Infections in Adult Solid Organ Transplantation

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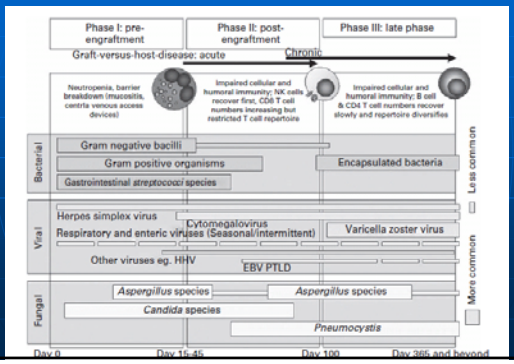
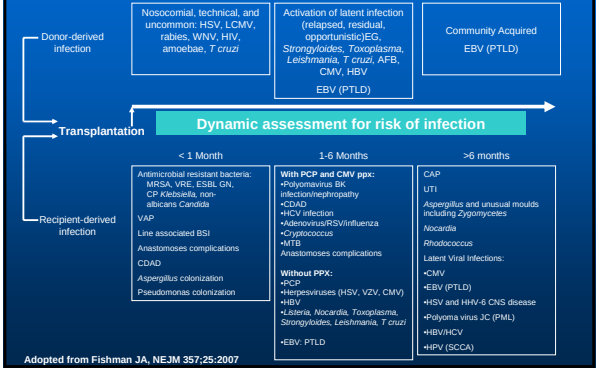
Focus

- Donor and Recipient Screening and Risk assessment
- Review of the induction and maintenance IS agents and infections associated with them
- Review standardization of the use of PCP and CMV prophylaxis
- Focus on CMV, EBV and Polyoma BK virus
- Emerging infections such as CDAD, MTB, arboviruses and parasites will be discussed separately

The "BMT Engraftment" Model

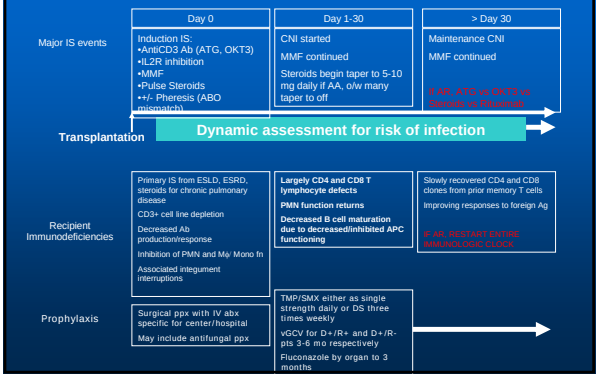


Stylized Timeline of Potential Infections post solid organ transplantation



Adopted from Fishman JA, NEJM 357;25:2007

Stylized Timeline of Immunosuppression



Donor Screening

Donor Screening

- Epidemiologic and risk factor assessment
- Chart review
  - reason for hospitalization and cause of present illness
  - If active or past infection, assessment for appropriate antibiotic management and course
  - Other possible infections? (e.g., encephalitis, sepsis/blood stream infection)
- Serologic testing, Routine
- Serologic testing, tailored
- Microbiologic review: blood, urine and respiratoroy cultures
- CXR and other pertinent radiography
- Per Center and OPO protocols, NAT for blood borne pathogens

Donor Screening

- **United Network of Organ Sharing**
  - CMV IgG
  - EBV – VCA or EBNA antibody test may be performed if the recipient is EBV seronegative
  - HIV 1,2 EIA
  - *HTLV I,2 EIA*
  - HBsAg, HBcAB, HBSAB
  - HCV EIA
  - RPR
  - Tuberculosis
    - o *Strongyloides* for donors from endemic areas
    - o *Trypanosoma cruzi* for donors from endemic areas
    - o West Nile for endemic areas
    - o Toxoplasmosis
  - Encouraged OPO specific policies re: NAT for HIV/HCV/HBV

HTLV 1-2 screening recently removed from UNOS screening criteria

Donor Related Infections

Nucleic Acid Amplification Technology and associated “windows” (NAT)

Virus	Serology Window (median, days)	NAT Window (median estimated, days)
HBV	60	25
HCV	70	8-10
HIV	23	13

Recipient Screening

Recipient Checklist

- **Epidemiologic history and screening**
  - Work, Travel/residence, hobbies, pets, military, healthcare employment, incarceration, family history including family members incarcerated or in military and where stationed
- **Vaccine history** (some centers confirm with serologies)
- **Standard serologies including**: RPR or VDRL, HIV, HBV (HBSAg, HBSAb, HBCAb), HCV, EBV and CMV. Some include Toxoplasma, VZV, HSV 1 and 2
- **PPD or equivalent**, and if prior reactive or evidence of LTBI, treatment history
- **Known infections** (e.g., MRSA, ESBL *Enterobacteracieae*, *C difficile* disease, LTBI and treatment course)
- **Assessment for latent infections** (e.g., Histoplasma, Coccidioides, Strongyloides, LTBI)
- **Possible Infections** (e.g., LCMV)
- NB: when possible, include NAT or Ag testing for pathogen if suscpected- in some cases, particulary BMT and heme malignancies, Ab screening will not be reliable.

