What You Don’t Know Can Hurt You:
Infections in Transplant Recipients

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September 24, 2010

General Pearls

- Immunocompromised patients with infections
  - are often sicker than they look
  - often have more extensive disease than is apparent
  - may require longer treatment than others
  - may have unusual infections
  - often require invasive procedures
  - may need to have immunosuppression reduced

Infection-related mortality in heart transplant recipients

Dummer JS, In Kaye MP et al eds, Heart and Lung transplantation 2000

Indication for hospitalization post-transplantation

Dhamidharka VR. AJT. 04
Case

- 42 year old male from Guam with ESRD secondary to glomerulonephritis, s/p living unrelated kidney transplant 4 months PTA (UCSF) presented with fevers to 39 and chills and soaking night sweats for 2 months
- One month ago he was discharged from UCLA after a “negative” fever workup
- HD#3: CXR: ill-defined nodular opacity seen on CXR
- HD#6: CT chest

What is the most likely scenario?
A. Tuberculosis
B. Organ Rejection
C. Invasive Aspergillosis
D. All of the Above
Case

What is the most likely scenario?
A. Tuberculosis
B. Organ Rejection
C. Invasive Aspergillosis
D. All of the Above
### Determinants of Infection

- **Technical aspects of surgery**
  - Liver, lung > heart > kidney
- **Environmental exposure**
  - TB, endemic mycoses, Strongyloides
  - Gardening: Aspergillus, Nocardia
  - Food and water: Salmonella, Listeria
- **Degree of immunosuppression**
  - **Medications**, host factors, immunomodulating infections (CMV)
- **Type of immunosuppression**

### Relationship of OR time to incidence of infections

![Image of bar chart showing the relationship of OR time to incidence of infections](chart.png)

Kusne et al, 1988, Medicine; 67:132

### Case

- 36 year old Latina s/p cadaveric renal transplant (chronic GN) 2 years ago presents with SOB X 3 weeks and fevers to 39.8.
- **Meds:** Mycophenolate
Pulmonary infections

Approach

1. When is the patient presenting in relation to the transplant?
2. What is the degree of immunosuppression?
3. What is the nature of the pulmonary infiltrates?
4. What is the tempo of the pulmonary symptoms?
5. What is the Aa gradient?

Pattern of Infiltrates

- **Segmental/lobar:**
  - Common bacterial pathogens: ACUTE
  - Legionella: ACUTE
- **Nodules:**
  - Cryptococcus, Histo, Cocci: SUBACUTE
  - Aspergillus: SUBACUTE
  - Nocardia: SUBACUTE
- **Diffuse:**
  - PCP: ACUTE
  - CMV: SUBACUTE
  - HHV-6, HHV-7: SUBACUTE
  - RSV: SUBACUTE
  - Adenoviruses: SUBACUTE
- **Non-infectious:** Drug reactions (azathioprine, sirolimus),
  - PE: ACUTE

Tempo

- **Segmental/lobar:**
  - Common bacterial pathogens: ACUTE
  - Legionella: ACUTE
- **Nodules:**
  - Cryptococcus, Histo, Cocci: SUBACUTE
  - Aspergillus: SUBACUTE
  - Nocardia: SUBACUTE
- **Diffuse:**
  - PCP: ACUTE
  - CMV: SUBACUTE
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  - RSV: SUBACUTE
  - Adenoviruses: SUBACUTE
- **Non-infectious:** Drug reactions (azathioprine): SUBACUTE,
  - PE: ACUTE

Aa gradient

- **Normal:**
  - TB
  - Common bacterial PNA
  - CHF
- **Increased:**
  - PCP
  - CMV
  - RSV
  - HHV-6, HHV-7
  - Adenovirus
CMV

- Single most important pathogen in transplant recipients
- >50% SOT patients affected by CMV
- Indirect effects: GNR/fungal infections, organ injury/rejection
- Risk factors: D+/R-, OKT3 rx, HHV-6 infection, cadaveric, lung/heart transplant >> kidney

<table>
<thead>
<tr>
<th>CMV Spectrum</th>
<th>CMV Ag/PCR</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>CMV infection</td>
<td>+</td>
<td>Asymptomatic</td>
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<tr>
<td>CMV “syndrome”</td>
<td>+</td>
<td>Fever, myelosuppression</td>
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<tr>
<td>CMV tissue invasive/end-organ disease</td>
<td>+</td>
<td>Pneumonia, GI, hepatitis, CNS, retinitis, nephritis, etc.</td>
</tr>
<tr>
<td>“Compartmentalized” CMV disease</td>
<td>-</td>
<td>Pneumonia, GI, retinitis, CNS</td>
</tr>
</tbody>
</table>

Ljungman. CID. 2002

CMV Diagnosis

- CMV shell vial culture:
  - Insensitive, late
- Antigenemia:
  - M.Ab detects pp65 early antigen in infected WBCs
  - Sensitive, specific, rapid – but need WBCs
  - Can detect CMV infection before disease onset by 1 week sooner than buffy coat shell vial culture
- PCR for CMV DNA:
  - Leukocyte PCR sensitivity > antigenemia
  - Not standardized
CMV Diagnosis

