Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

ID Bootcamp: Solid Organ and Stem Cell Transplant

Camille Nelson Kotton MD, FAST, FIDSA
Clinical Director, Transplant & Immunocompromised Host Infectious Diseases Group, Infectious Diseases Division, Massachusetts General Hospital
Associate Professor, Harvard Medical School

6/1/2022

Disclosures of Financial Relationships with Relevant Commercial Interests

Camille Nelson Kotton, Disclosures		
Company	Role	Details
Evrys	Consultant	CMV treatment in transplant
Merck	Consultant, Adjudication committee member, Data monitoring committee, symposium speaker (CME)	Transplant infections CMV antiviral trial, adjudication Pneumococcal vaccine, adjudication
Oxford Immunotec	Consultant, research, Symposium speaker (CME)	Novel diagnostics in transplant patients, TB in Immunocompromised Hosts
Shire/Takeda	Consultant, Adjudication committee member, symposium speaker (CME)	CMV management in transplant patients
Hookipa	Consultant, principal investigator on clinical trial CMV vaccine in kidney transplant recipients	CMV vaccine in kidney transplant recipients
AiCuris	Research	Local PI, use of pritelivir in immunocompromised patients with resistant herpes
Roche Diagnostics	Research	Review of risk factors for herpes viral infections after transplant

Outline: What I Hope You Will Learn

- Type of immunosuppression seen with organ transplant
- Timeline of infection
- Prevention is paramount
  - Gaps in prophylaxis help develop the differential diagnosis
- Syndromes
- Diagnostics
  - Differential diagnosis is broad, imperative to obtain diagnosis
- Treatment – including drug interactions
- Latest strategies for prevention, recognition, diagnosis, and treatment
  - Guidelines
  - Best practices for safety and practice improvement
- **Bootcamp: meant as an introduction to subsequent similar talks**

The More Immunocompromised Host

- Hematopoietic stem cell transplant (HSCT) < 2 years
  - ↑ if graft versus host disease
- Solid organ transplant (SOT) < 1 year
  - ↑ if rejection
- AIDS with low CD4 counts
- Active leukemia or lymphoma, generalized malignancy, aplastic anemia, recent radiation tx
- Congenital immunodeficiency
- Immunosuppressive medications
- Chronic hepatic or renal disease, diabetes
- Autoimmune diseases

https://wwwnc.cdc.gov/travel/yellowbook/2022/travelers-with-additional-considerations/immunocompromised-travelers, Kotton, Kroger, Freedman

The Less Immunocompromised Host

- Stem cell transplant recipients > 2 years post-transplant, not on immunosuppressive drugs, no graft versus host disease
- Chemotherapy for leukemia/lymphoma or cancer more than 3 months earlier with malignancy in remission
  - Those who have received immunotherapy with agents such as checkpoint inhibitors may need longer
- HIV patients with >500 CD4 lymphocytes
- Asplenia
- Nutritional deficiencies
- Steroid inhalers, topical steroids, intra-articular, bursal, or tendon injection of steroids, or on high-dose steroids over a month ago

https://wwwnc.cdc.gov/travel/yellowbook/2022/travelers-with-additional-considerations/immunocompromised-travelers, Kotton, Kroger, Freedman

Host considerations: *"Net state of immunosuppression"*

Dr. Robert Rubin, Massachusetts General Hospital

IMMUNOSUPPRESSION IS ADDITIVE

- Disease state may alter the immune system
  - Autoimmune diseases
  - Advanced organ failure
  - Other organ compromise: kidney, liver
- Comorbidities/conditions
  - Diabetes, obesity, malnutrition/weight loss
  - Hypogammaglobulinemia
  - Viral infections (HIV, CMV, EBV, HCV)
  - Altered microbiome
  - Advanced age
- Exogenous immunosuppression
  - Pre-transplant immunosuppression (i.e. autoimmune hepatitis)
  - Induction agents @ time of transplant
  - Chronic immunosuppression
  - Treatment of rejection

Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD

National Organ Transplant Data – USA

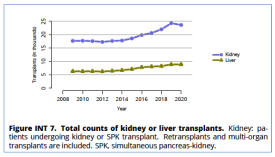


Figure INT 7. Total counts of kidney or liver transplants. Kidney: patients undergoing kidney or SPK transplant. Retransplants and multi-organ transplants are included. SPK, simultaneous pancreas-kidney.

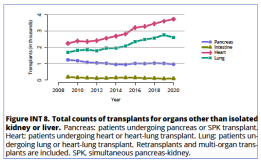


Figure INT 8. Total counts of transplants for organs other than isolated kidney or liver. Pancreas: patients undergoing pancreas or SPK transplant. Heart: patients undergoing heart or heart-lung transplant. Lung: patients undergoing lung or heart-lung transplant. Retransplants and multi-organ transplants are included. SPK, simultaneous pancreas-kidney.

>850,000 transplants done in USA since 1988

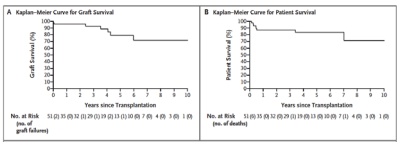
OPTN/SRTR 2020 Annual Data Report:
Introduction, AJT Feb 2022

What's Trendy? (Might be on boards?) Hepatitis C Donors and Organ Transplant

- Many programs are using hepatitis C positive donors into negative or positive recipients and treating after transplant
  - Yes, we are infecting people with hepatitis C
- Can be either HCV viral load and/or antibody positive
- For all organs, ~100% clearance
- Was often research protocol, now moving towards standard of care
- Need to have a good plan for medications (insurance)
- Trend towards shorter treatment protocols

Longer-Term Outcomes of *HIV-Positive–to–HIV-Positive Renal Transplantation*, Selhorst, Muller et al, NEJM 2018

- n=51
- 8 patients (16%) died after transplantation from non–graft-related causes
- No transmission of drug resistant virus
- **5-year overall survival and graft survival similar to the 3-year overall survival and graft survival observed among HIV-positive patients who received an organ from an HIV-negative donor in the United States**



HIV Organ Policy Equity (HOPE) Act: USA

- **Permits donated, HIV-positive organs to be used for transplantation in HIV-positive patients**
  - Previously prohibited by federal law
- **An active program at multiple centers**
  - Research setting only
- **+/- Half of organ donors have false positive testing**
  - Screening test positive, confirmatory test (done later, takes time) negative

10

Common Immunosuppression after Organ Transplant

Induction (step 1)
T cell depleting *or*
IL-2 antagonist *or*
High dose steroids

*T cell depleting= antithymocyte globulin (thymoglobulin), alemtuzumab (Campath®)
IL-2 antagonist= basiliximab (Simulect®)

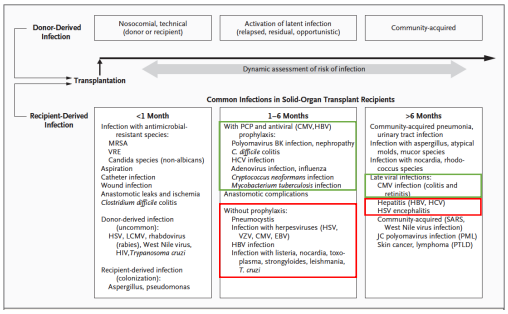
Chronic immunosuppression
Step 2

tacrolimus
(or cyclosporin)

