Infections in Transplant Recipients

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Infectious Disease

Outline

- Background
- Pretransplant
- Immunosuppression
- Infections
- Workup and other stuff

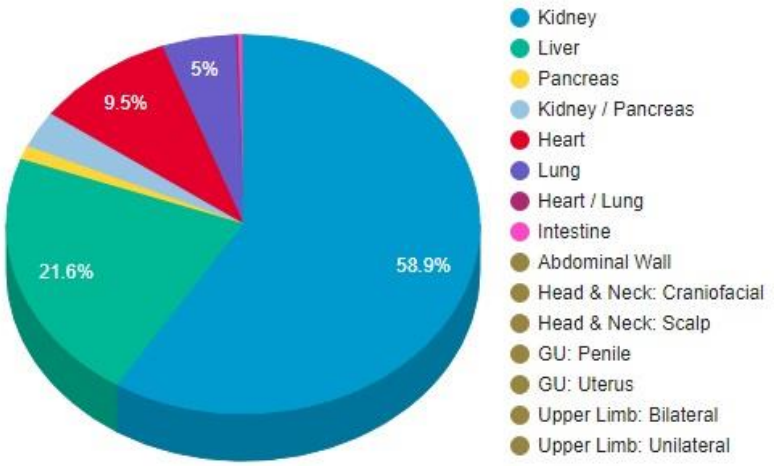
Introduction

- Solid Organ Transplant (SOT) started 1954 with kidney transplants between identical twins
- Bone marrow transplant started in 1956 between identical twins
- Success limited until development of azathioprine and corticosteroids in 1960's
  - Decreased allograft rejection
- Calcineurin inhibitors in 1980's moved transplant forward – cyclosporine
  - Allowed for expansion/development of heart and liver transplantation programs, also the start of lung transplant

SOT to date

Transplants By Organ Type January 1, 1988 - March 31, 2018
Based on OPTN data as of April 20, 2018

Organ	Transplants
Kidney	437,330
Liver	160,722
Pancreas	8,680
Kidney / Pancreas	23,395
Heart	70,905
Lung	37,261
Heart / Lung	1,245
Intestine	2,974
Abdominal Wall	1
Head & Neck: Craniofacial	6
Head & Neck: Scalp	1
GU: Penile	2
GU: Uterus	12
Upper Limb: Bilateral	6
Upper Limb: Unilateral	4
Total	**742,544**

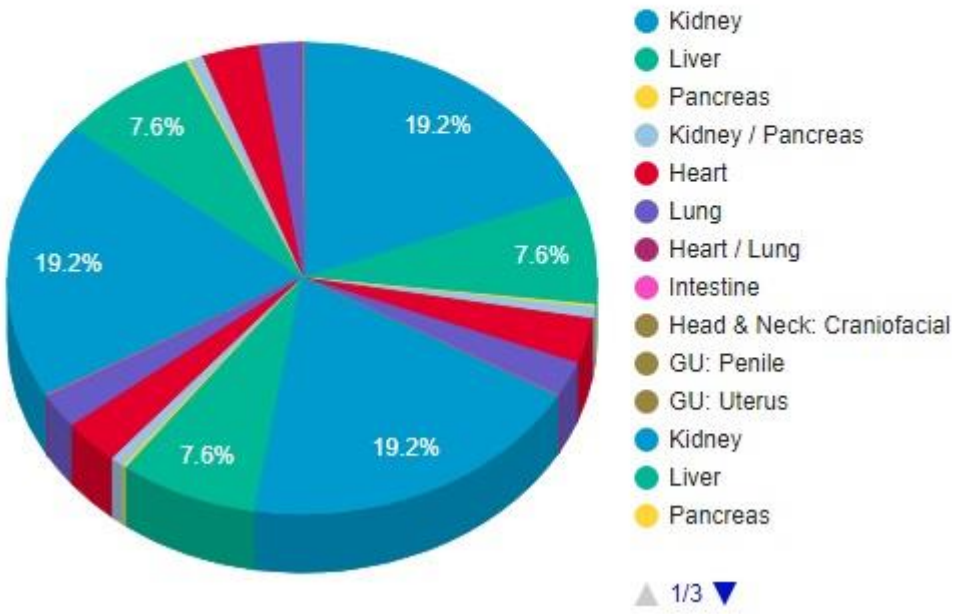


https://www.unos.org/data/

SOT 2018

Transplants By Organ Type - January - March 2018
Based on OPTN data as of April 20, 2018

Organ	Transplants
Kidney	12,138
Liver	4,798
Pancreas	121
Kidney / Pancreas	483
Heart	1,961
Lung	1,459
Heart / Lung	17
Intestine	60
Head & Neck: Craniofacial	1
GU: Penile	1
GU: Uterus	2



https://www.unos.org/data/

Current SOT

At a Glance

114,420

people need a lifesaving organ transplant (total waiting list candidates). Of those, **74,694** people are active waiting list candidates. Totals as of today 5:36pm

21,041

organ transplants performed so far in 2018

Total Transplants January - March 2018

as of 04/20/2018

10,119

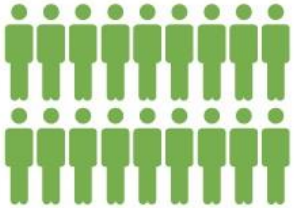
donors

Total Donors January - March 2018

as of 04/20/2018

Organ donation and transplantation can save lives

Every ten minutes, someone is added to the national transplant waiting list.



On average, 95 transplants take place each day in the U.S.

One organ donor can save eight lives. Sign up to be a donor in your state.

https://optn.transplant.hrsa.gov/ as of 8-20-18

Marrow donors to date

- National Marrow Donor Program founded 1986

Center for International Blood and Marrow Transplant Research
Transplant Activity Report Covering 2010-2014

Table 1. Total number of HCTs performed in the United States and reported to CIBMTR* by year 2010-2014

	YEAR											
	2010		2011		2012		2013		2014		Grand Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Grand Total	16,668	18	18,099	20	18,687	20	19,468	21	19,862	21	92,784	100

* CIBMTR captures data from U.S. transplant centers for > 95% of allogeneic (unrelated and related) HCT. CIBMTR captures data for approximately 80% of autologous HCT performed in the United States--these are reported voluntarily by HCT centers.

How many bone marrow or umbilical cord blood transplants are performed in the United States?

