Impact of Infection after transplantation

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athens-NEPHROLOGY

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Newer immunosuppressive regimens have reduced rates of acute graft rejection while post-transplant infections exceed rejection as a cause of hospitalization.

VR Dharnidharka et al, Am J Transplant 2004,4:384-389

Impact of Infection Post-Transplant

- **Pneumonia**: Increased over 4-fold in first year after renal transplantation vs. non-transplant, by almost 3-fold in second year (diabetic ESRD transplant patients)
- **Sepsis** post-renal transplantation:
  - ~18 episodes per 100 patient years (Year 1)
  - ~11 episodes (Year 2)
- High Mortality
- Decreased quality of life

Data from: USRDS 2002, KC Abbott et al, Am J Nephrol. 2001; DJ Tveit et al, J. Nephrol 2002.

Why new pathogens?

- Prolonged patient survival (travel, employment)
- Shifts in **nosocomial flora** (antimicrobial resistance) and prolonged hospitalizations
  - ✓ Routine prophylaxis (fluconazole, vancomycin, cephalosporins, antivirals)
  - ✓ Renal, hepatic, pulmonary dysfunction (sicker patients)
- Intensified Immune suppression
- Improved diagnostic assays
- New technologies (VADs, stem cells)
- Organ shortage and Expanded Criteria Donors

Risk for infection is a semiquantitative relationship between:

Epidemiologic exposures

(including latent infections)

and

"The net state of immune suppression"

Epidemiologic Exposures May Be Recent or Distant & from Donor or Recipient

Recent

- **Nosocomial flora**
- Catheter related
- Surgery
- Community acquired
- Urinary tract infection
- Aspiration
- *Cryptococcus*
- *Legionella*
- **Donor-derived**

Distant

- Tuberculosis
- Colonization (remote)
- Non-tuberculous mycobacteria
- *Strongyloides*
- Herpesviruses
- Toxoplasmosis
- *Leishmania*, *T. cruzi*
- Histoplasmosis, Coccidioides
- HTLV, HIV, HCV, HBV

HTLV, human T-cell lymphotrophic virus; HIV, human immunodeficiency virus.

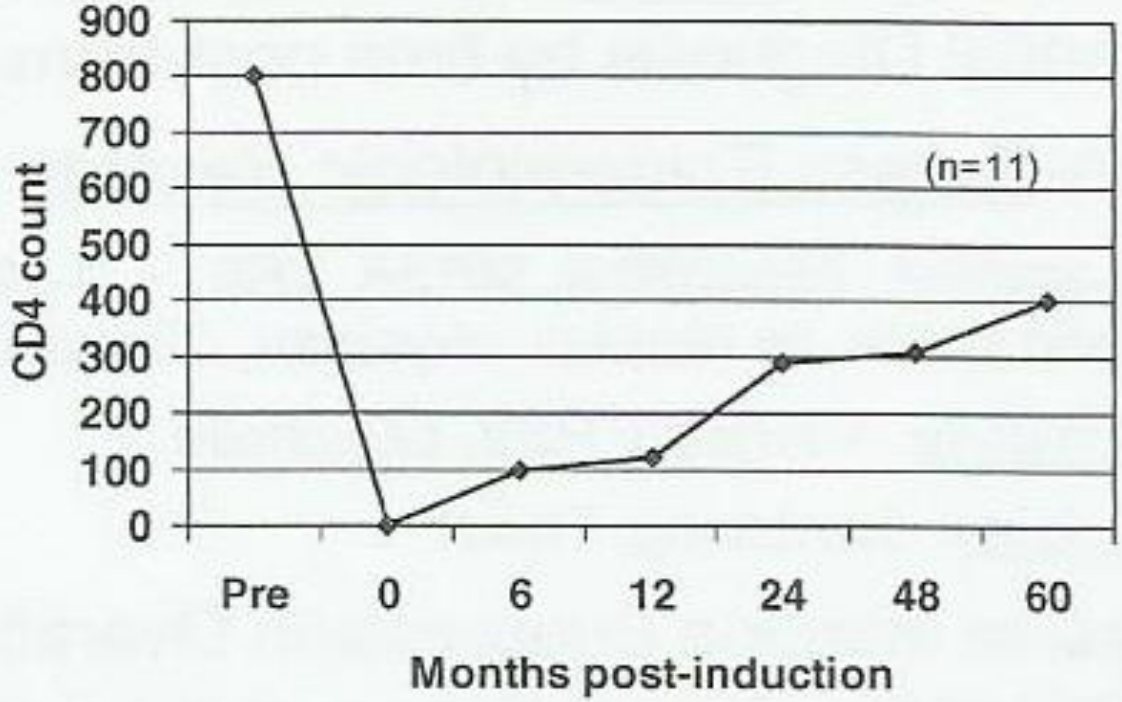
"Net State of Immune Suppression"

