Transplant associated infections

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What organs are transplanted?

Kidney, Heart, liver, Lung, Heart – lung, Bone marrow

Overview:

Infections and rejection are the most common complications of transplantation

- Type of infections differ depending on type of transplantation
- Type of infection is dependent on patient's past history and associated risk factors
- Timing of infection dependent on level of immunosuppression

Basic Principles of Transplant Infections

- Infections occur on a time scale
- Type and frequency of infection vary with transplant type: Heart-Lung>lung>liver>heart>kidney
- More surgery → more infection
- More immunosuppression → more infection
- No good marker is available for state of immunosuppression (unlike CD4 in HIV)
- Beware of donor as a source of infection especially early post-transplant
- Transplantation does not protect from infections "normal" people get

Time Scale of Infection after Transplantation

Types of Infections vary depending on time post-transplant:

- 0-30 days: mostly "surgical" infections, →common bacteria, Candida, HSV
- 1-6 months: → opportunistic pathogens, CMV, Pneumocystis, Nocardia, Aspergillus
- 6 months onward: →common community infections, occasional opportunists, endemic fungi (histo, crypto)

How do the infections occur?

- Reactivation or recurrence of prior infection
    - *Viral infections*
    - *Urinary tract infection*
- Hospital acquired infection at time of organ transplant
    - *Surgical site infection*
    - *Urinary Tract infection*
- Exposure to nature's microbes under immunosuppression
    - *Moulds, mycobacteria*

Partial List of Organisms Transmitted by Transplantation

- Viruses: CMV and other herpesviruses, HIV, hepatitis A, B C & D, HTLV-1, WNV, Rabies, LCMV, Polyoma- BK and JC viruses
- Fungi: Histoplasma, Coccidioides, Cryptococcus
- Protozoa: Toxoplasma, malaria, *T. cruzii*
- Bacteria: Most common following surgery.
    - TB, nosocomial pneumonia agents (lung), urinary bacteria (kidney), bacteraemia donor,
    - Atypical infections occur late following transplant
        - Listeria, mycobacterial
- Prions: Creutzfield-Jakob disease (cornea)

Bacterial Infections

- Most common is UTI
    - High risk related to GU surgery
        - Ureteral anastomosis
        - Postoperative stent
    - Often patients have history of UTIs preceding transplant
    - Indwelling Foley catheters
    - Leading cause of bacteremia following renal transplant

Increase in Multidrug Resistant Organisms (MDRO)

- Mechanisms of resistance
    - Beta-lactamases
    - Carbapenemases
    - Quinolone resistance

Nosocomial Infections

- Surgical Site
- Catheter related
    - Indwelling blood catheters
    - Indwelling urinary catheters
- Clostridium difficile
- Environmental
    - Aspergillosis
- Fungal Infections
- Most common cause is Candida
    - Urinary tract
    - Blood stream
- Other fungi can cause
    - Meningitis- Cryptococcosis
    - Pneumonia -Aspergillus, Mucormycosis, other moulds
    - Skin nodule- Dermatiaceous moulds, Blastomycosis, Histoplasmosis
- Esophageal Candidiasis

Viruses: Before and After transplantation

<u>Viruses infected before transplant which can reactivate after transplant</u>

- Hepatitis B and C
- HIV
- Herpes family of viruses- CMV, HSV, VZV, EBV, HHV8
- Papilloma viruses
- Polyoma - BK and JC virus

- Viruses infecting after transplant

Expose as normal people but more susuctible After transaplant:

- Respiratory viruses
- Adenovirus
- RSV
- Influenza
- Parainfluenza
- Metapneumovirus
- Enterovirus
- Rhinovirus
- Coronavirus

Effects of Viral Infection in Transplantation

- Directly causing infectious disease syndromes
  - Nephritis, hepatitis, neutropenia
  - Allograft injury often greater than systemic
- Immunomodulatory effets
  - systemic immune suppression
  - Cellular effects – graft rejection, GvHD
  - abrogation of tolerance
- Oncogenesis
  - Hepatitis B: hepatocellular carcinoma
  - Epstein Barr Virus: B-cell lymphoma (PTLD)
  - Hepatitis C: splenic lymphoma (villous lymphocytes)
  - Papillomavirus: Squamous cell & anogenital cancer
  - HHV8 (KSHV): Kaposi's sarcoma, effusion lymphoma

Herpes Viruses: (Refer text books)

