UniversitätsKlinikum Heidelberg

International Pediatric Transplant Association

Viral Infections after Transplantation

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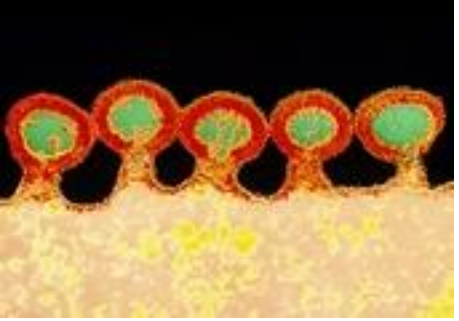
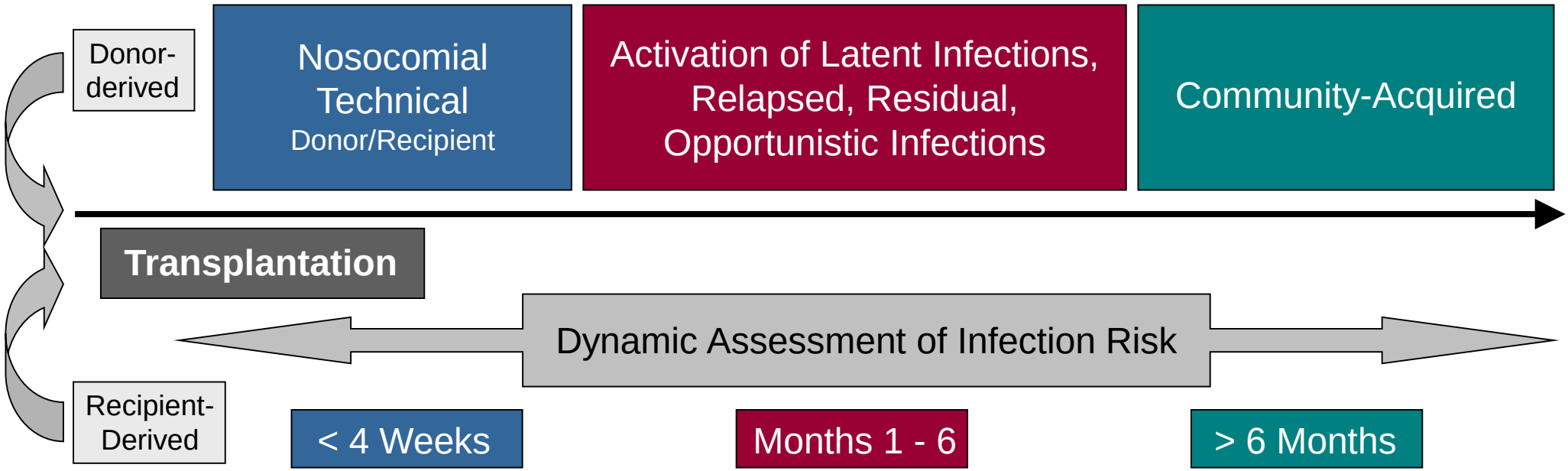
Pediatric Transplantation Teaching Course, Moscow 2016



OVERVIEW

- Timeline of post-transplant infections
- Selected infectious agents:
  - Cytomegalovirus (CMV)
  - Epstein-Barr virus (EBV)
  - Polyomavirus (BKV, JCV)

Timeline of Post-Transplant Infections



Resistant Species:
- MRSA, VRE, Candida
- Aspiration, Line/Wound Infection, Anastomotic Leaks/Ischemia
- Clostridium diff. Colitis

Donor-Derived (uncommon):
- HSV, LCMV, Rabies, West Nile Virus

Recipient:
- Aspergillus, Pseudomonas

With Prophylaxis:
- **Polyomavirus (BKV)**
- Clostridium diff. Colitis
- Adenovirus, Influenza, HCV
- Cryptococcus neoform.
- M. tuberculosis

Anastomotic Compl.

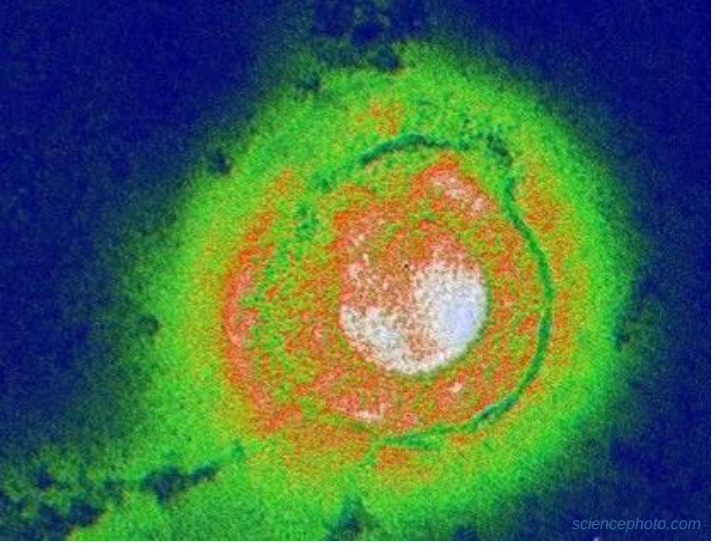
Without Prophylaxis (add.):
- Pneumocystis (PcP)
- HSV, VZV, **CMV**, **EBV**, HHV-6, HHV-8, HBV
- Listeria, Nocardia, Toxoplasma etc.

Community-Acq. Pneumonia
Urinary Tract Infection
- Aspergillus, Atypical Moulds
- Nocardia, Rhodococcus

Late Viral Infections:
- **CMV** (Colitis, Retinitis)
- Hepatitis (HBV, HCV)
- HSV Encephalitis
- SARS, West Nile Virus
- Polyomavirus (JCV)

Associated Malignancy:
- **PTLD**, Kaposi Sarcoma

Am J Transplant 2009, 9(S4): 3; Am J Transplant 2013, 13(S4): 3



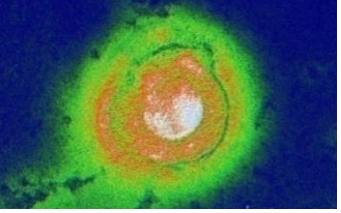
Cytomegalovirus (CMV)

Frequency of CMV Risk Constellation
in Pediatric Renal Transplant Patients

CMV-Serostatus	Pediatric Patients	Adult Patients[2]
D+/R-	29.2%	18.2%
D+/R+	25.9%	39.8%
D-/R+	9.3%	23.2%
D-/R-	35.6%	18.8%

Pediatric patients bear a higher risk of primary CMV infection than adults.

[1]*Höcker et al., Transplantation 2015*
[2]*Am J Transplant 2014; 14 Suppl 1: 11*



Definition of CMV Infection

Infection

Presence of CMV replication regardless of symptoms
(viremia (defined as pos. NAT and/or pos. pp65Ag), pos. culture and/or histopathological evidence)

Disease

Presence of CMV infection accompanied by clinical symptoms

Syndrome

CMV replication plus one or more of the following criteria:

- Fever
- Malaise
- Leukopenia
- Thrombocytopenia

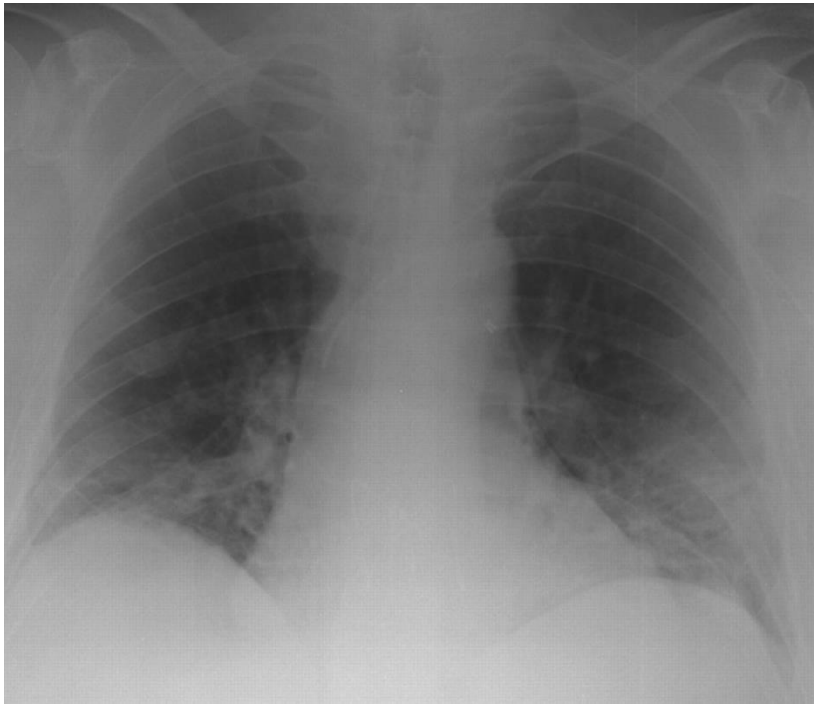
Tissue-Invasive Disease

CMV replication plus one or more of the following criteria:

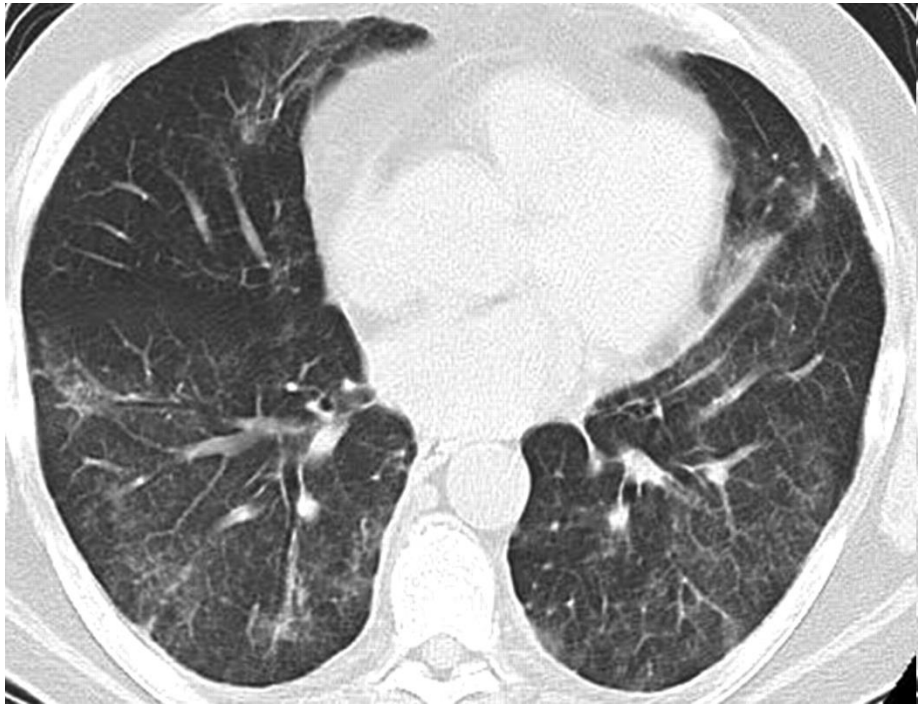
- Gastrointestinal disease
- Pneumonitis
- Hepatitis
- CNS disease
- Retinitis
- Other (nephritis, cystitis, myocarditis, pancreatitis, etc.)

