How to Deal with Emerging & Re-emerging Infections in Transplantation

The 46th Annual Meeting of IDAT, 10-11 October 2020: Emerging and Re-emerging Infectious Diseases: A Continuous Challenge

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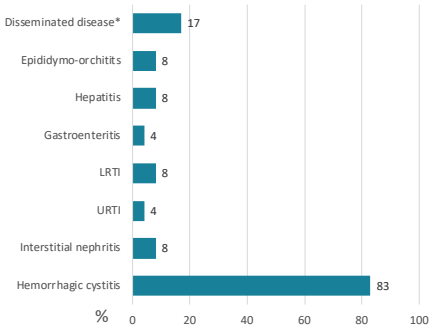
Outlines

- Emerging transplant infections
  - Adenovirus
  - BK polyomavirus
  - Cytomegalovirus

Adenovirus Infection in Thai KT Recipients

- Retrospective study 2015-2019 (Rama)
- Prevalence: 24/752 KT (3.2%)
- Early ≤ 3 mo (50%) vs. late-onset >3 Mo (50%)
- Early-onset infection tend to have
  - Lymphopenia(ALC <1,000 cells/mm^3)
  - More co-infection esp. CMV
  - More received IV cidofovir
  - Outcome: allograft dysfunction, rejection, mortality (P = NS)

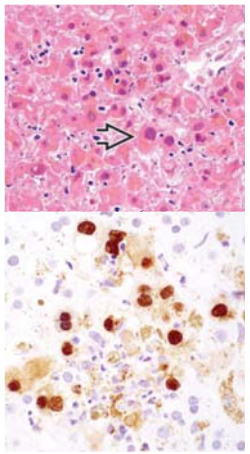


*Disseminated disease: Two or more organs are involved, not including viremia

Bruminhent J, Watcharananan SP. Open Forum Infect Dis. 2019 Nov 13;6(12):ofz489.

Lab Diagnoses

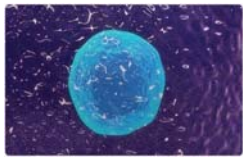
- Nucleic acid amplification testing
  - PCR
- Viral culture
- Rapid antigen assay
- Histopathology
  - ***"Smudge cells"***
  - Immunohistochemical staining



https://basicmedicalkey.com/adenovirus-6/

Management of Adenovirus infection

- **Immune reconstitution**
  - –Immunosuppression reduction
  - –IVIG
  - –Adoptive ADV-specific T cell



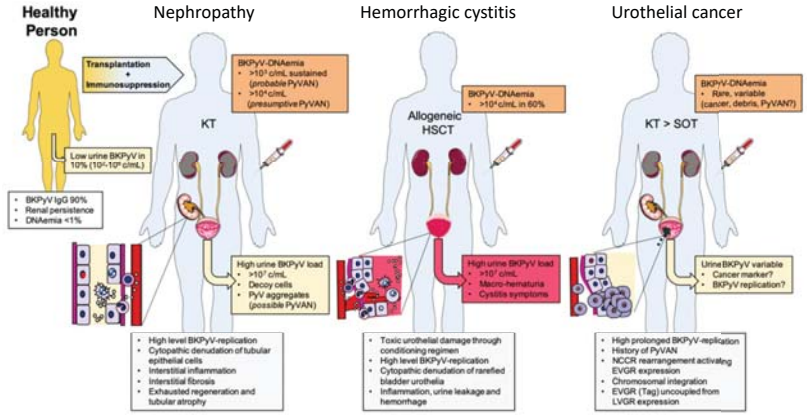
- **Antiviral therapy: cidofovir**
- **Dosing** + 0.9%NSS 100 mL IV drip in 90 mins
  - 1 mg/kg 3 times/wk
  - 5 mg/kg/wk for 2 wks then 5 mg/kg every other wk until clinical resolution and VL (-) x 3 1-wk apart, from the sites that were originally positive
  - 0.5 mg/kg 3 times/wk (CrCl <50 mL/min)
- **Probenecid**
  - 4 tabs PO 3 h prior to cidofovir infusion
  - 2 tabs PO at 2 h and 8 h after completion of cidofovir
- **Aggressive IV hydration**
  - 0.9%NSS 1,000 mL drip in 2 h prior to cidofovir
  - 0.9%NSS 1,000 mL drip in 3 h start with cidofovir

