Nosocomial Bacterial and Fungal Infections in Critically Ill Transplant Recipients

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Principles of Bacterial Infections in Organ Transplant Recipients

- Organ Specific Sites of Infection
- Multi-drug Resistant Pathogens
- Unique Aspects of Presentation
- Interrelatedness of risk factors for bacterial and fungal infections, such as cmv infection, surgical technical factors, and renal failure

Organ Specific Bacterial Infections

Organ	Infection
Kidney	Complex Urinary Tract Infections
Liver	Biliary Sepsis, Hepatic Abscess
Small Bowel	Intraabdominal Sepsis
Lung	Pneumonia
Heart	Mediastinitis
Pancreas	Pancreatic Abscess, Biliary sepsis

Nosocomial Bacterial Pathogens of Concern in Solid OrganTranspantation

- *S. aureus*
- Vancomycin Resistant Enterococci
- *C. difficile*
- ESBL producing Klebsiella and *E. coli*

Decline in Bacteremia in relation to Organ Transplantation

- Tufts New England Medical Center

  Over 5 year period about 40% decline in bacteremia in liver transplant recipients
- Heart Transplant Program in Madrid

  67% decline

One factor may be control of CMV

Effect of Ganciclovir Prophylaxis on Bacteremia in Liver Transplant Recipients

Multivariate Analysis of Risk Factors for Bacteremia

Factor	HR (95% CI)	P Value
Choledocochole-docostomy	0.39 (0.19-0.82)	0.01
Ganciclovir ≥ 14 d	0.44 (0.20-0.98)	0.04
< 10 units RBC's	0.31 (0.12-0.82)	0.02

Munoz-Price LS, Slifkin M, et al Clin Infect Disease 2004: 39: 1293-9.

Bacteremia in Heart Transplant Recipients

Blood Stream infection incidence has declined from 21% to 7.5%

Mortality associated with BSI (OR 1.8, 95% CI 1.2-2.8)

Risk Factors for Bloodstream infection

Hemodialysis (OR 6.5, 95% CI 3.2-13)

Prolonged ICU Stay (OR 3.6, 95% CI 1.6-8.1)

Viral Infection (OR 2.1, 95% CI 1.1-4.0)

Rodriguez C, et al Transplant 2006; 81: 384-391

Vancomycin Resistant Enterococcal Colonization and Infection in Liver Transplant Recipients

- Colonization Pretransplant - 13%
- Acquisition of VRE post transplant - 18%
- VRE colonization associated with 8x increased likelihood of VRE infection
- Bacteremia most common infection
- Colonized patients have 6 d longer ICU stay
- Colonized patients have higher mortality at 90 days 16% versus 9%
- VRE acquistion post transplant associated with higher mortality (OR: 4.9 (95% CI 1.2-19.3)

McNeil et al Clin Infect Dis 2006;42: 195-203

Vancomycin Resistant Enterococcal Colonization and Infection Awaiting Liver Transplantation

Factors Associated with acquisition of resistance in liver transplant recipients

- Admitted to liver unit
- Proton pump inhibitor
- Antibiotics (anti-anaerobe, others)
- Length of stay
- ICU stay
- ERCP
- Paracentesis

McNeil et al Clin Infect Dis 2006 42: 195-203

Vancomycin Resistant Enterococcal Infection in Liver Transplant Recipients

From Univ of Cincinnati group

- VRE infection associated with more abdominal surgery
- More frequent biliary complications
- Higher mortality (48% v 18%)
- Increased cost

Gearhart M, et al. Clin Transplant 2005; 19: 711-716

Infected Bilomas in Liver Transplant Recipients

Risk Factors	OR	(95% CI)	pValue
Hepatic artery thrombosis	90.9	(6.1-500)	< 0.001
Hepatic artery stenosis	13.1	(3.2-52.6)	< 0.001
Roux en Y anastomosis	5.8	(1.2-27.7)	0.03
Ursodiol Use	0.1	(0.0-0,4)	<0.001

Said A, et al. Amer J Transplant 2004; 4:574-82

Infected Bilomas in Liver Transplant Recipients

Microbiologic Findings

Early	Late
Enterococci (37%)	Enterococci (53%)
(VRE 48%)	(VRE 83%)
Coag neg Staph (26%)	Candida (79%)
Candida (26%)	Resistant Gram Negatives (35%)

