Epidemiology
- Testing Options & Challenges
  - Imaging – abnormal CXRs in many due to trauma, disease
  - Tuberculin Skin Test (TST)
  - Interferon Gamma Release Assays (IGRA)
- Clinical Specimens
  - AFB Smear & Culture
  - Nucleic Acid Amplification (NAA)
Properties of T-cell assays

<table>
<thead>
<tr>
<th></th>
<th>ELISA (e.g., QuantiFERON TB gold in tube)</th>
<th>ELISPOT (e.g., T-SPOT. TB)</th>
<th>Intracellular cytokine staining</th>
<th>Skin test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material</td>
<td>PBMC, whole blood</td>
<td>PBMC</td>
<td>PBMC, whole blood</td>
<td>in vivo (skin)</td>
</tr>
<tr>
<td>Volume of blood</td>
<td>3 ml</td>
<td>10 ml</td>
<td>1–2 ml</td>
<td>n.a.</td>
</tr>
<tr>
<td>Time need</td>
<td>20–26 h</td>
<td>20–26 h</td>
<td>8 h</td>
<td>48–72h</td>
</tr>
<tr>
<td>Unit</td>
<td>U or pg/ml</td>
<td>SFU/250,000 PBMC</td>
<td>percentage</td>
<td>mm induration</td>
</tr>
<tr>
<td>Stimuli</td>
<td>antigens, peptides (RD1 derived)</td>
<td>antigens, peptides (RD1 derived)</td>
<td>antigens, peptides (RD1 derived, PPD)</td>
<td>tuberculin PPD</td>
</tr>
<tr>
<td>APC dependence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>n.a.</td>
</tr>
<tr>
<td>Functional analysis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Phenotypical analysis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Knowledge of MHC status</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
</tr>
<tr>
<td>Knowledge of epitopes</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
</tr>
<tr>
<td>Performance in deceased donors/ICU setting</td>
<td>Not known</td>
<td>Not known</td>
<td>Not known/limited knowledge</td>
<td>Not known</td>
</tr>
</tbody>
</table>

Slide courtesy of Martina Sester, PhD.

Table 4: Comparison of TST and IGRA.

<table>
<thead>
<tr>
<th>Test</th>
<th>Availability</th>
<th>TAT</th>
<th>Advantages/disadvantages</th>
<th>Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>Widely available</td>
<td>48–72 h</td>
<td>Low cost; Need to return to have test reading; HCW expertise in administering and reading test; False positive after BCG vaccination, NTM</td>
<td>Living donors but not feasible in deceased donors</td>
</tr>
<tr>
<td>QuantiFERON-TB Gold</td>
<td>FDA approved</td>
<td>~24 h</td>
<td>+Cost; No need for second visit; Indeterminate results in immunosuppression; Lymphopenia may affect test; Not evaluated in deceased donors</td>
<td>Living or deceased donors</td>
</tr>
<tr>
<td>T-SPOT.TB</td>
<td>Widely available</td>
<td>~24 h</td>
<td>+Cost; No need for second visit; Indeterminate results in immunosuppression; Not evaluated in deceased donors</td>
<td>Living or deceased donors</td>
</tr>
</tbody>
</table>

There is no data yet on the clinical utility or test performance of IGRA in the deceased donor population, or similar populations such as critical care unit patients or patients with head injury. It is unknown whether brain death may impact the performance of this assay.

IGRA Performance in the Deceased Donor

The gamma-interferon assay for diagnosis of bovine tuberculosis in cattle: conditions affecting the production of gamma-interferon in whole blood culture

JS ROTHEL*, SL JONES†, LA CORNER*, JC COX† and PR WOOD*

SUMMARY: The recently developed gamma-Interferon (IFN-γ) assay system for the diagnosis of bovine tuberculosis in cattle has been accredited by the Standing Committee on Agriculture for use in Australia. In this test system, whole blood is incubated with tuberculin purified protein derivative (PPD) antigens for 16 to 24 h. The plasma is then collected and assayed for IFN-γ production using an enzyme immunoassay (EIA). The assay system has proven to be a rapid, sensitive and inexpensive method for measuring antigen specific cell-mediated reactivity when compared with the more traditional lymphocyte proliferation assay. The IFN-γ assay is the first in-vitro cellular assay to be used as a routine diagnostic test in veterinary medicine. While the IFN-γ EIA has been optimised, several conditions affecting the production of IFN-γ in whole blood culture needed investigation. We determined that optimal IFN-γ production required the use of heparinised blood, cultured with 20 μg/ml of PPD within 8 h of collection. The use of blood collected post mortem resulted in reduced sensitivity for the assay. The kinetics of IFN-γ release were established as were the effects of intradermal tuberculin testing on the IFN-γ assay. Aust Vet J 69: 1 – 4