± prednisone

mycophenolate
mofetil
(Cellcept)

Timeline of Infection after Organ Transplantation



Fishman, Infection in Solid-Organ Transplant Recipients, NEJM 2007

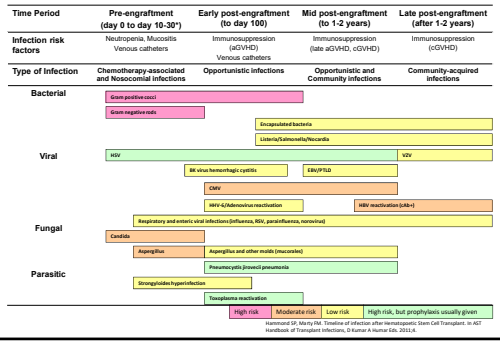
Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD

Common Immunosuppression after Stem Cell Transplant

- Chemotherapy
- Anti-graft versus host disease prophylaxis
  - Tacrolimus, cyclosporin
  - Methotrexate
  - Mycophenolate mofetil
  - Antithymocyte globulin (rabbit)
- Anti-graft versus host disease treatment
  - The first-line treatment of acute GVHD is methylprednisolone

Timeline of Infection after HSCT



Hammond SP, Marty FM. Timeline of infection after Hematopoietic Stem Cell Transplant. In: ACT Handbook of Transplant Infections, D Kumar A Humar Eds. 2011;4.

Prevention & Prophylaxis

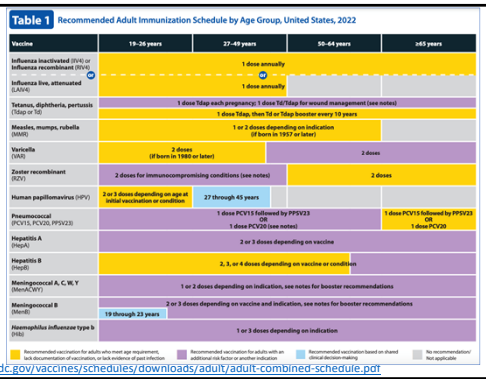
- Pre-immunosuppression evaluation**
  - Vaccines
  - Screening for latent infections
  - Plan for chronic infections
  - Optimize diabetes, stop smoking/marijuana use, etc
  - Education
- Management: peritransplant/initiation of immunomodulatory
- Prophylaxis and/or screening after transplant/immunomodulatory therapy started

Pre-Immunosuppression Evaluation (MGH)

	Everyone	If risk factors
Hepatitis B surface antigen	x	
Hepatitis B core antibody (IgG not IgM)	x	
Hepatitis B surface antibody	x	
Hepatitis C	x	
HIV	x	
Tuberculosis screening	x	
Coccidioides serology		x
Strongyloides serology		x
Trypanosoma cruzi (Chagas disease)		x

Pre-Solid Organ Transplant Evaluation (MGH)

	Everyone	Vaccinate if neg	If risk factors
Hepatitis A	x	x	
Hepatitis B surface antigen	x		
Hepatitis B core antibody (IgG not IgM)	x		
Hepatitis B surface antibody	x	x	
Hepatitis C	x		
HIV	x		
Tuberculosis screening	x		
Varicella	x	x	
Cytomegalovirus	x		
Mumps-measles-rubella	x	x	
Syphilis antibody	x		
Coccidioides antibody			x
Strongyloides serology			x
Trypanosoma cruzi (Chagas disease)			x



https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf

Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD

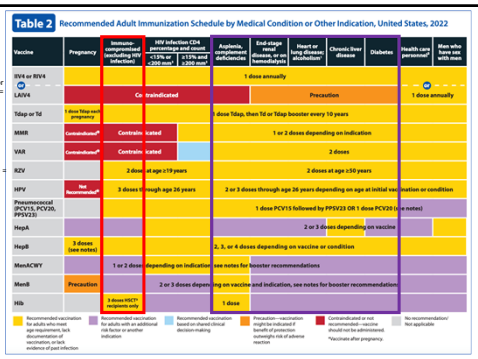


Table 2 Recommended Adult Immunization Schedule by Medical Condition or Other Indication, United States, 2022

Vaccine	Pregnancy	Immunocompromised (including HIV infection)	HIV infection CD4 percentage and count: ≤15% or <200 /mm³	HIV infection CD4 percentage and count: ≥15% and ≥200 /mm³	Asplenia, complement deficiencies	End-stage renal disease, or on hemodialysis	Heart or lung disease, alcoholism	Chronic liver disease	Diabetes	Health care personnel*	Men who have sex with men
IIV4 or RIV4				1 dose annually							
LAIV4	Contraindicated					Precaution				1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy			1 dose Tdap, then Td or Tdap booster every 10 years							
MMR	Contraindicated*	Contraindicated		1 or 2 doses depending on indication							
VAR	Contraindicated*	Contraindicated		2 doses							
RZV		2 doses at age ≥19 years		2 doses at age ≥50 years							
HPV	Not Recommended*	3 doses through age 26 years		2 or 3 doses through age 26 years depending on age at initial vaccination or condition							
Pneumococcal (PCV15, PCV20, PPSV23)				1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)							
HepA				2 or 3 doses depending on vaccine							
HepB	3 doses (see notes)			2, 3, or 4 doses depending on vaccine or condition							
MenACWY		1 or 2 doses depending on indication; see notes for booster recommendations									
MenB	Precaution	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations									
Hib		3 doses HSCT† recipients only		1 dose							

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection | Recommended vaccination for adults with an additional risk factor or another indication | Recommended vaccination based on shared clinical decision-making | Precaution—vaccination might be indicated if benefit of protection outweighs risk of adverse reaction | Contraindicated or not recommended—vaccine should not be administered. *Vaccinate after pregnancy. | No recommendation/ Not applicable

https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf

CDC: Who Should Get Tested for TB

- TB tests are generally not needed for people with a low risk of infection
- Certain people should be tested for TB bacteria because they are more likely to get TB disease, including:
  - People who have spent time with someone who has TB disease
  - **People with HIV infection or another medical problem that weakens the immune system**
  - People who have symptoms of TB disease (fever, night sweats, cough, and weight loss)
  - People from a country where TB disease is common (most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia)
  - People who live or work somewhere in the US where TB disease is more common (homeless shelters, prison or jails, or some nursing homes)
  - People who use illegal drugs

www.cdc.gov/tb/topic/testing/

Latent TB Screening

- Medical history
- Epidemiologic risk factors
- TB skin test (TST)
- Interferon gamma release assay (IGRA) (blood test) (sometimes preferentially vs TST, IDSA guidelines 2016)
  - T-SPOT.®*TB*
  - QuantiFERON®-TB Gold
- Radiographic findings
  - Old granulomatous disease, apical scarring

T-SPOT.®*TB* and QuantiFERON®-TB Gold

- Enumerates effector T-cell response to stimulation with a combination of peptides simulating ESAT-6 and CFP10 (+ TB7.7 for QFN) antigens
- Detects prior exposure to:
  - *M. tuberculosis* complex organisms (*M. tuberculosis, M. bovis, M. africanum, M. microti, M. canetti)*
  - *M. kansasii, M. szulgai,* and *M. marinum*
- Not + with prior BCG vaccine (bacille Calmette–Guérin)
- Interpret test correctly:
  - If either test or PPD positive, take as positive
  - Borderline results = partway b/w + and negative
  - **Indeterminate results = assay did not work**

Your patient has latent TB. Should and when should you start chemoprophylaxis? When can immunosuppressive medications be started?

