Management of post transplant infections

What’s new in 2016

Peter V. Chin-Hong, MD MAS
Twitter: PCH_SF
September 29, 2016

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

Case

- 71 y.o. female who has severe acute on chronic hypoxic respiratory failure due to interstitial lung disease, now s/p bilateral lung transplant

Case

- Donor has sputum +gram-negative rods

Question: Treat recipient?
A. Yes
B. No
Case

- POD#8 – purulent pleural & pericardial drainage
- Multi-drug resistant *Acinetobacter* infection (CRAB)
- Taken to the OR for wash out
- EMCO POD#9 for worsening hypoxemia
- POD#30 – increasing oxygen requirements. Comfort care

Multidrug-resistant bacterial donor-derived infections in SOT

- Between 2009-2015, 17/33 (52%) recipients infected with MDR gram-negative organisms
- 41% died; 59% died or suffered allograft loss
- Most cases unexpected


“Poop pills”

- Open-label feasibility study
- 20 patients
- Failed vancomycin taper for *C. difficile* infection
- 30 frozen FMT capsules on 2 consecutive days
- Diarrhea resolved in 14/20 and retreatment of 4/6 nonresponders

> Youngster I et al, 2014, JAMA 312(17)
Cliff vs Angus

Infection-related mortality in transplant recipients

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

Indication for hospitalization post-transplantation

Dharmidharka VR. AJT. 04

Infection-related mortality in transplant recipients

Dharmidharka VR. AJT. 04

Dharmidharka VR. AJT. 04

Dharmidharka VR. AJT. 04

Dharmidharka VR. AJT. 04

Dharmidharka VR. AJT. 04

### 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**

### Case

- 36 year old female s/p cadaveric renal transplant (chronic GN) 2 years prior to admission presents with SOB X 3 weeks and fevers to 39.8 C.
- Meds: Mycophenolate

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**Infection Timetable**

<table>
<thead>
<tr>
<th>Nosocomial, Technical</th>
<th>Opportunistic (Donor, recipient, exposure)</th>
<th>Community Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSI, VAP, C. diff, Biliary leak</td>
<td>Nocardia, Aspergillus, PCP, HSV, VZV, EBV, CRBSI, SSI</td>
<td>Pneumococcal, PNA, Respiratory viruses</td>
</tr>
</tbody>
</table>

**Treatment for rejection**

- Valganciclovir
- TMP-SMX

**Months post-transplant**

**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
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?
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

CMV Spectrum

<table>
<thead>
<tr>
<th>CMV Ag/PCR</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV infection</td>
<td>+</td>
</tr>
<tr>
<td>CMV “syndrome”</td>
<td>+</td>
</tr>
<tr>
<td>CMV tissue invasive/ end-organ disease</td>
<td>+</td>
</tr>
<tr>
<td>“Compartmentalized” CMV disease</td>
<td>-</td>
</tr>
</tbody>
</table>

Ljungman. CID. 2002

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
- Future: Monitor T-cell mediated response to CMV infection

CMV

<table>
<thead>
<tr>
<th>Method</th>
<th>Principle</th>
<th>Clinical use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral culture</td>
<td>Isolate virus</td>
<td>Dx CMV disease</td>
<td>↑Sensitivity ↓Specificity</td>
</tr>
<tr>
<td>Serology</td>
<td>Detect antibody</td>
<td>Pre-transplant assessment</td>
<td>CMV risk assessment</td>
</tr>
<tr>
<td>Antigenemia</td>
<td>Detect pp65 antigen in PMNs</td>
<td>Rapid dx, limited if ↓PMNs, Guide preemptive Rx, Guide duration of Rx</td>
<td>↓Sensitive vs. PCR ↑Specificity vs. Cx</td>
</tr>
<tr>
<td>PCR</td>
<td>Detect DNA</td>
<td>Rapid dx, Guide preemptive Rx, Guide duration of Rx</td>
<td>↑Sensitivity vs. Ag ↓Specificity at low copy numbers</td>
</tr>
<tr>
<td>Histology</td>
<td>Identify viropathic changes</td>
<td>Dx end-organ disease</td>
<td>Sensitive and specific</td>
</tr>
</tbody>
</table>
CMV Prophylaxis


Zika Transmission

- Mosquitoes
- Sex
- Sweat or tears?