- **Immunosuppressive Therapy:** Type/Temporal Sequence/Intensity -- "AUC"
- Prior therapies (Chemotherapy, Antimicrobials)
- Mucocutaneous Barrier Integrity (Lines)
- Neutropenia, Lymphopenia
- Underlying Immune Deficiency & Metabolic conditions: Uremia, Malnutrition, Diabetes, Alcoholism/cirrhosis, COPD/bronchiectasis
- Viral Co-Infection (CMV, Hepatitis B and C, RSV): Immune Modulation/Rejection/Cancer

Immunosuppression and Infection

- **Antilymphocyte globulin** mimics alloimmune response: Activation of latent (herpes)virus, fever, cytokines (timing varies with type)
- **Corticosteroids**: Bacteria, PCP, HBV, HCV
- **Azathioprine**: Neutropenia, papillomavirus?
- **MMF**: Early bacterial infection, late CMV?
- **Cyclosporine/Tacrolimus**: ⇑ viral replication, gingival infection, intracellular pathogens
- **Rapamycin**: Excess infections in combination with current agents, idiosyncratic pulmonary edema or pulmonary infections?

Anti-Thymocyte Globulins and CD4+ T-cell Depletion



- *CD4/CD8 ratio remains persistently inverted*

Muller et al, Transplantation 1997

What makes the transplant recipient unique?

- Technical issues – leaks, ischemia
- Graft Injury – Rejection, dysfunction
- Drug toxicities and interactions
- Mixed immune deficits
- Viral co-infections
- Metabolic derangements
- Prior infections and antimicrobials

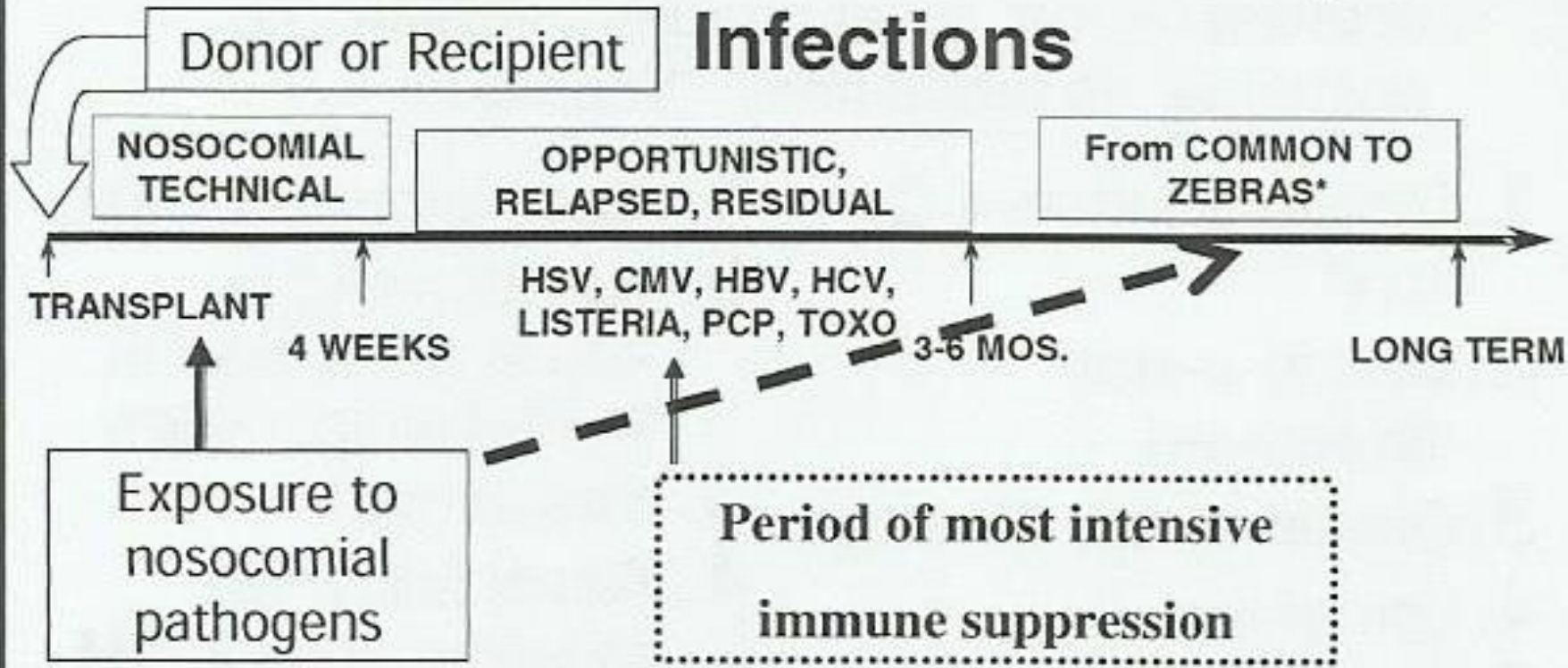
Measures of "Immune Deficits"

