Infections in Solid Organ Transplantation

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Outline

- CMV: prevalence, which preventative strategy (prophylaxis vs monitoring/preemptive therapy), what drugs, how long, what about ganciclovir resistance
- Polyomavirus: prevalence, outcomes, screening strategies, treatment interventions
- Hepatitis C: natural history on dialysis vs transplant, treatment options
- Hepatitis B: treatment post-transplant, use of Hep B cAg+ donors
- EBV: prevalence, outcomes, role of surveillance and preemptive treatment

Prevalence of Solid Organ Transplants

Type of Organ	# in 2006
Renal –	16,646
Liver –	6,136
Heart –	2,147
Lung -	1,401
Kidney + Pancreas –	914
Pancreas -	390
Heart-Lung -	31

OPTN/SRTR 2007 Annual Report

Incidence of Infections

Type of Infection	Liver	Kidney	Heart	Lung/heart-lung	Pancreas/ KP
Bacterial	33-68	47	20-30	35-66	35
CMV	22-29	8-32	9-35	53-75	50
HSV	3-14	53	1-42	10-18	6
VZV	5-10	4-12	1-12	8-15	9
Candida sp.	1-26	2	1-5	10-16	32
PCP	4-11	5-10	1-8	15	

CID 2001:33

Immunosuppressant Medications

- Glucocorticoids
  - Reduce neutrophil accumulation at site of inflammation
  - Inhibit IL-2 gene promoter
- Calcineurin inhibitors (cyclosporine, tacrolimus)
    - Inhibit T cell function by decrease IL-2 production
- Antiproliferative agents (mycophenolate, azathioprine)
  - Interrupts DNA replication of T cells
- Sirolimus
  - Inhibit intracellular signaling pathways of IL-2 receptor
  - Induce neutropenia

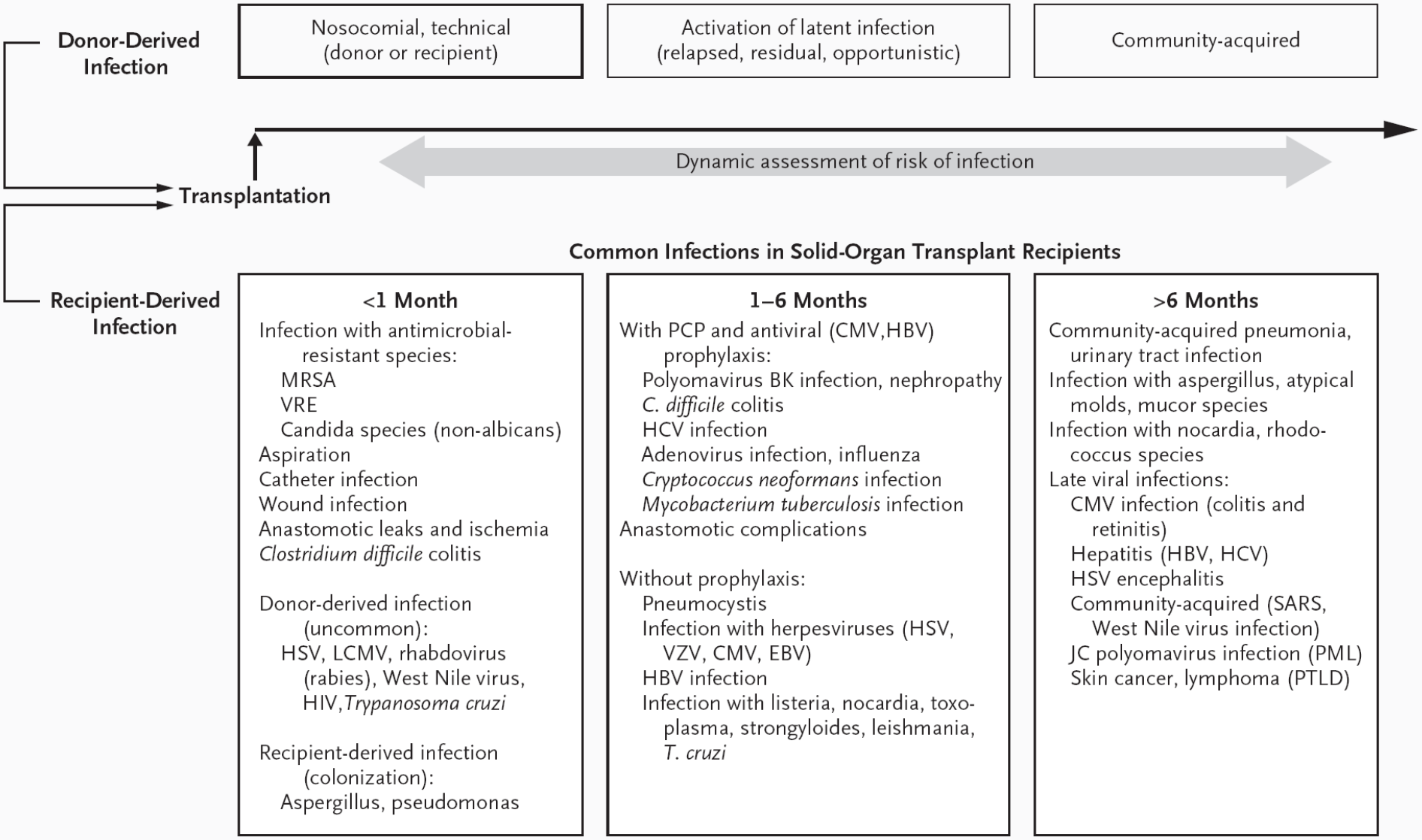
Immunosuppressant Medications

- Monoclonal antibodies
  - CD3 receptor blocker (OKT3)
  - IL-2 receptor blockers (basiliximab, daclizamab)
- Polyclonal antibodies
  - Anti-thymocyte globulin (Thymoglobulin, Atgam)

Immunizations

- Hepatitis B
  - Dialysis patients require higher dose
- Hepatitis A
- Polio, inactivated
- Tetanus
- Varicella (LA)
- Influenza
  - Inhaled influenza vaccine is live attenuated
- Pneumococcal
  - Repeat every 3 – 5 years

Infectious Complications



Common Infections in Solid-Organ Transplant Recipients

<1 Month

Infection with antimicrobial-resistant species:
- MRSA
- VRE
- Candida species (non-albicans)

Aspiration
Catheter infection
Wound infection
Anastomotic leaks and ischemia
Clostridium difficile colitis

Donor-derived infection (uncommon):
- HSV, LCMV, rhabdovirus (rabies), West Nile virus, HIV, *Trypanosoma cruzi*

Recipient-derived infection (colonization):
- Aspergillus, pseudomonas

1–6 Months

With PCP and antiviral (CMV,HBV) prophylaxis:
- Polyomavirus BK infection, nephropathy
- *C. difficile* colitis
- HCV infection
- Adenovirus infection, influenza
- *Cryptococcus neoformans* infection
- *Mycobacterium tuberculosis* infection

