Infections in Transplant Recipients

Justin Seroy, DO

Infectious Disease

Outline

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

Introduction

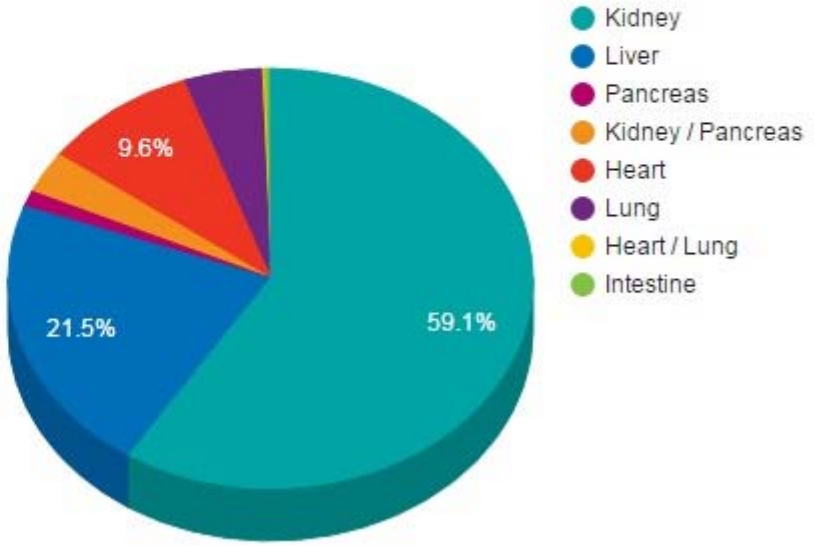
- Solid Organ Transplant (SOT) started 1954 with kidney transplants between identical twins
- Bone marrow transplant started in 1956 between identical twins
- Success limited until development of azathioprine and corticosteroids in 1960's
  - Decreased allograft rejection
- Calcineurin inhibitors in 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 - June 30, 2016

Based on OPTN data as of July 22, 2016

Organ	Transplants
Kidney	395,511
Liver	143,856
Pancreas	8,235
Kidney / Pancreas	21,727
Heart	64,085
Lung	32,224
Heart / Lung	1,186
Intestine	2,733
Total	**669,557**



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

Current SOT

- 2015: 30,969 donors (24,980 deceased; 5,989 living)

At a Glance

120,079

people need a lifesaving organ transplant (total waiting list candidates). Of those, **77,389** people are active waiting list candidates. Totals as of today 4:03pm

16,446

organ transplants performed so far in 2016

Total Transplants January - June 2016

as of 07/22/2016

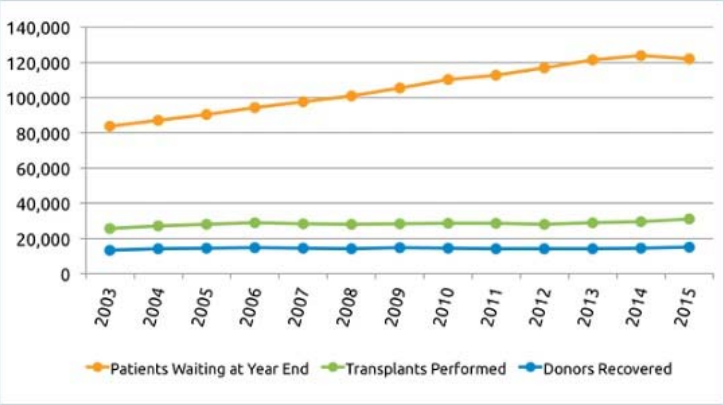
7,767

donors

Total Donors January - June 2016

as of 07/22/2016

The need continues to grow



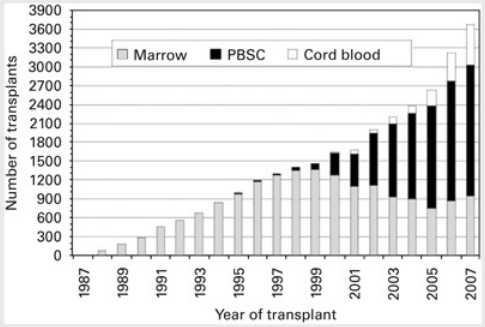
Despite advances in medicine and technology, and increased awareness of organ donation and transplantation, the gap between supply and demand continues to widen.

