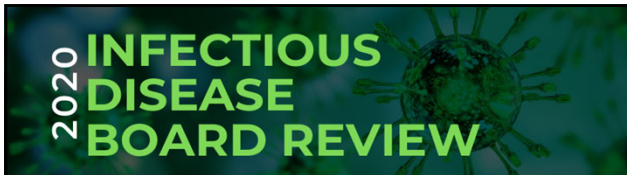


43 – Infections in Solid Organ Transplant Recipients

Speaker: Barbara Alexander, MD



2020 INFECTIOUS DISEASE BOARD REVIEW

Infections in Solid Organ Transplant Recipients

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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

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

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

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

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

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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

From Murray: Text, Principles and Practice of Infectious Diseases, 9th Edition, Chapter 51.3. Infections in Solid Organ Transplant Recipients by Mark Hersh and M. Louise Murray. © 2007 by McGraw-Hill. © 2007 by McGraw-Hill. © 2007 by McGraw-Hill. © 2007 by McGraw-Hill.

“LATE” BACTERIAL INFECTIONS FOLLOWING SOT

80% OF LATE BACTERIAL INFECTIONS ARE COMMUNITY ACQUIRED

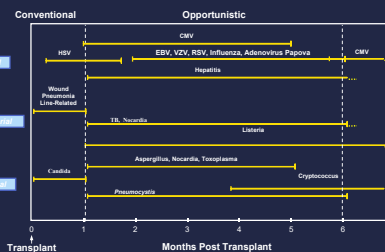
- *Streptococcus pneumoniae*
 - Incidence significantly > in SOT (146/100,000) vs general population (12/100,000)
 - Vaccination recommended
- *Listeria monocytogenes*
 - Bacteremia (Gram + Rods) / Diarrhea / Meningitis
 - Ampicillin treatment of choice
 - High relapse rate, treat for at least 3-6 wks

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

CLASSIC TIMING OF INFECTIONS FOLLOWING SOLID ORGAN TRANSPLANTATION

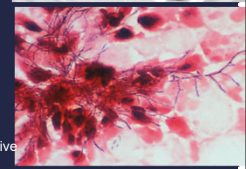
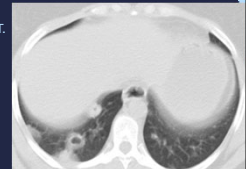
Timing altered by:

- Enhanced immunosuppression
- Prophylaxis regimen
- Unique exposures



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



“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

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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 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)

Lurain et al JID 2002; Limaye et al Lancet 2000; Limaye et al JID 2002; Kotton et al Transplantation 2013.

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 ANTIVIRAL RESISTANCE

Key mutations have been associated with resistance

- UL97 CMV Phosphotransferase gene mutations (most common)
 - Imply ganciclovir resistance

Mutations or Deletions	Ganciclovir Interpretation	Interpretation
M99V/I/T, V496G, S95 del, S95-403 del, C518Y, H320Q, A334V/G, L395S/V, K339T, G607M, S307Y	5-15	High-grade resistance
L407P, C593G, A334E/P/T, E396G, G307R	2-5	Low-grade resistance
V494M, A331Y, L395T, N357D, L406K, G305S, S307Y	<2	Insignificant grade resistance

* Boldface indicates the seven most common ("clinically") UL97 mutations conferring ganciclovir resistance.
 † % of mutant of wild type.

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

Lurain et al JID 2002; Limaye et al Lancet 2000; Limaye et al JID 2002; Kotton et al Transplantation 2013; Torre-Cisneros et al Transplantation Reviews 2016.

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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!

Piant J, Rowin C. Antiviral Research 2010; 163:91-105.

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

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.

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

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

QUESTION #1

The most appropriate treatment for this condition is:

- Cidofovir
- Ganciclovir
- Acyclovir
- Cyclophosphamide
- Rituximab

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

Pettit B et al. Transplantation. 2002;73(2):265.
Peters AC, et al. Transplantation. 2010; 102(9):1553.

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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

Allen et al. Am J Transplantation 2013;13:107-120

POLYOMAVIRUS BK VIRUS NEPHROPATHY

- Ubiquitous, DNA virus
 - 1° 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)

Hayashi RY et al. UNOS Database: Abstract 76, 2006 World Transplant Congress; Ramos et al. J Am Soc Nephrol 2002;13:2145; Hirsch et al. Transplantation 2005;79:1277-1286

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

Hirsch et al. Transplantation 2005;79:1277-1286; Nickenleit et al. NEJM 2000;342 (18):1309-1315; Ramos et al. J Am Soc Nephrol 2002;13:2145