Most patients have mixed immune deficits

- Multiple drugs (changing)
- Variable metabolism
- Unknown native "immune function"
- Unknown meaning of drug levels in individual
- Differing exposures and background immunity
- Few relevant assays – lymphocyte markers

Must individualize immune suppression, but generally lack appropriate assays

The Timeline of Post-Transplant Infections



COMMON VARIABLES in IMMUNE SUPPRESSION:

☹ MANY DIFFERENT REGIMENS (steroid-free, CNI-free, Antibody Induction)

☹ TREATMENT OF REJECTION

☹ NEUTROPENIA (virus or drug-induced)

☹ VIRAL INFECTIONS (CMV, HCV, EBV, RSV …)

Use of the Timelines

- ⇨ Differential Diagnosis by time post-transplant
- ⇨ Identify Excess Epidemiologic Hazards:
  - ⇨ Nosocomial: Aspergillus, MRSA, VRE, -- clustered in time and space, by hospital, physician, Clinical Unit
  - ⇨ Community: Influenza, RSV, Legionella
  - ⇨ Individual: Gardening, Travel
- ⇨ Excessive Immune Suppression Overall: Too many infections, too severe, or at the wrong time on time line

Timetable of Infection after Transplantation

First Month following Transplantation

- Infection carried with donor cells or organ
- Present in recipient prior to transplant
- Technical complications (unforgiving surgery)
  - Obstructed stents, organ damage in procurement
  - Hemorrhage, hematoma, leaks, ischemia
- Post-operative complications
  - Aspiration, pulmonary embolus
  - Lines, Drains, Catheters

Early Post-Transplant Infections

Infections carried by the allograft:

- Common bacteria/yeasts: Pneumococcus, Staphylococcus, Streptococcus, Pseudomonas, Salmonella, Aspergillus, Candida species
  - **Increasingly nosocomial, antimicrobial resistant**
  - Contamination at procurement
- Known viruses (CMV, HSV, EBV, HCV, HBV)
- Mycobacteria (NTBI)
- West Nile Virus, Rabies, LCMV, HIV
- Chagas' Disease, Leishmania, Histoplasma, Toxoplasma gondii, Paracoccidioides

Conditions Predisposing to Early Infection

- Immune Suppression (bolus steroids)
- Intubation (>3 days)
- Catheters: Urinary, Venous, Dialysis
- Graft dysfunction
- Constipation, Endoscopy, *C. difficile* colitis
- Broad-spectrum Antibiotics
- Deep vein thrombosis, Atelectasis
- Metabolic:Malnutrition/Uremia/Hyperglycemia

Early infections: Technical Complications in Organ Transplantation

- Anastamotic leaks or obstructions
- Hematomas, lymphoceles
- Iatrogenic damage to skin (tape)
- IV line or Urinary catheter-related
- Improper tissue typing
- Excess immune suppression (drug toxicity)
- Injury to donor organ in procurement
- Excessive organ ischemic time