Recipient Infection Risk Assessment: What's modifiable and what's not

- **High Risk, Peritransplant:**
  - Induction therapy with lymphocyte depletion
  - High-dose pulse steroids
  - Pheresis
  - High-risk for rejection (ABO mismatch, high PRA, etc)
  - Active infection in either donor or recipient
- **High Risk, Technical:**
  - Anastamotic leak
  - Bleeding
  - Return to OR
  - Wound site infection or dehiscence
  - Prolonged intubation
  - Prolonged use of invasive catheters
- **High Risk, Post Transplant:**
  - Graft dysfunction or DGF
  - Latent infection in Donor or Recipient
  - Acute or chronic rejection
- **Low(er) Risk**
  - Good HLA match
  - Low or Zero PRA/crossmatch
  - Immunologic tolerance
  - Short OR time
  - Technically "easy" transplant
  - Good or immediate graft function
    - "Bile on the table"
    - Urine flow
  - "Good" Antibiotic prophylaxis
    - Based upon Transplant Unit, ICU and hospital antibiograms
    - Preliminary risk assessment of patient and need for any adjustments (e.g., cefazolin won't be good for pt with recent ESBL *E coli* infection)
    - Directed therapy to latent infections (e.g., *Strongyloides, Schistosomiasis*)
- **Low(er) Risk, Post Transplant:**
  - Appropriate ABX and OI ppx
    - PCP ppx
    - Toxo ppx for hearts
    - CMV ppx
    - Directed to latent infections, e.g. LTBI, *coccidioides*, Histoplasmosis

Immunosuppression

Immunosuppression

- Goal: to prevent rejection events while minimizing collateral damage
  - CD= nonopportunistic and opportunistic infections and malignancies, and long term secondary drug effects
- Achieved by:
  - Induction Immunosuppression
    - Modified based upon organ transplanted (and amount of donor lymphoid tissue transplanted)
    - Immediately prevents any HLA or alloantigen processing
  - Maintenance immunosuppression
    - Lower level IS that permits recovery of recipient immunity to a point
    - Targeted to minimize signal transduction, signal triggering, or cell cycling.

Induction Immunosuppression

- Immediately eliminates or blocks T cell activation and antigen presentation/recognition
- Minimizes exposure to calcineurin inhibitors and reduces the need for prolonged steroid management
- Agents include:
  - Antilymphocyte Antibodies (eliminate target)
    - ATG, OKT3
  - IL-2 receptor blockade (eliminate signalling)
    - basiliximab and daclizimab
  - Block everything
    - alemtuzumab

Infectious Complications

- **ATG**:
  - **Largely bacterial**
    - K and K/P:
      UTIs>SSI>BSI>PNA
      - *Enterobacteriaceae* most common> *Enterococcus*
    - Lung, Lung-Heart:
      - *Nocardia*, despite TMP/SMX ppx. *Pseudomonas*
    - *Mycobacterium tuberculosis*
  - **Viruses:**
    - CMV- More on this later
    - HCV- higher rates of reactivation
    - BKV- primary data are conflicting and also include tacrolimus and MMF as independent risk factors, but prospective data finds strong relationship between ATG in AR and BK nephropathy
  - **Fungal Infections:**
    - PCP
    - ? *Histoplasma* (data are confounded as urinary Histo Ag may be falsely positive shortly after ATG infusion)
    - IFI not increased
- **OKT3**
  - Rarely used due to markedly increased risks of:
    - severe CMV infection,
    - invasive fungal infections and
    - EBV associated PTLD>>ATG
    - T1/2 effect markedly longer than ATG

Smith at al. Clin J Am Soc Nephrol 2007;2:1037-42

Wheat et al. Transpl Infect Dis 2004;6:23-7

Hibberd et al. Transplantation 1992;53:68-72

Abbott et al. Transpl Infect Dis 2001;3:203-11

Bustami et al. Am J Transplant 2004;4:87-93

IL-2R associated infections

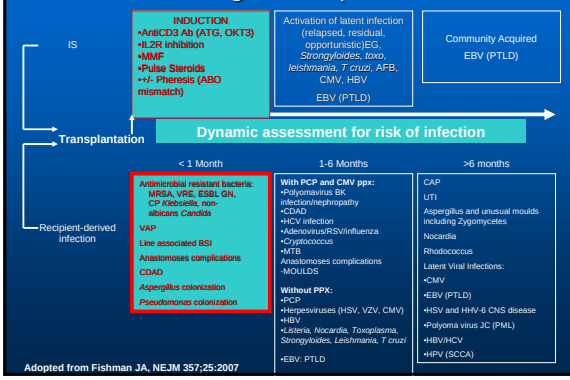
- Overall rates of bacterial, viral including CMV, and HCV reactivation, and fungal infections are not statistically different than that of placebo or other induction therapies *if appropriate PCP and CMV ppx are used*.
- Unlike OKT3, there was no increased risk for EBV-associated PTLD.

