Infections in Solid Organ Transplant (SOT) Recipients

- SOT is a life-saving intervention
  - 857,960 SOTs performed in U.S. since 1988
  - 39,036 SOTs performed in 2020
- SOT recipients
  - have compromised immunity / increased infection risk
  - are targets for common & emerging opportunistic pathogens encountered pre- and post-transplant
  - often have atypical infection presentation owing to their compromised immunity / decreased inflammatory response
  - are on complex medical regimens; drug interactions common

WHAT YOU SHOULD KNOW FOR THE BOARD EXAM:

- Infection risk varies based on
  - Organ transplanted
  - Time post transplant
  - Degree of immunosuppression
  - Prophylaxis regimen
  - Unique exposures
- Key drug interactions and drug-induced syndromes
  - Calcineurin inhibitors and azoles, macrolides, rifampin (covered in Dr. Gilbert’s antibiotic lecture)
  - Sirolimus associated pneumonitis
  - Calcineurin inhibitors and TIP and PRES

WHAT YOU SHOULD KNOW FOR THE BOARD EXAM:

- The following major clinical syndromes:
  - CMV syndrome & disease
  - EBV & Post Transplant Lymphoproliferative Disorder (PTLD)
  - BK virus nephropathy
  - Aspergillosis, Mucormycosis & Cryptococcosis
  - Tuberculosis
  - Toxoplasmosis
  - Donor derived infections

PLAY THE ODDS

The data in the stem let’s you “play the odds” as to the most likely diagnosis

- Patient completing valganciclovir prophylaxis 6 weeks prior presenting with fatigue, low grade fever and leukopenia
  - CMV Syndrome
- Donor died from skiing accident in fresh water lake in Florida and recipient presents 3 weeks post transplant with encephalitis
  - Naegleria
- Renal transplant recipient on valganciclovir prophylaxis presents with asymptomatic renal dysfunction
  - BK Virus
- Lung transplant recipient planted vegetable garden 2 weeks prior while on prophylaxis presents with productive cough and cavitary lung lesion
  - NOCARDIA
FREQUENCY, TYPE & INFECTION SOURCE IN THE 1ST POST TRANSPLANT YEAR

<table>
<thead>
<tr>
<th>Transplant Type</th>
<th>Infection Episodes per Patient</th>
<th>Bacteremia</th>
<th>CMV Disease * (%)</th>
<th>Fungal Infections (%)</th>
<th>Most Common Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Heart-Lung</td>
<td>3.19</td>
<td>8-25</td>
<td>39</td>
<td>8.6</td>
<td>Lung</td>
</tr>
<tr>
<td>Liver</td>
<td>1.96</td>
<td>10-23</td>
<td>29</td>
<td>4.7</td>
<td>Abdomen &amp; Biliary tract</td>
</tr>
<tr>
<td>Heart</td>
<td>1.36</td>
<td>8-11</td>
<td>25</td>
<td>3.4</td>
<td>Lung</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.98</td>
<td>5-10</td>
<td>8</td>
<td>1.3</td>
<td>Urinary tract</td>
</tr>
</tbody>
</table>

*CMV, Cytomegalovirus; CMV disease rates in the absence of routine antiviral prophylaxis

CLASSIC TIMING OF INFECTIONS FOLLOWING SOLID ORGAN TRANSPLANTATION

**“EARLY” BACTERIAL INFECTIONS FOLLOWING SOT**
Type & site of early bacterial infection varies based on organ transplanted, surgical approach/technique & transplant center
- Risk of peritoneal soilage/infection greater in liver transplantation with Roux-en-Y biliary drainage
- Recipient colonization with resistant organisms (e.g. MRSA, VRE, CRE) pre-transplant, confers risk of post-transplant infection
- Cluster with unusual pathogen - environmental problem? (e.g. Legionella, M. abscessus from hospital water distribution systems)

**“LATE” BACTERIAL INFECTIONS FOLLOWING SOT**
80% OF LATE BACTERIAL INFECTIONS ARE COMMUNITY ACQUIRED
- Streptococcus pneumoniae
  - Incidence significantly > in SOT (146/100,000) vs general population (12/100,000)
  - Vaccination recommended
- Listeria monocytogenes
  - Bacteremia (Gram + Rods) / Diarrhea / Meningitis
  - Ampicillin treatment of choice
  - High relapse rate, treat for at least 3-6 wks