Am J Transplant 2013; 13: 93; Transplantation 2013; 96: 333

Invasive CMV Disease
Clinical Manifestation of CMV Pneumonitis



Bilateral Interstitial Infiltrates

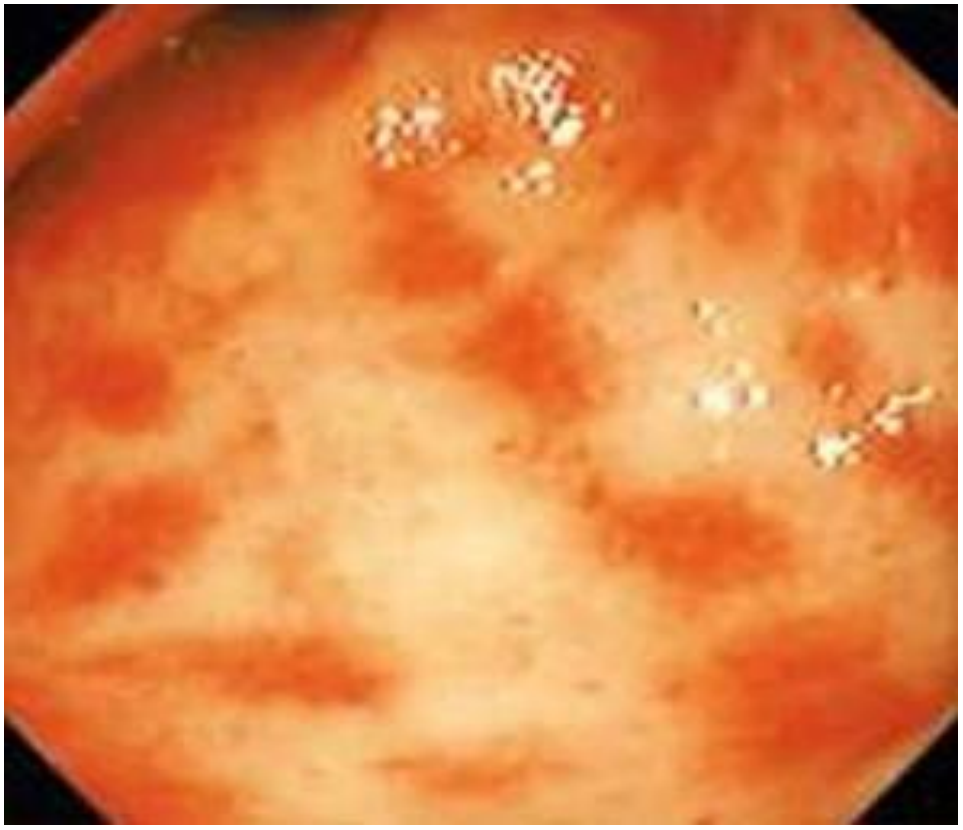


Ground-Glass Opacity

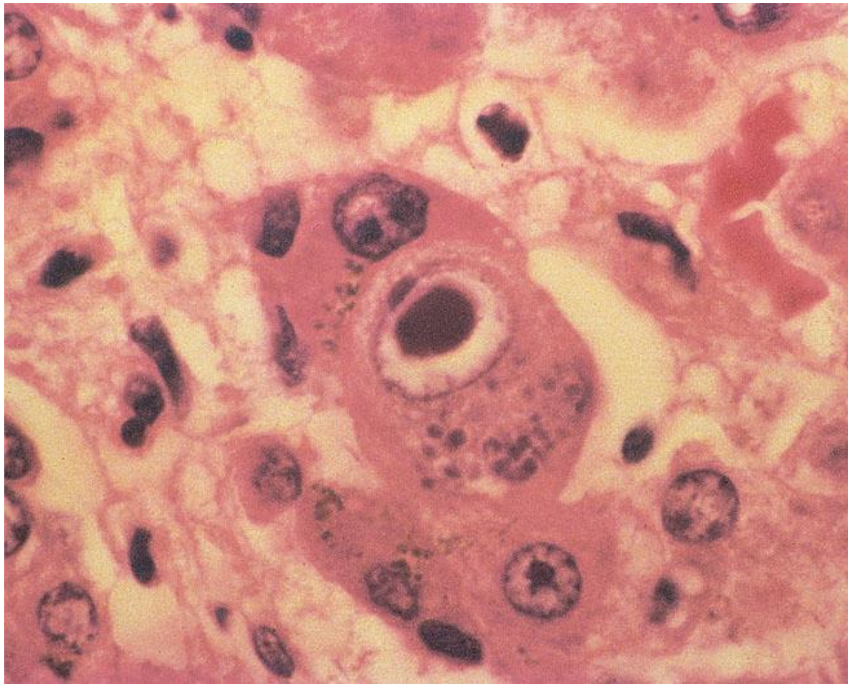
Am J Radiol 2009; 192: 1

Invasive CMV Disease
Clinical Manifestation of CMV Colitis

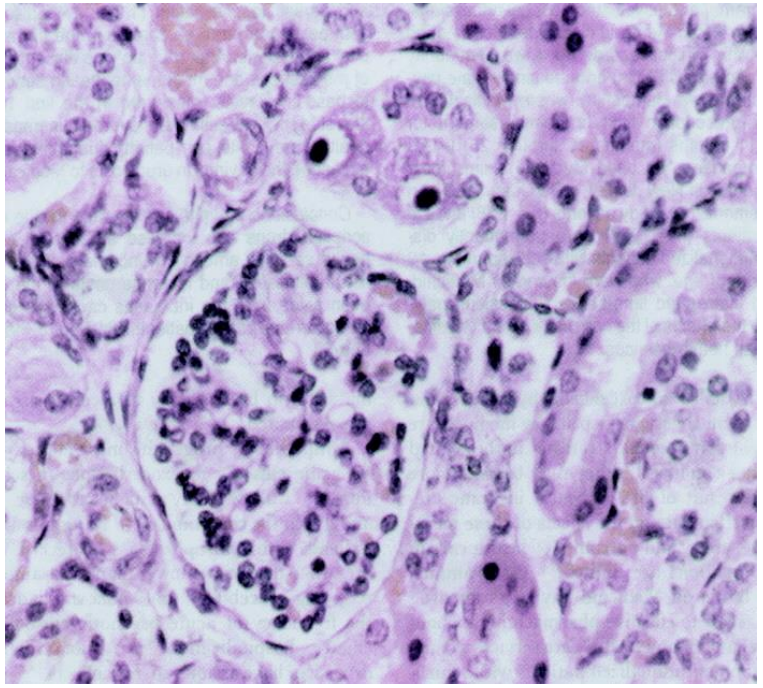
„Burning flame"



Invasive CMV Disease
Histopathology



CMV Hepatitis



CMV Nephritis

Diagnostics

Prior Kidney Transplantation

- **CMV serology (IgG)** in donor and recipient
  - Donor < 12 months and CMV IgG pos. → "CMV pos."
  - Recipient < 12 months and CMV IgG pos. → "CMV neg." (maternal antibodies)

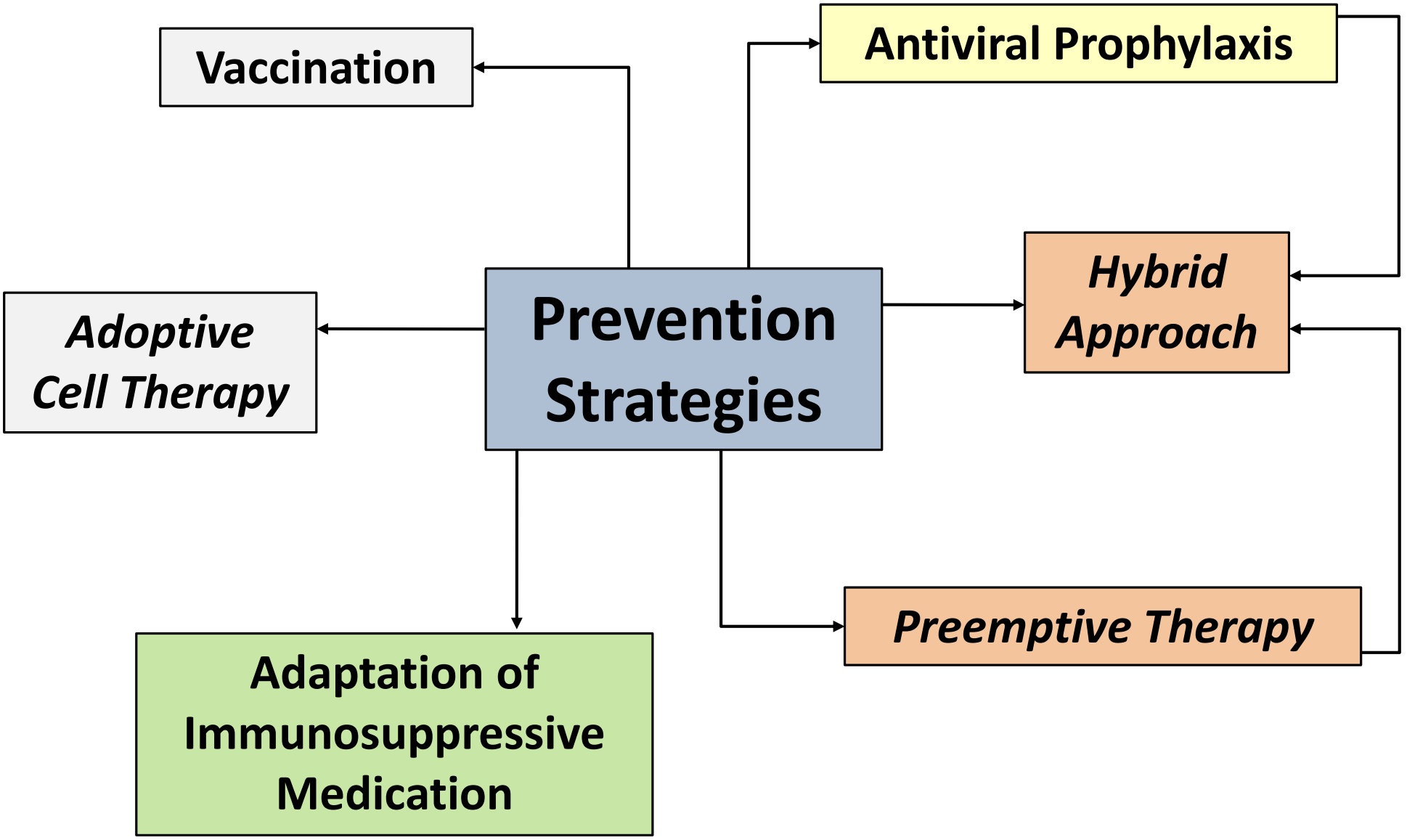
Post-Transplant

- **CMV quantitative NAT (QNAT)** in plasma or whole-blood
  (preferred method of diagnosis and monitoring response to therapy; calibration of assay according to WHO standard; no change of specimen type)
- **CMV pp65Ag** is an acceptable alternative.
  (cave: sample processing within 6 - 8 hrs; diagnostically less conclusive in case of leukocytopenia)
- **Histology/immunohistochemistry** for diagnosis of tissue-invasive disease
- **CMV culture and QNAT of tissue specimens** only in case of gastrointestinal disease and pneumonitis (BAL)

Am J Transplant 2013; 13: 93; Transplantation 2013; 96: 333

An ounce of prevention is worth a pound of cure.

