

BK Nephropathy: The Vanderbilt Experience

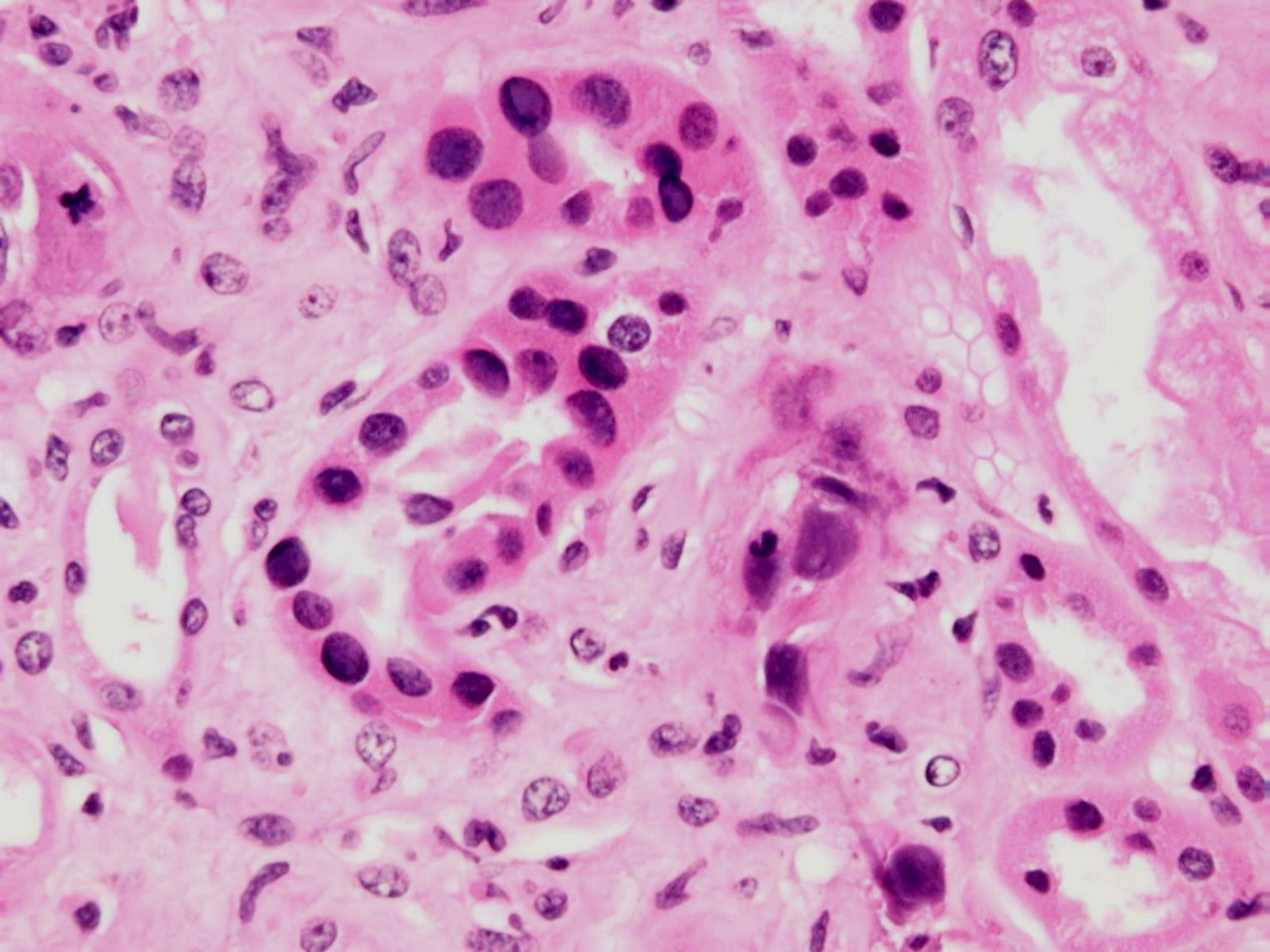
J. Harold Helderman

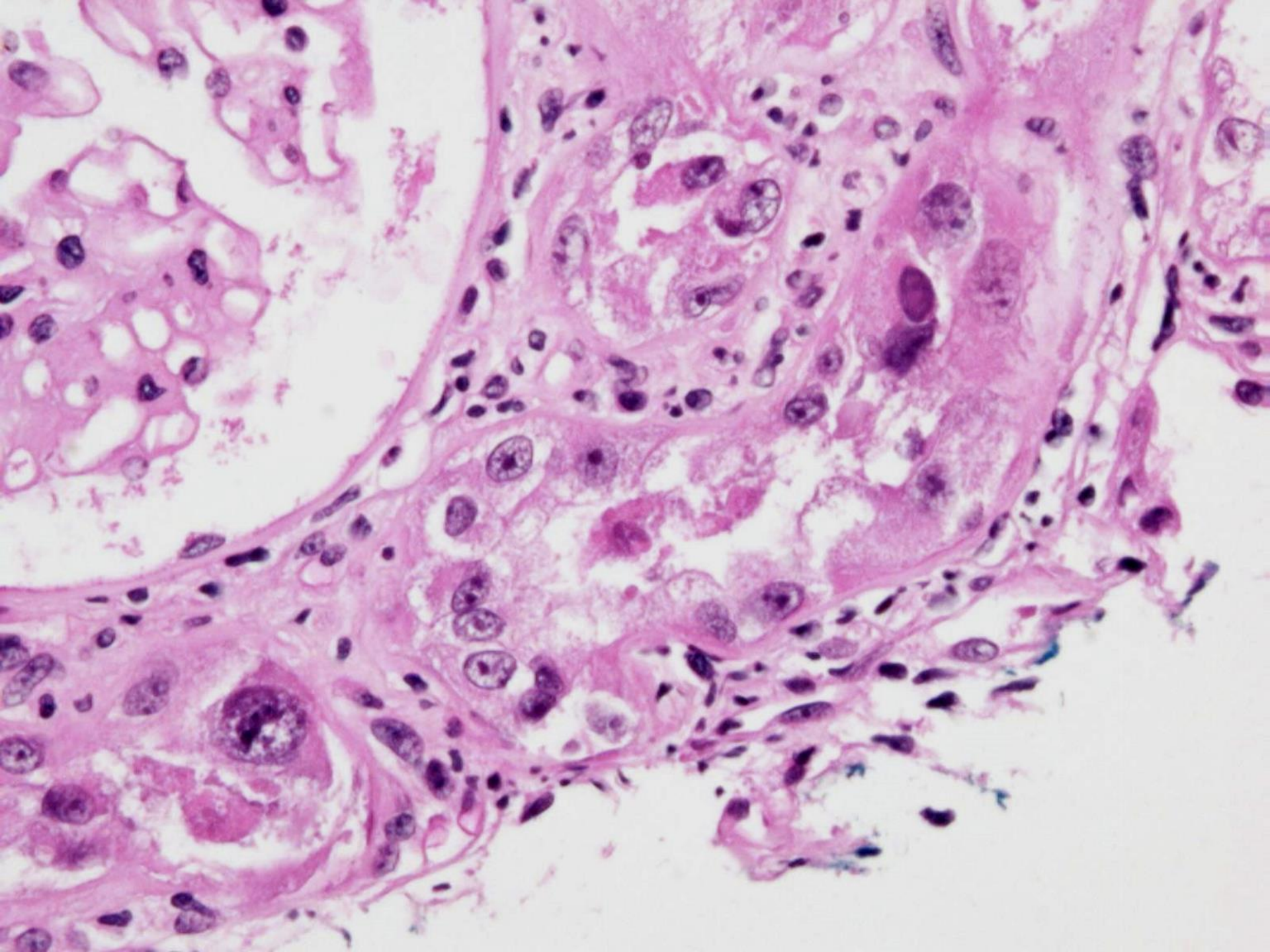
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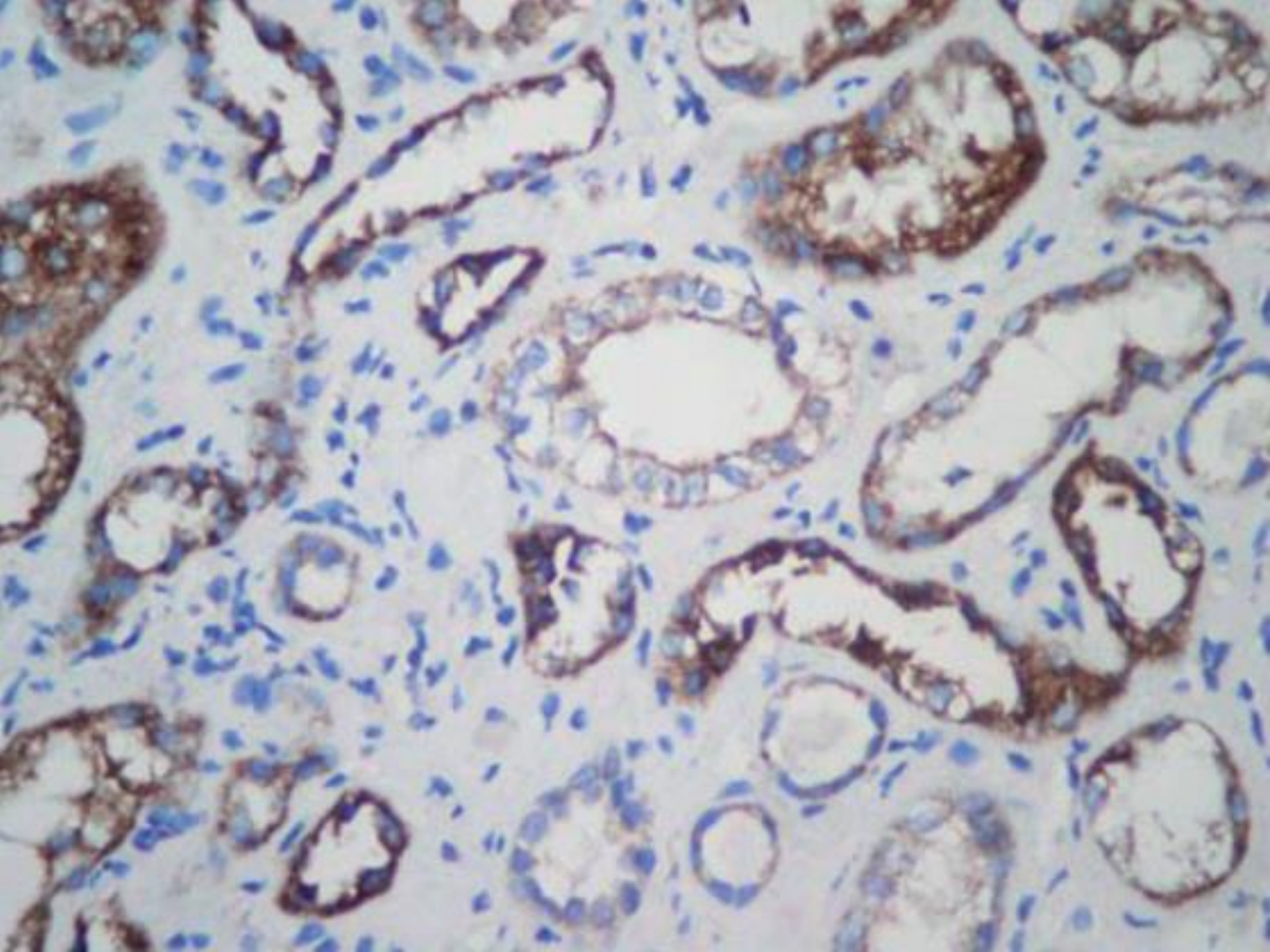
- 1. The Pathology**
- 2. Viral Taxonomy**
- 3. Testing & Screening**
- 4. Treatment literature**
- 5. The Vanderbilt Experience**

