Mahidol University
Faculty of Medicine
Ramathibodi Hospital

Transplant Infections

What's Hot/ What's New

Jackrapong Bruminhent, MD
Division of Infectious Diseases
Department of Medicine
Faculty of Medicine Ramathibodi Hospital
Mahidol University

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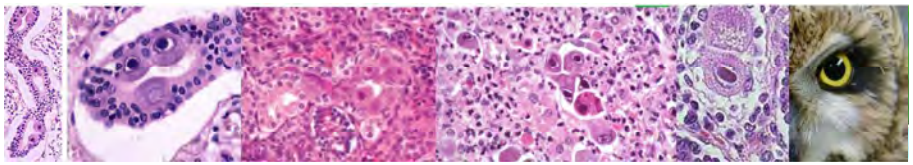
My Disclosure

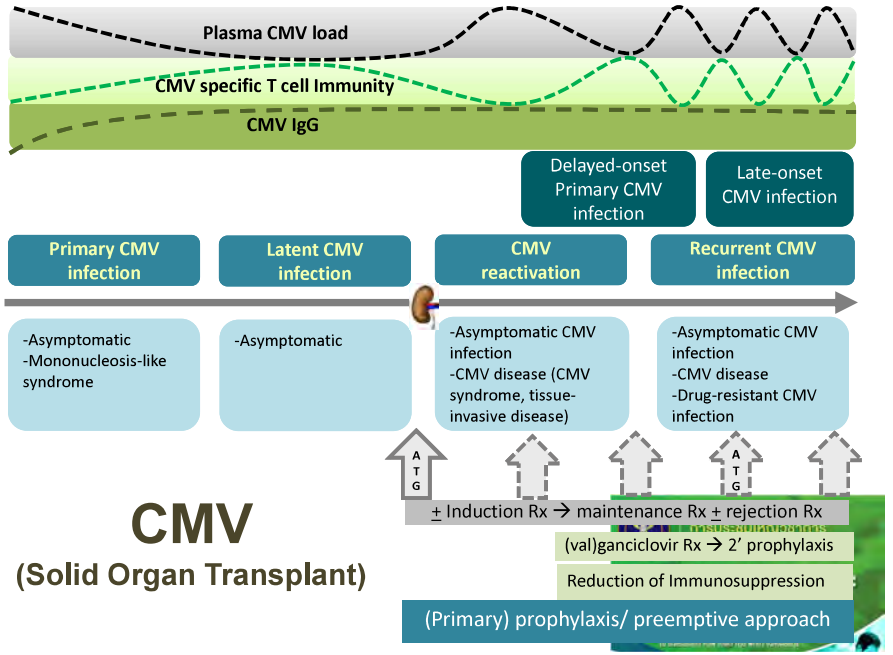
- **Speakers Bureau**
  - Pfizer, Astellas, MSD, Roche, Siam, SP Pharmaceutical
- **Congress Travel**
  - Astellas
- **Research Grant**
  - Qiagen, Q Bioscience

Outlines

New

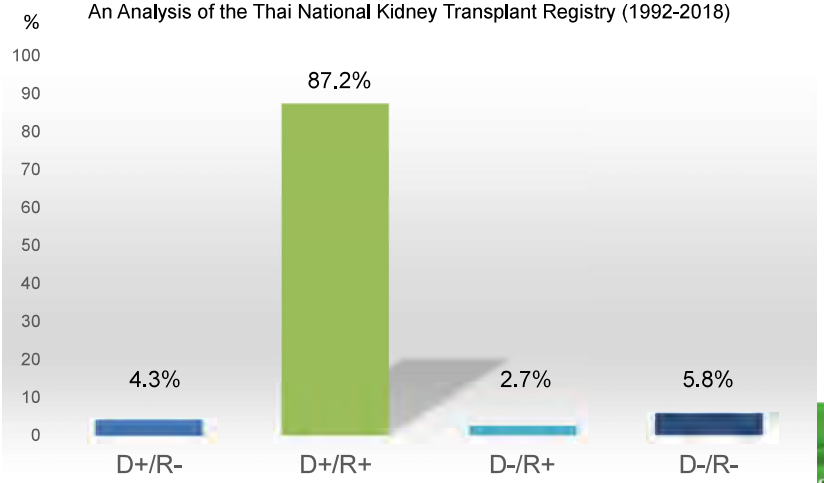
1. Updated guideline of CMV in SOT 2018
2. Definitions of CMV infection in transplant patients
3. CMV prevention in Thai kidney transplant recipients
4. CMV-specific T cell immunity in SOT
5. CMV prophylaxis in HSCT





CMV Serology Pair in Thailand

An Analysis of the Thai National Kidney Transplant Registry (1992-2018)



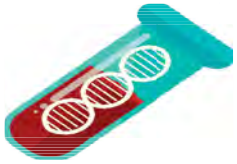
Bruminhent J. Watcharananan SP. 2018 Data to be published.