Florescu DF. Clin Transplant. 2019 Sep;33(9):e13527

Human Polyomavirus (PyV) Infection

Polyomavirus	PyV	Syndrome
BK virus	PyV1	Hemorrhagic cystitis, BKV associated nephropathy (BKVAN)
JC virus	PyV2	Progressive multifocal leukoencephalopathy, JCV-associated nephropathy
KI virus	PyV3	? Respiratory tract disease
WU virus	PyV4	? Respiratory tract disease
Merkel cell virus	PyV5	Merkel cell carcinoma
Human polyomavirus 6	PyV6	?clinical significance
Human polyomavirus 7	PyV7	pruritic rash and viremia in lung transplant recipients
Trichodysplasia spinulosa virus	PyV8	Trichodysplasia spinulosa
Human polyomavirus 9	PyV9	Identified in blood & urine of an asymptomatic KT recipient
MXPyV, MWPyV	PyV10	?diarrhea
STLPyV	PyV11	Detected in stool sample, ?clinical significance
Human polyomavirus 12	PyV12	Detected in stool sample, ?diarrhea
New Jersey PyV	PyV13	Detected from muscle biopsy in pancreas transplant recipient with systemic vasculitis, myositis and retinal blindness

Polyomavirus (PyV)

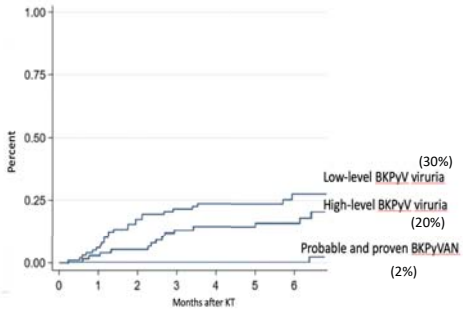


Graf FE, Hirsch HH. Emerging transplant infections. Cham, Switzerland: Springer Nature, 2020:1–26.

BKPyVAN in Thai KT Recipients

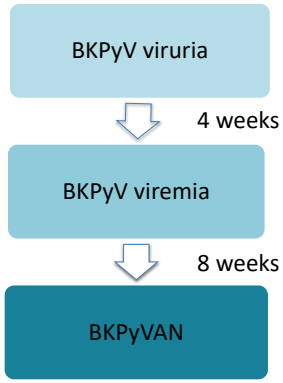
- A prospective study in 2019 (Rama)
- Preemptive BKV VL monitoring
- 90 patients, 37% female
- 64% deceased-donor KT
- 68 % induction therapy
- Incidence of high-level BKPyV viruria (urine BKV VL $>10^7$ cps/mL) within 6 months was 20%
- Risk factors (multivariate analysis)
  - Panel-reactive antibody of 11-50%
  - %NK cells
  - %VP1-specific NK cells

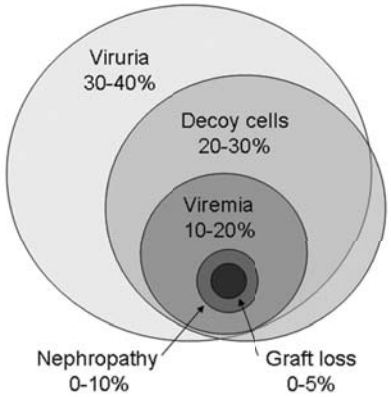
Cumulative incidence BKPyV infection within 6 months after KT



Siripoon T. Kantachuvesiri S, Apiwattanakul N, Bruminhent J. ID week 2020 Poster presentation No. 1189

