Consensus Recommendations on Management of BK Virus in Renal Transplantation

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Disclosures/Acknowledgents

- I have no conflicts relevant to this talk

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The Second International Consensus Guidelines on the Management of BK Polyomavirus in Kidney Transplantation

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Outline

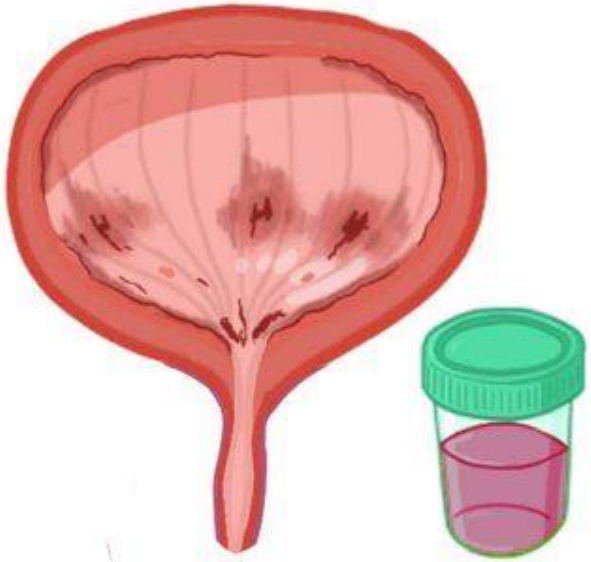
- Importance of BK
- Clinical Manifestations
- Screening Protocols
- Pathology
- Treatment
- Retransplantation
- Pediatric Recipients

Importance of BK Virus in Renal Transplantation

- BK viremia frequently occurs post transplantation
- Can lead to BK Nephropathy if persists
- Important cause of graft loss
- Reduction in immunosuppression usually helps but can lead to rejection
- Persistent BK viremia/nephropathy associated with urothelial carcinoma

BK VIRUS (BKV)