Infected Bilomas in Liver Transplant Recipients

Risk Factors for Mortality

- Pretransplant Renal Disease
- Infection with Candida
- Infection with Multidrug Resistant Gram negative organisms

Staphylococcus aureus Infection in Liver Transplant Recipients

- 20% of Liver Transplant Recipients develop S. aureus infection (57% MRSA)

Risk Factors for infection

- MRSA colonization
- MSSA colonization
- Alcoholic cirrhosis
- Prolonged prothrombin time

Bert F, et al. Liver Transplant 2005; 11: 1093-99

Staphylococcus aureus Infection in Liver Transplant Recipients

- Increase in MRSA infections in Pittsburgh VA program from 1990-1998
- Early onset infections
- High mortality for deep-seated infections
- Correlation with primary CMV infection

Singh N, et al. Clin Infect Dis 2000; 30: 322-7

Clostridium difficile infections in Solid Organ Transplant Recipients

- Incidence of *C difficile* in transplant recipients has increased from 5% to 27%
- Overall rate 15%
- Recurrent *C difficile* 14%
- Risk Factors for *C. difficile*

  Age

  Liver Transplant

  ATG induction

Mortality for Complicated *C.difficile* (graft loss, total colectomy, or death)= 72%

Colectomy had best survival

Boutros M, et al Abstract 2751, WTC, Boston, 2006

Sepsis in Renal Transplant Recipients

- Analysis of 19, 992 renal transplants from 1995-2000 from ESRDS data base
- Overall rate of 6.9% of patients
- Timing of Sepsis
  - 8.8 per 100 patient years first 3 months
  - 3.1 per 100 patient years months 6-12
  - 2.3 per 100 patient years for years 1-3
- Mortality rate - 13%
- Major Cardiovascular events in association – 13%

Gill JS, et al Abstract 2686, WTC 2006

Sepsis in Renal Transplant Recipients

Adjustment for patient age, gender, race, BMI, cause of ESRD, donor source, dialysis vintage, multi-organ transplant, delayed graft function, and albumin at time of transplant

Patients with Sepsis had:

Increased risk of graft loss (HR 2.3, 95% CI 2.1-2.5)

Death with graft function (HR 3.5, 95% CI 3.0-4.0)

Use of Activated Protein C in transplant recipients

Experience in U Pittsburgh ICU demonstrates that APC can be given despite thrombocytopenia and coagulopathy

18/38 (48%) had coagulopathy

6/38 (16%) had hemorrhage requiring discontinuation of APC

28 day survival 79%

69% able to be discharged

Linden PK Abstract 2750, WTC 2006

Invasive Fungal Infections in Solid Organ Transplantation

- Rates are decreasing due to surgical technical factors, changes in immunosuppression, control of Cytomegalovirus, use of prophylaxis
- Examination of clinical trial cohorts of OLT

  Rates of 29% in early 1980's have fallen to less than 5% in late 1990's in several trials encompassing all transplanted patients

Analysis of ESRDS Database for Fungal Infections

33,240 Recipients

- Primary Diagnosis

  5.22 episodes per 1000 patient years at risk

- Secondary Diagnosis

  10.79 episodes per 1000 patient years

Hospitalization: 21% within 2 months of transplant, 66% within a year, 76% at one year

Abbott KC, et al. Transplant Infect Dis 2001; 3: 203-11

Analysis of ESRDS Database for Fungal Infections

Sites of Infection

Site	%
Candida esophagitis	22%
Pneumonia	20%
Aspergillus	9%
Candida	6%
Other Mycoses	5%
Urogenital Candida	10%
Meningitis	8%
Disseminated Candida	5%

Analysis of ESRDS Database for Fungal Infections

Fungal Etiologies for hospitalization

Candida	83.5%
Aspergillus	6.8%
Cryptococcus	4.3%
Unspecified	1.6%
Coccidiomycosis	1.9%
Zygomycosis	0.8%
Histoplasmosis	0.5%

Analysis of ESRDS Database for Fungal Infections

Factors Associated with Hospitalization for Fungal Infection

- Diabetes
- Rejection
- Maintenance Tacrolimus
- Years of Pretransplant Dialysis and > 4 years of pretransplant dialysis
- Year of Transplant (risk reduction)

Risk Stratification for Fungal Infection in Liver Transplant Recipients

High Risk Patients have 2 or more factors

- Choledochojejunostomy
- Retransplantation
- Anastomotic Leak
- Intraoperative Blood Transfusions > 40 units or return for intraoperative bleeding
- Serum Creatinine > 2 mg/dl
- Perioperative Candida Colonization

Pappas PG, et al Amer J Transplant 2006; 6: 386-91.