B. Franklin


Vaccination
Antiviral Prophylaxis
Adoptive Cell Therapy
Prevention Strategies
Hybrid Approach
Preemptive Therapy
Adaptation of Immunosuppressive Medication

American Journal of Transplantation 2013; 13: 93–106
Wiley Periodicals Inc.

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doi: 10.1111/ajt.12103

Special Article

Cytomegalovirus in Solid Organ Transplantation

R. R. Razonable[a,*], A. Humar[b] and the AST Infectious Diseases Community of Practice

Updated International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation

Camille N. Kotton,[1,8] Deepali Kumar,[2] Angela M. Caliendo,[3] Anders Åsberg,[4] Sunwen Chou,[5] Lara Danziger-Isakov,[6] and Atul Humar,[7] on behalf of The Transplantation Society International CMV Consensus Group

Transplantation • Volume 96, Number 4, August 27, 2013

Chemoprophylaxis

Serostatus	Risk Level	Recommended	Alternate
D+/R-	Intermediate to high	**3 - 6 mths of valganciclovir** (or ganciclovir i.v.) as recommended in adults[A] OR **2 - 4 wks of valganciclovir** (or ganciclovir i.v.) with sequential monitoring	
R+	Low	**2 - 4 wks of valganciclovir** (or ganciclovir i.v.) with sequential monitoring	**3 - 6 mths of valganciclovir** (or ganciclovir i.v.) as recommended in adults[A]
D-/R-	Lowest	Monitoring for clinical symptoms	Preemptive monitoring

[A]T cell-depleting induction is associated with increased risk of CMV replication and disease; consider prolonged prophylaxis or more intensive monitoring.

Transplantation 2013; 96: 333

Valganciclovir Dosage for CMV Prophylaxis

FDA Issues New Dosing Recommendations For Valganciclovir:
… children with low body weight, low body surface area, and very low serum creatinine could have a high calculated creatinine clearance requiring a dose of the antiviral approaching the maximum 900-mg dose used in adults…
…To minimize the potential for overdose, the FDA has set a maximum value for the calculated creatinine clearance of 150 ml/min·1.73 m^2…
… formula yields a dose higher than 900 mg, the 900-mg dose should be used…

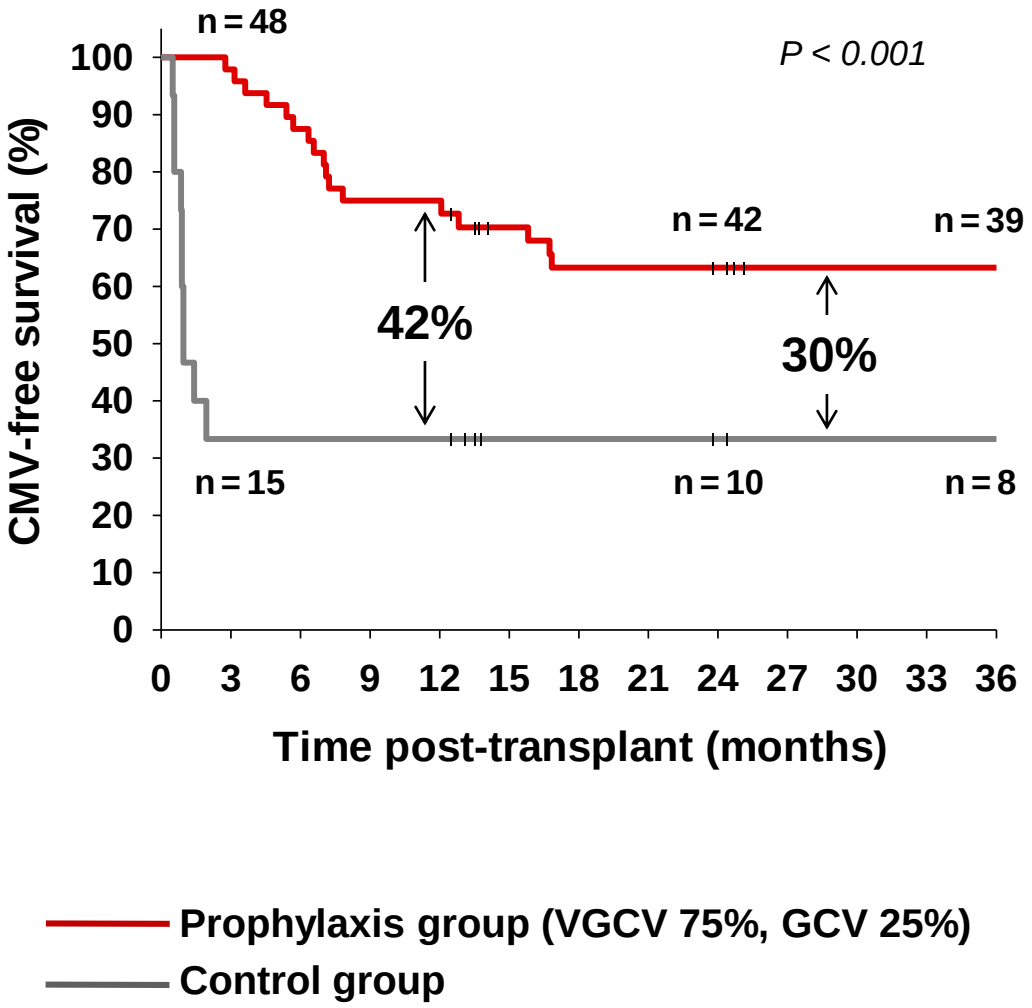
MedPage Today, September 15, 2010

Dose (mg/d) = 7 x BSA (m^2) x eGFR* (ml/min·1.73 m^2)

- *Schwartz formula: eGFR = height (cm)/serum creatinine (mg/dl) x 0.413
- Max. eGFR = 150 ml/min·1.73 m^2
- Max. daily dose 900 mg

Am J Transplant 2009; 9: 636

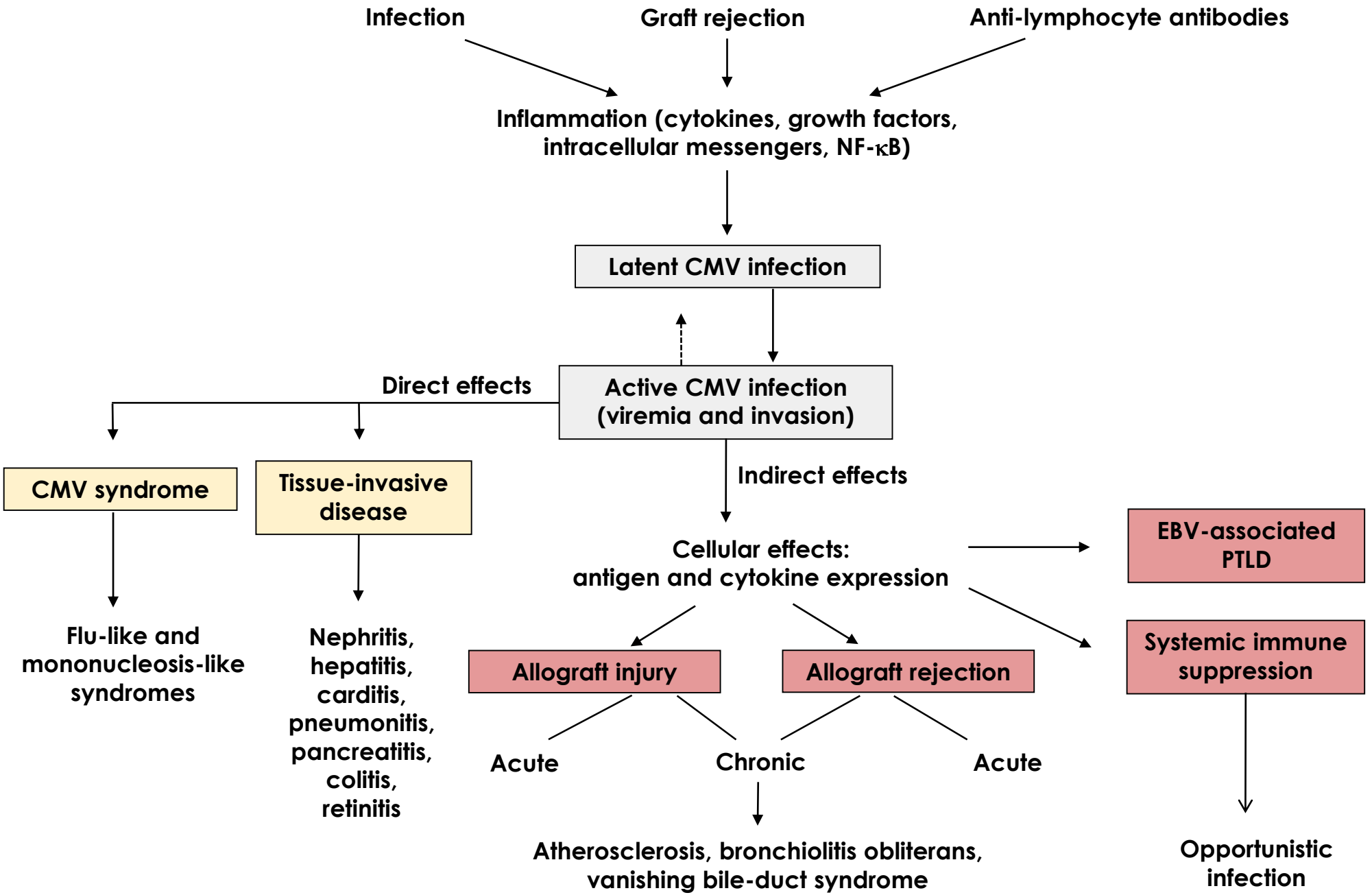
Association between VGCV Prophylaxis and CMV Replication in CMV High-risk (D+/R-) Patients



CERTAIN Cooperative EuropeanPaediatric Renal Transpl-Ant INitiative

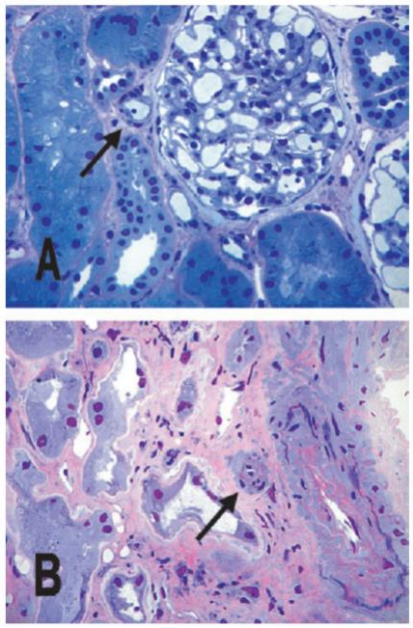
Höcker B et al., Transplantation 2015

Direct and Indirect Effects of CMV



Clin Transplant 2007; 21: 149

CMV-Associated Pathology of Kidney Allograft



- Intragraft CMV protein expression is associated with reduced renal allograft survival.