Anastomotic complications

Without prophylaxis:
- Pneumocystis
- Infection with herpesviruses (HSV, VZV, CMV, EBV)
- HBV infection
- Infection with listeria, nocardia, toxoplasma, strongyloides, leishmania, *T. cruzi*

>6 Months

Community-acquired pneumonia, urinary tract infection
Infection with aspergillus, atypical molds, mucor species
Infection with nocardia, rhodococcus species
Late viral infections:
- CMV infection (colitis and retinitis)
- Hepatitis (HBV, HCV)
- HSV encephalitis
- Community-acquired (SARS, West Nile virus infection)
- JC polyomavirus infection (PML)
- Skin cancer, lymphoma (PTLD)

NEJM 2007;357:2601

Month 0 - 1

- Recurrent infections
  - Donor and recipient
- Infectious complications related to surgery
  - Line sepsis
  - UTI from urethral stent
  - Pulmonary infections after lung transplant or prolonged ventilator support

Investigation of Rabies Infections in Organ Donor and Transplant Recipients — Alabama, Arkansas, Oklahoma, and Texas, 2004

On July 1, this report was posted as an MMWR Dispatch *on the* MMWR *website* (http://www.cdc.gov/mmwr).

Months 1 - 6

- Reactivation or primary infection of viral diseases
  - CMV, HSV, HBV, HCV, VZV, EBV
  - Polyoma virus nephropathy in renal transplant
- Emergence of opportunistic pathogens
  - Bacterial
    - Nocardia
  - Fungal
    - Candida, aspergillosis, PCP
- Higher risk of “common infections”

After 6 months

- Higher risk of “common infections”
- Continued risk of opportunistic infections
  - Endemic fungal infections
  - PCP, CMV, nocardia
- Post-transplant lymphoproliferative disorder secondary to Epstein Barr Virus
- Polyoma virus nephropathy in renal transplant

MMWR – Sept 5, 2003

Public Health Dispatch

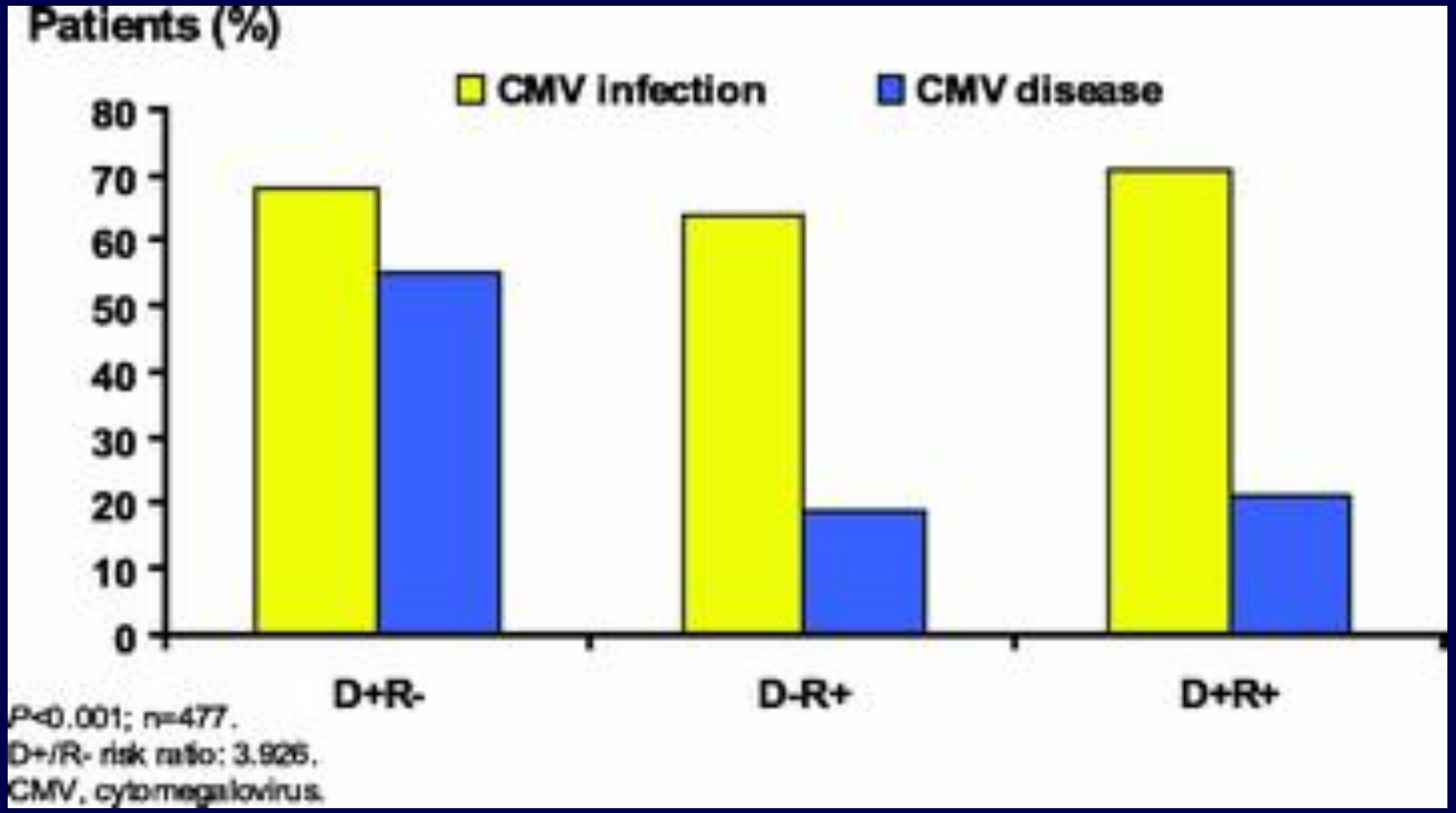
Multistate Outbreak of Hepatitis A Among Young Adult Concert Attendees — United States, 2003

Cytomegalovirus (CMV)

- A member of herpes virus family
- Most frequent infectious complication in renal transplant recipients
- Infection: CMV viremia by PCR analysis
- Disease: CMV viremia + clinical symptoms
  - Fever, leukopenia, increase LFTs, increase creatinine, increase LDH
  - Localized symptoms varies on type of transplant

CMV:
Prevalence in an untreated population

477 consecutive KTx recipients without prophylaxis from 1994-97:



At day+100: 64% with CMV infection, 24% with CMV disease

Hartmann A et al, Transplantation 2006; 82: S15

CMV

- Antibody positive: IgG by ELISA
  - Indicated prior exposure
  - Present in 30 – 80 % of patients
- Diagnosis
  - PCR testing
  - Antigenemia
  - Biopsy

Effects of CMV

- Direct
  - Neutropenia & thrombocytopenia
  - Flu-like symptoms
  - Inflammatory response & tissue injury
  - Organ infection & accompanying symptoms
- Indirect
  - Injury or rejection of transplanted organ
    - Up regulation of HLA antigens & activation of cytokines
  - Increase risk of fungal and bacterial superinfections

CMV: How best to prevent?

