Late allograft dysfunction: non-rejection causes

Jiranat Sriswasdi, M.D.

Division of Nephrology

Department of Medicine Phramongkutklao Hospital

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Outline

- Late allograft dysfunction
- Recurrent glomerular diseases
- Transplant renal artery stenosis
- Infection: BKPyV-nephropathy
- Chronic allograft failure
- Take home message

Allograft dysfunction: definitions

Post transplant onset

- **Immediate** < 1 week
- **Early** 1 week - 3 months
- **Late** > 3 months

Allograft Dysfunction

- **SCr** ↑ 25-30% from baseline

Or same criteria **as AKI** in native kidney

- **DGF**: dialysis within 1 week post KT

Progression of dysfunction

- **Acute** < 3 months (≈AKI/AKD on top CKD)
- **Chronic** > 3 months – years (≈CKD progression)

UpToDate.
Josephson MA. Clin J Am Soc Nephrol. 2014 Mar;9(3):590-7.
Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. Am J Transplant. 2009 Nov;9 Suppl 3:S1-155.

Late allograft dysfunction

NEPHROLOGY

Chronic allograft injury

Immune mediated

- Chronic Rejection
  - ABMR
  - TCMR
  - Mixed
- MVI, C4d & DSA negative

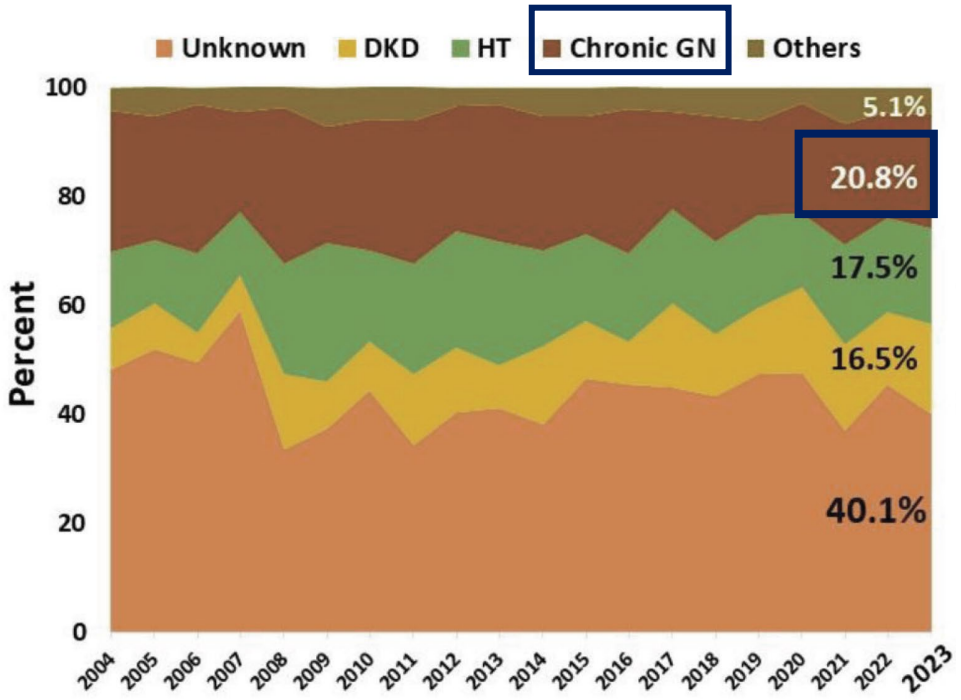
Non-immune mediated

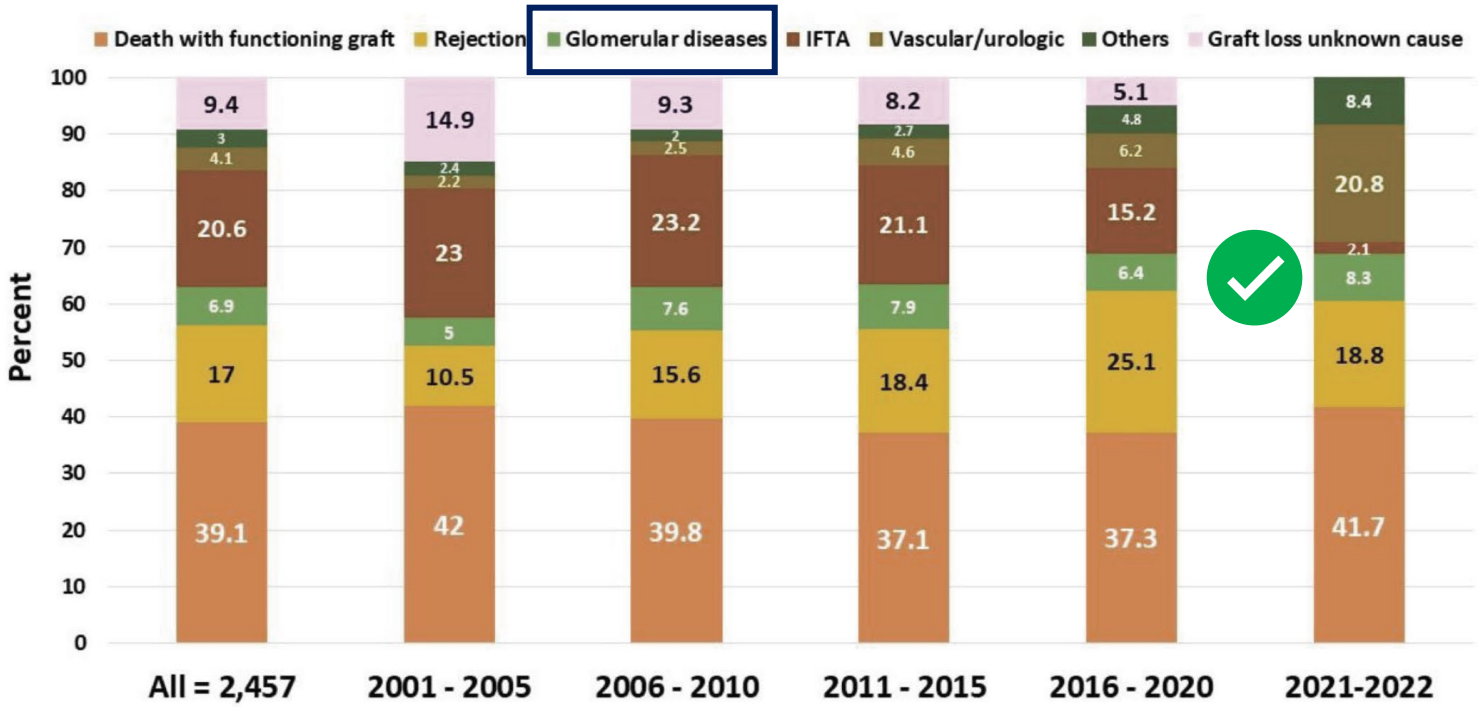
- Transplant renal artery stenosis
- Recurrent/de novo glomerular diseases
- Infection: BKPyV nephropathy
- CNI nephrotoxicity
- Urinary obstruction
- Others: PTLD, Graft AVF, Nephrotoxic, TMA

Haq K, et al. Adv Kidney Dis Health. 2024 Sep;31(5):416-426.
Van Loon E, et al. Transplantation. 2020 Feb;104(2):e46-e56.

Recurrent glomerular diseases

Glomerular disease and KT: Thailand



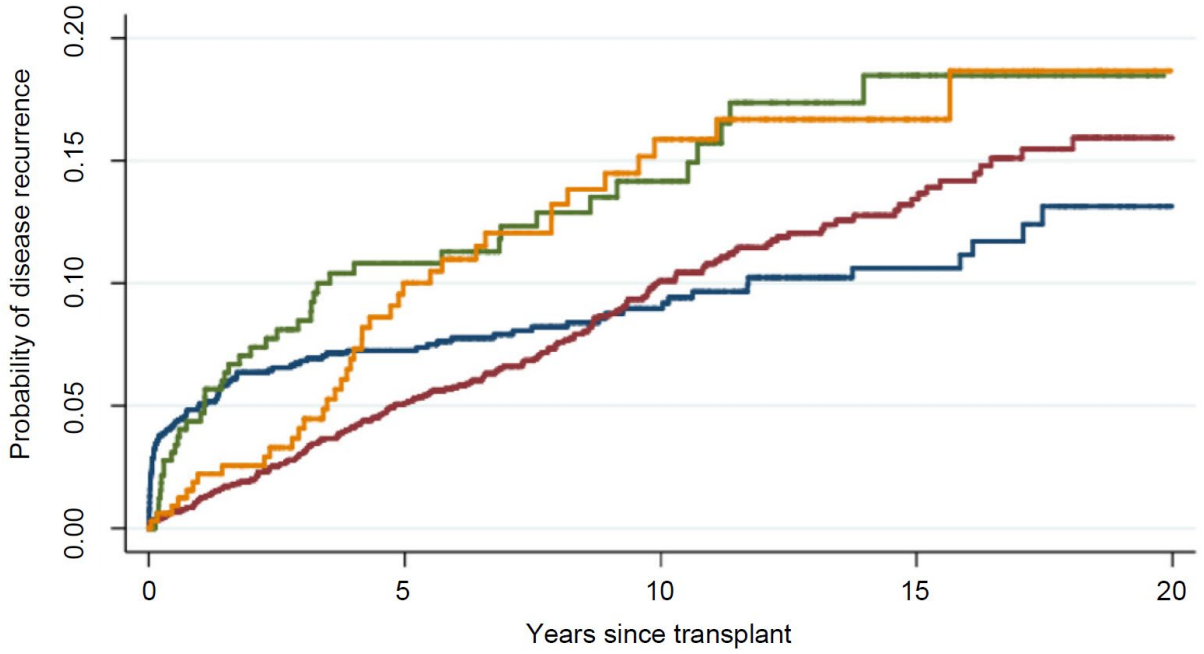


Glomerular disease is the leading cause (20.8%) of CKD receiving KT in Thailand

Glomerular disease (de novo or recurrent) is the 3rd common cause of "death-censored graft loss"