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

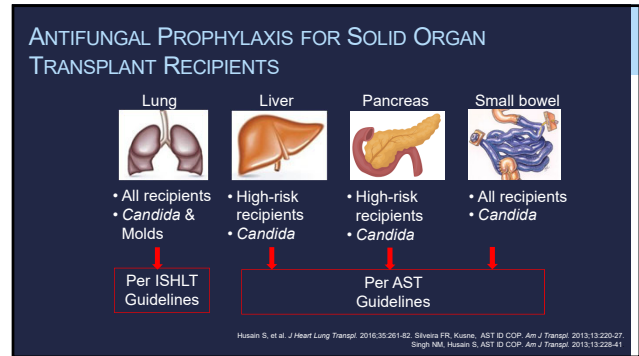
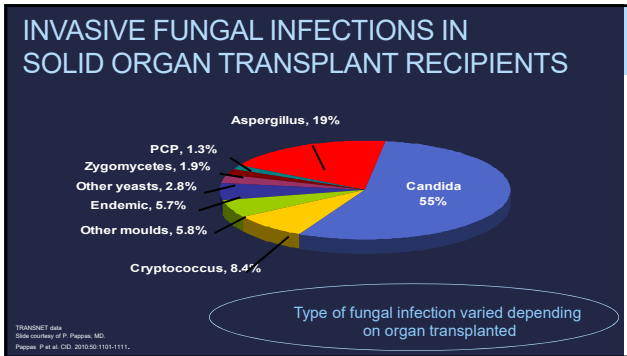
BK VIRUS NEPHROPATHY TREATMENT

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

Hirsch et al. Transplantation 2005;79:1277-1286; Farasati et al. Transplantation 2004;79:116; Vats et al. Transplantation 2003;75:105; Kabambi et al. Am J Transplant 2003;3:186; Williams et al. N Engl J Med 2005;352:1157-58.

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INVASIVE FUNGAL INFECTIONS ACCORDING TO ORGAN TRANSPLANTED

N=16,808

	Kidney	Heart	Pancreas	Liver	Lung	Small Bowel
12 Month IFI Incidence (%)	1.3	3.4	4.0	4.7	8.6	11.6
IFI Type (%)						
Candidiasis	49	49	76	68	23	85
Aspergillosis	14	23	5	11	44	0
Other molds	7	10	3	6	26	0
Cryptococcosis	15	10	5	6	2	5
Endemic	10	3	6	5	1	0
Pneumocystosis	1	3	1	0	2	0
Other	4	2	4	4	2	10

Pappas P, Alexander B, Andes D, et al. CID 2010;50:1101-1111

- ### 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

INVASIVE FUNGAL INFECTIONS RISK FACTORS AFTER SOT

Each solid organ group will have unique risks for IFIs
Strongly influenced by medical & surgical factors including technical complexity

Liver

- Re-transplantation
- Pre-tx fulminant hepatic or renal failure
- Heavy *Candida* colonization peri-tx
- Large volume intra-operative transfusions
- Bleeding complications requiring re-operation
- Choledochojunostomy

Lung

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

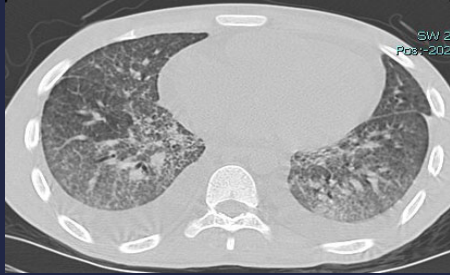
CANDIDA ASPERGILLUS

- ### 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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CHEST CT



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
- DIAGNOSIS:
 - PCR
 - Giemsa smear of BAL
 - Brain aspirate for tachyzoites
 - Immunoperoxidase stain of endocardial biopsy or other tissue
- TREATMENT: sulfadiazine-pyrimethamine-leucovorin

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 calcofluor 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 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 #3

Assuming trimethoprim-sulfamethoxazole was causing her improvement, which additional test on the BAL might have explained her improvement?

- PCR for CMV
- PCR for toxoplasmosis
- PCR for tuberculosis
- Galactomannan
- Cold enrichment culture for Listeria

QUESTION #4

This presentation is most consistent with:

- CMV encephalitis
- HHV6 encephalitis
- VZV encephalitis
- Rabies encephalitis
- Cryptococcal meningitis

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“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.

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:

- Pneumococcal
- Tetanus-diphtheria toxoid
- Inactivated Influenza

Live virus vaccines are NOT recommended after SOT including:

- Measles Mumps Rubella
- Varicella
- Inhaled influenza
- Oral polio
- Yellow fever
- BCG
- Small pox
- Salmonella typhi (oral)

“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)



Reiber SI et al. N Engl J Med. 2003;349:2252-2258. MWRW Moss M et al. WMO Rep. 2005;37:799-801. Kuzin S et al. Transpl. 2002;11:1295-1297. Miller T et al. CID 2010;50:1112-1119. Mamer F et al. Infection. 2007;35(4):219-24. Grossh PA, et al. Am J Transpl. 2009;9:519-526.

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
 - 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)

PATHOGEN	PRESENTATION
LYMPHOCYTIC CHORIOMENINGITIS VIRUS	ENCEPHALITIS
RABIES	ENCEPHALITIS
TOXOPLASMOSIS	DIFFUSE PNEUMONIA MYOCARDITIS RETINITIS ENCEPHALITIS
WEST NILE VIRUS	MENINGITIS ENCEPHALITIS POLIOMYELITIS-LIKE FLACCID PARALYSIS
CHAGAS' DISEASE	FEVER MYOCARDITIS
ACANTHAMOEBA	SKIN LESION ENCEPHALITIS
BALAMUTHIA MANDRILLARIS	ENCEPHALITIS
VISCERAL LEISHMANIASIS	PANCYTOPENIA HEPATOSPLENOMEGALY
MALARIA	FEVER

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. Ann Intern Med 2006;144:505. Weiner SM et al. Nephrol Dial Transplant. 2007;22(12):3631.

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OTHER PEARLS FOR BOARDS...

If you're thinking PCP but its 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 PRESS (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