Donor-Derived infections: Viral

- Herpesviruses – CMV, EBV, HHV6, HSV, VZV
- HTLV I and II
- HIV
- West Nile Virus – mosquitoes and birds
- Rabies – bat bite
- LCMV – hamsters and rodents
- Respiratory Viruses: influenza (avian), adenovirus, SARS coronavirus, metapneumovirus?
- Risks of Xenotransplantation – Porcine Endogenous Retrovirus

Therapeutic Alternatives- Early Infections

1. Identify and remove infected sites
   - intravascular clot
   - catheters
   - devitalized tissues (debride hematoma, collections)
2. Reduce immune suppression
3. Treat (viral) co-infections
4. Antimicrobial agents

Timetable of Infection: Months 2-6 following Transplantation

- Residual (technical) from first month
- Undiagnosed nosocomial infections
- Community acquired infections
- Classic "opportunistic infections"
  - P. carinii, T. gondii
- Endemic/Geographic pathogens
  - T. cruzi, Strongyloides stercoralis, Leishmania
  - Geographic fungi: Histoplasma, Coccidioides, Paracoccidioides
  - Tuberculosis
- Community acquired: Ubiquitous
  - Cryptococcus neoformans
  - Nocardia asteroides
  - Aspergillus sp.

The Growing Family of Viral Pathogens in Transplantation

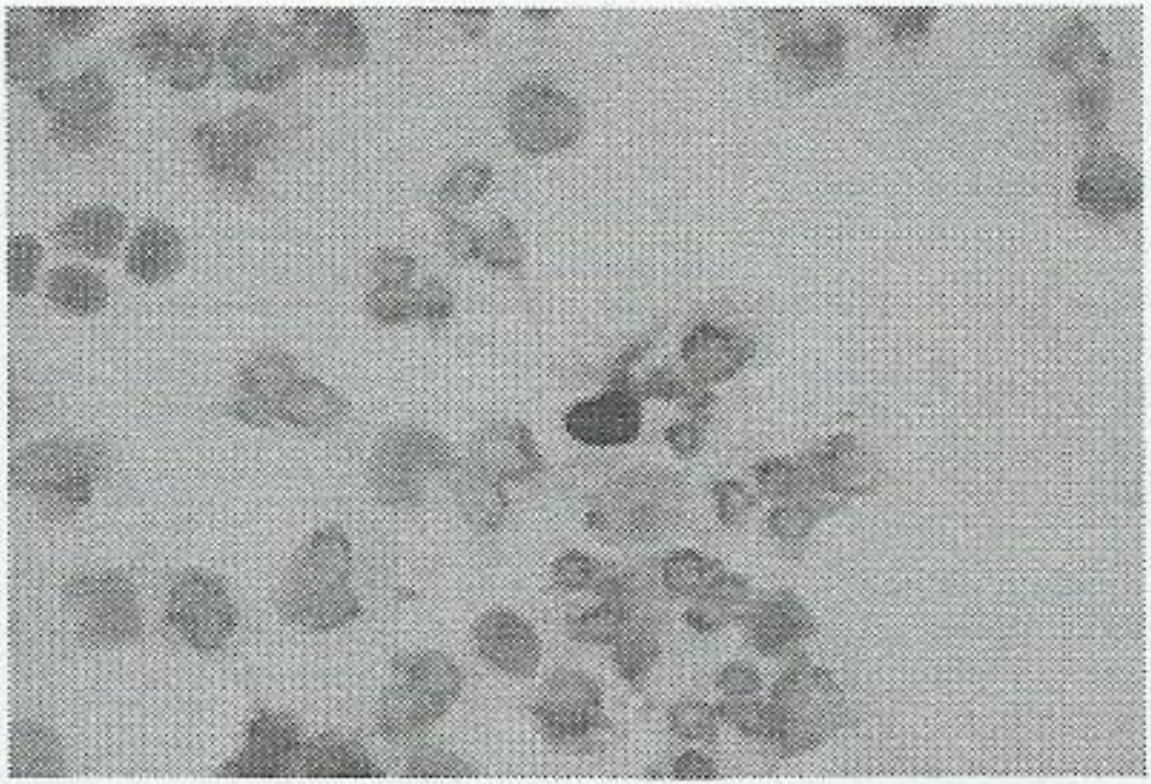
- HERPES SIMPLEX
- VARICELLA ZOSTER
- EPSTEIN-BARR VIRUS
- CYTOMEGALOVIRUS
- HHV6 (& role with CMV)
- HHV7 (role?)
- HHV8/KSHV
- HIV, LCMV
- WEST NILE, RABIES