- BAL
  - Low predictive value for positive CMV culture
  - Bronchoscopy cannot distinguish viral shedding vs. invasive disease
- Transbronchial lung biopsy
- CT Scan: Bad

CMV Treatment

- GCV induction 5mg/kg BID x 14-21 days plus IVIG 500mg/kg QOD x 14-21 days
- But poor evidence:
  - Survival: 15% historical vs. 52% GCV + IVIG
  - CMV-specific IVIG does not improve outcome
- Prevention: V-ACV, GCV po, **V-GCV**

CMV Prophylaxis


Polyomaviruses

**BK and JC**

- Usually activated post-transplant
- **JC Virus**
  - PML
  - Presentation: Progressive motor, sensory and cognitive deficits
  - Rx: None
- **BK Virus**
  - Tubo-interstitial nephritis
  - Risk factor: Immunosuppression (esp. tacrolimus and mycophenolate)
  - Rx: Reduce immunosuppression
Fungus

<table>
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<tr>
<th>Organ Transplanted</th>
<th>Incidence (%)</th>
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<tbody>
<tr>
<td>Liver</td>
<td>7-42</td>
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<tr>
<td>Pancreas</td>
<td>18-38</td>
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<tr>
<td>Heart-Lung/Lung</td>
<td>15-36</td>
</tr>
<tr>
<td>Heart</td>
<td>5-32</td>
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<tr>
<td>Kidney</td>
<td>1-14</td>
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Singh, CID 2000:31 Paya, CID 1993:16

Fungus Mortality

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Fatality rate (%)</th>
</tr>
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<tbody>
<tr>
<td>Aspergilosis</td>
<td>45-54</td>
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<tr>
<td>Non-Aspergillus hyalohyphomycetes</td>
<td>80</td>
</tr>
<tr>
<td>(Scedosporium spp, Fusarium spp)</td>
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</tr>
<tr>
<td>Zygomycosis</td>
<td>100</td>
</tr>
<tr>
<td>(Rhizopus, Mucor)</td>
<td></td>
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<tr>
<td>Phaeohyphomycosis</td>
<td>20</td>
</tr>
<tr>
<td>Candida</td>
<td>29</td>
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</table>

Hussain et al, CID 2003:37 Pappas, ICAAC 2003

Fungus Trends

- 53 consecutive heart and liver transplant recipients with invasive mold infections in 11 centers 1998-2002
- Spectrum of fungus is changing dramatically:
  - ↓ Aspergillus infections 70%
    - prior studies in 1990s: 98%
  - ↑ Non-Aspergillus mold infections 30%
    - Scedosporium, Fusarium, Zycomycetes, Phaeohyphomycetes
    - prior studies in 1990s: 2%

Singh et al, Transplantation 2002:73
Fungus

Diagnosis

- Patient characteristics
- Radiology
- Microbiology
- Non-culture tests
  - Galactomannan (Antigen) assay
  - PCR
- Pathology: the best way to demonstrate invasive disease

Kontoyiannis et al, JID, 2005
Halo sign

Crescent sign

Fungus
Galactomannan

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size, no. of patients</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
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</thead>
<tbody>
<tr>
<td>Kawasaki et al. [114]</td>
<td>Variable</td>
<td>84</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Maatman et al. [115]</td>
<td>Hematologic malignancies</td>
<td>188</td>
<td>90.8</td>
<td>95.4</td>
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<td>Urbanzki et al. [116]</td>
<td>Hematologic malignancies</td>
<td>115</td>
<td>98</td>
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<td>Saliken et al. [117]</td>
<td>Hematologic malignancies</td>
<td>105</td>
<td>77</td>
<td>NA</td>
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<tr>
<td>Fortun et al. [118]</td>
<td>Liver transplant</td>
<td>240</td>
<td>96</td>
<td>94</td>
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<tr>
<td>Kani et al. [119]</td>
<td>Hematologic malignancies</td>
<td>122</td>
<td>88</td>
<td>97</td>
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<td>Siemens and Koch-Davila [120]</td>
<td>Pulmonary diseases</td>
<td>52</td>
<td>100</td>
<td>23</td>
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<tr>
<td>Maatman et al. [121]</td>
<td>Hematologic malignancies, HCT</td>
<td>294</td>
<td>90</td>
<td>98</td>
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<td>Saliken et al. [122]</td>
<td>Hematologic malignancies, HCT</td>
<td>797</td>
<td>90</td>
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<td>Maatman et al. [123]</td>
<td>HCT</td>
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<td>94</td>
<td>99</td>
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<td>Herbrecht et al. [124]</td>
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<td>Farnoe and Kopper [125]</td>
<td>Variable</td>
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<tr>
<td>Rosk et al. [126]</td>
<td>Variable</td>
<td>60</td>
<td>50</td>
<td>100</td>
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<td>Bender et al. [127]</td>
<td>Hematologic malignancies</td>
<td>192</td>
<td>47</td>
<td>93</td>
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<tr>
<td>Buchheit et al. [128]</td>
<td>Hematologic malignancies</td>
<td>165</td>
<td>55</td>
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<tr>
<td>Kashi et al. [129]</td>
<td>Liver transplant</td>
<td>154</td>
<td>NA</td>
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<tr>
<td>Huisman et al. [130]</td>
<td>Lung transplant</td>
<td>70</td>
<td>50</td>
<td>93</td>
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<tr>
<td>Reza et al. [131]</td>
<td>HCT</td>
<td>74</td>
<td>75</td>
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<tr>
<td>Mir et al. [134]</td>
<td>HCT</td>
<td>67</td>
<td>82</td>
<td>75</td>
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</tbody>
</table>

