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# Approach to Respiratory Infections in Immunocompromised Hosts



Thailand  
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# Conflict of Interest Disclosure

I have no financial or intellectual disclosures related to this topic

# Learning Objectives

- We have only 40 minutes together, so I am going to predominantly focus on the approach to these patients and pearls of wisdom to recall
- Cannot cover all the specific diseases.....but we will touch on a few....and others in the rest of the pulmonary infections presentations; will not touch on prophylaxis
- At the conclusion of this presentation, you will be able to:
  - Describe the approach to pulmonary infections in immunocompromised hosts
  - Recall that the type of immune deficiency and timeline are key in the differential diagnosis
  - List the common radiographic patterns that can be helpful in the approach to these patients
  - Recognize that non-infectious complications can occur as well

# General Principles

- Type of immunodeficiency and timeline are the most important factors in narrowing the differential diagnosis
- Consider previous therapies, previous infections/cultures, travel, other exposures (cause of death and infections in organ donor)
- Early diagnosis and micro-organism specific therapy is the key
- BE AGGRESSIVE IN PURSUING A SPECIFIC MICROBIOLOGIC DIAGNOSIS\*
- Multiple simultaneous pulmonary complications are common

# General Principles

- Serological testing is generally not useful
- Microbiological testing should focus on antigen detection and nucleic acid detection (PCR)
- CT Chest is a key component of diagnostic work up
- Empiric anti-microbials should be started as soon as possible

# Clinical Presentation

- Patients may not present with classic signs and symptoms of pneumonia due to their immunosuppressed state
- Signs and symptoms are non-specific and may include:
  - Fever, cough, and dyspnea

# General Principles

- Certain subgroups are highly susceptible to infection
  - Aggressive tumors
  - Recent HSCT (esp. with GVHD)
  - Recent infections with CMV or known colonization with fungi or resistant bacteria
  - ANC below 500 (especially below 100)
  - High dose glucocorticoid therapy or recent intensification of immunosuppression

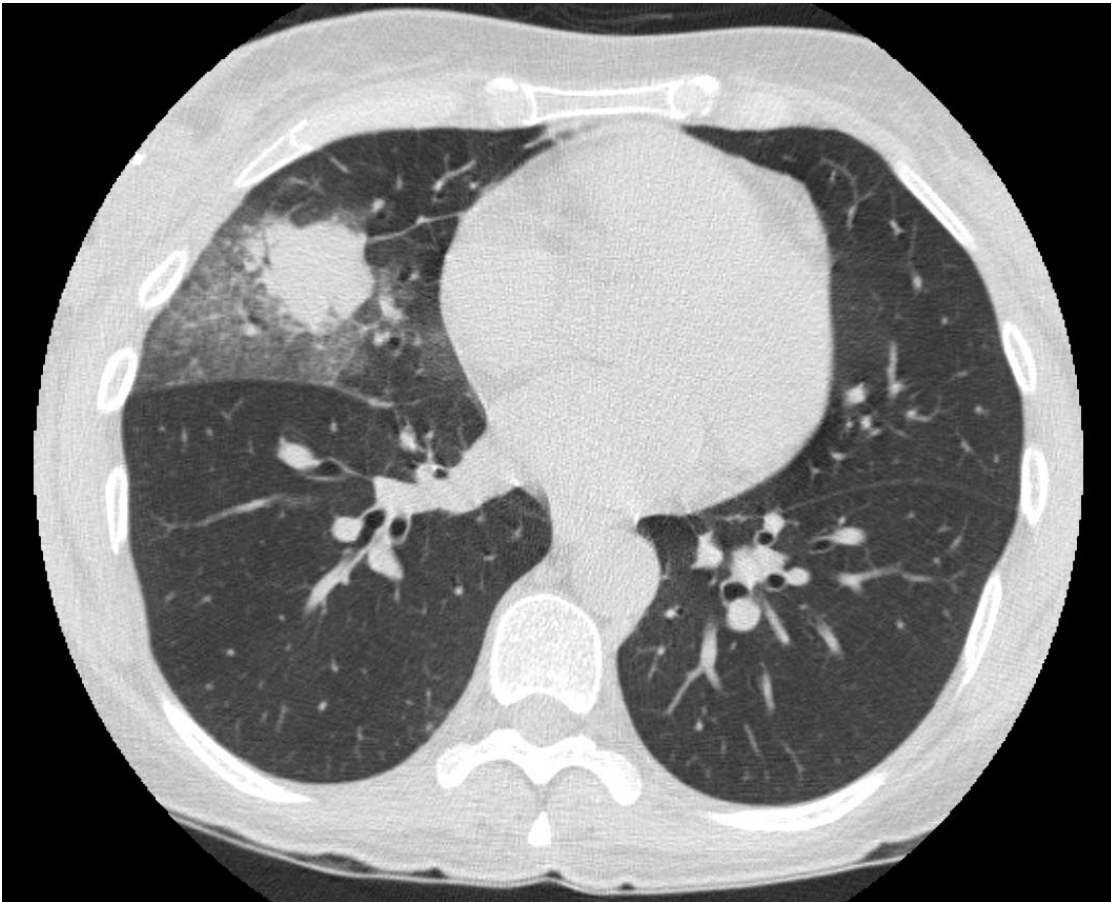




The type and degree of immunocompromise determine risk for infection

## Question 1

- A 23 year-old man with chronic granulomatous disease presents with fever and non-productive cough
- On physical examination, he is afebrile with normal oxygenation and faint crackles in the mid-right lung zone. The skin and cardiac exams are normal
- After a chest radiograph reveals a focal nodular opacity, a chest CT is obtained



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## Question 1

Which of the following is the most appropriate next step?

- A. BAL galactomannan
- B. Serum galactomannan
- C. Sputum fungal culture
- D. Transbronchial biopsy
- E. No additional testing; begin empiric antifungal therapy

## Question 1

Which of the following is the most appropriate next step?