Nearly 20,000 bone marrow or umbilical cord blood transplants were performed in the United States in 2014.[a]

Number of Transplants Performed	Type of Transplant
11,392[b]	**Autologous** (the cells for transplant were provided by the patient)
3,544	**Related allogeneic** (the cells for transplant were provided by the patient's sibling or another family member)
4,926	**Unrelated allogeneic** (the cells for transplant were provided by a volunteer donor)

FROM:
The US National Marrow Donor Program role in unrelated donor hematopoietic cell transplantation
D Confer and P Robinett

Pretransplant

- Pretransplant history of utmost importance
  - Prior exposures, travel, occupations, hobbies
- Chronic diseases may be affected by transplant
  - ?re-infection of transplanted organ (HBV, HCV)
  - Diabetes mellitus affecting graft healing
  - Pre-existing cardiac disease, pulmonary, gall bladder
- Prior exposures/immunity play a role in immunosuppressed persons
- Prior colonization/infections
- Reactivation of latent infection

TABLE 311-5 Routine Laboratory Studies before and after Transplantation

BEFORE TRANSPLANTATION*	AFTER TRANSPLANTATION
Cytomegalovirus IgG antibody	Viral load monitoring for cytomegalovirus
Epstein-Barr virus IgG antibody	Antibody studies (as clinically indicated)
Herpes simplex (types 1 and 2) antibody	
Varicella-zoster IgG antibody	
Toxoplasma IgG antibody (heart transplant recipients)	
Hepatitis B screen†	
Hepatitis C enzyme immunoassay‡	
Human immunodeficiency virus antibody	
Tuberculin skin test or interferon gamma release assay for tuberculosis	
Stool for ova and parasites; *Strongyloides* antibody§	
Trypanosoma cruzi antibody‖	

Mandell: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th *ed.*; Chapter 311: Risk Factors and Approaches to Infections in Transplant Recipients. 3414-3424.

Risk factors for infection

- Patients are undergoing major surgery, many will be in ICU setting post operatively
- Organ was outside the body for hours
  - Ischemia leading to allograft injury?
- Many patients have been in the ICU setting prior to transplantation
- ?Immune suppression making the patient more susceptible to infection (BMT)
- SOT infections are most common at the site of transplantation
- Surgical procedure itself
  - OR time, blood loss, etc.

Immunosuppression

- We make our patients susceptible to infections to prevent rejection
- Corticosteroids:
  - Broad inhibition of immune response (innate inflammatory response, phagocytic function, cellular immunity, possible antibody formation)
  - Hyperglycemia
  - Avoidance may reduce post-txp CMV infections (liver)
- Cytotoxic agents
  - Suppress bone marrow, peripheral blood counts
  - Cyclosporine, Tacrolimus, Mycophenolate mofetil, sirolimus

Immunosuppression

TABLE 311-2 Biologic Preparations Used to Prevent or Treat Rejection

AGENT	ADVERSE EFFECTS
Polyclonal Antibodies	
Antithymocyte globulins*	Serum sickness, thrombocytopenia, lymphopenia (can last up to 2-3 yr with Thymoglobulin), increased risk of CMV, PTLD
Anti–human thymocyte immune globulin (rabbit) (Thymoglobulin)	
Lymphocyte immune globulin, antithymocyte (equine) (Atgam)	
Monoclonal Antibodies	
Anti-CD25 (interleukin-2 receptor) antibodies† Basiliximab (Simulect)	Hypersensitivity reactions, infection risk not significantly increased
Anti-CD20 antibody‡ Rituximab (Rituxan)	Infusion reactions, hepatitis B virus reactivation
Anti-CD52 antibody§ Alemtuzumab (Campath)	Infusion reactions, increased risk of CMV, *Pneumocystis jirovecii* pneumonia, invasive fungal infections, immunosuppression effects that can last up to 12 mo.
Other Agents	
Anti-B7 fusion protein (co-stimulation ligand)‖ Belatacept (Nulojix)	Increased rate of Epstein-Barr virus–associated PTLD

CMV, cytomegalovirus; PTLD, post-transplantation lymphoproliferative disease.

Mandell: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th *ed.*; Chapter 311: Risk Factors and Approaches to Infections in Transplant Recipients. 3414-3424.

Immunosuppression

- Patients have continued immunosuppression after initial prophylaxis
- Treatment of episodes of acute rejection, especially with high dose steroids “resets” the clock
- Increased risk of opportunistic infections after steroid boluses
- Toxicity associated with immunosuppressive therapy
  - Tacrolimus – renal toxicity, neurologic, diarrhea, diabetes
  - Mycophenolate – bone marrow suppression, diarrhea

Timeline of Infection

The NEW ENGLAND JOURNAL of MEDICINE

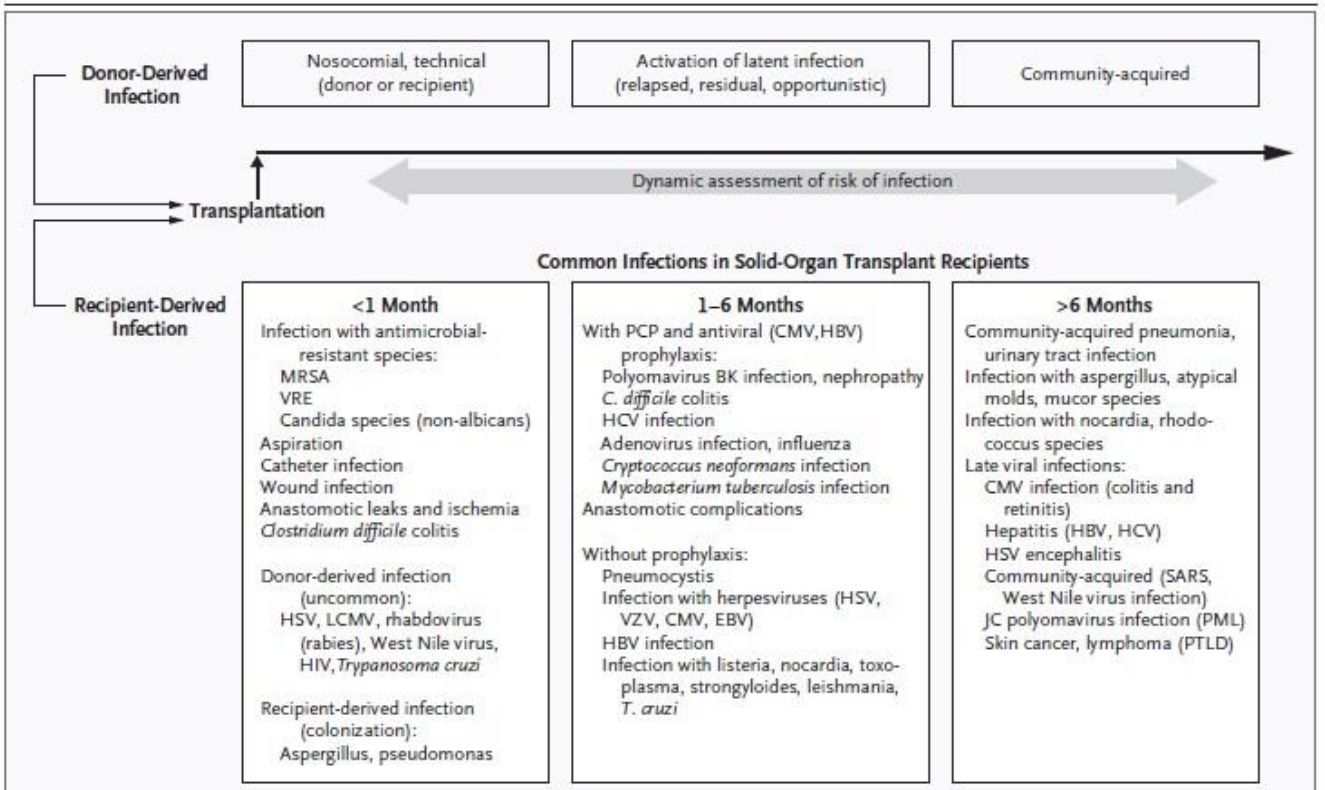


Figure 4. Changing Timeline of Infection after Organ Transplantation.