While national rates of donation and transplant have increased in recent years, more progress is needed to ensure that all candidates have a chance to receive a transplant. [Graph description of Need continues to grow]

https://optn.transplant.hrsa.gov/ as of 7-29-16

Marrow donors to date

- National Marrow Donor Program founded 1986



Annual transplants from the unrelated donors facilitated by the National Marrow Donor Program since its inception. Annual figures are by fiscal year (October–September) and include products collected outside the United States of America and imported, as well as those collected within the United States of America and exported. Before July 1999, only BM was used for initial transplantation, but PBSC were available in the setting of retransplantation. Stippled bars—BM, solid bars—PBSC and open bars—umbilical cord blood units. 2007 numbers are estimated.

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

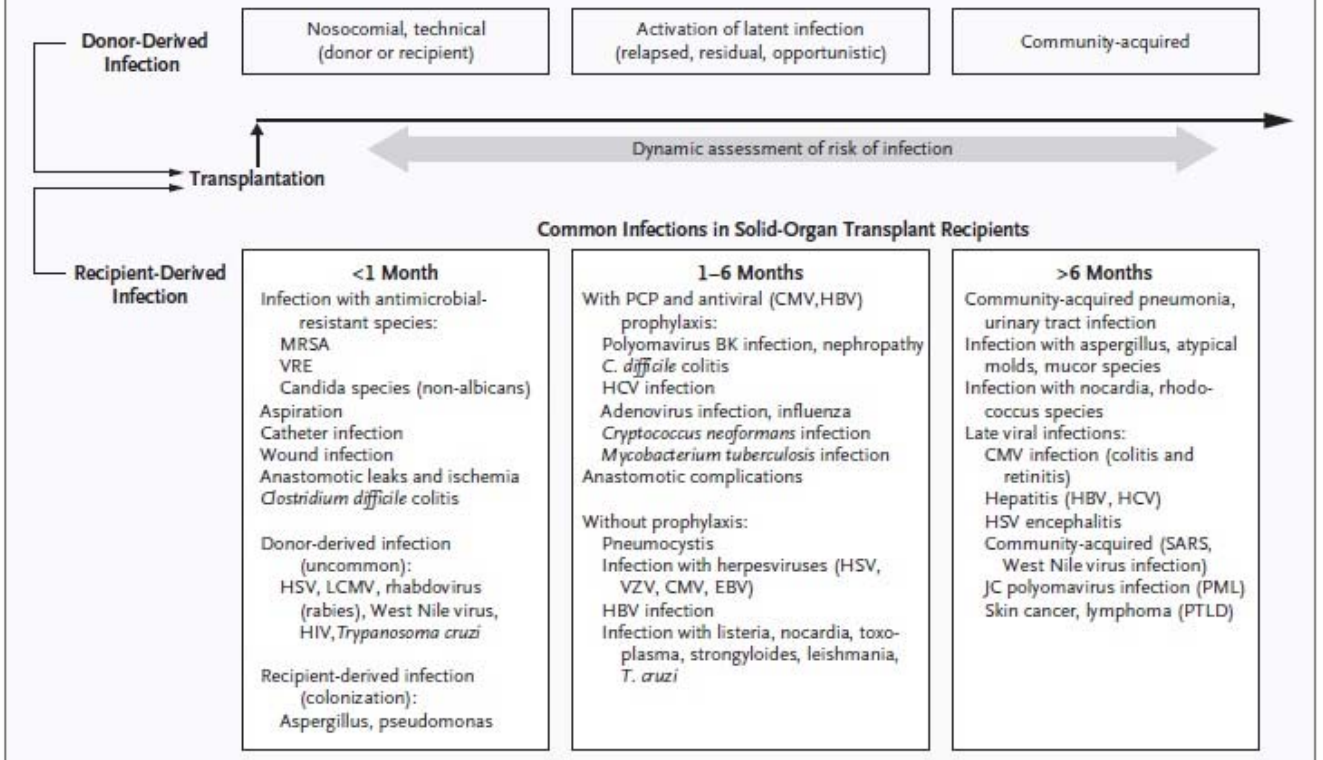


Figure 4. Changing Timeline of Infection after Organ Transplantation.