  Clin Infect Dis 2011

- CMV increases tubular apoptosis through the TNF-α–TNF-R1 pathway in a rat model of chronic renal allograft rejection.

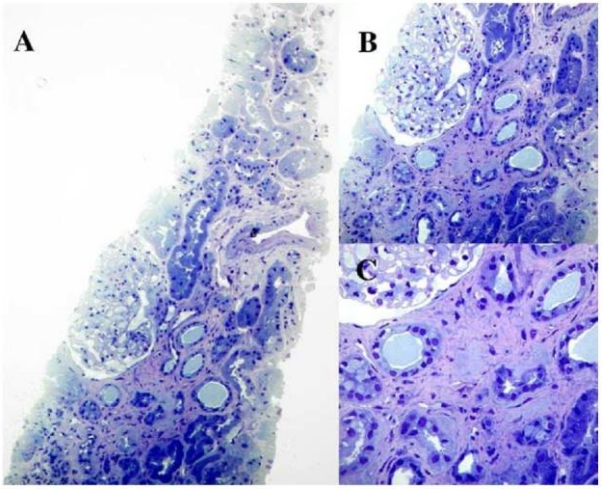
  Transpl Immunol 2008

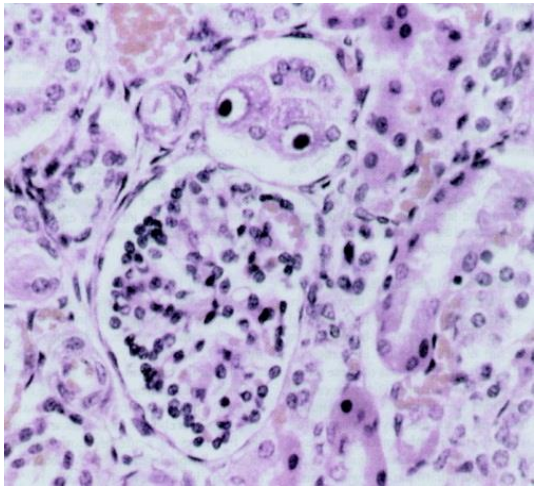
- Persistent CMV infection is associated with increased expression of TGF-β_1, PDGF-AA and ICAM-1 and arterial intimal thickening in kidney allografts.

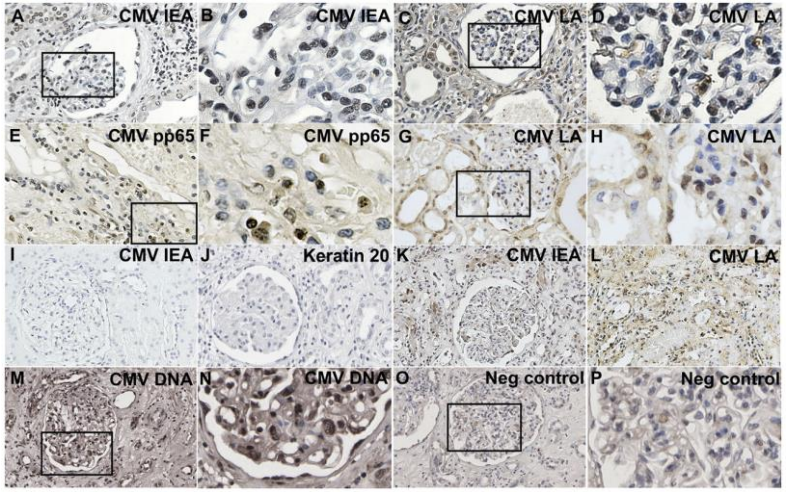
  NDT 2005; Transpl Immunol 2006

- CMV induces TGF-β_1 activation in renal tubular epithelial cells after epithelial-to-mesenchymal transition.

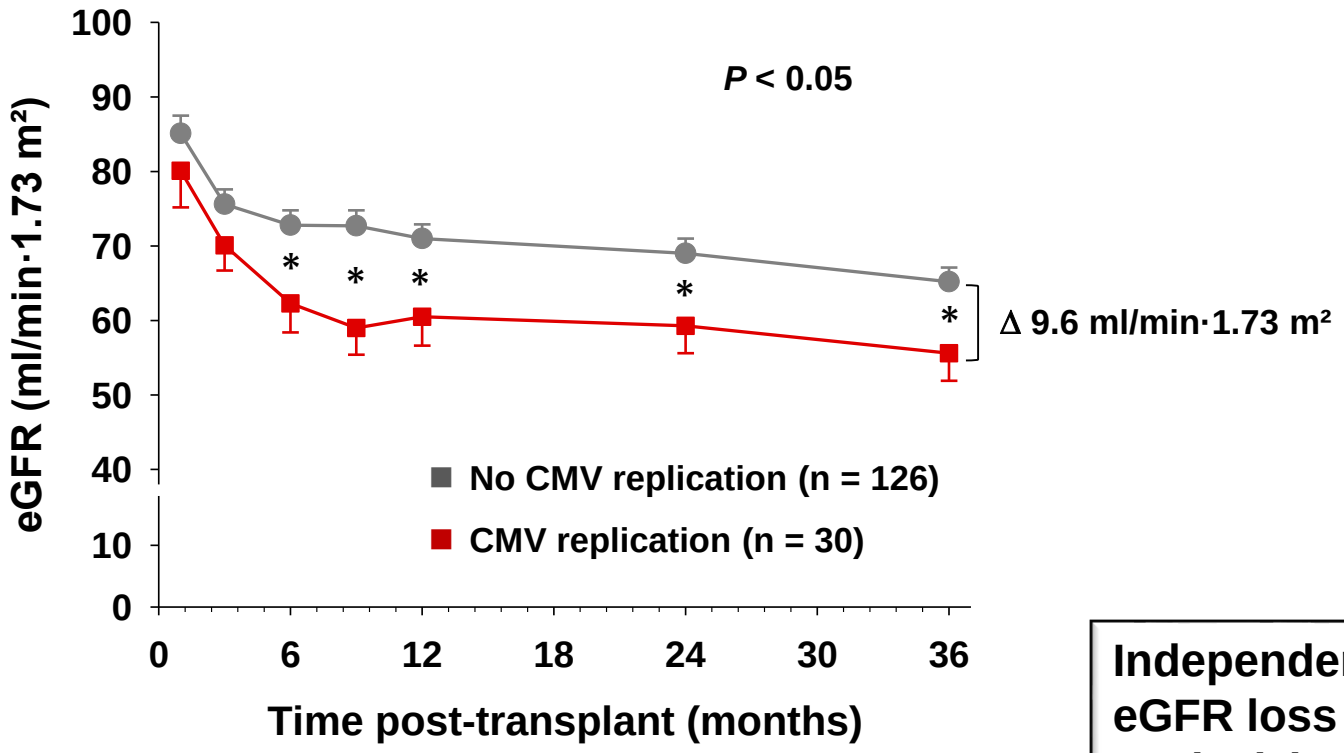
  PLoS Path 2010







Reduced Graft Function in Pediatric RTx Patients with CMV Replication



Independent risk factors for eGFR loss (multivariate analysis):

- **CMV replication (*P* < 0.05)**
- Acute rejection (*P* < 0.05)
- Recipient's age (*P* < 0.001)

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Höcker B et al., Transplantation 2015

Hematological Data

Hematological data	Prophylaxis group (n = 99)	Control group (n = 143)	*P* value
Anemia [Hb < 8 g/dl], n (%)			
Up to 100 days post-transplant	18/99 (18%)	12/143 (9%)	0.023
During 1st year post-transplant	24/99 (24%)	26/143 (18%)	0.252
Leukopenia [leukocytes < 3500/µl], n (%)			
Up to 100 days post-transplant	22/99 (22%)	12/143 (9%)	0.002
During 1st year post-transplant	34/99 (34%)	27/143 (19%)	0.006
Neutropenia [neutrophils < 1300/µl], n (%)			
Up to 100 days post-transplant	15/64 (23%)	10/103 (10%)	0.016
During 1st year post-transplant	19/58 (33%)	17/84 (20%)	0.092
Agranulocytosis [granulocytes < 500/µl], n (%)			
Up to 100 days post-transplant	8/64 (13%)*	1/103 (1%)	0.001
During 1st year post-transplant	11/58 (19%)	2/84 (2%)	0.001
Thrombocytopenia [thrombocytes < 100/µl], n (%)			
Up to 100 days post-transplant	4/99 (4%)	8/143 (6%)	0.584
During 1st year post-transplant	6/99 (6%)	8/143 (6%)	0.879

*3 of 8 (38%) patients received overdosing of VGCV by 46 - 64% prior to agranulocytosis.