Swaminathan S et al, 2016, NEJM 9/28/16

Zika Guidance for OPOs

<table>
<thead>
<tr>
<th>Regulatory body</th>
<th>Medical &amp; Social History</th>
<th>Exclude as donor if:</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human cells and tissues</td>
<td>FDA</td>
<td>Screen for Zika</td>
<td>Zika diagnosed in past 6 months (live and deceased)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sex with male with above risk factors (live)</td>
</tr>
<tr>
<td>Organs</td>
<td>Organ Procurement and Transplantation Network (OPTN)</td>
<td>Screen for Zika “focus on recent travel history, epidemiologic risk factors, &quot;symptoms&quot; of donor”</td>
<td>Zika, Dengue, and Chikungunya</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 4 days symptoms: RT PCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 4-7 days: IgM Ab and convalescent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 7 days: IgG Ab</td>
</tr>
</tbody>
</table>
What MIA is doing (LAORA and transplant centers)

- No screening recipients
- No screening living donors
- For all deceased donors (8/1/16):
  - OPTN Policy 2.9
  - Urine and plasma PCR
  - Plasma Zika IgM & IgG
  - Not sure what to do with positives

“Still no clear answer as to what to do with positives. We are evaluating on each positive (not many so far) based on risk:benefit on a case by case basis. I wish I had more answers.”

Transplant ID specialist
University of Miami

Global distribution of *A. aegypti* mosquitos
Kraemer M et al, Oxford

Global distribution of *A. albopictus* mosquitos
Kraemer M et al, Oxford
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

Who is this handsome guy?
A. Julio Iglesias
B. Johnny Cash (circa 1972)
C. Peter Stock

Obama lifts ban on HIV organ transplants
SF Gate
11/21/13

HIV-positive organ donation: HOPE Act signed into law
Slate
11/22/13
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

Fungus

<table>
<thead>
<tr>
<th>Organ Transplanted</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>7-42</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18-38</td>
</tr>
<tr>
<td>Heart-Lung/Lung</td>
<td>15-36</td>
</tr>
<tr>
<td>Heart</td>
<td>5-32</td>
</tr>
<tr>
<td>Kidney</td>
<td>1-14</td>
</tr>
</tbody>
</table>

Singh, CID 2000:31        Paya, CID 1993:16
### Fungus Mortality

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size</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>Mattesini et al. [18]</td>
<td>Hematologic malignancies</td>
<td>196</td>
<td>90.8</td>
<td>96.4</td>
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<tr>
<td>Umemura et al. [16]</td>
<td>Hematologic malignancies</td>
<td>138</td>
<td>69</td>
<td>95</td>
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<tr>
<td>Sallan et al. [17]</td>
<td>Hematologic malignancies</td>
<td>105</td>
<td>77</td>
<td>NA</td>
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<tr>
<td>Torok et al. [14]</td>
<td>Lung transplants</td>
<td>93</td>
<td>95</td>
<td>94</td>
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<tr>
<td>Kane et al. [14]</td>
<td>Hematologic malignancies</td>
<td>122</td>
<td>56</td>
<td>97</td>
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<tr>
<td>Siemens and Koch-Dorfler [20]</td>
<td>Pulmonary diseases</td>
<td>52</td>
<td>100</td>
<td>23</td>
</tr>
<tr>
<td>Mattesini et al. [21]</td>
<td>Hematologic malignancies, HCT</td>
<td>254</td>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td>Schall et al. [22]</td>
<td>Hematologic malignancies, HCT (many children)</td>
<td>797</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>Monnevez et al. [24]</td>
<td>HCT</td>
<td>97</td>
<td>94</td>
<td>99</td>
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<tr>
<td>Herbrecht et al. [4]</td>
<td>Hematologic malignancies</td>
<td>79</td>
<td>66</td>
<td>96</td>
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<tr>
<td>Rimele and Kope [25]</td>
<td>Variable</td>
<td>90</td>
<td>59</td>
<td>NA</td>
</tr>
<tr>
<td>Ross et al. [26]</td>
<td>Variable</td>
<td>807</td>
<td>50</td>
<td>100</td>
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<tr>
<td>Beckler 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>53</td>
<td>99</td>
</tr>
<tr>
<td>Koch et al. [29]</td>
<td>Lung transplant</td>
<td>154</td>
<td>NA</td>
<td>97</td>
</tr>
<tr>
<td>Hazen et al. [30]</td>
<td>Lung transplant</td>
<td>50</td>
<td>50</td>
<td>93</td>
</tr>
<tr>
<td>Reque et al. [31]</td>
<td>HCT</td>
<td>34</td>
<td>76</td>
<td>100</td>
</tr>
<tr>
<td>Miet et al. [32]</td>
<td>HCT</td>
<td>67</td>
<td>82</td>
<td>75</td>
</tr>
</tbody>
</table>

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

* Denotes number of episodes, not number of patients.

