Infectious Diseases in Transplantation

Janis E. Blair, MD
Division of Infectious Diseases
Mayo Clinic Scottsdale

Outline

- Impact of Infections
- Risk of Infections
- Timeline of Infection
- Overview of Major Pathogens
- Specific Infections among various Types of Transplantation
- Infection Prevention

Impact of Infections on Transplantation

- **Infections are a leading causes of morbidity and mortality in all transplantation.**
- **More than 50% of all organ recipients have active infection post transplant**
  - **Direct effects of infection**
  - **Indirect effects of cytokines, growth factors**
    - **global depression of host defenses**
    - **opportunistic superinfection**
    - **allograft injury**
    - **contribute to some malignancies**

Challenges In Transplant Related Infections

- Diversity of organisms is greater than in the general population
- Rate of progression of infection is greater
- Immunosuppression may obscure signs and symptoms
- Emphasis on preventing infection

Risk of Infection

- Interaction of 3 factors
  - Epidemiological exposures of the patient
  - Prophylaxis
  - Net state of immunosuppression

Risk of Infection-1
Epidemiologic Exposures

- History of:
  - Hospitalization?
  - Ill persons in household?
  - Cocci or other endemic fungal infection?
  - TB exposures, ever?
  - Travel overseas, Mexico?
  - Military, location?
  - Travel related illnesses?
  - City, suburb, rural home?
  - Pets, birds, livestock, rodents, reptiles, aquarium, insect bite/attach?
  - STDs?
  - HIV risk behavior?
  - Outdoors activities?
  - Raw meat/dairy? What is water source?
  - Hobbies?
  - Types of employment?

Risk of Infection-2

Prophylaxis

- TMP/SMX
  - PCP, nocardia, others
- Acyclovir
  - HSV
- Valganciclovir
  - CMV
- Pyrimethamine/sulfa
  - Toxoplasmosis
- Fluconazole
  - Cocci, candida

- Note: each program may have a different schedule of prophylaxis

Risk of Infection-3

- Net state of immunosuppression
  - Dose, duration and sequence of medications
  - Defects in host defenses by underlying disease
  - Neutropenia
  - Defects in mucocutaneous barrier
  - Indwelling foreign bodies
  - Metabolic derangements
  - Immunomodulating viruses

Immunosuppressive Agents

- Corticosteroids
- Calcineurin inhibitors
- Antiproliferative agents
- Antibodies
- Miscellaneous

Immunosuppressive Agents

- Corticosteroids
  - Alter a broad range of normal immune functions:
  - Humoral immunity
  - Cellular immunity
  - Wound healing
  - Inflammatory responses
- Infections:
  - Bacterial, fungal, viral, opportunistic

Immunosuppressive Agents

- Cyclosporin, tacrolimus
  - Inhibit T cell activation, suppresses humoral immunity, DTH, GVHD
- ID implications
  - Vaccinations less effective
  - Difficult to interpret skin tests
  - Infections: Fungal, CMV/other viral, bacterial
  - Drug interactions

Immunosuppressive Agents

- Mycophenolate moffetil (Cellcept, Myfortic)
- Potent anti-proliferation effect on T&B lymphocytes
- Neutropenia
- Infections
  - Herpesvirus infections

Immunosuppressive Agents

- Sirolimus (Rapamune)
- Inhibits T&B cell, NK and LAK cells activation and proliferation
- Novel mechanism.
- Opportunistic infections, fatal infections, sepsis

Immunosuppressive Agents

- Polyclonal Antibodies
  - Profound lymphocyte depletion
  - Thymoglobulin (antithymocyte globulin/rabbit)
  - Antilymphocyte globulin (horse)
- Monoclonal OKT3
  - Murine anti CD3, rapidly depletes Tcells
- Common a/e: fever, chills, hTN, leukopenia
- Opportunistic infections

Immunosuppressive Agents

- Chimeric or humanized recombinant anti-IL-2 monoclonal Abs
  - Dacluzumab (Zenapax), basaliximab (Simulect)
  - Inhibits the IL-2 mediated activation of T cells
  - Impaired wound healing, cellulitis; no added infectious risks

Timing of Infections in Transplantation

- Most clinically important infections occur in the first 3-4 months
- Convergence of many factors:
  - Underlying disease
  - Major surgery
  - ICU stays, sometimes prolonged
  - Heavy immunosuppression
  - Nosocomial infections/colonizations

Timeline of Infections

- First month
- Months 1-6
- Greater than 6 months

Timeline of Infections
First Month

- Post op nosocomial bacterial or fungal (90%)
  - Pneumonia, UTI, vascular-access devices
  - Surgical site infections

Timeline of Infections
First Month

- Untreated recipient infection present prior to transplant
  - Pneumonia
  - UTI,
  - HSV reactivation

Timeline of Infections
First Month

- Allograft derived
  - Donor bacteremia, fungemia, or viremia may seed the organ
    - HIV, WNV, CMV, others
    - Candida, Cocci

Timeline of Infections
Months 2 - 6

- Residual effects from 1st month, surgical site issues
- Effects of immunomodulating viruses
    - CMV
    - EBV, other HHVs, HBV, HCV, HIV
- Opportunists
    - Pneumocystis, aspergillus, listeria, mycobacteria
    - Toxoplasmosis, Strongyloidiasis, endemic fungal infections

Timeline of Infections
6 months and beyond

- Infection profile depends on the recipient category:
  - Recipients with good transplant outcome
  - Recipients with chronic/progressive infection with HBV, HCV, CMV, EBV.
  - Recipients with recurrent or chronic rejection

Timeline of Infections
6 months and beyond

- Recipients with good transplant outcome
  - Immunosuppression at baseline
  - Good allograft function
  - Infections similar to those in community, unless intense environmental exposure has occurred.