Therapy

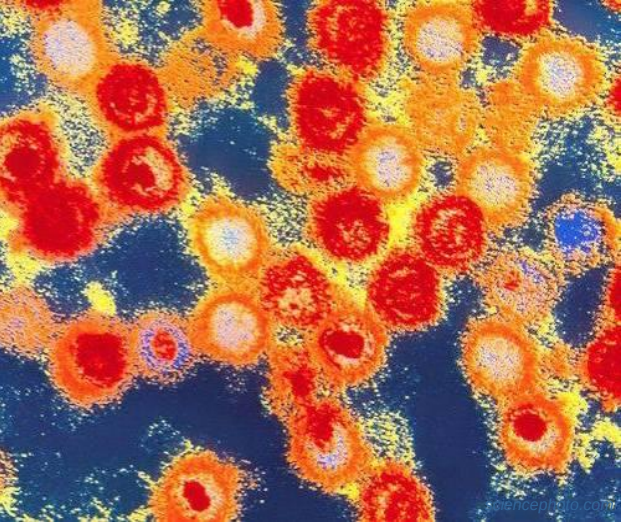
Asymptomatic CMV Infection

- Ganciclovir i.v. (5 mg/kg b.i.d.) in children aged < 5 years
- Valganciclovir p.o. (2-fold prophylactic dosage) in older patients
- Reduction of immunosuppression where indicated

CMV Disease

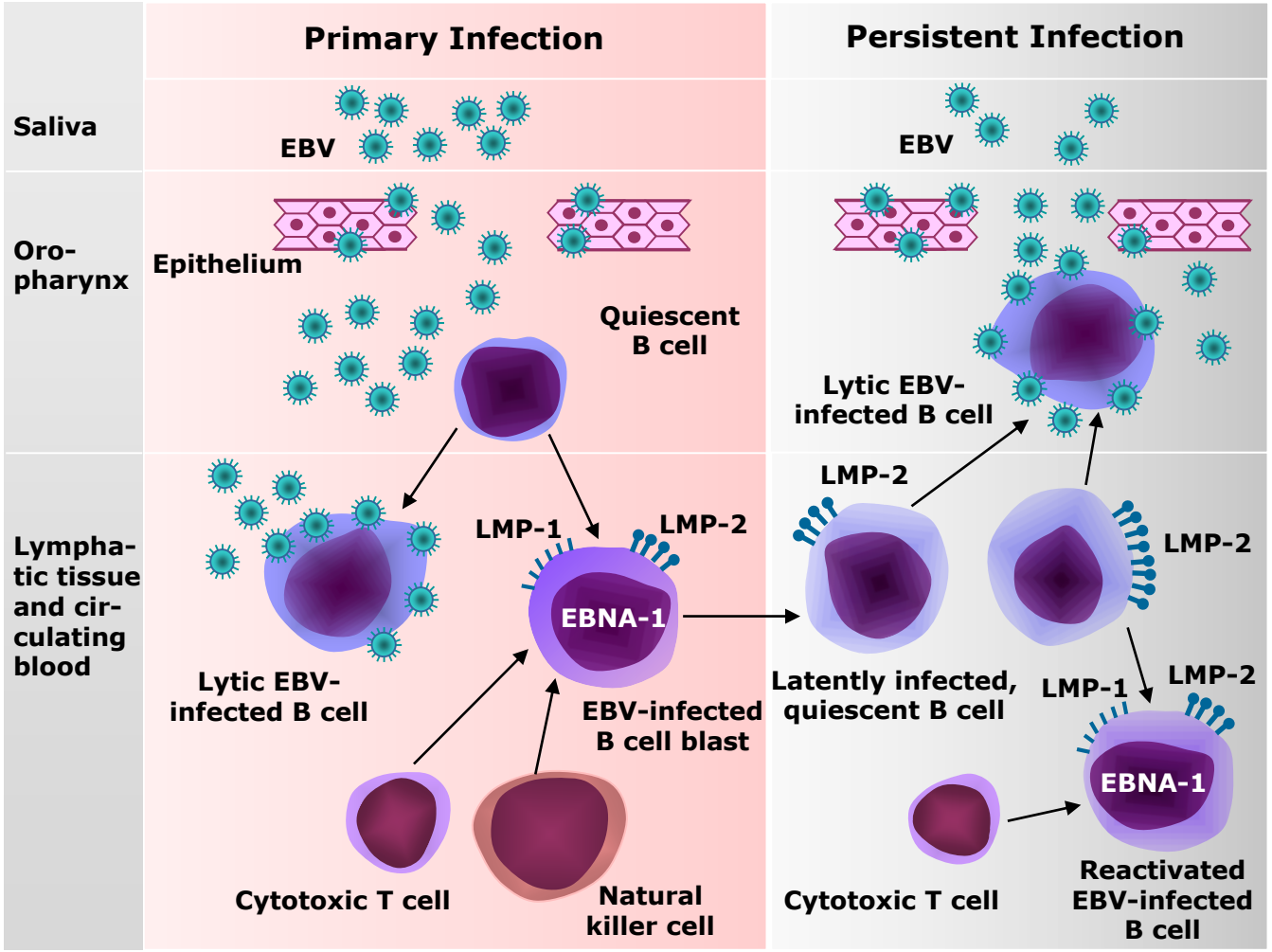
- Ganciclovir i.v. (5 mg/kg b.i.d.) in children aged < 12 years
- Valganciclovir p.o. (2-fold prophylactic dosage) in older patients
- CMV Ig i.v. (in addition to above-mentioned antiviral agents) in patients with severe CMV disease (i.e., pneumonitis, enteritis) and in those with hypogammaglobulinemia during CMV infection or disease

Am J Transplant 2013; 13: 93; Transplantation 2013; 96: 333



Epstein-Barr-Virus (EBV)

Epstein-Barr Virus (EBV) Infection and Post-Transplant Lymphoproliferative Disease (PTLD)



- Mostly mild cytopathic properties
- But ability to immortalize B cells
- Under immunosuppression risk of malignant B cell transformation
- 90% of PTLDs in pediatric patients induced by EBV

Modified according to N Engl J Med 2000; 343: 481

Risk Factors For PTLD

Early PTLD (≤12 months post-transplant)

- Primary EBV infection
- OKT3 and polyclonal antilymphocyte antibodies
- Young recipient age (i.e., infants and young children)
- CMV mismatch or CMV disease

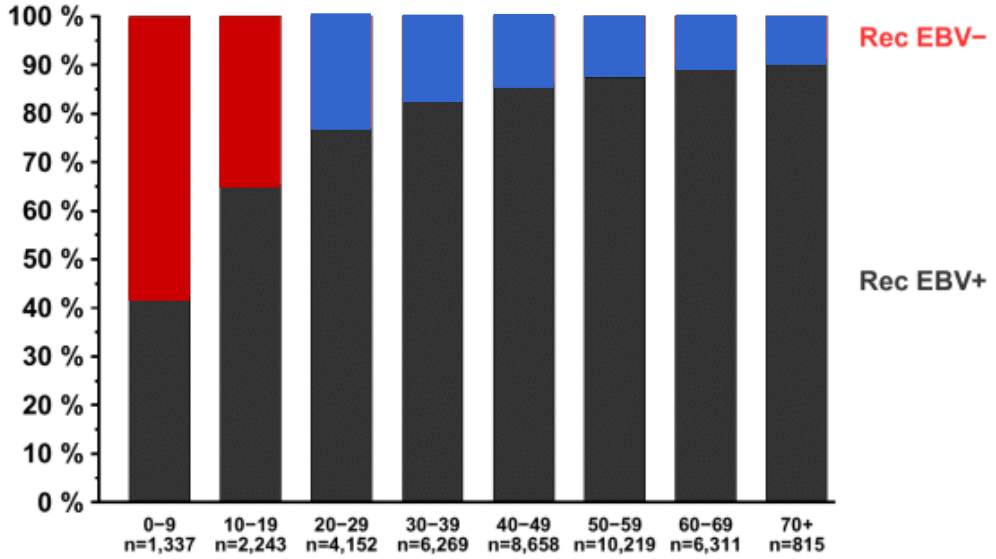
Late PTLD (>12 months post-transplant)

- Duration of immunosuppression
- Older recipient age (i.e., adults)

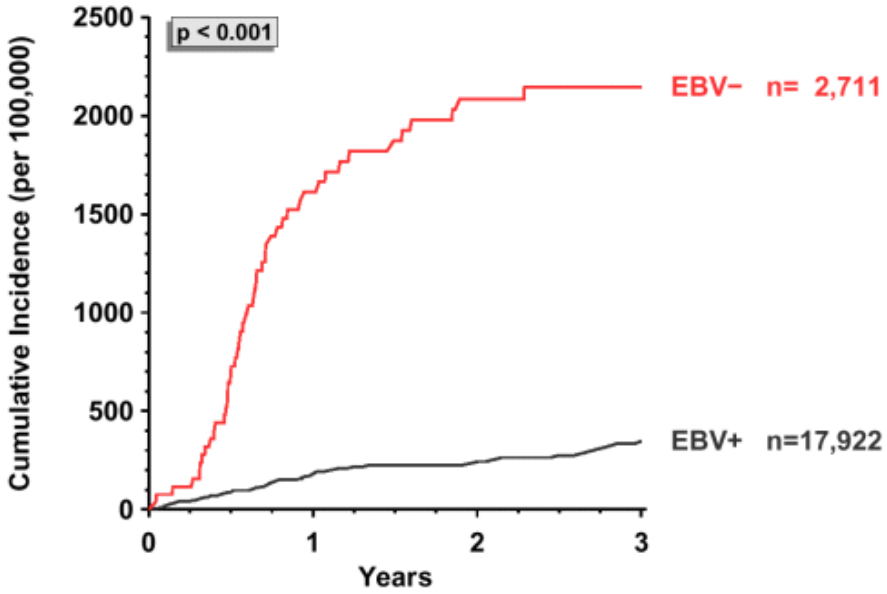
Am J Transplant 2013; 13: 41 ; Am J Transplant 2013; 13: 107

EBV-Seronegativity at RTx as Risk Factor for the Development of Non-Hodgkin Lymphoma (NHL)

Recipient EBV Serostatus at RTx



Incidence of NHL



Transplantation 2009; 88: 962

Spectrum of EBV Infection and Disease

- Asymptomatic EBV infection
- Unspecific flu-like symptoms
- Infectious mononucleosis

PTLD Categories (WHO Classification)
I. Early lesions
- Plasmacytic hyperplasia
- Infectious mononucleosis-like lesion
II. Polymorphic PTLD
III. Monomorphic PTLD (B-, T- or NK-cell type)
IV. Classical Hodgkin lymphoma-type PTLD

