Prevention and Management of Infectious Complications in Patients with Kidney Disease Receiving Immunosuppressive Therapy

Martha Pavlakis, MD

Medical Director, Kidney and Pancreas Transplantation

Beth Israel Deaconess Medical Center

How immunosuppressed is this patient?

- Most renal patients are somewhat immunosuppressed
- Degree of immunosuppression depends on what they've been treated with and for how long
- History of immunosuppression regimen and duration is crucial to both intelligent prevention and effective management

Prevention and Management

- Prevention is important, not always possible
- Prophylaxis by guidelines
- Successful management depends on accurate and timely diagnosis
- KEY POINTS:
  - Pursue diagnosis aggressively
  - Get tissue-based diagnosis when possible
  - Work with an infectious disease doctor who specializes in immunosuppressed patients
  - Sometimes a cold is just a cold

Prevention

- Starts with knowing what infections to avoid
- Learn the risks in the short, intermediate and long term in your immunosuppressed patient
- Education critical
  - If you get a fever, you must call MD
  - If someone is ill, you should stay a safe distance
  - Do not eat food if it looks/smells spoiled
  - Avoid uncooked or undercooked foods
  - Wash all fruits and vegetables before consumption
  - Sensible handwashing
  - Get vaccinations prior to immunosuppression if possible

Prevention-testing

- Pre-immunosuppression or pre-transplant
  - Hepatitis serology panels
  - HIV testing, RPR, Review history of infections
  - CMV and EBV testing pre-transplant to risk stratify
  - Complete physical exam and history of travel, antibiotic use etc
  - Chest Xray and PPD testing
  - Update relevant vaccines (yearly flu etc)
  - As indicated by residency: Strongyloides, Toxoplasmosis, other parasites (flukes, malaria)

Vaccinations

- Vaccinations-(responses often sub-optimal)
- Inactivated vaccines are safe (AVOID LIVE)
  - Hep A, B, inactivated polio, DPT, menigitis and pneumovax, yearly flu
- Ideally household contacts should also be vaccinated
- Pre-immunosuppression or pre-transplant
  - Treat HIV to suppress viral load, optimize CD4 count
  - Treat Hepatitis C if possible (variable response)
  - Begin to treat positive PPD

What are the major pathogens?

- Community acquired-viral, bacterial
  - Common airborne and blood borne pathogens
- Latent Pathogens (CMV, HSV, HPV)
- Nosocomial - bacterial, fungal
- Opportunistic (ie PJP, aspergillus)

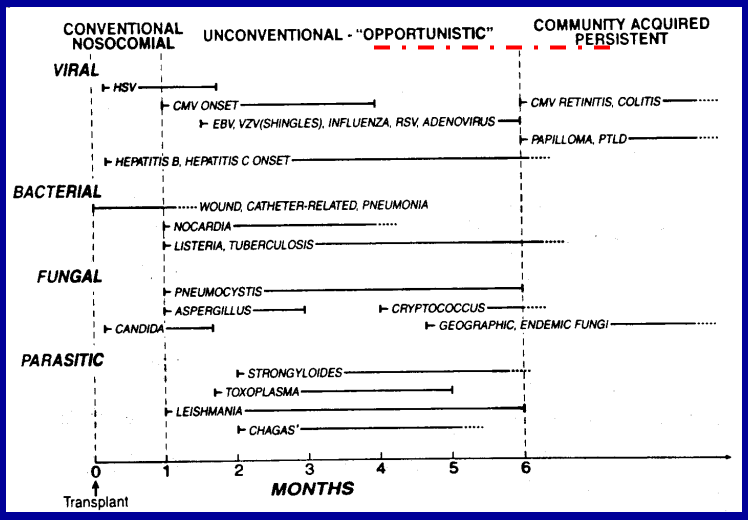
Major risk factors for infection

- Age, co-morbid conditions such as diabetes
- Duration and intensity of immunosuppression
  - Treatment for acute rejection, use of plasma exchange
- Antibiotic exposure
- Colonization
- Parentarel nutrition, recent surgery
- Duration and frequency of hospitalizations
- Prolonged foley catheter drainage
- Mechanical ventillation
- Leukopenia

