

Post liver transplant infectious complications

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Objective

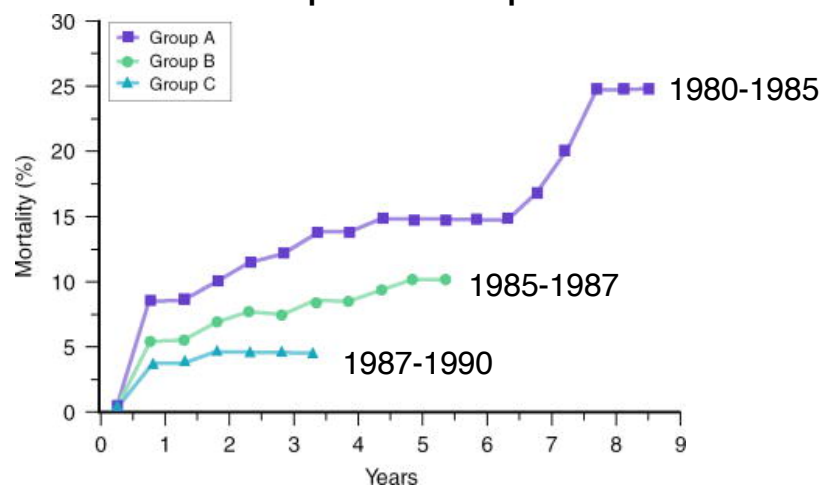
- Discuss the immediate post-operative and long-term management of liver transplant recipients

General pearls

- **Liver transplant** patients with infections
 - are often sicker than they look
 - often have more extensive disease than is apparent
 - may require longer treatment than others
 - may have unusual infections