- A. BAL galactomannan
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# Type of Immunosuppression and Infection Risk

Immuno-deficiency	Example(s)	Clinical Pattern	Organisms
Defects in immunoglobulins and/or complement proteins	Common variable immune deficiency	<ul style="list-style-type: none"><li>• Sinopulmonary infections</li><li>• Chronic GI infections</li><li>• Meningitis</li></ul>	<ul style="list-style-type: none"><li>• Encapsulated bacteria (<i>S. pneumo</i>, <i>H. flu</i>, <i>N. meningitidis</i>)</li><li>• <i>Giardia</i></li><li>• <i>Campylobacter</i></li></ul>
Granulocyte defects	<ul style="list-style-type: none"><li>• Neutropenia</li><li>• Chronic granulomatous disease</li></ul>	<ul style="list-style-type: none"><li>• Recurrent skin and soft tissue infections</li><li>• Abscesses</li></ul>	<ul style="list-style-type: none"><li>• <i>S. aureus</i></li><li>• Gram negative bacilli</li><li>• <i>Aspergillus</i></li><li>• <i>Nocardia</i></li></ul>
Defects in cell-mediated immunity	HIV Post transplant CTD	Progressive infections	<ul style="list-style-type: none"><li>• Viruses</li><li>• Mycobacteria</li><li>• Fungi</li></ul>

# Diagnostic Assessment

- Vital signs, exam
- Blood, urine, sputum, CSF cultures
- CBC, chemistries
- Urinary antigens
- Antigen and PCR assays of serum, BAL, CSF
- Skin examination
- **Imaging**

# Radiographic Patterns

Classical imaging signs/pattern indicative of lung infections and probable differential diagnosis.

Signs	Diagnosis	Differential diagnosis
Consolidation & air bronchogram	Pneumonia	Atelectasis, neoplasia, aspiration
Silhouette sign	Segmental or bronchopneumonia	Atelectasis, neoplasia
Bulging fissure sign	Lobar pneumonia, abscess	Neoplasia
Feeding vessel sign	Septic emboli	Metastasis
Air fluid level sign	Empyema, abscess	Neoplasia, Wegener's granulomatosis
Inhomogeneous enhancement	Abscess, empyema	Neoplasia
Split pleura sign	Empyema, bronchopulmonary fistula	Postoperative and pleurodesis associated changes
Ground glass opacities (GGO)	Atypical pneumonia	Neoplasia, drug toxicities, cardiac failure, vasculitis
Halo sign	Aspergillosis	Pseudomonas, HSV, CMV, Wegener granulomatosis,
Air crescent sign	Aspergillosis	Hydatid cyst of lung
Monad sign	Mycetoma	Wegener's granulomatosis, neoplasia
Reverse Halo	Aspergillosis, cryptogenic organizing pneumonia	Tuberculosis, bacterial infections, Sarcoidosis, Wegener's granulomatosis
Crazy paving	PCP, viral like influenza	Alveolar proteinosis, pulmonary edema and hemorrhages
Miliary pattern	Tuberculosis	Metastasis

S.K. Bajaj, B. Tombach / Radiology of Infectious Diseases 4 (2017) 29e37



Common HRCT imaging patterns with frequent immunocompromise-related infections.

Imaging patterns	Associated infections
Ground-glass opacity	<ul style="list-style-type: none"><li>● Pneumocystis</li><li>● Cytomegalovirus</li></ul>
Nodules	
<1 cm diameter	<ul style="list-style-type: none"><li>● Viral pneumonia</li></ul>
>1 cm diameter	<ul style="list-style-type: none"><li>● Invasive aspergillosis</li><li>● Septic embolism</li></ul>
“Halo sign”	<ul style="list-style-type: none"><li>● Invasive aspergillosis</li><li>● Candidiasis</li><li>● Cytomegalovirus pneumonia</li></ul>
Cavitated nodules	<ul style="list-style-type: none"><li>● Septic embolism</li><li>● Invasive aspergillosis</li></ul>
Tree-in-bud pattern	<ul style="list-style-type: none"><li>● Infectious bronchiolitis</li></ul>
Consolidation	
Lobar	<ul style="list-style-type: none"><li>● Pneumococcus</li><li>● Klebsiella</li></ul>
Rounded	<ul style="list-style-type: none"><li>● Pneumococcus</li><li>● Legionella</li></ul>
Bronchopneumonia	<ul style="list-style-type: none"><li>● Gram-negative bacteria</li><li>● Staphylococcus</li></ul>

X. Zheng, G. Zhang / Radiology of Infectious Diseases 1 (2014) 37e41

# Radiographic Patterns

Imaging findings of pneumonia caused by fungi and virus in immunocompromised patients.

	Common radiographic findings	Common CT findings
Pneumocystis pneumonia	<ul style="list-style-type: none"><li>• Bilateral symmetric ground-glass opacities or fine reticulonodular pattern, mainly involving perihilar regions.</li><li>• May be diffuse or involve mainly the lower or upper lung zones</li></ul>	<ul style="list-style-type: none"><li>• Bilateral symmetric ground-glass opacities</li><li>• May be patchy or diffuse</li><li>• May have “crazy paving” pattern</li></ul>
Pulmonary candidiasis	<ul style="list-style-type: none"><li>• Unilateral or bilateral areas of consolidation</li><li>• Poorly defined nodules</li></ul>	<ul style="list-style-type: none"><li>• Multiple bilateral nodules</li><li>• CT halo sign</li><li>• Patchy or confluent consolidation</li></ul>
Angioinvasive pulmonary aspergillosis	<ul style="list-style-type: none"><li>• Bilateral poorly defined nodules</li><li>• Single or multiple foci of consolidation</li></ul>	<ul style="list-style-type: none"><li>• Multiple nodules, 1–3 cm diameter</li><li>• CT halo sign</li><li>• Wedge-shaped areas of consolidation</li><li>• Cavitation, with or without air-crescent sign</li></ul>
Pulmonary histoplasmosis	<ul style="list-style-type: none"><li>• Single or multiple nodules</li><li>• Unilateral or bilateral areas of consolidation</li><li>• Cavitation is rare</li></ul>	<ul style="list-style-type: none"><li>• Diffuse nodular opacities 3 mm or less in diameter</li><li>• Nodules greater than 3 mm in diameter</li><li>• Small linear opacities</li><li>• Focal or patchy areas of consolidation</li><li>• cavitation is rare</li></ul>
Viral pulmonary infections	<ul style="list-style-type: none"><li>• Bilateral reticulonodular pattern</li><li>• Patchy bilateral areas of consolidation</li></ul>	<ul style="list-style-type: none"><li>• Multiple small centrilobular nodules</li><li>• Unilateral or bilateral</li><li>• Patchy areas of consolidation</li><li>• Ground-glass opacities</li></ul>

X. Zheng, G. Zhang / Radiology of Infectious Diseases 1 (2014) 37e41

# Radiographic Patterns

## CT changes in atypical Pneumonia.

Pneumonia	GGO with lobular distribution	GGO diffuse pattern	Centrilobular nodules	Segmental consolidation	Interlobular septal thickening	Pleural effusion
Viral	++	+++	++	+	++	-
Legionella	+++			+++		++
Mycoplasma	++		++	++	+	
Chlamydia	++		++	++	+	
Aspergillosis	++	+	++ (+/- halo)	++		
Candida	+		++		+	