Thai Transplantation Society: Registry book 2023

Recurrent glomerular diseases



MPGN and FSGS recurrent earlier (within 3 years) than IgAN and MN (at 5 years)

Table 1 | Recurrence of primary GN diagnosed by protocol or clinical biopsies

Diagnosis pre-transplantation[a]	N	Year 1, %	Year 3, %	Year 5, %[b]	Actual graft survival, %	*P*[c]	Follow-up (mo)
No GN	1282	–	–	–	82.6	–	87.5 ± 46
FSGS	148	10.5	30.7	35.1	73.0	0.009	90.3 ± 49
MN	49	18.9	45.4	55.0	79.6	0.908	99.7 ± 51
MPGN	52	18.3	41.4	41.4	53.8	<0.0001	81.3 ± 49
IgAN	165	12.5	42.0	51.0	80.9	0.382	96.2 ± 45[d]

FSGS and MPGN have the lowest long term graft survival

Allen PJ, et al. Kidney Int. 2017 Aug;92(2):461-469.
Cosio FG, Cattran DC. Kidney Int. 2017 Feb;91(2):304-314.

Recurrent FSGS: risk

Risk of recurrence	
Strong risk/high level of evidence	**Low-moderate risk (some evidences)**
- History of recurrence in previous KT esp. within a year post KT (strongest risk) - Primary FSGS - Rapid disease progression (< 3 years before ESKD) **- Nephrectomy of native kidneys** - Anti-Nephrin Ab positive prior to transplant	- Younger age at transplant - White race - Histology with diffuse mesangial proliferation - LRKT - Younger at diagnosis (onset < 6 years of age but not genetic FSGS) - Lower BMI

No evidence of association: Type of FSGS variants (hilar, collapsing, tip, etc.), type of immunosuppression, HLA-mismatch

Protective factor: **Non-nephrotic** syndrome, **genetic FSGS**

Shirai Y, et al. Kidney Int. 2024 Mar;105(3):608-617.
Ivanyi B. Nat Clin Pract Nephrol. 2008 Aug;4(8):446-57.
Uffing A, et al. Clin J Am Soc Nephrol. 2020 Feb 7;15(2):247-256.
Allen PJ, et al. Kidney Int. 2017 Aug;92(2):461-469.

FSGS: diagnosis

Clinical features (1˚)	Investigation
- **Proteinuria within a month** (can be early in a week esp. children) & full-blown nephrotic - HT, microscopic hematuria not uncommon - **Graft dysfunction**	- **Proteinuria screening and SCr *daily for 1 week***, twice weekly in week 2, weekly for 4 weeks, monthly for 1st year, every 3 months thereafter - ***MCD-like*** in 1st 3 months (early disease)

Characteristics	Recurrent FSGS	De novo FSGS
Onset of proteinuria	**Within a month** (median 1.5 Mo)	**> 3 months** (mostly > 12 months)
Nephrotic syndrome	**Common**	Uncommon
Causes	Primary FSGS	***CNIs, mTORIs***, Infection (**CMV**, Parvovirus), Chronic rejection, TRAS
Allograft dysfunction	Early	**Late**
Foot process effacement	**Diffuse**	Varied (diffuse if severe)

Raina R, et al. Kidney Int. 2024 Mar;105(3):450-463.
Uffing A, et al. Clin J Am Soc Nephrol. 2020 Feb 7;15(2):247-256.
Allen PJ, et al. Kidney Int. 2017 Aug;92(2):461-469.

Recurrent FSGS: treatment

- **TPE/IA** (CAT1, Gr1B): **3 daily TPEs** followed by at least 6 more TPEs in the subsequent 2 to 3 weeks (3 TPEs/week) then weekly-monthly tapered (duration varied; weeks to months until proteinuria < 1 g/d)
- **Monitor:** proteinuria for treatment titration
- **Adjunct**: **CNIs** (high level), **high dose steroids** (prednisolone 1 MKD and tapered to 10 mg/d over 8-12 weeks, **ACEIs/ARBs**
- **± Rituximab**: contraindication to TPE or refractory to TPE
- **Prognosis**: ↓ remission rate if ***TPE later than 2 weeks*** after onset
- **Prophylaxis**: ***NO*** indication for ***prophylaxis*** TPE/Rituximab

Candidate with FSGS: *Not* excluding from transplant, but risk should be informed

Raina R, et al. Kidney Int. 2024 Mar;105(3):450-463.
Connelly-Smith L, et al. J Clin Apher. 2023 Apr;38(2):77-278.

Recurrent IgAN: risk

Risk of recurrence	
Candidate related	**Transplant related**
- Recurrent IgAN in previous graft (esp. graft loss due to recurrence within 10 years) - Rapid CKD progression of native kidney - Transplant at ***young age*** - Presence of preformed DSA	- Induction with ATG (vs IL-2RA) - Well matched HLA - Living related donor (but no effect on graft outcome) ***- Steroid withdrawal*** - Preemptive transplant - Elevated IgA (after KT), Gd- IgA1-specific IgG Ab (at time of KT)

Recurrence rates are varied: 10-30% if clinical-based biopsy and 50% if protocol biopsy

Ivanyi B. Nat Clin Pract Nephrol. 2008 Aug;4(8):446-57.
Allen PJ, et al. Kidney Int. 2017 Aug;92(2):461-469.
Uffing A, et al. Clin J Am Soc Nephrol. 2021 Aug;16(8):1247-1255.
Ong SC, Julian BA. Semin Nephrol. 2024 Sep;44(5):151570.

Recurrent IgAN: diagnosis

Characteristics	Details
Onset (clinical)	- ***Insidious onset*** with median ***3 years*** but usually within 5 years post-transplant
Urine sediments	***- 64% absence of hematuria*** - 28% present with isolated SCr rising - 39% SCr rising with hematuria/proteinuria - Macroscopic hematuria is rare
Biopsy	- Maybe C1q positive (up to 60%) in IF (no long-term outcome significance) with concurrent crescent **- Oxford classification (MEST-C)** has been validated for prognosis in some studies

Ivanyi B. Nat Clin Pract Nephrol. 2008 Aug;4(8):446-57.
Allen PJ, et al. Kidney Int. 2017 Aug;92(2):461-469.
Uffing A, et al. Clin J Am Soc Nephrol. 2021 Aug;16(8):1247-1255.
Ong SC, Julian BA. Semin Nephrol. 2024 Sep;44(5):151570.
Moroni G, et al. Front Immunol. 2019 Jun 19;10:1332.

Recurrent IgAN: treatment

- **No definite treatment** in recurrent diseases
- **ACEI/ARBs** remain drug of choice for proteinuria reduction (no strong evidence of long- term outcome benefit, however)
- SGLT2i?
- No evidence of cyclophosphamide or high dose steroids
- ***Avoid steroids withdrawal strategy***
- Tonsillectomy in ***Japanese/Chinese*** population (↓ recurrent incidence)

Very limited data regarding recurrent IgAN treatment

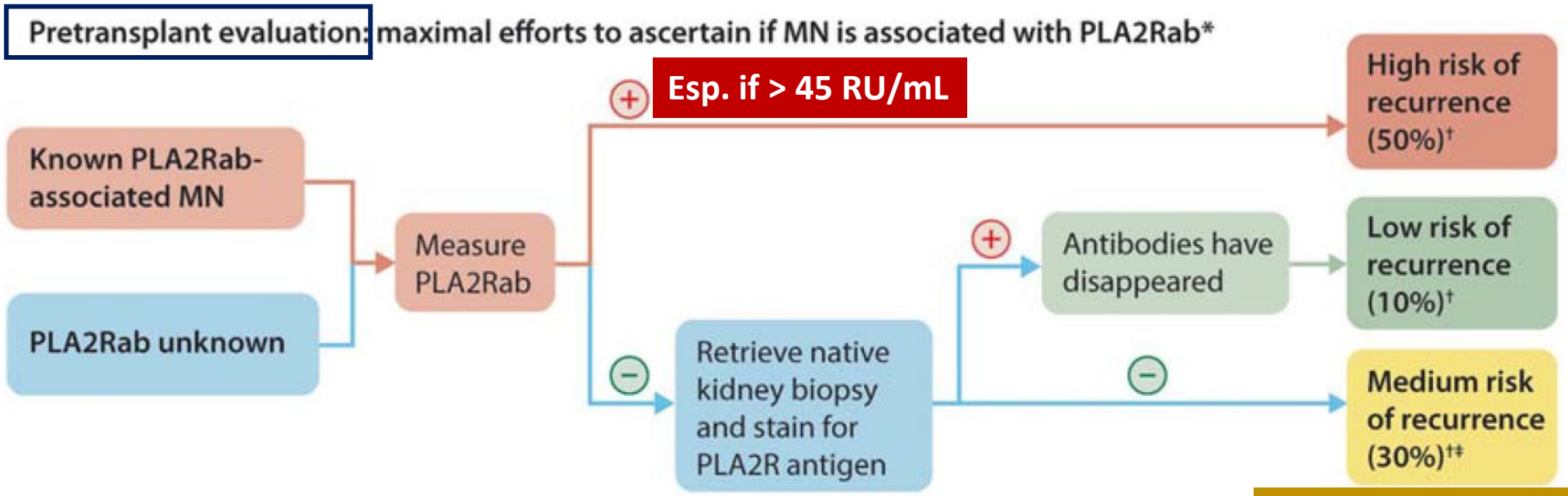
Ivanyi B. Nat Clin Pract Nephrol. 2008 Aug;4(8):446-57.
Allen PJ, et al. Kidney Int. 2017 Aug;92(2):461-469.
Uffing A, et al. Clin J Am Soc Nephrol. 2021 Aug;16(8):1247-1255.
Ong SC, Julian BA. Semin Nephrol. 2024 Sep;44(5):151570.
Moroni G, et al. Front Immunol. 2019 Jun 19;10:1332.