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**CYTOPLASMIC MEMBRANE**
- Polyenes – bind ergosterol
- AMB
- Lipid AMB drugs
- Allylamines
- Terbinafine
- Azoles
- Ketoconazole
- Itraconazole
- Fluconazole
- Voriconazole
- *Posaconazole

**CELL WALL**
- Echinocandins – inhibit glucan synthesis
- Caspofungin
- Micafungin
- Anidulafungin

**PROTEIN/DNA SYNTHESIS**
- Fluconosine

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)

**Number of Days of Treatment**

N=277, SOT=9

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

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**Isavuconazole vs voriconazole**

- SECURE: prospective double blind RCT
- N=527
- Global: 26 countries
- Isavuconazole (19% mortality) is non-inferior to voriconazole (20%) for IA
- Fewer adverse effects with isavuconazole (hepatobiliary, eye, skin)
- Bottom line: isavuconazole is viable alternative


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**Prophylaxis in Lung Transplant**

*Incidence of invasive aspergillus infection by date of transplant*

Cohen S et al, IDSA 2011; ATC 2012
Case
• 34 year-old W male with DM s/p kidney pancreas transplant 6 weeks prior
• Gram negative rod sepsis and abdominal rash
• U.S. born, no foreign travel. From Fresno, CA
• Donor was immigrant from Mexico. Immigrated 6 years ago. Farmer

Case
What is this thing anyway?
A. Bacteria
B. Virus
C. Parasite
D. Spirochete

Case
• 45 year-old kidney transplant recipient presents with abdominal pain, shortness of breath and this rash on his buttocks

Case
• Strongyloides rhabditiform larvae complete life cycle via peri-anal skin in immunocompromised hosts
• Spread to lungs, skin, other areas
• Can cause bacteremia with GI bugs. Mortality rate is high
• Often no eosinophilia
Recent outbreaks reported to CDC and DTAC

- Three donors from Strongyloides endemic areas
- Transmission 1
  - 5 organs transplanted; 1 recipient affected (CTDN)
- Transmission 2
  - 5 organs; 2 recipients dead. Results known but not reported to TC
- Transmission 3
  - 4 organs; donor tested prior to transplantation; all recipients treated. No disease (NYODN)
- CDC
  - Since 2009, 7 other clusters; 20 recipients; 2 deaths
- NYODN
  - Screening since 2010
  - 10 positive donors
  - 355 screened

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>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis C</td>
<td>9</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HIV</td>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>6</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>West Nile Virus</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>EBV</td>
<td>3</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Cryptococcus</td>
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<td>0</td>
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<tr>
<td>Ichilatosomiasis</td>
<td>2</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Strongyloides</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Syphilis</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Bacterial Meningitis</td>
<td>1</td>
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<tr>
<td>Cytomegalovirus</td>
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<td>ACL</td>
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<td>Influenza A</td>
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<tr>
<td>LCMV</td>
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<td>3</td>
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<tr>
<td>Legionella</td>
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<tr>
<td>Listeria</td>
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<tr>
<td>M ycotic Aneurysm</td>
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<tr>
<td>RMSF</td>
<td>1</td>
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<td>0</td>
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<tr>
<td>St. aureus in transport fluid</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Zygoamyecetes</td>
<td>1</td>
<td>0</td>
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</tr>
</tbody>
</table>

Trypanosoma cruzi and vector

Abanyie F, Chin-Hong PV et al, 2015, Am J Transplant

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. Zika and other viruses are increasing in importance
• Donor derived infections should be considered in recipients with unexplained illness. Multidrug resistant organisms are a growing problem

U.S. Children Getting Majority Of Antibiotics From McDonald's Meat

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 heaping helping 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?”

Visit my blog and twitter PCH_SF
http://www.healio.com/infectious-disease/blogs