- **HEPATITIS B and C**
- **PAPILLOMAVIRUS**
- **POLYOMAVIRUS BK/JC**
- **ADENOVIRUS, RSV**
- **INFLUENZA, PARAINFLUENZA**
- **METAPNEUMOVIRUS**
- **PARVOVIRUS B19**
- **SMALLPOX/VACCINIA**
- **SARS coronavirus**

Effects of Viral Infection in Transplantation

- "DIRECT EFFECTS" -- CAUSATION OF INFECTIOUS DISEASE SYNDROMES
  - Fever and neutropenia, hepatitis
  - Colitis, Retinitis, Nephritis, Pancreatitis
- "INDIRECT"or Immunomodulatory EFFECTS
  - Systemic Immune Suppression → OI's
  - Graft Rejection, GVHD
  - Abrogation Of Tolerance
- Oncogenesis/Cellular Proliferation
  - 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
  - Accelerated atherogenesis, BK-ureteric obstruction

CMV Antigenemia Assay



Early Detection of CMV: Assays

- For early detection, both PCR (molecular) and antigenemia assays are useful. Quantitative molecular (PCR) assays are preferable for routine monitoring (sensitivity).
- Monitoring of infection and the success of therapy require quantitative or semi-quantitative assays.
- Resistance Assays with molecular sequencing.

Responds poorly to therapy

- Discharged on oral valganciclovir
- CMV antigenemia assay rises to 5126 cells on two slides → intravenous ganciclovir
- CMV antigenemia drops to 2111 cells in 10 days, 350 cells at 2 weeks, but never drops below 279 cells; Cr = 2.9
- Virus resistant to ganciclovir by molecular analysis → Foscarnet; Mg to 1.1, Cr = 1.1

PATTERNS OF TRANSMISSION OF CMV In Solid Organ Transplant Patients

Primary Infection (D+/R-):

- CMV seronegative individual receives "cells" containing latent virus from a seropositive donor
- CMV is reactivated with clinical disease in 40-60%
- Asymptomatic viremia >50% with prophylaxis
- The allograft is generally the source of infection
- Infection may be acquired in the community or from viable leukocytes from blood products

Indirect Effects: Examples

- Cytomegalovirus: best studied, global immune suppression, increased graft rejection
- Hepatitis B and C: increased incidence of opportunistic infection
- Epstein-Barr virus: link to non-Hodgkin's lymphoma
- Parvovirus B19: elaboration of cytokines, autoimmune effects, Cellular apoptosis
- Leishmania: immune suppression
- RSV, Coronavirus, influenza: ciliary injury, local suppression

Opportunistic Infections Promoted by CMV Infection in Transplant Patients

- *Pneumocystis carinii*
- Fungal infections (esp. intra-abdominal transplants):
- *Candidemia and intra-abdominal infection* in OLTx; patients with initial poor graft function
- *Aspergillus spp.* Role of CMV in promoting fulminant HCV hepatitis rather than direct effect
- Bacteremia: *Listeria monocytogenes*
- Epstein-Barr virus infection (RC Walker et al, CID, 1995, 20:1346-55), HHV6, HHV8/KSHV?
- HCV: risk for cirrhosis, retransplantation, mortality

Viral Oncogenesis and Proliferative Events in Transplantation

CMV: Early arteriosclerosis, role in PTLD.

Epstein Barr Virus: PTLD (B-cell), Hodgkin's, T-cell (Asia), Burkitt's (*c-myc, P. falciparum*), Cofactor in Kaposi's?

Papillomavirus: Squamous, Anogenital Cancers

HHV8/KSHV: Kaposi's sarcoma, Castleman's ds.