Infections occur in a generally predictable pattern after solid-organ transplantation. The development of infection is delayed by prophylaxis and accelerated by intensified immunosuppression, drug toxic effects that may cause leukopenia, or immunomodulatory viral infections such as infection with cytomegalovirus (CMV), hepatitis C virus (HCV), or Epstein–Barr virus (EBV). At the time of transplantation, a patient's short-term and long-term risk of infection can be stratified according to donor and recipient screening, the technical outcome of surgery, and the intensity of immunosuppression required to prevent graft rejection. Subsequently, an ongoing assessment of the risk of infection is used to adjust both prophylaxis and immunosuppressive therapy. MRSA denotes methicillin-resistant *Staphylococcus aureus*, VRE vancomycin-resistant *Enterococcus faecalis*, HSV herpes simplex virus, LCMV lymphocytic choriomeningitis virus, HIV human immunodeficiency virus, PCP *Pneumocystis carinii* pneumonia, HBV hepatitis B virus, VZV varicella–zoster virus, SARS severe acute respiratory syndrome, PML progressive multifocal leukoencephalopathy, and PTLD post-transplantation lymphoproliferative disorder. Modified from Fishman and Rubin[1] and Rubin et al.[45]

Fishman, J. *Infection in Solid-Organ Transplant Recipients*. N Engl J Med 2007;357:2601-14.

A 57 year old female undergoes orthotopic liver transplantation for HCV related cirrhosis. Due to her medical condition, she has been an inpatient for over one month and was in the ICU for several weeks prior to her transplant. 13 days after her transplant, she becomes febrile to 101.1F and her WBC rises to 18.7K. She has been on an empiric course of vancomycin and zosyn since the transplant. Blood cultures turn positive for Gram + cocci in pairs and chains. What is your next course of action?

- A) Repeat blood cultures and remove/exchange any central lines. Await ID of the isolate.
- B) Repeat blood cultures and order a CT of the abd/pelvis. Change her antibiotics to include VRE activity.
- C) Repeat blood cultures, continue vancomycin and zosyn. Add linezolid.
- D) Review donor cultures and information. Repeat blood cultures. Order MRSA swab of nares. Continue your current antibiotics.