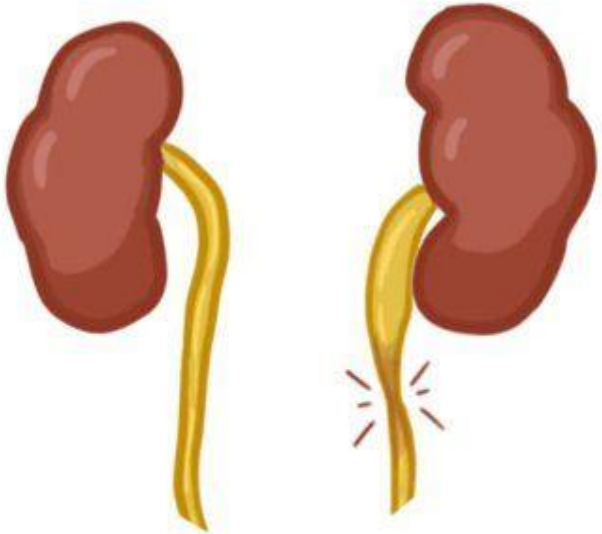
CLINICAL MANIFESTATIONS



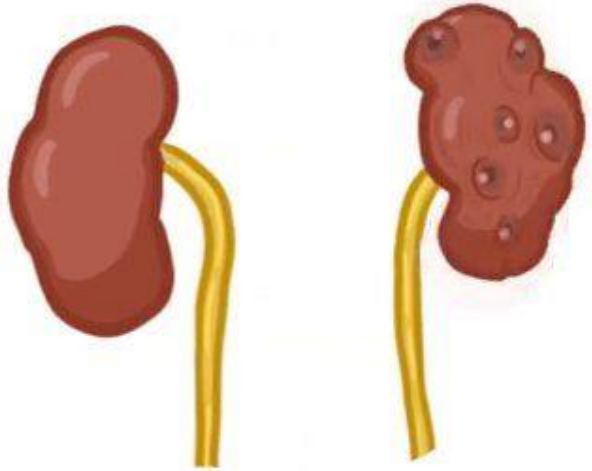
HEMORRHAGIC CYSTITIS

↳ BLOODY URINE

↳ BONE MARROW TRANSPLANT RECIPIENTS

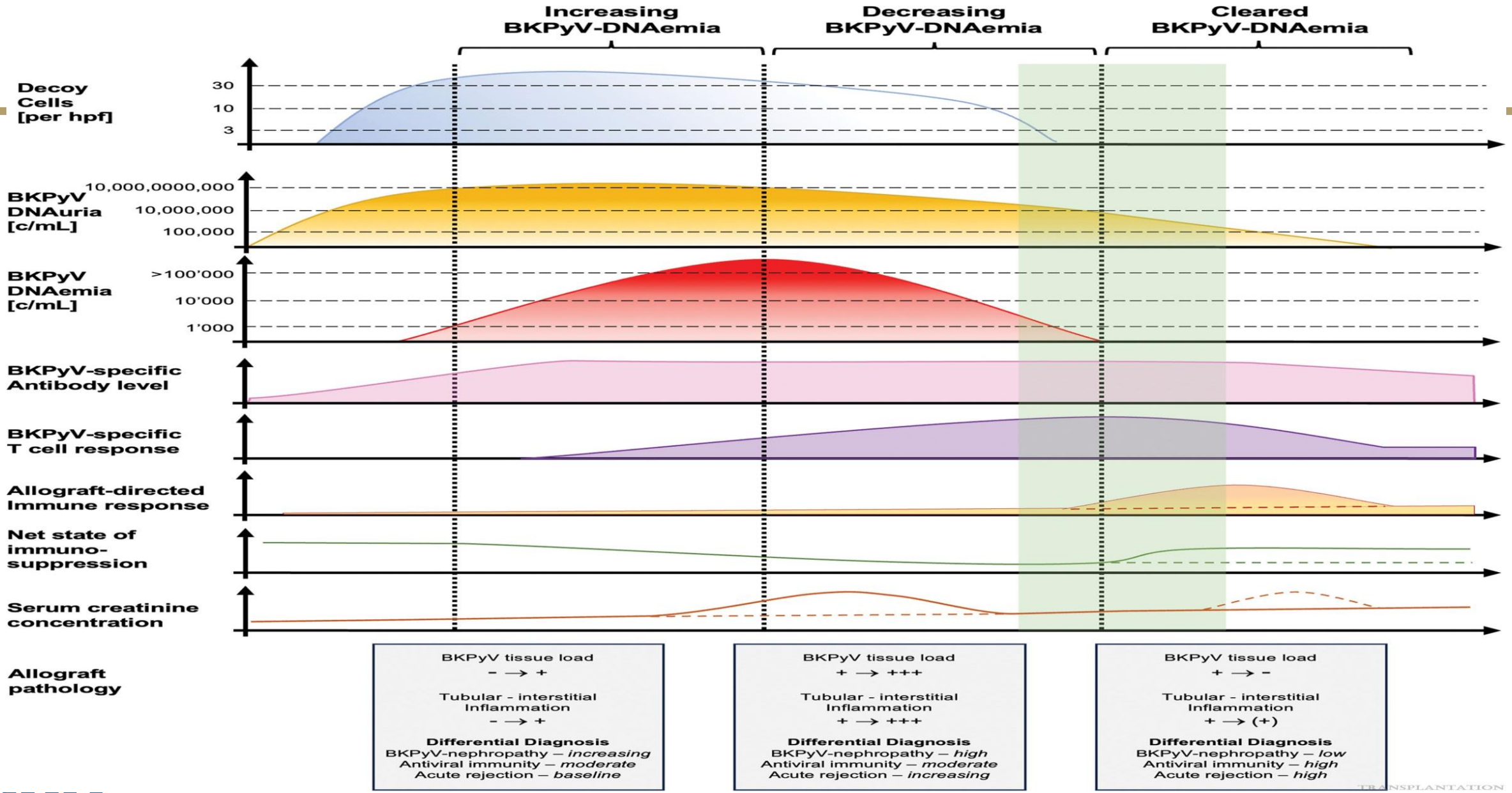


URETERAL STENOSIS



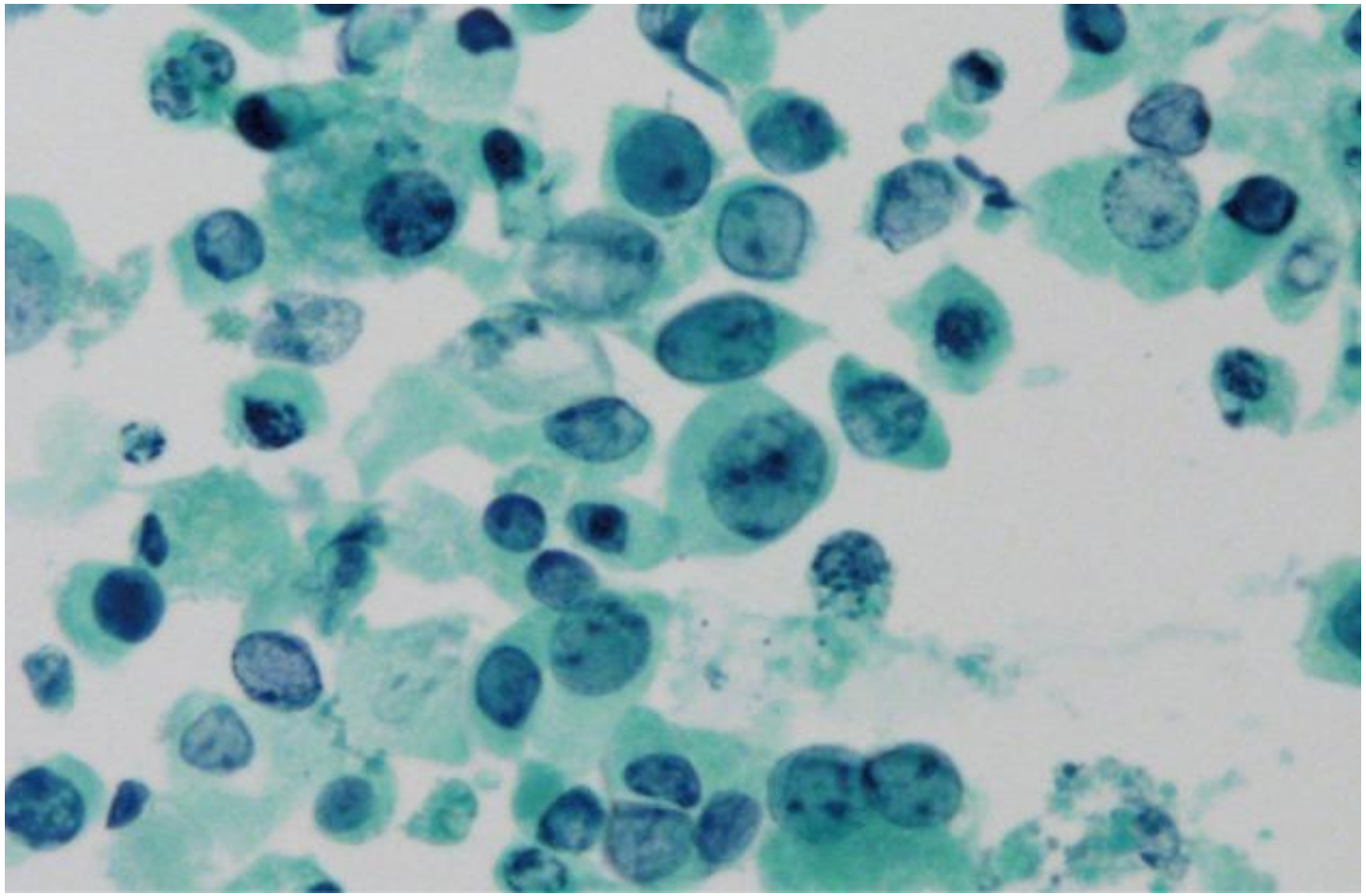
NEPHROPATHY

↳ KIDNEY TRANSPLANT P



Kotton et al Transplantation, 108, 1834; 2024

Voided urine cytology shows many decoy cells displaying nuclear enlargement, high N/C ratio and basophilic 'ground-glass' intranuclear inclusion with marginated chromatin.



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Incidence/Prevalence

- In 1st 12 mo post transplant, viruria with BK pcr > 10 million or decoy cells seen in 20-40% of patients post transplant
- BK DNA emia in 10-20%
- BK Nephropathy in about 8%

- In next 24 mo 10-20% DNA emia and/or BK Nephropathy
- In next 3 to 5 years 1 to 10%

Risk Factors for BK Viremia/Nephropathy

- Older recipient age- Moderate
- Male recipient- Moderate
- Tacrolimus instead of cyclosporine as CNI- High
- T cell depleting anti lymphocyte products (ATG, Alemtuzimab)- Low
- Higher dose steroids- Moderate
- Acute rejection episodes- Low
- Ureteric Stents- Low
- High levels of donor anti BK antibody/recipient negative but not generally tested- Moderate