Campath (alemtuzemab, Anti CD52)

- Humanized mouse monoclonal antibody directed against the CD52 surface antigen.
  - Mature and long-lived T cells,
  - B cells including plasma cells,
  - APC including monocytes, macrophages, and dendritic cells.
  - PMNs and NK Cells
- Mechanisms for lymphcyte depletion includes:
  - complement fixation
  - ADCC
  - growth inhibition as a result of crosslinking the CD52 target antigen.
  - Duration of action may be as long as 3-12 months (dose dependent)

- The doses of alemtuzumab in SOT induction are lower than what are used in heme-malignancies. Complications have included:
  - Pseudomonas sepsis
  - Pulmonary and disseminated nocardiosis
  - MTB reactivation with dissemination
  - NTM infection (PNA, *M kansasii*)
- Infectious complications clearly dose related:
  - Peleg et al, CID 2007:
    - Re-use of alemtuzumab in AR increased infectious complications minimum of 5 fold vs IS induction alone
    - Lung, multi-organ or repeat organ, small intestine were independent predictors of infectious complicaitons

Stylized Timeline of Potential Infections post solid organ transplantation



Adopted from Fishman JA, NEJM 357;25:2007

Antimicrobial Resistance in Primary Bacterial Isolates, BIDMC Transplant Unit 2002-2005

Organism	N	Antimicrobial	% Susceptible		OR (95% CI)	*P*
			HOSP	OLT		
Klebsiella	13	ceftriaxone	82	38	7 (2-28)	0.0001
		pip/tazo	91	38	15 (4-61)	<0.001
		gentamicin	86	38	10 (3-38)	<0.001
Pseudomonas	11	ceftazidime	78	82	0.8 (0.1-3.9)	ns
		imipenem	85	91	0.5 (0.01-3.9)	ns
		gentamicin	77	91	0.3 (0.1-2.4)	ns
E coli	9	ceftriaxone	98	78	13 (1.3-70)	0.001
		levofloxacin	86	55	5 (0.1-100)	0.001
Enterobacter	6	ceftazidime	81	33	9 (1.1-100)	0.006
		gentamicin	100	33	*	<0.001
S. aureus	11	oxacillin	43	45	0.9 (0.2-4)	ns
Enterococcus	39	vancomycin	73	33	5.3 (2.5-11.3)	<0.001

Fungal Infections Associated with SOT

Table 2
Timetable and clinical syndromes of invasive fungal infections in solid organ transplant recipients

Infection and Time of Occurrence	Setting, Risk Factors	Clinical Manifestations
Early (first month)		
Acute disseminated candidiasis	Complications of surgery, no azole prophylaxis	Fever ± hypotension
Intermediate (1–6 mo)		
Invasive aspergillosis*	Immunosuppression for the prevention or treatment of rejection; reactivation of immunomodulating viruses (CMV, others)	Fever (may be absent), dry cough, dyspnea
Late (>6 mo)		
Cryptococcosis	Chronic immunosuppression; risk increases with chronic rejection	Headache, fever, mental status changes, skin lesions
Endemic mycoses	Chronic immunosuppression; risk increases in chronic rejection	Fever of insidious onset, respiratory complaints, signs of metastatic infection (manifestations depend on the organs involved)

* Less frequently caused by other molds such as *Fusarium* spp, Zygomycetes, and others.

Nucci and Anaissie, Clin Chest Med 2009;30:295-306

Preliminary univariate risk factor analysis for invasive fungal infection in OLT, 2002-2005

Variable	IFI		OR (95% CI)	*P* value
	No (%) N=40	Yes (%) N=13		
Age (years)	54	45	---	0.07
DDLT	37 (92)	10(77)	0.3 (-.03-2.4)	0.12
Roux-en-Y anastamoses	**4 (10)**	**5(38)**	**5.6 (1-34)**	**0.02**
Median Warm ischemic time (minutes)	55	33	---	0.23
Median Cold ischemic time (minutes)	452	469	---	0.8
Blood Products >40 Units	**7 (18)**	**9 (69)**	**10.3 (2-57)**	**<0.001**
Colonization Pre-Transplant	**2(5)**	**11(84)**	**104.5(10-1329)**	**<0.001**
Repeat OR <5 days not including re-transplant	**2(5)**	**7 (54)**	**22 (3-244)**	**<0.001**
Repeat Transplant	**1 (2.5)**	**3 (23)**	**11.7 (0.8-629)**	**0.002**
Vascular complication	**3 (7.5)**	**7 (54)**	**14.4 (2.3-103)**	**<0.001**

Preliminary multivariate logistic regression analysis for risk factors associated with IFI*

Variable	Adjusted OR (95% CI)	*P* value
Pre-transplant colonization	104.3 (9-1250)	<0.001
Return to OR < 5 days excluding re-transplant	22 (1.3-381)	0.03

*Vascular complications included HAT/HAS, portal vein thrombosis or anastomotic repair, and could not be included in the model.

Modifiable risk and effect of antifungal prophylaxis in a priori defined high risk OLT pts who developed IFI by day 100.

Kaplan-Meier (KM) day 100 estimates and 95% confidence intervals (CI) for risk of fungal infection: modified intent-to-treat population

	Day 100 KM estimate (95% CI)		
Fungal infection endpoint	Combined treatments	L-amB	Fluconazole
Proven or probable IFI	0.17 (0.09–0.29)	0.18 (0.09–0.36)	0.15 (0.06–0.35)
Proven or probable IFI or empiric systemic antifungal therapy	0.37 (0.26, 0.50)	0.43 (0.28, 0.62)	0.29 (0.16, 0.50)

L-amB, liposomal amphotericin B; IFI, invasive fungal infections.