Timing & Prevalence of BKPyVAN





Randhawa P, Transplant Infections 2012, Bohl D L et al. CJASN 2007

Definition & Intervention for BKPyVAN

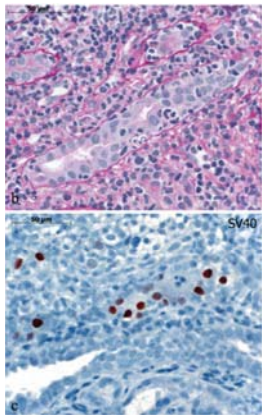
Testing		Possible	Probable	Presumptive	Proven
Urine	High level viruria -Decoy cells -BKV DNA load > $7\log_{10}$ cp/mL -BK VP1 mRNA load >6.5 log10cp/ng RNA -PyV particles	+	+	+	+
Plasma	Viremia -BKV DNA load > $3\log_{10}$ cps/mL (sustained in < 3 wks) -BKV DNA load > $4\log_{10}$ cps/mL	-	+ +	+ +	+
Biopsy	Nephropathy -Viral cytopathic changes -Inflammatory infiltrates/tubulitis -More than mild interstitial fibrosis/tubular atrophy	-	-	-	+
Therapy		No	(Yes)	Yes	Yes

Hirsch HH. Clin Transplant 2019 Sep;33(9):e13528.

Histologic Diagnosis

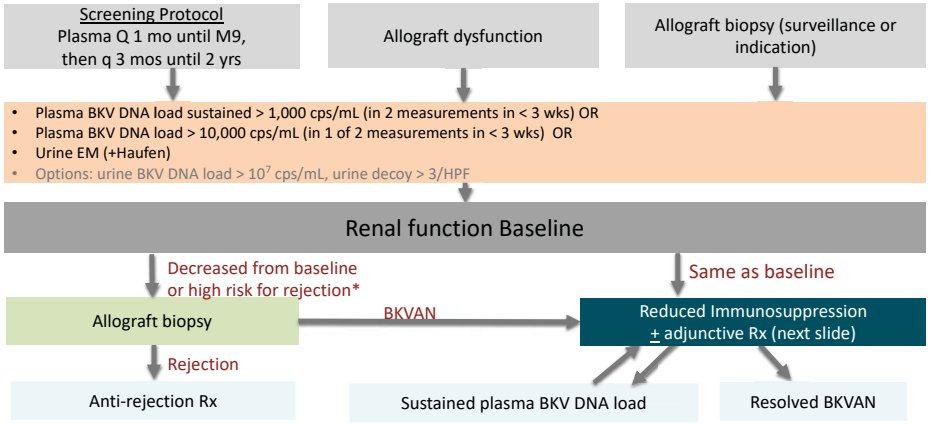
- **(Multi) focal distribution, medulla**
  A minimum of 2 biopsy cores should be taken, preferentially medullary tissues
- **Viral basophilic nuclear inclusion in epithelial cells**
  Renal tubular and/or Bowman's capsular lining urothelium
- **Positive immunohistochemical staining**
  Antibodies directed against BKV or the cross-reacting Simian virus SV40 large T antigen

Negative biopsy cannot R/O early focal BKVAN



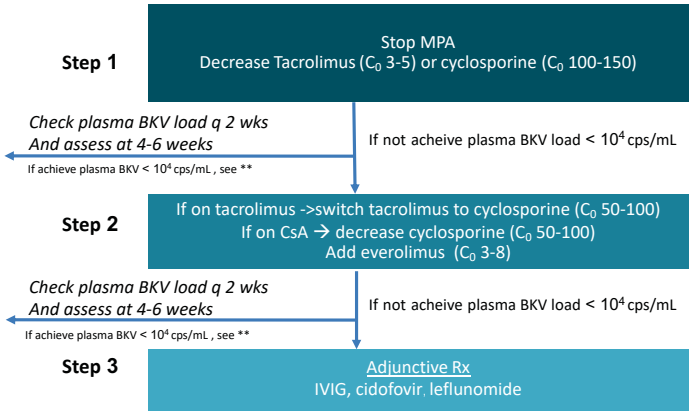
Hirsch HH. Clin Transplant 2019 Sep;33(9):e13528 Graf FE, Hirsch HH. Emerging transplant infections. Cham, Switzerland: Springer Nature, 2020:1–26.

AST-IDCOP BKV in KT Guideline 2019



Hirsch HH. Clin Transplant 2019 Sep;33(9):e13528. *Highly-sensitized status (+PRA, +DSA, ABO incompatibility, Re-KT)

Adjustment of Immunosuppressants



** If achieve plasma BKV < 10^4 cps/mL, back to protocol and resume immunosuppression gradually

Hirsch HH. Clin Transplant 2019 Sep;33(9):e13528.

