Lecture outline

- Why is this topic important?
- General principles of infection and SOT?
  - Case 1
  - Case 2
  - Case 3

Why is evaluation and treatment of SOT recipients with infection so challenging?

1. Infectious differential diagnosis is broad
2. Clinical manifestations often atypical
3. Diagnostic testing is slow and insensitive
4. Treatments are associated with toxicity and drug interactions

Why such a broad infectious DDx?

- Multiple means of acquisition
- Often opportunistic infections (OIs)
- Routine infections with resistant pathogens
- Difficult to risk stratify OI risk in each patient
Acquisition of infection to organ transplant recipients

Reactivation of latent infections
- Herpesviruses
- TB
- Strongyloides

Environmental exposures
- Community vs. Nosocomial
- Opportunistic vs. Common

Surgery-related infection
- Obstruction or leaks at anastomoses

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

Prophylaxis

Treatment of latent infections

Impact of OI prophylaxis on the post-transplant “timeline”

How do you determine which patients are at risk for which Ois?

How do they determine OI risk in HIV patients?
- CD4 count follows closely with risk
  - PCP < 200
  - Cryptococcus < 100
  - CMV < 50

Does CD4 help in SOT?

Kowalski R. Clin Transplantation. 2003
Assays to assess T-cell function

- **ImmuKnow™**
  - Stimulates CD4 cells and measures ATP production
  - Studies have shown mixed results
  - Low ATP production correlates with infection (BK)
  - May be useful in select cases

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Clinical, radiographic, and pathologic manifestations may be atypical

- Immunosuppression = *inflammation suppressive*

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Diagnostic testing in IS patients

- Diagnosis may require pathology specimens
- Cultures for mycobacteria and fungi take weeks
- Many PCR and antigen tests are send-out
- False positives (or low level positive) common
- Serology may be falsely negative
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Treatment of infection SOT

**Drug interactions**

- CYP450 inhibitors
  - Vor, -Posa, -Itra, -Fluc
  - Clarithromycin
- CYP450 inducers
  - Rifampin
  - Rifabutin

**Toxicities**

- Renal
  - Ampho B
  - Aminoglycosides
- Heme
  - Valganciclovir
- Hepatic/GI
  - Isoniazid
  - Tigecycline

An ounce of prevention really is worth a pound of cure

- Evaluate and treat for latent infections
- Evaluate for common donor-derived infections
- Educate to avoid exposures post-transplant
- Prophylaxis
- Immunize

Case 1

- 65 year-old Chinese woman 10 months post liver transplant presents w/ ear fullness and pain
- Diagnosed with mastoiditis by MRI
- Mastoid biopsy:
  - Bacterial and fungal cultures: negative
  - Path: lymphocytic inflammation with no granulomas, bacteria or fungi

Case 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 the most likely diagnosis?

A. *Aspergillus fumigatus*
B. *Candida albicans*
C. *Mycobacterium tuberculosis*
D. *Pseudomonas aeruginosa*
E. *Scedosporium prolificans*

Dx: Disseminated TB w/ mastoiditis

Why was the Dx missed on pathology?

- Pathologists did not stain for Mycobacteria (AFB) because there were no granulomas present

Why was her latent TB not treated pre-transplant?

- Presented with fulminant hepatitis B and went to transplant quickly
- Screening for LTBI did not take place

TB in SOT recipients

- Active TB Risk: > 25x risk vs. gen population
  - Lung transplant recipients had 100x risk
- 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?

![Graph showing % of TB cases post-transplant over time](attachment:graph.png)

Singh N. CID. 1998

**Prevent Active TB. Treat LTBI.**

So...which candidates have LTBI?

- TST ≥ 5mm induration
- Positive Quantiferon TB Gold test
- History of TST ≥ 5mm induration without prior treatment, regardless of present TST size
- Prior exposure to active TB case, without prior treatment, regardless of present TST size
- Chest X-ray findings concerning for prior TB**
  - (apical scarring/calcified nodules)

**These patients should have 3 sputum sent for AFB smear/mycobacterial culture to evaluate for active pulmonary TB before determining treatment strategy.

**Treatment of LTBI in transplant candidates**

- Non-Liver
  - Pre-transplant, INH x 9 mo
- Liver
  - Pre-transplant, Rif x 4 mo
  - Post-transplant INH x 9 mo
- Avoid rifampin post-transplant, rifabutin can be consider in select cases

**Case 1: Summary**

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

**Case 2**

- 54 year-old M 9 months s/p bilateral lung transplant for interstitial lung disease presents for routine evaluation
- On routine evaluation he admits to increased fatigue and cough over the last couple weeks
- MEDS: Prograf 2mg BID, Cellecept 1000 mg BID, Prednisone 5 mg QD, Septra TIW, valcyte 900 QD

**Chest X-ray: Today**

**Chest X-ray: 3 months ago**
Pulmonary nodules in SOT recipients

- Retrospective analysis of all SOT patients who were dx w/ pulmonary nodules 1990-2005
- Transplant type:
  - Liver - 42%
  - Heart - 22%
  - Kidney- 18%; Kidney-Pancreas - 5%
  - Lung - 8%
- Mean days post transplant to diagnosis: 1060

Copp DH. AJT. 2006

Risk factors for types of PNs

- Infectious
  - Non-lung Tx OR: 20.7, p=0.02
  - Associated consolidation OR: 20.2, p<0.01
- Aspergillus
  - Heart Tx OR: 4.4, p=0.04
  - < 90 d post-Tx OR: 13.7 p <0.01
- PTLD
  - Lung Tx OR 14.6, p=0.003
  - EBV neg pre-transplant OR 11.3, p=0.04


Case cont.