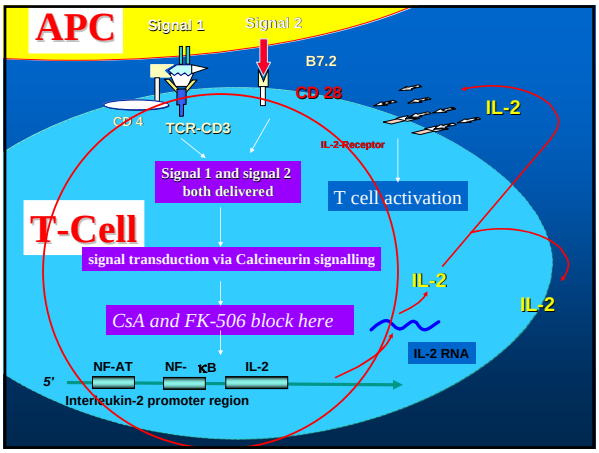
Hadley et al. Transplant Infect Dis 2009;11:40-8

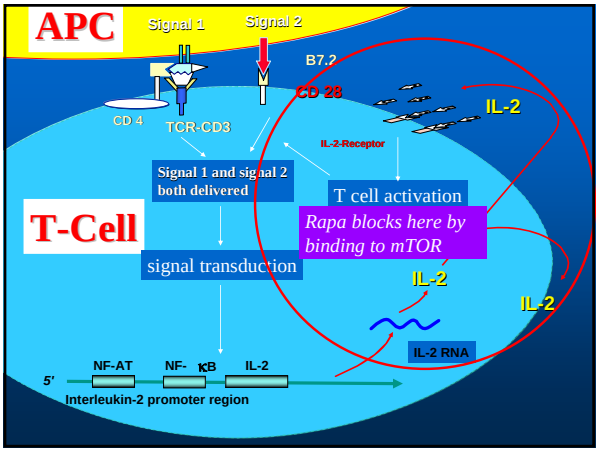
Maintenance Immunosuppression

- 1 from:
  - Calcineurin Inhibitors (CNI)
    - cyclosporin or tacrolimus or
  - Rapamycin
    - (conversion from CNI, never used initially due to inhibition of endo and epithelial cell proliferation)
  - PLUS:
- 1 from: antimetabolite
    - mycophenylate mofeteil or azathioprin
- Sometimes, low dose prednisone
  - associated with race/ethnicity

Calcineurin inhibition

- Cyclosporin (Neoral®, Sandimmune®, Gengraf®)
- Tacrolimus (FK506, Prograf®)
- The mechanisms of calcineurine inhibitors (CNIs) converge at the inhibition of the calcineurin
  - (a signal transduction pathway that leads to NFkB activation and upregulation of IL-2 production).
- This inhibition ultimately inhibits the production and secretion of IL-2.
  - The interaction between IL-2 and the IL-2 receptor is crucial in the activation and differentiation of B and T cells.
  - Therefore, halting the rejection process at this step is highly effective at combating rejection.





Antimetabolites

- Mycophenolate Mofetiel-
  - Inhibits activated lymphocytes preventing cell cycling
  - Uncertain therapeutic window
- Azathioprine
  - Precursor to 5 Mercaptopurine
  - This ultimately prevents mitosis and proliferation of rapidly dividing cells, such as activated B and T lymphocytes.
    - blocks most T-cell functions
    - inhibits primary antibody synthesis
    - little effect on established immune responses, and is therefore effective only in the prevention (not treatment) of acute rejection.

CMV

- Association with ATG well known and is the result of TNFα release at the time of fever with ATG infusion. Cellular NFκB binds to a promotor region of the CMV immediate early antigen gene.
- Other factors associated with CMV activation include:
  - Donor/recipient status
  - Degree of T lymphocyte depletion (both CD4 and CD8, and ratio as TH-2 responses far less protective than TH-1/CMI)
  - Type and dosage of lymphocyte depleting agents, including re-treatment for AR
  - Prolonged high-dose maintenance agent like MMF, AZA, pred if used,
  - CMV prophylaxis used or not

Reinke P, et al. *Transpl Infect Dis.* 1999;1:157-164.

Pathways for CMV Reactivation From Latency

- Up regulation of TNF-alpha, IL-2, and proinflammatory cytokines
- Activation of leukocytes, endothelial cells, smooth muscle cells, and dendritic cells
- Despite use of IL-2 and cell cycle inhibiting agents, the CMV activation overcomes maintenance IS effects, and graft alloantigens becoming targets, resulting in acute rejection
- The Converse is also true: AR events even prior to IS intervention can result in CMV reactivation

Reinke P, et al. *Transpl Infect Dis.* 1999;1:157-164.

Mechanisms by Which CMV May Harm the Allograft: Cellular Effects

- Endothelial cells infected with CMV⇒↑ neutrophil and CTL responses
- Increase of MHC antigens
  - Sequence homology and immunologic cross-reactivity between CMV IE antigen and HLA-DRβ chain
  - CMV-infected cells produce glycoprotein homologous to MHC class I antigens
- Upregulation of proinflammatory adhesion molecules
- CMV⇒ autoantibodies; humoral rejection

Toyoda M, et al. *Transpl Immunol.* 1997;5:104-111. Iwamoto GK, et al. *J Clin Invest.* 1990;85:1853-1857. Waldman WJ, et al. *Transplantation.* 1998;66:67-77. Craigen JL, et al. *Immunology.* 1997;92:138-145. Fujinami RS, et al. *J Virol.* 1988;62:100-105. Beck S, Barrell BG. *Nature.* 1988;331:269-272.