Recurrent membranous nephropathy

- **Bimodal onset** (early within 1-2 years then at 5th year)
- Anti-PLA2R positive in 70% (same as native)
- Recurrence rate ≈ 30-50% (↑ if protocol biopsy)
- **Risk factor**: **Anti-PLA2R positive prior to KT**, older recipient, higher proteinuria at KT, steroid withdrawal, rapid ESKD in native kidney
- **Insidious** but ***not*** as benign as native (unlikely to spontaneous remission = ***need active treatment***)
- **Diagnosis**: LM maybe missed (early), IF (anti-PLA2R stained, IgG_4) and EM for EDD at subepithelial area should be sought

Leon J, et al. Transplantation. 2019 Oct;103(10):1990-2002.
Hullekes F, et al. Am J Transplant. 2024 Jun;24(6):1016-1026.
Cosio FG, Cattran DC. Kidney Int. 2017 Feb;91(2):304-314.

Recurrence risk and monitoring



Peri- and post-transplant monitoring:

- Measure proteinuria every month → if proteinuria 1 g/d → biopsy of kidney

0.3-1 g/d if increasing/persistent PLA2Rab

- In patients with known PLA2Rab-associated MN: measure PLA2Rab every 1–3 months depending on pretransplant antibody status
  - → PLA2Rab increasing → increased likelihood of recurrence, consider early kidney biopsy
  - → PLA2Rab decreasing → lower likelihood of recurrence, perform kidney biopsy only if clinically indicated

Esp. 1st 6 month

Rovin BH, et al. Kidney Int. 2021 Oct;100(4):753-779.

Recurrent MN: treatment

- **RASi** with closed monitoring of graft function (hemodynamic effect)
- **If proteinuria < 1 g/d**
  - **Maximized RASi,** BP control and monitor proteinuria and Anti-PLA2R titer
- **If proteinuria > 1 g/d**
  - **Rituximab** 1 g iv at D0 and D15 (≈ MENTOR trial; anti-CD20 + CNIs)
  - If refractory: cyclophosphamide (withdraw of anti-metabolites)
  - ***No*** indication for ***prophylaxis*** TPE or Rituximab

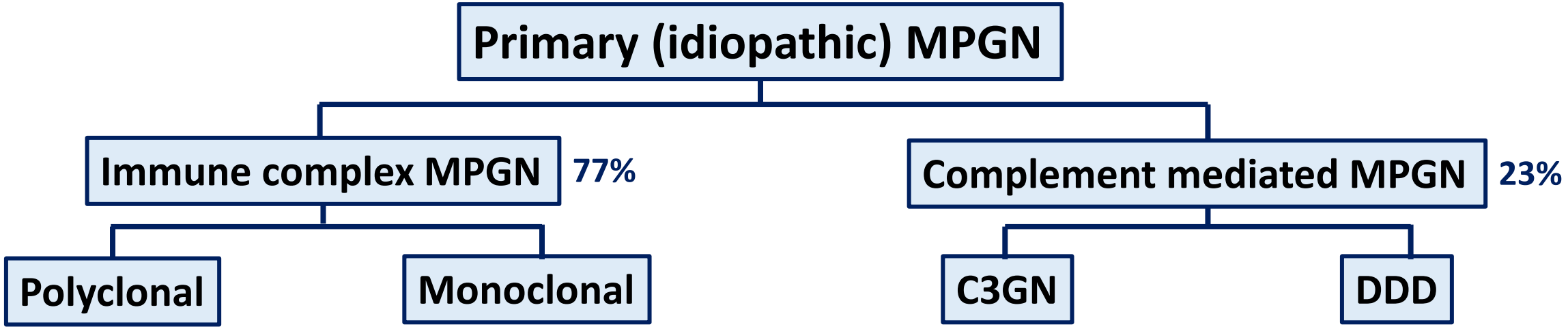
Rovin BH, et al. Kidney Int. 2021 Oct;100(4):753-779.
Leon J, et al. Transplantation. 2019 Oct;103(10):1990-2002.
Alsharhan L, Beck LH Jr. Am J Kidney Dis. 2021 Mar;77(3):440-453.

Recurrent VS De novo MN

Characteristics	Recurrent MN	De novo MN
Onset	**Earlier** (2-3 years)	**Later** (> 2-3 years; mean 5 y); 5.3% at 8 years
Association	**Anti-PLA2R** (70%)	Transplant glomerulopathy, **chronic ABMR & DSA**
Histology	**Diffuse** involvement, **Anti-PLA2R tissue stained, IgG4**, few C3, maybe C4d positive	**Focal**/segmental involvement, mesangial hypercellularity, concurrent rejection, ***Negative Anti-PLA2R, IgG1, FAT1 Ag***
Treatment	RASi & **Rituximab**	↑ Maintenance immunosuppression

Leon J, et al. Transplantation. 2019 Oct;103(10):1990-2002.
Alsharhan L, Beck LH Jr. Am J Kidney Dis. 2021 Mar;77(3):440-453.
Sethi S, et al. Kidney Int. 2024 Nov;106(5):985-990.