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.

Recipient derived infections

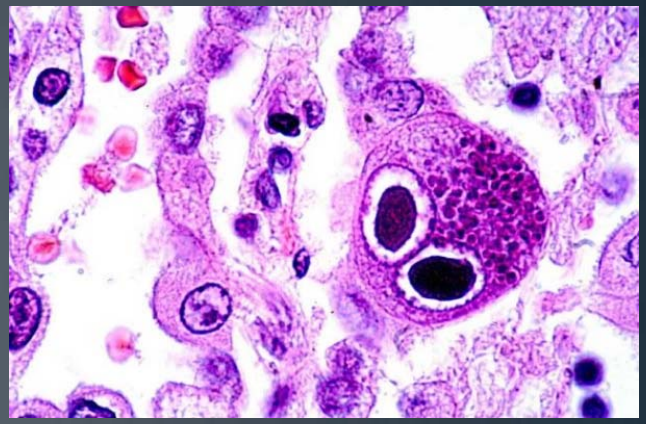
- Active infections should be eradicated/controlled prior to transplant
  - Immune suppressions worsens this
- Endogenous flora
  - Candida
  - VRE
  - ?Staphylococcus aureus/MRSA
  - Aspergillus
  - Pseduomonas
- Latent infections
  - Toxoplasma
  - Herpes viruses
  - Tuberculosis
  - Coccidiodes, Histoplasmosis

Donor derived infections

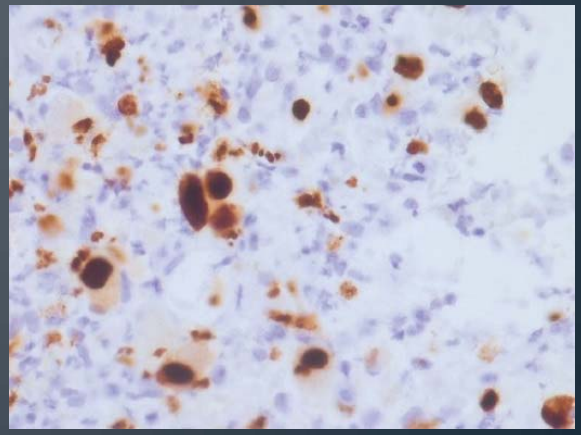
- Donor information made available to physicians
- Generally uncommon but still do occur
- Follow donor culture results for acute infections
- Donor history/serology
- Other transplant recipients with similar infections
- Types of donor derived infections
  - HSV
  - LCMV
  - WNV
  - HIV
  - Rabies
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

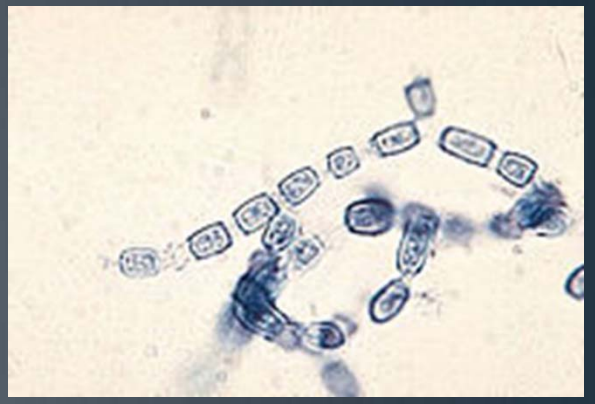
Table 1. Clinical Presentations of Post-Transplantation Lymphoproliferative Disorder Associated with Epstein–Barr Virus.