- Prophylaxis-
  - Therapy for all patients at risk
- Monitoring and preemptive therapy-
  - periodic PCR screening and treatment only if viremic
- Ganciclovir vs. Valganciclovir
  - Oral: 7% vs 70% bioavailability
  - IV GCV 2.5-5.0 mg/kg/d = Valcyte 450 mg qD

Drug Therapy for CMV

- Prophylaxis
  - Given to all D+/R- transplants
  - Utilize during and after polyclonal/monoclonal antibody therapy for moderate risk patients

Agents

- Ganciclovir
- Valganciclovir
- IVIG – CMV
- Valacyclovir

Drug Therapy for CMV

- Preemptive therapy
  - Monitor CMV viral replication
  - Treat positive results with “treatment doses of antiviral therapy.”
  - Preememptive vs. prophylaxis:
    - Cost neutral
    - Equal efficacy in prevent symptomatic CMV disease
    - Requires extra monitoring

Am Journal of Transplantation 2006;6:2134-43.

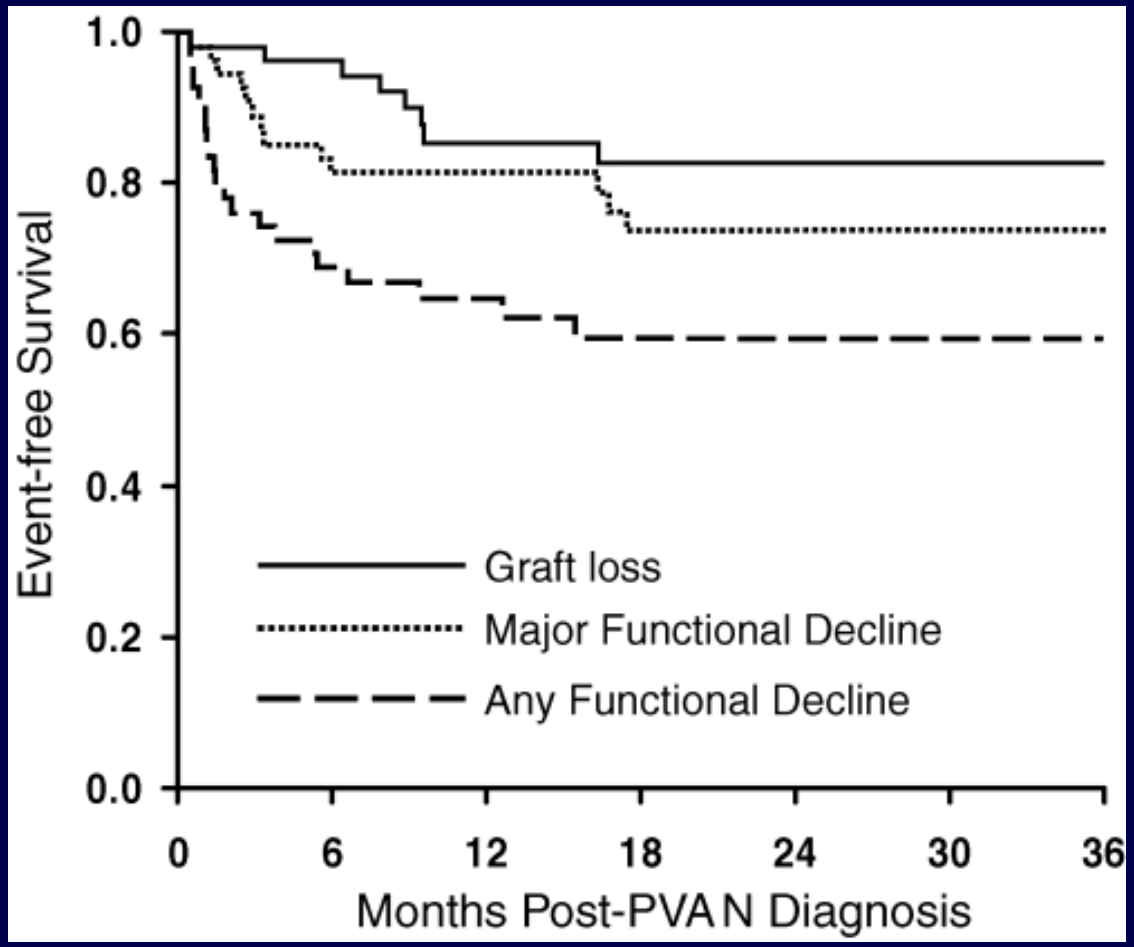
BK Virus

Polyoma Virus (BK Virus)

- DNA virus causing interstitial nephritis (nephropathy) after renal transplant
  - Can appear like acute rejection on biopsy
- BK & JC Virus
  - Primarily seen in renal transplant patients
- Developing knowledge of pathogenesis
- Infection in 10 – 45% or renal transplant
- High rate of graft failure with nephropathy
- Risk Factors
  - Over immunosuppression, age, DM, - serostatus

Prognosis after PVAN diagnosis:

- 55 cases of PVAN diagnosed from 2002-04:
  - 31 with renal dysfunction
  - 24 diagnosed by protocol biopsy
- Mean 20 month f/u:
  - 15% graft loss
  - 24% with major functional decline (>50%) from diagnosis