Am J Transplant 2013; 13: 41 ; Am J Transplant 2013; 13: 107

Diagnostics

Prior Kidney Transplantation

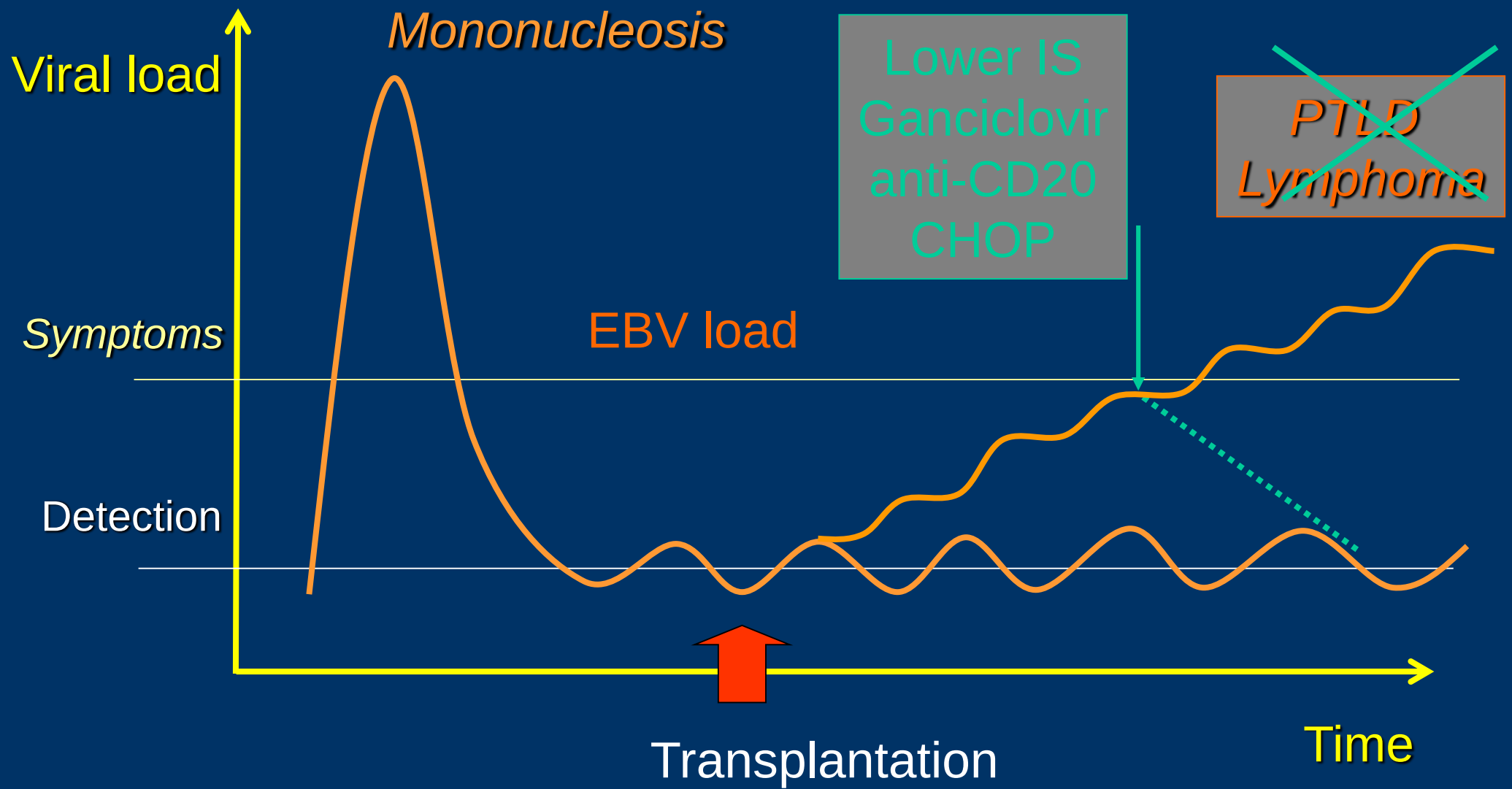
- EBV serology (IgG) in donor and recipient for risk assessment

Post-Transplant

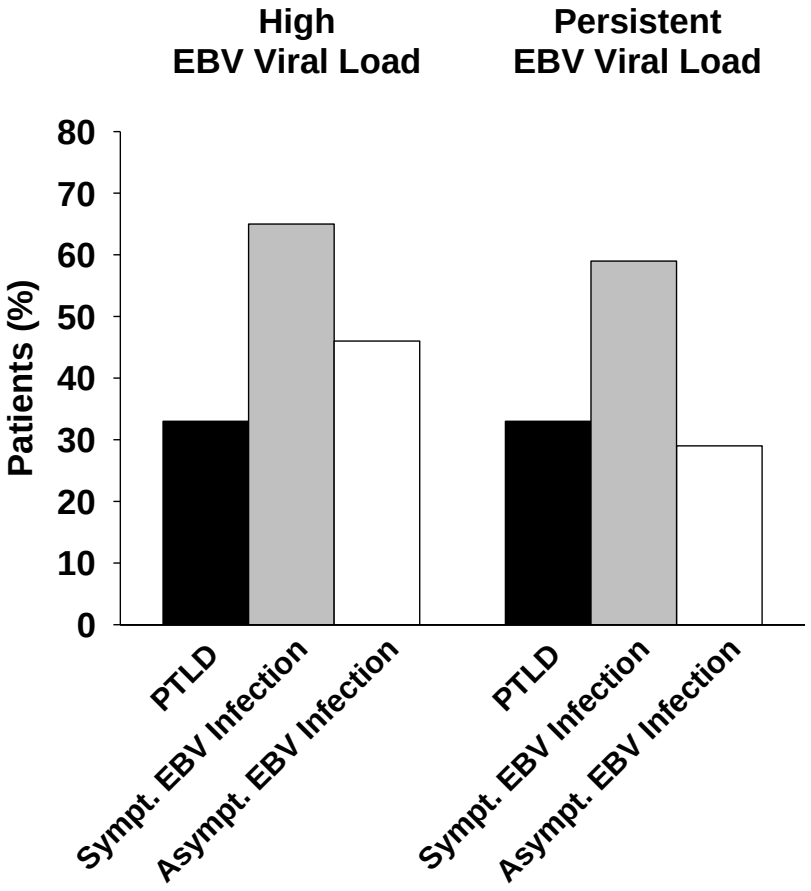
- EBV viral load
  - Lack of standardization in terms of specimen (whole-blood, lymphocyte, plasma), cut-off value (WHO international standard has yet to be validated.)
  - Monitoring schedule?
  - Poor positive predictive value for PTLD (28 – 65%)
- EBV-specific T cell response
  - Assays are complex, costly and difficult to implement in routine diagnostic laboratory.

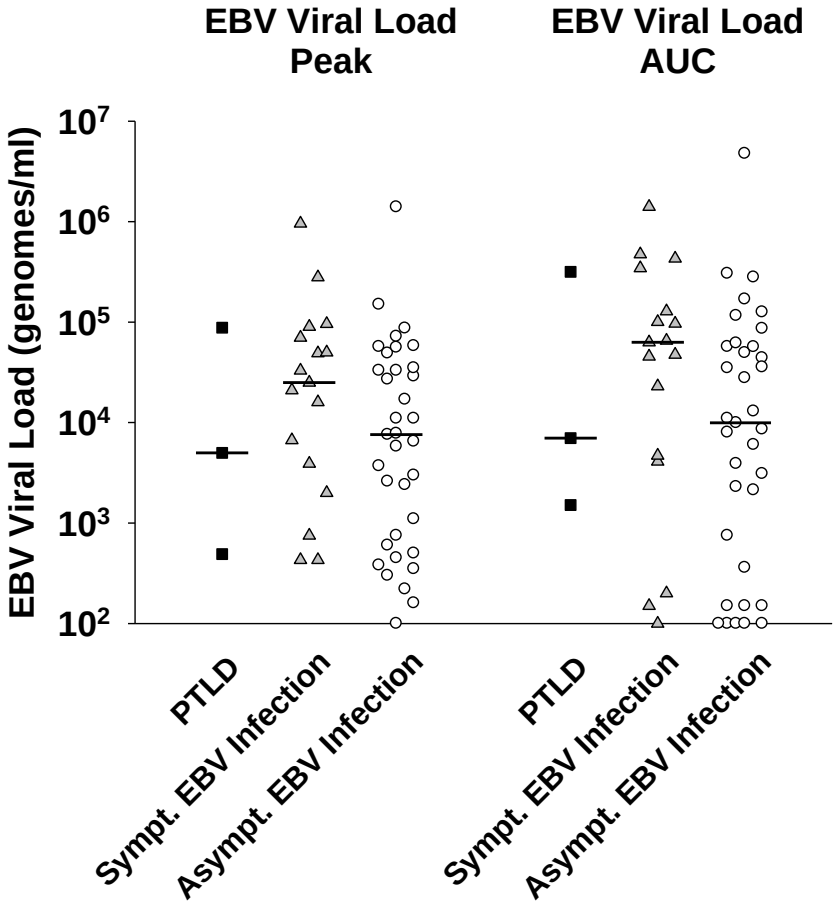
Am J Transplant 2013; 13: 41 ; Am J Transplant 2013; 13: 107

EBV load screening and monitoring



EBV Viral Load and EBV-Associated Clinical Symptoms





Clin Infect Dis 2013; 56: 84

Antiviral Prophylaxis

- EBV-naïve (R-) recipients of EBV-positive kidney allograft (D+) carry a high risk of primary EBV infection. *Am J Hematol 2011; 86: 206*
- Subclinical EBV infection is accompanied by chronic allograft dysfunction. *J Am Soc Nephrol 2010; 21: 1579*
- Cumulative incidence of NHL is significantly increased ($p<0.001$) in EBV-negative kidney allograft recipients. *Transplantation 2009; 88: 962*
- CMV Ig is associated with significantly lower ($p<0.02$) NHL risk. *Lancet Oncol 2007; 8: 212*
- Antiviral chemoprophylaxis (ganciclovir/aciclovir) is accompanied by an up to 83% reduction of the PTLD risk. *Am J Transplant 2005; 5: 2894*

Effect of antiviral prophylaxis with (val-)ganciclovir on the incidence and morbidity of primary EBV infection in high-risk (D+/R-) patients?