- Herpes 1 and 2: Cold sores, Genital ulcers

- Varicella
    - Shingles/herpes zoster
- Epstein-Barr
    - Mononucleosis and Post-transplant lymphoproliferative disease
- HHV-8
    - Post transplant Kaposi's sarcoma
- CMV (single most important pathogen in transplant recipients)
    - Hepatitis
    - Diarrhoea or intestinal ulcers
    - Anemia, low white cells, low platelets
- Labial Herpes

CMV disease

- Levels of CMV virus can be monitored in the blood
    - Potentially allows for detection of virus before illness
    - Patients who have never been exposed are at greatest risk (antibody negative)
- Patients who have been previously infected (50-80%) can reactivate

Cytomegalovirus (CMV) infection

- Most commonly occurs within the first 6 months following transplant
- Higher incidence in patients with stronger immunosuppression
- Associated with rejection
- Patients who receive steroids and increase in immunosuppression are at risk for CMV independent of time from transplantation

CMV Prevention and Treatment

- New treatments in the last decade
- IV and oral formulations now
- Ganciclovir (Cytovene) and valganciclovir (Valcyte)
- Patients who have no antibody to CMV at transplant receive prophylaxis if donor organ is CMV +

- Patients with CMV antibody are followed with CMV levels every 2 weeks and treated if number reaches a certain level

Epstein-Barr Virus (EBV) and Transplantation

- Epstein-Barr virus can cause lympho-proliferative disease after transplantation
- Some cases are polyclonal proliferations that respond to reduction of immunosuppression; others are true lymphomas
- Risk varies by transplant group - lowest in renal transplants (~0.3%) and highest in lung transplants and pediatric transplants (~4%)
- As with CMV primary infection and level of immunosuppression are the main risks
- Lymphoproliferative Disease in the Abdomen related to EBV
- Human Herpes Virus – 8 and Kaposi's Sarcoma (KS)
- Strongly associated with KS in AIDS and transplantation
- May respond to reduction of immunosuppression

Polyoma Viruses

- Most common after renal transplant is BK
    - Common cause of renal nephropathy
    - Can lead to allograft dysfunction
    - Difficult to treat
        - Reduce immunosuppression
        - Cidofovir
        - Ciprofloxacin
        - Leflunomide
    - Monitored by PCR - Blood or urine

Respiratory Viral Infections

- Influenza
- Parainfluenza
- Adenovirus
- Metapneumovirus
- Adenovirus

- Enterovirus
- Rhinovirus
- Coronavirus

Prevention

- Screening for prior illnesses
- Up to date immunizations
    - Pneumovax (pneumonia vaccine) every 5 years
    - Influenza (flu vaccine) yearly
    - Hepatitis A/B vaccine one series
    - Prophylaxis antibiotics/antivirals
    - TMP-SMX
    - Valcyte (valganciclovir)

Prevention of Exposure to Infection

- Respiratory viruses: - avoid persons with colds, public places during flu outbreaks, vaccinate family members
- Airborne molds:
    - avoid barns, grain store, chicken cages etc.
    - STD's: Practice safer sex
- Exotic infections: - Before international travel confer with infectious disease expert

What personal habits effect risk of infections?

- Sick exposures
- Hobbies - Gardening, Hunting, Fishing
- Prior residences
- Travel history and future travel
- Common Sense Prevails
- Wash hands
- Avoid sick contacts
- Wash food
- Cook food

Case 1

1. A donor kidney becomes available for a 50 year old man with renal failure who was on renal dialysis for the past 2 years.

- 1.1. What microbiological investigations should be performed on donor and recipient Immediately prior to transplantation? Give reasons.
- 1.2. What other virological screening assays should be considered. Give reasons.

After successful transplant, patients wasdischarged. 7 weeks later he presented with general malaise and noted to be febrile.

- 1.3. What is the differential diagnosis?
- 1.4. What investigations should be started?
- 1.5. Why correct diagnosis is essential?
- 1.6. How these investigation results interpreted?

Lab investigation results

- Hb = 9.7/dl
- White cell count = 3.2 x 10^9/l
- Differential: PMNs 30%, lymphocytes 65%, monocytes 5%
- Urea and electrolytes: within normal ranges
- ALT : 75 IU/l (normal range up to 45)
- Bilirubin, alkaline phosphatase, g- glutamyl transferase – within normal ranges
- Chest x ray = normal
- MSU = no growth