A. Start TB chemoprophylaxis ASAP as per guidelines. (Ensure no active TB, pulmonary or extrapulmonary.) Can start immunosuppression any time.

B. Avoid TB chemoprophylaxis. Too many side effects, and too much hassle.

C. Most of my patients had BCG vaccine as children, and test false + as older adults. I don't give TB chemoprophylaxis.

Your patient has latent TB. Should and when should you start chemoprophylaxis? When can immunosuppressive medications be started?

A. Start TB chemoprophylaxis ASAP as per guidelines. (Ensure no active TB, pulmonary or extrapulmonary.) Can start immunosuppression any time.

B. Avoid TB chemoprophylaxis. Too many side effects, and too much hassle.

C. Most of my patients had BCG vaccine as children, and test false + as older adults. I don't give TB chemoprophylaxis.

Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD

Excellent Prophylaxis is Paramount… and provides important clues on boards questions

- Antivirals
- Pneumocystis/Toxoplasmosis
- Antifungals

Prophylaxis: Solid Organ Transplant Massachusetts General Hospital

CMV/Herpes Antiviral Prophylaxis

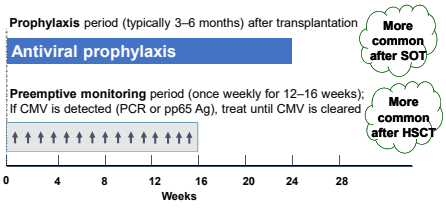
- Valganciclovir if any CMV risk (if either donor and/or recipient are CMV positive)
  - Prevents CMV, herpes, varicella/zoster
- Acyclovir/valacyclovir/famvir **if no CMV risk**
  - Prevents herpes, varicella/zoster
- Duration varies, 3-6 months is common (longer for lung transplant)
- Main side effect is leukopenia and cost with valganciclovir

Donor CMV Antibody	Recipient CMV Antibody	Prophylaxis	Duration
+	+	Valganciclovir	Antithymocyte globulin and D+R- → 6 months
-	+		
+	-		All others 3 months
-	-	ACV/Famvir/ValACV	

Anti-*Pneumocystis*/anti-bacterial

- Trimethoprim-sulfamethoxazole x 6-12 months (longer for heart/lung transplants)
- *or* dapsone or atovaquone if true allergy

CYTOMEGALOVIRUS PREVENTION: Prophylaxis vs. Preemptive Therapy

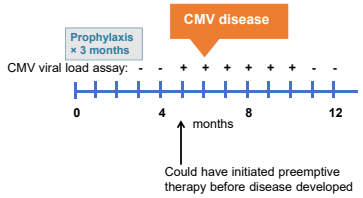


Humar A, Snydman D; AST Infectious Diseases Community of Practice. *Am J Transplant.* 2009;9 (Suppl 4):S78-S86.

Hybrid Strategy for SOT: CMV Surveillance After Prophylaxis

Consider "net state of immunosuppression"

- Weekly monitoring after end of prophylaxis, for ~12 weeks
- High risk (D+/R-) may be highest yield population (for late disease)
  - Other high-risk groups (potent immunosuppression)
- Guidelines experts use approach, not strongly evidence-based



Kotton CN et al, The Third International Consensus Guidelines on The Management of Cytomegalovirus In Solid Organ Transplantation, Transplantation 2018

Antiviral Prophylaxis: Stem Cell Transplant

- Acyclovir/valacyclovir/famvir for everyone
  - Prevents herpes, varicella/zoster
  - Duration varies a lot across programs, 6-12+ months is common
- Letermovir x 100 days if higher CMV risk
  - if recipient is CMV positive – opposite of solid organ (D-R+ is high risk after HSCT)
  - Prevents CMV, NOT herpes, varicella/zoster
  - Decreased mortality
  - If small viral load "blips", carry on and retest a week later – only stop therapy if high blips (>1,000 IU/ml)
- Main side effect is cost with letermovir

Antiviral Prophylaxis/Treatment Agents

Antiviral agent	CMV	HSV	Varicella	BK	Adeno-virus	EBV
Commercially available						
ganciclovir IV/valganciclovir PO	x	x	x			
acyclovir/valacyclovir/famciclovir*	high dose +/-	x	x			
letermovir	x					
maribavir	x					*in vitro*
foscarnet**	x	x	x			
cidofovir**	x	x	x	poor	+/- (IC50)	
Novel/investigational antiviral agents (SOT)						
brincidofovir (not available)	*x*	*x*	*x*	*x*	*x*	*x*

*acyclovir/valacyclovir/famciclovir and letermovir for prophylaxis only
**foscarnet, cidofovir not usually used for prophylaxis

Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD

Pneumocystis/Toxoplasmosis

- First line:
  - Bactrim SS daily or DS three times a week
- Second line (only if real Bactrim allergy or intolerance) alternatives:
  - Atovaquone (Mepron) 1500 mg QD
  - Dapsone 100 mg QD
    - √ G6PD
    - watch for methemoglobinemia, low white blood cell count
  - Pentamidine IV q month (does not cover Toxoplasmosis)
- Duration variable, usually until end of PPx

Antifungal Prophylaxis: Solid Organ Transplant

Organ	Common Practice	Comments
Kidney, liver, heart	None for most; some programs give fluconazole/echinocandins peri-liver	Some Nystatin swish and swallow
Pancreas	Fluconazole post-op for variable time, < 1 month	
Lung	**Voriconazole, posaconazole, itraconazole for variable times after transplant**	Voriconazole and augmented skin cancer, osteitis risks a major concern
Intestinal transplant, Composite tissue	Often longer courses of fluconazole/echinocandins	

32

Antifungal Prophylaxis: Hematopoietic Stem Cell Transplant

- Fluconazole often used in first 100 days after HSCT
  - Generally for higher risk receipts
  - Classic population for *C. krusei,* R to fluconazole
- Posaconazole generally reserved for higher risk patients
  - Only FDA approved agent for this indication
- Voriconazole – higher risk of mucormycosis seen

33

Sources of Infection after Transplant

- Community-acquired
- Nosocomial
- Prior colonization
  - + Intraoperative *Aspergillus* culture w/ cystic fibrosis & lung transplant → OR 4.36 invasive aspergillosis (Luong *et al*, Transplantation 2014)
- Emerging
- Donor-derived infection
  - Organ graft, blood products

Ten years of donor-derived disease: A report of the disease transmission advisory committee

