Infection in the (non-HIV) Immunocompromised Host

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Lecture outline

• Background/why is this topic important?
• Solid organ transplantation
• Heme malignancy/stem cell transplantation
• Biologics

• No financial relationships to disclose

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• Solid organ transplantation
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Most to least?

- Heme malign/stem cell transplant
- Organ transplantation
- Treatment for autoimmune diseases
- Treatment for solid tumors
- Acquired/genetic immune deficiencies
- Hyposplenism

Type of immune defect?

Humoral immunity
- Rituximab (anti-CD20)
- Hyposplenism
- CVID (Low IgG)

Cell-mediated immunity
- Solid organ transplant
- Stem cell transplant
- TNF inhibitors
- Steroids
- Other IS Rx

Innate (PMN) immunity
- Cancer chemoRx
- Chronic Gran Dz (CGD)

A challenge: diagnosis and treatment of infection in the non-HIV IS host?

1. Infectious DDx is broad
2. Clinical manifestations often atypical
3. Diagnostic tests are insensitive and slow
4. Treatments = toxicity & drug interactions

How is this different from HIV immunosuppressed patients?

<table>
<thead>
<tr>
<th>Immune defect</th>
<th>HIV</th>
<th>Non-HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death of CD4+ T-cells</td>
<td>Heterogeneous</td>
<td></td>
</tr>
<tr>
<td>CD4+ count</td>
<td>No reliable tests available</td>
<td></td>
</tr>
</tbody>
</table>
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Immunosuppression in SOT

- **Depleting antibodies**: Thymoglobulin, Campath
- **IL-2 receptor blockers**: Basiliximab
- **Antimetabolites** (Mycophenolate)
- **Calcineurin inhibitors** (Tacrolimus, Cyclosporine)
- **Corticosteroids**
- **T-cell costimulation blocker** (Belatacept)

Acquisition of infection to organ transplant recipients

- **Reactivation of latent infections**
  - Herpesviruses
  - TB
  - Strongyloides
  - Hepatitis B
- **Surgery-related infection**
  - Obstruction and/or leaks

- **Prophylaxis**
- **Environmental exposures**
  - Community vs. Nosocomial
- **Opportunistic**

- **Screening and treatment of latent infections**

- **Donor-derived infections**
  - Bacteria
  - Viruses
  - Fungi
  - Parasites

Treatment of rejection

- **CMV**
- **Aspergillus**
- **PCP**
- **Cryptococcus**
- **HSV**
- **VZV**
- **EBV**
- **Nocardia**
- **Listeria**
- **Toxoplasmosis**
- **Endemic mycoses**
- **Tuberculosis**

Degrees of immunsuppression

**Timeline** of infection post-transplant

**Nosocomial, Technical Opportunistic, Community Acquired**

Months post-transplant
Case 1
- 65 year-old woman 10 months post liver transplant presents w/ ear fullness and pain
- Diagnosed with mastoiditis by MRI
- Mastoid biopsy:
  - Bacterial cultures: negative
  - Path: lymphocytic inflammation with no granulomas or organisms identified

Case 1: continued
- Patient was discharged with IV cefepime
- Readmitted with continued ear pain, fatigue
- ID team evaluated the patient and ordered retesting of prior pathology specimens

What is your diagnosis?
A. Aspergillus fumigatus
B. Candida albicans
C. Cefepime-resistant Pseudomonas
D. Mucormycosis
E. Mycobacterium tuberculosis
Dx: Disseminated TB w/ mastoiditis

Why was the Dx missed on pathology?
• Pathologists did not stain for mycobacteria because there were no granulomas present

Tuberculosis in SOT recipients
• Active TB Risk: >25x risk vs. gen population
• At Dx- 30-50% will have extrapulmonary disease
• Treatment complicated by drug interactions
• Attributable mortality 9.5-20%

Singh N. CID. 1998, Torre-Cisneros J. CID. 2009
When do SOT recipients present with TB post-transplant?