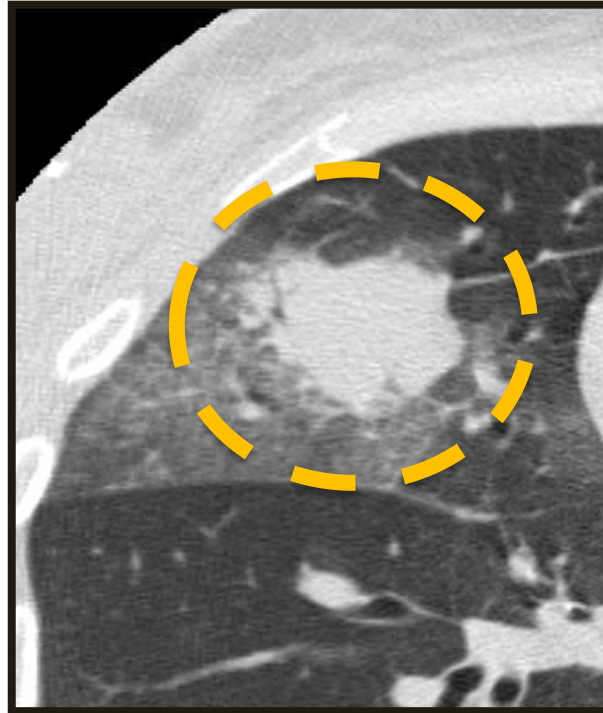
+Sign indicate the relative frequency of the findings from lowest to highest.

S.K. Bajaj, B. Tombach / Radiology of Infectious Diseases 4 (2017) 29e37

## Halo Sign

Ground glass opacity surrounding a nodule or mass

Histopathology: focus of infarction surrounded by alveolar hemorrhage



# Halo Sign Associations

Category	Examples
Fungi	Aspergillosis, Mucormycosis, Cryptococcosis
Viruses	HSV, VZV, RSV, CMV, influenza A
Bacteria	Actinomyces, bacterial pneumonia, septic emboli
Mycobacteria	Mycobacterium tuberculosis, MAC
Parasites	Paragonimus westermani, Toxocara canis
Systemic diseases	Granulomatosis with angiitis, sarcoidosis, amyloidosis
Neoplasms	Lung cancer, lymphoma, metastases

Georgiadou SP, et al. *Clin Infect Dis*, 2011;52(9):1144-55

- The incidence of HS on:
  - Day 0 was 96%
  - Day 3 was 68%
  - Day 7 was 22%,
  - Day 14 was 19%



Caillot D, et al. *J Clin Oncol.* 2001

# Diagnostic Criteria for Invasive Fungal Disease

## Host Factors

- Neutropenia
- Allogeneic stem cell transplant
- Corticosteroids

## Clinical Criteria

- CT findings
- Tracheobronchitis
- Sinonasal infection
- CNS infection

## Mycologic Criteria

- Direct test (cytology, direct microscopy, culture)
- Indirect test (antigen detection)

EORTC/MSG Consensus Group. *Clin Infect Dis*, 2008;46(12):1813-21

# Galactomannan (GM) Antigen Detection

**Polysaccharide in  
the cell wall of  
*Aspergillus***

Thought to be  
released during  
angioinvasion

## False positives

- Other fungi (e.g.,  
*Penicillium*,  
*Fusarium*,  
*Histoplasma*)
- Use of  
tazobactam
- Plasmalyte

## BAL GM

- Higher  
sensitivity
- Higher PPV
- Higher  
diagnostic  
odds ratio  
than serum  
GM

Guo YL, et al. *Chest*, 2010;138(4):817-24

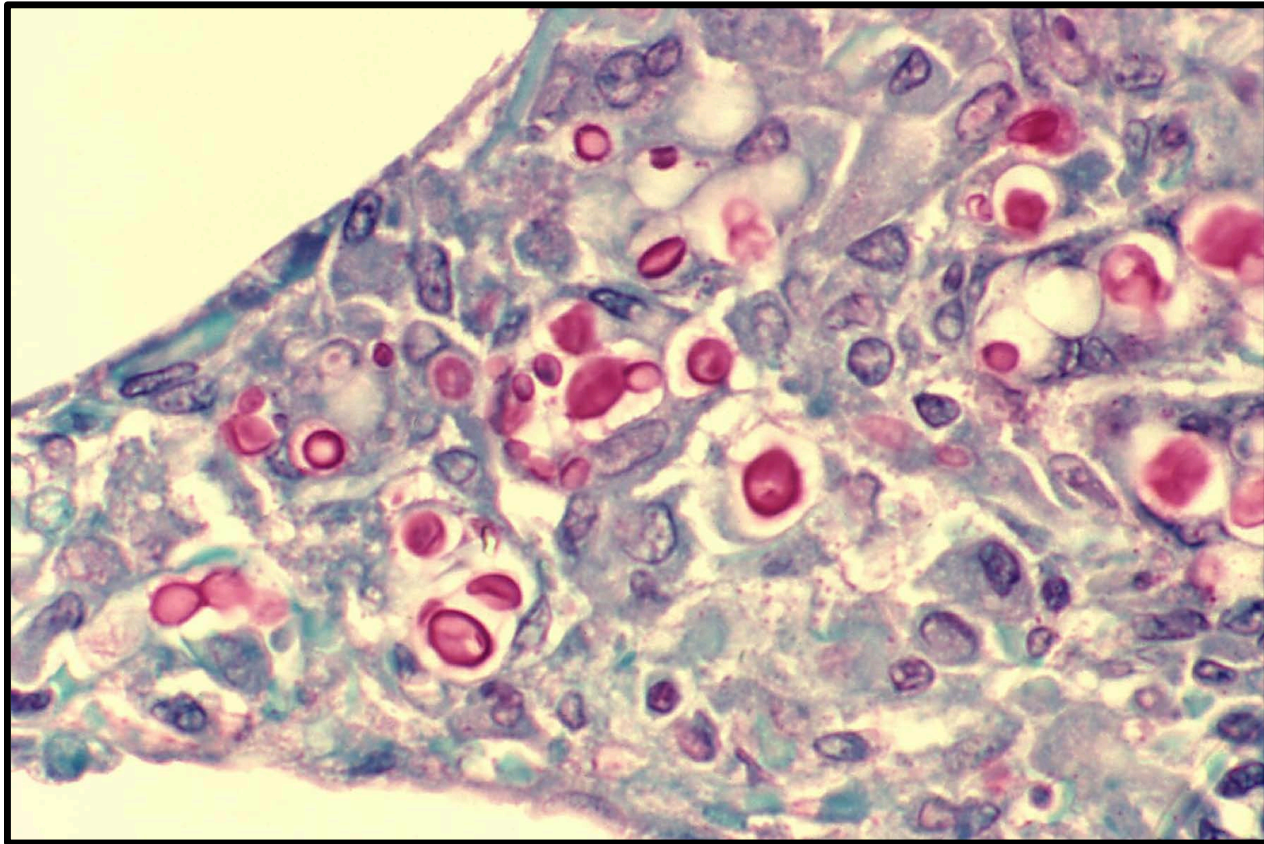


## Question 1

- A. BAL galactomannan
- B. Serum galactomannan (less sensitive than BAL GM)
- C. Sputum fungal culture (very low sensitivity)
- D. Transbronchial biopsy (more invasive option)
- E. No additional testing; begin empiric antifungal therapy (OK to begin therapy, but additional testing necessary)