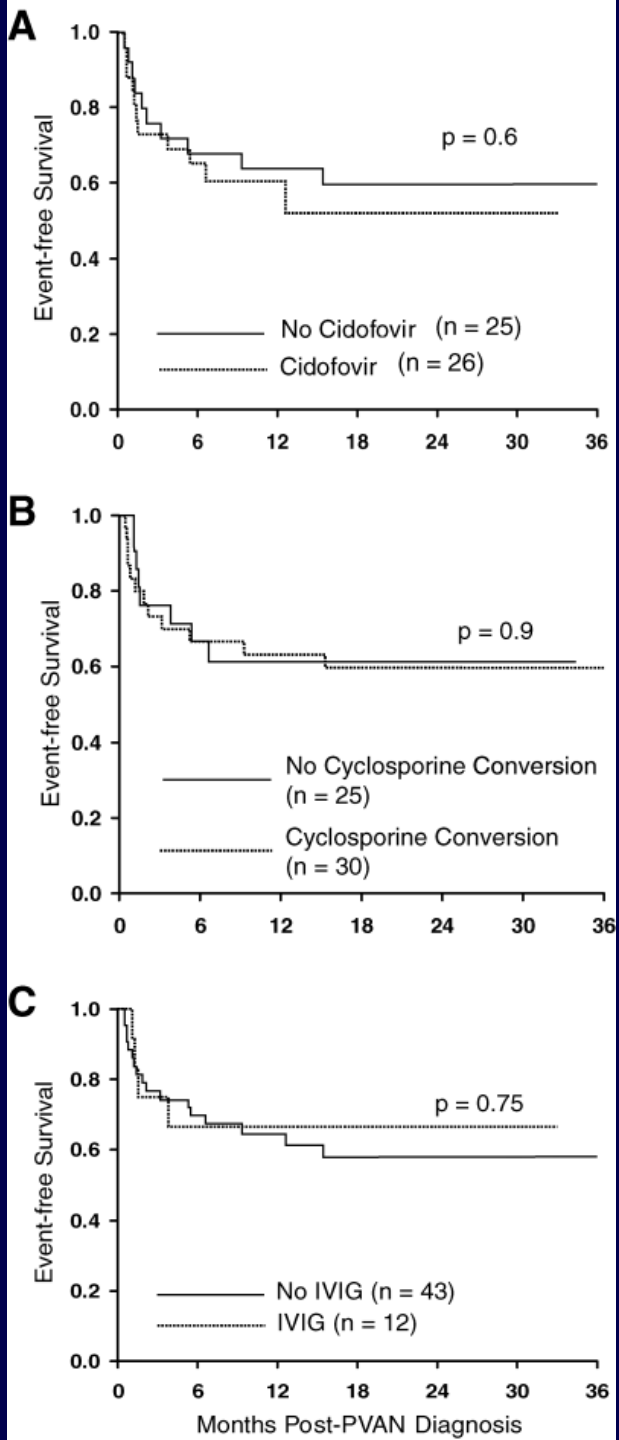


Wadei HM et al, Am J Transplant 2006; 6: 1025

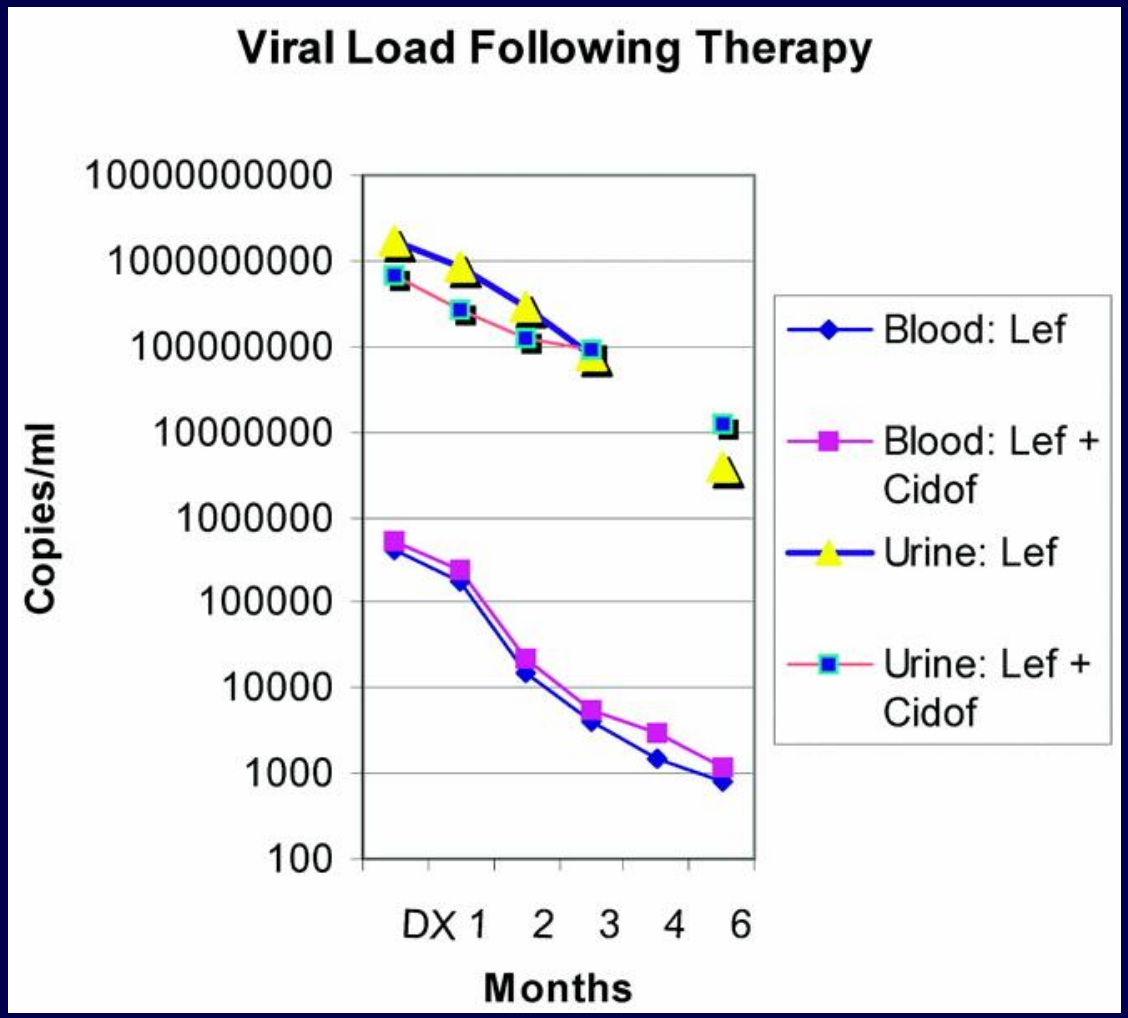
Interventions to slow progression: does anything work?

- Possible interventions:
  - Cidofovir 0.25 mg/kg q 2 weeks x 4
  - Transition to CSA (trough125-175 ng/ml) vs reduction of TAC (4-6 ng/ml) combined with reduction of MMF (250 mg BID)
  - IVIg 1.25 g/kg x 2
- None demonstrated a benefit

Wadei HM et al, Am J Transplant 2006; 6: 1025



Lefunomide +/-cidofivir in addition to immunosuppression reduction



- 26 patients with biopsy-proven BKVAN:
- 17 leflunomide alone
- 9 leflumomide + cidofovir
  - Leflunomide: started at 100 mg/d x 3, then 20mg/d with goal trough 50-100 ng/ml
  - Cidofovir: started at 0.25mg/kg IV biweekly x 4 doses