Infection-related mortality

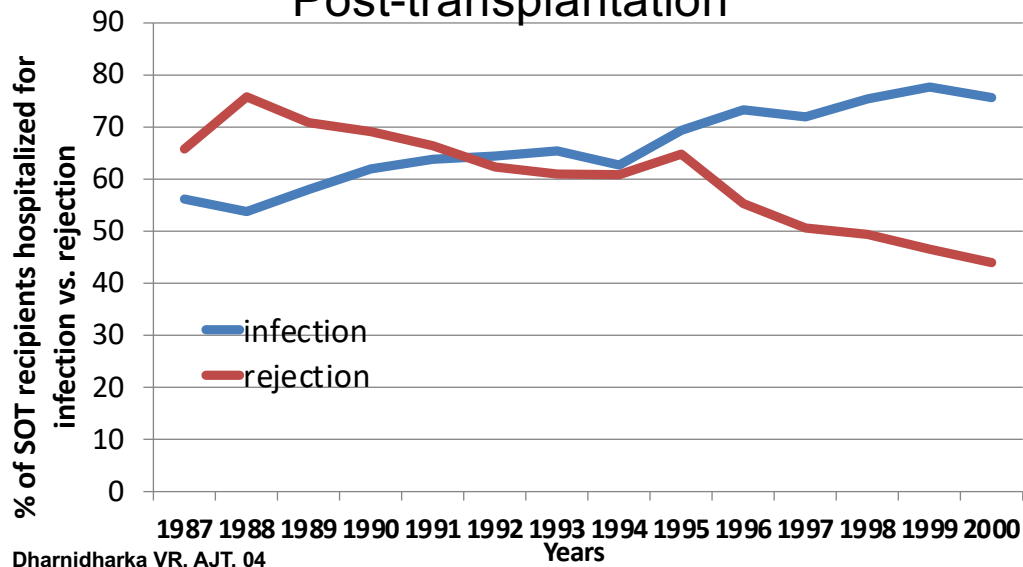
Heart transplant recipients



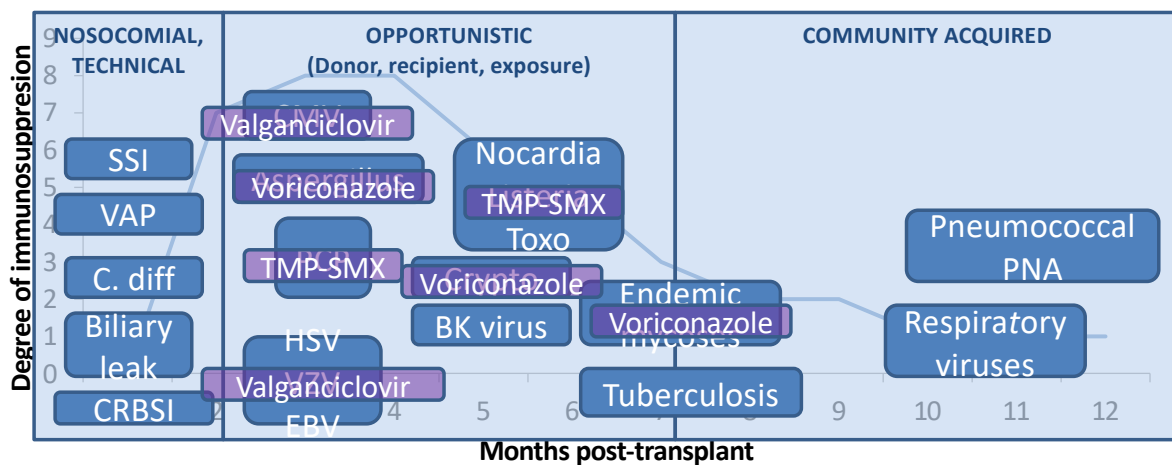
Dummer JS, In Kaye MP et al eds, Heart and Lung transplantation 2000

Indication for hospitalization

Post-transplantation



Infection Treatment for rejection



Aspergillus

Clinical

- Colonization
- Allergic bronchopulmonary aspergillosis (ABPA)
- Aspergilloma (fungus ball)
- **Invasive pulmonary aspergillosis (immunocompromised)**
 - Sinus
 - Lung (nodules)



Aspergillus rhinocerebral disease

Aspergillus

Diagnosis

- Risk factors: immunocompromised
- **Radiology: CXR, CT chest with nodules**
- Non-culture tests: Galactomannan (Antigen) assay
- Pathology. Biopsy: septate hyphae, acute angle branching
- Microbiology (cultures)



Multiple pulmonary nodules

Aspergillus

Diagnosis

- Risk factors: immunocompromised
- Radiology: CXR, CT chest with nodules
- **Non-culture tests: Galactomannan (Antigen) assay**
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N=160	Sensitivity	Specificity
Serum	47	93
BAL	85	100

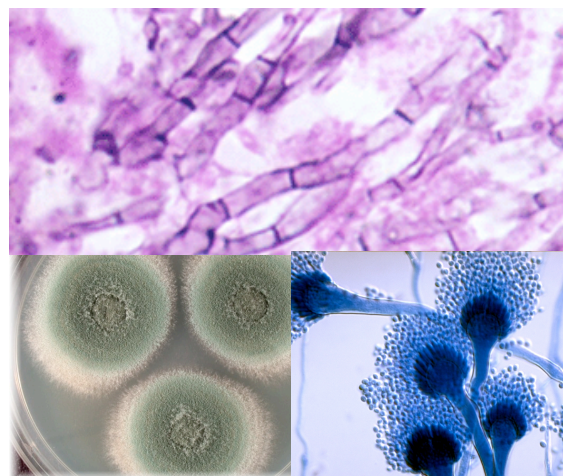
Becker et al, Br J Haematology, 2003; 121:448

D'Haese J et al, J Clin Microbiol, 2012; %0:1258

Aspergillus

Diagnosis

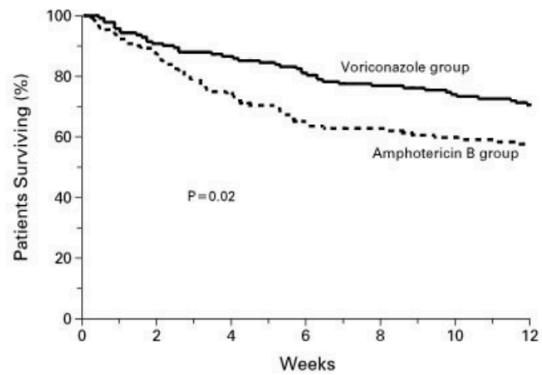
- Risk factors: immunocompromised
- Radiology: CXR, CT chest with nodules
- Non-culture tests: Galactomannan (Antigen) assay
- **Pathology. Biopsy: septate hyphae, acute angle branching**
- **Microbiology (cultures)**



Hyphae, plate colonies and conidia

Aspergillus Treatment

- Treatment
 - **Voriconazole**
 - \pm Echinocandin
 - Isavuconazole
 - \pm Echinocandin