IGRA Use in Deceased Donors

- Insufficient evidence to recommend IGRA use
- Results usually not available in 24 hrs
- High rate of indeterminate results (0-16%)
- Repeat testing generally not feasible
- Cell-mediated immunity depressed following head injury → non-response to mitogen control
- Limited data in pediatrics
- Does not distinguish between latent & active TB
IGRA Challenges in Transplant Donors

- Positive tests in low risk population may represent false positive
- More useful in living donors
  - Epidemiologic history available
  - Healthy donor → reliable test performance
  - Transplant may be delayed
    - Diagnostic evaluation
    - Treatment for latent or active TB

IGRA Use in Deceased Donors

- Donors with an indeterminate or positive IGRA should not be excluded from donation, they should be screened for active TB
- Highest risk of transmission to recipients is unrecognized active TB, not latent TB
- IGRA testing may be used to follow & offer treatment to recipient
- Donation should be deferred for active TB
Molecular Testing of Deceased Donors

- Lung donors should be screened by bronchoscopy with AFB smear & culture
- Nucleic acid amplification preferred → rapid results
- High TB incidence countries have access to Xpert MTB/Rif → results in < 2 hours

TB Management of the Transplant Donor
### Clinical Management of Latent TB in Donors

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Transmission Risk</th>
<th>Recommendation – Living Donor</th>
<th>Recommendation – Deceased Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/O TB Exposure or Significant Risk Factors – not tested</td>
<td>Variable</td>
<td>Test</td>
<td>Insufficient data on testing; Monitor clinically</td>
</tr>
<tr>
<td>H/O Latent TB – treated appropriately</td>
<td>Lower</td>
<td>Monitor recipient clinically</td>
<td>Monitor recipient clinically</td>
</tr>
<tr>
<td>H/O Latent TB – treated insufficiently OR not treated OR not documented OR new diagnosis LTBI with no evidence active TB</td>
<td>Moderate</td>
<td>Consider deferring transplant until donor has taken some/all LTBI treatment &amp; consider treatment of recipient; Monitor clinically</td>
<td>Monitor recipient clinically; consider LTBI treatment. Recommend LTBI treatment of lung recipients.</td>
</tr>
</tbody>
</table>

Adapted from Morris MI. Amer J Transpl 2012.

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### Clinical Management of Latent TB in Recipients

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Transmission Risk</th>
<th>Recommendation – Living Donor</th>
<th>Recommendation – Deceased Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>New diagnosis LTBI with TST or IGRA found during pre-transplant evaluation with no evidence of active TB</td>
<td>Moderate</td>
<td>Consider deferring transplant until donor has taken some/all LTBI treatment &amp; consider treatment of recipient; Monitor clinically</td>
<td>Monitor recipient clinically; consider LTBI treatment. Recommend LTBI treatment of lung recipients.</td>
</tr>
<tr>
<td>Unexplained pulmonary fibrosis in donor without cavitiation without additional testing. (Try to rule out other causes of apical fibrosis such as endemic mycoses, malignancy)</td>
<td>Variable</td>
<td>Defer donation pending further evaluation</td>
<td>Consider testing donor (BAL). If tests are pending, consider whether high or low risk for TB before deciding whether to proceed. If all definitive tests negative, accept as donor (non-lung) BUT consider treatment; Monitor clinically.</td>
</tr>
</tbody>
</table>
### Clinical Management of Active TB in Donors

