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

Peter V. Chin-Hong, MD MAS
March 7, 2014
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

% of SOT recipients hospitalized for infection vs. rejection

Years


Dharnidharka VR. AJT. 04
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Meta-analysis SIR (95% CI)</th>
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<tbody>
<tr>
<td><strong>EBV-related cancers</strong></td>
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<tr>
<td>Hodgkin’s lymphoma</td>
<td>HIV/AIDS 11.03 (8.43-14.4)</td>
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<td>Transplant 3.89 (2.42-6.26)</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>HIV/AIDS* 76.67 (39.4-149)</td>
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<td>Transplant 8.07 (6.40-10.2)</td>
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<tr>
<td><strong>HHV-8 related cancer</strong></td>
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<tr>
<td>Kaposi’s sarcoma</td>
<td>HIV/AIDS* 3640.0 (3326-3976)</td>
</tr>
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<td>Transplant 208.0 (114-349)</td>
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<tr>
<td><strong>HBV/HCV-related cancer</strong></td>
<td></td>
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<tr>
<td>Liver</td>
<td>HIV/AIDS 5.22 (3.32-8.20)</td>
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<td>Transplant 2.13 (1.16-3.91)</td>
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<tr>
<td><strong>Helicobacter pylori-related cancer</strong></td>
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<tr>
<td>Stomach</td>
<td>HIV/AIDS 1.90 (1.53-2.36)</td>
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<td></td>
<td>Transplant 2.04 (1.49-2.79)</td>
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</table>

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
Case

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
Infection

**Treatment for rejection**

- **NOSOCOMIAL, TECHNICAL**
  - SSI
  - VAP
  - C. diff
  - Biliary leak
  - CRBSI

- **OPPORTUNISTIC**
  - (Donor, recipient, exposure)
  - CMV
  - Aspergillus
  - Nocardia
  - Listeria
  - Toxo
  - BK virus
  - HSV
  - VZV
  - EBV

- **COMMUNITY ACQUIRED**
  - Pneumococcal PNA
  - Respiratory viruses

- **Months post-transplant**

- **Degree of immunosuppression**
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

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?
Pulmonary infections
Pattern of Infiltrates

- **Segmental/lobar:**
  - Common bacterial pathogens
  - Legionella

- **Nodules:**
  - Cryptococcus, Histo, Cocci
  - Aspergillus
  - Nocardia

- **Diffuse:**
  - PCP
  - CMV
  - HHV-6, HHV-7
  - RSV
  - Adenoviruses

- **Non-infectious**: Drug reactions (azathioprine, sirolimus),
  - PE
Pulmonary infections

Tempo

• **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): SUBACUTE,
  - PE: ACUTE
Pulmonary infections

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>
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<th>CMV Ag/PCR</th>
<th>Clinical</th>
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<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>
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</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
  - Tubointerstitial nephritis
  - Risk factor: Immunosuppression (esp. tacrolimus and mycophenolate)
  - Rx: Reduce immunosuppression
# Fungus

<table>
<thead>
<tr>
<th>Organ Transplanted</th>
<th>Incidence (%)</th>
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<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>
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<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>
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<tbody>
<tr>
<td>Aspergillosis</td>
<td>45-54</td>
</tr>
<tr>
<td>Non-Aspergillus hyalohyphomycetes</td>
<td>80</td>
</tr>
<tr>
<td>(Scedosporium spp, Fusarium spp)</td>
<td></td>
</tr>
<tr>
<td>Zygomycosis</td>
<td>100</td>
</tr>
<tr>
<td>(Rhizopus, Mucor)</td>
<td></td>
</tr>
<tr>
<td>Phaeohyphomycosis</td>
<td>20</td>
</tr>
<tr>
<td>Candida</td>
<td>29</td>
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</tbody>
</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
Broad and hyposeptate, with wide angle branching
Phaeohyphomycosis
Incidence of IA per 1000 Patient-Days