## Question 2

- A 52 year old man who underwent cadaveric kidney transplant four months ago presents with 6 days of fever, dyspnea, chest pain, and headache. Medications include cyclosporine, mycophenolate mofetil, and prednisone 15 mg/day
- On physical examination, temperature is 38.5°C and oxygen saturation is 92% on ambient air. He appears lethargic. The cardiopulmonary and skin exams are normal. The neurologic exam is non-focal and there is no nuchal rigidity
- Chest radiograph reveals several nodular opacities in both lungs abutting the pleura. Lumbar puncture demonstrates a lymphocytic pleiocytosis with increased CSF protein. A CT-guided biopsy of the largest pulmonary nodule is obtained



## Question 2


Which of the following is the most appropriate therapy?

- A. Acyclovir
- B. Ampicillin
- C. Fluconazole
- D. Liposomal amphotericin B and flucytosine
- E. Trimethoprim/sulfamethoxazole

## Question 2

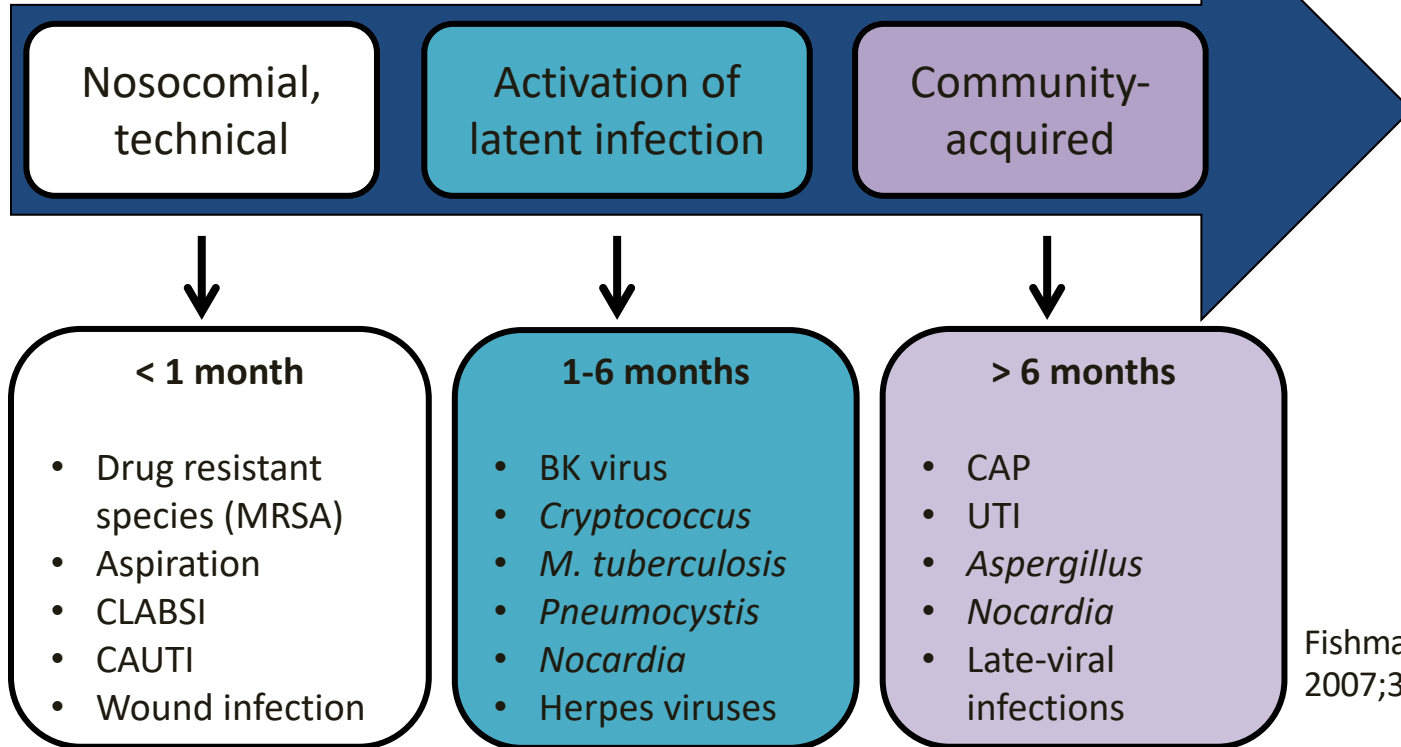
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- C. Fluconazole
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- E. Trimethoprim/sulfamethoxazole



For transplant patients, infections occur in a predictable pattern based on time from transplant