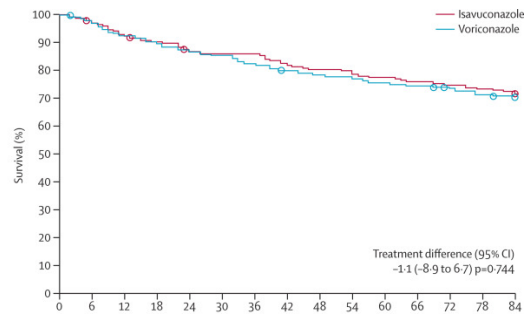


Voriconazole vs. Amphotericin B

Herbrecht et al. NEJM 2002: 347

Aspergillus Treatment

- Treatment
 - Voriconazole
 - \pm Echinocandin
 - **Isavuconazole**
 - \pm Echinocandin

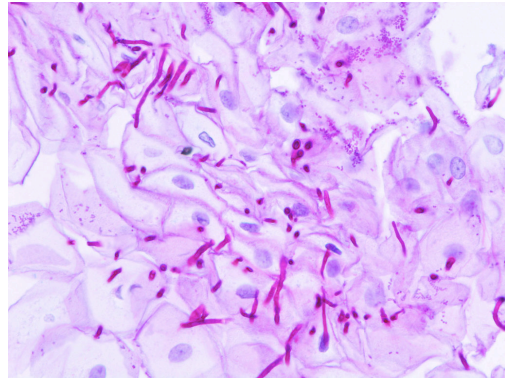


Voriconazole vs. Isavuconazole

Maertens JA et al. Lancet 2015 Dec 9.

Fungus

Organ Transplanted	Incidence (%)
Liver	7-42 (most candida)
Pancreas	18-38
Heart-Lung/Lung	15-36
Heart	5-32
Kidney	1-14



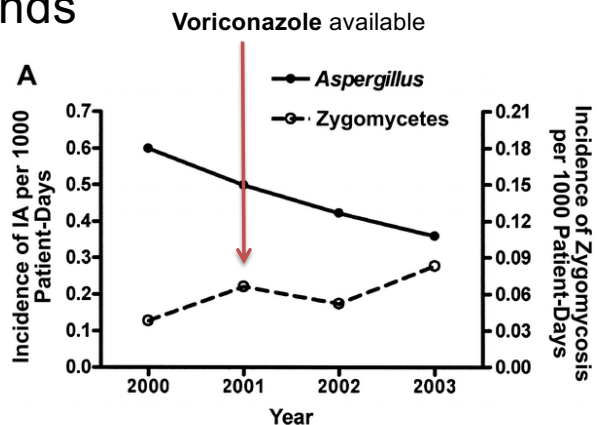
Esophageal candidiasis

Singh, CID 2000:31

Paya, CID 1993:16

Fungus Trends

- Spectrum of fungus is changing dramatically:
 - ↓ *Aspergillus* infections 70%
 - Prior studies in 1990s: 98%
 - ↑ **Non-*Aspergillus* mold infections 30%**
 - *Scedosporium*, *Fusarium*, *Zygomycetes*, *Phaeohyphomycetes*
 - Prior studies in 1990s: 2%



Singh et al, Transplantation 2002:73

Kontoyiannis et al, JID, 2005

Lum et al, Transpl Infect Dis 2020

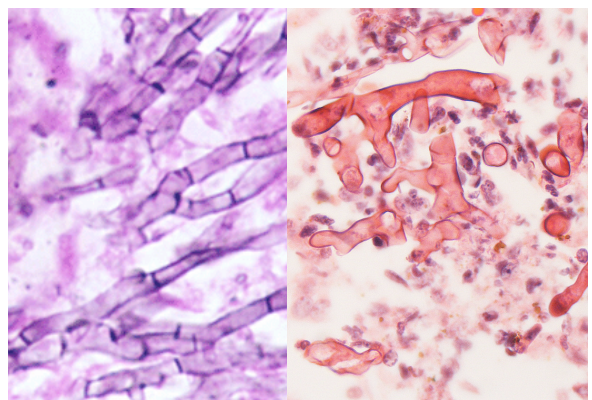
Case

- 57 year-old female s/p liver transplant recently treated for rejection with thymoglobulin presents with DKA and L eye proptosis
- Biopsy shows non-septate hyphae at 90°
- Diagnosis?
- Treatment?