CMV Infection in Thai KT Recipients

Ramathibodi[1]	Chulalongkorn[2]
Retrospective study (2006-2010)	Retrospective study (2012-2014)
CMV D+/R+ (99%)	CMV D+/R+ (99%)
CMV disease (4.6%) within 1 yr post-KT	Asymptomatic CMV infection (21%) CMV disease (7%), median F/U of 16 mos -20% (IL-2 RA) -50% (low-dose ATG) -67% (standard-dose ATG)
Median onset 3 months (range, 1-7)	Onset within 3 months (86% of cases)
GI disease (44%)	GI disease (mainly)
Risk factors: Acute cellular rejection (OR 7.3) Acute tubular necrosis (OR 3.4)	Risk factors: Older recipients/10 yr (OR 1.5) Standard ATG induction (OR 8.19) Low-dose ATG induction (OR 3.87)

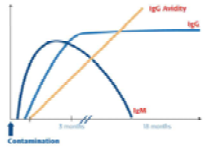
1. Watcharananan SP. Transpl Proc. 2012 Apr;44(3):701-5. 2. Chiasakul T. Transplant Proc. 2015 Oct;47(8):2460-41.

Laboratory CMV Diagnoses



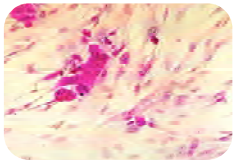
Nucleic acid amplification testing (NAAT)

Qualitative/quantitative PCR



Serology

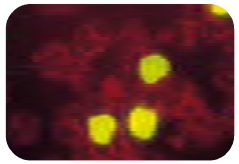
no role for the diagnosis



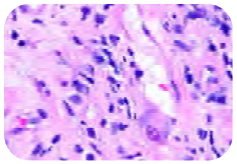
Viral culture

Conventional culture

Shell vial assay



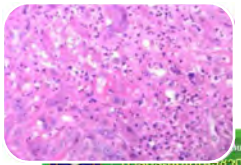
pp65 antigenemia assay



Histopathology

Cytopathic changes

(viral inclusion; Owl's eye)



Special staining

Immunohistochemical staining

in situ DNA hybridization

Kotton CN. Transplantation. 2013 Aug 27;96(4):333-60.

New

Original Clinical Science—General

The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation

Camille N. Kotton, MD.[1] Deepali Kumar, MD.[2] Angela M. Caliendo, MD, PhD.[3] Shirish Huprikar, MD.[4] Sunwen Chou, MD,[5] Lara Danziger-Isakov, MD, MPH,[6] and Atul Humar, MD[7]
on behalf of the The Transplantation Society International CMV Consensus Group

June 2018

Abstract: Despite recent advances, cytomegalovirus (CMV) infections remain one of the most common complications affecting solid organ transplant recipients, conveying higher risks of complications, graft loss, morbidity, and mortality. Research in the field and development of prior consensus guidelines supported by The Transplantation Society has allowed a more standardized approach to CMV management. An international multidisciplinary panel of experts was convened to expand and revise evidence and expert opinion-based consensus guidelines on CMV management including prevention, treatment, diagnostics, immunology, drug resistance, and pediatric issues. Highlights include advances in molecular and immunologic diagnostics, improved understanding of diagnostic thresholds, optimized methods of prevention, advances in the use of novel antiviral therapies and certain immunosuppressive agents, and more savvy approaches to treatment resistant/refractory disease. The following report summarizes the updated recommendations.

(*Transplantation* 2018;102: 900-931)

TTS CMV in SOT Guideline 2018

	What's New
Diagnosis	More emphasize on QNAT, IU/mL, (less preferred pp65 antigen)
Treatment	A minimum of 2 wks, until clinical resolution and eradication of CMV DNAemia -below LLOQ (< 200 IU/mL) (highly sensitive assays) or -until 2 undetectable VLs (less sensitive assays)
	Secondary prophylaxis after treatment (not routinely recommended)
	CMV drug resistance (more codon noted)
	CMV-specific immune monitoring to guide Rx duration
Prevention	CMV-specific immune monitoring to guide strategy
	Valacyclovir 2 gram PO QID prophylaxis in KT recipients (recent RCT), neurotoxicity is concerning
	Hybrid approach → Surveillance after prophylaxis

Kotton CN. et al. Transplantation. 2018 Jun;102(6):900-931.