Am J Transplant. 2021;21:689–702

Daniel R. Kaul[1] | Gabe Vece[2] | Emily Blumberg[3] | Ricardo M. La Hoz[4] | Michael G. Ison[5] | Michael Green[6] | Timothy Pruett[7] | Michael A. Nalesnik[8] | Susan M. Tlusty[2] | Amber R. Wilk[2] | Cameron R. Wolfe[9] | Marian G. Michaels[4]

- The Organ Procurement and Transplantation Network (OPTN) created The Disease Transmission Advisory Committee (DTAC) to review and classify reports of potential disease transmission to inform national policy and improve patient safety.
- January 1, 2008 to December 31, 2017, DTAC received 2185 reports
  - 335 (15%) classified as a proven/ probable donor transmission event
- ~2/3 infection, ~1/3 malignancy
- **Overall risk 17.8/10,000 or 0.178%**
- **All types of infections (!)**
- **Note: initial trigger is transplant center reporting to local organ bank (you!)**

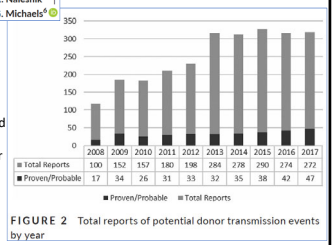


FIGURE 2 Total reports of potential donor transmission events by year

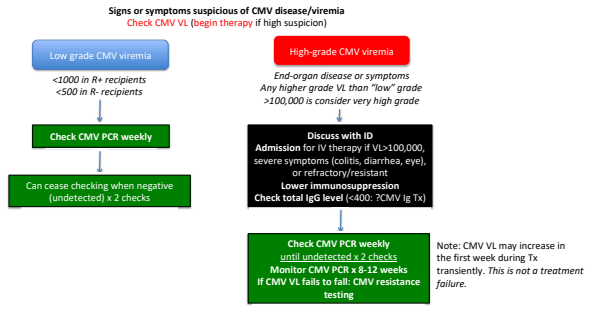
Syndromes

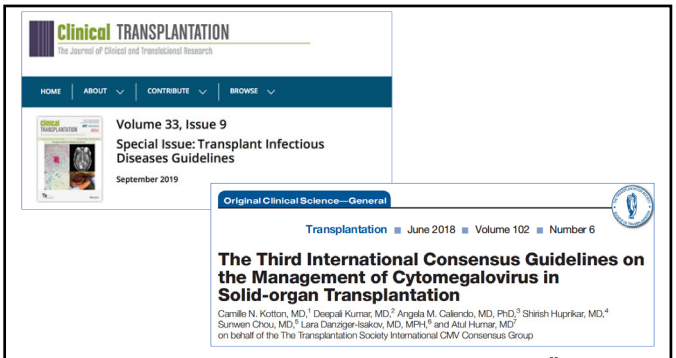
Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD

CMV: the most common pathogen after transplant, one of the "*great masqueraders*"

- Asymptomatic viremia**
- CMV syndrome
- End organ disease:
  - Colitis
  - Pneumonitis
  - Retinitis
- Best diagnosed by CMV viral load
- Best treated with valganciclovir or ganciclovir IV
- Treat to resolution of infection and/or viral load – check weekly
- If low absolute lymphocyte count at end, consider secondary prophylaxis or monitoring





39

https://onlinelibrary.wiley.com/toc/13990012/2019/33/9

The Dreaded Pulmonary Nodule

For the boards (and clinical medicine), consider the prophylaxis and what's not covered

Let the prophylaxis and epidemiology drive your differential diagnosis

Who gets fungal infections?

- Post-solid organ transplant: Incidence of invasive fungal infections in the first year has been reported to be 3%[1]
  - Candidiasis (sterile space), esp liver transplant*surgery
  - Cryptococcal disease
    - Among most common causes of meningitis
  - Invasive aspergillosis in 1-15%[2]
    - Accounts for significant % of deaths in first year
    - Mortality dropping in recent times, however
  - Mucormycosis less common, higher mortality
- Stem cell transplant: similar, longer risk if graft-vs-host disease
- Non-transplant immunocompromised hosts: less frequent/"net state of immunosuppression"

41

1 Shoham S, Marr K. Invasive fungal infections in solid organ transplant recipients. Future Microbio 2012; 7(5): 639-655
2 Singh N, Husain S, Aspergillosis in Solid Organ Transplantation, AJT, 2013

Diagnostics

- Culture
  - Fungal stain and culture
  - Notify lab not to mince specimen if suspicion of mucormycosis
  - Fungal isolators (blood) very rarely +
    - *Candida* will grow in routine cultures
    - *Histoplasma* better; lysis centrifugation isolators is best
- Pathology: Morphology
  - Septate (*Aspergillus*) vs non-septate (*Mucor/Zygomycetes*) hyphae
  - Grocott-Gomori's (or Gömöri) methenamine silver stain
  - Periodic acid-Schiff (PAS)

42

Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD

Diagnostics: Fungal Markers

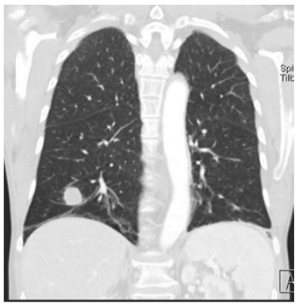
Diagnostic Assay	Specimen	Comments
Cryptococcal antigen	Blood, CSF	High sensitivity/specificity
1,3 beta – D - glucan	Blood	Primarily for yeast; Low sensitivity/moderate specificity *Excellent for Pneumocystis*
Galactomannan	Blood, BAL, other body fluids	Primarily for Aspergillus; Low sensitivity/high specificity on blood, higher sensitivity on body fluids
Aspergillus PCR	Blood, BAL, other body fluids	

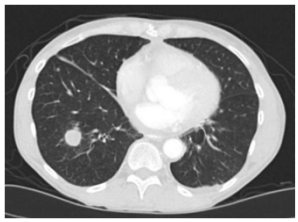
43

Clinical Vignette

- 54 yo woman with history of primary systemic AL amyloidosis, complicated by cardiac amyloidosis, treated cytoxan/bortezomib/dexamethasone initially, followed by lenalidomide/dexamethasone
- Orthotopic cardiac transplant Feb 2016
- Autologous stem cell transplant, Day 0=7/11/16.
- CMV DNA VL on Day 0 was 29,800 IU/ml.
- Neutropenic sepsis with a blood culture on Day 5 with *Strep salivarius*.
- Ongoing fevers, new 2 cm pulmonary nodule by CT on Day 18

44





45

After ordering bronchoscopy, next best step?

- Start voriconazole
- Start posaconazole or isavuconazole
- Start amphotericin B product
- Start echinocandin (caspofungin/micafungin/anidulafungin)
- Combination therapy

46

After ordering bronchoscopy, next best step?