# Timeline of Infections after Solid Organ Transplantation



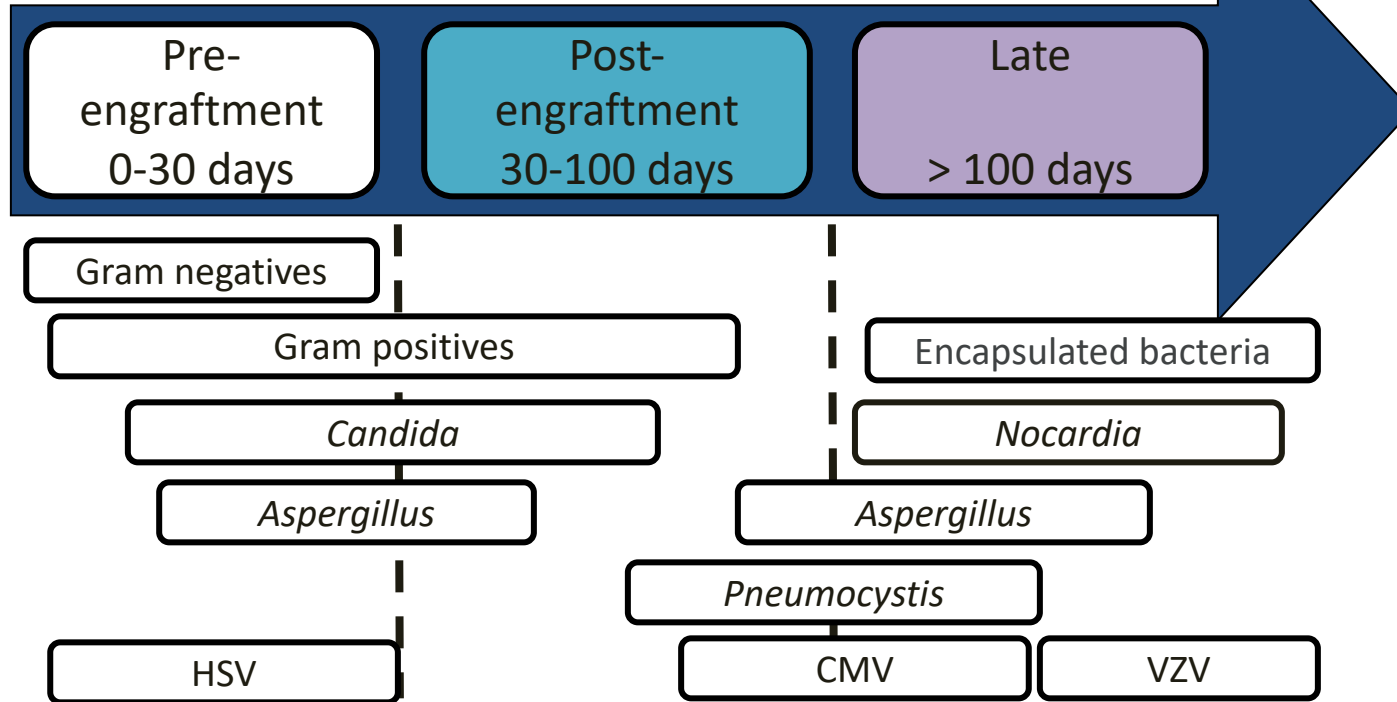
Fishman JA. *N Engl J Med.* 2007;357(25):2601-14

# Infections in SOT

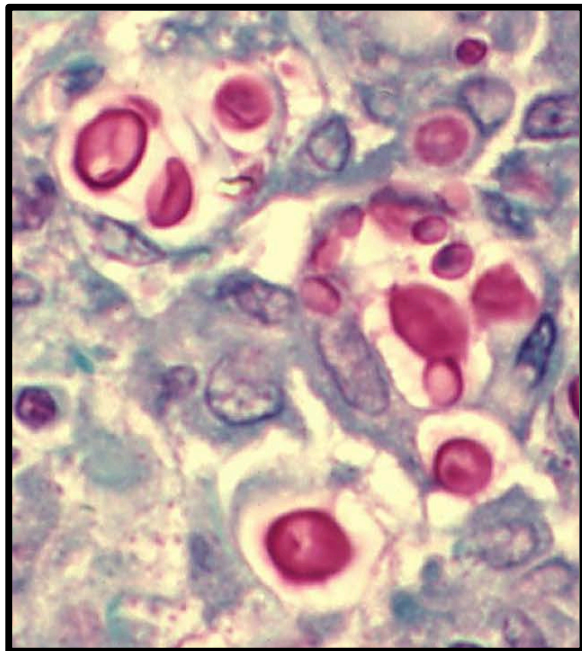
- Treatments result in dysfunctional neutrophils
- Lung is the primary site of infection in heart and lung transplant
- In liver, kidney, small bowel recipients, abdominal infections, followed by lung
- IMI more common in lung and small bowel transplants
  - Use of prophylaxis has led to increase in non-aspergillus infections
  - Liver transplant patients particularly susceptible to *mucorales* spp
- In lung transplant patients, must also consider airway anastomotic infections



# Timeline of Infections after Hematopoietic Stem Cell Transplantation



Chi AK. *Chest*. 2013;144(6):1913-22



## Forms of Disease

- Meningoencephalitis
- Pulmonary
- Cutaneous
- Disseminated disease

Third most common invasive fungal infection in SOT recipients after candidiasis and aspergillosis

Singh N, et al. *Clin Infect Dis*. 2008;47(10):1321-7

# Cryptococcosis: Clinical Features

## Meningoencephalitis

Fever, headache, lethargy,  
personality changes

CSF: Lymphocytic pleiocytosis, low  
glucose, elevated protein, elevated  
opening pressure

## Pulmonary disease

Fever, chest pain, dyspnea, cough,  
hemoptysis

Imaging: Solitary-few nodules  $\pm$   
cavitation, hilar/mediastinal  
adenopathy, pleural effusions