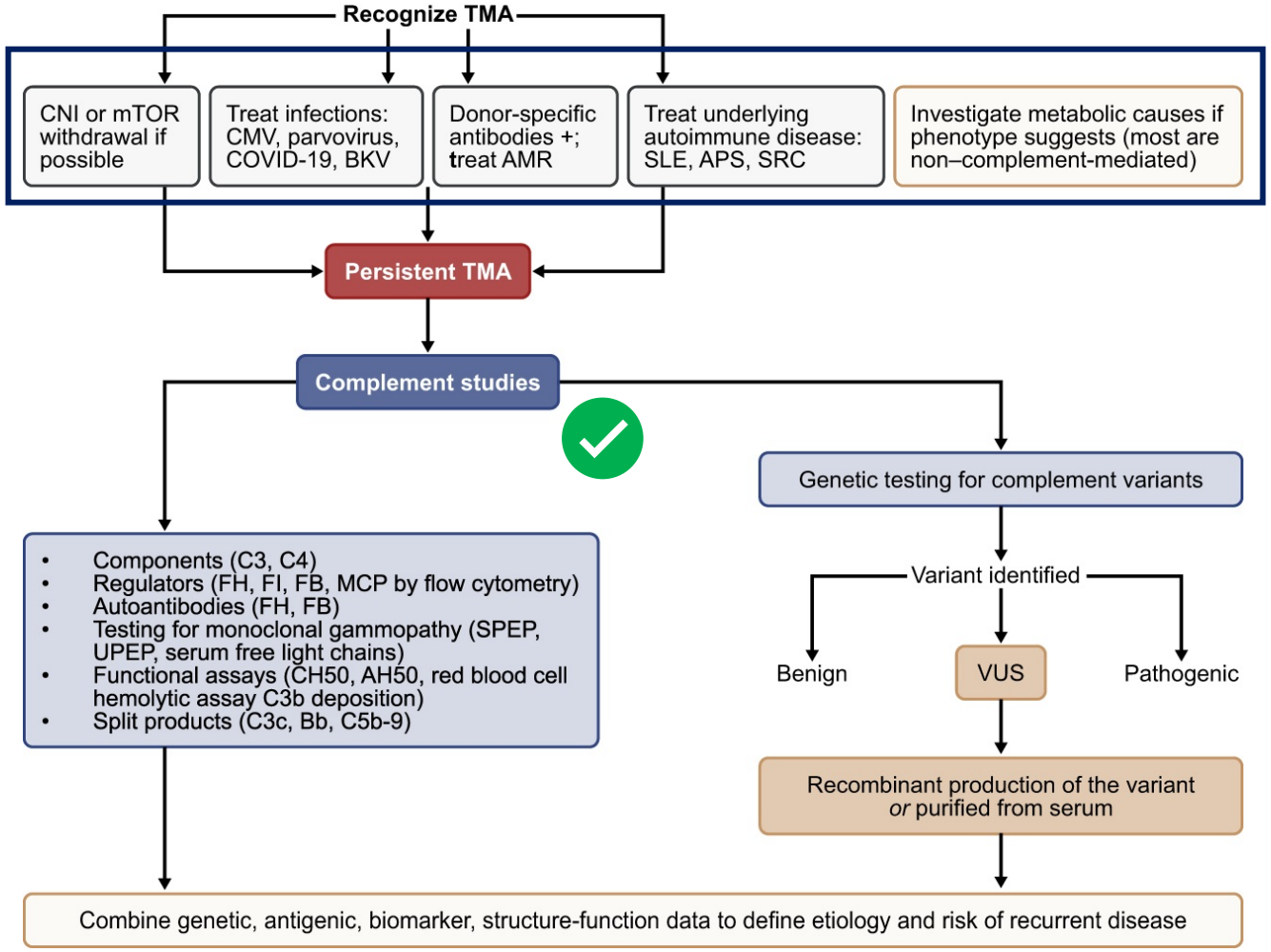
Recurrent MPGN



Polyclonal	Monoclonal	C3GN	DDD
Recurrent: 30-35% Allograft loss: 10%	Recurrent: 66% Allograft loss: 50%	Recurrent: 70% Allograft loss: 50%	Recurrent: 80-90% Allograft loss: 25%
Late (5y) recurrent C4d positive ↑recurrent if C3C4 low	Early (6month) recurrent SPEP neg 70% & no MM 30% serum monoclonal (MGRS)	Early (1-2y) recurrent with graft failure in 18 mo ↑recurrent if C3 low, young, heavy proteinuria, crescentic disease	Late recurrent ApoE stained (80%) can be differentiate from C3GN (0%)

Lorenz EC, et al. Kidney Int. 2010 Apr;77(8):721-8. Chadban SJ, et al. Transplantation. 2020 Apr;104(4S1 Suppl 1):S11-S103. Attieh RM, et al. Clin Kidney J. 2025 Apr 30;18(5):sfaf134. Uffing A, et al. Clin J Am Soc Nephrol. 2021 Nov;16(11):1730-1742.

Complement mediated-TMA (aHUS)



Recurrence risk	Treatment regimen
High risk (50-100%) • Previous early recurrence • Pathogenic mutation[a] • Gain-of-function mutation	Prophylactic eculizumab[b,c] Note: Start on the day of transplantation due to potential for severe recurrence and limited recovery of function in renal grafts compared with native kidneys
Moderate risk • No mutation identified • Isolated *CFI* mutations • Complement gene mutation of unknown significance • Persistent low titer FH autoantibody	Prophylactic eculizumab or plasma exchange[d]
Low risk (<10%) • Isolated *MCP* mutations • Persistently negative FH autoantibodies	No prophylaxis

R/O drugs (CNIs), infection (CMV), autoimmune (APS), ABMR then work up for recurrent aHUS (complement studies)

Java A, et al. J Am Soc Nephrol. 2025 May 1;36(5):940-951.
Goodship TH, et al. Kidney Int. 2017 Mar;91(3):539-551.

Recurrent GN: paraproteinemia

Characteristics	AL-amyloidosis	MIDD	Fibrillary GN	PGNMID
Common Causes	MGRS 80%, MM 16%, lymphoma 4%	MGRS 64%, MM 34%, Lymphoma 2%	Autoimmune, Solid cancer, infection	MGRS 96%, MM 3%, lymphoma 1%
SPEP positive	66-88%	64%	13%	20-30%
Rate of recurrent	22% (CR), 50% (PR/NR)	> 85%	36% (esp. monoclonal)	86%
Time to recurrent	<5y(PR/NR), >10 y(CR)	22 months	51 months	5.5 months
Rate of graft loss	12.5%	63%	7% (similar to other causes)	44%
Treatment	Chemotherapy	Chemotherapy	Treat underlying cause	Rituximab?
Transplant eligibility	Exclude unless “cured” (CR/VGPR) + no cardiac amyloid	Exclude unless “cured”	Yes, but inform rate of recurrent	If no monoclonal (FLC or SPEP) detected

Due to high recurrent rate, discussion with patient and hematologist is mandate

Sprangers B, et al. Transplantation. 2023 May 1;107(5):1056-1068.
Angel-Korman A, et al. Transplantation. 2020 Oct;104(10):2035-2047.
Ponticelli C, et al. Clin J Am Soc Nephrol. 2011 May;6(5):1214-21.
Said SM, et al. Kidney Int. 2018 Jul;94(1):159-169.
Leung N, et al. N Engl J Med. 2021 May 20;384(20):1931-1941.
Rosenstock JL, Markowitz GS. Kidney Int Rep. 2019 Apr 29;4(7):917-922.

Recurrent GN: miscellaneous

Diseases	Risk of recurrence	Graft loss from recurrence
Lupus Nephritis	30% (Histology), 2-9% (clinical)	2-4%
ANCA-GN	6% (60% renal ± extrarenal, 40% extrarenal only)	3-7%
IgA Vasculitis	78% (histology), 29-42% (clinical)	10% (esp. crescentic)
Anti-GBM disease	< 5% (55% if Anti-GBM +)	Rare
Diabetic nephropathy	100% (esp. histology)	Rare

Ponticelli C, et al. Clin J Am Soc Nephrol. 2011 May;6(5):1214-21.
Tang W, et al. Kidney Int. 2013 Mar;83(3):503-10.
Ivanyi B. Nat Clin Pract Nephrol. 2008 Aug;4(8):446-57.
Riella LV, et al. Transplant Rev (Orlando). 2017 Jan;31(1):1-9.

Transplant Renal Artery Stenosis

Transplant renal artery stenosis

Epidemiology	Risk factor
- Most common vascular complications - **Diagnosis within 3 months to 2 years** (rarely in the 1st month) - The early onset suggest surgical technique (peri-anastomosis), late onset suggest atherosclerosis (adjacent iliac A) or inflammation (diffuse stenosis-rejection?) - Incidence 1-23% - Hazard ratio for graft loss or death **= 2.8**	- **Elderly** donor or recipients - Donor or recipients **(PAD, high atherosclerosis risk)** - **Expanded criteria donor, DGF** (↑IRI) - History of rejection (cellular)?, Class II DSA **- CMV infection** - **Redundant/multiple** renal arteries - Right > Left renal A (longer artery than vein; prone to kinking) - Surgical technique

Fervenza FC, et al. Am J Kidney Dis. 1998 Jan;31(1):142-8.
Chen W, et al. Clin Kidney J. 2015 Feb;8(1):71-8.
Bruno S, et al. J Am Soc Nephrol. 2004 Jan;15(1):134-41.

TRAS: clinical manifestation

- Asymptomatic (from routine surveillance)
- Unexplained Cr rising (**bland sediment** and R/O CNI intoxication, rejection, obstruction)
- >30% Cr rising ***after ACEIs/ARBs*** initiation in 4 weeks
- Uncontrolled hypertension
- Flash pulmonary edema (Pickering syndrome)
- Bruit over allograft
- Rarely hypokalemia (“one-clip, one-kidney” model)

+ Aforementioned risk factors

Fervenza FC, et al. Am J Kidney Dis. 1998 Jan;31(1):142-8.
Chen W, et al. Clin Kidney J. 2015 Feb;8(1):71-8.
Bruno S, et al. J Am Soc Nephrol. 2004 Jan;15(1):134-41.