- Start voriconazole
- Start posaconazole or isavuconazole
- Start amphotericin B product
- Start echinocandin (caspofungin/micafungin/anidulafungin)
- Combination therapy

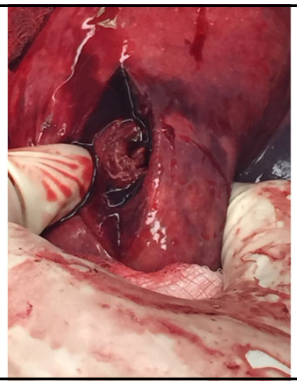
47

- "She has had a dry cough but denies any sputum production, chest pain, SOB or headache. She has felt very well, and was quite determined to be discharged in the next few days."
- Voriconazole started
- She was underwent bronchoscopy, radial EBUS, washings, brushings and transbronchial biopsy → **nonseptate hyphae seen**
- **Diagnosis: likely Zygomycetes**
- She was switched from voriconazole to dual antifungal therapy with loading of isavuconazole and Ambisome.
- Repeat CT scan performed 2 days later showed significant increase in size of the nodule with new satellite lesions. She proceeded to RLL resection that evening by the cardiothoracic surgeons.

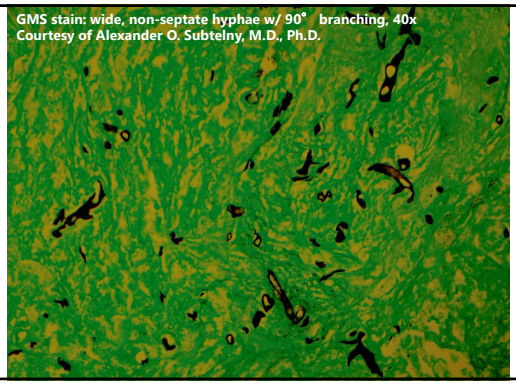
48

Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD



49



50

Very Rare RHIZOPUS SPECIES

SUSCEPTIBILITY Performed at UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER, Dept of Pathology, San Antonio, TX

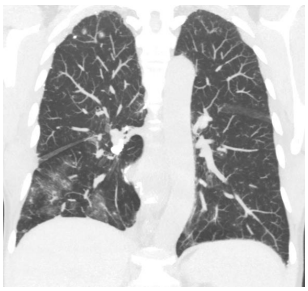
MIC DILUTION METHOD

No CLSI interpretive guidelines available

Amphotericin B	MIC=1
Isavuconazole	MIC=1
Miconazole	MIC=2
Posaconazole	MIC=0.5

In view of this, Ambisome was stopped on POD #9 and isavuconazole converted to 372mg daily for months/indefinite, plan is for radiographic resolution, immune reconstitution (heart transplant immunosuppression is for life).

51

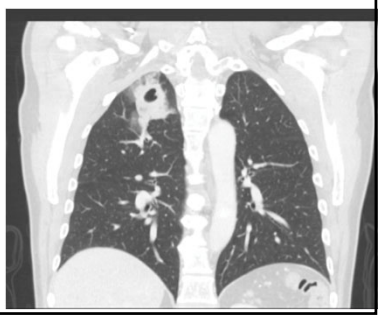


A year after transplant, she presented with disseminated zoster, new patchy infiltrates. Responded well to IV acyclovir.

52

What's This?

- Man in 50s diagnosed with multiple myeloma in 2011 → autologous stem cell transplant in March 2019.
- Due to disease progression in June 2020, he was treated with daratumumab and pomalidomide. He received radiation therapy to the thoracic and cervical spine.
- He consented to participate in a clinical trial protocol and underwent CAR infusion in January 2021. On fluconazole and acyclovir prophylaxis.
- Routine screening PET 4 months later "new thick walled multiloculated cavitary lesion in the right upper lobe with surrounding groundglass and clustered nodularity is concerning for infection, including bacterial as well as atypical and fungal infections in an immunocompromised patient". No symptoms at all



Epidemiology (ID fellow note)

- Living situation - lives with wife, 3 kids
- Outdoor exposures - rare, walks outside with dog in rode, has stopped dirt biking/hiking with thrombocytopenia
- Occupational exposures - Denies, works as a contractor for DoD, currently working at home
- Hobbies - mostly spending time at home right now
- Travel - Frequent travel pre-pandemic for work, has been to Australia, multiple countries in Asia and Europe, never to Africa or South America
- TB – no history of TB or known TB exposures; homeless or incarcerated? Denies
- Animals - Dog
- Food - raw or unpasteurized foods? Denies
- Dental work - None recent, does have a wisdom tooth pressing on a facial nerve
- Smoking - Denies
- Alcohol - Denies
- Recreational drugs - Denies
- Sex and prior STIs- Denies

Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD

What would you do next?

A. Start voriconazole, loading dose then maintenance based on weight
B. Start "vancopime" (cefepime plus vancomycin)
C. Start azithromycin
D. A-C (all of the above)
E. Bronchoscopy

Pseudomonas!

All other studies negative:

- BAL mycobacterial, fungal stains/cultures
- Cryptococcal antigen (blood)
- 1,3 beta D glucan (blood)
- Galactomannan (BAL and blood)
- Pathology: Bronchial epithelium with rare scattered neutrophils. Alveolated lung with fibroinflammatory changes and chronic inflammation. There is no evidence of malignancy. No microorganisms are seen on Brown-Hopps, GMS, Steiner, PAS-D, FITE, and AFB stains. Immunohistochemical stains for CMV, HSV, VZV, and adenovirus are negative. Trichrome and elastic stains were examined. The histologic findings are compatible with acute infection.

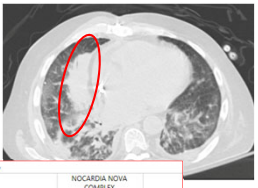
04/19/2021 1657	04/29/2021 1323	Wound culture/smear [818905205] (Abnormal) Other from Biopsy RUL LUNG TBBX

Susceptibility

	Pseudomonas aeruginosa MIC METHOD	
Amikacin	<=2	Susceptible
Cefepime	2	Susceptible
Ceftazidime	2	Susceptible
Ciprofloxacin	<=0.25	Susceptible
Levofloxacin	1	Susceptible
Meropenem	<=0.25	Susceptible
Piperacillin-tazobactam	<=4	Susceptible
Tobramycin	<=1	Susceptible

Pneumonia

- 45yo s/p heart transplant 3 months earlier on posaconazole, atovaquone prophylaxis (not on TMP-SMX due to renal failure)
- New pneumonia, right middle lobe
- What is the cause?



Susceptibility

	NOCARDIA NOVA COMPLEX MIC METHOD	
Comment	SEE NOTES	Note[1]
Amikacin		Susceptible
Amoxicillin + Clavulanate		Resistant
Ceftriaxone		Susceptible
Ciprofloxacin		Resistant
Clarithromycin		Susceptible
Doxycycline		Intermediate
Imipenem		Susceptible
Linezolid		Susceptible
Minocycline		Susceptible
Moxifloxacin		Resistant
Tobramycin		Resistant
Trimethoprim/sulfamethoxazole		Susceptible

[1] SUSCEPTIBILITY TESTING Performed at the University of Texas Health Center at Tyler, Tyler TX

Let's Switch to Parasites

Clinical Vignette

64yo man from Dominican Republic with end-stage liver disease, chronic abdominal pain, listed for liver transplant

- Eosinophilia (up to 70%) x 6 months
- Recurrent enteric Gram negative rod bacteremias
- Fluffy pulmonary infiltrates
- What does he have?