Role of mTOR Inhibitors for BKPyV Infection

- **De novo:** TRANSFORM study[1]
  - A 24-month RCT in **de novo** KT concentration-controlled EVR with rCNI vs. mycophenolate with standard CNI
  - Significant reduction of incidences in BKV infections for patients on the EVR + rCNI regimen (P<0.001)
- **Conversion:** A Prospective Controlled Study[2]
  - A 36-month study in conversion KT with proven BKVAN with EVR with rCNIs vs. rCNIs and halved-dose antimetabolites
  - Better allograft outcome, BKV load decline, higher survival free of adverse graft outcome for patients on the EVR + rCNI regimen (P< 0.05)

[1]Berger SP. Am J Transplant. 2019 Nov;19(11):3018-3034.
[2]Everolimus for BKV Nephropathy in Kidney Tx Recipients: A Prospective, Controlled Study (2020, Abstract)
EVR: everolimus, rCNI: reduced–dose calcineurin inhibitors

Adjunctive Therapies for BKPyVAN

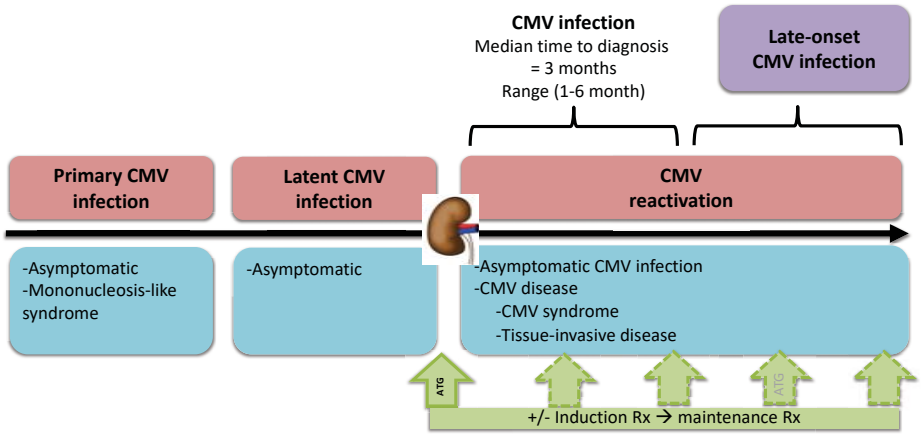
Drug	Dosing	Toxicity/comments
Cidofovir (IV)	0.25 to 1.0 mg/kg at 1–3 weekly intervals **Probenecid use: no**	-Impaired kidney function, proteinuria, neutropenia, anterior uveitis
Leflunomide (PO)	100 mg daily for 5 days (loading), followed by 40 mg daily (maintenance)	-hepatitis, hemolysis, thrombotic microangiopathy, BM suppression
Quinolones (PO)	Ciprofloxacin 500-1000 mg daily Levofloxacin 500 mg daily	-QT prolongation, tendinitis -Drug interaction with CNI -Levofloxacin 500 mg/day failed to Rx BK viremia*
IVIG	0.2 to 2.0 g/kg divided for 4 doses	-Consider in cases with intense inflammation on the biopsy and/or concomitant acute rejection

Hirsch HH. Clin Transplant 2019 Sep;33(9):e13528. *Lee BT. Clin J Am Soc Nephrol. 2014 Mar;9(3):583-9.

Human Herpes Viruses

Virus	HHV	Primary infection	Reactivation
HSV-1	HHV-1	Herpes labialis	Recurrent herpes labialis
HSV-2	HHV-2	Herpes genitalis	Recurrent herpes genitalis
VZV	HHV-3	Varicella	Zoster
EBV	HHV-4	Acute mononucleosis	EBV-related posttransplant lymphoproliferative disease (PTLD)
CMV	HHV-5	Acute mononucleosis-like syndrome	CMV syndrome/ CMV disease (colitis, retinitis)
HHV-6	HHV-6	Roseola infantum	HHV-6 encephalitis (anterograde amnesia)
HHV-7	HHV-7	Roseola infantum	HHV-7 and CMV coinfection
HHV-8	HHV-8	?URI	KS/primary effusion lymphoma/castleman dis.