TRANSPLANT
INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

(Val-)Ganciclovir prophylaxis reduces Epstein-Barr virus primary infection in pediatric renal transplantation

Britta Höcker,[1] Stephan Böhm,[2,3] Helmut Fickenscher,[2,4] Uta Küsters,[2] Paul Schnitzler,[2] Martin Pohl,[5] Ulrike John,[6] Markus J. Kemper,[7] Henry Fehrenbach,[8] Marianne Wigger,[9] Martin Holder,[10] Monika Schröder,[11] Reinhard Feneberg,[1] Sabine Köpf-Shakib[1] and Burkhard Tönshoff[1]

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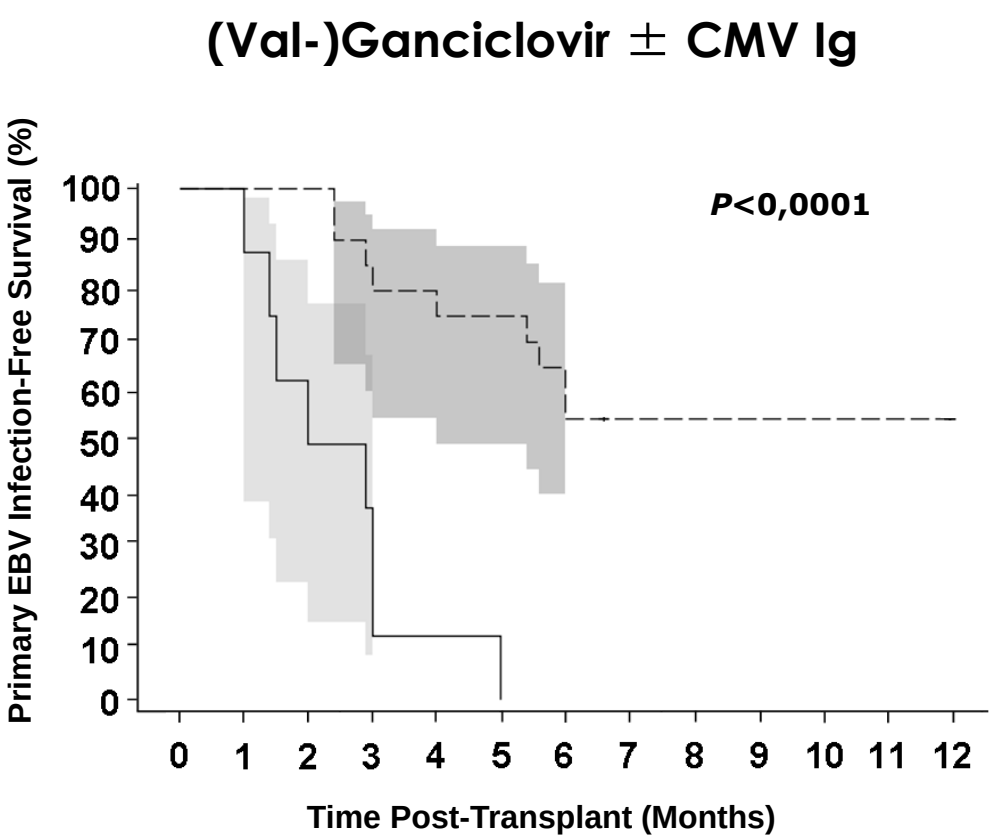
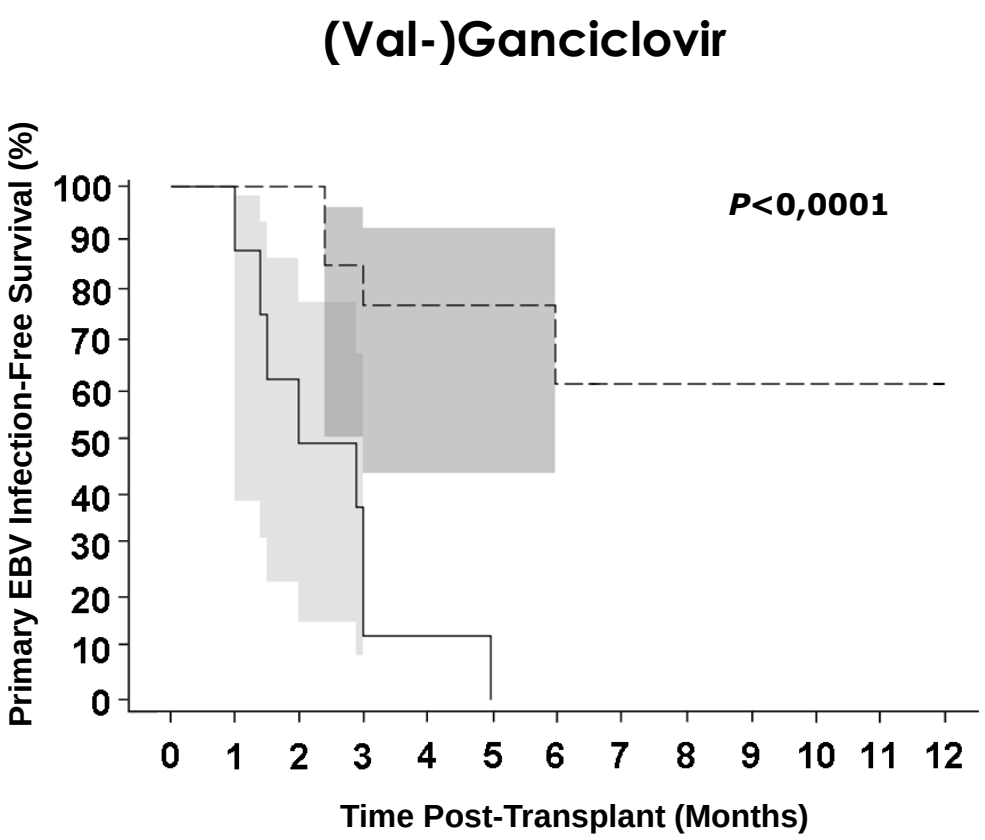
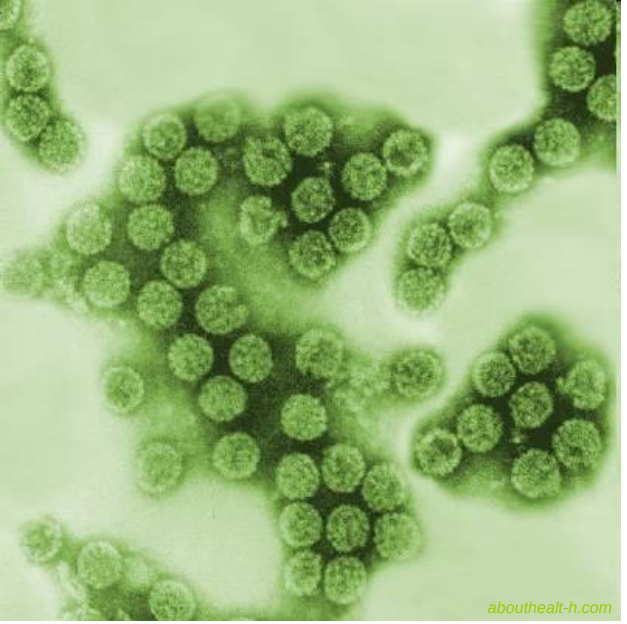
5 University Children's Hospital, Freiburg, Germany
6 University Children's Hospital, Jena, Germany
7 University Children's Hospital, Hamburg, Germany
8 Children's Hospital, Memmingen, Germany
9 University Children's Hospital, Rostock, Germany
10 Olga Children's Hospital, Stuttgart, Germany
11 Clementine Children's Hospital, Frankfurt, Germany

Effect of Antiviral Chemoprophylaxis with (Val-)Ganciclovir on the Incidence of Primary EBV Infection in High-Risk (D+/R-) Patients





Transpl Int 2012; 25: 723



Polyomavirus (BKV)

Primary Infection

- Occurs during first decade (seropositivity ~90%).
- Unspecific flu-like symptoms
- Transmission via respiratory tract

Persistent / Latent Infection

- Kidney, urothelial cells
- CNS? Leukocytes? Gastrointestinal tract?

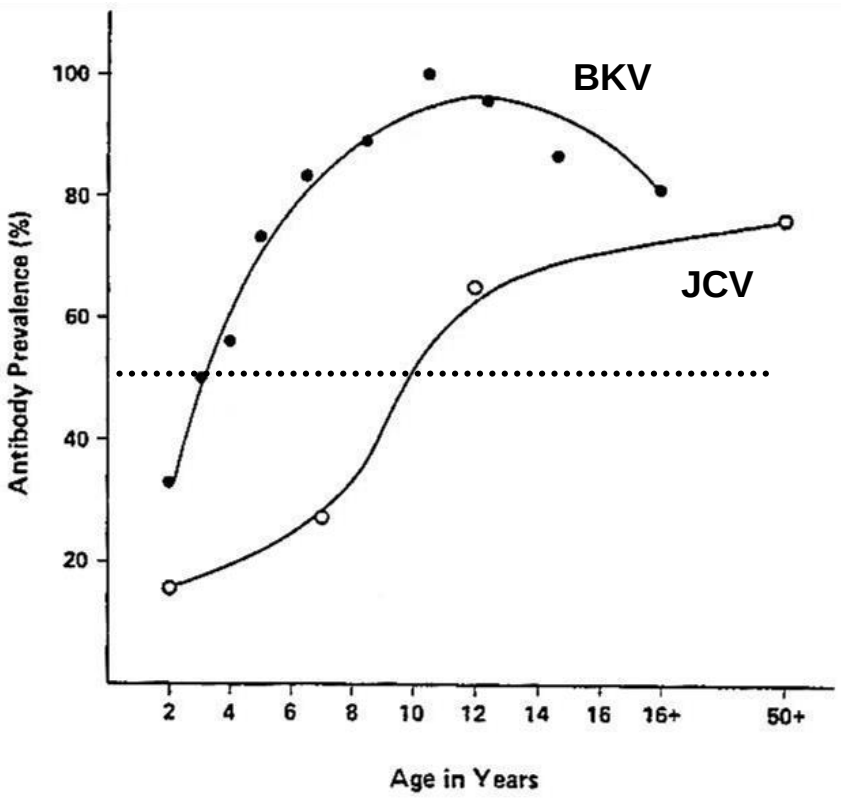
Reactivation

Immunological Competence

- Reactivation ~ 10% → viruria <10^5 cp/ml

Immunosuppression

- RTx: reactivation of BKV in donor urothelial cells
- Shedding of “decoy cells”
- High-level viruria in 30 - 50% of patients after RTx → viruria >10^7 cp/ml
- 30% of patients with high-level viruria develop BKV viremia
- Premature graft failure in 1 - 15% due to BKV



J Infect Dis 1973; 128(6):784-787

Am J Transplant 2009; 9: 136; Am J Transplant 2013; 13: 179

Diagnostics

Urine

- **Cytology** („decoy cells“, not pathognomonic: CMV, adenovirus)
- **Viral Load** (BKV DNA load >10^7 cp/ml; BKV VP1 mRNA load >$10^{6.5}$/ng RNA)

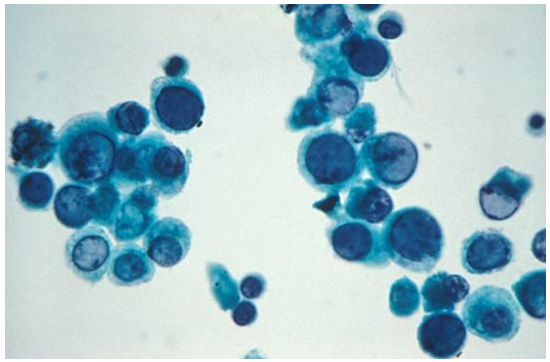
  Advantages: high negative predictive value for polyomavirus-associated nephropathy (PyVAN), window period of 6 – 12 wks before viremia and nephropathy