TRAS: diagnosis

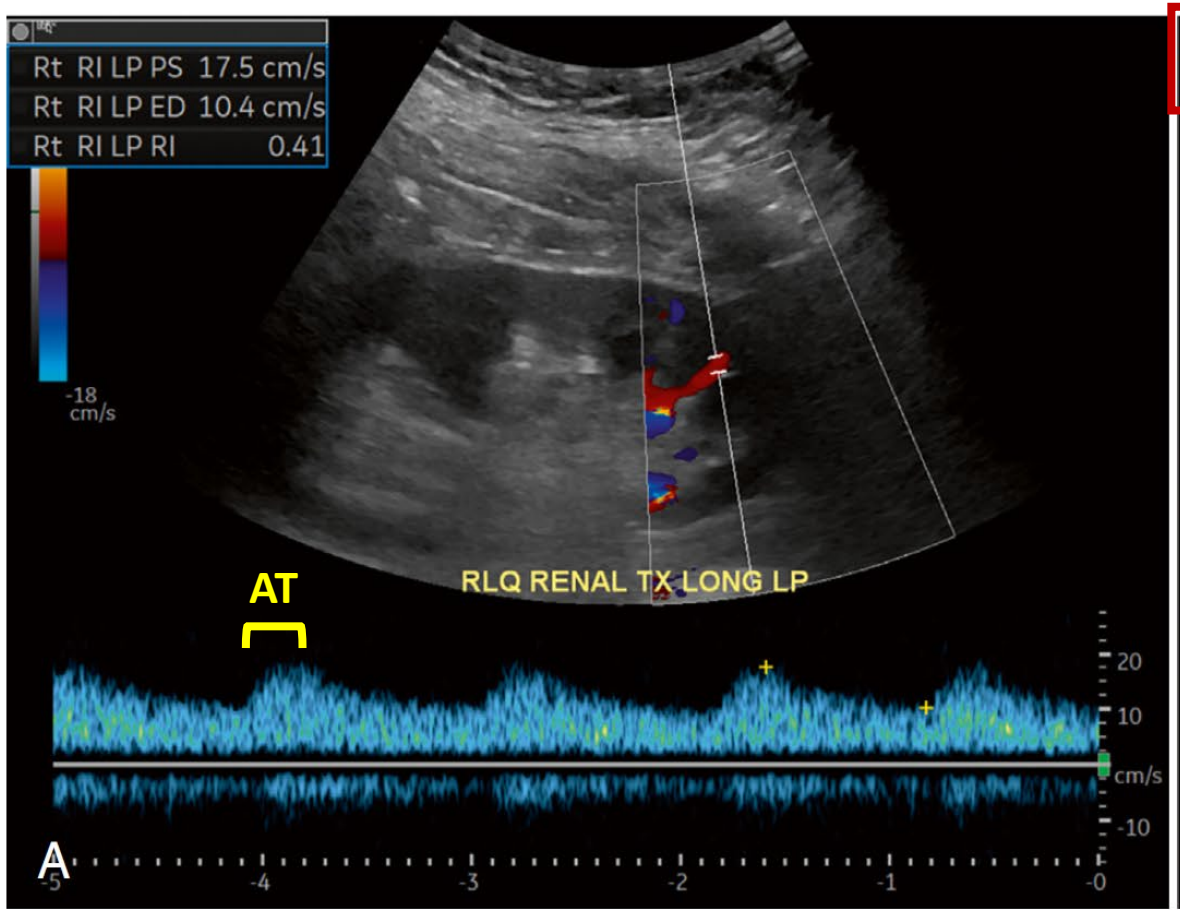
Imaging Modality	Advantage	Disadvantage	Sensitivity and Specificity
Duplex ultrasonography **Screening**	1. Availability 2. No radiation of contrast exposure 3. Multiple duplex parameters that can be combined for increased sensitivity and specificity	1. Operator dependable 2. Findings can be confounded by factors such as tortuosity of the renal artery and the complexity of its anatomy 3. The value of duplex parameters such as AT and RI are debatable	87%-94% and 86%-100%
CTA	Excellent images especially after 3D reconstruction	1. Need for iodinated contrast which itself is nephrotoxic 2. Exposure to ionizing radiation	No data available as CTA is not a first-line imaging choice for TRAS
MRA	1. No ionizing radiation 2. Noncontrast MRI can provide acceptable images	1. Poor availability 2. Gadolinium can cause nephrogenic systemic fibrosis in patients with severely depressed GFR 3. Not compatible with certain metallic prosthesis 4. Claustrophobia is a contraindication 5. Metallic lips within the vicinity of the renal artery can lead to false positives/overestimation of stenosis	67%-100% and 75%-100%
DSA **Confirm + therapeutics**	Ability to intervene in addition to diagnosis	1. Need for iodinated contrast 2. Exposure to ionizing radiation 3. Arterial dissection, hematomas, embolic phenomena, and puncture site pseudoaneurysm	Gold standard imaging modality against which other methods are compared for sensitivity and specificity

No role for PRA or PAC (one-clip, one-kidney model)

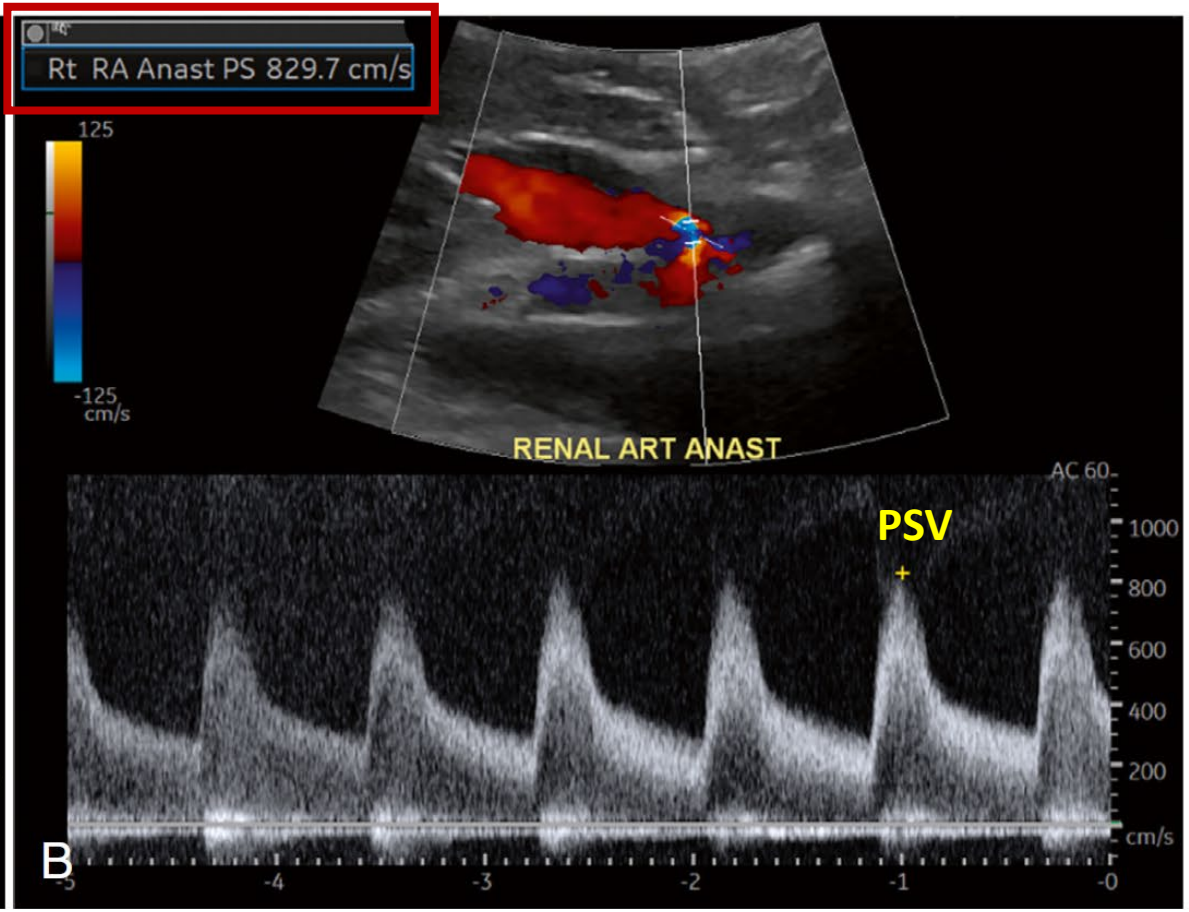
Fervenza FC, et al. Am J Kidney Dis. 1998 Jan;31(1):142-8.
Chen W, et al. Clin Kidney J. 2015 Feb;8(1):71-8.
Bruno S, et al. J Am Soc Nephrol. 2004 Jan;15(1):134-41.
Gunawardena T, et al. Exp Clin Transplant. 2022 Dec;20(12):1049-1057.

TRAS: diagnosis

Indirect signs



Direct signs



Post-stenotic **area: "parvus et tardus" pattern**
Resistance index↓, Acceleration time > 0.08 s

Stenotic **area: Peak systolic velocity > 250-300 cm/s**
PSV renal A/iliac A > 2, turbulence flow

Carol M. Rumack, Diagnostic Ultrasound, 6th edition.

TRAS: treatment

- No RCTs; low grade evidence
- Revascularize only in "**hemodynamic significant lesion**" = (confirmed by renal angiogram) > 70% or 50-69% stenosis with mean pressure gradient > 10 mmHg or systolic gradient > 20 mmHg or post-stenosis dilatation
- **Symptomatic** (unexplained cr rising, uncontrolled HT, heart failure): treatment of choice = Percutaneous transluminal renal angioplasty **(PTRA) with stent** (↓recurrent stenosis & stabilize renal function)
- Surgery only in **difficulties for endovascular treatment** due to higher morbidity and complications
- **Supportive**: RASi (**very closed** monitoring), anti-platelet, statins

Mazzolai L, et al. *Eur Heart J*. 2024;45(36):3538-3700.
Hicks CW, et al. *Am J Kidney Dis*. 2022;79(2):289-301.
Hinojosa-Gonzalez DE, et al. J Endovasc Ther. 2022 Apr;29(2):294-306.