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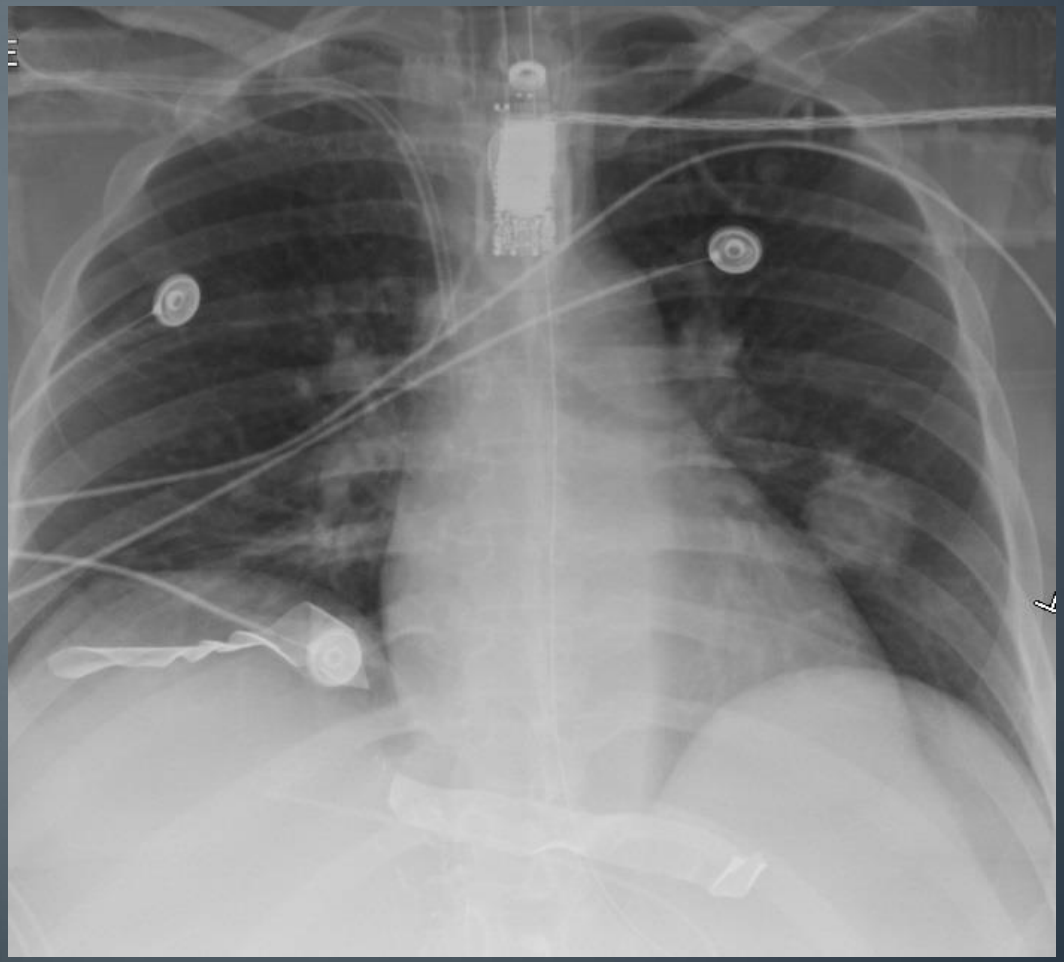
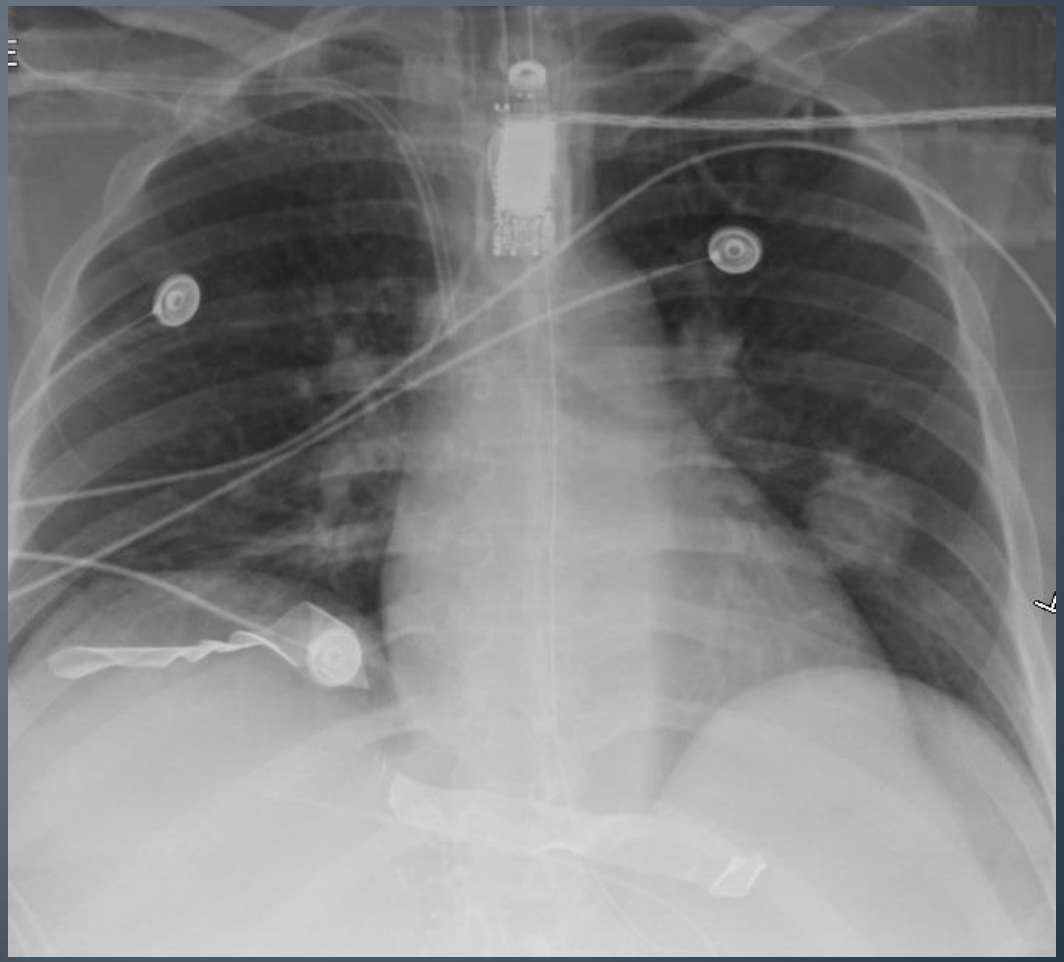
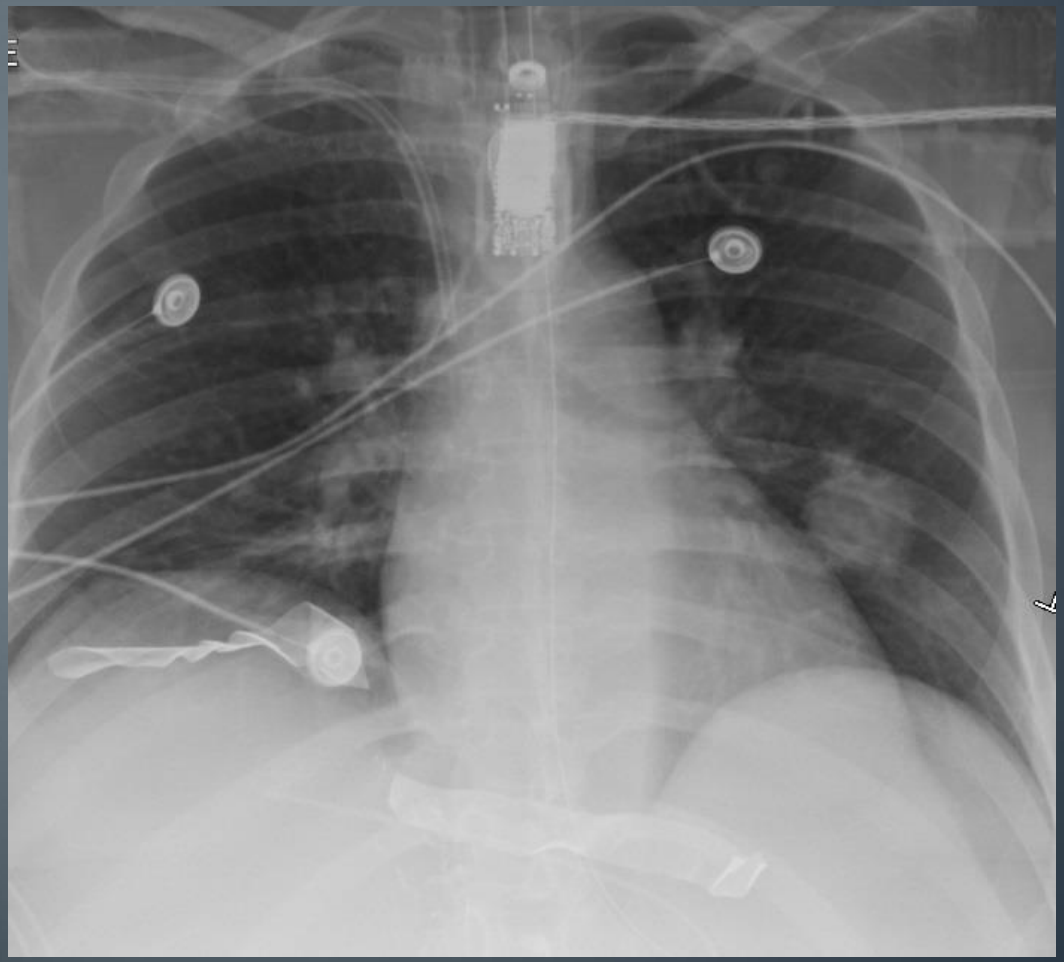
A 57 year old female undergoes orthotopic liver transplantation for HCV related cirrhosis at BUMCP. Due to her medical condition, she has been an inpatient for over one month and was in the ICU for several weeks prior to her transplant. 61 days after her transplant, she becomes febrile to 100.8F. She is currently being treated for VRE bacteremia and candida albicans fungemia with daptomycin and micafungin. She is not on any O2 and does not have a cough but you order a CXR, which is shown below. She takes tacrolimus, MMF, prednisone for IS. She takes Bactrim and valganciclovir for prophylaxis.



What is your next step?



You notice she was previously positive for Coccidiodes IgG and has been off fluconazole for one month now due to starting micafungin.