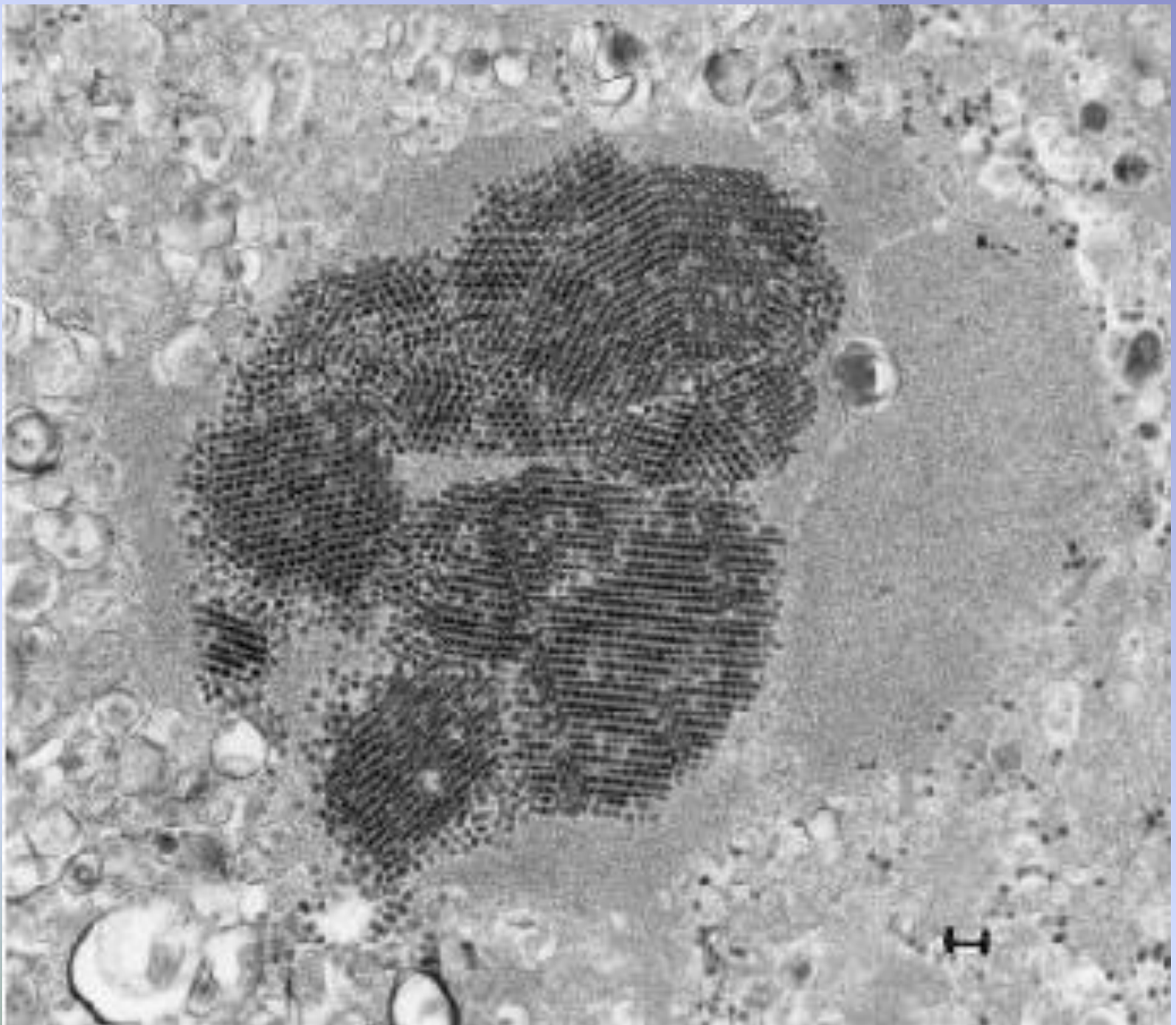
PATHOLOGY

- Path: consistent with BK nephropathy
 - Viral cytopathic effect-**intranuclear inclusion bodies**
 - Degenerative **tubular epithelial changes** with sloughing and cellular and granular casts
 - Variable **interstitial nephritis**







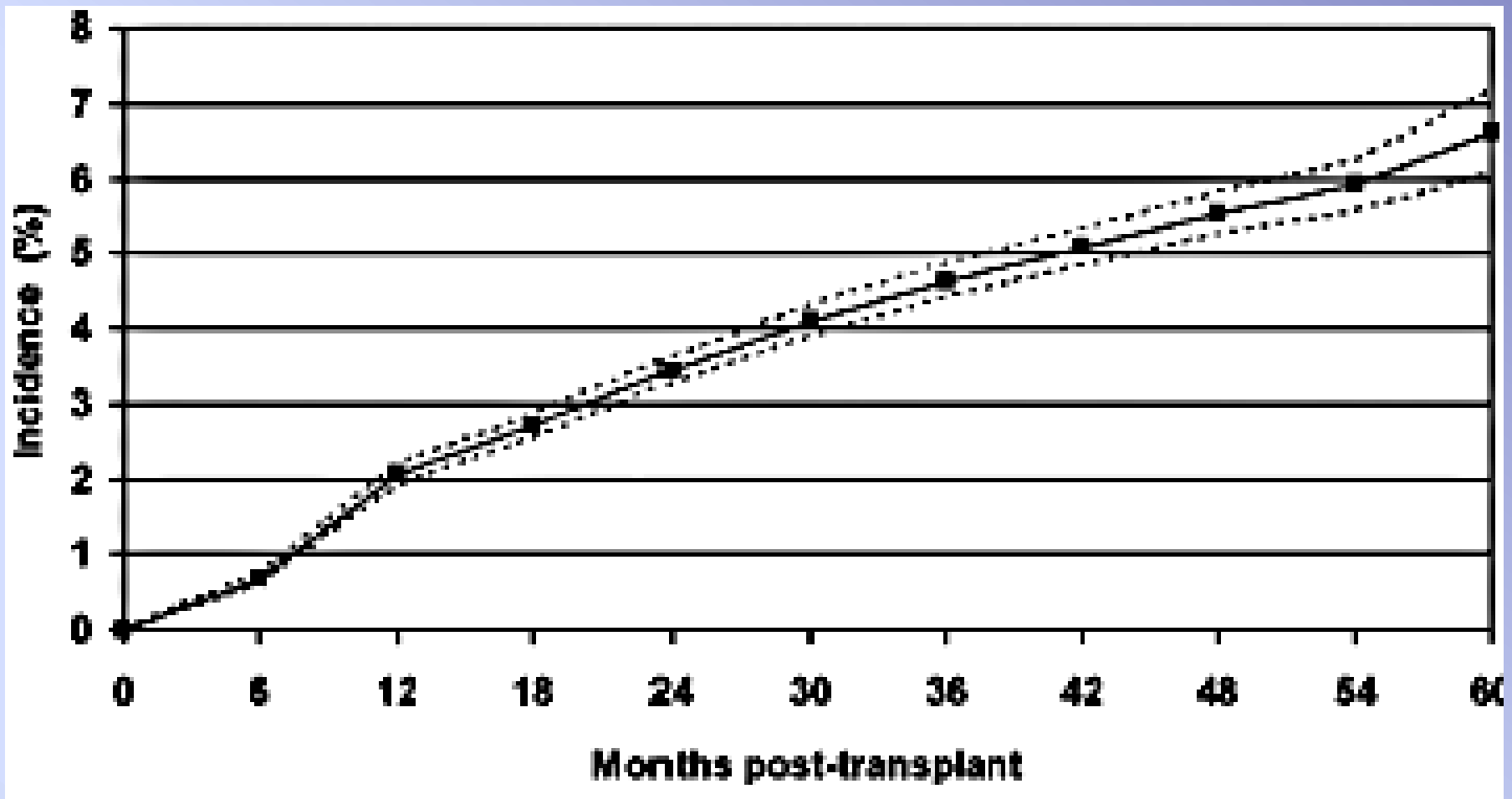


BK Virus

- 1971: described by Gardner SD and colleagues in Lancet: “isolated from urine after renal transplantation”-named BK virus (the initials of the patient who had ***ureteric stenosis***)
- 1983: first report on ***tubulointerstitial nephritis*** (6 year old boy with primary immune deficiency)
- Not truly appreciated until mid 1990's

Gardner SD, et al. Lancet 1971

Rosen S, et al. NEJM 1983



Kaplan-Meier estimated incidence of treatment of BK virus , 2003 to 2006 OPTN database (n=48,292): 0.7% at 6 months posttransplant; 2.18% at 1 year, 3.45% at 2 years, and 6.6% at 5 years

Higher center volume and living kidney donation: protective; more BK in more recent transplant years

Dharnidharka VR, et al. Transplantation 2009

BK Virus

- Belongs to a family of DNA viruses called polyomaviruses-originally Papovavirus-(includes JC virus, KI, WU and MC viruses)
- Reported in 10-60% of kidney transplant recipients→BK nephropathy in 1-5% of patients→ graft loss in up to 60% of patients

BK Virus

- Primary Infection:
 - Childhood nonspecific viral illness-respiratory
- Long-lived latency in uroepithelium and renal tubular cells (not in reticuloendothelial cells-like herpes viruses)
- Antibodies against BKV: 50% of children by age 3, 60-90% by age 10, and 80-90% by age 20
- Reactivation in immunocompromised individuals

Linear Progression of Disease

- Asymptomatic **viruria** → **viremia** → parenchymal damage → progressive deterioration of graft function (**BK nephropathy**), hemorrhagic cystitis, ureteral ulceration/stenosis, and progressive multifocal leukoencephalopathy (PML)