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Transmission Risk</th>
<th>Recommendation – Living Donor</th>
<th>Recommendation – Deceased Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/O Active TB – Site remote from transplant (i.e. pulmonary in a kidney donor),</td>
<td>Lower to Moderate</td>
<td>Monitor recipient clinically; consider culture of previous TB sites if possible. Verify adequate treatment. May consider LTBI treatment of recipient.</td>
<td>Same as living donor</td>
</tr>
<tr>
<td>treated appropriately over 2 years ago (most relapses occur within 2 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H/O Active TB – Site remote from transplant, treated appropriately within 2 years</td>
<td>Lower to Moderate</td>
<td>Monitor recipient clinically; consider culture of previous TB sites if possible. Verify adequate treatment. Consider/suggest LTBI treatment of recipient if treatment adequacy not verifiable.</td>
<td>Same as living donor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H/O Active TB – site remote from transplant, treated insufficiently or with</td>
<td>Higher</td>
<td>Defer until adequately treated; consider consult with ID specialist. Culture previous TB sites prior to transplant.</td>
<td>Monitor clinically; recommend LTBI treatment &amp; cultures of previous TB sites; consider consult with ID specialist</td>
</tr>
<tr>
<td>nonstandard regimen NOT disseminated or CNS</td>
<td>Increased risk if less than 2 years since Active TB diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H/O Active TB – site same as transplanted organ – rare due to likely scarring/fibrosis of organ</td>
<td>Moderate</td>
<td>Verify treatment; Monitor clinically; LTBI treatment for recipient; Culture previous TB sites before transplant; consult ID</td>
<td>Same</td>
</tr>
</tbody>
</table>

**Clinical Scenario Transmission Risk Recommendation – Living Donor Recommendation – Deceased Donor**

- **H/O Active TB – Site remote from transplant (i.e. pulmonary in a kidney donor), treated appropriately over 2 years ago (most relapses occur within 2 years)**
  - Lower to Moderate
  - Monitor recipient clinically; consider culture of previous TB sites if possible. Verify adequate treatment. May consider LTBI treatment of recipient.
  - Same as living donor

- **H/O Active TB – Site remote from transplant, treated appropriately within 2 years**
  - Lower to Moderate
  - Monitor recipient clinically; consider culture of previous TB sites if possible. Verify adequate treatment. Consider/suggest LTBI treatment of recipient if treatment adequacy not verifiable.
  - Same as living donor

- **H/O Active TB – site remote from transplant, treated insufficiently or with nonstandard regimen NOT disseminated or CNS**
  - Higher
  - Increased risk if less than 2 years since Active TB diagnosis
  - Defer until adequately treated; consider consult with ID specialist. Culture previous TB sites prior to transplant.
  - Monitor clinically; recommend LTBI treatment & cultures of previous TB sites; consider consult with ID specialist

- **H/O Active TB – site same as transplanted organ – rare due to likely scarring/fibrosis of organ**
  - Moderate
  - Verify treatment; Monitor clinically; LTBI treatment for recipient; Culture previous TB sites before transplant; consult ID
  - Same
Highest TB Risk Donors

- Reject deceased donors & defer living donors until adequately treated in the following cases:
  - Active TB at time of donation
  - Positive TB culture/Nucleic acid amplification (NAA)
  - Findings suggest possible active or latent TB but no special cultures/NAA available pre-transplant

Adapted from Morris MI. Amer J Transpl 2012.
Take Home Messages

- 1/3 of world population has latent TB infection
- Transmission risk highest with unrecognized active rather than distant latent TB
- Currently available diagnostic tests have not been validated in the deceased donor population AND do not distinguish active from latent infection
- Identifying recipients of high risk donors for close monitoring may optimize outcomes
- Many patients die on the transplant waiting list while few die of post-transplant infection
Meeting Report

Diagnosis and Management of Tuberculosis in Transplant Donors: A Donor-Derived Infections Consensus Conference Report†

M. I. Morris‡, J. S. Daly‡, E. Blumberg‡,
D. Kumar‡, M. Senter‡, N. Schluger‡, S.-H. Kim‡,
B. S. Schwartz‡, M. G. Iserl‡, A. Humar‡,
N. Singh‡, M. Michaels‡, J. P. Otolowski‡,
F. Delmonico‡, T. Ptuet‡, G. T. John‡
and C. N. Kotton‡

†Endorsed by American Society of Transplantation, Canadian Society of Transplantation, and The Transplantation Society

Mycobacterium tuberculosis is a ubiquitous organism that infects one-third of the world’s population. In previous decades, access to organ transplantation...