Case

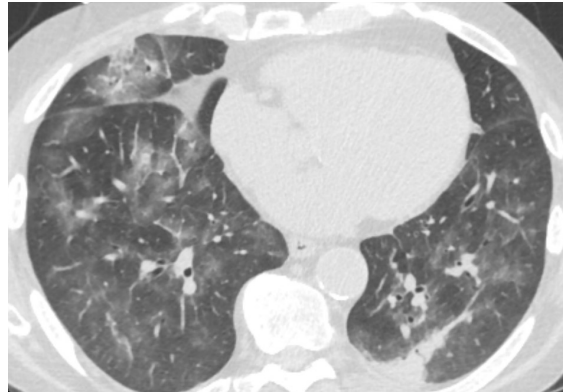
- 57 year-old female s/p liver transplant recently treated for rejection with thymoglobulin presents with DKA and L eye proptosis
- Biopsy shows non-septate hyphae at 90°
- Diagnosis? **Mucormycosis**
- Treatment? **Surgery & Amphotericin B**



Aspergillus (left) vs Mucor (right)

CMV



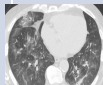
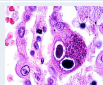
- Most important infection in SOT recipients
- Infects 60-100% of humans by adulthood
- Immunocompetent hosts: 1° infection is often asymptomatic, virus then remains latent
- In SOT recipients infection is due to
 - 1° infection from donor graft D+/R-
 - Reactivation in setting of immunosuppression (esp. T cell depleting agents)



Chest CT showing diffuse ground glass opacities

CMV

Clinical

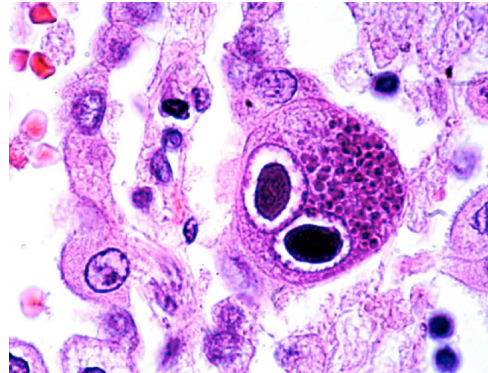
	PCR	Clinical	
Asymptomatic CMV viremia	+	No symptoms	
CMV syndrome	+	Fever, malaise, myelosuppression	
CMV with end-organ disease	+	Pneumonia , hepatitis, colitis , retinitis, CNS	
Compartmentalized CMV disease*	-	Pathologic evidence of end-organ disease	

*Consider colonoscopy in high-risk patient with negative CMV PCR who is having diarrhea to r/o compartmentalized CMV disease

CMV

Diagnosis

- Viral culture
 - Slow, ↓Specificity
- Serology
 - Detects antibody
 - CMV risk assessment pre-transplant
 - Highest risk D+/R-
- PCR
 - Detects DNA
 - Fast, ↑Sensitivity (but ↓specificity if low VL)
- Histology
 - Sensitive and specific



“Owl’s eyes” inclusion bodies of CMV

CMV

Treatment

- What kind of CMV? Asymptomatic viremia? CMV syndrome? Organ disease?
- In general:
 - Start with **valganciclovir 900 BID** (induction)
 - IV ganciclovir if severe or if bad GI disease
 - Minimum **2 weeks** (3 weeks for GI) if PCR undetectable
 - **Cidofovir** or **foscarnet** if resistant CMV
- Nitpicky pearls:
 - Cutoff for treating **asymptomatic** viremia: **1500 IU/mL**
 - **No routine secondary prophylaxis**. Can monitor high-risk patients x 3 months (pre-emptive)



CMV Prevention

Focus on D+R- for CMV prophylaxis

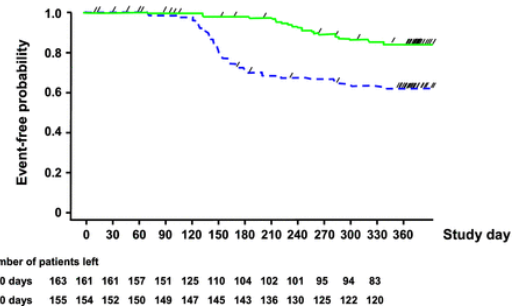
Risk	D	R	% Symptomatic Disease*
High	+	-	60%
Mod	+	+	10-30%, up to 50% with ALA**
Low	-	-	0-4%