What's New?

TTS 2013	TTS2018
Treatment	
Induction Rx until 1-2 undetectable VLs	A minimum of 2 wks, until clinical resolution and eradication of CMV DNAemia -below LLOQ (< 200 IU/mL) (highly sensitive assays) or -until 2 undetectable VLs (less sensitive assays)
Secondary prophylaxis may be given, with the longer duration employed in high-risk patients as outlined above (weak, low).	Secondary prophylaxis after treatment (not routinely recommended)
CMV drug resistance	CMV drug resistance (more codon noted)
Prevention	

What's New? (1)

TTS 2013	TTS2018
Diagnostic	
CMV viremia	CMV DNAemia
Copies/mL	International units/mL
Treatment	
Induction Rx until 2 undetectable VLs	A minimum of 2 wks, until clinical resolution and eradication of CMV DNAemia -below LLOQ (< 200 IU/mL) (highly sensitive assays) or -until 2 undetectable VLs (less sensitive assays)
Secondary prophylaxis may be given, with the longer duration employed in high-risk patients as outlined above (weak, low).	Secondary prophylaxis after treatment (not routinely recommended)
	Role of maribavir, letermovir, brincidofovir for salvage

What's New (2)

TTS 2013	TTS2018
Prevention	
Preemptive approach for CMVR+	(Targeted) prophylaxis in those with high risk e.g. ATG use, desensitization or ABO incompatible protocols (rituximab, bortezomib, eculizumab, plasmapheresis/ immunoadsorption), and HIV)
Hybrid approach	Surveillance after prophylaxis
	Cell-mediated immunity to guide strategy (more)
	mTOR inhibitor-regimen in CMV R+
Threshold to initiate preemptive Rx (promising)	Recommend that centers establish their own thresholds and audit clinical outcomes to verify the thresholds used
	Valacyclovir 2 gram PO QID prophylaxis in KT recipients (recent RCT), neurotoxicity is concerning
	Preemptive therapy has not been well studied in some seropositive populations including lung, heart, vascularized composite, pancreas, islet, and intestinal transplant; we suggest prophylaxis may be preferable (weak, low).

CMV GI Disease
(in Transplant Patients)

New

Definition	Clinical symptoms and/or signs	Nucleic acid testing (eg, PCR)	Histopathology findings
Proven	Upper and/or lower GI symptoms		Macroscopic mucosal lesions plus CMV documented in tissue*
Probable	Upper and/or lower GI symptoms		No macroscopic mucosal lesions plus CMV documented in tissue
Possible	Upper and/or lower GI symptoms	CMV documented in blood** or CMV documented in tissue	**? no cut-off value for the diagnosis**

*by histopathology, virus isolation, rapid culture, immunohistochemistry, or DNA hybridization
** by PCR or antigen

Ljungman P. Clin Infect Dis. 2017 Jan 1;64(1):87-91.

Compartmentalized Disease

- Clinical syndromes wherein the virus is detected in the affected tissues but is minimally detectable/ undetectable in the blood[1]
  - e.g. CMV GI disease, retinitis
- Risk of absence of CMV viremia in CMV GI disease[2]
  - CMV D+/R+ (compared to CMV D+/R-)
  - Diagnosis > 6 months post-transplant

Colonoscopy should be performed in case suspected for CMV GI disease esp. CMV D+/R+

1. Razonable RR. Am J Transplant. 2013 Mar;13 Suppl 4:93-106. 2. Fisher CE. Transpl Infect Dis. 2016 Jun;18(3):372-80.

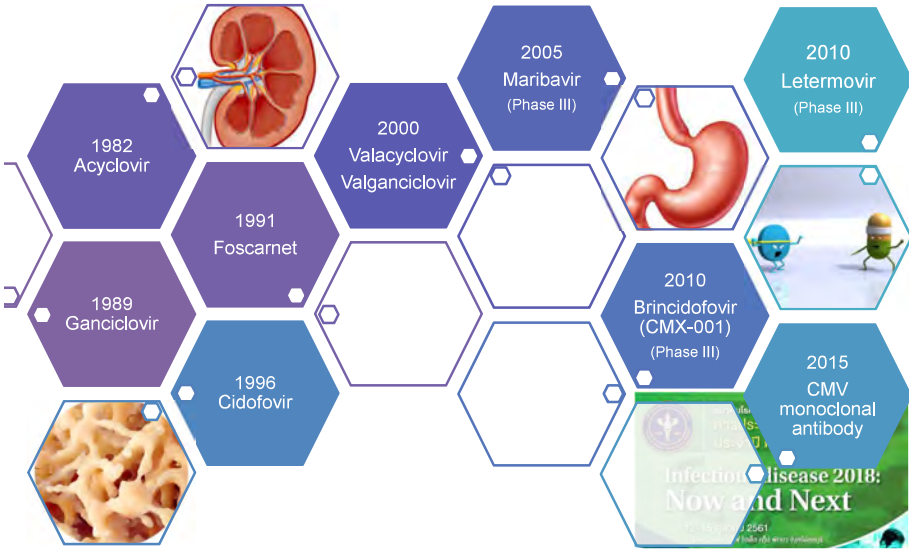
CMV Pneumonitis
(in Transplant Patients)