Kumar D et al., Am J of Transplant 2007;7:1209

**LATE BACTERIAL INFECTIONS, CONT.**
- Nocardia species
  - 1%-6% of all SOT recipients
  - Presents most often as pulmonary nodules, CNS (15-20%), skin (15%), or bone (2-5%) lesions
  - Diagnosis: Culture and/or histopathology
    - Branching, filamentous Gram + Rods
    - Partially acid-fast by modified Kinyoun stain
    - Nocardia is Neurotropic; brain imaging critical
  - Treatment:
    - High dose TMP-SMX drug of choice
    - Otherwise, based on susceptibility data & site of infection
    - TMP-SMX dose used for PCP prophylaxis not protective

**CMV DISEASE AFTER SOT**

**INDIRECT AND DIRECT EFFECTS**

**INDIRECT Effects:**
- Acute and Chronic Rejection
- Opportunistic Super-Infections (Gram negative bacteria & Molds)

**DIRECT Effects:**
- CMV Syndrome – most common presentation
  - CMV in blood + fever + malaise, leukopenia, atypical lymphocytosis, thrombocytopenia, or elevated liver enzymes
- Tissue Invasive Disease
  - Evidence of CMV on biopsy + compatible signs/symptoms
RISK OF CMV DISEASE AFTER SOT

<table>
<thead>
<tr>
<th>CMV Serologic Status</th>
<th>Risk Category</th>
<th>Incidence of Disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D+/R-</td>
<td>High</td>
<td>50+</td>
</tr>
<tr>
<td>D+/R+ or D-/R+</td>
<td>Intermediate</td>
<td>10-15</td>
</tr>
<tr>
<td>D-/R-*</td>
<td>Low</td>
<td>0</td>
</tr>
</tbody>
</table>

ALA Therapy (R+)

- Induction: Intermediate 25-30
- Rejection: High 65

*Should receive leukocyte depleted blood products

CMV DISEASE AFTER SOT

PROPHYLACTIC APPROACHES

UNIVERSAL
All SOT recipients receive therapy during highest risk periods
- Expensive
- May induce resistance
- Some pts exposed unnecessarily

PREEMPTIVE
Treatment based on asymptomatic viral replication in blood
- Optimal viral threshold for initiating therapy not well defined
- Requires serial monitoring with detection assay

NOTE: Letermovir not studied or approved for use in SOT population, only HSCT

CMV DISEASE AFTER SOT

PROPHYLAXIS

Bottomline:
- D+/R- or ALA for rejection → Universal
  - First 3-6 months post-transplant
  - At least 1 month post-ALA for rejection
- R+ → Universal or Preemptive
  - First 3-6 months post-transplant

CMV DISEASE AFTER SOT

GANCICLOVIR RESISTANCE

- Suspect resistance if prolonged (> 6 weeks) ganciclovir exposure AND:
  - No reduction in viral load after 14 days of treatment
  - No clinical improvement after 14 days of treatment

- Management of suspected ganciclovir resistance:
  - Reduce immunosuppression
  - Switch to foscarnet (± CMV hyperimmune globulin)

CMV DISEASE AFTER SOT

ANTIVIRAL RESISTANCE

Key mutations have been associated with resistance
- UL97 CMV Phosphotransferase gene mutations (most common)
  - Imply ganciclovir resistance

- UL54 CMV DNA Polymerase gene mutations
  - May confer resistance to ganciclovir, foscarnet, & cidofovir

Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD

CMV Disease After SOT

Letermovir (LMV)
- Inhibits CMV terminase complex, interferes with viral genome cleavage/packaging
- Activity against strains with UL97 & UL54 mutations
- Only a few case reports of use for GCV resistant infections some which resulted in LMV resistant dz
- No activity against other herpes viruses

Maribavir (MBV)
- Interferes with viral nuclear egress by inhibiting UL97 kinase
- UL97 kinase activates ganciclovir (GCV), thus MBV inhibits GCV activity
- MBV & GCV should not be used together
- MBV is active against many GCV resistant strains
- Phase 3 structural or GCV resistant dz just finished enrolling!