Timeline of Infections
6 months and beyond

- Recipients with chronic or progressive infection
  - HBV, HCV, CMV, EBV
  - Cause injury to the infected organ or contribute to cancer

Timeline of Infections
6 months and beyond

– Recipients with recurrent or chronic rejection
  - greater immunosuppression
  - continued risk for opportunistic pathogens

Major Pathogens

- CMV
- EBV
- HHVs
- Hepatitis B & C
- Aspergillus
- Candida
- Pneumocystis
- Multiply resistant bacteria
- Listeria
- Endemic fungi
- Toxoplasmosis
- Nocardiosis
- Mycobacteria
  - TB
  - Non-TB

Cytomegalovirus in Transplantation

- Primary disease vs. reactivation
- Mononucleosis syndrome
- Fever and aches
- GI mucosal ulcers
- Hepatitis
- Bone marrow suppression
- Interstitial pneumonia
- Immune suppression
- Retinitis

Coccidioidomycosis in Transplantation

- Cocci usually occurs in the 1st year post transplant
- Risk factors for cocci
  - Prior cocci
  - Positive cocci serology at tx
  - ? Rejection
- Targeted prophylaxis
- Rate of cocci is 1-2% with targeted px

Coccidioidomycosis in Transplantation

- Most are manifested as pneumonia.
- 20% extrapulmonary infections
- Mortality is high
- Treatment with azoles or AMB
- Azoles successfully prevent reactivation of cocci infections
- Cocci can be transmitted from donor to recipient

When to Hospitalize?

- Keep a low threshhold for hospitalization
  - Fever
  - Unknown etiology
- Can be discharged when
  - Defined
  - On appropriate therapy
  - Improving

Infections Specific to Transplant Type

- Kidney
- Liver
- Heart
- Lung

Kidney Transplant Infections

- Urinary tract infections
  - Most common bacterial infections in kidney tx.
  - Gram negative rods, Candida spp.
  - Viral: BK, JC viruses
- Surgical site infections
- Viral infections: CMV and other herpes viruses
- Fungal infections are less common

Liver Transplant Infections

- Early: bacterial or fungal infections in the abdomen and GI tract.
  - Deep candida infections, liver abscesses, cholangitis
- Later: viral infection, systemic opportunists
  - CMV: Viremia, hepatitis, contribution to allograft injury
  - Hepatitis C, B
  - Opportunists

Heart Transplant Infections

- Pulmonary infections are the most frequent and severe type of infections.
  - community and nosocomial organisms
- Mediastinitis: coagulase positive or negative staphylococci
- Toxoplasmosis
- No increased risk of endocarditis

Lung Transplant Infections

- Highest rate of infection.
- Exquisite vulnerability of lung:
  - High level immunosuppression, rejection, lost cough reflex, obliterative bronchiolitis, colonization of native lung
- Lung infxns are more severe than heart tx
- Higher rates of mediastinitis, invasive fungal infections
- Bacterial, CMV, fungal pneumonias common

Preventing Infections

- Pre-transplant evaluation
  - History of previous infections
  - Serologies
  - Immunizations
  - Treat any active infections
  - Plans for prophylaxis

Preventing Infections

- Post Transplantation
  - Routine prophylaxis dependent on serology, history
  - Avoid indiscriminate antibiotic use
  - Narrow empiric antibiotics when possible, based on cultures

Preventing Infections

Annual or periodic immunization schedule

- Annual influenza vaccine
- Pneumovax every 5 years
- Tetanus booster every 5 years
- Avoid live virus vaccines

Preventing Infections

- Patient education
- Hand hygiene
- Keep hands from face
- Avoid viral situations
- Food safety
  - Avoid raw meat, fish & dairy products
- Animal contacts
  - Avoid litter box, cage cleaning, aquarium duty

Further Reading

- **Tolkoff-Rubin NE, Rubin RH. Recent advances in the Diagnosis and Management of Infection in the Organ Transplant Recipient. Seminars in Nephrology 2000;20:148-163**
- **Chaparro C, Kesten S. Infections in Lung Transplant Recipients. Clinics in Chest Medicine 1997;18:339-351.**
- **Montoya JG, et al. Infectious Complications among 620 Consecutive Heart Transplant Patients at Stanford University Medical Center. Clinical Infectious Diseases 2001;33:629-40.**
- **Singh N. The Current Management of Infectious Diseases in the Liver Transplant Recipient. Advances in Liver Transplantation 2000;4:657-673.**
- **VanBurik JH, Weisdorf DJ. Infections in Recipients of Blood and Marrow Transplantation. Hematology/Oncology Clinics of North America 1999;13:1065-1089**