Case 1: Summary

- Pathological (and clinical) manifestations of infection may be atypical in SOT recipients
- Risk of reactivation is >25 fold in SOT
- Treatment for LTBI pre-transplant or early post-transplant decreases risk of active TB

Case 2

- 38 y/o F s/p renal transplant 8 mo ago presents with fever and cough progressive over 1 week
- No improvement on levofloxacin x 7 days
- Exam: 39.4, 98, 122/87, 28, 94% on 4L NC
- General: Increased work of breathing
- Lungs: scattered crackles

Case 2

**Medications**

- Tacrolimus
- Mycophenolate
- Prednisone 5 mg
- TMP-SMX DS 3x/wk

**PMH**

- Trisomy 21
- Congenital heart dz
- IgA nephropathy
Case 2: Labs

- WBC: 2.5
- Hematocrit: 25
- Platelets: 75
- Cr: 1.7
- LFTs: WNL

DDx of bilateral ground glass opacities

- Infection
  - PCP
  - Viral infection
- Edema
- Hemorrhage
- Interstitial lung diseases

DDx of ground glass opacities (GGO) on CT scan

- Infection
  - PCP
  - Viral infection
- Edema
- Hemorrhage
- Interstitial lung diseases
Our Infectious DDx

<table>
<thead>
<tr>
<th></th>
<th>PCP</th>
<th>Resp virus (flu, RSV, etc.)</th>
<th>CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pancytopenia?</td>
<td>No</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>On prophylaxis?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Other</td>
<td>Serum β-D-glucan: negative</td>
<td>Season: yes</td>
<td>Donor CMV IgG+: recipient IgG-</td>
</tr>
<tr>
<td>Empiric Rx?</td>
<td>No</td>
<td>Oseltamivir</td>
<td>Ganciclovir</td>
</tr>
</tbody>
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Case 2: Results

- Results:
  - Resp virus PCR panel (nasal swab): negative
  - CMV PCR blood: 930,000 copies/ml

- Rx: Ganciclovir IV for CMV pneumonitis

- Course
  - WBC and platelets slowly normalized
  - ICU for 2 weeks

Spectrum of CMV disease in SOT

Asymptomatic viremia
  - “CMV syndrome”
    - Fever/malaise
    - Pancytopenia

End-organ disease
  - GI disease (colitis)
  - Hepatitis
  - Pneumonitis
  - Rare (CNS, retinitis)

Diagnosis and treatment of CMV

- Diagnosis:
  - CMV PCR serum (if low viral load consider other Dx)
  - Biopsy of infected organ

- Treatment:
  - IV Ganciclovir or PO Valganciclovir
  - Treat until PCR undetectable and at least 2-3 weeks
  - Secondary prophylaxis in select cases
Case 2: take home points

- “Ground-glass” on CT: PCP, CMV, resp virus
- CMV common post SOT, often "late-onset"
- Fever, pancytopenia +/- end-organ disease
- Dx: Serum CMV PCR (antigen) +/- tissue biopsy
- Rx: Ganciclovir (IV) or valganciclovir (PO)

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Risk of infection in patients with hematological malignancies

- Underlying disease:
  - Hypogammaglobulinemia (MM and CLL)
  - Neutropenia due to BM infiltration
- Treatment:
  - Chemotherapy
  - Stem cell transplant

Chemotherapy induced neutropenia

Neutropenia + Mucositis + Central venous catheters + Prior antibiotic exposure
Neutropenia-associated infections

- Bacterial pathogens
  - Bacteremias (oral and GI flora)
  - Typhlitis
  - Pneumonia and CRBSI
- Fungal infections
  - Candidemia
  - Aspergillus (if prolonged)
- Viral infections
  - HSV

Management of high-risk, febrile neutropenic patient?

- Empiric therapy 1st (medical emergency):
  - Cefepime, carbapenem*, or pip-tazo
  - Add Vancomycin if CRBSI, SSTI, PNA, or critically ill
- Diagnostics: Pan-culture and image
- No response to empiric therapy?
  - Continue work-up for source
  - Consider escalate antibiotics → add antifungal

*anti-pseudomonal carbapenem (aka not ertapenem)

Initial management of febrile stem cell transplant recipient?

- Empiric therapy:
  - Empiric antibiotics based on likely source
- Diagnostics:
  - How far post-transplant?
  - GVHD?
  - Specific signs/symptoms?

Cell recovery and infection risk post stem cell transplant

- Neutrophils → NK cells → CD 8+ → B-cells → CD4+
- Encapsulated bacteria, Respiratory viruses
- CMV, VZV, PCP, Molds (Ols)
- GVHD

Weeks post-transplant

Mackall C. BMT.2009

Freifeld AG. Clin Infect Dis. 2011

Freifeld AG. Clin Infect Dis. 2011
Case 3

- 21 year-old with refractory AML has been neutropenic for over 8 weeks and has been on prophylactic levofloxacin, fluconazole, and acyclovir
- He presents to clinic with 3 days of fatigue, mild cough, and pleuritic chest pain
- LABS: 0.9>33<31, ANC = 0.2

Chest X-ray: 3 months ago

Chest X-ray: Today
DDx of cavitary lung lesions?