BK Virus-Donors

- Pretransplant samples from donor and recipients
- 54/81 adult kidney donors (67%): seropositive for BK virus
- BKV infection developed in 25 (46%) of 54 recipients who received kidneys from seropositive donors compared to 4 (15%) of 27 recipients who received kidneys from seronegative donors

Bohl DI, et al. Am J Transplant 2005

BK Virus-Donors

- BK viruria in recipients from seropositive donors occurred earlier (median onset: 45 days vs. 370 days, $p < 0.001$) with longer durations (median duration: 157 vs. 7 days, $p = 0.009$) and higher peak urine titers
- Donor seropositivity: associated with a significantly elevated odds ratio of 3.1
- Early BKV infection in kidney transplant recipients is usually of donor origin
- Testing for BK virus serostatus is neither routine, not mandated at this time

Risks for BK Nephropathy

- Degree of overall immunosuppression-USE OF TACROLIMUS
- Prior treatment for acute rejection, especially treatment with pulse steroids or lymphocyte-depleting agents
- Donor seropositivity; seronegative recipients
- Male Sex; older age; deceased donor
- Degree of HLA mismatch and prolonged cold ischemia time
- Ureteral stent placement (four-fold increase)
- Renal injury (I.e. immune injury-rejection, proinflammatory cytokines, ischemia-reperfusion injury)

Fishman JA. Am J Transplant 2003

Matlosz B, et al. Transplant Proc 2005

Burgos D. Transplant Proc 2006

Diagnostic Testing

- **Urine:**

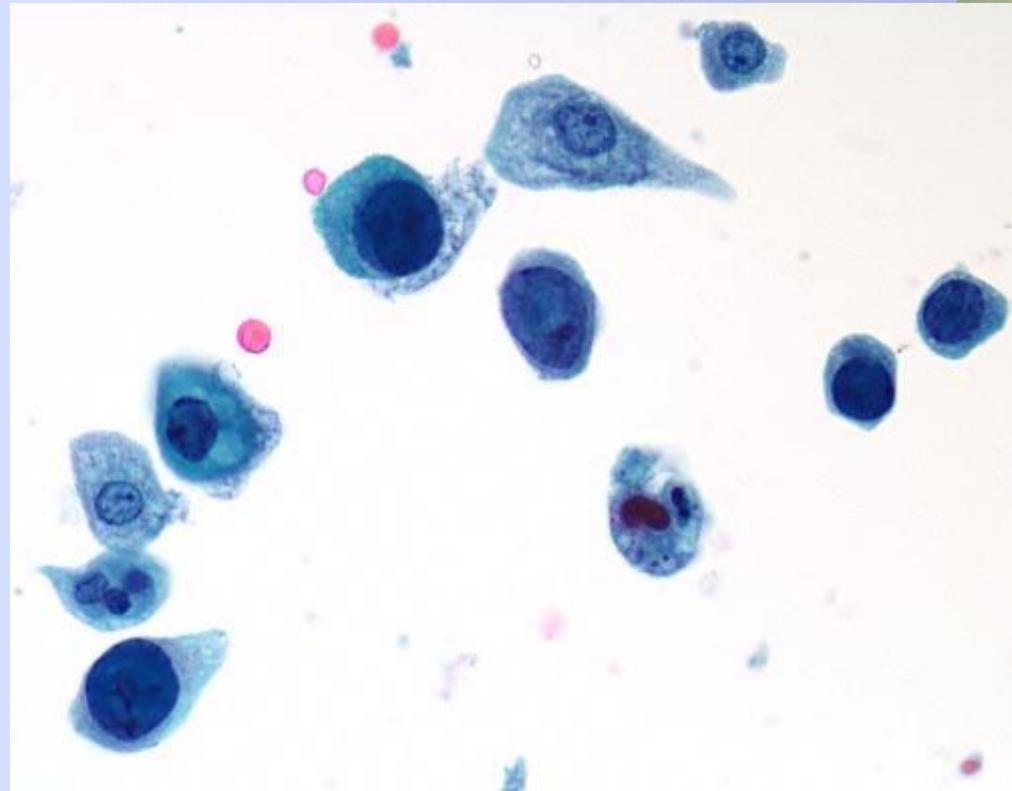
- Decoy Cells
- DNA PCR
- EM-Haufen
- Urinary cytokines: IL-3 and IL-6 (Opelz et al)
- Urinary cell mRNA profiles (Suthanthiran et al)

- **Blood**

- DNA PCR (Quant); PPV ~60% (plasma BK level >10,000 copies/ml-associated with 93% specificity for presence of BK nephropathy- *Hirsch HH, et al. 2006*)

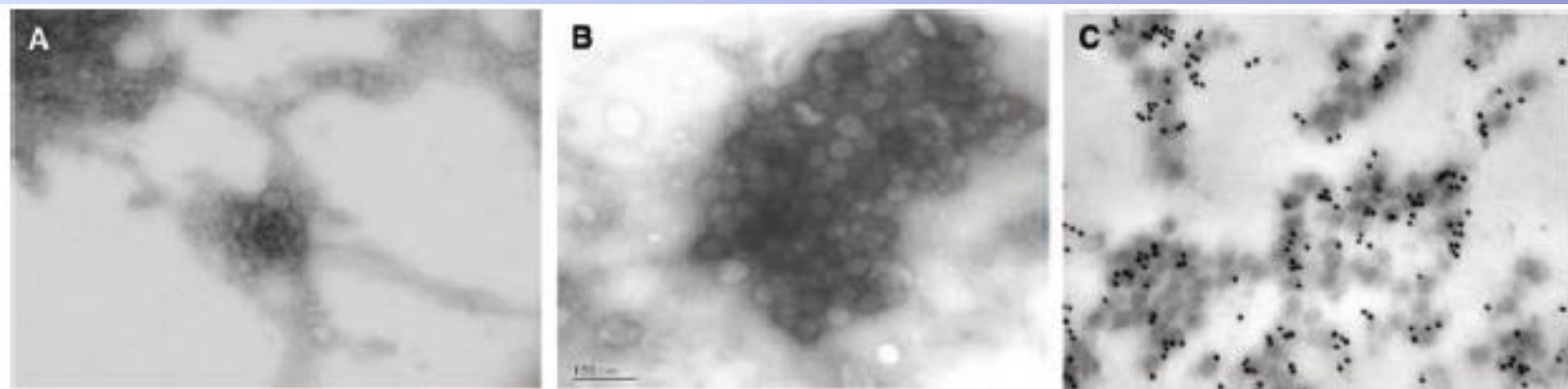
- **Renal biopsy:** gold standard

Urine “Decoy cells” (intranuclear viral inclusions in tubular epithelial cells)



- May be mistaken for degenerative or tumor cells

Haufen: Cast-like, Three-dimensional Polyomavirus Aggregates in the Urine



- Negative-staining electron microscopy: 194 urine samples from 139 controls (negative) and 143 samples from 21 patients (all positive) with BK nephropathy
- Detection of Haufen (cluster or stack in German) in the urine correlated tightly with biopsy confirmed BK (concordance rate 99%)

Singh HK, et al. JASN 2009

Haufen: Cast-like, Three-dimensional Polyomavirus Aggregates in the Urine

- Densely arranged viral aggregates
- Haufen-positive urine sample: multiple small and large polyoma virus aggregates with significant Tamm-Horsfall protein content
- Comes from the injured renal tubular segments/out of the affected nephrons
- 100% sensitive and 99% specific for identifying biopsy-proven BK nephropathy
- Biomarker for intrarenal BK virus infection-noninvasive; not recommended as a mass screening tool at this time

Table 1. Diagnostic Testing for BK Virus Nephropathy

Test	Threshold Value	Correlation With PVAN on Biopsy
Decoy cells	>10 cells/cytospin	+
Urine BK virus DNA quantitative PCR	>1 × 10 ⁷ copies/mL	++
Blood/plasma BK virus DNA quantitative PCR	>1 × 10 ⁴ copies/mL	+++

Abbreviations: PCR, polymerase chain reaction; PVAN, polyomavirus-associated nephropathy.