Year

2000
2001
2002
2003

Incidence of Zygomycosis

Aspergillus

Zygomycetes

Per 1000 Patient-Days
Fungus
Diagnosis

• Patient characteristics
• Radiology
• Microbiology
• Non-culture tests
  – Galactomannan (Antigen) assay
  – PCR
• Pathology: the best way to demonstrate invasive disease
“Halo 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>
</tr>
</thead>
<tbody>
<tr>
<td>Kawamura et al. [14]</td>
<td>Variable</td>
<td>94</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Maertens et al. [15]</td>
<td>Hematologic malignancies</td>
<td>186</td>
<td>92.6</td>
<td>95.4</td>
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<tr>
<td>Ulusakarya et al. [16]</td>
<td>Hematologic malignancies</td>
<td>135</td>
<td>69</td>
<td>96</td>
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<tr>
<td>Salonen et al. [17]</td>
<td>Hematologic malignancies</td>
<td>105</td>
<td>77</td>
<td>NA</td>
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<tr>
<td>Fortun et al. [18]</td>
<td>Liver transplant</td>
<td>240</td>
<td>56</td>
<td>94</td>
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<tr>
<td>Kami et al. [19]</td>
<td>Hematologic malignancies</td>
<td>122</td>
<td>58</td>
<td>97</td>
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<td>Siemann and Koch-Dorfler [20]</td>
<td>Pulmonary diseases</td>
<td>52</td>
<td>100</td>
<td>23</td>
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<tr>
<td>Maertens et al. [21]</td>
<td>Hematologic malignancies, HCT</td>
<td>294</td>
<td>90</td>
<td>98</td>
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<tr>
<td>Sulahian et al. [22]</td>
<td>Hematologic malignancies, HCT (many children)</td>
<td>797</td>
<td>91</td>
<td>94</td>
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<tr>
<td>Maertens et al. [23]</td>
<td>HCT</td>
<td>97</td>
<td>94</td>
<td>99</td>
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<tr>
<td>Herbrecht et al. [24]</td>
<td>Hematologic malignancies</td>
<td>797(^a)</td>
<td>65</td>
<td>95</td>
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<tr>
<td>Rimke and Kappe [25]</td>
<td>Variable</td>
<td>90</td>
<td>59</td>
<td>NA</td>
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<tr>
<td>Pinel et al. [26]</td>
<td>Variable</td>
<td>807</td>
<td>50</td>
<td>100</td>
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<tr>
<td>Becker et al. [27]</td>
<td>Hematologic malignancies</td>
<td>160</td>
<td>47</td>
<td>93</td>
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<tr>
<td>Buchheidt et al. [28]</td>
<td>Hematologic malignancies</td>
<td>165</td>
<td>33</td>
<td>99</td>
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<tr>
<td>Kwak et al. [29]</td>
<td>Liver transplant</td>
<td>154</td>
<td>NA</td>
<td>87</td>
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<tr>
<td>Husain et al. [30]</td>
<td>Lung transplant</td>
<td>70</td>
<td>30</td>
<td>93</td>
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<tr>
<td>Rovira et al. [31]</td>
<td>HCT</td>
<td>74</td>
<td>75</td>
<td>100</td>
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<tr>
<td>Marr et al. [4]</td>
<td>HCT</td>
<td>67</td>
<td>82</td>
<td>75</td>
</tr>
</tbody>
</table>

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

\(^a\) Denotes number of episodes, not number of patients.
Dismukes WE, Clin Infect Dis 2006; 42:1289-96
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)

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

courtesy Steve Hays MD
Bronchoscopy revealed nodular polypoid lesions

courtesy Steve Hays MD
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
37 y.o. kidney-pancreas tx
Fever

1. Bacteria
2. Virus
3. Parasite
4. Spirochete
Trypanosoma cruzi trypomastigotes on a peripheral blood smear from a patient aged 37 years

MMWR March 15, 2002 / 51(10);210-2
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 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
<table>
<thead>
<tr>
<th>Infections</th>
<th>Donor Reports</th>
<th>Confirmed Recipients</th>
<th>Recipient Deaths</th>
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<tbody>
<tr>
<td>Hepatitis C</td>
<td>9</td>
<td>4</td>
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<tr>
<td>Tuberculosis</td>
<td>8</td>
<td>3</td>
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<td>HIV</td>
<td>7</td>
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<td>Chagas</td>
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<td>Hepatitis B</td>
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<td>Toxoplasmosis</td>
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<td>Legionella</td>
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<td>Mycotic Aneurysm</td>
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<td>RMSF</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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2005-2007

Courtesy Mike Ison, MD, MS
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
WASHINGTON, DC—According to a Department of Health and Human Services report released Monday, McDonald's meat from antibiotics-injected livestock is now the primary source of antibiotics for U.S. children, particularly for uninsured youths...

"Unfortunately, some children still fall through the cracks in our health-care system, but luckily, McDonald's is there to lend a helping hand," the Secretary of Health and Human Services said at a press conference announcing the findings. "So even if a child's family has no health insurance and can't afford medicine, virtually anyone can afford a delicious 99-cent Big Mac with pickles, cheese, and a heapin' helpin' of [the antibiotic] quinupristin-dalfopristin." “All children tend to eat at McDonald's a lot, which is a good thing. If you think about it, where else are these kids going to get their fluoroquinolone?"