Josephson M et al, Transplantation 2006;81: 74

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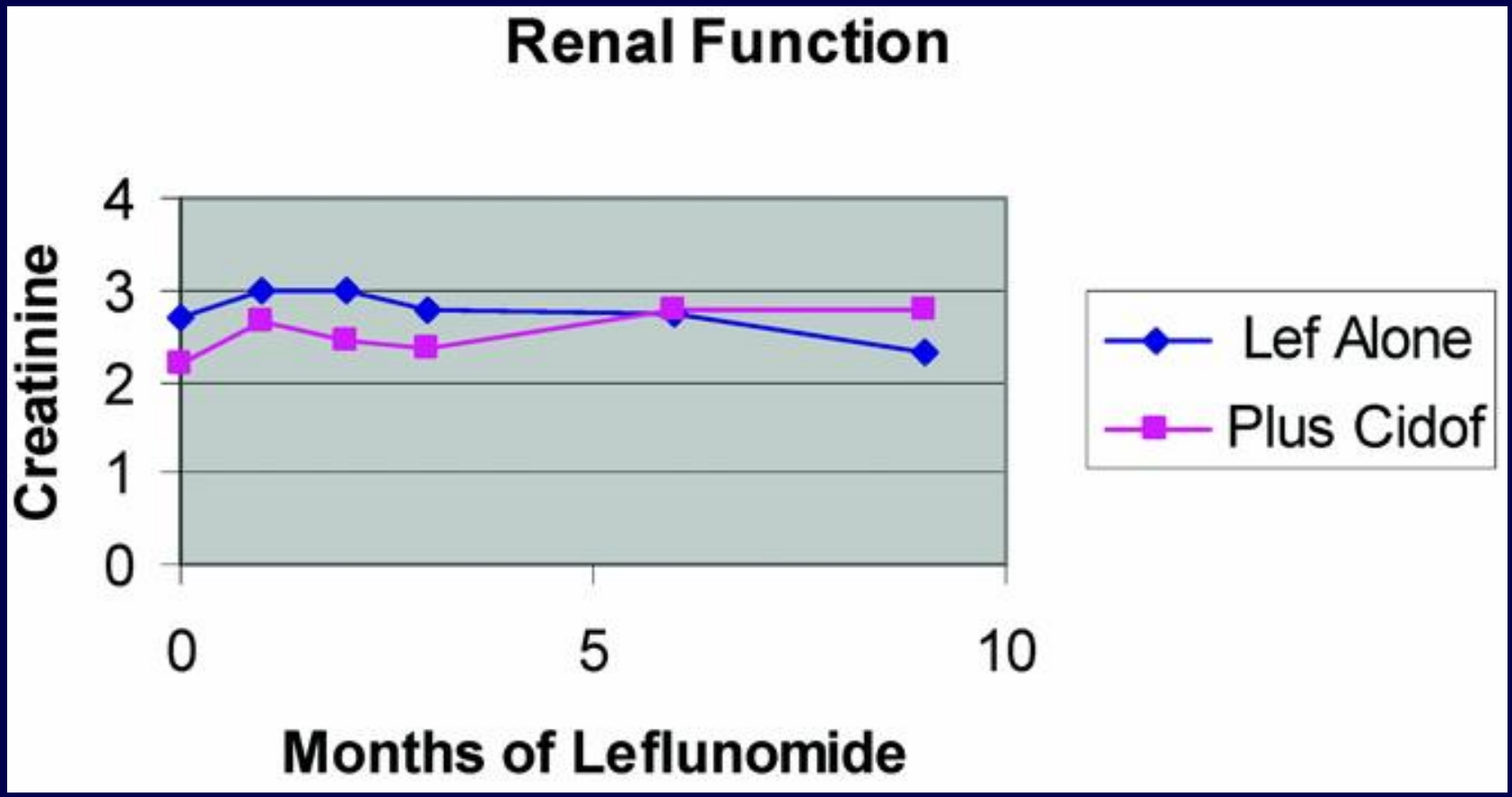


Josephson M et al, Transplantation 2006 ;81: 74

Polyoma Virus (BK Virus)

- Monitoring
  - Urine or serum viral load (PCR), biopsy
  - Role still to be determined
- Management (no clear guidelines)
  - 1st line therapy: modify immunosuppression
  - Antiviral therapy
  - Miscellaneous

Modification of immunosuppression

TABLE 5. Treatment of PVAN by modification of maintenance immunosuppression

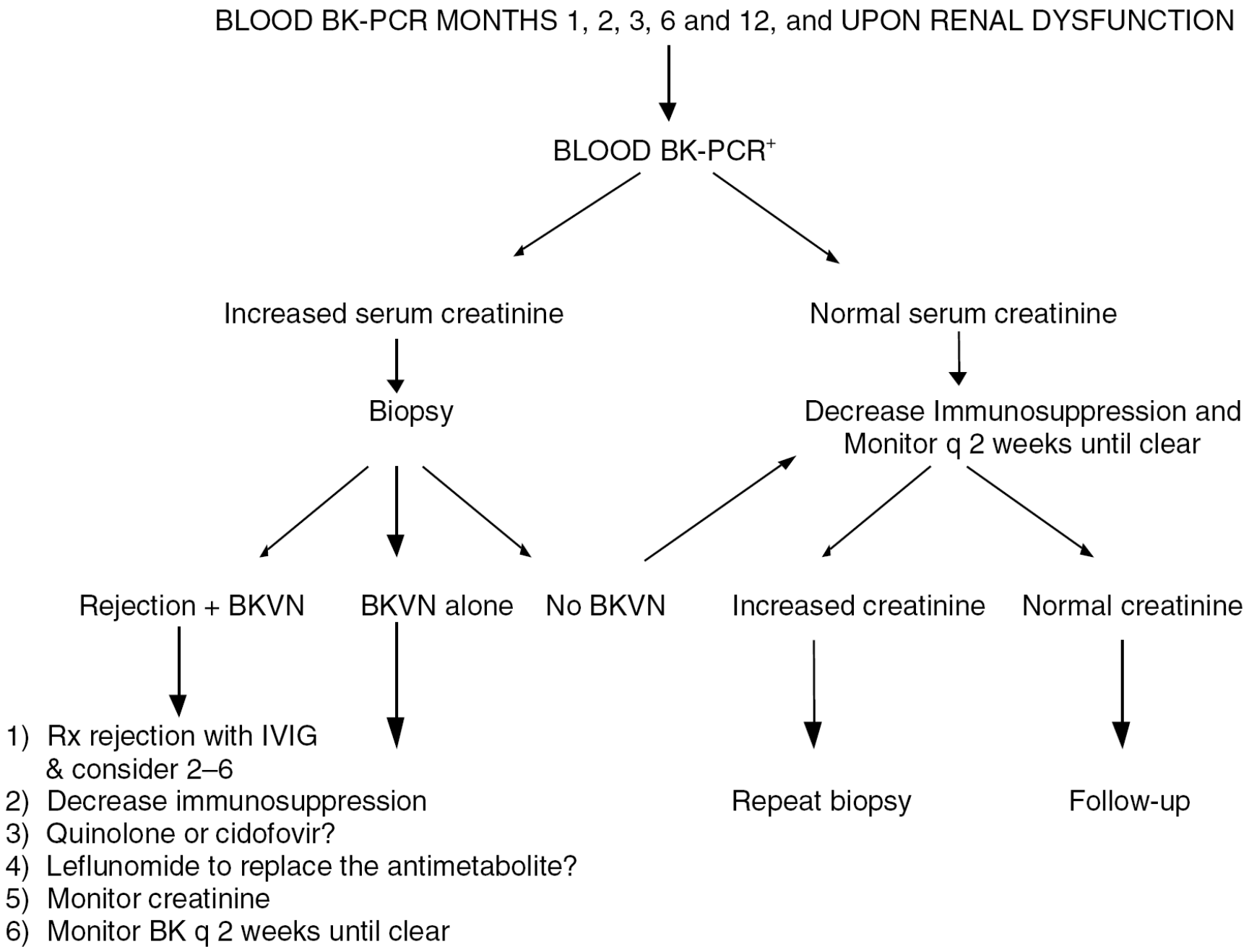
Switching	Decreasing	Discontinuing
Tacrolimus→CsA (trough levels 100–150 ng/mL) (***B-III***)	Tacrolimus (trough levels <6 ng/mL) (***B-III***)	Tacrolimus or MMF (maintain or switch to dual drug therapy):
MMF→azathioprine (dosing ≤100 mg/d) (***B-III***)	MMF dosing ≤1 g/day (***B-III***)	CsA/prednisone (***B-III***)
Tacrolimus→sirolimus (trough levels <6 ng/mL) (***C-III***)	CsA (trough levels 100–150 ng/mL) (***B-III***)	Tacrolimus/prednisone (***B-III***)
MMF→sirolimus (trough levels <6 ng/mL) (***C-III***)		Sirolimus/prednisone (***C-III***)
MMF→leflunomide (***C-III***))		MMF/prednisone (***C-III***)