CMV Infection in CMV Seropositive (R+) SOT Recipients



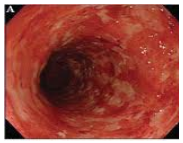
CMV Infection in Thai KT Recipients

- A retrospective study (Jan 2016 - Dec 2018)(Rama)
- Prevalence 61/518 (11.7%)
- Early ≤ 6 Mo (9.7%) vs. late-onset > 6 Mo (2%)
- Late-onset CMV infection
  - median onset of 14 (IQR 8-15) months
  - Asymptomatic CMV infection (40%) and tissue-invasive disease (60%)
  - Risk factors (univariate analysis): CMV D^+/R^- serostatus, prior episode of rejection within 6 months
  - No difference in rate of allograft failure and mortality compared to early-onset infection (p = NS).

Nuansri S, Kantachuvesiri S, Bruminhent J. The 36th RCPT Annual Meeting 2020, Chonburi, Thailand. 2020.

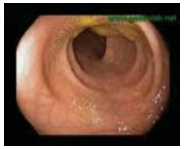
CMV Management in KT recipients

Duration of therapy?



Diarrhea

(val) ganciclovir
Induction Rx: q 12 H for at least 2 weeks
Maintenance Rx: q 24 H (not routinely recommended)



Reduction of immunosuppression
Off MPA, keep low-dose CNI & steroids

How soon should we resume immunosuppressants?

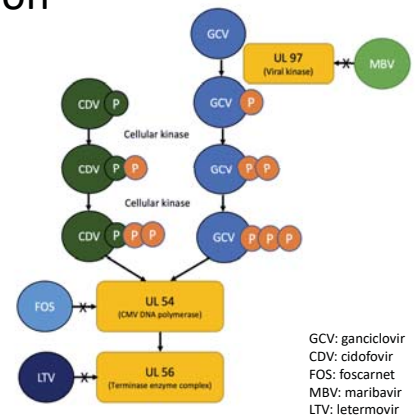
Resolving diarrhea

Undetectable plasma CMV load ≥ 1 time
*highly sensitive assay (LLOQ < 200 IU/mL

QFT-CMV - reactive

Drug-resistant CMV Infection

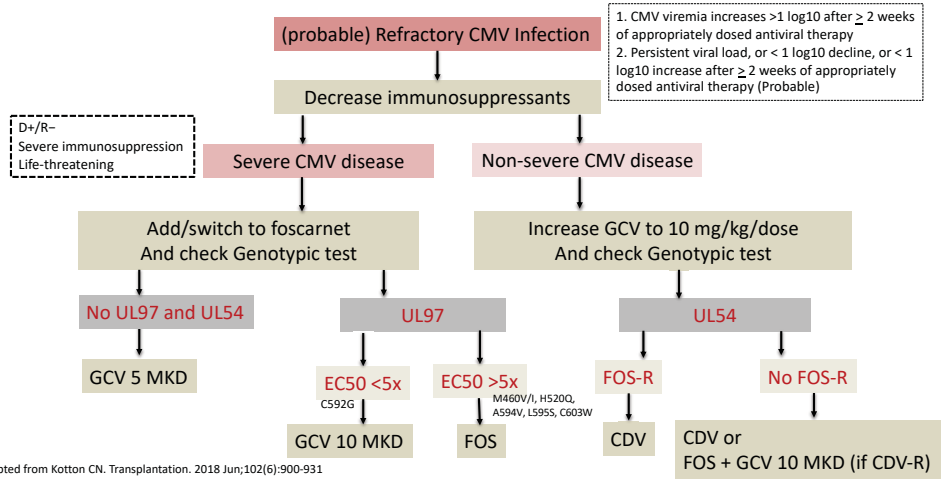
Drugs	Resistant genes	Codon range
Ganciclovir	UL97, UL54	353-653, 301-987
Cidofovir	UL54	301-987
Foscarnet	UL54	301-987
Maribavir	UL27, UL97	22-426, 353-653
Letermovir	UL56, UL51	229-396, 91-91



