Infections in Solid Organ Transplant (SOT) Recipients

- SOT is a life-saving intervention
- >750,000 SOTs performed in U.S. since 1988
- 39,718 SOTs performed in 2019

- 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

Data from Organ Procurement and Transplantation Network database as of June 29, 2020

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 TTP and PRESS

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
  - ACANTHAMOEBA

- Renal transplant recipient on valganciclovir prophylaxis presents with asymptomatic renal dysfunction
  - NOCARDIA

- Lung transplant recipient planted vegetable garden 2 weeks prior while on posaconazole prophylaxis and presents with productive cough and cavitary lung lesion

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant – Scynexis, Astellas, Shionogi
- Research Grant – Lediant
- Clinical Trials (Site PI/Study PI) – Ansun, Astellas, Cidara, Scynexis, Shire, F2G
- Royalties (Chapter Author) – UpToDate

©2020 Infectious Disease Board Review, LLC
FREQUENCY, TYPE & INFECTION SOURCE IN THE 1ST POST TRANSPLANT YEAR

| Transplant Type | Infection Episodes per Patient | Bacteremia | CMV Disease * (%) | Fungal Infections (%) | Most Common Source |
|-----------------|-------------------------------|------------|-------------------|----------------------|-------------------|
| Kidney          | 0.98                          | 5-10       | 8                 | 1.3                  | Urinary tract     |
| Heart           | 1.36                          | 8-11       | 25                | 3.4                  | Lung              |
| Lung Heart-Lung | 3.19                          | 8-25       | 39                | 8.6                  | Lung              |
| Liver           | 1.86                          | 10-23      | 29                | 4.7                  | Abdomen & Biliary tract |

*CMV: Cytomegalovirus. Numbers reflect CMV disease rates in the absence of routine antiviral prophylaxis.

CLASSIC TIMING OF INFECTIONS FOLLOWING SOLID ORGAN TRANSPLANTATION

Timing altered by:
- Enhanced immunosuppression
- Prophylaxis regimen
- Unique exposures

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

“EARLY” BACTERIAL INFECTIONS FOLLOWING SOT

Type & site of early bacterial infection varies based on organ transplanted, surgical approach/technique & transplant center
- Risk of peritoneal 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)

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

| CMV Serologic Status | Risk Category | Incidence of Disease (%) |
|----------------------|---------------|--------------------------|
| D+/R-                | High          | 50+                      |
| D+/R+ or D-/R+       | Intermediate  | 10-15                    |
| D-/R-*               | Low           | 0                        |
| ALA Therapy (R+)     |               |                          |
| Induction            | Intermediate  | 25-30                    |
| Rejection            | High          | 65                       |

D, Donor; R, Recipient; ALA, Antilymphocyte Antibody
*Should receive leukocyte depleted blood products

CMV DISEASE AFTER SOT

- Typically occurs 1-3 months post-transplant
  - Or after prophylaxis is stopped
- Disease of GI Tract and Eye may not have concurrent viremia
  - Diagnosis often requires biopsy/aspiration
- Viral load may continue to rise during first 2 weeks of Rx
  - Don't repeat PCR until Day 14 of treatment
- Treat for 2-3 weeks...
  - DO NOT STOP TIL VIREMIA CLEARs (high risk for relapse)

CMV DISEASE AFTER SOT
PROPHYLACTIC APPROACHES

**UNIVERSAL**
- All SOT recipients receive therapy during highest risk periods
  - Options include IV or oral ganciclovir or valganciclovir
  - Expensive, may induce resistance, some pts exposed unnecessarily

**PREEMPTIVE**
- Treatment based on asymptomatic viral replication in blood
  - Requires serial monitoring with detection assay
  - Optimal duration of treatment, drug to use, & viral threshold for initiating therapy not yet determined

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

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

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

©2020 Infectious Disease Board Review, LLC
CMV DISEASE AFTER SOT
ANTIVIRAL RESISTANCE (ON THE HORIZON)

Letermovir (LMV)
- Interferes with cleavage / packaging of viral genome by inhibiting pUL56 subunit of CMV terminase complex
- Resistance mutations usually in pUL56 (rarely pUL89 or pUL51 subunits) of CMV terminase complex; do not confer cross-resistance to other antiviral drugs
- Appears to have low barrier to resistance; only a few case reports for use in SOT with GCV resistant infections
- Only approved for prophylaxis in HSCT population
- No activity against other herpes viruses

Maribavir (MBV)
- Interferes with viral nuclear egress by inhibiting viral pUL97 kinase.
- UL97 inhibition also prevents 1st phosphorylation step of ganciclovir (GCV) resulting in antagonistic effect when used together
- Resistance mutations usually in UL97 gene; can confer cross-resistance to GCV
- Phase 3 clinical trial of GCV resistant disease just finished enrolling...stay tuned!

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)
• ~3% Cumulative 10 year incidence in SOT population
• Incidence varies based on organ transplanted
  - Small Bowel / Multivisceral – up to 32%
  - Lung / Heart / Liver - 3-12%
  - Kidney - 1-2%
• Biphasic pattern of disease after SOT:
  - First peak (20% cases) occurs 1st post-tx year
  - Second peak occurs 7-10 years post-tx

Olagne, J, et al. Am J Transplant. 2011 Jun;11(6):1260-9.