BKPyV-Nephropathy

BKPyV-nephropathy

NEPHROLOGY

Virology & Epidemiology

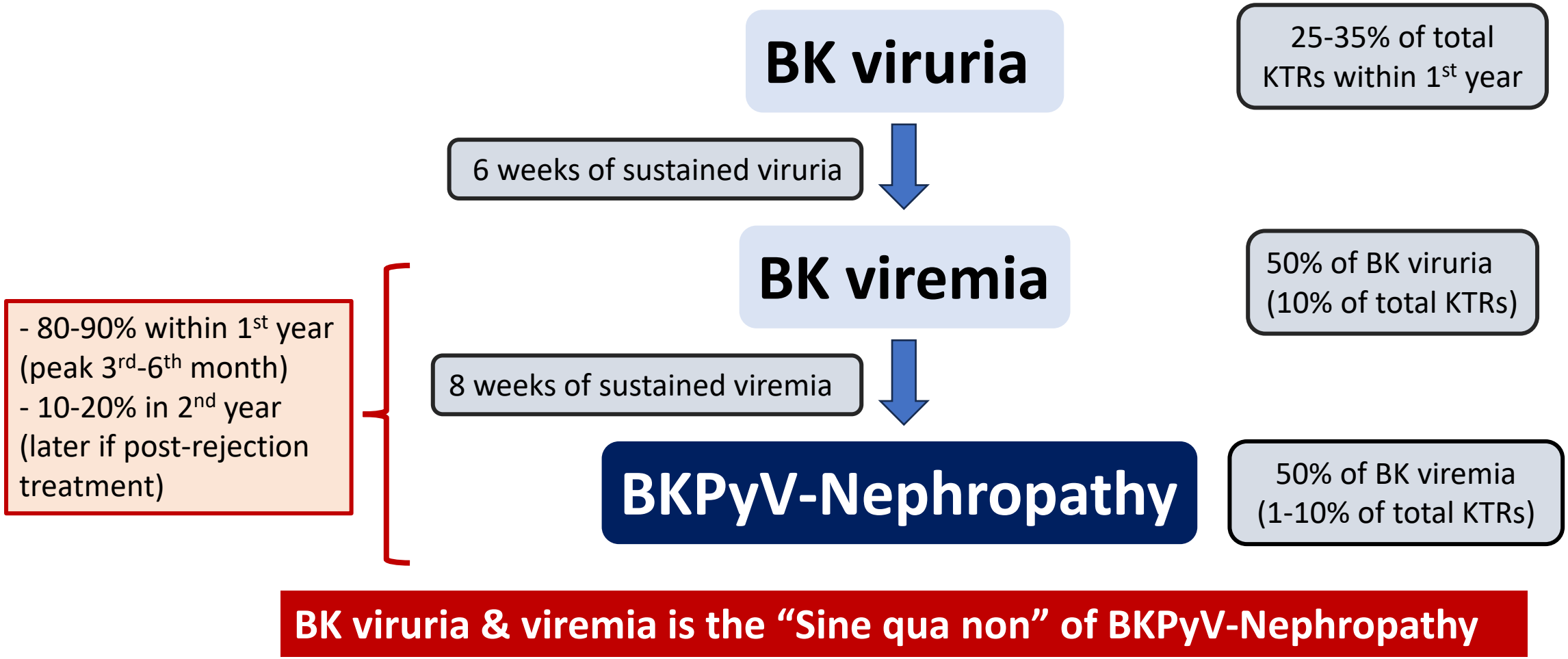
- **Ubiquitous** (> 90% infection within 4 years-old), **member of polyoma virus** (SV and JC virus)
- **Latent within renal tubular epithelial cell and uroepithelial cell** (controlled by cellular mediated immunity) 5% asymptomatic viruria ***prior to KT***
- **Reactivation** of virus replication from **immunosuppression** & cell differentiation (local inflammation)
- < 2% for single cause of graft loss but ***↑risk of all-cause graft loss***

Risk factors

- **Transplantation**
  - **TAC > CsA, High CNIs level**
  - **ATG > IL-2 RA**
  - **High corticosteroids, Rituximab, ± MPAA**
  - **ABOi, HLA-MM, DGF, Rejection, Multi-organ SOT**
  - **Ureteric stent (> 3 weeks)**
  - **mTORi (↓ risk)**
- **Recipient**
  - **Old, male, previous KT, some HLAs**
  - **ADPKD (↓ risk)**
- **Donor**
  - **Serology D^+/R^-**
  - **Urinary BKPyV shedding**

Kotton CN, et al. Transplantation. 2024 Sep 1;108(9):1834-1866.
Kant S, Dasgupta A, Bagnasco S, Brennan DC. Viruses. 2022;14(8):1616.
Eder M, et al. Kidney Int. 2025 Jul 2:S0085-2538(25)00506-X.
Al-Talib M, et al. Nephrol Dial Transplant. 2025 Apr 1;40(4):651-661.

Natural history



BK viruria & viremia is the "Sine qua non" of BKPyV-Nephropathy

Myint TM, Chong CHY, Wyld M, Nankivell B, Kable K, Wong G. *Transplantation*. 2022;106(1):e76-e89.
Hirsch HH, Randhawa PS; AST Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13528.
Kant S, Dasgupta A, Bagnasco S, Brennan DC. Viruses. 2022;14(8):1616.
Kotton CN, et al. Transplantation. 2024 Sep 1;108(9):1834-1866.

Clinical manifestation

- **Asymptomatic** (histologic confirmed but stable graft function) to **progressive Scr rising** (mostly bland & sub-nephrotic range proteinuria)
- ***No systemic symptoms***
- **Rarely hemorrhagic cystitis** (in hematopoietic stem cell transplant)
- **Rarely ureteric stenosis** (distal ureter: anastomosis at the ureterovesical junction) onset 4-6 months
- **± Malignancy** (uroepithelial CA / RCC): controversy

Myint TM, Chong CHY, Wyld M, Nankivell B, Kable K, Wong G. *Transplantation*. 2022;106(1):e76-e89.
Hirsch HH, Randhawa PS; AST Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13528.
Kant S, Dasgupta A, Bagnasco S, Brennan DC. Viruses. 2022;14(8):1616.
Gardner SD, Field AM, Coleman DV, Hulme B. Lancet. 1971;1(7712):1253-1257.
Al-Talib M, et al. Nephrol Dial Transplant. 2025 Apr 1;40(4):651-661.

BKPyV nephropathy definitions

Definitions	BKPyV VL	Management
Possible	**Urine** BKPyV-DNAuria > **10^7 c/mL** Or **decoys** cell/virion from EM but negative for DNAemia	**Check plasma BKPyV VL**
Probable	Sustained **plasma** BKPyV-DNAemia **> 10^3 c/mL** for **> 2 wk**	**↓ Immunosuppression**
Presumptive	**Plasma** BKPyV-DNAemia **> 10^4 c/mL**	**↓ Immunosuppression**
Biopsy-proven	**Cytopathic change** plus **IHC** and specific test **identifying BKPyV** as opposed to JC polyomavirus*	**↓ Immunosuppression**

IHC for SV40 is positive in both JC and BKPyV, plasma BKPyV-DNAemia is required for confirmation

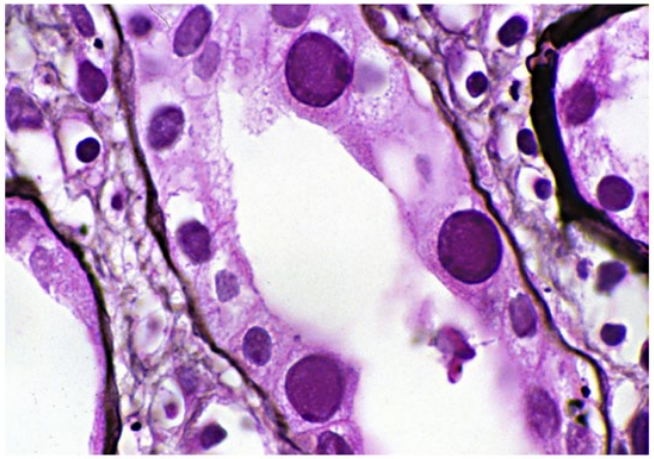
Kotton CN, et al. Transplantation. 2024 Sep 1;108(9):1834-1866.

Investigation

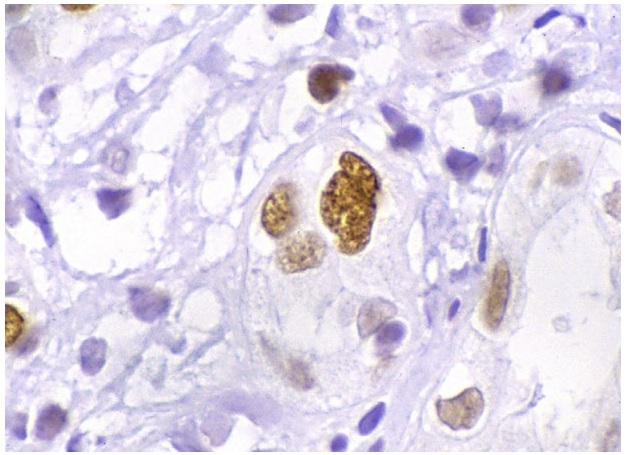
- Regular screening of KTRs to identify patients for treatment of ***probable/presumptive/biopsy-proven*** BKPyV-nephropathy
- **When** to screen BKPyV-DNAemia
  1) Plasma BKPyV loads **monthly** until **mo 9, then every 3 mo until 2 y** post-transplantation (routine screening every case)
  2) Increased immunosuppression or **antirejection therapy**, ***monthly*** screening for BKPyVDNAemia for the ***next 3 mo***
  3) Allograft dysfunction; Scr. ↑ > 15-20% (esp. unexplained & recent ↑ immunosuppression)
  4) Protocol biopsy
- **In resource limited**/blood sampling not available, **urine** decoy or **urine** BKPyV can be used with ***same interval as plasma VL***
- **Biopsy** is indicated in ***allograft dysfunction*** or ***high immunologic risk***

Kotton CN, et al. Transplantation. 2024 Sep 1;108(9):1834-1866.