Screening Protocols

- Based on disease development BK Viruria> BK DNA emia> BK Nephropathy

- Best strategy for nephropathy is prevention
- Screening with Blood BK pcr is best method based on positive predictive value for BK nephropathy
- Urine decoy cells are non specific but high predictive value if negative. In resource restricted environments can use decoy cells and only do blood pcr if positive
- Urine DNA emia less reliable method but if used do plasma testing when urine > 10 million

- Q mo X 9 mo
- Then q 3 mo until 2 years
- If positive q 2 to 4 weeks until < 1000 or negative
- Also initiate monitoring after treatment for rejection

Diagnosis/Management

- If BK DNA emia >/=1000 c/ml repeat in 2 to 3 weeks – weak
- If sustained at that level or higher, immunosuppression reduction suggested – strong
- Monitor BK q 2-4 weeks to see effect of intervention - weak
- In general, earlier identification and reduction of immunosuppression results in shorter duration of viremia, less nephropathy, and better allograft function

Strategies to Reduce Immunosuppression

- Reduce immunosuppression enough to allow for BK control without precipitating acute rejection
- Reduce Anti-Proliferative first
- If DNA around 1000c/ml can reduce by 50% first
- If DNA >/= to 10 million suggest stop Antiproliferative
- If DNA>/= 1000 after 1 to 2 mo, reduce CNI gradually to tacrolimus level 3 to 5 ng/ml or CSA 50-75 ng/ml
- Generally safe and effective with success in 80 – 100%
- Consider DSA and biopsy if creatinine rises to look for rejection/BK Nephropathy

Other Options

- Reduce CNI first by 25% and then 50% gradually down to Tac 3-5 and CSA 50-125 ng/ml
- Then reduce and DC antiproliferatives if not at least 10 fold reduction in BK
- In either case add low dose steroids to avoid monotherapy if initially steroid free

- I prefer first approach as 10-30% risk of rejection from immunosuppression reduction and CNI more potent against rejection
- It has worked well for me in most cases

- Insufficient data to recommend switching to TOR inhibitors as primary approach
- Use of belatacept with MPA and steroids not shown to be associated with higher BK incidence but no data on reduction of immunosuppression with this regimen

Cost Benefit Analysis of Monitoring

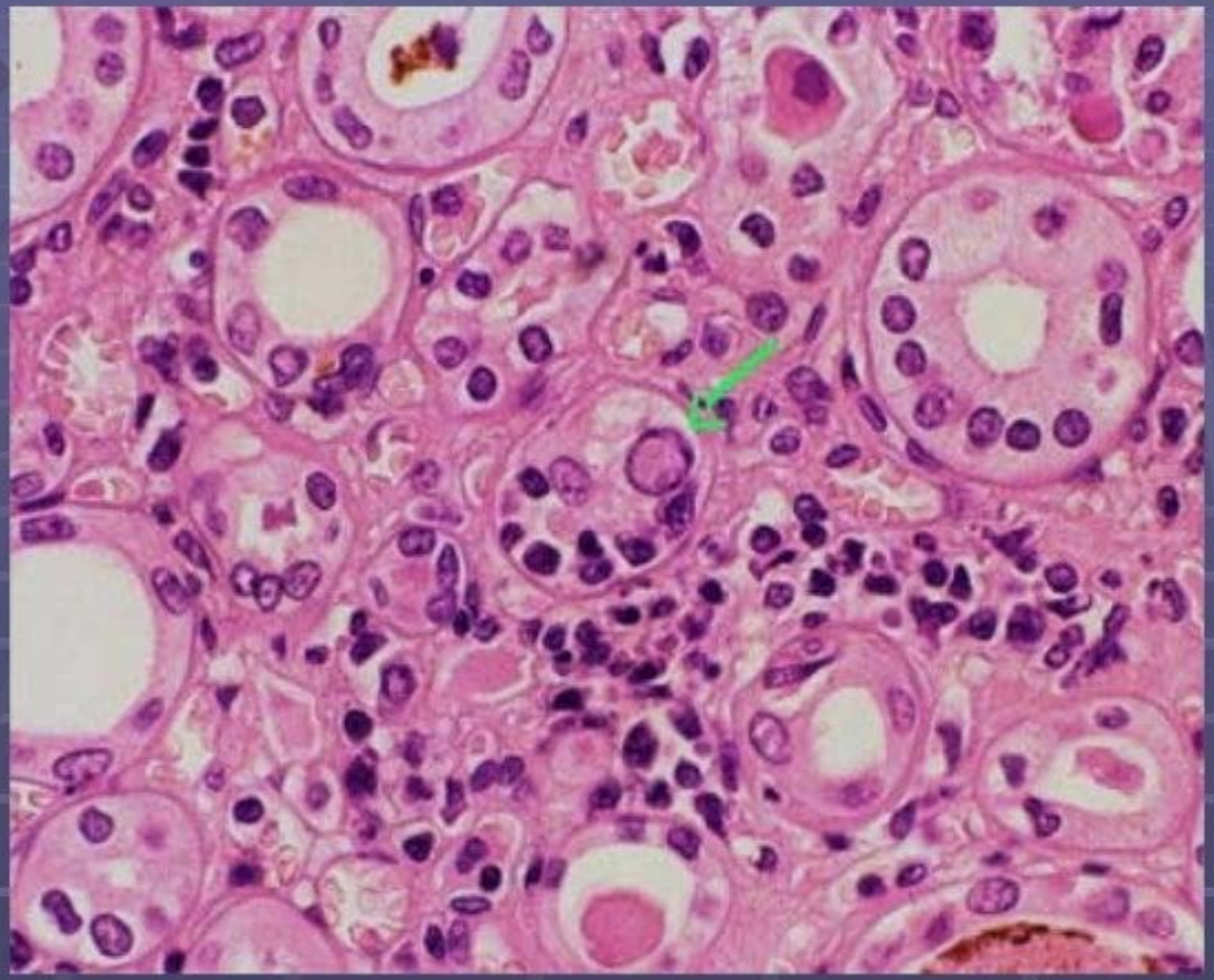
- No randomized trial data to use
- Thus data depend on arbitrary decision on BK nephropathy rate, acute rejection rate, graft failure rate and difference in cost between dialysis and transplantation
- Three cost utility analyses have been done with different results
- But all show that screening results in net survival benefits and is cost effective