Incidence of Graft Failure in Hepatitis C Liver Recipients Based on CMV Infection

Infection Status	Graft Failure
CMV (negative)	13/18 (19%)
CMV (positive)	13/25 (52%)

P=0.02

Graft failure definition – cirrhosis, listing for retransplantation, or death.
Courtesy of Russell Wiesner, MD.

Risk of CMV Disease in SOT Recipients

Serologic Status

Donor	Recipient	Immunosuppressive Regimen	Incidence of Disease
+	-	CyA or FK, pred, MMF or Aza	50+%
?	+	CyA or FK, pred, MMF or Aza	10%-15%
?	+	Induction antilymphocyte Ab, followed by standard 3 drugs	25%-30%
?	+	Antirejection antilymphocyte Ab, followed by standard 3 drugs	65%
-	-	Any	0%*

CyA = cyclosporine; FK = tacrolimus; pred = prednisone; MMF = mycophenolate mofetil; Aza = azathioprine; ab = antibody. *Provided "pedigreed" leukopheresed blood products used.

Slifkin et al. Drugs 2004;64:2763-92

Rate of CMV Disease Despite Antiviral Prophylaxis in High Risk recipients (D+/R-)

	Renal Transplants	
	Placebo	Valacyclovir
Prophylaxis (3 mo)	45%	3%
Postprophylaxis (6 mo)	45%	16%

	Hepatic Transplants	
	Placebo	Ganciclovir (po)
Prophylaxis (3 mo)	44%	5%
Postprophylaxis (6 mo)	44%	15%

Lowance D, et al, for the International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. *N Engl J Med.* 1999;340:1462-1470.
Razonable RR, et al. *J Infect Dis.* 2001;184:1461-1464.
Gane E, et al, for the Oral Ganciclovir International Transplantation Study Group. *Lancet.* 1997;350:1729-1733.

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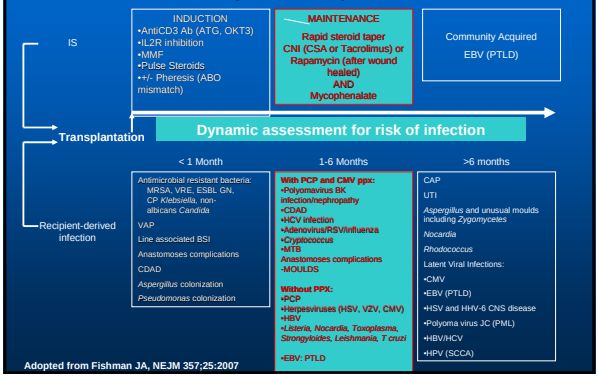


Adopted from Fishman JA, NEJM 357;25:2007

Modalities to prevent OIs

- TMP/SMX[1]-
  - well proven for PJP/PCP ppx;
  - may limit *Nocardia* complications such as dissemination,
  - very useful in heart/heart-lung transplants and preventing toxoplasma reactivation
  - Other bacterial infections may be prevented (e.g., *Listeria*, staphylococci, GN UTIs)
- Fluconazole[2]-
  - Colonization and invasive rates statistically reduced in fluconazole treated OLT recipients
  - Useful for secondary prophylaxis for endemic mycoses*

*primary agent for *Coccidiodes immitis* and *Cryptococcus neoformans*; secondary agent for *Histoplasma capsulatum*[3-5]

1. Fishman, N Engl J Med 2007;357:2601-14
2. Winston et al. Ann Intern Med 1999;131:729-37
3. IDSA guidelines for treatment of Coccidioides 2005; 41:1217–1223
4. IDSA guidelines for the management of Cryptococcal disease, 2010;50 e version
5. Histoplasmosis Clinical Infectious Diseases 2007; 45:807–25

Modalities to Prevent Viral Infections in SOT

Modality	CMV	HSV	VZV	EBV	Other
Avoidance	+	-	+	-	HCV, HBV, HIV
Vaccine	-	-	+	-	HBV, HAV
Passive Immunity	CMVIg	-	Vzig	-	HBIG
Immune Modulation	-	-	-	-	IFN for HBV and HCV
Antiviral agents	GCV, ACV, vGCV	ACV, vACV, fACV, vGCV	ACV, vACV, fACV, vGCV	?vGCV	3TC, FTC, TDF, ADF, ECV

Slifkin et al. Drugs 2004;64:2763-92

DEFINITIONS OF PROPHYLAXIS AND PRE-EMPTIVE THERAPY

Strategy	Definition	Advantages	Disadvantages
Prophylaxis	Administration of an agent prior to infection or disease	Ease of administration to defined individuals	Low risk persons exposed to unnecessary agent with known toxicities Prolonged or incorrect dosing may lead to emergence of resistance
Pre-Emptive	Highly directed therapy to persons who exhibit positive marker (pDNA PCR, bDNA PCR, or antigenemia	Minimizes unnecessary exposure to drug Minimizes risk of emergence of resistance	Requires validated highly sensitive surveillance at biologically reasonable intervals