CASE 1
- 54 yo male 60 days post-cardiac transplant was treated for rejection with steroids when fever and a non-tender anterior cervical mass appeared.
- Biopsy showed nodal replacement by lymphocytes, many of which stained positively for Epstein-Barr virus as well as for the B cell marker, CD20.
- His plasma EBV viral load was 10,000 copies /ml.

QUESTION #1
The most appropriate treatment for this condition is:
A. Cidofovir
B. Ganciclovir
C. Acyclovir
D. Cyclophosphamide
E. Rituximab

EPSTEIN BARR VIRUS POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

EBV transformed B-lymphocytes give rise to PTLD
- A few cases may arise from T-lymphocytes

Risk factors:
- 1° EBV infection
  - Donor seropositive, Recipient seronegative
  - Antilymphocytic antibody therapy (T-cell depletion)
- Organ transplanted
  - Intestine > Lung > Heart > Liver > Kidney

EPSTEIN BARR VIRUS POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

Clinical manifestation - wide range
- Fibrillary meningitis-like illness with lymphadenopathy
- Solid tumors
  - Often involve transplanted graft
  - 50% any extranodal masses
  - 25% involve CNS

Definitive diagnosis requires tissue biopsy
- Classification based on histology and clonality
- Molecular (PCR) tests available
  - WHO Standard for Assay Calibration available
  - Whole Blood vs Plasma controversy
  - Misses EBV-negative, localized, and donor-derived PTLD
- Used as an aid for Diagnosis and Pre-emptive monitoring with stepwise reduction in immunosuppression to reduce PTLD rates

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**EPSTEIN BARR VIRUS POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)**

**Treatment:**
- Antivirals not effective on latently infected lymphocytes
- Reduce Immunosuppression (Response ~ 45%)
- Rituximab: Anti-CD20 monoclonal antibody (Response ~ 55%)
- Cytotoxic Combination (CHOP, ACVBP) Chemotherapy
  - Reserved for non-responsive disease
  - High treatment associated mortality (13%-50%)
- Adoptive Immunotherapy (EBV cytotoxic T-cells)
  - Under study, not readily available

**CASE 2**

52 yo female S/P cadaveric renal transplant receiving tacrolimus, prednisone and mycophenolate.
- Week 30 post transplant serum creatinine rose from 1.5 to 2.3 mg/dl.
- Tacrolimus levels were in therapeutic range.
- Urinalysis revealed one plus protein and no cells or casts.

**QUESTION #2**

Which would be most helpful in understanding if BK virus was causing her renal failure?
A. Presence of decoy cells in urine cytology
B. Urine BK viral load
C. Urine culture for BK virus
D. Plasma BK viral load
E. Demonstration of BK inclusions in renal tubular epithelium on renal biopsy

**POLYOMAVIRUS BK VIRUS NEPHROPATHY**

- Ubiquitous, DNA virus
  - 1st infxn – URI during early childhood
  - 80% worldwide population sero+
- Renal & uroepithelial cells, site of latency
- Cause of nephropathy post renal transplant
  - Up to 15% of renal recipients effected
  - Time to onset 28-40 weeks (majority within 1st yr post tx)
- Manifests as unexplained renal dysfunction (as does rejection)

**DIAGNOSIS**

- Replication in urine precedes replication in blood precedes nephropathy
- Renal Bx - “Gold Standard” for diagnosis
- Blood PCR
  - Sensitive (100%) but less specific (88%)
  - Cannot rule out rejection
  - Useful as indicator for biopsy
- Urine Cytology, Electronmicroscopy, & PCR
  - Detection in urine: Low PPV but High NPV

**TREATMENT**

- Reduce immunosuppression
- Case series with variable success using:
  - Low-dose cidofovir
  - Leflunomide
- New drugs & randomized controlled trials needed
- Preemptive monitoring key to prevention

**REFERENCES**

Hirsch et al. Transplantation 2006;79:1277-1286
Farasati et al. Transplantation 2006;79:242; 161/165; 1252

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58 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD

INVASIVE FUNGAL INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS

Type of fungal infection varied depending on organ transplanted

- Candida: 55%
- Aspergillus: 19%
- Cryptococcus: 8.4%
- PCP: 1.3%
- Other yeasts: 2.8%
- Other moulds: 5.8%
- Zygomycetes: 1.9%