NOTE: HCT, hematopoietic cell transplantation; NA, not available.

* Denotes number of episodes, not number of patients.
**Fungus Therapy**

- Voriconazole +/- OLAT (77)
- Amphotericin B +/- OLAT (10)

Survival at wk 12
- Voriconazole ± OLAT 70.8%
- AmB ± OLAT 57.9%

Hazard ratio = 0.59 (95% CI 0.42-0.88)

**Number of Days of Treatment**

N=277, SOT=9

Herbrecht et al. NEJM 2002: 347
OLAT: Other Licensed Antifungal Therapy

**Case**

- Patient with DKA, renal failure, immunosuppressed
- Black necrotic lesions of nose with invasion
- Broad, branching, non-septate hyphae
- Almost 100% mortality in immunosuppressed
- Rx: Surgery and Ampho
- Diagnosis?

**50 y.o. DKA with necrotic palate**

1. Actinomycosis
2. Aspergillus
3. MRSA
4. Mucormycosis
5. Norcardia
50 y.o. DKA with necrotic palate

1. Actinomycosis  
2. Aspergillus  
3. MRSA  
4. Mucormycosis  
5. Nocardia

Case

62 y/o female who is one year s/p double lung transplant for IPF

3 weeks of increasing LUQ discomfort

SOB and cough

Low grade fevers

Bronchoscopy revealed nodular polypoid lesions

62 y.o. female s/p lung tx

Dyspnea and cough

1. Actinomycosis  
2. Aspergillus  
3. MRSA  
4. Mucormycosis  
5. Nocardia
62 y.o. female s/p lung tx
Dyspnea and cough

1. Actinomycosis
2. Aspergillus
3. MRSA
4. Mucormycosis
5. Nocardia

Nocardia

- 4% renal transplants
- Lung (90%), brain (50%)
- Skin, bone
- Rx: TMP/SMX, minocycline, imipenem

Case

- 37 year-old woman s/p cadaveric kidney and pancreas transplant 6 weeks prior to admission presented with fever

What is this in blood?
37 y.o. kidney-pancreas tx

Fever

1. Bacteria
2. Virus
3. Parasite
4. Spirochete

Case

• U.S. Centers for Disease Control contacted
• Nifurtimox x 4 months
• Donor investigation: immigrant female from Central America
• Two other organ recipients from same donor (kidney, liver) found to be infected with T. cruzi (hemoculture)
• Outcome: recurrent reactivation several weeks after completing therapy; died of Chagas myocarditis

Trypanosoma cruzi trypomastigotes on a peripheral blood smear from a patient aged 37 years

MMWR March 15, 2002 / 51(10):210-2
Trypanosoma cruzi and vector

Donor derived infections

Disease Transmission Advisory Committee (DTAC)
Transplant Transmission Surveillance Network (TTSN)
UNOS Patient Safety Specialist:
Shandie Covington, Kimberly Parker & Kimberly Taylor
(804) 782-4929

Infections

<table>
<thead>
<tr>
<th>Infections</th>
<th>Donor Reports</th>
<th>Confirmed Recipients</th>
<th>Recipient Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis C</td>
<td>9</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>8</td>
<td>3</td>
<td>2</td>
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<tr>
<td>HIV</td>
<td>7</td>
<td>4</td>
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</tr>
<tr>
<td>Chagas</td>
<td>6</td>
<td>1</td>
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<tr>
<td>Hepatitis B</td>
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<tr>
<td>Toxoplasmosis</td>
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<td>West Nile Virus</td>
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<tr>
<td>Histoplasmosis</td>
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<td>Bacteremias</td>
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<td>LCMV</td>
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<td>Legionella</td>
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<td>Mycotic Aneurysm</td>
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<td>S. aureus in transport fluid</td>
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<tr>
<td>Zygomycetes</td>
<td>1</td>
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</tbody>
</table>

Take home points

- Opportunistic infections in transplant can occur late
- SOT recipients may not present with normal signs and symptoms of infection
- CMV disease is the most important infection in SOT recipients
- Donor derived infections should be considered in recipients with unexplained illness