Freifeld AG, et al. *Clin Infect Dis*. 2011;52(4):e56

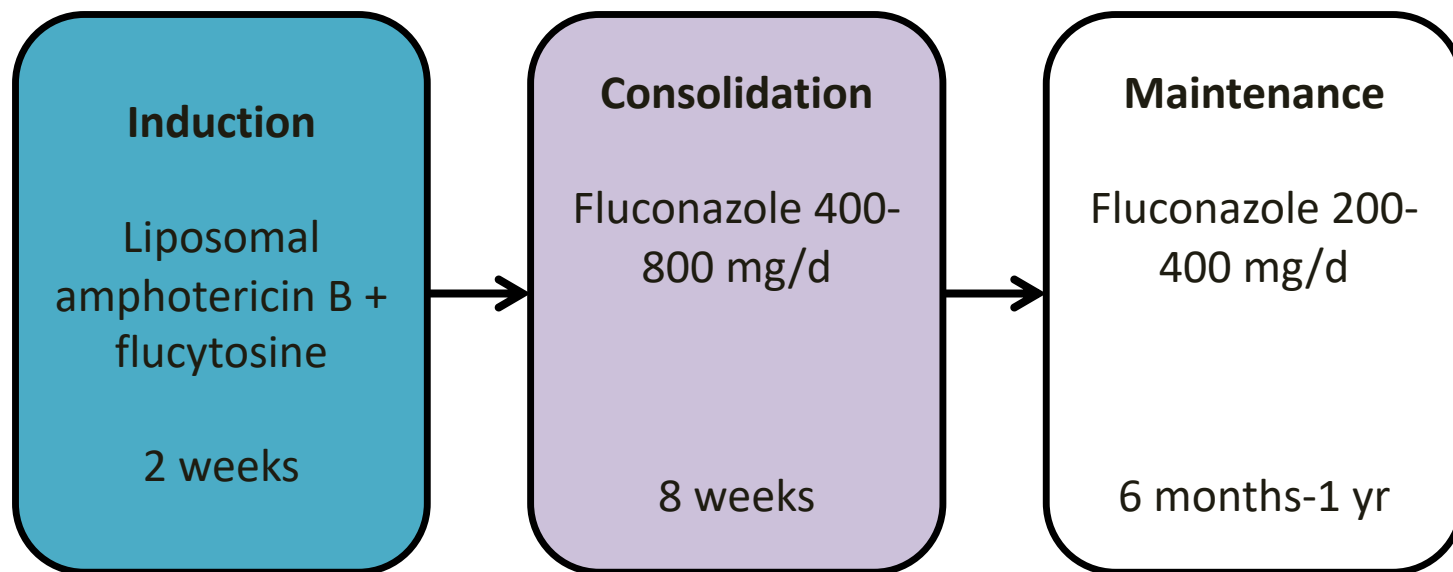
# Cutaneous Cryptococcosis



Most common: papulonodular lesions with umbilicated center resembling molluscum contagiosum

Fine HF, et al. *Arch Ophthalmol.* 2004;122(11):1726-1727

# Cryptococcosis: Treatment



Perfect JR, et al. *Clin Infect Dis*. 2010;50(3):291-322

## Question 2

Which of the following is the most appropriate therapy?

- A. Acyclovir (drug of choice for HSV encephalitis)
- B. Ampicillin (drug of choice for *Listeria* meningitis)
- C. Fluconazole (used for consolidation/maintenance, but inadequate for induction)
- D. Liposomal amphotericin B and flucytosine
- E. Trimethoprim/sulfamethoxazole (drug of choice for PJP and *Nocardia*)

## Question 3

- A 46 year old non-smoking woman with HIV presents with two weeks of dyspnea on exertion and non-productive cough. She was diagnosed with HIV five years ago and has intermittently received care. When last seen six weeks ago, she had a CD4 count of 185 cells/ $\mu$ L and a HIV RNA of 53,000 copies/mL. She has not been taking any medications and has not had recent travel
- On exam, temperature is 38.0 $^{\circ}$ C and oxygen saturation is 82% breathing ambient air. She has bilateral crackles and egophany. There are no rashes. A representative image from chest CT is shown





## Question 3

In addition to community-acquired pneumonia coverage, which of the following should be started?

- A. Acyclovir
- B. Amphotericin B
- C. Ganciclovir
- D. Trimethoprim/sulfamethoxazole
- E. Voriconazole

## Question 3

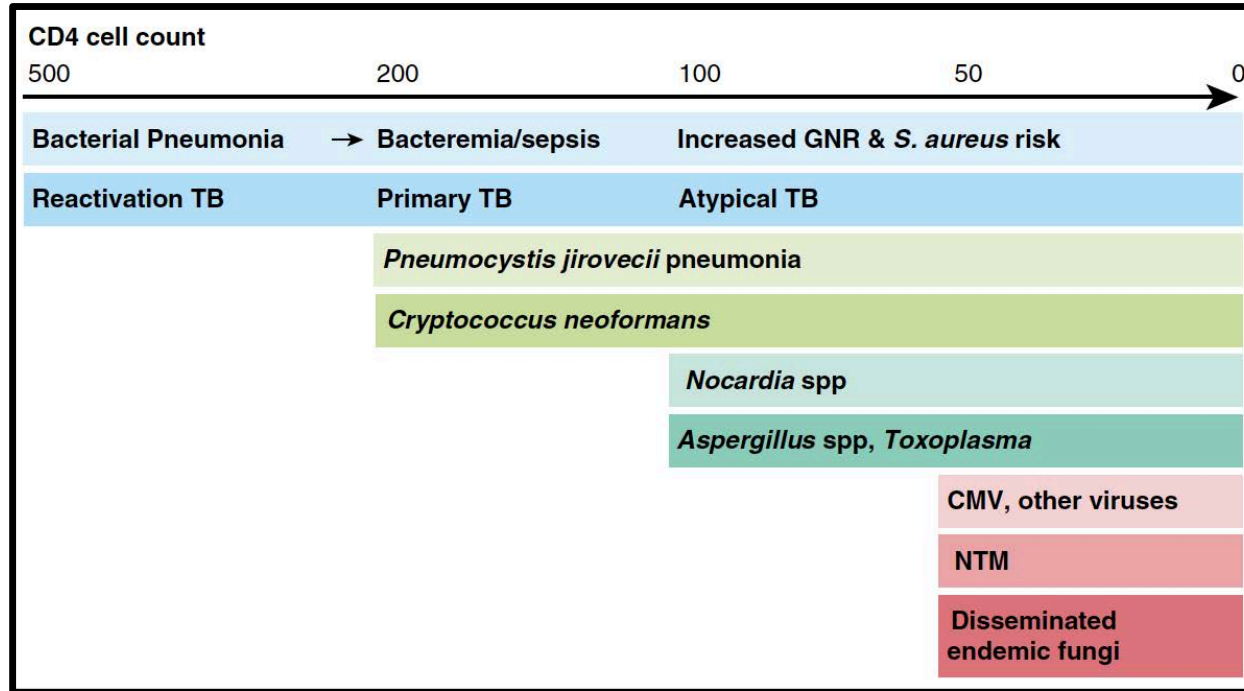
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- C. Ganciclovir
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In patients with HIV, the CD4 count correlates with infection risk