Efficacy and Safety of Valganciclovir vs. Oral Ganciclovir for Prevention of Cytomegalovirus Disease in Solid Organ Transplant Recipients

Carlos Paya[a,*], Atul Humar[b], Ed Dominguez[c], Kenneth Washburn[d], Emily Blumberg[e], Barbara Alexander[f], Richard Freeman[g], Nigel Heaton[h], Mark D. Pescovitz[i] on behalf of the Valganciclovir Solid Organ Transplant Study Group

[a]Mayo Clinic, Rochester, MN, USA
[b]University Health Network, Toronto General Hospital,

was comparable by 12 months (48.5% valganciclovir vs 48.8% ganciclovir). Time-to-onset of CMV disease and to viremia were delayed with valganciclovir; rates of acute allograft rejection were generally lower with valganciclovir. Except for a higher incidence of neutropenia with valganciclovir (8.2%, vs 3.2% ganciclovir) the safety profile was similar for both drugs. Overall, once-daily oral valganciclovir was as clinically effective and well-tolerated as oral ganciclovir tid for CMV prevention in high-risk SOT recipients.

Am J Transplant 2004;4:611-20

Table 3: (A) Summary of cytomegalovirus (CMV) disease up to 6 and 12 months post-transplant in the intent-to-treat (ITT) population, as assessed by the Endpoint Committee (data are cumulative, i.e. events up to 12 months post-transplant include the events up to 6 months). (B) Summary of cytomegalovirus (CMV) disease up to 6 and 12 months post-transplant (intent-to-treat (ITT) population)

	Percentage (no.) of patients			
	Valganciclovir (n = 239)		Ganciclovir (n = 125)	
(A)	6 months	12 months	6 months	12 months
CMV disease*	12.1% (29)	17.2% (41)	15.2% (19)	18.4% (23)
CMV syndrome	5.0% (12)	7.9% (19)	10.4% (13)	12.0% (15)
Tissue-invasive	7.1% (17)	9.2% (22)	4.8% (6)	6.4% (8)
Hepatitis	6	6	1	2
Pneumonia	2	3	1	2
Gastrointestinal tract disease	12	17	4	5
Other	1	1	0	0
Patients inevaluable	5.0% (12)	9.2% (22)	5.6% (7)	9.6% (12)

*95% CI difference in proportions (−0.042, 0.110 at 6 months and −0.068, 0.098 at 12 months).

	Percentage (no.) of patients	
(B) CMV disease*	Valganciclovir (n = 239)	Ganciclovir (n = 125)
Endpoint Committee		
6 months	12.1% (29)	15.2% (19)
12 months	17.2% (41)	18.4% (23)
ASSE*		
6 months	11.3% (27)	12.8% (16)
12 months	15.1% (36)	15.2% (19)
Investigator-treated CMV disease events		
6 months	23.0% (55)	21.6% (27)
12 months	30.5% (73)	28.0% (35)

*All Signs, Symptoms and Laboratory criteria fulfilled (i.e. strict protocol definition of CMV disease).

Conclusions

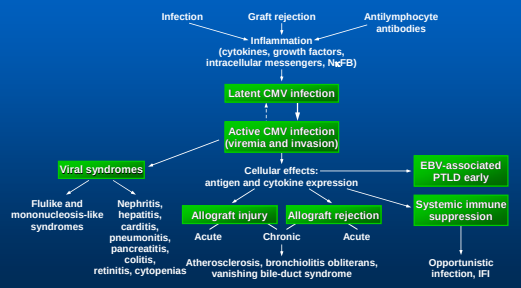
- By understanding the pharmacology, epidemiology and associated risk factors associated with infectious complications post organ transplant, we can modify those outcomes
  - Careful pre-transplant screening of the recipient and donor
  - Appropriate antimicrobial prophylaxis
  - Remembering to “restart” the immunologic clock with Acute Rejection therapies

More slides

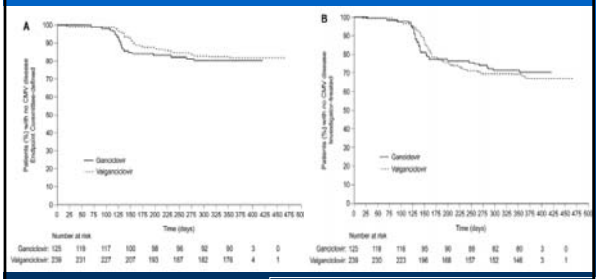
- More Slides

CMV

Effects of CMV: Overview



Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med.* 1998;338:1741-1751.



Paya et al. Am J Transplant 2004;4:611-20

Survival analyses demonstrating statistical non-inferiority between vGCV and oral GCV ppx arms by end-point defined and ITT analyses

Table 5: Summary of acute graft rejection by organ type up to 6 and 12 months post-transplant (intent-to-treat (ITT) population)

	Percentage (no.) of patients			
	Valganciclovir (n = 239)		Ganciclovir (n = 125)	
Organ type	6 months	12 months	6 months	12 months
Total	29.7% (71)	32.6% (78)	36.0% (45)	36.0% (45)
Liver (n = 177)	27.1% (32)	28.8% (34)	35.6% (21)	35.6% (21)
Kidney (n = 120)	21.0% (17)	23.5% (19)	23.1% (9)	23.1% (9)
Heart (n = 56)	57.1% (20)	65.7% (23)	71.4% (15)	71.4% (15)
Kidney-pancreas (n = 11)	40.0% (2)	40.0% (2)	0% (0)	0% (0)

While overall, the results showed noninferiority of valGCV to GCV with regards to CMV disease, there was overall superiority regarding acute rejection rates. Though the investigators did not show the CMV rates by organ transplanted, the clear superiority was in the KT recipients receiving valGCV. There was a suggestion that GCV was superior in OLT.