Test Results

Strongyloides Antibody by ELISA: 100.00

INTERPRETATION: POSITIVE

All reactions of <=1.7 units/ml should be considered NEGATIVE.
All reactions >1.7 units/ml should be considered POSITIVE, indicative of infection with *Strongyloides stercoralis* at some indeterminate time.
Sensitivity of the test is 93% and specificity is 98%.

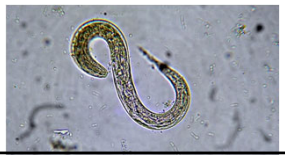
Centers for Disease Control testing

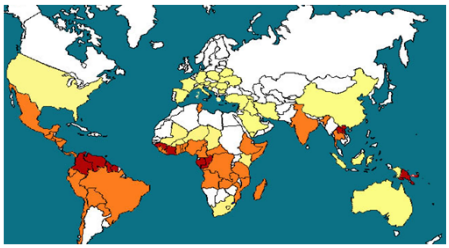
Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD

Strongyloides

- Nematode "roundworm"
- 100-200 million people worldwide are infected
- Autoinfection*
- >50% mortality immunocompromised patients with disseminated disease

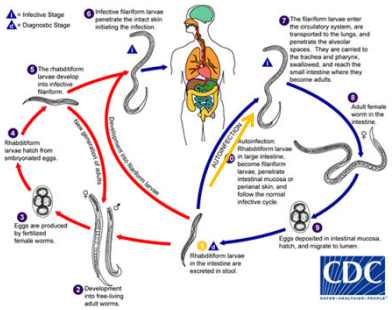




The countries highlighted in **yellow** have sporadic endemicity, on the range of 1-3%. Those that are **orange** are endemic, while those that are **red** are generally hyperendemic, with the highest frequency of *Strongyloides* infection.

http://web.stanford.edu/group/parasites/ParaSites2006/Strongylodiasis/epidemiology.html

Strongyloides stercoralis lifecycle



http://www.cdc.gov/dpdx/strongyloidiasis/

Drug Interactions: Transplant & Antimicrobials

- Azoles
  - Voriconazole, posaconazole > fluconazole
  - Isavuconazole – much less interaction
  - Increase tacrolimus (or cyclosporine, rapamycin)
- Rifamycins
  - Rifabutin < rifampin (=rifampicin)
  - Decrease tacrolimus (or cyclosporine, rapamycin)
  - Increase prednisone
- QT prolongation
  - Combination effect
  - May be present with liver disease
- Recommended: Use of on-line drug interaction calculator

Cardinal Rules 2022: Immunosuppression and Infection

1. Immunosuppression and infections not always straightforward
2. Be prepared to be surprised – think broadly
3. Prepare patient for immunosuppression – role for ID specialists
4. Prophylaxis & vaccines alter the risk equation
   Primary and secondary prevention
5. Consider the source of infection: donor, recipient, blood products, geographic, more antibiotic resistance

Questions? ckotton@mgh.Harvard.edu

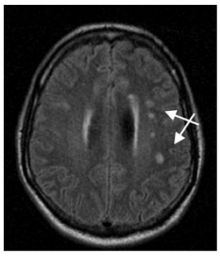
MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

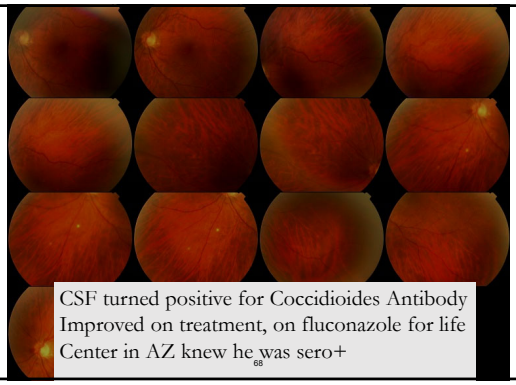
Speaker: Camille Kotton, MD

Meningoencephalitis after OLT

- 45yo man moved back home to Boston, cirrhosis/end stage liver disease
- 6 weeks after liver transplant, fevers, headache, seizure
- CSF glucose <20, protein 180, WBC 250 lymph predominant
- Started mycobacterial, fungal coverage



67



CSF turned positive for Coccidioides Antibody
Improved on treatment, on fluconazole for life
Center in AZ knew he was sero+

68

Lip Lesion in a Solid Organ Transplant Recipient

Nicole Theodoropoulos and Michael Angarone

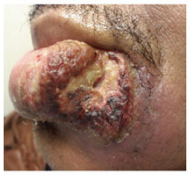


Figure 1. Photograph of lower lip ulcerated lesion at initial presentation.

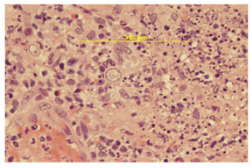
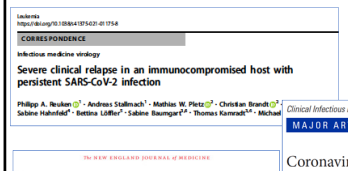


Figure 2. Histopathology of section through lip lesion tissue (hematoxylin-eosin, high-power magnification).

Clinical Infectious Diseases 2012;54(9):1332

COVID-19 and Immunocompromised Hosts



Leukemia
https://doi.org/10.1038/s41375-021-01154

CORRESPONDENCE

Infectious medicine virology

Severe clinical relapse in an immunocompromised host with persistent SARS-CoV-2 infection

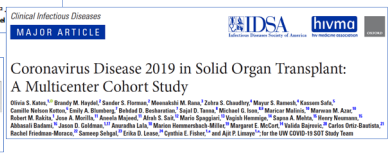
Philipp A. Reuken[1] · Andreas Stallmach[1] · Mathias W. Pletz[2] · Christian Brandt[2] · Sabine Hahnfeld[2] · Bettina Löffler[2] · Sabine Baumgart[2,3] · Thomas Kamradt[3,4] · Michael

THE NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host

Best treatments?
Role of immunomodulatory therapies?
Best management of immunosuppression?
Optimizing vaccination strategies?



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA hivma

Coronavirus Disease 2019 in Solid Organ Transplant: A Multicenter Cohort Study

Donor-Derived Infections

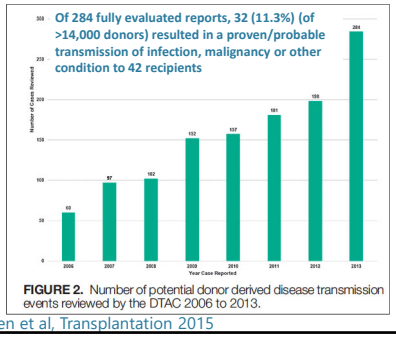


FIGURE 2. Number of potential donor derived disease transmission events reviewed by the DTAC 2006 to 2013.