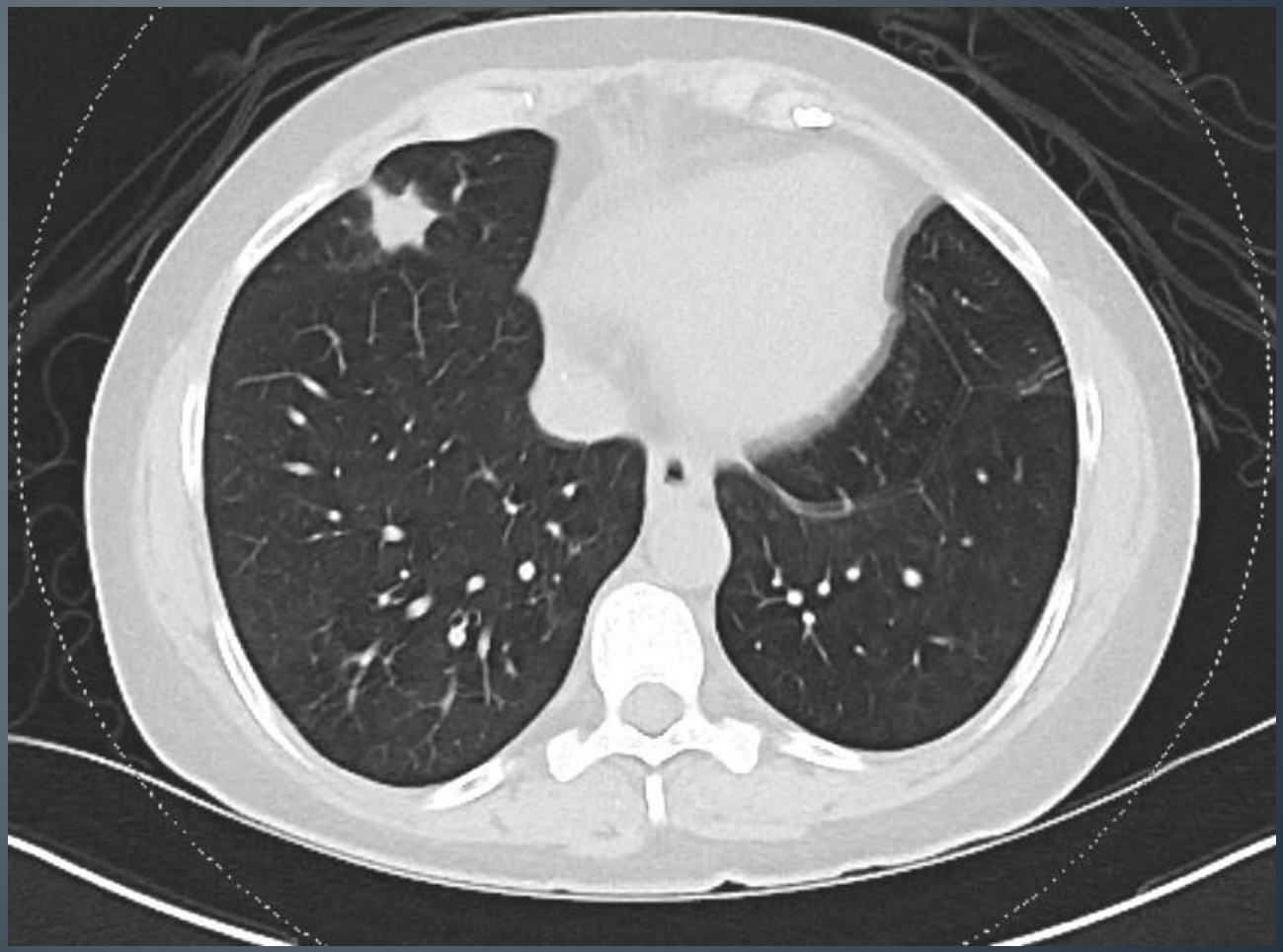
What is your suspected diagnosis?

- A) Round atelectasis
- B) Aspergillus pneumonia
- C) Pulmonary Coccidioides
- D) Pulmonary Nocardiosis
- E) MRSA pneumonia

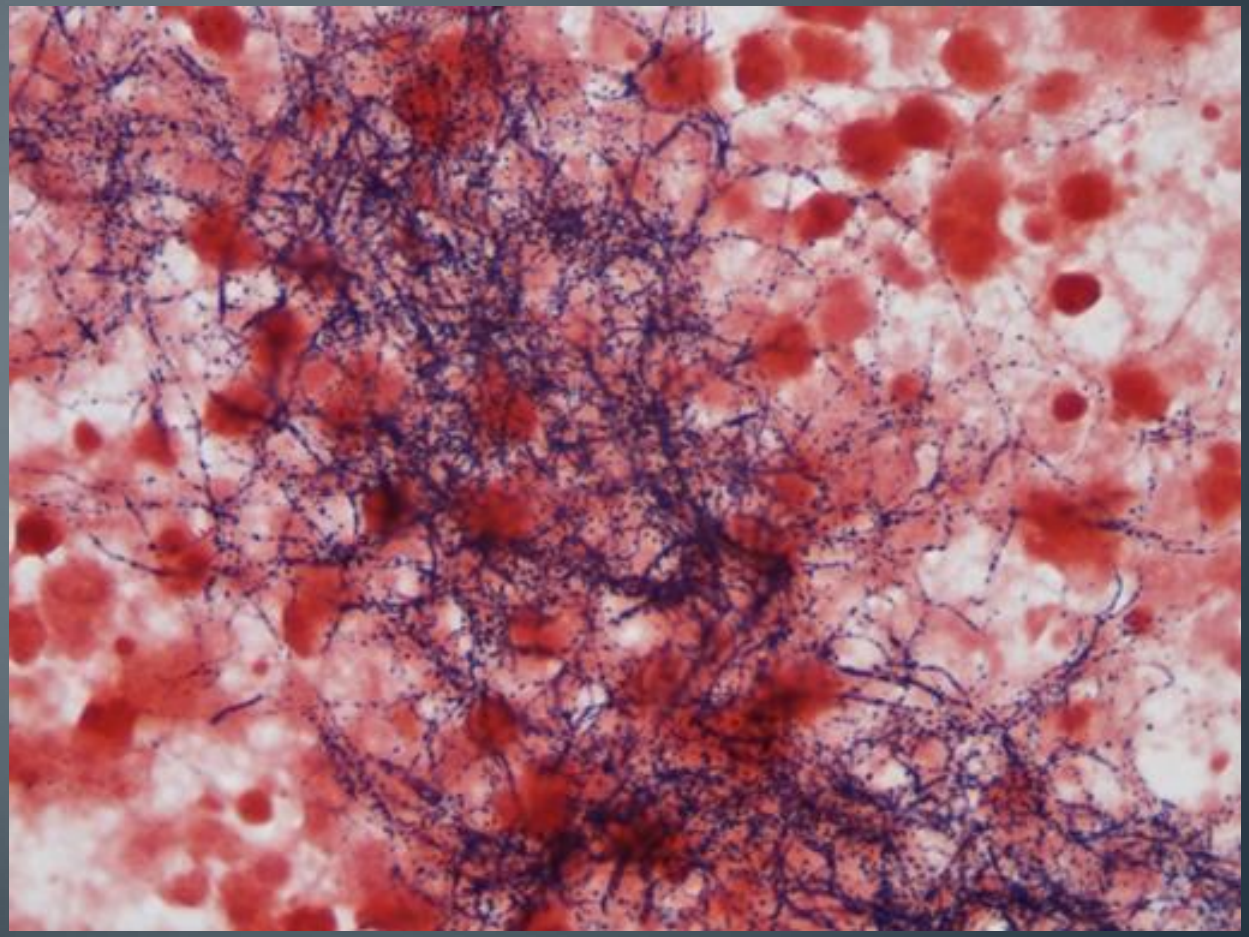
What is your suspected diagnosis?