Paya et al. Am J Transplant 2004;4:611-20

EBV

- EBV induced post-transplant lymphoproliferative disorders (PTLD):
  - Heterogenous group of lymphoproliferative disease associated with EBV infections in solid and liquid organ transplant recipients.

- Allogeneic BMT/Stem Cell Transplant
  - EBV transformation of **donor** B cells (occassionally T cells)
  - T-cell depleted or antigen-mismatch transplants (MUD), cord-blood allogeneic HSCT are primary risk factors.
    - NB- this is highly correlated to the type of marrow conditioning regimen applied at the time of transplantation.
- Solid Organ Transplant
  - EBV transformation of **recipient** cells in majority of cases;
  - EBV transformation of **donor** lymphocytes within the donor organ has been described
  - ALAb used at induction, with repeat exposure due to 1) retransplantation (new organ, second organ); 2) AR that is steroid unresponsive.

Incidence

- Pediatric population
  - 3-4% (OLT with cyclosporin)
  - 6-13% (tacrolimus)
  - 14-27% (OKT3 and prednisone resistant rejection)
  - Mortality: 10-20%
- Adult population
  - 0.8-3% (OLT with cyclosporin)
  - 5-10% (thoracic organ transplant)
  - >20% (steroid resistant rejection)
  - Mortality: 50-80%

Ho, et al. Transplantation 1988;45:719 Sokol et al. Transplantation 1993;56:1394

Reyes et al. Transplant Proc 1996;14:214 Putnam, et al Transplant Proc 1996;28:2777

Cacciarelli et al. Liver Transpl Surg 1997;3:C-47

Incidence of EBV+ and EBV- PTLD by Organ Transplanted

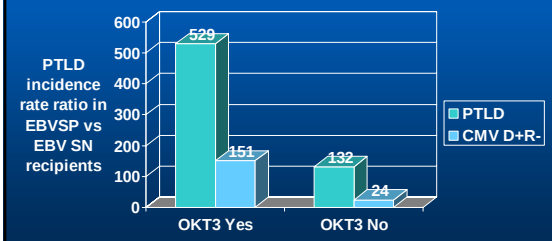
Table XII. Incidence of post-transplant lymphoproliferative disorders (PTLD) in solid organ transplantation

Organ	Overall [% (no.)]	Reported (%)
Kidney	1.3 (27/2017)	0.2–6.5
paediatric	12 (10/81) [EBV R– 10/46 (22%) vs EBV R+ 0/35 (0%)]	na
Liver	2.2 (8/359)	2.1–2.6
paediatric	5 (2/40) [protocol for PTLD prophylaxis]	na
Heart	2.5 (20/813)	1.9–7.2
Pancreas-kidney	5.4 (6/111)	2.7–11
Lung ± heart	6.5 (24/372)	1.8–20
paediatric	14 (2/14)	na
Intestine	9.4 (3/32)	na
paediatric	32 (13/41) [EBV R– 31% (4/13) vs EBV R+ 32% (9/28)]	na

EBV = Epstein-Barr virus; **na** = not applicable; **R+** = recipient seropositive; **R–** = recipient seronegative.

Slifkin et al. Drugs 2004;64:2763-92

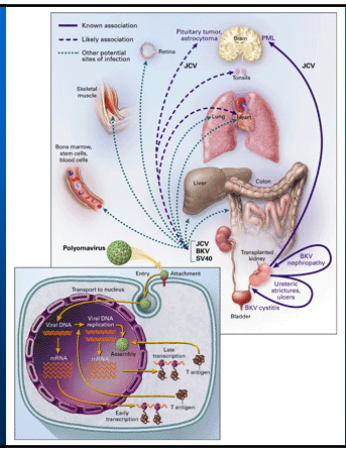
Incidence of PTLD in EBV+/- Recipients by risk factors



Walker et al. Clin Infect Dis 1995;20:1346

BK

Human Polyomaviruses	Date identified	Major Cell type infected	Associated disease
BKV	1971 (Gardner et al)	Kidney epithelial and uroepithelial cells	Hemorrhagic cystitis, BK nephropathy, encephalitis
JCV	1971 (Padgett et al)	Kidney epithelium, B cells, oligodendrocytes	PML
KI	2007 (allander et al)	?	?
WU	2007 (Gaynor et al)	?	?
MCV	2008 (Feng et al)	Merkel Cells	Merkel Cell Carcinoma



Adopted from Fishman JA, NEJM 2002 347,527

BK complications

- BK viruria and viremia is reported in up to 80% of renal transplant recipients with 10% progressing to BKN with graft loss occurring in up to 90% of these cases
  - Clearly more strongly associated with BK viremia as most viruria is asymptomatic shedding
  - Pathology is proximal tubular necrosis and denudation of the basement membrane directly associated with lytic phase of viral replication
    - Pathognomonic cells shed in urine are the Decoy Cells (uroepithelium with viral inclusions)

- No single risk factor for development of BKN
  - Overall degree of IS and not the specific agents employed is a key factor, though it's clear that BKN rarely occurs in other non-renal solid organ transplants or in allogeneic stem cell transplants
    - In these cases, only asymptomatic viruria occurs or hemorrhagic cystitis
  - In renal transplantion, other factors appear to be donor seropositive, male sex, older age (>55), specific HLA loci and HLA mismatches, and use of AL Ab antirejection therapy.