INVASIVE FUNGAL INFECTIONS ACCORDING TO ORGAN TRANSPLANTED N=16,808

<table>
<thead>
<tr>
<th>Organ</th>
<th>12 Month IFI Incidence (%)</th>
<th>IFI Type (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>1.3</td>
<td>Candidiasis</td>
</tr>
<tr>
<td>Heart</td>
<td>3.4</td>
<td>Aspergillosis</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4.0</td>
<td>Other moulds</td>
</tr>
<tr>
<td>Liver</td>
<td>4.7</td>
<td>Cryptococcus</td>
</tr>
<tr>
<td>Lung</td>
<td>8.6</td>
<td>Endemic</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>11.6</td>
<td>Pneumocystosis</td>
</tr>
</tbody>
</table>

INVASIVE FUNGAL INFECTIONS RISK FACTORS AFTER SOT

Each solid organ group will have unique risks for IFIs

Liver
- Re-transplantation
- Pre-existing hepatic or renal failure
- Heavy Candida colonization peri-tx
- Large volume intra-operative transfusions
- Bleeding complications requiring re-operation
- Choledochojejunostomy

Lung
- Vulnerable anastomotic site
- Continuous environmental exposure
- Aspergillus colonization of airways
- CMV pneumonitis
- Acute rejection
- Obliterative bronchiolitis

ANTIFUNGAL PROPHYLAXIS FOR SOLID ORGAN TRANSPLANT RECIPIENTS

Lung
- All recipients
- Candida & Molds

Liver
- All recipients
- High-risk recipients
- Candida

Pancreas
- All recipients
- High-risk recipients
- Candida

Small bowel
- All recipients
- Candida

Per ISHLT Guidelines
Per AST Guidelines

TUBERCULOSIS

- 34-74 fold higher risk of active disease in SOT recipients than general population
- Incidence 1% - 6% (up to 15% in endemic areas)
- Median onset 9 months post-tx (0.5-144 months)
- 33% of infections are disseminated at diagnosis
- Treatment
  - Rifampin-based regimens associated with graft loss/rejection in 25%
  - Mortality ~30%
  - Treat latent TB prior to transplant when possible

CASE 3

- 35 yo female s/p heart transplant in France 90 days prior presented with fever, dyspnea and a diffuse pneumonia on chest CT.
- She was receiving prednisone, tacrolimus & mycophenolate.
- Both recipient & donor were CMV negative; she was not on CMV prophylaxis.
- She was on inhaled pentamidine for PCP prophylaxis.

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CASE 3
Trimethoprim-sulfamethoxazole was started empirically and she began improving.
Bronchoalveolar lavage (BAL) was negative for:
- pneumocystis by direct fluorescent antibody stain & PCR,
- fungi by calcifour white / potassium hydroxide stain,
- mycobacteria by AFB smear,
- bacteria by Gram stain, and
- respiratory viruses by multiplex PCR
Routine bacterial BAL and blood cultures were negative.

QUESTION #3
Assuming trimethoprim-sulfamethoxazole was causing her improvement, which additional test on the BAL might have explained her improvement?
A. PCR for CMV
B. PCR for toxoplasmosis
C. PCR for tuberculosis
D. Galactomannan
E. Cold enrichment culture for Listeria

TOXOPLASMOSIS
- Acquired from donor, reactivation, blood transfusion or ingestion of contaminated food or water
- Donor seropositive/Recipient seronegative at high risk
- HEART > LIVER > KIDNEY TRANSPLANT
- Presents with myocarditis, pneumonitis, & meningitis
- DIAGNOSIS:
  - PCR
  - Giemsa smear of BAL
  - Brain aspirate for tachyzoites
  - Immunoperoxidase stain of endocardial biopsy or other tissue
- TREATMENT: sulfadiazine-pyrimethamine-leucovorin

CASE 4
Liver transplant recipient presented 21 days post transplant with confusion, tremors, lethargy, anorexia
- On bactrim & valganciclovir prophylaxis
- Rapid progressive neurologic decline → agitation & delirium → intubation
- Blood & urine cultures: negative
- CSF: lymphocytic pleocytosis (25 WBCs/mm³) & elevated protein
- Gram stain, bacterial, fungal cultures negative
- Brain MRI: non-revealing
- Empiric intravenous ganciclovir, vancomycin, ceftriaxone & ampicillin
- Day 6 Repeat MRI: diffuse encephalitis
- Expired 13 days after neurologic symptom onset
- Donor was previously healthy presenting with subarachnoid hemorrhage
  - Toxicology screen: + cocaine & marijuana
  - Brain CT: expanding subarachnoid hemorrhage
  - Recently on camping trip