GCV: ganciclovir
CDV: cidofovir
FOS: foscarnet
MBV: maribavir
LTV: letermovir
P: phosphate

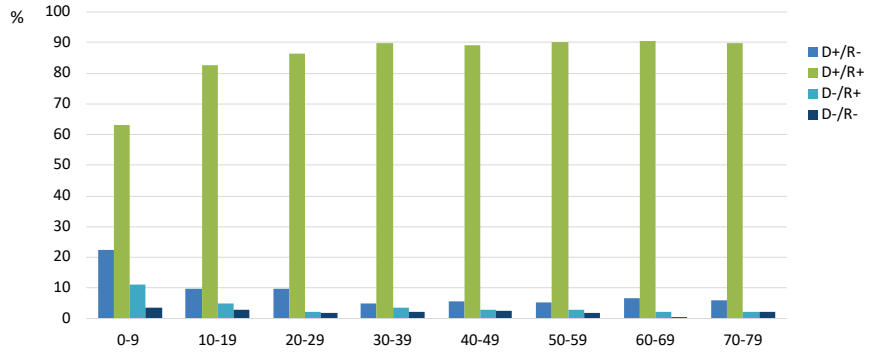
Bruminhent J. Razonable RR. Expert Opin Orphan Drugs. 2020 Submitted.

Management of Anti-CMV Drug Resistance



Adapted from Kotton CN. Transplantation. 2018 Jun;102(6):900-931

Distribution of CMV seroprevalence in KT donors and recipients



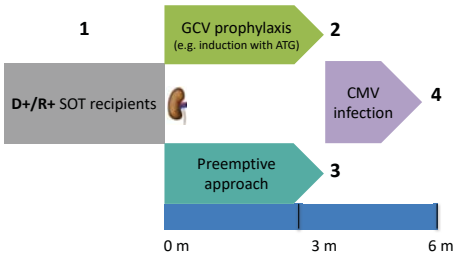
Bruminhent J, An Analysis of the National Transplant Registry. Transplant Proc. 2020 Apr;52(3):829-835.

CMV Prevention among Thai KT Recipients

Serostatus	CMV D+/R-	CMV D+/R+ with ATG	CMV D+/R+ without ATG
Risk of CMV infection after KT	High (small population)	Moderate → high (ATG=known risk factors among Thai KT population).	Moderate
Prevention strategy	-(val)ganciclovir prophylaxis for 6 months	-(val)ganciclovir prophylaxis for 3 months	-Preemptive approach (check plasma CMV VL weekly)
Real-world practice	Ganciclovir (during admission) then switch to preemptive approach (hybrid approach) -Follow CMV IgG -Follow QFT-CMV	Ganciclovir (during admission) then switch to preemptive approach (hybrid approach)	-Preemptive approach (check plasma CMV VL with Nephro visit)
Comments	-Remain at risk of delayed-onset primary CMV infection beyond prophylaxis -	-Proposed cut-off value to initiate anti-CMV therapy (center-specific). -3,090 cps/mL or 2,812 IU/mL (distinguish with & without symptoms) -2,000 to 3,000 cps/mL or 1,820 to 2,730 IU/mL. (survey among ID and Nephro)	

Bruminhent J, Vanichanan J, Watcharananan SP. J Infect Dis Antimicrob Agents 2020; 37: 105-110.

Potential Uses of CMV-specific Immune Monitoring



1. Risk assessment prior to transplant

CMI positive → wkly CMV VL
CMI negative→ wkly CMV VL or ?prophylaxis

2. At the end of prophylaxis

CMI positive → done
CMI negative→ continue prophylaxis or switch to wkly CMV VL (hybrid approach)

3. During preemptive approach (≥1 month)

CMI positive → ?continue wkly CMV VL
CMI negative→ continue wkly CMV VL

4. End of induction therapy for CMV infection

CMI positive → ?need for maintenance Rx/secondary prophylaxis
CMI negative→ maintenance Rx/secondary prophylaxis

Adapted from Kotton CN. Transplantation. 2018 Jun;102(6):900-931

Thank you

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