	Sensitivity	Specificity	PPV
Decoy Cells (>10/cytospin)	25%	84%	5-20%
Viruria (>10⁷ copies/ml)	100%	92%	31%
Viremia (>10⁴ copies/ml)	100%	96%	50-60%

Wiseman AC. Am J Kid Dis 2009

Viscount HB, et al. Transplantation 2007

BK Virus Testing

- Viremia detection by molecular PCR amplification is associated with higher PPV and NPV for BK nephropathy than viruria by decoy cells or PCR
- **Same laboratory and same assay-different primers and assay techniques**
- A negative biopsy does NOT rule out BK nephropathy due to the possibility of sampling error and the focal nature of the infection (sensitivity is not 100%)
- Biopsy: viremia is accompanied by elevation in serum creatinine or high-level viremia despite reduction of immunosuppression

Screening and Diagnostic Testing for BK

- AST Infectious Disease Community of Practice guidelines and KDIGO guidelines: earlier (**starting at 1 month posttransplant**) and more frequent screening (**monthly plasma screening for the first 6 months, then every 3 months until 2 years posttransplant**)-may be more appropriate in high incidence transplant centers

Hirsch HH, et al. Am J Transplant 2013
Kasiske BL, et al. Kidney Int 2010

Treatment of BK Nephropathy

- Cidofovir, leflunomide, quinolones, and intravenous immunoglobulin: no randomized prospective clinical trial
- Careful reduction of immunosuppression and close follow-up for development of acute rejection- remains the cornerstone
- **No specific antiviral drug treatment**

Treatment of BK Nephropathy

- Multicenter prospective studies are needed:
 - Stratifying histologic grading and renal function
 - Use of viral load or other techniques for diagnosis
 - Evaluation of different treatment strategies: assessing the possibility of chronic allograft dysfunction due to systematic reduction of immunosuppression
 - Longer follow-up

Re-transplantation

- Possible despite persistent/increased risks
 - The short-term graft and patient survival with re-transplantation after BK appears to be excellent
 - Longer-term outcomes remain unknown

Dhamidharka VR, et al. Am J Transplant 2010

- Not enough data to recommend nephrectomy of failed allograft prior to re-transplantation
 - **Nephrectomy is not necessarily protective**
- Pre-transplant clearance of viremia is necessary

Recent Articles

Polyomavirus BK Replication in *De Novo* Kidney Transplant Patients Receiving Tacrolimus or Cyclosporine: A Prospective, Randomized, Multicenter Study

- DIRECT study: a prospective 6-month, open-label multicenter study; with a follow-up visit at month 12; randomizing *de novo* KT patients to CsA or Tac between 2003-2005
- Tac dosing was based on C0 targets: 10–15 ng/mL during months 1–3 and 5–10 ng/mL during months 4–6

Polyomavirus BK Replication in *De Novo* Kidney Transplant Patients Receiving Tacrolimus or Cyclosporine: A Prospective, Randomized, Multicenter Study

- Univariate analysis: CsA-MPA with lower rates of viremia than Tac-MPA at month 6 (10.6% vs. 16.3%, $p = 0.048$) and 12 (4.8% vs. 12.1%, $p = 0.004$) and lower plasma BKV loads at month 12 (3.9 vs. 5.1 \log_{10} copies/mL; $p = 0.028$)
- Multivariate models: CsA-MPA with less viremia than Tac-MPA at month 6 and month 12
- Viremia at month 6 was also independently associated with higher steroid exposure until month 3 (OR 1.19 per 1 g), and with male gender (OR 2.49) and recipient age (OR 1.14 per 10 years) at month 12

Polyomavirus BK Replication in *De Novo* Kidney Transplant Patients Receiving Tacrolimus or Cyclosporine: A Prospective, Randomized, Multicenter Study

- At baseline, BK viruria was detected in 19 (5.0%) of 378 patients with residual urine production: none of these developed viremia, and only 8 remained viruric posttransplant : less than 5 log₁₀ copies/mL
- Baseline BK viremia was found in 3 (0.5%) of 609 patients, but none had detectable viruria or viremia posttransplant
- The highest rates of viruria and **viremia** were observed at month 6 (25.4% and **13.7%**, respectively) which then decreased at month 12 (20.3% and **8.6%**, respectively)

Hirsch HH, et al. Am J Transplant 2013

Recent Articles

- Lower prevalence of BK virus infection in African American renal transplant recipients: a prospective study (23% vs 47%)
Sood P, et al. Transplantation 2012
- Ciprofloxacin Prophylaxis (250 mg twice daily for 30 days) in Kidney Transplant Recipients Reduces BK Virus Infection at 3 Months But Not at 1 Year
Wojciechowski D, et al. Transplantation 2012
- Factors influencing viral clearing and renal function during polyomavirus BK-associated nephropathy after renal transplantation: peak viral load, tacrolimus treatment, delayed diagnosis, and viral reduction time influence outcomes in patients with BKVN
Schwarz A, et al. Transplantation 2012

Study Design

- 1. Patient Population – all patients with histologically proven BK Nephropathy 2002 – 2011 (n = 25)**
- 2. Anti – metabolite stopped; CNI switched from tacrolimus to CSA modified (<150 ng/ml C12) in all**
- 3. Out come Variables**
 - a.) BK Viremia**
 - b.) Renal Function**
 - c.) Graft Survival**

Tables and Figures

Table 1. Patient demographics

Demographic	Mean	St Deviation	Median
Age at Transplant	51 years	11 years	54 years
Gender			
Male	88%		
Female	12%		
Race			
Caucasion	56%		
African American	40%		
Other	4%		
Donor			
Deceased	58%		
Living	42%		
Induction			
Thymoglobulin	62%		
Campath	19%		
Simulect	15%		
Prednisone Use	81%		
Tacrolimus Level pre KKVN	8.7 ng/dl	2.5 ng/dl	8.35 ng/dl
Rejection pre BKVN	23%		
Rejection post BKVN	11%		
Time to diagnosis BKVN	14 months	8 months	14 months
Time to BK Viremia Clearance	161 days	138 days	90 days

Figure 1. Trend in mean BK Viremia at time of diagnosis and the following three months with treatment