PVAN, polyomavirus-associated nephropathy; CsA, cyclosporine A; MMF, mycophenolate mofetil.

B-III: Moderate evidence to support a recommendation based on clinical experie descriptive studies, or reports of expert committees.

C-III: Poor evidence to support a recommendation based on clinical experience descriptive studies, or reports of expert committees.

Transplantation 2005;79:1277


BLOOD BK-PCR MONTHS 1, 2, 3, 6 and 12, and UPON RENAL DYSFUNCTION
BLOOD BK-PCR+
Increased serum creatinine
Normal serum creatinine
Biopsy
Decrease Immunosuppression and
Monitor q 2 weeks until clear
Rejection + BKVN
BKVN alone
No BKVN
Increased creatinine
Normal creatinine
1) Rx rejection with IVIG
& consider 2–6
2) Decrease immunosuppression
3) Quinolone or cidofovir?
4) Leflunomide to replace the antimetabolite?
5) Monitor creatinine
6) Monitor BK q 2 weeks until clear
Repeat biopsy
Follow-up

Polyomavirus Nephropathy
Take-home points

- DNA virus causing interstitial nephritis (nephropathy) after renal transplant
- Related to over-immunosuppression, reactivation of virus latent in transplanted kidney
- Usually leads to inexorable graft loss unless identified early
- MONITOR! MONITOR! MONITOR!

PCP (PJP?)

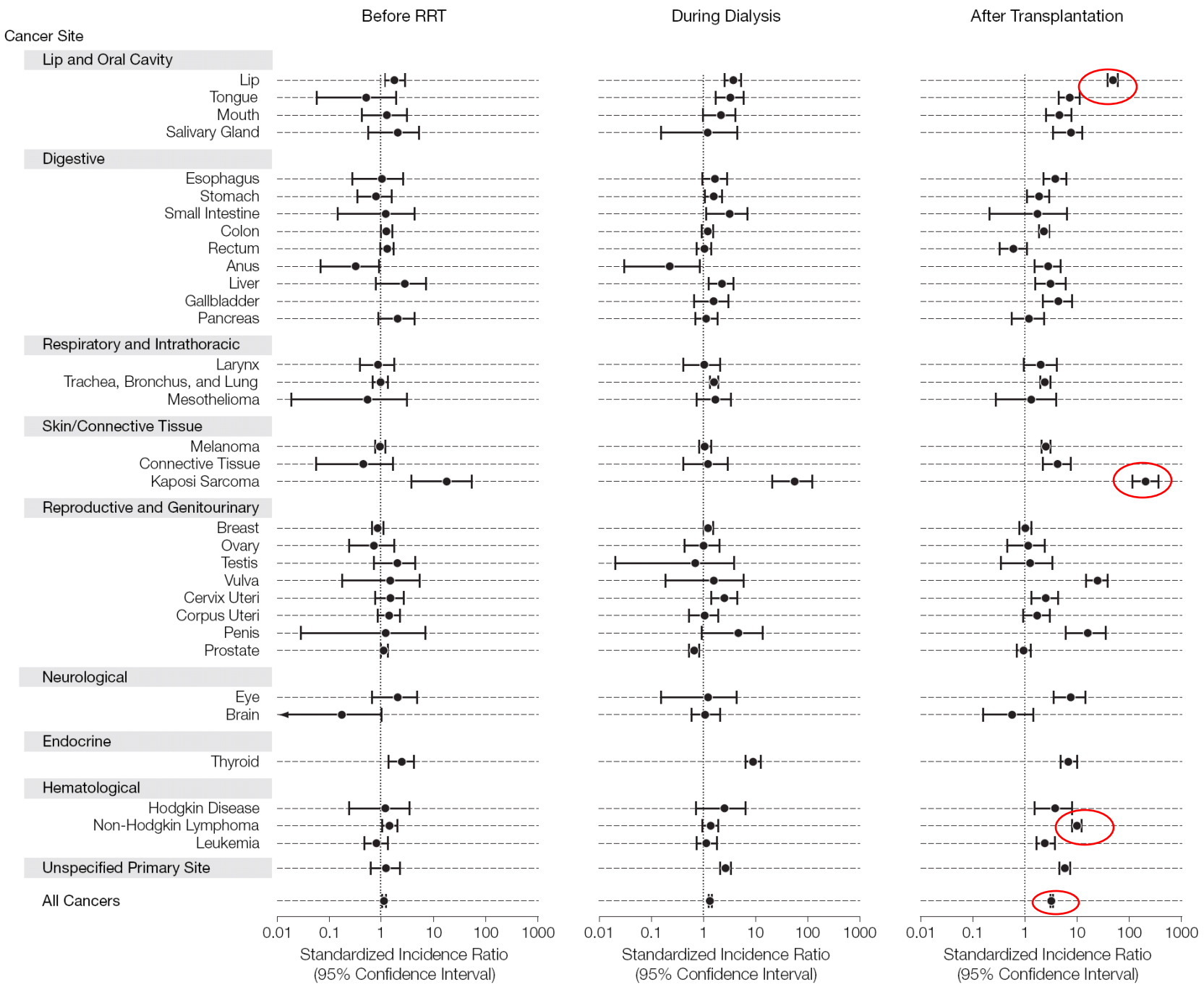
- *Pneumocystis jiroveci* causing pulmonary infection
  - Insidious onset
- High mortality rates
- Effective prophylaxis
  - *SMX/TMP, pentamidine, or dapsone*

Hepatitis C (HCV)

- Overall incidence increasing in the U.S
  - >30% of liver transplant pts are HCV +
- Recurrence in virtually all patients
- Risks
- Primary treatment is prevention
  - Steroid sparing/free immunosuppression for liver transplant
- Treatment
  - Concern for increase acute rejection with Interferon alpha

Cancer after transplant

- Skin/lip most common – Majority of all malignancies
  - More squamous cell (250x higher vs general pop) vs. basal cell (10x higher vs. general pop)
- Anogenital- 2-3% of all malignancies
- Renal carcinomas- 0.5 -3.9% of malignancies
- PTLD- 1 -5% of malignancies
  - EBV with causative role



NEJM 2006;296:2827

What is PTLD?