Green et al, Transplantation 2015

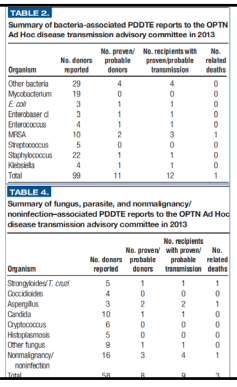


TABLE 2.
Summary of bacteria-associated PDDTE reports to the OPTN Ad Hoc disease transmission advisory committee in 2013

Organism	No. donors reported	No. proven/ probable donors	No. recipients with proven/probable transmission	No. related deaths
Other bacteria	29	4	4	0
Mycobacterium	19	0	0	0
E. coli	3	1	1	0
Enterobaser cl	3	1	1	0
Enterococcus	4	1	1	0
MRSA	10	2	3	1
Streptococcus	5	0	0	0
Staphylococcus	22	1	1	0
Klebsiella	4	1	1	0
Total	99	11	12	1

TABLE 4.
Summary of fungus, parasite, and nonmalignancy/ noninfection–associated PDDTE reports to the OPTN Ad Hoc disease transmission advisory committee in 2013

Organism	No. donors reported	No. proven/ probable donors	No. recipients with proven/ probable transmission	No. related deaths
Strongyloides/*T. cruzi*	5	1	1	1
Coccidioides	4	0	0	0
Aspergillus	3	2	2	1
Candida	10	1	1	0
Cryptococcus	6	0	0	0
Histoplasmosis	5	0	0	0
Other fungus	9	1	1	0
Nonmalignancy/ noninfection	16	3	4	1
Total	58	8	9	3

TABLE 3.
Summary of virus-associated PDDTE reports to the OPTN Ad Hoc disease transmission advisory committee in 2013

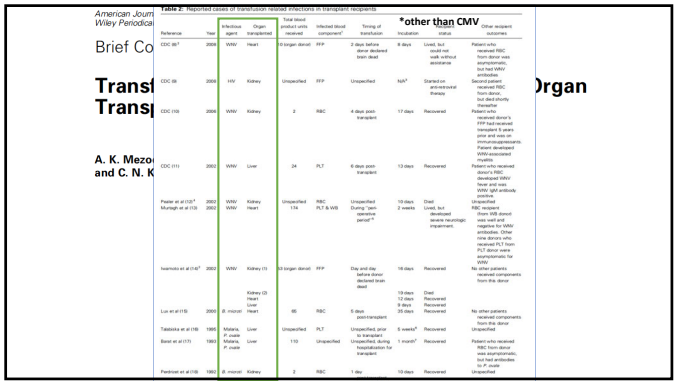
Organism	No. donors reported	No. proven/ probable donors	No. recipients with proven/probable transmission	No. related deaths
HBV	12	2	2	0
HCV	11	0	0	0
Adenovirus	4	1	1	0
Community respiratory virus	6	1	2	0
CMV	6	2	4	0
HSV	2	0	0	0
West Nile Virus	10	1	3	0
Other viral	11	1	1	1
Total	62	8	13	1

HCV, hepatitis C virus; HBV, hepatitis B virus.

Green et al, Transplantation 2015

Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD


American Journ
Wiley Periodica

Brief Co

Transl Organ
Transp

A. K. Mezo and C. N. K

Table 2: Reported cases of transfusion-related infections in transplant recipients

Reference	Year	Infectious agent	Organ transplanted	Total blood product units received	Infected blood component[a]	Timing of transfusion	Incubation	*other than CMV status	Other recipient outcomes
CDC (6)[7]	2008	WNV	Heart	10 (organ donor)	FFP	2 days before donor declared brain dead	8 days	Lived, but could not walk without assistance	Patient who received RBC from donor was asymptomatic but had WNV antibodies
CDC (9)	2009	HIV	Kidney	Unspecified	FFP	Unspecified	N/A[b]	Started on anti-retroviral therapy	Second patient received RBC from donor, but died shortly after surgery
CDC (10)	2009	WNV	Kidney	2	RBC	4 days post-transplant	17 days	Recovered	Patient who received donor's FFP had received transplant 5 years prior and was on immunosuppressants. Patient developed WNV-associated myelitis
CDC (11)	2002	WNV	Liver	24	PLT	6 days post-transplant	13 days	Recovered	Patient who received donor's RBC developed WNV fever and was WNV IgM antibody positive
Pealer et al (12)[7] Murugh et al (13)	2002 2002	WNV WNV	Kidney Heart	Unspecified 11[c]	RBC PLT & WB	Unspecified During "peri-operative period"[d]	10 days 2 weeks	Died Lived, but developed severe neurologic impairment.	Unspecified RBC recipient (from WB donor) was well and negative for WNV Platelet recipients (nine donors who received PLT from PLT donor) were asymptomatic for WNV
Iwamoto et al (14)[7]	2002	WNV	Kidney (1) Kidney (2) Heart Liver	10 (organ donor)	FFP	Day and day before donor declared brain dead	16 days 19 days 12 days 9 days	Recovered Died Recovered Recovered	No other patients received components from this donor
Lui et al (15)	2003	B. microti	Heart	65	RBC	5 days post-transplant	35 days	Recovered	No other patients received components from this donor
Talaiska et al (16)	1995	Malaria, P. ovale	Liver	Unspecified	PLT	Unspecified, prior to transplant	5 weeks[e]	Recovered	Unspecified
Barat et al (17)	1993	Malaria, P. ovale	Liver	110	Unspecified	Unspecified, during hospitalization for transplant	1 month[f]	Recovered	Patient who received RBC from donor was asymptomatic, but had antibodies to P. ovale
Pentlovet et al (18)	1990	B. microti	Kidney	2	RBC	1 day	10 days	Recovered	Unspecified

Testing for HBV Infection

- Testing for HBV infection (consisting of testing for HBV surface antigen, HBV surface antibody, and HBV core IgG antibody) is recommended for the following persons:
  - persons born in countries of high and intermediate HBV endemicity (HBsAg prevalence ≥2%);
  - U.S.-born persons not vaccinated as infants whose parents were born in countries with high HBV endemicity (≥8%);
  - persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders; donors of blood, plasma, organs, tissues, or semen.

Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, MMWR Jan 2018

HBV Levels of Risk –UpToDate

- **Very high risk** — Patients are at very high risk of reactivation (>20 percent risk of reactivation) if they are HBsAg positive and are going to receive anti-CD20 therapy (ie, rituximab, ofatumumab, obinutuzumab) or undergo hematopoietic cell transplantation.
- **High risk** — Patients are considered at high risk for reactivation (11 to 20 percent risk of reactivation) if they are HBsAg positive and are going to receive high-dose glucocorticoids (eg, ≥20 mg/day for at least four weeks) or the anti-CD52 agent, alemtuzumab.

Antiviral therapy ⬆

- **Moderate risk** — HBsAg-positive individuals are at moderate risk of reactivation (1 to 10 percent) if they are going to receive any of the following: cytotoxic chemotherapy **without** glucocorticoids; anti-TNF therapy; or anti-rejection therapy for solid organ transplants.
- Patients who are HBsAg negative and anti-HBc positive are at moderate risk for reactivation if they are going to receive anti-CD20 therapy or undergo hematopoietic cell transplantation.