D Donor CMV Ab, R Recipient CMV Ab

*Incidence of symptomatic disease if no prophylaxis

**Anti-lymphocyte antibodies

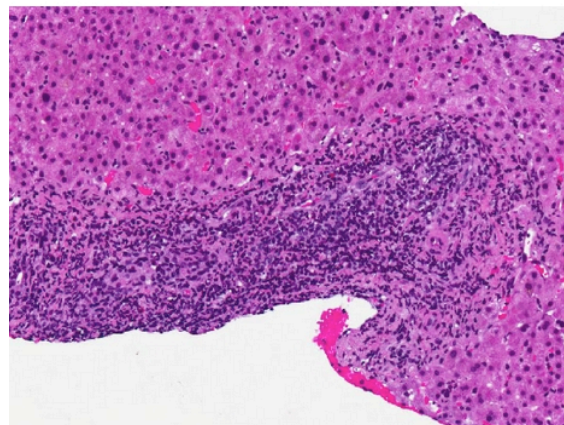
And for 6 months



Humar A et al, 2010, Am J Transplant. 2010 May;10(5):1228-37

Bonus Case

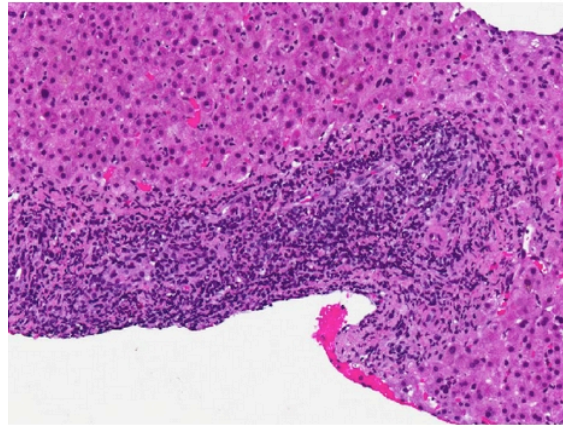
- 40 year-old male 3 months s/p liver transplant in Asia (Hep B hepatocellular CA) on tacrolimus, mycophenolate and prednisone presenting with persistent ↑LFTs
- Serology and blood PCR negative for EBV, CMV, HSV, HBV, HCV, parvovirus, HHV-6
- Biopsy shows moderate acute cellular rejection vs hepatitis with no viral inclusions
- Diagnosis?
- Treatment?



Marked portal inflammation with mixed lymphoplasmacytic infiltrate

Bonus Case

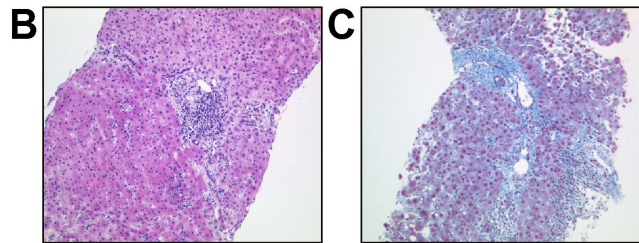
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- Serology and blood PCR negative for EBV, CMV, HSV, HBV, HCV, parvovirus, HHV-6
- Biopsy shows moderate acute cellular rejection vs hepatitis with no viral inclusions
- Diagnosis? **Hepatitis E infection**
- Treatment? ↓**Immunosuppression, antivirals**



Marked portal inflammation with mixed lymphoplasmacytic infiltrate

HEV

- Chronic HEV almost always in immunocompromised
- 50-70% of those affected post-transplant develop chronic HEV
- Can progress to cirrhosis
- Dx: Detection of serum HEV RNA >6 months
- May be mistaken for rejection
- Rx: ↓**Immunosuppression, ribavirin**



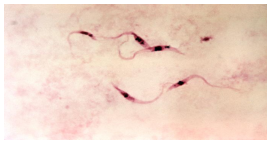
B: 5 months s/p OLT with portal hepatitis

C: 12 months s/p OLT with persistent hepatitis and fibrosis

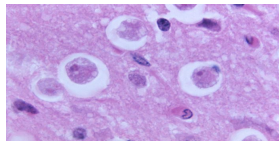
Schlosser et al, J Hepatology 2012:56
Kamar et al, Gastroenterology, 2011:140

Case

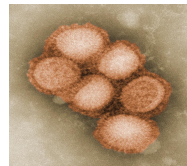
Which of these organisms is safe to transplant?



T. cruzi



Naegleria



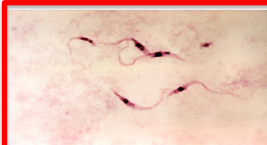
H1N1



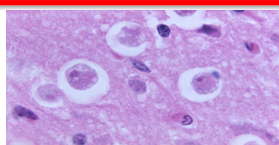
Strongyloides

Case

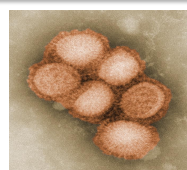
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T. cruzi



Naegleria



H1N1



Strongyloides

Chin-Hong et al, Am J Transplant. 2011; (11)4
Roy et al, Am J Transplant. 2014; (14)1
Kumar et al, Am J Transplant. 2010; (10)1
Chin-Hong et al, ATC 2013

Don't forget about donor-derived infections