The infection timeline

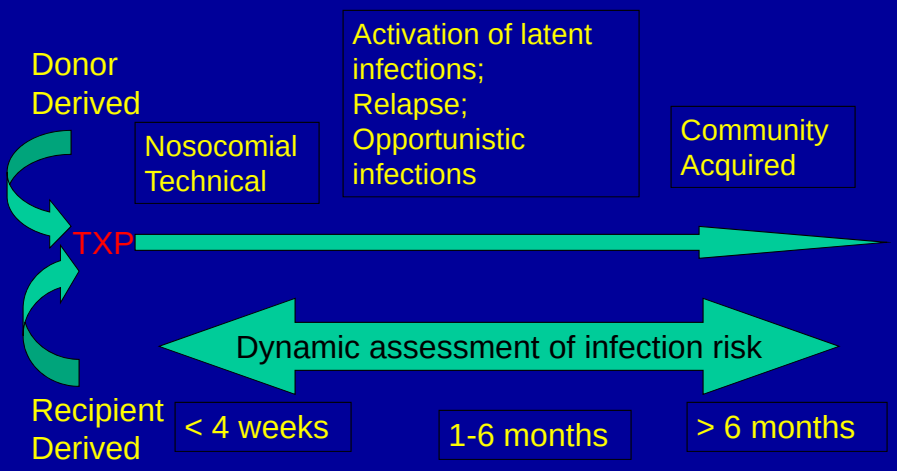
- Helps focus the work up
- Reminds us of pathogens to think about
- The time line re-sets each time immunosuppression is augmented

1998 Classic overview



Fishman & Rubin, NEJM 1998

2009 update-timeline of infections



Adapted from Fishman AJT Infections in SOT Supplement 4 2009

< 4 weeks	1-6 months	> 6 months
Abx-resistant sp -VRE MRSA Candida	Assume Prophylaxis for PJP, CMV	Comm. Acquired PNA
Aspiration Pneumonia	BK, Hep C, Adeno, Flu	UTI
Line infection	Cryptococcus M. Tb	Aspergillus, Mucor
Wound infection	Anastomos. leak	Nocardia (TMP-S)
Anastomos leak	Without prophylaxis	Late Viral:
C. Diff colitis	Pneumocystis	CMV, Hep B, C
Donor derived (UNCOMMON) Rabies, LCMV, HSV, WNV	Herpes (HSV, CMV VZV, EBV) HBV, Listeria, Nocardia, Toxo, Strongyloides, Leishmania, T. Cruzi	HSV eceph SARS, WNV JC (PML) EBV (PTLD) HPV (Skin cancer)

Prophylactic treatment

- Valcyte dose adjusted for 900 mg daily
  - Prevents CMV, HSV
  - High risk transplant: 6 months
  - Medium or low risk: 3 months
- Nystatin four times daily swish and swallow OR Clotrimazole troche TID
  - Prevents oro-pharyngeal thursh
  - Duration of therapy 1 month or longer
- Bactrim DS BIW or SS daily
  - Prevents UTI, PJP, Nocardia
  - Duration of therapy 6 months-life

Prophylactic treatment

- Fungal prophylaxis can be with Nystatin OR Azole therapy (Clotrimazole, Fluconazole)
- The Azoles will suppress CNI metabolism, raising levels with initiation and dropping them with cessation of therapy
- Beware CNI toxicity or under immunosuppression when stopping/starting azole therapy

Prophylactic treatment

- Hepatitis B - prophylaxis NOT ROUTINE
- Used in setting of transplant recipient of intermediate risk organ (Hep B core antibody positive, surface antigen negative)
- Use of NAT testing increasingly common
- HGIg at time of transplant if recipient not immunized
- Epivir therapy for 3-6 months vs longer

Screening

- For high impact, easily detected infections
- Urinalysis for UTI
- Blood or urine testing for BK post transplant
  - Urine or blood BK PCR
  - Urine Decoy cells