New

Definition	Clinical symptoms and/or signs	Nucleic acid testing (eg, PCR)	Histopathology findings
Proven	New infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea		CMV documented in lung tissue by virus isolation, rapid culture, histopathology, immunohistochemistry, or DNA hybridization techniques
Probable	New infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea	Detection of CMV by viral isolation, rapid culture of BAL fluid, or the quantitation of CMV DNA in BAL fluid	
Possible	New infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea	Quantitative PCR on lung tissue biopsy	**? no cut-off value for the diagnosis**

Ljungman P. Clin Infect Dis. 2017 Jan 1;64(1):87-91.

Anti-CMV Drugs



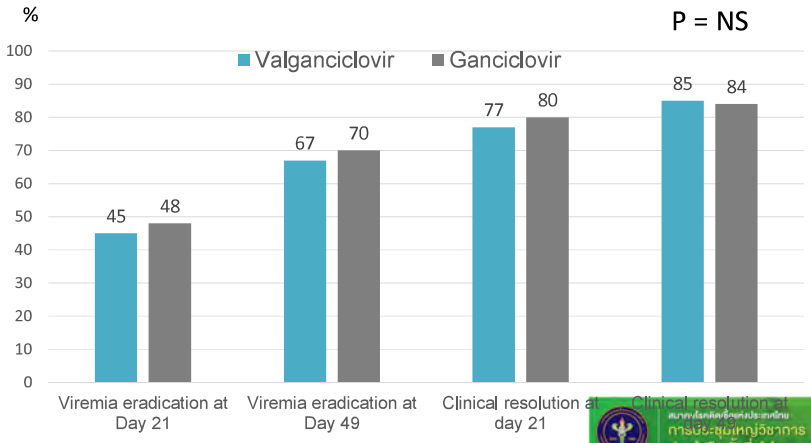
How to monitor CMV after Rx?

Anti-CMV Drugs

Drug	Dosing*	Toxicity/comments
Valganciclovir	900 mg PO q 12 h	-Bone marrow suppression (leukopenia)
Ganciclovir (IV)	5 mg/kg IV q 12 h	-Bone marrow suppression (leukopenia)
Foscarnet	60 mg/kg IV q 8 h (or 90 mg/kg q 12 h)	-Nephrotoxic Used in high level UL97 mutant ganciclovir resistance
Cidofovir	5 mg/kg once wkly x 2 then q 2 weeks thereafter	-Nephrotoxic -Used as alternative drug in UL97 mutant ganciclovir resistance

*Dose adjustment for renal impairment.
Adapted from Bruminhent J. World J Hepatol. 2014 Jun 27;6(6):370-83.

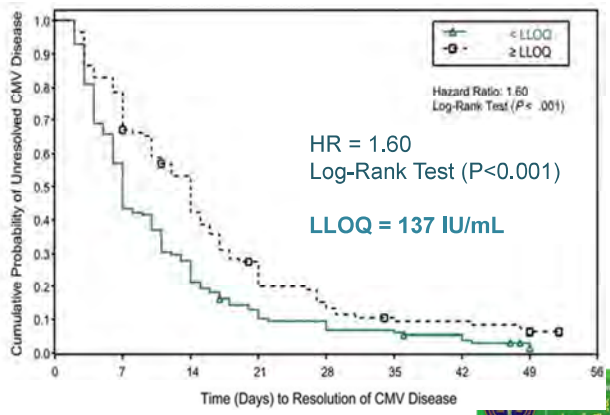
VICTOR Trial



Oral Valganciclovir Is Noninferior to IV Ganciclovir for the Treatment of CMV Disease in SOT Recipients

Asberg A. Am J Transplant 2007; 7: 2106–2113

Viral Suppression at Day 21 & Clinical Resolution of CMV Disease in SOT recipients



Relative CMV load reductions from baseline were not significantly associated with faster resolution of CMV disease

Razonable RR. Clin Infect Dis. 2013 Jun;56(11):1546-53