- An **EBV-related disease**- B cell proliferation induced by EBV infection

Reactive Hyperplasia

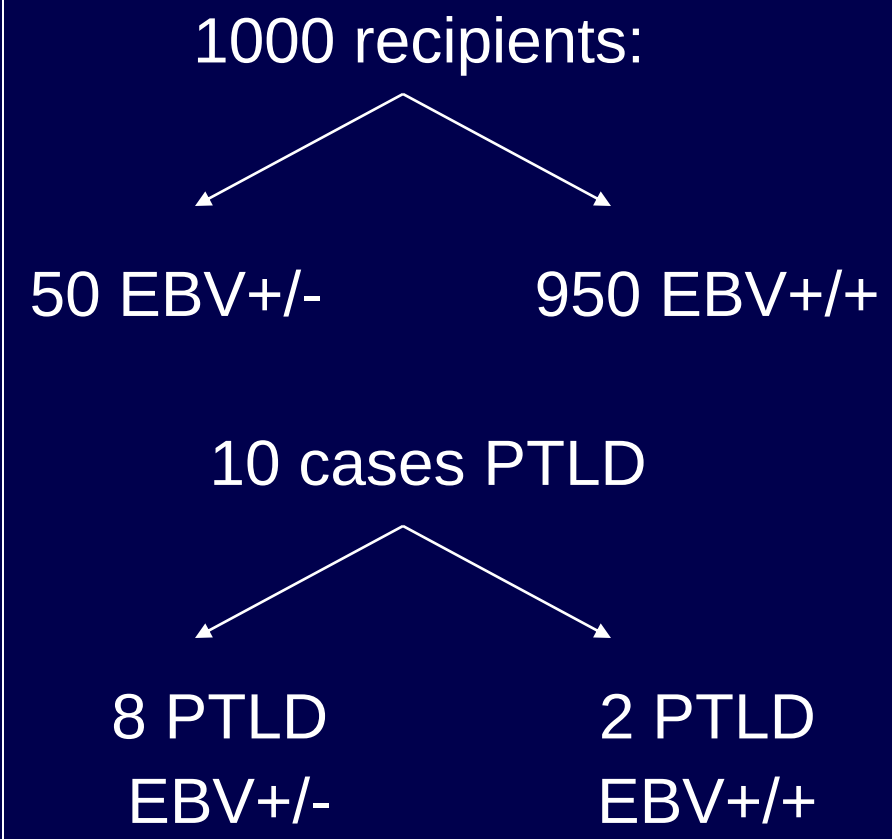
- Post-transplant infectious mononucleosis
- Plasma cell hyperplasia

Neoplasia

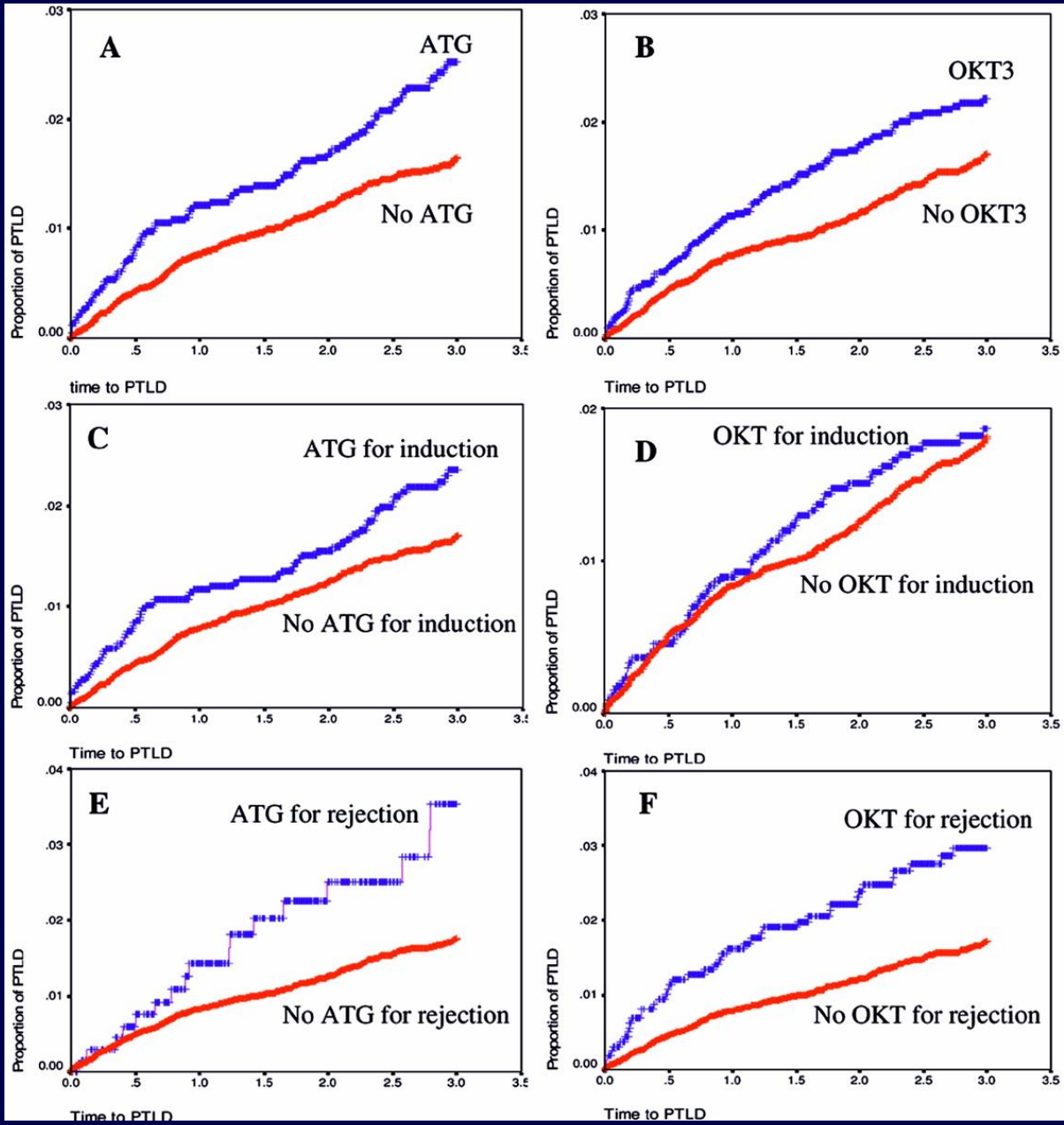
- Polymorphic B cell hyperplasia
- Polymorphic lymphoma

EBV and PTLD

- 95% of population is EBV IgG+
- ~5% of KTx recipients are EBV- recipients of EBV+ kidneys
- PTLD occurs in ~1% overall
- 80% of PTLD occurs in EBV- recipients
- Incidence of PTLD in EBV- recipients is as high as 20%!