Management-diagnose early

- Get tissue if possible (biopsy, LP, bronchoscopy, laparotomy etc), involve surgery early
- Low threshold for initiating anti-infectious treatment
- Use imaging, examine the skin carefully
- Obtain routine cultures plus fungal isolators and viral PCRs as appropriate
- Make early decisions about ongoing immunosuppression management

Management-other causes of fever

- INFECTION is always number one on the differential
- Allograft rejection - rarely causes fever in modern drug era
- Non-infectious causes of inflammation such as pancreatitis, pulmonary embolism
- Drug fevers are <u>diagnoses of exclusion</u>
  - Rapa related pneumonitis
  - ATG induced fever

Selected infections

- VRE - within 1-2 months of transplant or initiation of immunosuppression
  - Colonization rates vary
  - Single positive Culture may be contaminant
  - Take in context of symptoms, colonization, or concomitant presence of VRE in wounds or other sterile sites such as urine
  - Multiple positive blood cx's should be treated as active infection.
  - First line options: Daptomycin, linezolid, synercid,
  - Second line options: chloramphenicol, doxycycline, bactrim

Selected infections

- Listerosis often 6 months post transplant
  - Presents as menino-encephalitis, septicemia or febrile gastroenteritis
  - First line therapy: Amoxacillin 2-3 weeks
- Nocardiosis 1- 6 months post transplant
  - Much less frequent with bactrim prophylaxis
- Mycobacterial infections
  - Increased risk of disseminated disease
  - 12 months drug treatment, 4 agents
  - Significant drug interactions with immunosuppressants
  - Rifamp decreases CNI levels, INH increases withint 1-3 days of therapy

Selected infections

- Fungal infections- difficult to differentiate colonization from infection in non-sterile sites
- Most common: Candida, Aspergillus, Cryptococcus
- More common in kidney pancreas recipients, pancreas after kidney recipients (enteric drainage)
- Therapy: Caspofungin useful for azole resistant candidate and non-albicans infections

Cytomegalovirus (CMV)

- ~70% of adult recipients and donors are IgG seropositive at time of transplant or immunosuppression induction
- Major cause of morbidity and mortality prior to era of routine prophylaxis.
- CMV infection- recent seroconversion or presence of viremia in absence of overt symptoms.
- CMV disease- symptomatic infection.

Cytomegalovirus (CMV)

- Presenting symptoms: Fever, leucopenia, malaise, thrombocytopenia, hepatitis, pneumonitis, pancreatitis, colitis, meningoencephalitis, and rarely myocarditis
- Retinitis rare in renal transplant recipients
- Risk stratification is essential
- Onset usually after cessation of prophylactic Valcyte, but resistant strains do occur

CMV Disease Treatment

- Treatment dose Valgancyclovir or ganciclovir for 12 weeks (or until viremia has cleared). DOSE ADJUST FOR RENAL FUNCTION
  - GCV IV 5 mg/kg q12 5-7 days, then q24 hours
  - Valgan p.o 900 mg BID
- Consider decrease IS at diagnosis
- Maintenance dose Valgan for 8-12 weeks
- Resistance is rare - UL97 mutation
- Cytogam reserved for CMV pneumonitis

Infections and malignancy

- Some infections are associated with increased risk of malignancy
- EBV and post transplant lymphoma
- HHV 8 and Kaposi's sarcoma
- HPV and skin/anogenital squamous cancers

Infection Prevention and Management

- Risks of infection are part of the informed consent of transplant or non-transplant related immunosuppression
- Preventive measures go a long way towards avoiding morbidity and mortality
- Use effective prophylactic treatment strategies
- Pursue diagnosis with imaging, biopsy etc.

Infectious Disease Guidelines

- American Journal of Transplantation Volume 9 Issue S4 , Pages S1 - S281 (December 2009)
- Available at AST website:
- www.a-s-t.org
- These are invaluable guidelines

QuickTime™ and a
decompressor
are needed to see this picture.

Dubberke AJT Volum 9 2009 S35