• Fungal:
  – Molds: Aspergillus >>> mucormycosis
  – Endemic mycoses: cocci, histo, etc.

• Bacterial:
  – Septic pulmonary emboli
  – S. aureus, Gram negatives, Nocardia

• Mycobacteria: TB and NTM

Case 3: micro results

• Galactomannan serum: 0.3 (normal <0.5)
• β-D-glucan serum: < 40 (normal < 40)
• Bronchoscopy
  – Bacterial culture: negative
  – Mycobacterial: negative
  – Fungal culture: negative
  – Galactomannan: 10.1 (normal < 0.5)

Aspergillus diagnostics (sensitivity)

• Biopsy: gold standard
• Fungal cultures BAL: 25-50%
• Galactomannan (aspergillus specific)
  – Serum: 60%
  – BAL: 70-95%
• Beta-D glucan (asperg, candida, PCP)
  – Serum: 55-95%

False positives

Galactomannan
• Piperacillin-tazobactam
• Amoxicillin-clav acid
• Fungal cross-reactivity

B-D glucan
• IV Ig
• Albumin
• Select HD filters
• Gauze packing


Kędzierska A. Eur J Clin Microbiol Infect Dis. 2007
**Treatment of invasive aspergillosis: Voriconazole vs. Ampho B**

Herbrecht R. NEJM. 2002

- **P=0.02**

**Isavuconazole vs. Voriconazole for invasive aspergillosis**

(Marr KA. Ann Intern Med. 2015)

- **Isavuconazole vs. Voriconazole**
- **(primary outcome: all cause mortality at 6 weeks)**

**Case 3: take home points**

- DDx for cavitary nodules: mold>bacteria> AFB
- Fungal testing limited sensitivity and specificity
- BAL GM has increased sensitivity for aspergillus
- Biopsy is the gold standard for diagnosis
- Voriconazole is 1st-line treatment of aspergillus
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TNF inhibition

- Clinical scenarios
  - Rheumatoid arthritis
  - Inflammatory bowel disease
  - Psoriasis/psoriatic arthritis

TNF inhibition in the treatment of septic shock

Fischer CJ. NEJM. 1996

TNF inhibit: tuberculosis

- Post-marketing survey of TB cases following release of infliximab (1998-2001)
- 70 cases of TB
- Median time to diagnosis: 12 wks (range 1-52)
- TB characteristics
  - Extrapulmonary disease: 40/70 (57%)
  - Disseminated disease: 17/70 (24%)

Keane J. NEJM. 2001
TNF inhib: fungal infections

- Survey of serious infection on TNF inhibit in U.S.
  - Non-tuberculous mycobacteria: 32
  - Tuberculosis: 17
  - Histoplasmosis: 56
- FDA Alert 2008: 256 cases of histoplasmosis in patients on TNF inhibitors

Case 4

- 43 y/o female with Crohn’s disease on infliximab (Remicade®) presents with 3 weeks of cough and fever. Works as a CPA in Bakersfield, CA. No pets.
- She received 1 week of moxifloxacin without improvement.

Which infections are in the DDx?

- Bacterial, mycobacterial, and endemic mycoses
- Cocci IgM/IgG sent
  - Negative
- Now what?

Coccidioides risk regions

http://updates.clltopics.org/
KOH stain from BAL fluid

*Coccidioides immitis*

Serological testing can be insensitive in immunocompromised patients!

Blair J. Mycopathologia. 2006

Biologics and viral infections

- Hepatitis B reactivation
  - Reactivation with TNF inhibitors reported
  - Rituximab (Rituxan®) - common
- JC virus (progressive multifocal leukoencephalopathy)
  - Natalizumab (Tysabri) – must check JCV IgG
  - Rituximab (Rituxan®) – reports, less common

Evaluation prior to TNF inhibitor use?

- Evaluate for LTBI
  - Check PPD or IGRA, CXR, take TB history
- Evaluate for recent endemic mycoses infection
  - Take travel history, symptom check
- Evaluate for HBV
  - Check hepatitis B surface antigen and core antibody


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