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

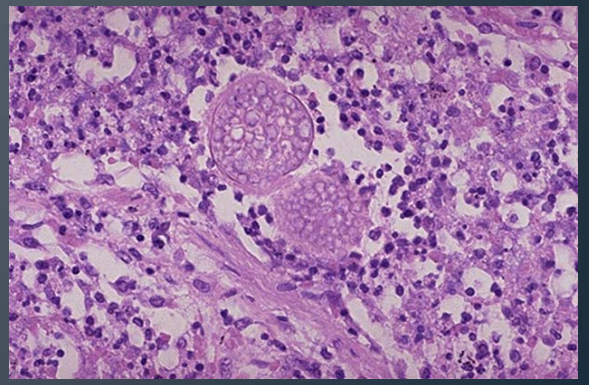
Fishman, J. *Infection in Solid-Organ Transplant Recipients*. N Engl J Med 2007;357:2601-14.

Coccidiodes 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



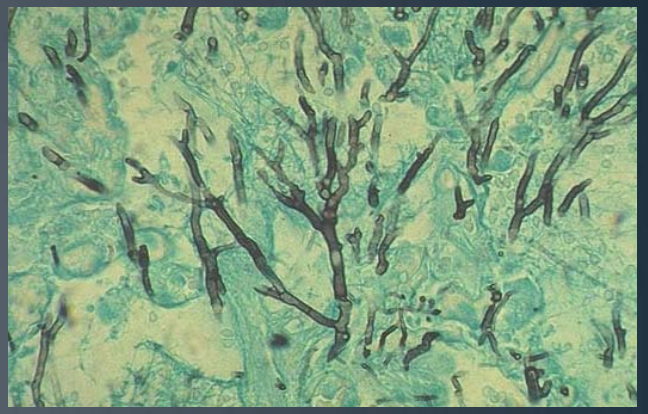
http://phil.cdc.gov/PHIL_Images/11121998/00004/39G0040_lores.jpg



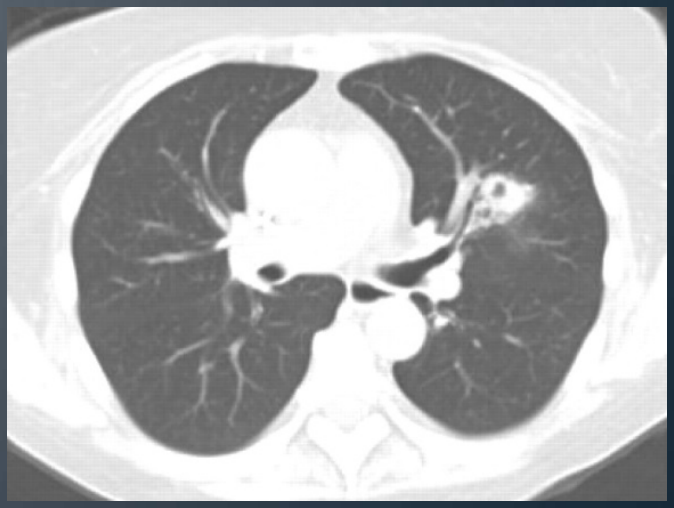
http://library.med.utah.edu/WebPath/INFEHTML/INFEC024.html

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 vorizonazole if suspected
- Interactions with IS meds (raises tacrolimus levels)
- Be aware of azole-resistant species