Risk Stratification of Fungal Infection in Liver Transplant Recipients

Others have shown a relationship between invasive fungal infection and

- Bacteremia
- Cytomegalovirus infection
- Prolonged Operative time (> 8 hrs)
- Post operative renal failure requiring dialysis
- Intensive Care Unit pretransplant stay
- Use of broad spectrum antibiotics

Prospective Observational Cohort Study of Low Risk Of Invasive Fungal Infection in Liver Transplant Recipients

- Invasive Fungal infection – 4%

  Candida in 3 patients (2%)

  Aspergillus in 3 patients

Of those with Candida in retrospect 2 fell into high risk after transplantation and could have benefited from prophylaxis

Prevention of Invasive Fungal Infection in Solid Organ Transplant Recipients

Cochrane Database Conclusions

- Significant reduction in invasive fungal infections 72% reduction (95% CI 43%-87%) for fluconazole (liver transplant recipients)
- Less data available for intraconazole, and liposomal amphotericin B
- Fluconazole use did not increase fungal infections with fluconazole resistant fungi
- Renal and cardiac transplants limited data for comparisons
- No impact on mortality

The Cochrane Database of Systematic Reviews 2006

Case Control Study of the Spectrum of Invasive Candidiasis in Liver Transplantaton

Risk Factor	OR	(95% CI)
Prophylaxis for SBP	11.0	(3.0-33.8)
Retransplantation	11.0	(3.3-36.4)
Post trans dialysis	8.0	(3.1-20.0)
CMV viremia	3.0	(1.2-7.3)

1/3 Non Albicans species, these were less likely to have anti-fungal prophylaxis, and have a higher mortality

Husain A, et al Transplantation 2003; 75: 2023-29

Observational data from Prospective Liver Transplant Data base

- Florida Group Analysis
- 1150 Transplants/1047 patients over 15 years
- High risk defined as retransplant, reop for bleeding, or bile duct complication first month, preop dialysis, fulminant hepatic failure, or recent fungal infection
- High risk invasive fungal infection – 19.1%
- Invasive fungal infection in low risk - 4%
- Prophylaxis with 5 days of ABLC once risk identified – 6.9%

Reed A, et al Abstract 1122 WTC, July 2006

Risk Factors for Invasive Aspergillosis after Heart Transplantation

Retrospective Analysis of Risk Factors for Invasive Aspergillosis

- **Reoperation (RR 5.8, 95% CI 1.8-18)**
- **CMV Disease (RR 5.2, 95% CI 2-13.9)**
- **Post Transplant Dialysis (RR 4.9, 95% CI 1.2-18)**
- **Invasive Aspergillosis prior to Transplant (RR 4.6, 95% CI 1.5-14.4)**
- **Itraconazole Prophylaxis (RR 0.2, 95% CI 0.3-0.8)**

Dose 600 mg per day x 4 d, then 400 mg daily

Munoz P, et al. Amer J Transplant 2004; 4: 636-43

Emergence of Non Aspergillus Mycelial Mold Infections

- Approximately 30 % of “mold like” infections are not Aspergillus

  Species such as Fusarium, Scedosporium, Cladophialophora, Exophiala, Rhizopus
- More likely to be disseminated
- More likely to infect central nervous system
- High mortality but not different than Aspergillus

Husain S, et al. Clin Infect Dis 2003; 37: 221-9

Combination of Voriconazole and Caspofungin for Primary Aspergillosis

Observational Multicenter Trial

Results difficult to interpret

Controls treated with lipid ampho B

Authors suggest that for subsets of those with A. flavus and renal failure may benefit from this combination

CMV infection and renal failure independently associated with increased risk for mortality

Singh N, et al Transplantation 2006; 81: 320-6

Prospects for the future for fungal infections in Solid Organ Transplant Recipients

- New Diagnostic Techniques
  - Molecular Diagnosis for Aspergillus
  - Galactomannin utility
- Risk Stratification methodology
- Treatment of Established Disease
  - Combination Therapy
- New Antifungals
  - Posaconazole
  - New Echinocandins