- A) PE and infarcted lung
- B) Aspergillus pneumonia
- C) Pulmonary Coccidioides
- D) Pulmonary Nocardiosis
- E) MRSA pneumonia

A 37 year old female is admitted for fatigue, nausea and fever. She previously underwent a renal/pancreas transplant which failed. She underwent a second renal transplant 18 months ago and received campath at the time of her transplant. She has not been treated for rejection. She takes tacrolimus, MMF and valganciclvor. On admission she has a CT chest show below:



While performing your incredibly thorough physical exam, you note a mass in her posterior thigh that is mobile, non tender and without signs of inflammation. An u/s of this reveals concern for abscess. IR aspirates this collection and sends the fluid for gram stain and culture. Gram stain is below:



What antibiotics do you empirically start?

- A) Vancomycin and Zosyn
- B) Linezolid and Zosyn
- C) Ambisome
- D) Bactrim and Imipenem
- E) Vancomycin, Cefepime and Tobramycin

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Recipient derived infections

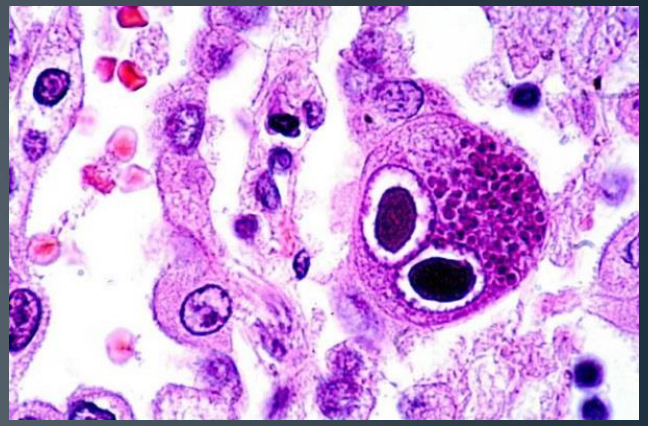
- Active infections should be eradicated/controlled prior to transplant
  - Immune suppression worsens this
- Endogenous flora
  - Candida
  - VRE
  - ?Staphylococcus aureus/MRSA
  - Aspergillus
  - Pseudomonas
- Latent infections
  - Toxoplasma
  - Herpes viruses
  - Tuberculosis
  - Coccidioides, Histoplasmosis

Donor derived infections

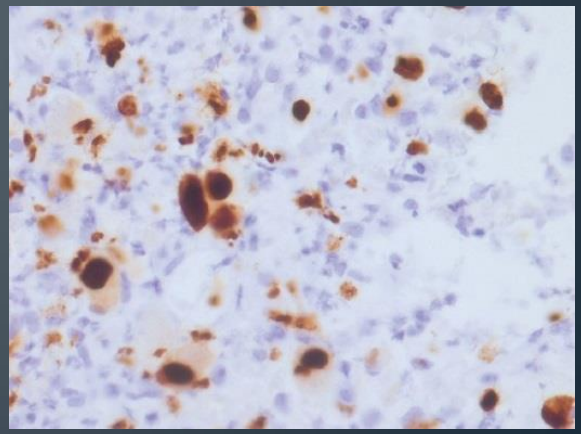
- Donor information made available to physicians
- Generally uncommon but still do occur
- Follow donor culture results for acute infections
- Donor history/serology
- Other transplant recipients with similar infections
- Types of donor derived infections
  - HSV
  - LCMV
  - WNV
  - HIV
  - Rabies
  - Trypanosoma cruzi

CMV (HHV 5)

- Infects 1/3 kids by age 5, over 50% persons by age 40. Some estimates over 90% adults
- Primary infection viral-type illness
- Remains latent in cells for life
- Highest reactivation in CMV +/- cases, IS with thymoglobulin, ATG, alemtuzumab
- Variety of manifestations as reactivation illness
- Tissue to differentiate between viremia/invasive disease
- TX: Ganciclovir followed by valganciclovir



Hematoxylin-eosin–stained lung section showing typical owl-eye inclusions (480X). Courtesy of Danny L Wiedbrauk, PhD, Scientific Director, Virology & Molecular Biology, Warde Medical Laboratory, Ann Arbor, Michigan.



Nasa M, Sharma Z, Sud R, Lipi L. Cytomegalovirus infection of gastrointestinal tract . Community Acquir Infect [serial online] 2016 [cited 2016 Aug 7];3:4-9. Available from: http://www.caijournal.com/text.asp?2016/3/1/4/179226

EBV (HHV4)

- Primary infection asymptomatic or mononucleosis syndrome (cervical LAD, splenomegaly, pharyngitis)
- 90% have immunity/past infection by age 40
- Post transplant lymphoproliferative disorder (PTLD) spectrum of disease.
  - Polyclonal B cell mononucleosis syndrome to malignant monoclonal lymphoma
- 3-10% of SOT recipients
- Mortality 40-60%
- Suspect with EBV pcr positive
- Confirm diagnosis with tissue biopsy
- Treatment is chemotherapy – usually rituxan. No active antiviral therapy

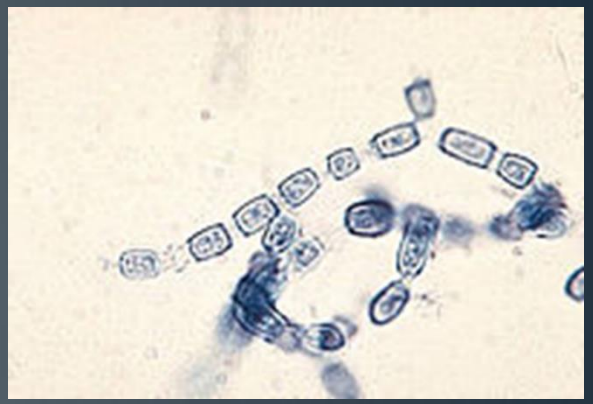
Table 1. Clinical Presentations of Post-Transplantation Lymphoproliferative Disorder Associated with Epstein–Barr Virus.

Unexplained fever (fever of unknown origin)
Mononucleosis-like syndrome (fever, malaise, pharyngitis, tonsillitis)
Gastrointestinal bleeding, obstruction, or perforation
Abdominal-mass lesions
Infiltrative disease of the allograft
Hepatocellular or pancreatic dysfunction
Central nervous system disease

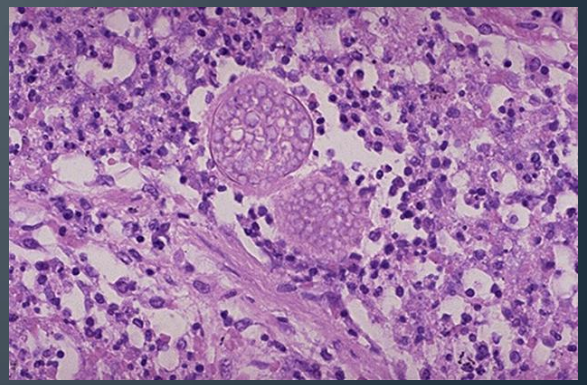
Fishman, J. *Infection in Solid-Organ Transplant Recipients*. N Engl J Med 2007;357:2601-14.