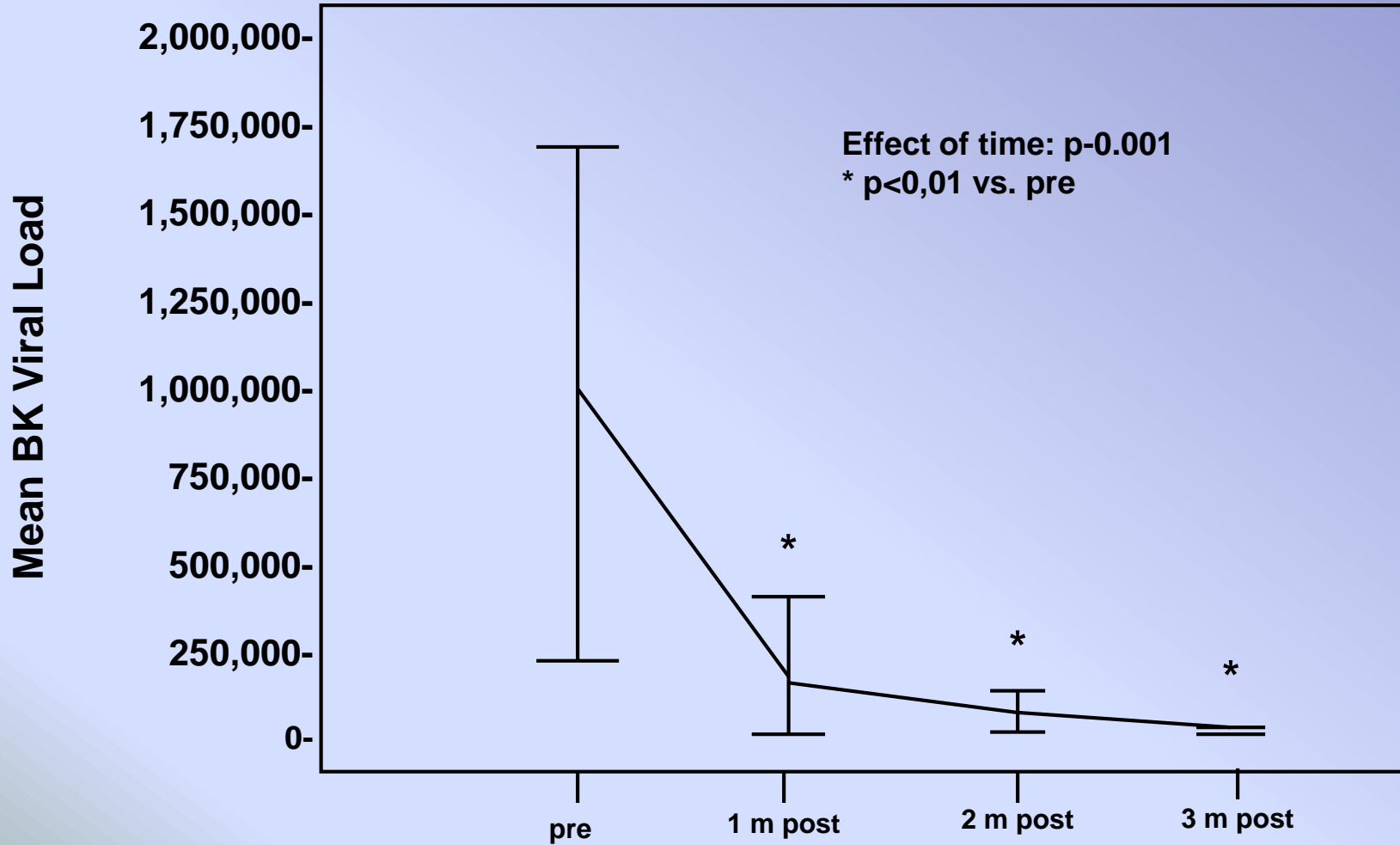


Table 2. Analysis of Death-Censored Survival Data

Length of Death - Censored Graft Survival	Estimate of Death - Censored Graft Survival	Standard Error	Confidence Interval
1 Year	96%	3.9%	
2 Years	92%	5.4%	
3 Years	87%	7.0%	
5 Years	81%	8.8%	
10 Years	68%	1.1%	
Mean Survival	98 months	8 months	81 - 115 months

Table 3. Analysis of Cumulative Survival Data

Length of Cumulative Graft Survival	Estimate of Cumulative Graft Survival	Standard Error	Confidence Interval
1 Year	96%	3.9%	
2 Years	88%	6.6%	
3 Years	88%	6.6%	
5 Years	77%	9.2%	
10 Years	50%	12.8%	
Mean Survival	88 months	9 months	71 - 106 months

Figure 2A. Mean Serum Creatinine (mg/dl) prior to infection, at time of diagnosis of bkvn, and nadir function within 6 months after treatment