EPSTEIN BARR VIRUS POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)
• Clinical manifestation - wide range
  • Febrile mononucleosis-like illness with lymphadenopathy
  • Solid tumors
  • Often involve transplanted graft
  • 50% are 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 controversial
    - 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

Petit B, et al. Transplantation. 2002;73(2):265.
Peters AC, et al. Transplantation. 2018; 102(9):1553.
**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

---

**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 affected
    - Time to onset 28-40 weeks (majority within 1st yr post bi)
    - Manifests as unexplained renal dysfunction (as does rejection)

---

**CASE 2**

- 52 yo female S/P cadaveric renal transplant receiving tacrolimus, prednisone and mycophenylate.
- 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.

---

**BK VIRUS NEPHROPATHY 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

---

**BK VIRUS NEPHROPATHY TREATMENT**

- Reduce immunosuppression
- Case series with variable success using:
  - Low-dose cidofovir
  - Leflunomide
- New drugs & randomized controlled trials needed
- Preemptive monitoring key to prevention
INVASIVE FUNGAL INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS

Type of fungal infection varied depending on organ transplanted:
- Aspergillus, 15%
- Candida, 55%
- Cryptococcus, 5.4%
- Zygomycetes, 1.9%
- Other yeasts, 2.8%
- Endemic, 5.7%
- Other molds, 5.8%

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

| Type          | Kidney | Heart | Pancreas | Liver | Lung | Small Bowel |
|---------------|--------|-------|----------|-------|------|-------------|
| 12 Month IFI  | Incident (%) | 1.3 | 3.4 | 4.0 | 4.7 | 8.6 | 11.6 |
| IFI Type (%)  | Candidiasis | 49  | 49 | 76 | 66 | 23 | 55 |
|               | Aspergillosis | 14 | 23 | 5 | 11 | 44 | 0 |
|               | Other molds | 7 | 10 | 3 | 6 | 26 | 0 |
|               | Cryptococcus | 15 | 10 | 5 | 6 | 26 | 5 |
|               | Endemic | 10 | 3 | 6 | 5 | 1 | 0 |
|               | Pneumocystosis | 1 | 3 | 1 | 0 | 2 | 0 |
|               | Other | 4 | 2 | 4 | 4 | 2 | 10 |

ANTIFUNGAL PROPHYLAXIS FOR SOLID ORGAN TRANSPLANT RECIPIENTS

- Per ISHLT Guidelines
- Per AST Guidelines

- Lung
  - All recipients
  - High-risk recipients: Candida

- Liver
  - All recipients
  - High-risk recipients: Candida

- Pancreas
  - All recipients
  - Candida

- Small bowel
  - All recipients
  - Candida

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.
Trimethoprim-sulfamethoxazole was started empirically and she began improving. Bronchoalveolar lavage (BAL) was negative for:

- pneumocystis by direct fluorescent antibody stain & PCR
- fungi by calcoflour 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.

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 WBC/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
**43 – Infections in Solid Organ Transplant Recipients**

*Speaker: Barbara Alexander, MD*

---

**“EXPECTED” DONOR- DERIVED INFECTIONS**

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

*United Network for Organ Sharing / Organ Procurement and Transplant Network
  Ison M et al. Am J Transplant. 2009;9:1929-1935.

**“UNEXPECTED” DONOR- DERIVED INFECTIONS**

**VIRUSES, VIRUSES, & PARASITES, OH MY...**

- Lymphocytic choriomeningitis virus (LCMV) & Hamsters and rodents
  - 4 outbreaks (3 USA, 1 Australia); 9 deaths
- Rabies virus & Unreported bat bite in donor
  - 3 outbreaks (2 USA, 1 Germany); 8 deaths
- Chagas’ Disease (Trypanosoma cruzi) & Reduviid bug (Latin America)
  - Screening tests lack sensitivity
  - Multiple transmissions reported
- HIV, Hep C, Hep B, West Nile Virus (WNV)
  - Remember the “Window” prior to development of antibodies
  - Nucleic Acid Tests decrease “window” to ~5-10 days (HIV), 6-9 days (HCV)

Fisher SA et al. N Engl J Med. 2006;354:2235-2249.  MMWR Morb Mortal Wkly Rep. 2008;57:799-801.  Kusne S et al. Transpl. 2005;11:1295-1297.

**SOLID ORGAN TRANSPLANT PATIENT TRAVEL**

- REGIONAL EXPOSURES
  - COCCIDIODOMYCOSIS: 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
  - STDs
  - MDR-TB
  - BLOOD SUPPLY (need for TRANSFUSIONS), etc....
- AVOID LIVE VACCINES: Yellow Fever, Oral typhoid, etc.
- DRUG INTERACTIONS → Transplant meds + travel related prophylactic agents

**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. donor from Latin America)

**KEY DRUG TOXICITIES / SYNDROMES**

- TTP / PRESS (RPLS) induced by calcineurin inhibitors
- 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

Euvrard S et al. N Engl J Med. 2012;367(4):329. Champion L et al. Am J Transplant 2006;6:144-156. Weinb M et al. Hepatol Clin Transplant 2017;21(1):A101.

---

©2020 Infectious Disease Board Review, LLC
OTHER PEARLS FOR BOARDS...

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 PRES (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