QUESTION #4
This presentation is most consistent with:
A. CMV encephalitis
B. HHV6 encephalitis
C. VZV encephalitis
D. Rabies encephalitis
E. Cryptococcal meningitis
"EXPECTED" DONOR-DERIVED INFECTIONS

- Expected = known before tx or for which there are recognized standard prevention guidelines
  - Cytomegalovirus (CMV)
  - Epstein–Barr virus (EBV)
  - Toxoplasmosis

"UNEXPECTED" DONOR-DERIVED INFECTIONS

VIRUSES, VIRUSES, & PARASITES, OH MY…

- Lymphocytic choriomeningitis virus
  - Rodents
  - 4 outbreaks (3 USA, 1 Australia); 9 deaths
  - Nucleic Acid Tests decrease "window" to ~5-10 days (HIV), 6-9 days (HCV)

"EXPECTED" DONOR-DERIVED INFECTIONS

- Enterovirus
  - 2 outbreaks (1 USA, 1 Italy); 5 deaths
- Pneumocystis jiroveci
  - N/A

TYPICAL PRESENTATIONS OF UNEXPECTED DONOR DERIVED INFECTIONS

- Most present in the first 3 months post transplant
- Look for epidemiologic clues for potential donor exposure in the stem (e.g. bat bites, new pets, recent travel to an endemic region)

VACCINATION RECOMMENDATIONS FOR SOT

- Update vaccinations pre SOT:
  - Hepatitis A, Hepatitis B, Flu, TDaP, Pneumococcal
  - Live Varicella, MMR vaccines (only if ≥ 8 weeks until transplant)
  - HIB, Meningococcal if planned splenectomy (e.g. Multivisceral Tx)

- Recommended post SOT: (Delay 3–6 months to maximize response)
  - Pneumococcal
  - Tetanus-diphtheria toxoid
  - Inactivated Influenza

- Live vaccines are NOT recommended after SOT including:
  - Measles Mumps Rubella
  - Varicella
  - Inhaled influenza
  - Oral polio
  - Yellow fever
  - BCG
  - Small pox
  - Salmonella typhi (oral)

SOLID ORGAN TRANSPLANT PATIENT TRAVEL

- REGIONAL EXPOSURES
  - COCCIDIOIDOMYCOSIS: Southwest U.S.
  - HISTOPLASMOSIS: Central/Mid-Atlantic U.S.
  - VISCERAL LEISHMANIASIS: Spain, Mediterranean Basin
  - MALARIA: Tropics
  - BABESIA MICROTI: Northeast & Upper Midwest U.S.

- AND ALL THE "NORMAL" RISKS TO TRAVELERS
  - DIARRHEA
  - BTDS
  - MDR-TB
  - BLOOD SUPPLY (need for TRANSFUSIONS), etc....
  - AVOID LIVE VACCINES: Yellow Fever, Oral typhoid, etc....
  - DRUG INTERACTIONS - Transplant meds + travel related prophylactic agents

KEY DRUG TOXICITIES / SYNDROMES

- Calcineurin inhibitors and TTP and PRESS (RPLS)
- Sirolimus-induced pneumonitis
  - Progressive interstitial pneumonitis (22% in one study)
  - Risk factors: late switch to sirolimus & impaired renal function
  - Symptoms: dyspnea, dry cough, fever, and fatigue
  - Radiographic & bronchoalveolar lavage consistent with bronchiolitis obliterans organizing pneumonia & lymphocytic alveolitis
  - Recovery with sirolimus withdrawal

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If you’re thinking PCP but it’s not → think TOXO
Patient presenting atypically during first month post transplant →
  think donor transmitted infection
  • Rabies, WNV, Coccidioides, Chagas, LCMV (look for epidemiologic clues in stem)
Remember drug interactions and syndromes
  • TTP and PREESS (RPLS) induced by calcineurin inhibitors
  • Sirolimus-induced pneumonitis
Remember Strongyloides hyperinfection syndrome
TB- Don’t miss a case!
BK, CMV and EBV/PTLD – know how to diagnose and manage

Thank You!