Indications for Biopsy

- To diagnose BK Nephropathy vs rejection/other pathology

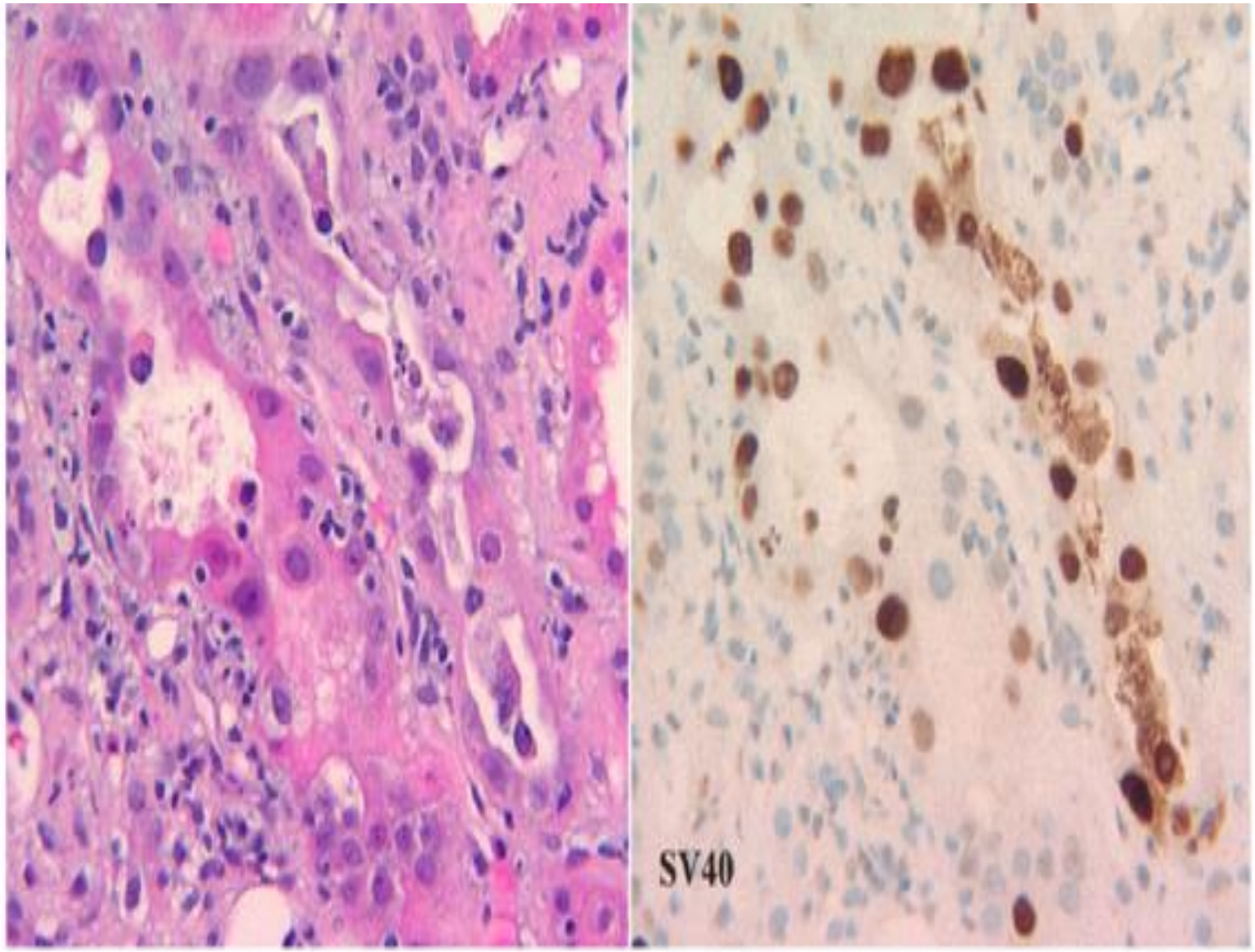
- Change in renal function
- Hematuria with normal lower tract
- Proteinuria