Coccidioides species

- Dimorphic – existing as either mycelium or spherule
- Two species – C. *immitis* and C. *posadasii*
  - C. *imimitis* from California San Joaquin Valley
  - C. *posadasii* – all other endemic areas
- 0.5% cases are disseminated disease
- Pulmonary lesions, skin manifestations
- Prophylaxis for SOT 200mg daily 6-12 months
- Treatment for life after tx course for active disease
- AmB for severe infection



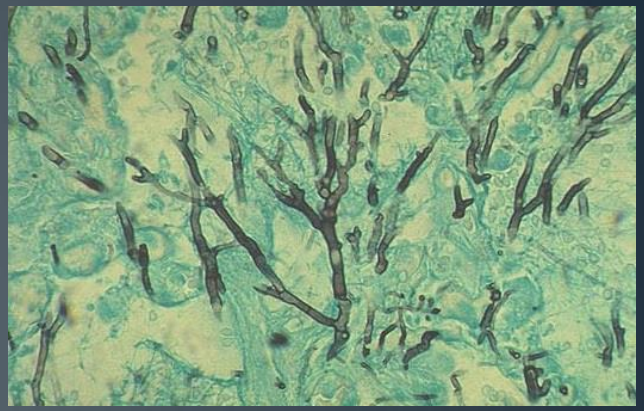
http://phil.cdc.gov/PHIL_Images/11121998/00004/39G0040_lores.jpg



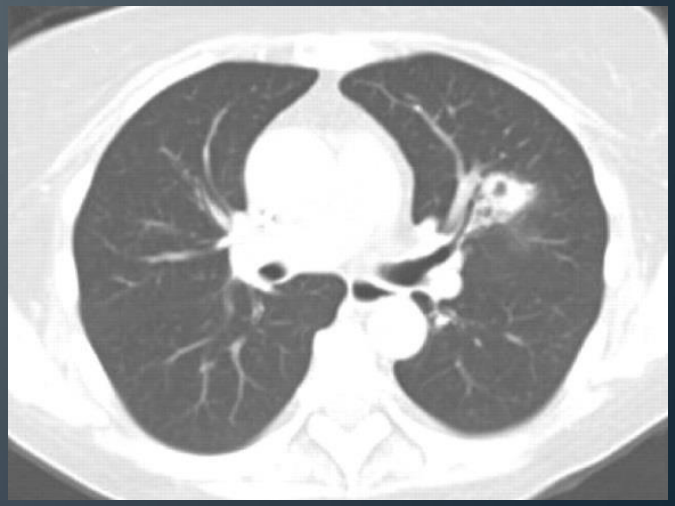
http://library.med.utah.edu/WebPath/INFEHTML/INFEC024.html

Aspergillus species

- Major cause morbidity/mortality
- Grow on most media within 48 hours
- Acute angle branching, true septate hyphae
- Aspergillus Ag (Galactomannan) used to detect cell wall for invasive Aspergillosis
  - Not recommended for SOT – only BMT
  - Need tissue/fluid for culture/path
  - Causes wide spectrum of clinical syndromes
- Treat empirically with voriconazole or posaconazole if suspected
- Interactions with IS meds (raises tacrolimus levels)
- Be aware of azole-resistant species

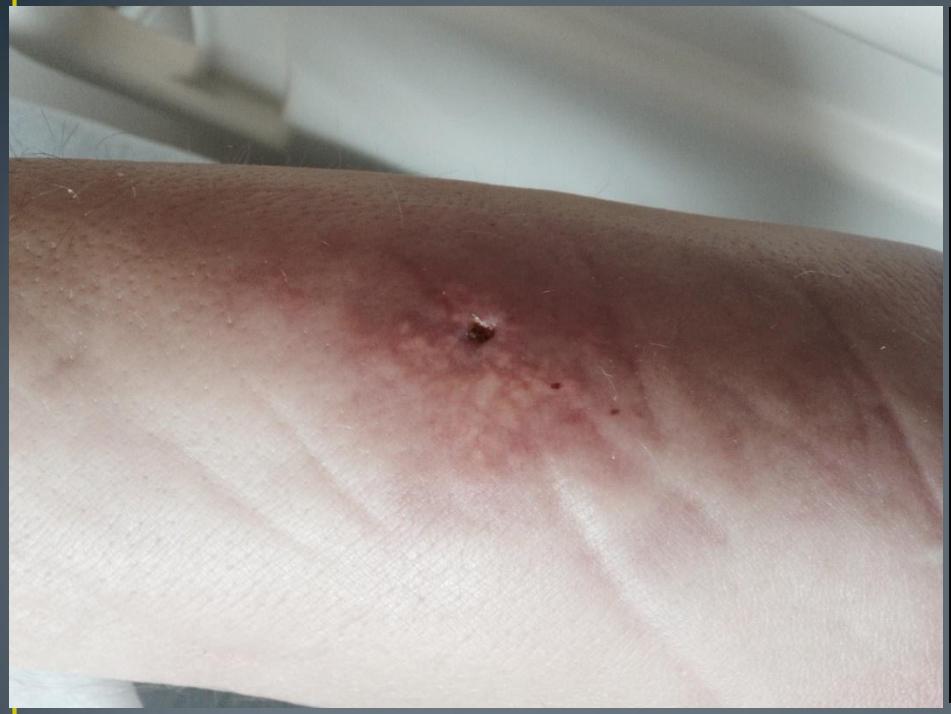


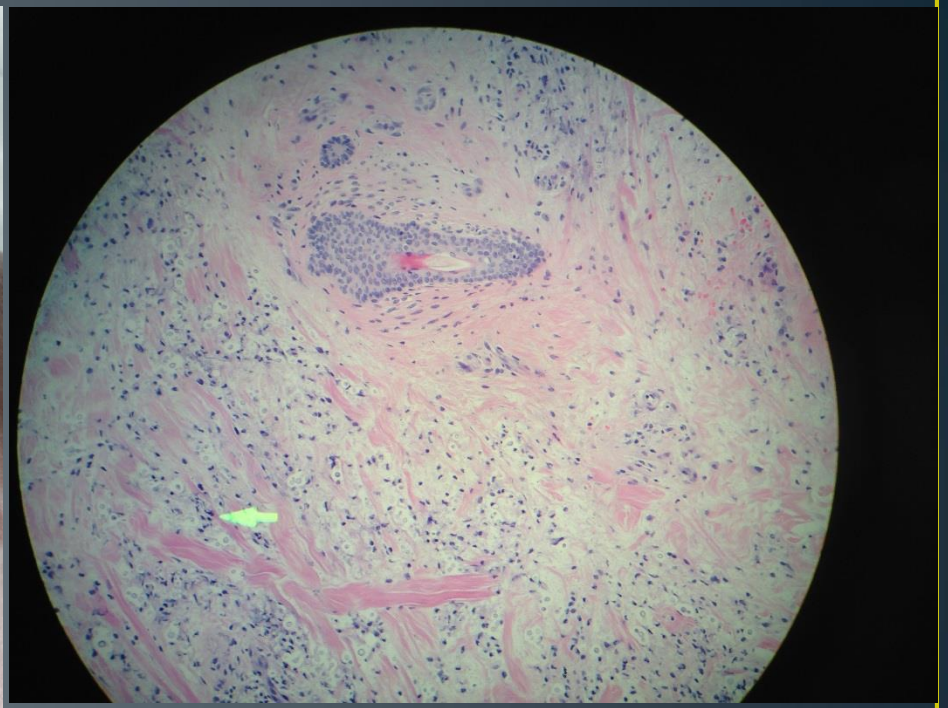
http://www.pathologyoutlines.com/topic/liveraspergillus.html