- Bronchoscopy
  - Bacterial: negative
  - mycobacterial: negative
  - fungal cultures: negative
- Galactomannan serum: 0.3 (normal <0.5)
- β-D-glucan serum: < 40 (normal < 40)
- Galactomannan BAL: 10.1 (normal < 0.5)
Aspergillus diagnostics (sensitivity)

- Fungal cultures BAL: 25-50%
- Galactomannan serum: 60% (all)/ 41% (SOT)
- Galactomannan BAL: 70-95%
- Beta-D glucan serum: 55-95%
- Biopsy: gold standard


Aspergillosis in SOT recipients

![Graph showing invasive Aspergillosis attack rate by Transplant Type and Time post-transplant.]

Case 2: Summary

- DDx for pulmonary nodules includes both infection and malignancy
- Serum GM, BDG, and sputum culture have limited sensitivity
- BAL GM has increased sensitivity
- Biopsy is the gold standard for diagnosis
- Voriconazole is the gold standard for treatment

Case 3

- 73 y/o man 8 days post cadaveric renal transplant presents with confusion
- Cyclosporine levels were markedly elevated, Na was 127 and possible pneumonia on CXR
- Electrolytes corrected, antibiotics given for pneumonia and cyclosporine level normalized
- Mental status deteriorated to coma

DDx of CNS infection in SOT recipient?

- Meningitis
- Encephalitis
- Brain abscess
CNS lesions in liver transplant recipients (n=60)

- Vascular events
- Infection
- Other malignancies
- Cont post retransplant
- Infection

DDx
- Nocardia
- Tuberculosis
- PTLD
- Toxoplasmosis
- Bacterial abscess
- Cryptococcus
- Other molds
- Zygomycoses
- Aspergillus

Meningoencephalitis in SOT
- Bacterial: routine meningitis, listeria, TB
- Fungal: cryptococcus, endemic mycoses (e.g. coccidioidomycosis)
- Viral:
  - Herpes viruses: HSV, VZV, CMV, EBV, HHV-6
  - WNV, rare: LCMV, Rabies
- Parasites: amoeba (rare)

Diagnostic evaluation of CNS infection in SOT recipient?
1. MRI with and without contrast
2. Lumbar puncture
   - Cell count, protein, glucose, freeze tube!!
3. CSF studies and serological testing guided by MRI and LP findings
4. If “focal lesion” – chest CT

Case 3 continued
- MRI of the brain was without acute changes
- CSF
  - WBC: 32 (79% lymphs, 5% PMNs); RBC: 2
  - Total protein: 142 and glucose: 105
- EEG showed diffuse slowing

“Timeline” of infection post-transplant

Donor-derived infections
- < 1% of transplants but are associated with significant morbidity and mortality

Donor-derived infection can also present early
Donor-derived Infections

- Common, screened for,
  - CMV, bacteremia, bacteriuria, syphilis, toxo
- Less common, not screened for, treatable
  - Tuberculosis, endemic fungal infection, Chagas
- Uncommon, not screened for, not treatable
  - Lymphocytic choriomeningitis virus, rabies, balamuthia, and west nile virus

Back to the case...

- Many serum and CSF studies were sent...
- Recipient:
  - CSF WNV IgM+
  - Serum WNV IgM+
- Donor
  - Serum WNV PCR +
- Donor had no signs or symptoms of infection at the time of death.

WNV clinical manifestation (General population)

- < 1% NEUROINVASIVE DISEASE
  - WNV Encephalitis (55-60%)
  - WNV Meningitis (35-40%)
  - WNV Poliomyelitis (5-10%)

- 80% ASYMPTOMATIC

- 20% WEST NILE FEVER
  - Abrupt onset of fever and HA
  - Malaise/Fatigue
  - Anorexia

WNV clinical manifestation (Donor-derived infections)

- 64% NEUROINVASIVE DISEASE

- 26% WEST NILE FEVER

How to prevent donor-derived WNV infection?

- Preventing donor-derived infection
- False-positives (wasted organs)

WNV activity 2012 – protect your recipients from WNV now!

- West Nile Virus Activity in California Counties 2012 YTD
- Counties with West Nile virus activity
- Counties with West Nile virus activity by county
- Counties with West Nile virus activity by county and zip code
- Counties with West Nile virus activity by county and zip code

- Map shows West Nile virus activity in California counties.


- Peterson LR. JAMA. 2004

- Rhee C. Transp Infect Dis. 2011
Protect your recipients against post-transplant infection

- Use insect repellent
- Dusk and dawn – high risk periods
  - Wear long sleeves and pants or stay indoors
- Keep mosquitoes out of home
- Emptying standing water from around home

WNV Diagnosis/Treatment

- Diagnosis
  - Serum or CSF IgM (may be negative early in disease)
  - Serum or CSF PCR (immunocompromised hosts)
  - Convalescent titers
- Treatment
  - Supportive care, consider IVIG but unproven
  - Mosquito control/prophylaxis (DEET)

Case 3: Summary

- CNS infection evaluation includes MRI, LP, and CSF/serum testing
- Consider donor-derived infection (DDI) in the early post-transplant period
- If concerned for DDI contact OPO
- Know how to prevent WNV in your post-transplant patients

QUESTIONS?

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