- **Low risk** — HBsAg-positive individuals are at low risk (<1 percent) for reactivation if they receive methotrexate or azathioprine. HBsAg-negative and anti-HBc-positive individuals are at low risk if they receive high-dose glucocorticoids (eg, ≥20 mg/day) or the anti-CD52 agent alemtuzumab.
- **Very low risk** — HBV reactivation occurs rarely in HBsAg-negative and anti-HBc-positive patients receiving the following: cytotoxic chemotherapy without glucocorticoids, anti-TNF therapy, methotrexate, or azathioprine.

Feb 2021

HBV Prevention Based on Levels of Risk -UpToDate

- "**Moderate to very high risk** – We recommend that antiviral therapy be administered concurrently or prior to initiating immunosuppressive therapy to patients who are at moderate to very high risk of HBV reactivation. In such patients, we prefer preventive therapy, rather than waiting for evidence of reactivation, since studies in this population have demonstrated that antiviral therapy started after the onset of reactivation may not prevent a flare."
  - Entecavir, tenofovir (not lamivudine)
- "**Low risk or very low risk** — Among those at low risk or very low risk of reactivation, we perform frequent monitoring so that HBV reactivation can be detected early in its course and appropriate therapy can be initiated."

Feb 2021

Clinical Vignette

- 70yo man from Syria needs moderate immunosuppression… what do you think?

	10/31/2011 1245	10/6/2011 1130	9/21/2010 1133
HEPATITIS			
HBV Core Ab(s)		Positive *	
HBV Core Ab, IgM	Negative *		Negative *
HBV e Ab	Positive *		
HBV e Ag	Negative *		
HBV Surface Ab		<5.0 *	<5.0 *
HBV Surface Ag		Negative	Negative
HBV DNA (IU/mL)	see comment *		
HCV Ab		Non-Reactive	Non-Reactive

Clinical Vignette

70yo man originally from Syria needs moderate immunosuppression… what do you think?

	10/31/2011 1245	10/6/2011 1130	9/21/2010 1133
HEPATITIS			
HBV Core Ab(s)		Positive *	
HBV Core Ab, IgM	Negative *		Negative *
HBV e Ab	Positive *		
HBV e Ag	Negative *		
HBV Surface Ab		<5.0 *	<5.0 *
HBV Surface Ag		Negative	Negative
HBV DNA (IU/mL)	see comment *		
HCV Ab		Non-Reactive	Non-Reactive

	12/31/2018 1115	10/12/2018 1315	3/14/2018 1323	2/16/2018 1145	1/16/2018 1307	8/21/2015 1050	7/20/2015 0833	7/6/2015 1049	12/3/2014 0912
HEPATITIS									
HBV Core Ab(s)									NON-REACTIVE *
HBV Core Ab, IgM									NON-REACTIVE *
HBV e Ab									
HBV e Ag									
HBV Surface Ab									NON-REACTIVE *
HBV Surface Ag									
HBV DNA (IU/mL)	1,380 *	1,720 *	336,000 *	740,000 *	>170000000 *	<20 NOT DETECTED *	<20 NOT DETECTED *	<20 NOT DETECTED *	

← More immunosuppression
← Started on entecavir

Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

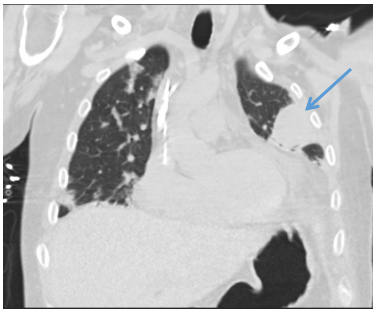
Speaker: Camille Kotton, MD

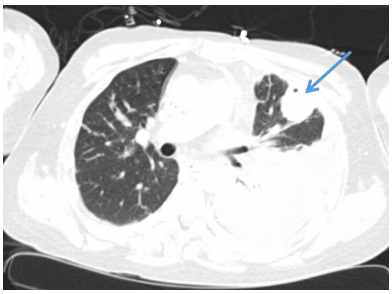
Approach to EBV monitoring

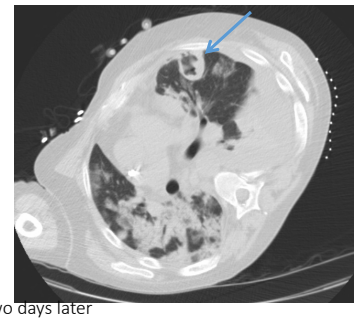
- Only routinely indicated in EBV seronegative recipients of a positive donor
- EBV monitoring post-transplant is done to assess risk for PTLD.
- Screening with EBV PCR periodically (every 1-3 months) for 1 year post-transplant
- If viral load is positive, monitor every month, and if >5,000 or if persistent, reduce IS and consult transplant ID.

Clinical Vignette

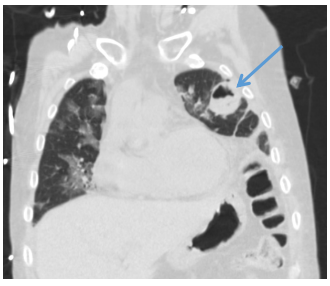
- 36yo male, Type I diabetes, 3 months after kidney/pancreas transplant (on prednisone 5 mg/day, mycophenolate mofetil (Cellcept) 1000mg twice a day, tacrolimus 4 mg twice a day)
- Transferred with three days of worsening left sided abdominal and flank pain
- Chest CT findings concerning for necrotizing pneumonia/cavitating lesion.
- On valganciclovir and TMP/SMX prophylaxis
- Exam: jaundiced, cachectic, dull breath sounds at left base, crackles both lungs







Two days later



Online Only Lectures - ID Bootcamp: Solid Organ and Stem Cell Transplant

Speaker: Camille Kotton, MD

Diagnostics

- Fungal markers all negative (blood)
  - 1,3 beta D glucan
  - Galactomannan antigen
  - Cryptococcal antigen
- Thoracentisis → exudate, chest tube placed
- Bronchoscopy, biopsy

What is the diagnosis?

A. *Aspergillus*
B. Mucormycosis
C. Necrotizing Gram negative
D. Mycobacterial (M. kansasii, etc)
E. *Nocardia*

Culture Data

LEFT EFFUSION/PLEURAL FLUID (and BAL)

Gram Stain –abundant polys, moderate red blood cells, few mononuclear cells, **no organisms seen**

Fluid Culture - **NOCARDIA NOVA COMPLEX, subspecies *veterana***

MIC DILUTION METHOD

Amikacin	Susceptible
Amoxicillin/Clavulanate	Susceptible **
Ceftriaxone	Intermediate
Ciprofloxacin	Resistant
Clarithromycin	Susceptible
Doxycycline	Resistant
Imipenem	Susceptible
Linezolid	Susceptible
Minocycline	Intermediate
Moxifloxacin	Resistant
Tobramycin	Resistant
Trimethoprim/Sulfa	Susceptible

Treatment

- Brain CT negative for metastatic infection
- Imipenem + azithromycin until radiographic improvement**
- Markedly improved in first few days (?chest tube placement)
- Doing well at 6 months, double treatment stopped
- Will need long term secondary prophylaxis with TMP/SMX