# Risk of Pulmonary Infection by CD4 Cell Count



Huang et al. *Respirology*. 2009;14(4):474-85

# Bacterial Pneumonia

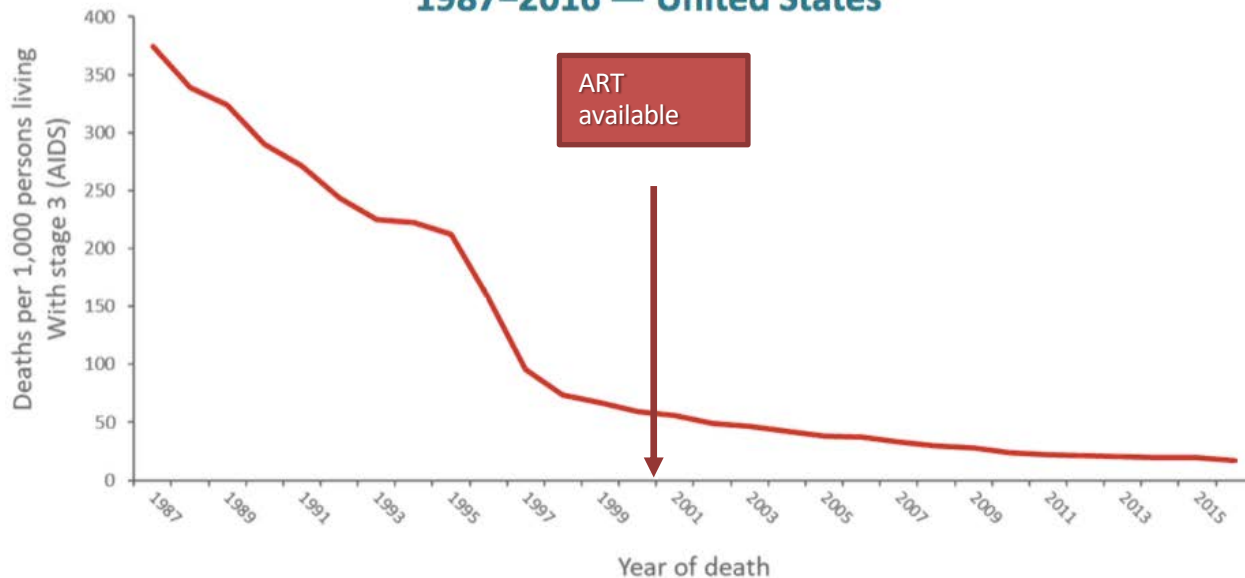
- Most frequent infection in HIV infected patients
- IVDU, smoking, older age, viral load, and previous recurrent pneumonia
- Can occur at any CD4 count, but incidence and severity increase as the CD4 count decreases
- Clinical presentation similar to non HIV infected patients
- CDC added recurrent pneumonia as an AIDs defining illness in 1992

# Bacterial Pneumonia

- *Streptococcus pneumoniae* most common cause
  - Effectiveness of vaccination controversial
- *Haemophilus influenzae* second most common
- *Pseudomonas aeruginosa* and *Staphylococcus aureus* can be seen as community acquired pathogen in these patients
- *Legionella* infection uncommon, but still more prevalent than in non HIV infected individuals and may portend a worse prognosis
- Other uncommon include *Rhodococcus equi* and *Nocardia* spp

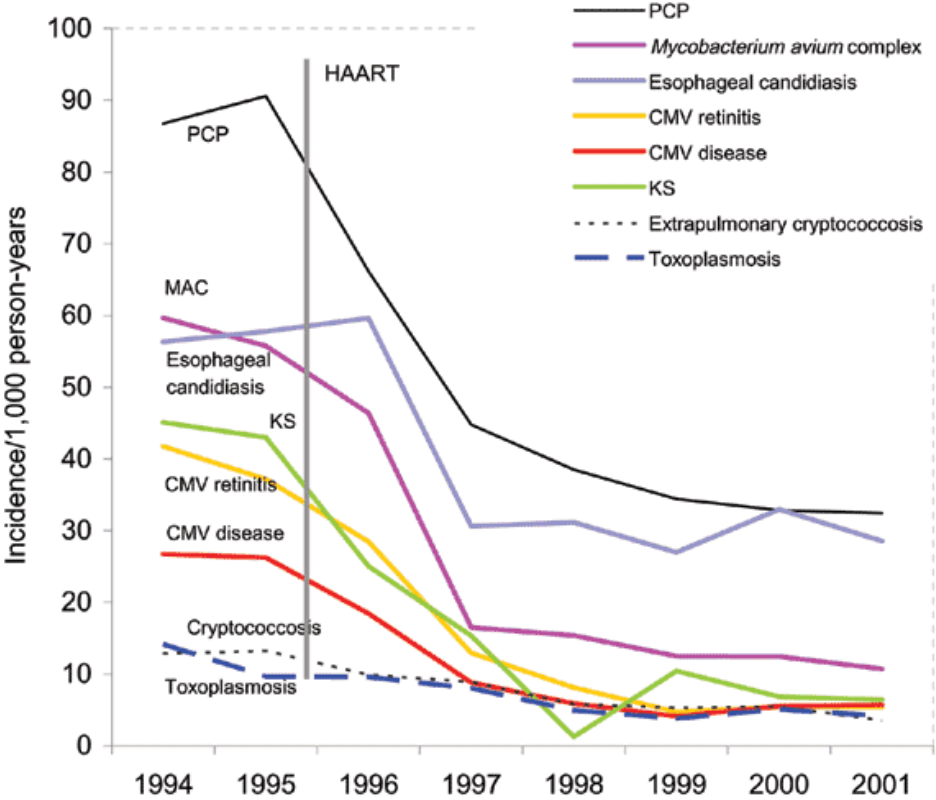
# Decline in HIV/AIDS Mortality Rates

## Trends in Annual Age-Adjusted\* Rates<sup>†</sup> of Death among Persons Living with Diagnosed HIV Infection Ever Classified as Stage 3 (AIDS) 1987–2016 — United States



\*Standard: age distribution of 2000 US population  
<sup>†</sup>Per 1,000 persons ever classified as having stage 3 infection (AIDS).

# Effect of ART on Incidence of Infections



Morris A, et al. Emerg Inf Dis Oct 2004  
<http://www.cdc.gov/ncidod/EID>



# HIV Chest Radiographic Patterns

## Focal

- bacteria, TB, PCP  
lymphoma

## Mediastinal LN

TB, MAC, KS, fungi,

## Diffuse

PCP, TB, bacteria,  
fungi, CMV, KS

## Pleural Effusion

bacteria, TB, KS, ↓albumin  
CHF, fungi, lymphoma (PEL)

## • Diffuse Nodules

- TB - miliary
- KS - large
- Fungi - small

## Cavities

TB (high CD4+),  
PCP, *R. equi*, Nocardia

# Pneumocystis Pneumonia

- PCP caused by *Pneumocystis jirovecii*, a ubiquitous fungus that shares some biological features with protozoa
- Use of routine prophylaxis and HAART have led to sharp decline in incidence, but still the most common AIDs defining illness
- HIV patients typically have a more subacute course and longer duration of symptoms

	HIV-Positive	HIV-Negative
Clinical	Subacute (weeks) Survival >80%	<b>Acute (&lt;1 week)</b> <b>Survival 50-90%</b>
Radiology	Diffuse bilateral opacities	Diffuse bilateral opacities
$\beta$ -D-Glucan	Sensitivity: 90-95% Specificity: 65-90%	Sensitivity: 90-95% <b>Specificity: 85-90%</b>
LDH	Sensitivity: 92-100% Specificity: 25-85%	<b>Sensitivity: 64-100%</b> Specificity: 25-85%
BAL microscopy	>90% sensitive (high organism burden)	<b>62-85% sensitive</b> <b>(low organism burden)</b>