BKPyV nephropathy: histology

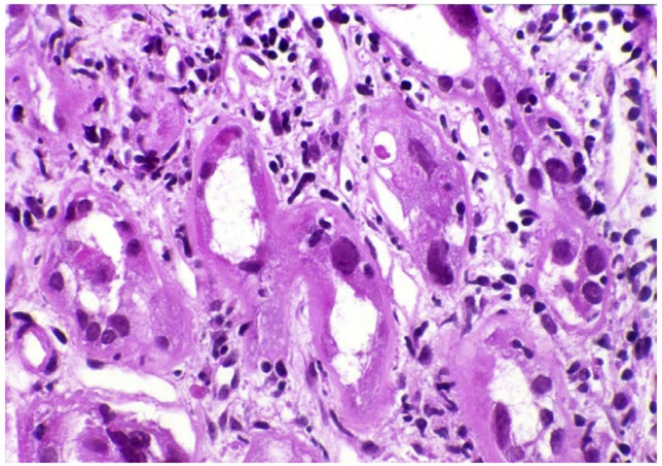


Viral cytopathic changes: **enlarged basophilic rim**, smudgy & **ground glass** viral nuclear inclusions in tubular epithelium

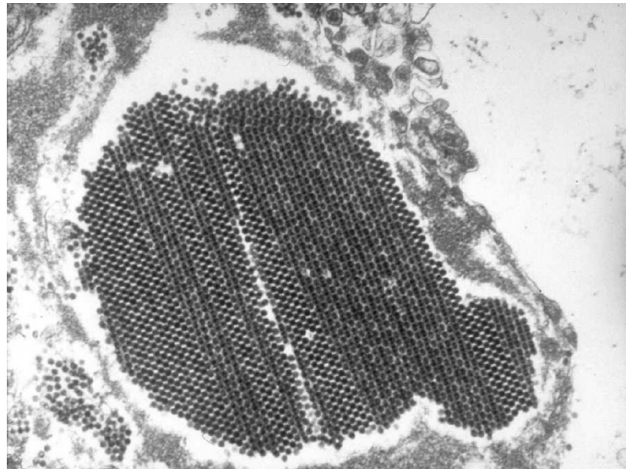


IHC: **positive for SV40** of enlarged nuclear inclusion

IF: ± positive IF for IgG, C3 and **C4d** at TBM **(not PTC)***



Viral inclusions and viral **pleomorphic** interstitial **infiltrate** composed of lymphocytes, **plasma cells**, and occasional neutrophils
+ **tubulitis**



EM: Polyomavirus particles,40-45 nm, are present in nuclei of infected cells, with a **lattice-like** arrangement

Involvement: **Renal tubular cell** (spare glomerular, vessel, podocyte) predominant at **medulla** and **focal** area

Adequate sample = 2 cores with medulla

Kotton CN, et al. Transplantation. 2024 Sep 1;108(9):1834-1866.
Lusco MA, et al. *Am J Kidney Dis*. 2016;68(6):e37-e38.

BKPyV nephropathy: Banff classification

Biopsy-Proven PVN[a] Class 1		Biopsy-Proven PVN[a] Class 2		Biopsy-Proven PVN[a] Class 3	
pvl	Banff ci Score	pvl	Banff ci Score	pvl	Banff ci Score
1	0–1	1	2–3	—	—
—	—	2	0–3		
—	—	3	0–1	3	2–3

Pvl (polyoma virus load): tubule with intranuclear viral inclusion bodies or a positive IHC for SV40 antigen in one or more cells per tubular cross-section is considered "a positive tubule"
Pvl 1 = ≤ 1% of all tubules with viral replication
Pvl 2 = > 1 or ≤ 10% of all tubules with viral replication
Pvl 3 = > 10% of all tubules with viral replication

ci Score: Interstitial fibrosis
ci 1 = Interstitial fibrosis in 6 to 25% of cortical area
ci 2 = Interstitial fibrosis in 26 to 50% of cortical area
ci 3 = Interstitial fibrosis in >50% of cortical area

Banff PVN class = combined viral load & fibrosis

Graft failure at 2 y
PVN class 1 = 16%
PVN class 2 = 31%
PVN class 3 = 50%

Nickeleit V, et al. J Am Soc Nephrol. 2018 Feb;29(2):680-693.

BKPyV management

No specific anti-viral medications: immunosuppression reduction is the main treatment

Steps	Anti-metabolite reduced first	CNIs reduced first
1st step	Reduce anti-metabolite dose by **50%**	Reduce CNIs **25-50%**, 1-2 steps to target **TAC trough 3-5 ng/mL**, CsA 75-125 ng/mL
Check BKPyV DNAemia	Check if BKPyV DNAemia **↓ 1log (10-fold) c/mL within 4 weeks** If not then 2nd step	
2nd step	**Discontinue anti-metabolite** Keep prednisolone 5-10 mg/d (avoid monotherapy of CNIs)	**Reduce anti-metabolite to 50%** Keep prednisolone 5-10 mg/d
Check BKPyV DNAemia	Check if BKPyV DNAemia **↓ 1log (10-fold) c/mL within 4 weeks** If not then 3rd step	
3rd step	**Reduce CNIs** TAC trough 5 ng/mL, CsA 100 ng/mL	**Discontinue anti-metabolite**

Plasma BKPyV is monitored q 2-4 weeks (until < 1,000 c/mL), serum creatinine q 1 week

Kotton CN, et al. Transplantation. 2024 Sep 1;108(9):1834-1866.

BKPyV adjunctive management

- **IVIG** (which adequately contained neutralizing Ab) may be considered
  - Incase of failed (persistent BKPyV DNAemia > 1,000 c/mL) treatment after ***steps of immunosuppressive reduction***, Or
  - Facilitate immunosuppressive reduction in those with ***high risk of rejection*** (weak recommendations)
- Dose: 0.1-0.3 g/kg/dose q 2-4 weeks or 0.5-2 g/kg/dose q 1-3/week
- ***No role*** of leflunomide, cidofovir, fluroquinolones, statins (***strong*** recommendations)

Insufficient data **to evaluate the efficacy of** ***switching to mTOR inhibitors*** **for treating BKPyV-DNAemia or biopsy-proven BKPyV-nephropathy (no recommendation, statement only)**

Kotton CN, et al. Transplantation. 2024 Sep 1;108(9):1834-1866.

Insights from the BKEVER Trial comparing everolimus versus mycophenolate mofetil for BK Polyomavirus infection in kidney transplant recipients

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods and cohort

- From January 2018 to June 2020
- 15 French transplant centers
- 130 kidney transplant recipients with BKPyV> 2.8 log copies/mL
- CNI + MMF ± steroids
- 1: 1 randomization
- Primary end point = BKV clearance at M6

Intervention group: Everolimus, n = 65

(discontinue drug 38)

Everolimus 3-8 ng/mL

+

Tacro 3-6 ng/mL
or CsA 50-75 ng/mL

Control group: MMF, n = 65

(discontinue drug 4)