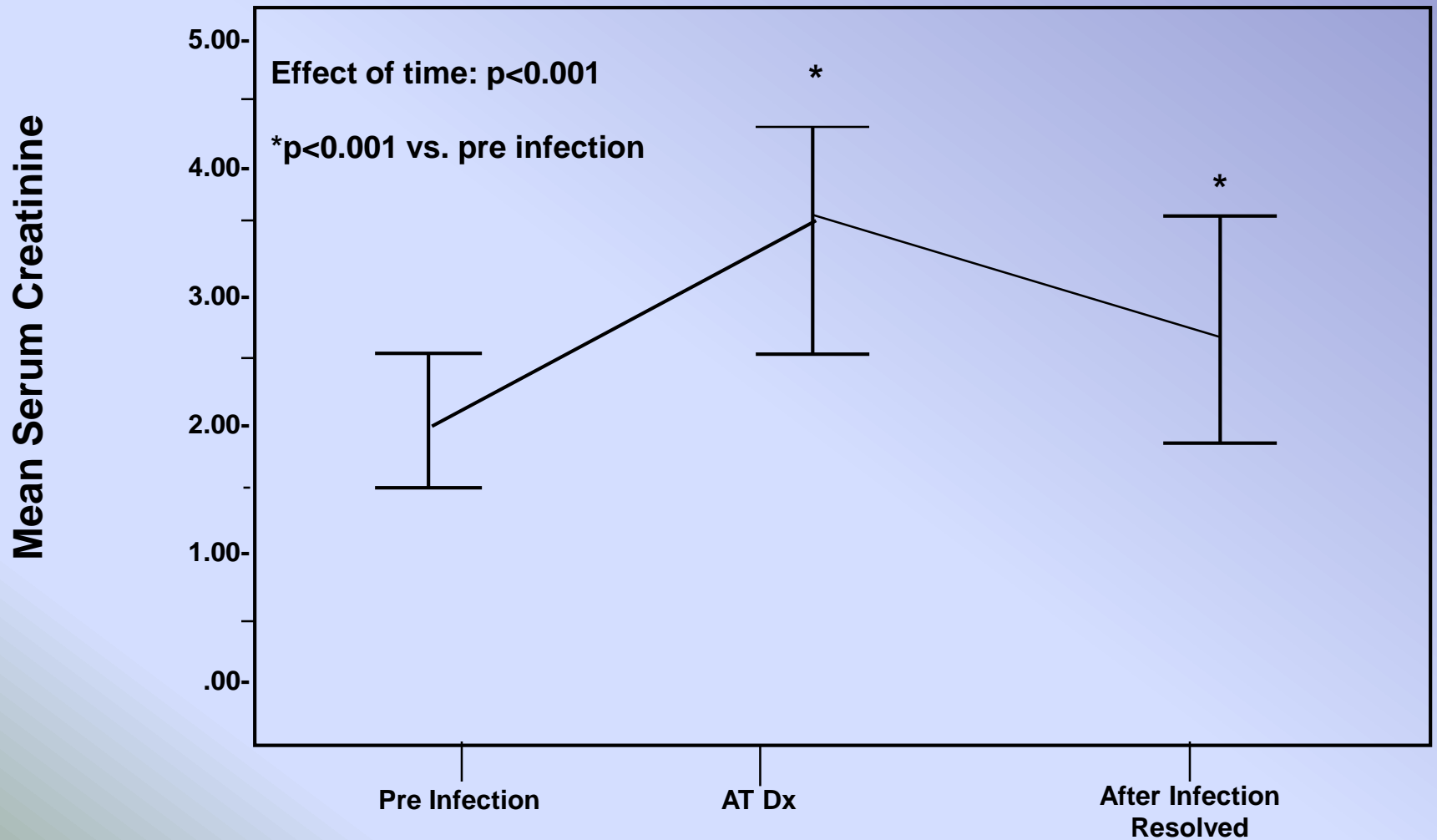


Figure 2B. Mean GFR (cc/min) prior to infection, at time of diagnosis of bkvn, and peak function within 6 months after treatment.