Hepatitis B (C?): Hepatocellular carcinoma

Hepatitis C: Splenic, non-Hodgkin's lymphoma (immunostimulation of villous B-lymphocytes)

HTLV-1: Adult T-cell leukemia & lymphoma

BK virus: Ureteric smooth muscle proliferation

JC virus: PML, neuroglial tumors?

CMV and Graft Dysfunction: Renal

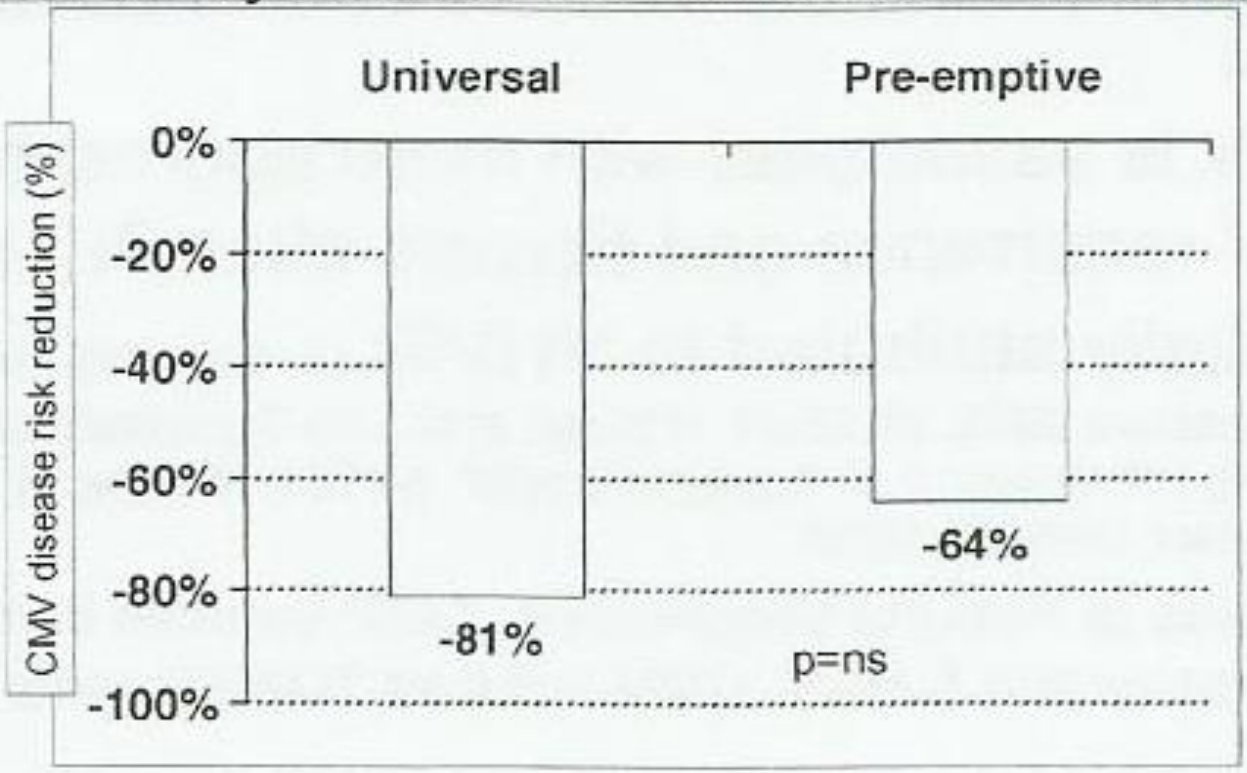
- CMV Disease causes poor renal graft function at 6 mos; CMV & HHV6 are associated with chronic dysfunction (3 yrs) (CY Tong et al, Transplant. 2002, 74:576-8)
- Acute but not Chronic allograft rejection is reduced by CMV prevention in liver and kidney (D+/R-) Tx (D Lowance et al, NEJM 1999, 340:1462-70; E. Gane et al, Lancet 1998, 350:1729-33)
- HHV6 increases CMV infection and OI's and possibly some acute rejection in renal (A. Humar, Transplant 2002, 73:599-604) & liver recipients (JA DesJardin CID 2001, 33:1358-62; PD Griffiths et al, J Antimicrob Chemother, 2000, 45 sup 29-34)
- HHV7 associated with increased CMV infection and with acute rejection (IM Kidd et al, Transplant 2000, 69:2400-4)