Risk for PTLD/ Lymphoma is increased with ATG (Thymoglobulin) and OKT3



Transplantation 2005; 80(9):1233-43.

Treatment of PTLD: Immunosuppression reduction

- Limited Disease:
  - 25% reduction
    - if triple therapy, may D/C antiproliferative (i.e. mycophenolate) medication

- Extensive Disease:

  Critically ill:
  - Stop all immunosuppression
  - Prednisone at 7.5-10 mg/d
  - Frequent biopsies, avoid rejection
  - Bolus with steroids prn rejection

  Not critically ill:
  - D/C antiproliferative agent,
  - decrease calcineurin inhibitor by 50%,
  - maintain prednisone at 7.5-10 mg/d

ASTS/ASTP EBV-PTLD Task Force, Transplantation 1999; 68: 1517-25

PTLD: Rituximab or Chemotherapy?

- Of 117 patients treated for PTLD from 1996-2005 at a single center, 35 failed immunosuppression dose reduction and survived to receive rituximab, chemotherapy, or both:

- 22 received rituximab:
  - 13 had complete response (59%), those without response received chemotherapy
  - Median survival 31 months
- 23 received chemotherapy:
  - 13 had complete response (57%)
  - Median survival 42 months
  - 26% died due to toxicities of therapy

Elstrom R et al, Am J Transplantation 2006; 6: 569

PTLD:
Take-home points

- EBV related lymphoma
- Anti-Thymocyte Globulin (ATG) and OTK3 use increase risk
- Know your patient's EBV serostatus, consider more rapid IS taper in EBV+/- recipients
- If PTLD develops:
  - Reduction in immunosuppression is 1st line
  - Rituximab +/- chemotherapy next step

Candidiasis

- Most common fungal infection
- Seeing rise of resistant species
  - *C. krusei & C. glabrata*
- Pathogenesis
  - Disruption of normal defense mechanisms
    - IV lines and broad spectrum antibiotic use

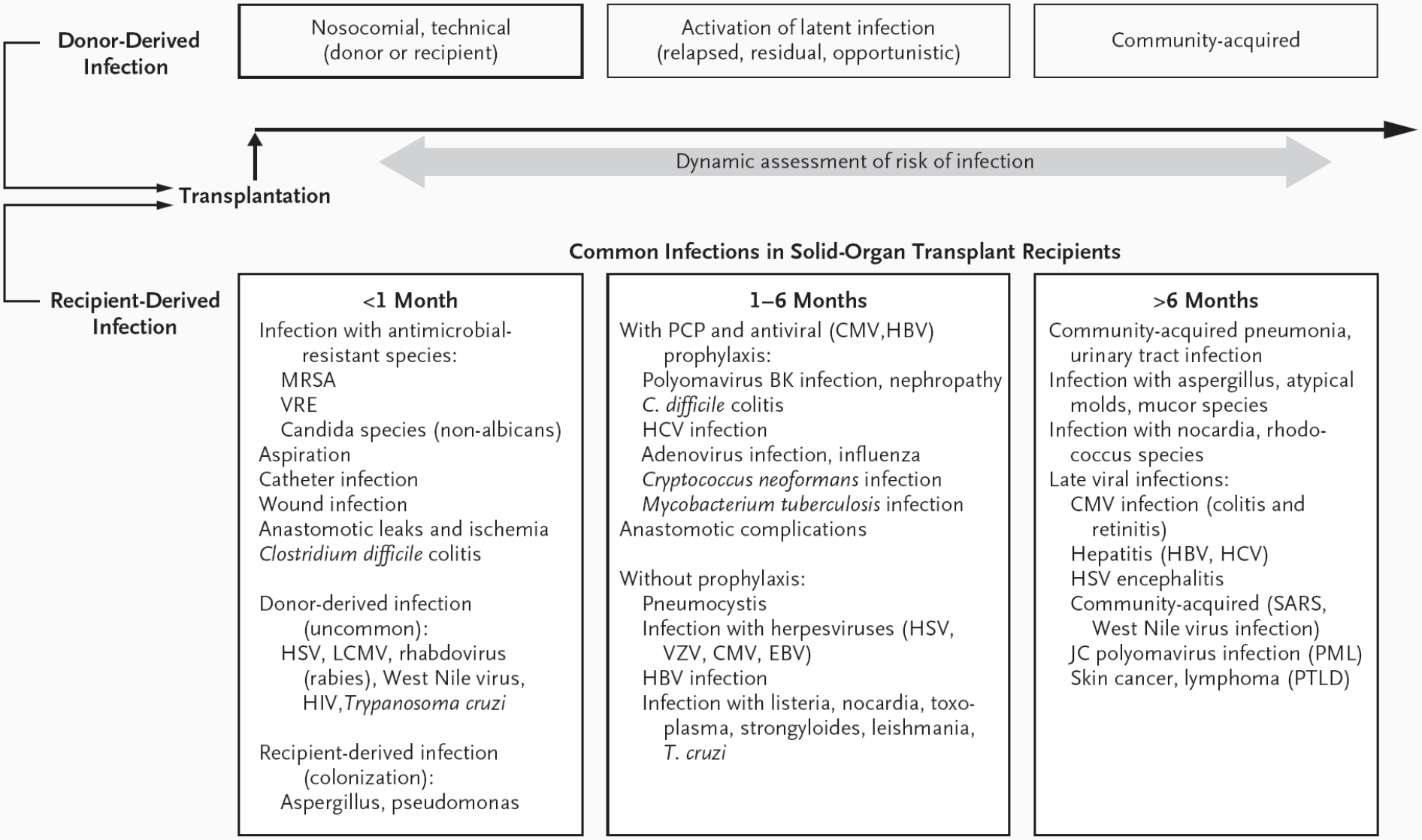
Aspergillosis

- Grows in soil and decaying organic material
- Acquired via inhalation
- Case clusters reported in oncology and transplant units
  - Mainly invasive aspergillosis

Miscellaneous Fungal Infections

- Cryptococcosis
- Endemic Infections
  - Prophylaxis often utilized
- Zygomycosis

Infectious Complications



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Catheter infection
Wound infection
Anastomotic leaks and ischemia
Clostridium difficile colitis

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- HSV, LCMV, rhabdovirus (rabies), West Nile virus, HIV, *Trypanosoma cruzi*

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1–6 Months

With PCP and antiviral (CMV,HBV) prophylaxis:
- Polyomavirus BK infection, nephropathy
- *C. difficile* colitis
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- Adenovirus infection, influenza
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Without prophylaxis:
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- Infection with herpesviruses (HSV, VZV, CMV, EBV)
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- JC polyomavirus infection (PML)
- Skin cancer, lymphoma (PTLD)

NEJM 2007;357:2601

Prophylactic Therapy Summary

- CMV
  - 3 - 12 months valgancyclovir or gancyclovir
- PCP
  - 6 – 12 months TMP/SMX
- Candidasis
  - 1 to 3 months (agents vary)
- Fungal infections
  - 6 – 12 months fluconazole for endemic fungus
  - Lifelong itraconazole in lung transplant