BK Nephropathy



- Variable degree of interstitial inflammation, fibrosis, atrophy
- Similar in appearance to cellular rejection
- Immunohistochemistry useful

BK Nephropathy



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Acute Rejection vs BK Nephropathy vs Both

- Acute cellular rejection without arteritis, in presence of BK Nephropathy, can be hard to diagnose as no distinguishing morphologic, immunohistochemical or molecular features
- Except for peritubular capillaritis, pathology of BK Nephropathy does not overlap with antibody mediated rejection
- The presence of intimal arteritis as well as chronic arteriolopathy suggests acute rejection

Management of Acute Rejection

- DSA positivity and/or acute rejection reported in 10-30% during or after clearance of BK
- If acute rejection occurs most recommend treating with high dose steroids and monitoring BK.
- No clear strategy for increasing immunosuppression but may need to reduce if rise in BK titres after treatment of rejection
- When BK cleared some cautiously increase immunosuppression with careful monitoring to prevent subsequent rejection

Additional Approaches for Resistant Viremia/Nephropathy

- IVIg have high anti BK antibody
- Few studies and uncertain benefit but well tolerated with few complications
- We use it at our centre if lack of response to usual strategies

- Cidofovir has in vitro anti BK effect but lack of good in vivo data plus important nephron and eye toxicity
- Conflicting data on leflunomide and can be hepatotoxic
- No demonstrated benefit of fluoroquinolones or statins in vivo

Retransplantation

- Retrospective studies have confirmed safe to retransplant patients whose grafts failed from BK Nephropathy
- Patient , graft survival and acute rejection rate similar compared to patients losing grafts for other reasons
- Recurrent BK nephropathy in only 2.3%
- No good information on optimal immunosuppression for subsequent transplant
- Ideally BK DNA emia should be negative before retransplantation but if positive, reduction of BK >2 logs is indicator of sufficient BK immunity pre transplantation
- No evidence of benefit from pre transplant nephrectomy whether BK negative or positive

Pediatric Patients

- Recommendations similar to adults re screening and immunosuppression reduction
- For pediatric patients with stable kidney transplant function and persistent BKPyV-DNAemia >10 000 c/mL (or equivalent) despite reducing immunosuppression, suggest performing a renal allograft biopsy because serum creatinine rise may be delayed in children with significant renal injury including rejection

Summary

- BK Nephropathy is an important cause of renal allograft failure
- Regular screening allows earlier detection
- Immunosuppression reduction results in reduction of titres and avoidance of nephropathy in most cases
- BK nephropathy more difficult to treat
- If immunosuppression reduction ineffective, IVIg can be used. Other strategies are not recommended
- Retransplantation in patients with previous BK related graft loss results in good results if BK negative or at least significant reduction in titres