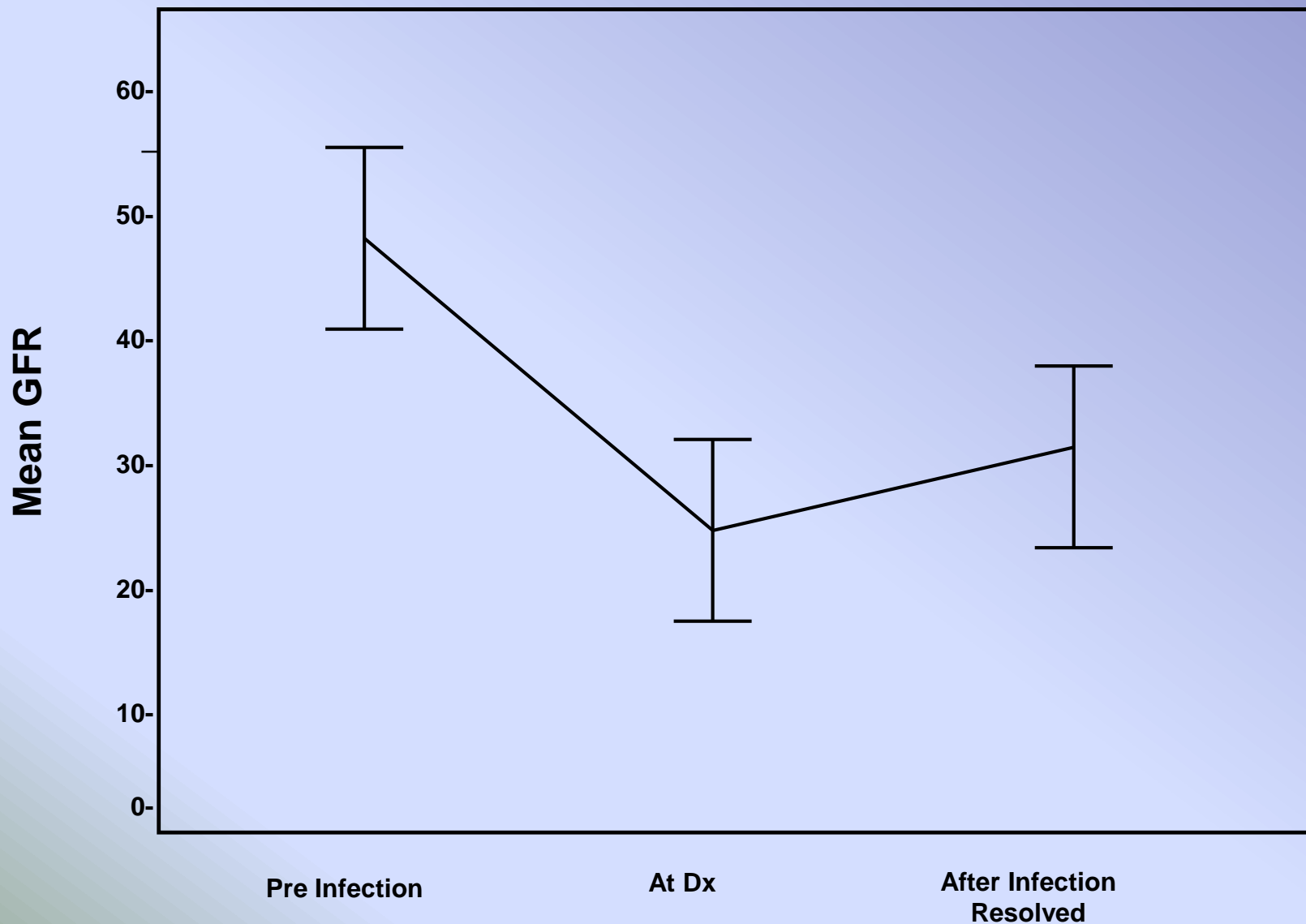


Figure 3. Death-censored graft survival with respect to time of transplant

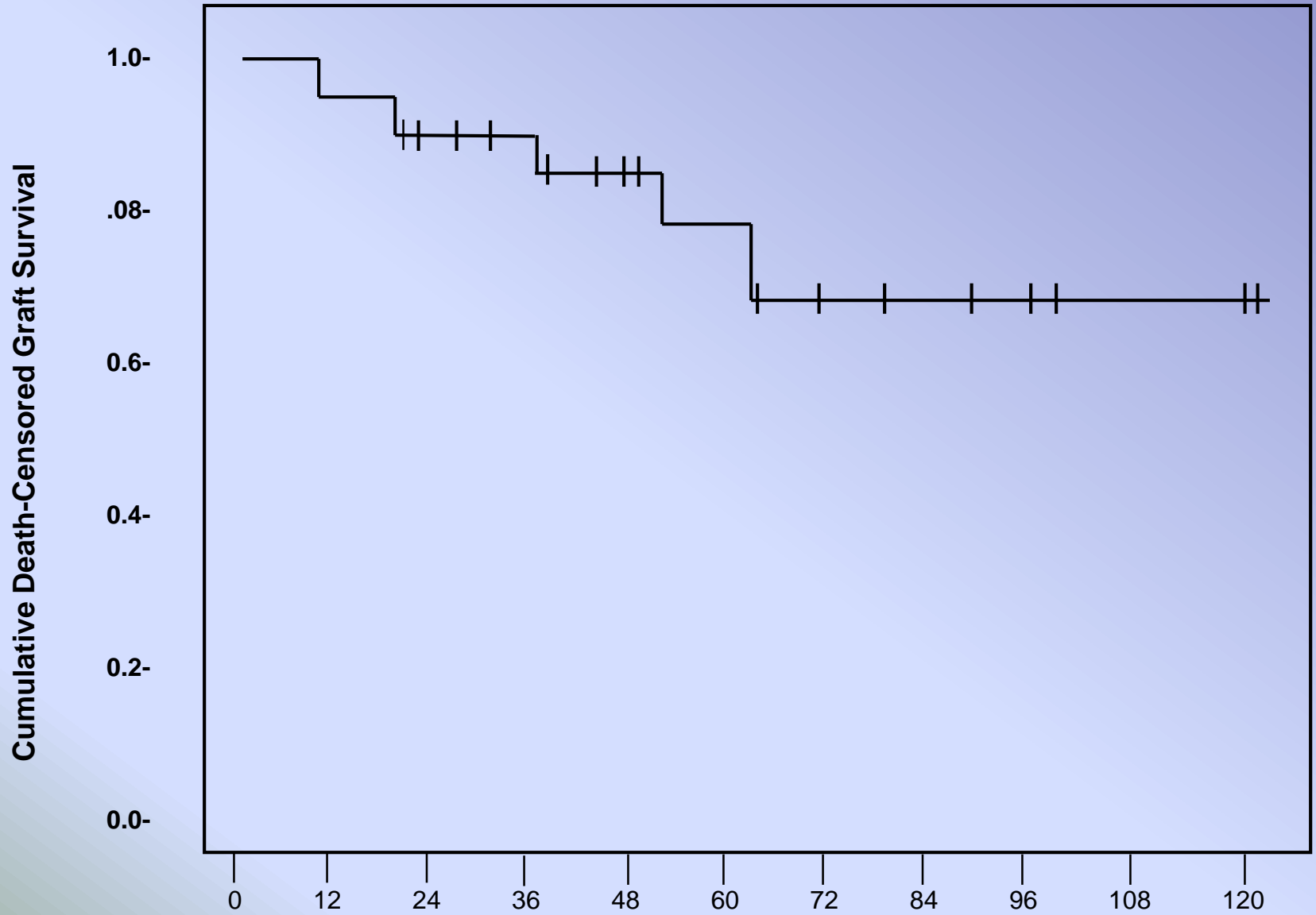
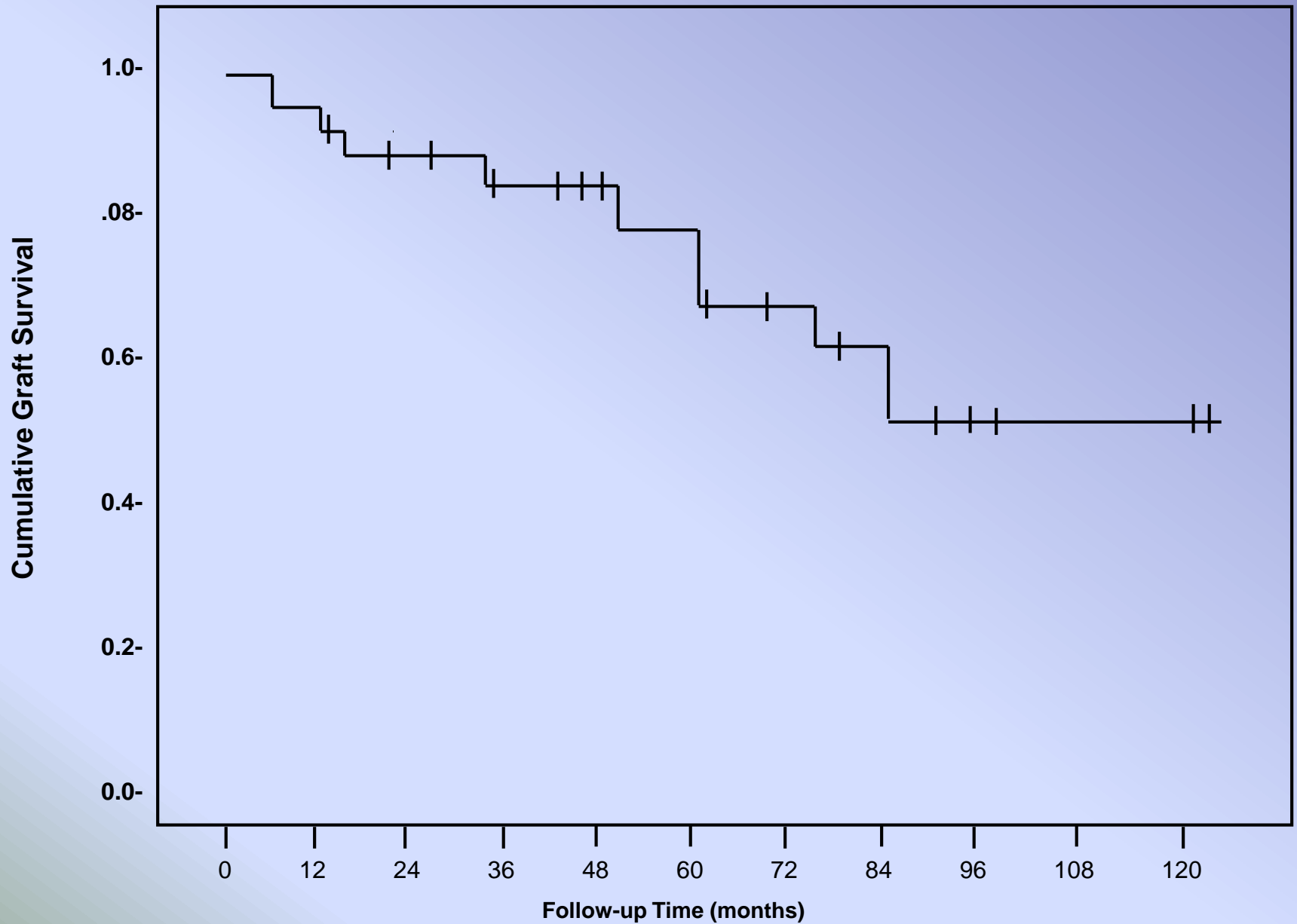


Figure 4. Cumulative graft survival with respect to time of transplant



New Vanderbilt Data

- 2012-2017
- N= 32
- Graft Loss=1
- Stabilization= 20
- Improvement=11

Conclusions

- 1. CNI switch and reduction in total Immunosuppression cleared viremia and led to graft stabilization in all**
- 2. 80% of the cohort had marked functional improvement**
- 3. No grafts were lost despite the literature citation of 50% graft loss**

Ongoing Studies

- Quinolone Prophylaxis for the Prevention of BK Virus Infection in Kidney Transplantation: A Pilot Study: randomized, placebo-controlled: levofloxacin use for 3 months-500 mg daily: BK viruria-Canada
- Safety and Efficacy of Mycophenolic Acid Withdrawal With Conversion to Zortress (Everolimus) in Renal Transplant Recipients With BK Virus Infection: randomized, open-label-UCSF
- Using mTOR Inhibitors in the Prevention of BK Nephropathy: randomized, open-label, low dose TAC and MPA vs rapamycin and MPA: Columbia University