Treatment

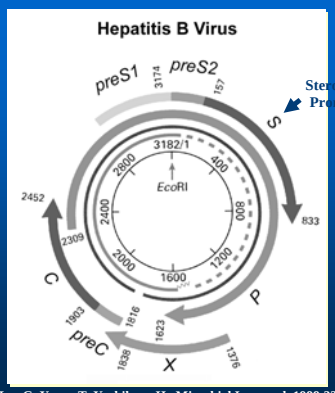
- Primary treatment of BKN is decreasing immunosuppression
- Alternatives is to replace MMF with lefluonomide
- Antiviral therapy with cidofovir is controversial but may be useful
- Some weak anecdotal data suggesting quinolones may play a roll in preventing or decreasing severity of BKN in viremic pts

HBV

- **HBSAg+**
  - expressing viral surface protein and active replication
- **HBCAb+**
  - Indicates prior infection; may be false positive (up to 10% of pts with ESRD can have weakly positive HBCAb EIA); in case of lost HBSAb, only useful for marker of prior infection. NOT protective
- **HBSAb+**
  - Minimum EIA titer of 10IU/mL to trigger "positive" result in labs; strongly neutralizing
- In pts who had prior HBV infection (ie., HBSAb+/CAb+ OR HBSAb-/CAb+), though they do not have circulating or replicating virus, they have nonreplicating HBVcccDNA dormant in the hepatocyte nucleus. This serves as a reservoir for potential future reactivation within the recipient. Must also be considered in OLT if the DONOR is HBCAb+

Agents associated with HBV reactivation

- Pulse steroid exposure
- Rituximab therapy
- Antilymphocyte antibodies
- IL2R antibodies
- alemtuzumab
- Pheresis
- Acute rejection therapy



Masuda M, Lee G, Yuasa T, Yoshikura H., Microbiol Immunol. 1988;32(7):741-7.

Table 1. Etiologic Classification of Acute Flares in Chronic Hepatitis B

Spontaneous reactivation of chronic hepatitis B
Reactivated hepatitis due to immunosuppressive medications
Cancer chemotherapy
Antirejection drugs
Corticosteroids
Resulting from antiviral therapy
Interferons
Nucleoside analogues
Corticosteroid withdrawal
Induced by HBV genotypic variation
Precore mutant
Core promoter mutant
HBV DNA polymerase mutant
Due to superimposed infections with other hepatotropic viruses
Hepatitis A virus
Hepatitis C virus
Hepatitis delta virus
Caused by interaction with HIV infection
Reactivated hepatitis
Effect of immune reconstitution therapy

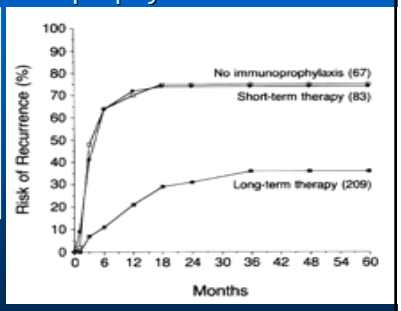
Perrillo RP. Acute flairs in chronic hepatitis B: the natural and unnatural history of an immunologically mediated liver disease. Gastroenterology 2001;120:1009-22.

HBV recurrence post orthotopic liver transplantation with and without passive immunoprophylaxis

359 patients evaluated from 372 consecutive patients expressing HBSAg transplanted in 17 centers from 1977-1990.

Short Term = 2 months HBIG

Long Term = 6 months HBIG



Samuel D, et al. N Engl J Med 1993;329:1842-7.

Antiviral Agents

- Various studies are assessing the utility of lamivudine vs adefovir vs entecavir for secondary ppx in HBV D+/R- or R+. Much is center specific; at present, standard of care is use of HBIG.

Summary and Conclusions

- Organ and recipient survival as well as acute rejection rates have markedly improved with more targetted immunosuppression approaches
- Post-transplant recipient infections are the result of both recipient and donor factors

- Modifiable risk factors include:
  - Good pre-transplant screening of both the donor and the recipient
  - Use or modified use of antilymphocyte depleting antibodies induction
  - Minimizing steroid exposure
  - Protocolizing OI prophylaxis based upon Donor and Recipient serologic history and automatically reinitiating in cases of AR

- Nonmodifiable risk factors are largely technical and include:
  - Time of transplant surgical complications
  - Post-surgical complications such as anastamotic dehiscence, post-surgical bleeding in high-risk patients
  - ABO or high-grade HLA mismatches in the cases of Priority 1 transplants

- It is a must for the Transplant ID specialist to understand the immunologic alterations associated with IS and to be available for ad hoc discussions at time of donor assessment.