  Disadvantage: low positive predictive value for PyVAN

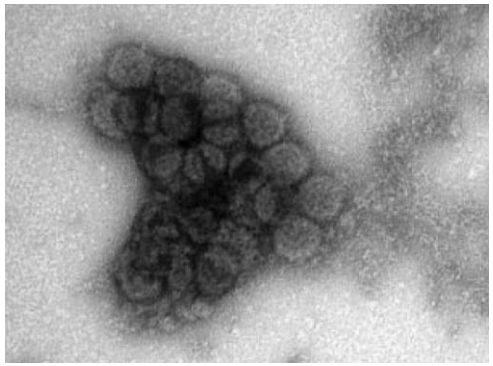
- **PyV Aggregates** (“Haufen”)

  Advantage: high (>90%) positive and negative predictive value for PyVAN

  Disadvantage: expertise in EM of PyV aggregates required



„Decoy Cells“



PyV „Haufen“

J Am Soc Nephrol 1999; 10: 1080; Lancet Infect Dis 2003; 3: 611; J Am Soc Nephrol 2009; 20: 416; Am J Transplant 2013; 13: 179

Diagnostics

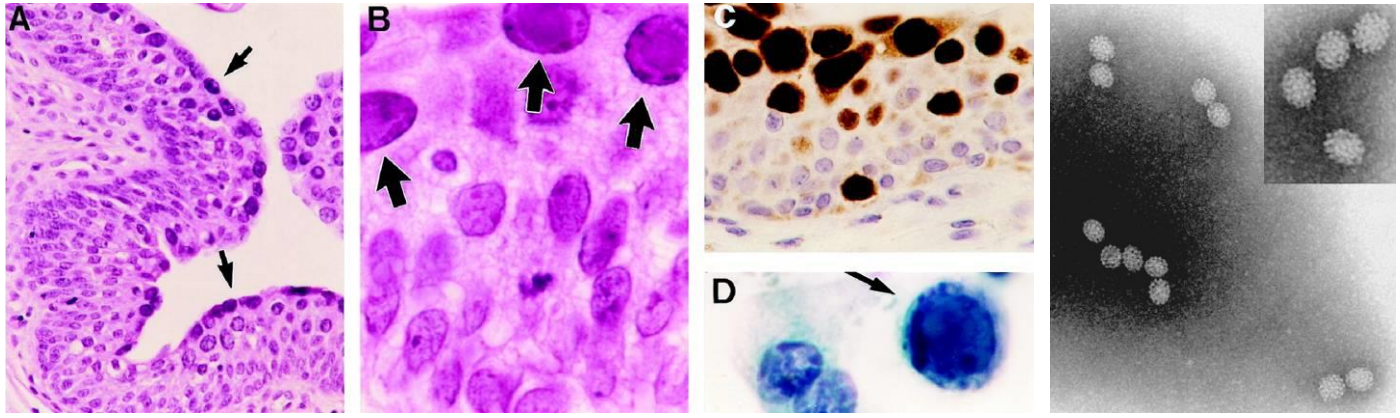
Blood

- **Viral Load** (BKV DNA load >10^4 cp/ml)

  Positive predictive value (PPV) for PyVAN 30 – 50%, window period of 2 – 6 wks before PyVAN, BKV DNA load >10^4 cp/ml → "presumed" PyVAN, BKV DNA load >10^6 cp/ml → "proven" PyVAN (PPV 90%)

Graft Biopsy

- **Immunohistochemistry** (T-Ag SV40, VP1)
- **≥2 cylinders, also medullary tissue** (sampling error in 10 - 30%)



J Am Soc Nephrol 1999; 10: 1080; Lancet Infect Dis 2003; 3: 611; J Am Soc Nephrol 2009; 20: 416; Am J Transplant 2013; 13: 179

Histology	Description	Extent of Bx Core	Risk of Graft Loss
PyVAN A • Viral cytopathic changes • Interstitial inflammation • Tubular atrophy • Interstitial fibrosis	Mild Minimal Minimal Minimal	≤25% ≤10% ≤10% ≤10%	<10%
PyVAN B • Viral cytopathic changes • Interstitial inflammation • Tubular atrophy • Interstitial fibrosis ▪ **PyVAN B1** - Interstitial inflammation ▪ **PyVAN B2** - Interstitial inflammation ▪ **PyVAN B3** - Interstitial inflammation	Variable Significant Moderate Moderate Moderate Significant Extensive	 11 - >50% 11 - >50% <50% <50% 11 - 25% 26 – 50% >50%	50% 25% 50% 75%
PyVAN C • Viral cytopathic changes	Variable Variable	Variable Variable	*Am J Transplant 2013; 13: 179* >80%

Therapy of PyVAN: Reduction of Immunosuppression

Strategy 1

1. CNI (TAC, CSA) dose reduction by 25 - 50%
2. Reduction of antimetabolite (MMF, AZA) dosage by 50% or discontinuation

Strategy 2

1. Reduction of antimetabolite (MMF, AZA) dosage by 50%
2. CNI (TAC, CSA) dose reduction by 25 - 50%
3. Discontinuation of antimetabolite

Immunsuppressant	Pre-Dose Level / Dosage
TAC	<6 ng/ml (target 3 ng/ml)
CSA	<150 ng/ml (target 100 ng/ml)
SRL	<6 ng/ml
MMF	<1000 mg/d (corresp. <600 mg/m²·d)
Prednisone	<10 mg/d (corresp. <5.8 mg/m²·d)

Conversion of immunosuppressive regimen

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Adjunctive Therapy of PyVAN

Cidofovir (Vistide®)

- 0.25 - 1 mg/kg i.v. at 1- to 3-week intervals
- Cave: nephrotoxicity, anterior uveitis (12 - 35%)

Leflunomide (Arava®)

- Substitute for MMF
- Loading dose 100 mg/d for 5 days, maintenance dose 40 mg/d
- Cave: hepatitis, hemolysis, thrombotic microangiopathy, bone marrow suppression, fungal pneumonia

IVIG

- 0.2 – 2 g/kg i.v. in conjunction with reduced immunosuppression

Fluoroquinolones?

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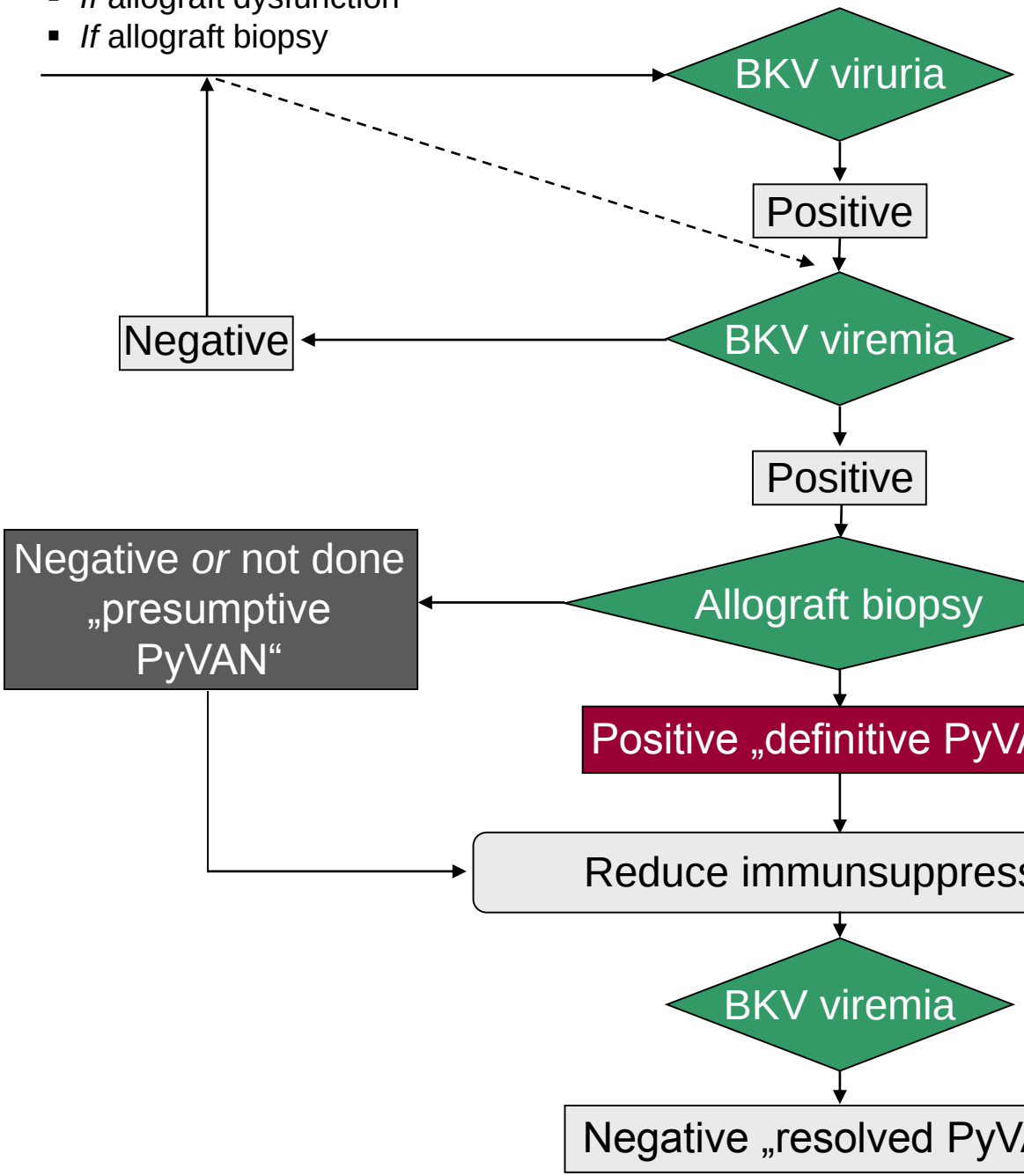
Screening

- Every 3 mths during first 2 yrs post-transplant *or*
- *If* allograft dysfunction
- *If* allograft biopsy



- Urine cytology (decoy cells) *or*
- Urine EM (PyV aggregates) *or*
- Urine BKV load (>10^7 cp/ml)

- Plasma BKV load >10^4 cp/ml

Other diagnosis
- Acute rejection?
- Drug toxicity?
- Recurrent disease?

- Staging (PyVAN A, B_1, B_2, B_3, C)

- Reduce CNI, MMF…
- Add cidofovir? Leflunomide? IVIG?

Follow-up
- Serum creatinine weekly
- Plasma BKV load every 1 - 2 wks (clearing 8 - 36 wks)
- Allograft biopsy?
- Raise immunosuppression?

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THANK
YOU!