CMV and Graft Dysfunction: Liver

- CMV is associated with cirrhosis, graft failure, retransplantation, and death in liver allograft recipients (KW Burak et al, Liver Transplant 2002, 8:362-9)
- CMV is associated with more aggressive HCV recurrence and fibrosis after OLTx (partially attributed to HHV6) (A. Sanchez-Fueyo et al, Transplant 2002, 73:56-63; N Singh et al, Clin Transplant 2002, 16:92-6; HR Rosen et al, Transplant 1997, 64:721; R. Patel et al, Transplant 1996, 61:1279)
  - Roles of immune suppression, CMV-induced immune suppression & HCV, CMV-induced TGFβ/fibrosis

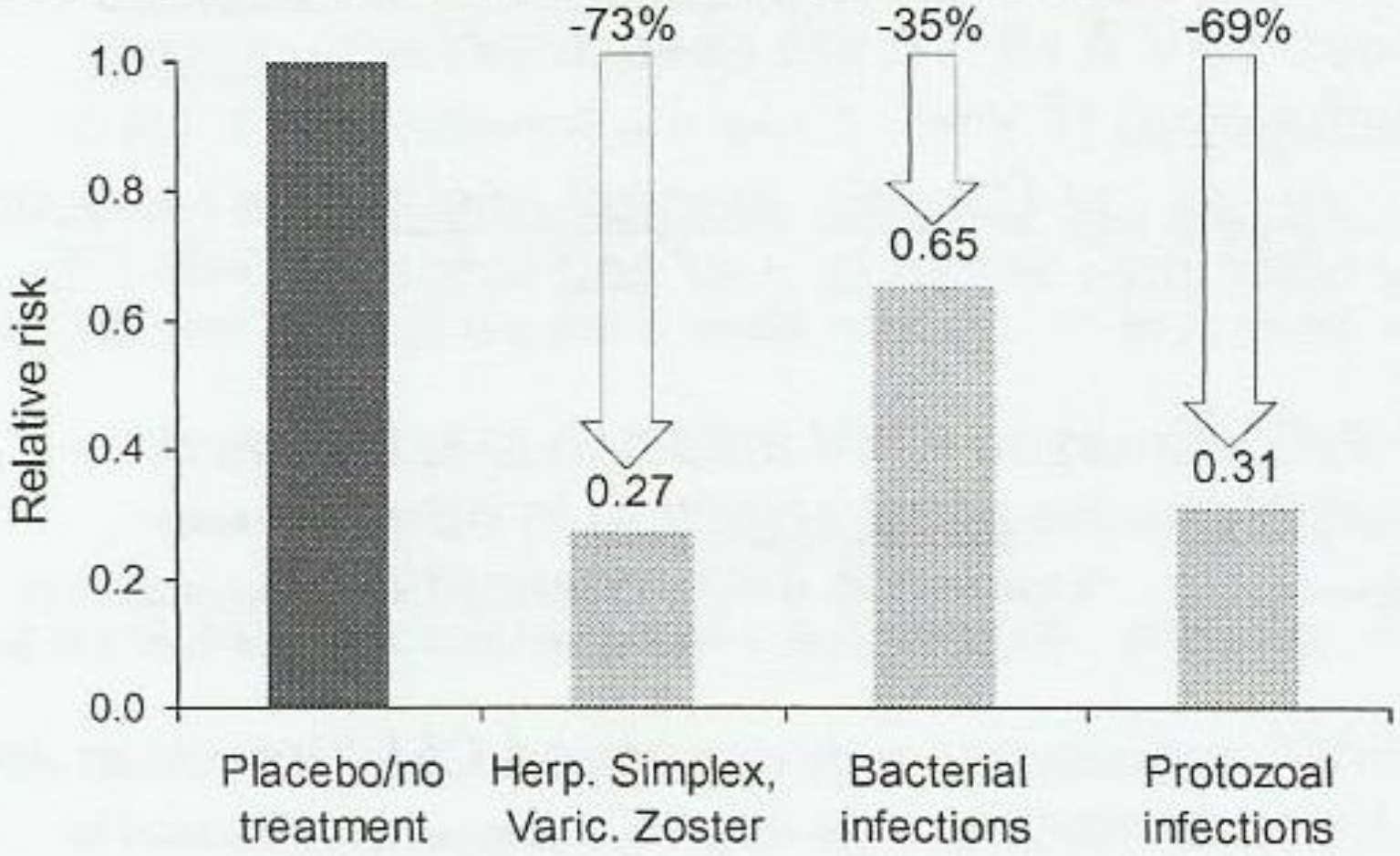
CMV disease in D+/R- renal recipients: Meta-analysis (all agents)