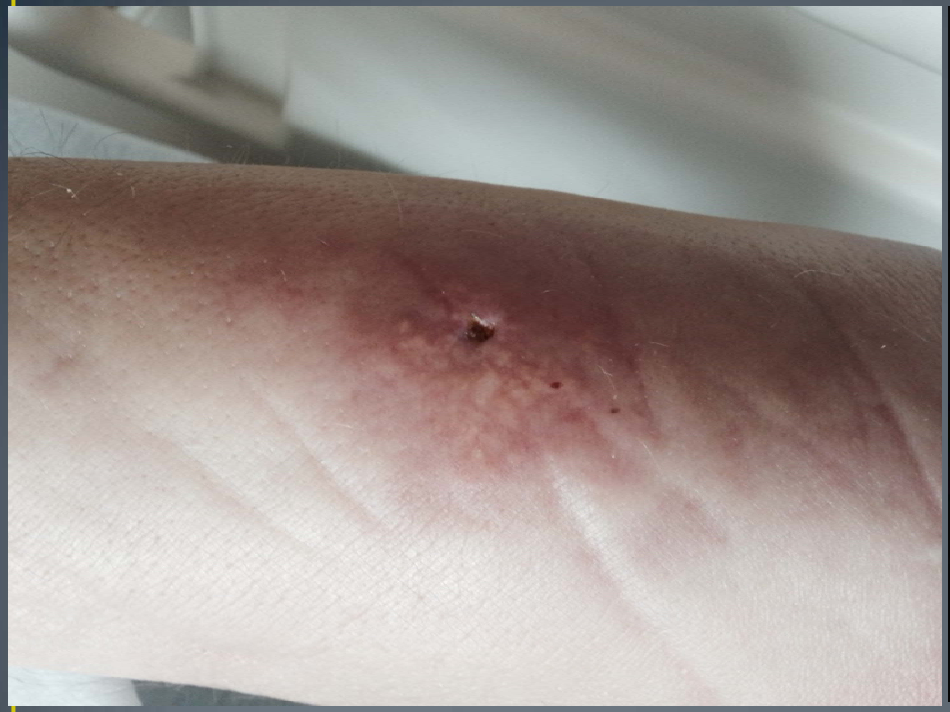


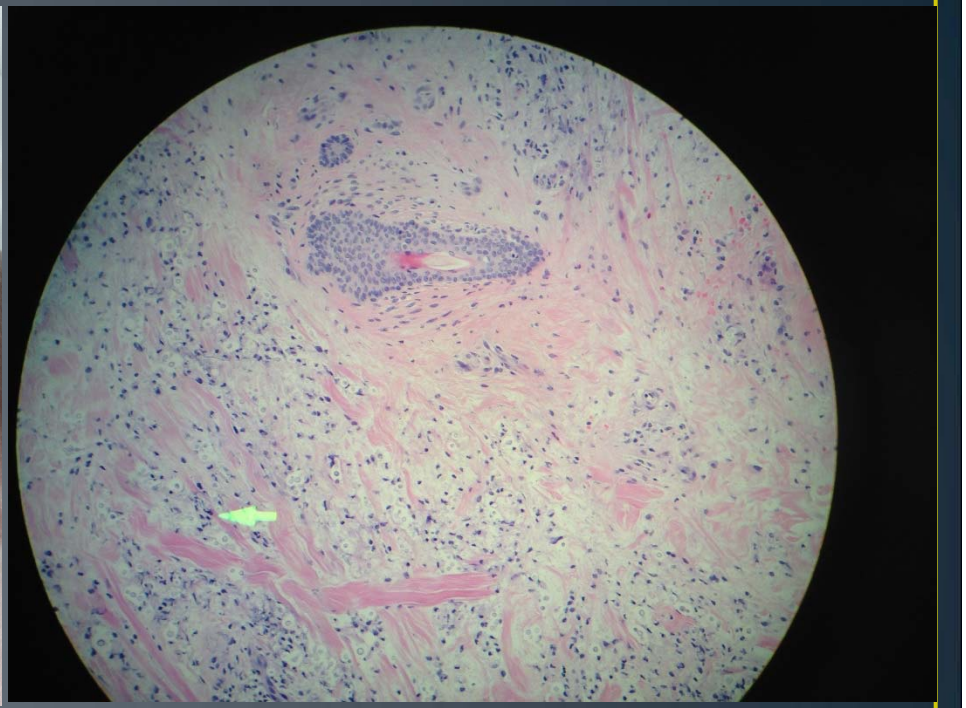
http://www.pathologyoutlines.com/topic/liveraspergillus.html



