Objective

• Discuss the immediate post-operative and long-term management of liver transplant recipients
General pearls

- **Liver transplant** 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

Infection-related mortality
Heart transplant recipients

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

• Colonization
• Allergic bronchopulmonary aspergillosis (ABPA)
• Aspergilloma (fungus ball)

• Invasive pulmonary aspergillosis (immunocompromised)
  – Sinus
  – Lung (nodules)

Aspergillus rhinocerebral disease

Aspergillus
Diagnosis

• Risk factors: immunocompromised
• Radiology: CXR, CT chest with nodules
  • Non-culture tests: Galactomannan (Antigen) assay
  • Pathology. Biopsy: septate hyphae, acute angle branching
  • Microbiology (cultures)

Multiple pulmonary nodules
Aspergillus Diagnosis

- Risk factors: immunocompromised
- Radiology: CXR, CT chest with nodules
- Non-culture tests: Galactomannan (Antigen) assay
- Pathology. Biopsy: septate hyphae, acute angle branching
- Microbiology (cultures)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>47</td>
<td>93</td>
</tr>
<tr>
<td>BAL</td>
<td>85</td>
<td>100</td>
</tr>
</tbody>
</table>

Becker et al, Br J Haematology, 2003; 121:448
D’Haese J et al, J Clin Microbiol, 2012; %0:1258

Hyphae, plate colonies and conidia
Aspergillus
Treatment

- Treatment
  - **Voriconazole**
    - ± Echinocandin
  - **Isavuconazole**
    - ± Echinocandin

Voriconazole vs. Amphotericin B
Herbrecht et al. NEJM 2002: 347

Aspergillus
Treatment

- Treatment
  - **Voriconazole**
    - ± Echinocandin
  - **Isavuconazole**
    - ± Echinocandin

Voriconazole vs. Isavuconazole
Fungus

Organ Transplanted | Incidence (%) |
--- | --- |
Liver | 7-42 (most candida) |
Pancreas | 18-38 |
Heart-Lung/Lung | 15-36 |
Heart | 5-32 |
Kidney | 1-14 |

Singh, CID 2000:31 Paya, CID 1993:16

Fungus Trends

- Spectrum of fungus is changing dramatically:
  - ↓ Aspergillus infections 70%
    - Prior studies in 1990s: 98%
  - ↑ Non-Aspergillus mold infections 30%
    - Scedosporium, Fusarium, Zycomycetes, Phaeohypomycetes
    - Prior studies in 1990s: 2%

Case

- 57 year-old female s/p liver transplant recently treated for rejection with thymoglobulin presents with DKA and L eye proptosis
- Biopsy shows non-septate hyphae at 90°
- Diagnosis?
- Treatment?

Mucormycosis

Treatment? Surgery & Ampho
CMV

- Most important infection in SOT recipients
- Infects 60-100% of humans by adulthood
- Immunocompetent hosts: 1° infection is often asymptomatic, virus then remains latent
- In SOT recipients infection is due to
  - 1° infection from donor graft D+/R-
  - Reactivation in setting of immunosuppression (esp. T cell depleting agents)

Chest CT showing diffuse ground glass opacities

CMV

Clinical

<table>
<thead>
<tr>
<th></th>
<th>PCR</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic CMV viremia</td>
<td>+</td>
<td>No symptoms</td>
</tr>
<tr>
<td>CMV syndrome</td>
<td>+</td>
<td>Fever, malaise, myelosuppression</td>
</tr>
<tr>
<td>CMV with end-organ disease</td>
<td>+</td>
<td>Pneumonia, hepatitis, colitis, retinitis, CNS</td>
</tr>
<tr>
<td>Compartmentalized CMV disease*</td>
<td>-</td>
<td>Pathologic evidence of end-organ disease</td>
</tr>
</tbody>
</table>

*Consider colonoscopy in high-risk patient with negative CMV PCR who is having diarrhea to rule out compartmentalized CMV disease
CMV

Diagnosis

- **Viral culture**
  - Slow, ↓Specificity

- **Serology**
  - Detects antibody
  - CMV risk assessment pre-transplant
  - Highest risk D+/R-

- **PCR**
  - Detects DNA
  - Fast, ↑Sensitivity (but ↓specificity if low VL)

- **Histology**
  - Sensitive and specific

“Owl's eyes” inclusion bodies of CMV

CMV

Treatment

- What kind of CMV? Asymptomatic viremia? CMV syndrome? Organ disease?

- In general:
  - Start with **valganciclovir 900 BID** (induction)
  - IV ganciclovir if severe or if bad GI disease
  - Minimum 2 weeks (3 weeks for GI) if PCR undetectable
  - **Cidofovir** or **foscarnet** if resistant CMV

- Nitpicky pearls:
  - Cutoff for treating **asymptomatic** viremia: **1500 IU/mL**
  - **No routine secondary prophylaxis.** Can monitor high-risk patients x 3 months (pre-emptive)

Razonable R et al, Clin Transplant 2019:33
CMV Prevention

Focus on D+R- for CMV prophylaxis

<table>
<thead>
<tr>
<th>Risk</th>
<th>D</th>
<th>R</th>
<th>% Symptomatic Disease*</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>+</td>
<td>-</td>
<td>60%</td>
</tr>
<tr>
<td>Mod</td>
<td>+</td>
<td>+</td>
<td>10-30%, up to 50% with ALA**</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>up to 50% with ALA**</td>
</tr>
<tr>
<td>Low</td>
<td>-</td>
<td>-</td>
<td>0-4%</td>
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</table>

D Donor CMV Ab, R Recipient CMV Ab
*Incidence of symptomatic disease if no prophylaxis
**Anti-lymphocyte antibodies

And for 6 months


Bonus Case

- 40 year-old male 3 months s/p liver transplant in Asia (Hep B hepatocellular CA) on tacrolimus, mycophenolate and prednisone presenting with persistent LFTs
- Serology and blood PCR negative for EBV, CMV, HSV, HBV, HCV, parvovirus, HHV-6
- Biopsy shows moderate acute cellular rejection vs hepatitis with no viral inclusions
- Diagnosis?
- Treatment?

Marked portal inflammation with mixed lymphoplasmacytic infiltrate
Bonus Case

- 40 year-old male 3 months s/p liver transplant in Asia (Hep B hepatocellular CA) on tacrolimus, mycophenolate and prednisone presenting with persistent ↑LFTs
- Serology and blood PCR negative for EBV, CMV, HSV, HBV, HCV, parovirus, HHV-6
- Biopsy shows moderate acute cellular rejection vs hepatitis with no viral inclusions
- Diagnosis? **Hepatitis E infection**
- Treatment? ↓Immunosuppression, antivirals

**HEV**

- Chronic HEV almost always in immunocompromised
- 50-70% of those affected post-transplant develop chronic HEV
- Can progress to cirrhosis
- Dx: Detection of serum HEV RNA >6 months
- May be mistaken for rejection
- Rx: ↓Immunosuppression, ribavirin

Schlosser et al, J Hepatology 2012:56
Kamar et al, Gastroenterology, 2011:140
Which of these organisms is safe to transplant?

T. cruzi  Naegleria  H1N1  Strongyloides

Chin-Hong et al, Am J Transplant. 2011; (11)4
Roy et al, Am J Transplant. 2014; (14)1
Kumar et al, Am J Transplant. 2010; (10)1
Chin-Hong et al, ATC 2013
Don’t forget about donor-derived infections

Potential transmission events reported to UNOS/DTAC

2005 2006 2007 2008 2009 2010 2011 2012
7 60 97 102 152 157 181 198

Good luck!