- Universal and Pre-emptive prophylaxis significantly reduce the risk of CMV disease



Kalil AC *et al. Ann Intern Med* 2005; 143: 870

Effect of anti-CMV prophylaxis on concomitant infections



Hodson EM *et al. Lancet* 2005; 365: 2105

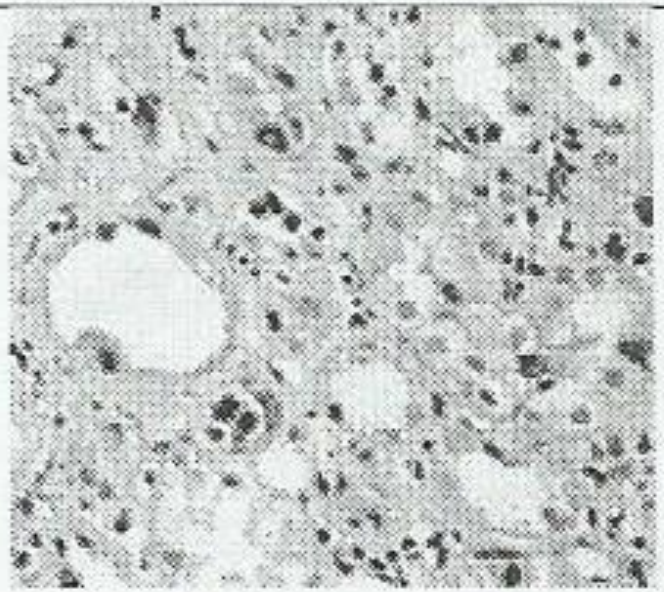
BK polyomavirus – a recent pathogen

- Associated with sterile pyuria, ureteral ulceration and obstruction, hemorrhagic cystitis in renal transplant patients -- rise in serum creatinine
- JC virus (PMLE) and SV40 in same family
- Asymptomatic viruria in 10-45% of renal transplant recipients only; disease in 2-4% of all renal Tx. Few in extra-renal transplants thus far.
- Up to 50 % of BMT recipients; cystitis
- 50% of nephritis in first 3 months post-transplant; many later. May coexist with rejection.
- Linked to intensity of immune suppression (not specific agents). Steroid responsive element in promoters.

BK Virus: Diagnosis

- **Urine decoy cells (cytology) - highly sensitive**
- **Tissue Biopsy**
  - Histology: tubular injury cellular enlargement, inflammation, intranuclear &intracytoplasmic inclusion bodies
  - Electron microscopy: intracellular crystalline arrays
  - Nucleic acid hybridization in situ
- PCR (blood): higher incidence of viremia in symptomatic patients but many asymptomatic
- Urine cellular PCR (VP1 mRNA): $\geq 6 \times 10^5$ copies/ng (R. Ding, Transplantation 74:987, 2002)

BK Virus:
Mononuclear Infiltrate with Nuclear Inclusions



Renal allograft biopsy 9 months post-cadaveric transplant in patient treated with tacrolimus and mycophenolate mofetil. Serum creatinine rose to 2.4 with evidence of hydronephrosis on ultrasound. Many tubular epithelial nuclei are enlarged with lavender homogeneous inclusions. A mild mononuclear infiltrate is seen in the interstitium and occasionally in tubules. H&E stain. (R. Colvin, MGH)

BK Virus: Therapy

- None at present
- **Reduction in immune suppression** results in graft loss of 16.4 to 80%
- Many maintain Cr ~ 2.5
- Exclude rejection, PTLD
- Low dose cidofovir with both anecdotal successes & failures, with some renal dysfunction.
- leflunomide (immunosuppressive agent) has some useful antiviral activity for BK and herpes viruses