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

Cryptococcus neoformas

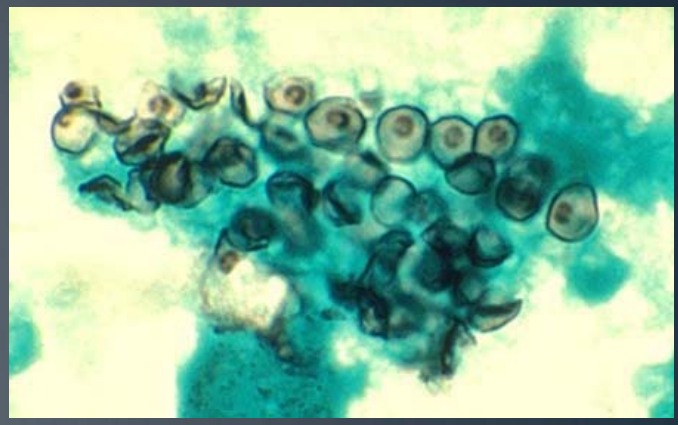




- Common immune compromised pathogen
- Encapsulated
- Associated with pigeons, woods
- Grow on most agar in 2-3 days
- Wide manifestations – most common CNS, pulmonary, cutaneous
- Serum/CSF cryptococcal Antigen useful in diagnosis
- Treat disseminated disease like CNS – Amphotericin/flucytosine initially

Pneumocystis jirovecii

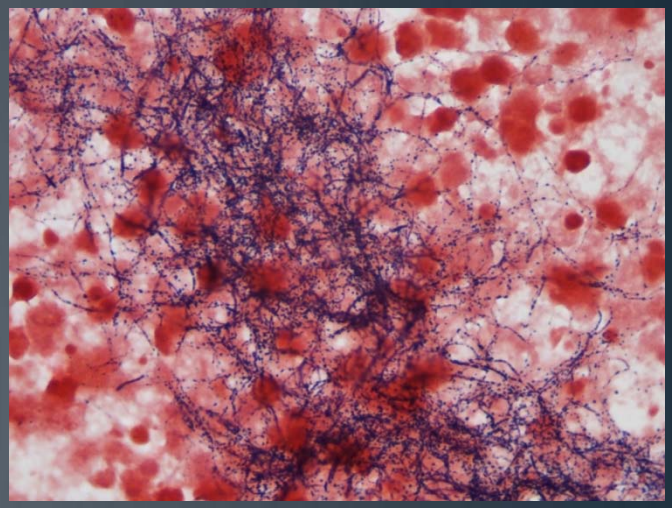
- Opportunistic fungal pathogen
- Primarily causes pulmonary disease
- In non-HIV patients who are immune suppressed, rapid development of disease
- Diagnose by immunoflourescent or silver stain
- Bactrim is treatment of choice
- Much lower incidence in post SOT due to Bactrim prophylaxis
- At higher 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 hyperintese white matter lesions on T2, flair. Hypointese 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.
- 2. https://www.unos.org/data/
- 3. https://optn.transplant.hrsa.gov/
- 4. *Bone Marrow Transplantation* (2008) **42**, S3–S5; doi:10.1038/bmt.2008.102
- 5. http://bloodcell.transplant.hrsa.gov/research/transplant_data/transplant_activity_report/index.html
- 6. Fishman, J. *Infection in Solid-Organ Transplant Recipients*. N Engl J Med 2007;357:2601-14.
- 7. 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