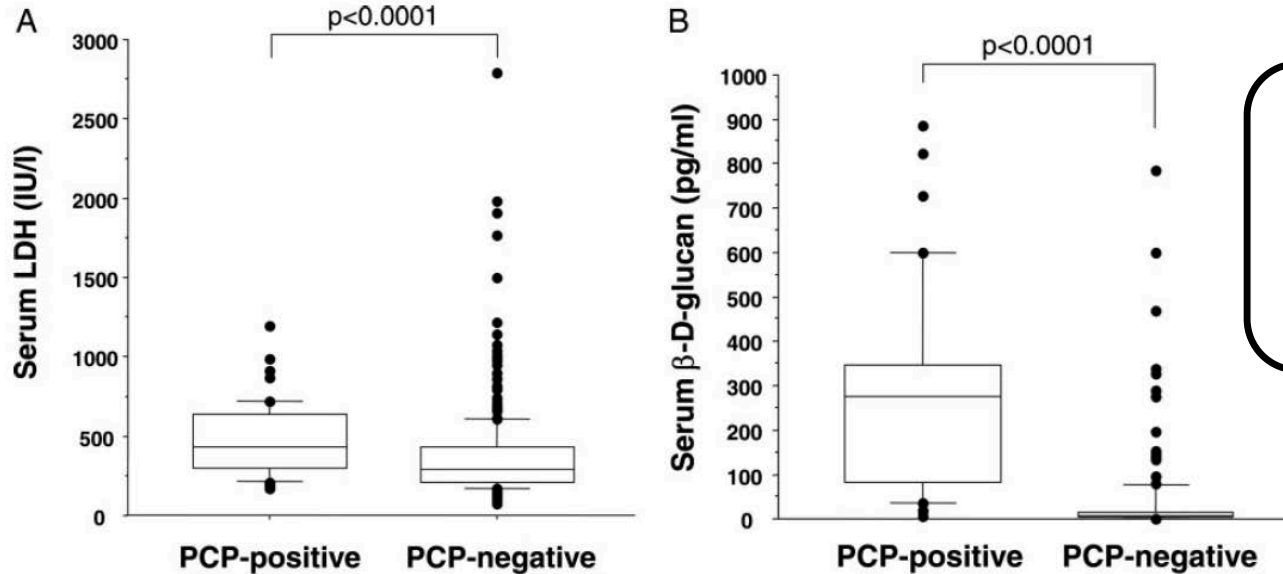
Tasaka S, et al. *Chest*, 2007;131(4):1173-80

deBoer MG, et al. *J Infect*. 2011;62(1):93-100

Tasaka S, et al. *J Infect Chemother*, 2012;18(6):793-806

- CXR is initially normal in many patients; eventually develop bilateral interstitial infiltrates emanating from the hila
- HRCT extremely sensitive for detecting PCP
- FOB with BAL preferred diagnostic procedure
- TMP-SMX remains DOC; adjunctive corticosteroids can be used in severe disease

*Pneumocystis* cannot be cultured; gold standard is staining



Serum biomarkers are suggestive but non-specific

Tasaka S, et al. *Chest*, 2007;131(4):1173-80

# TB in HIV Infected Patients

- HIV is currently the largest risk factor for developing TB disease
- Second most common opportunistic infection (may be most common in some geographic regions)
- May be new infection or reactivation, depending on geography
- Rates are lower when ART is initiated sooner
  - Ongoing viral replication a risk factor
- Presentation dependent on CD4 count; higher levels present with postprimary infection; lower counts will present with military/disseminated disease

# TB in HIV infected Patients

- Treatment principles similar to those in HIV- patients
- Can be complicated by drug interactions and overlapping toxicities, which can lead to subtherapeutic levels
- ART should be initiated as soon as TB therapy tolerated
  - This may lead to increased incidence of IRIS
  - One month of concomitant prednisone can reduce incidence

## Question 3

In addition to community-acquired pneumonia coverage, which of the following should be started?

- A. Acyclovir (CD4 not low enough for viruses, HSV pneumonia rare)
- B. Amphotericin B (radiographic pattern less consistent with fungal disease)
- C. Ganciclovir (CD4 not low enough for viruses, drug of choice for CMV)
- D. Trimethoprim/sulfamethoxazole
- E. Voriconazole (radiographic pattern less consistent with fungal disease)





Consider non-infectious complications of immunosuppressive medications

# Non-Infectious Complications

- Drug reactions
  - Consider and exclude infective and other potential causes
  - Establish a temporal relationship
  - Radiological findings are wide and include ARDS, NSIP, HP, and OP patterns
- Lymphoproliferative disorder
  - Often related to EBV
  - Multiple bilateral nodules/masses, lymphadenopathy and patchy air space opacification are common

# Non-Infectious Complications

- Rejection
  - Acute rejection: Volume loss and septal thickening fl/pleural effusion
  - Chronic rejection: BOS mosaic attenuation, air-trapping, and bronchial dilatation
- Alveolar hemorrhage
  - High mortality. Bilateral infiltrates on radiographs,
  - bilateral ground-glass opacification and consolidation on HRCT
  - Hemoptysis is not always a feature.
- Pulmonary edema/emboli
  - Remember PE and pulmonary edema as a cause for respiratory symptoms

- Neoplastic
  - Kaposi's sarcoma (almost exclusively in MSM)
  - Lymphoma, usually B-cell
  - Primary effusional lymphoma: “liquid lymphoma”, associated with HHV-8, poor prognosis
  - Lung cancer (adenocarcinoma)

# PAH in HIV

- WHO Group 1
- 1/200 cases of HIV infection
- Not related to HIV infection of pulmonary vascular endothelium
- NOT associated with HHV8
- Unrelated to CD4+ count
- Treat as other Group 1 PAH

# Immune Restoration Inflammatory Syndrome (IRIS)

- “Unmask” current or latent infection
  - CMV: retinitis, uveitis, vitritis, colitis, pancreatitis
  - MAC: lymphadenitis, adrenals, skin
  - Hepatitis C: acute hepatitis
- “Paradoxical worsening” TB, PCP, cryptococcal meningitis, Kaposi sarcoma
- Sarcoidosis

# Summary

- Type of immune deficiency is paramount
- Timing of symptoms post-transplant (SOT or HSCT) helps narrow the DDX
- Radiographic patterns are helpful
- Consider non-infectious etiologies as well

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