Pulmonary aspergillosis: a clinical review
M. Kousha, R. Tadi, A.O. Soubani
European Respiratory Review 2011 20: 156-174;

Cryptococcus neoformas





- Common immune compromised pathogen
- Encapsulated
- Associated with pigeons, woods
- Grow on most agar in 2-3 days
- Wide manifestations – most common CNS, pulmonary, cutaneous
- Serum/CSF cryptococcal Antigen useful in diagnosis
- Treat disseminated disease like CNS – Amphotericin/flucytosine initially

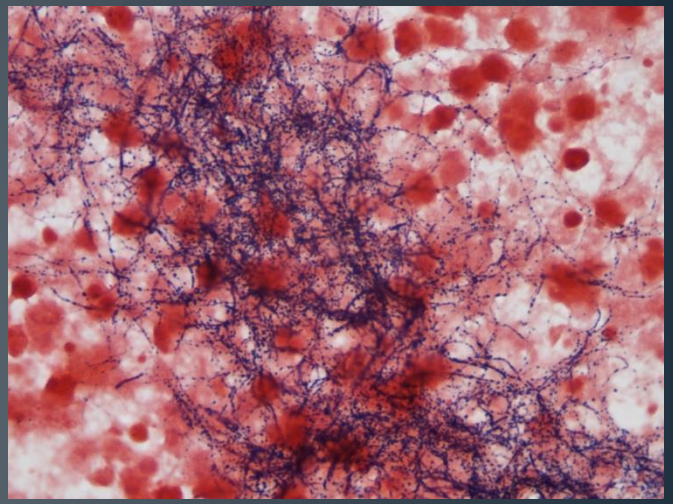
Pneumocystis jirovecii

- Opportunistic fungal pathogen
- Primarily causes pulmonary disease
- In non-HIV patients who are immune suppressed, rapid development of disease
- Diagnose by immunoflourescent or silver stain
- Bactrim is treatment of choice
- Much lower incidence in post SOT due to Bactrim prophylaxis
- At higher risk when steroids are increased

Credits
Arthur Ammann, MD, Global Strategies for HIV Prevention
Description
Lung biopsy using silver stain to demonstrate organisms in tissue.

Nocardia species

- Ubiquitous environmental organism
- Gram positive beaded branching rods
- Direct inoculation or inhalation causes infection
- Many times subacute/chronic presentation
- Pulmonary, cutaneous, CNS disease
- CNS imaging in all cases of pulmonary disease
- Bactrim mainstay of treatment, also carbapenem, amikacin, linezolid
- Prolonged course of treatment
- Less common due to Bactrim prophylaxis



Polyomaviruses – JC, BK

- Up to 90% adults seropositive for BK, 86% for JC
- Do not cause disease in immunocompetent persons
- BK – hemorrhagic cystitis in renal txp, HSCT
  - Up to 10% post renal txp have BK nephropathy
  - PCR for blood, urine. Cytopathic changes on biopsy.
  - Treatment – reduce immunosuppression
- JC – Lytic infection of oligodendrocytes in brain – leads to PML
  - PCR of CSF to diagnose
  - MRI with hyper intense white matter lesions on T2, flair. Hypo intense on T1
  - Lower immune suppression

Fever workup in transplant recipient

- Comprehensive history and exam
- CBC w/diff, CMP, CXR, UA, Blood and urine cultures
- Symptom/timeline appropriate workup
  - ?Respiratory pcr
  - CMV pcr
  - CT scanning or other imaging
- LP if headache, neurologic deficits
- Fevers >7days?
  - CMV, EBV, HHV6
  - Fungal?
  - Mycobacterial or other atypical
  - PJP, cryptococcal disease, tick borne illness
  - TB

Fever workup in transplant recipient

- Consider non infectious etiology of fever
  - Rejection
  - Drug reaction
- Some infections may present without fevers
  - Are they receiving steroids?
  - PJP – cough, shortness of breath
  - Cryptococcal infection – headache, non responsive cellulitis
  - PML – neurologic deficits

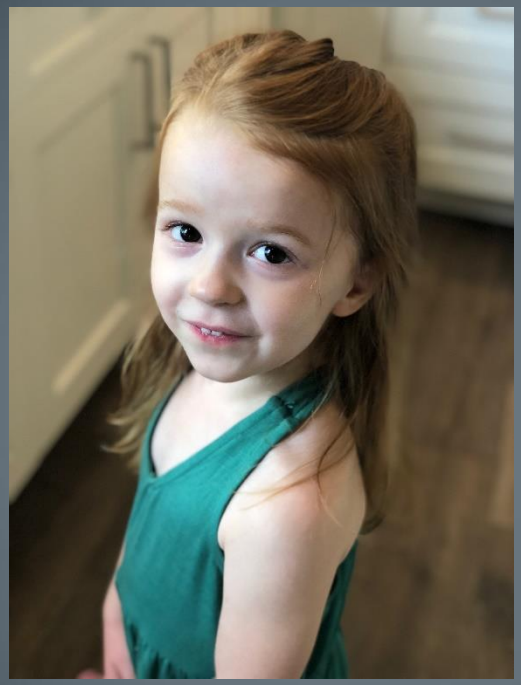
Post-transplant Prophylaxis

- Usually protocol, risk factor dependent
- TMP/SMX well tolerated, generally at least 3 months
  - Protection against PJP, Toxoplasma, Nocardia, Listeria, Legionella
  - Alternatives – Dapsone, Atovaquone, inhaled pentamidine
- Valganciclovir
- Fluconazole
- Fluoroquinolone (BMT)

Vaccination

- Evaluate before transplant, less response once immunosuppressed
  - MMR
  - TdaP
  - HAV/HBV
  - Pneumonia (Prevnar, pneumovax)
  - Influenza
  - ?Varicella (usually can't give after transplant)

Questions



References

- 1. Mandell: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed.; Chapter 311: Risk Factors and Approaches to Infections in Transplant Recipients. 3414-3424.
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