MMF half dose

+

Tacro 3-6 ng/mL
or CsA 50-75 ng/mL

Intervention outcomes

55.7%
M6
BKPyV clearance

121 days
Time to viral clearance

n = 11 (17%)
BKPyVN

n = 12 (18%)
Rejection

Control outcomes

81.3%
M6 BKPyV clearance
OR = 3.4, P = 0.003

63 days
Time to viral clearance

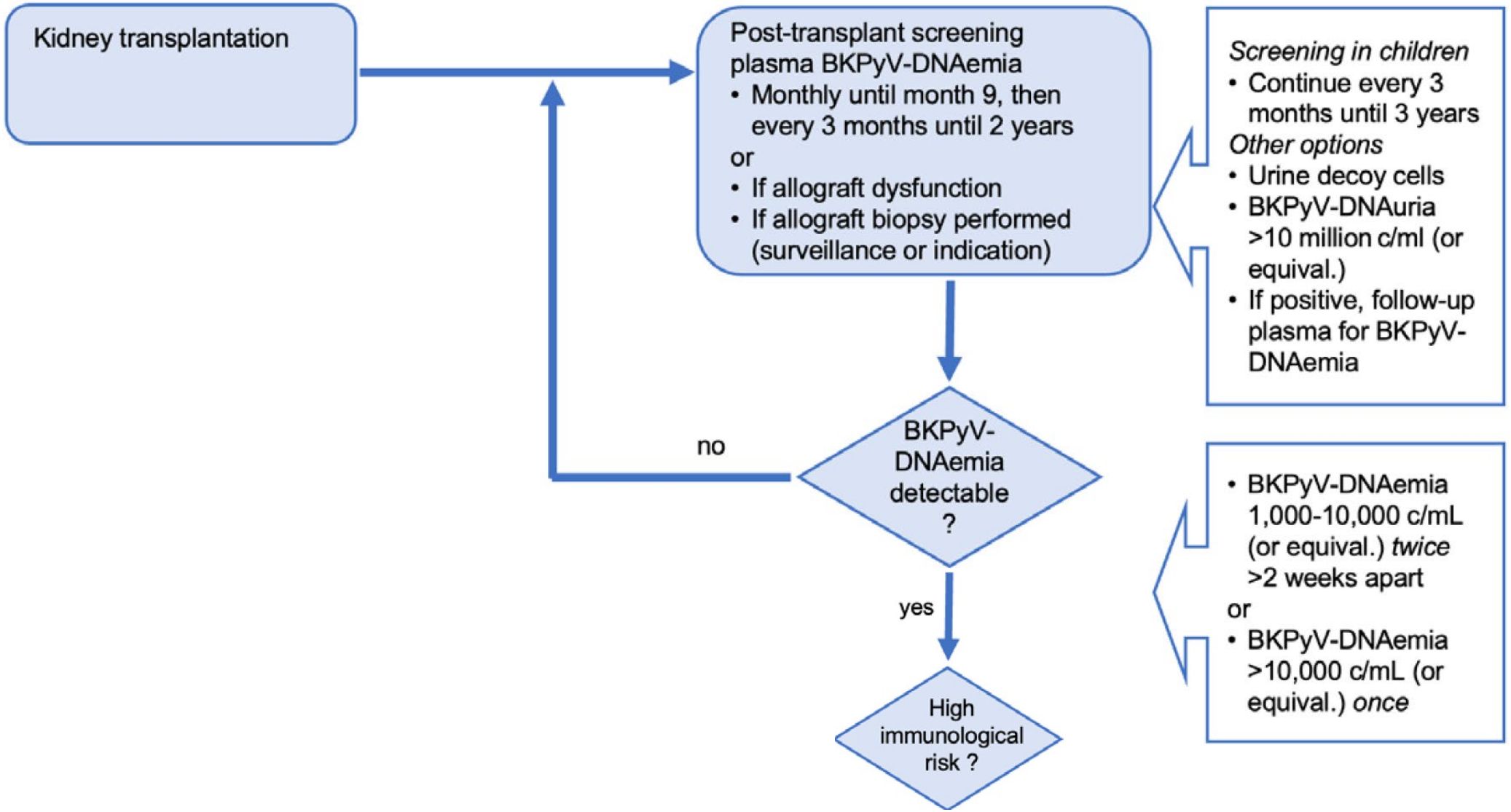
n = 6 (9%)
BKPyVN

n = 9 (14%)
Rejection

At 6 months, 50% MMF + low CNIs has better VL clearance than mTORi + low CNIs (81% vs 55%, OR 3.4 P 0.003)
50% MMF + low CNIs clears VL faster than mTORi + low CNIs (63 vs 121 d) without significant graft outcome

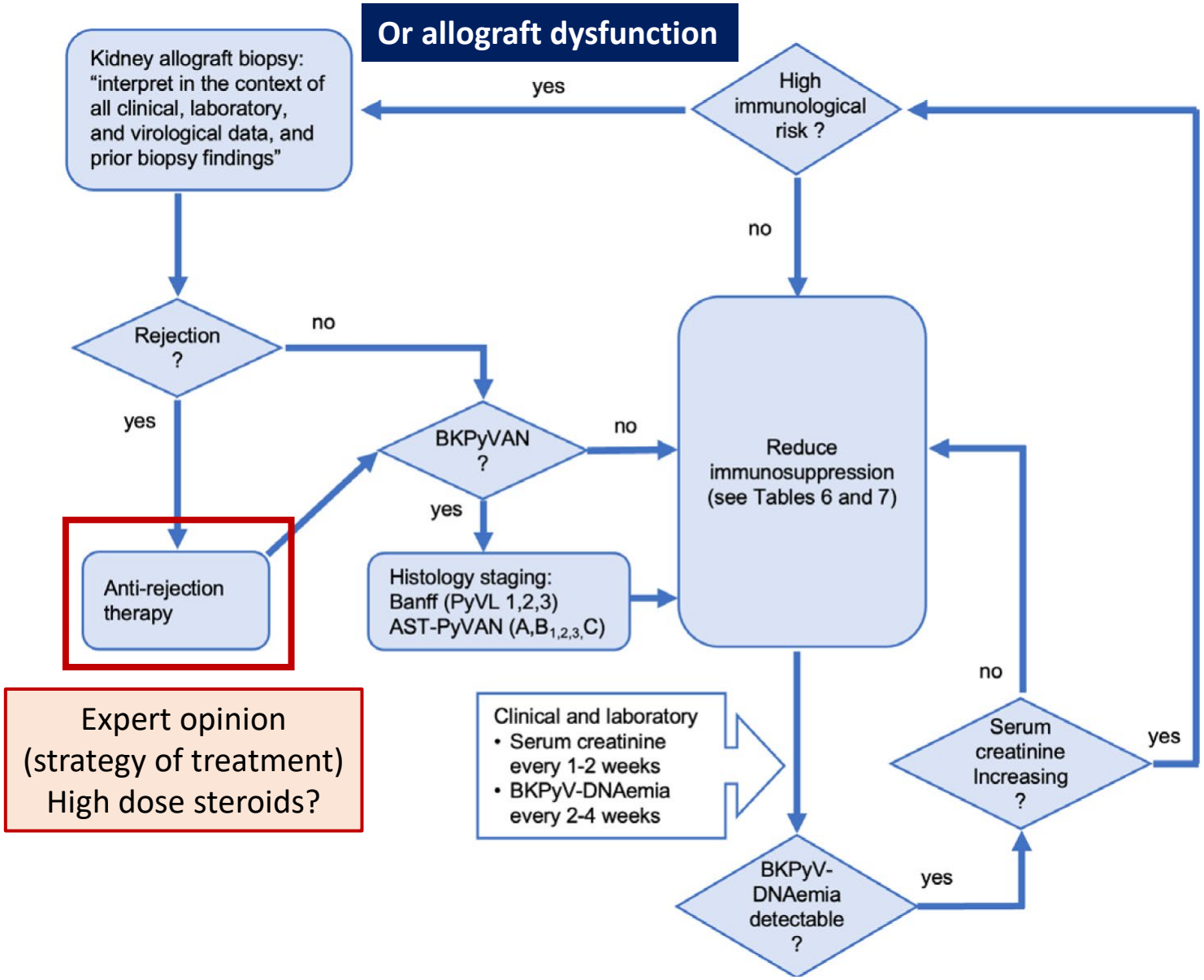
Caillard S, et al. Kidney Int. 2025 Feb;107(2):338-347.

BKPyV management



Kotton CN, et al. Transplantation. 2024 Sep 1;108(9):1834-1866.

BKPyV management



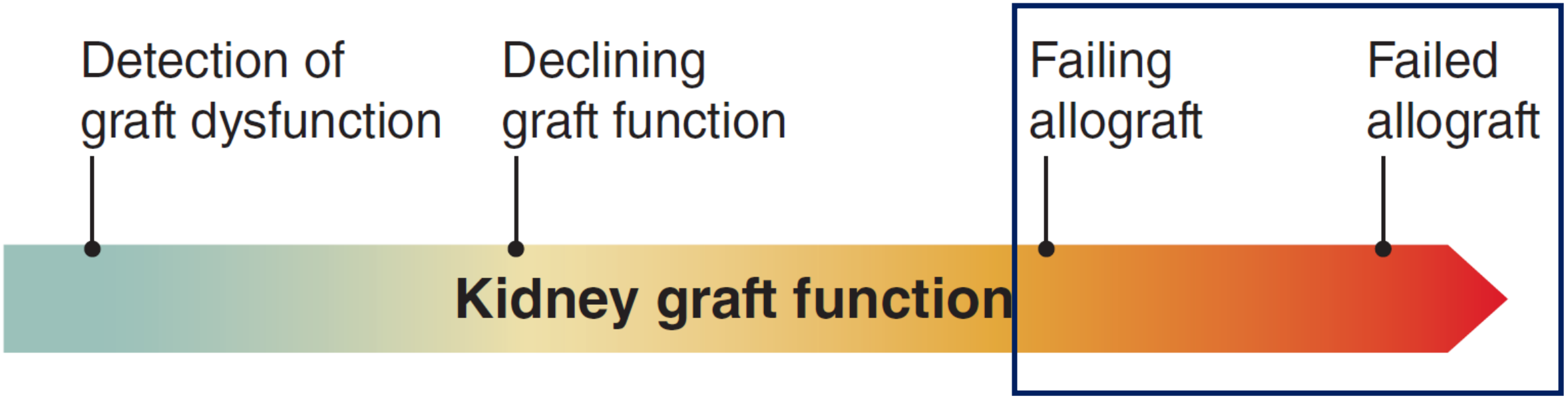
Expert opinion
(strategy of treatment)
High dose steroids?

Concurrent rejection with BKPyVAN

- Rare manifestation (8%)
- Rejection after treatment of BKVAN is more common (4-15% TCMR, 14% DSA, 7% ABMR)
- **Corticomedullary** in BK vs **cortex** in rejection
- Plasma cell rich & pleomorphic cells in BK
- **Rejection: endarteritis/MVI, C4d+ in PTC** (C4d+ in TBM in BK)
- ± Inflammation beyond viral cytopathic change
- TCMR (gr I) cannot be diagnosed confidently with BKPyVAN

Kotton CN, et al. Transplantation. 2024 Sep 1;108(9):1834-1866.
McGregor SM, Chon WJ, Kim L, Chang A, Meehan SM. World J Transplant. 2015;5(4):292-299.
Hirsch HH, Randhawa PS; AST Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13528.

Chronic allograft failure



Failing graft = "stable but low allograft function, declining function (when there is ***irreversible*** and ***progressive*** decline in kidney function with anticipated allograft survival ***of less than 1 year***), and return to KRT."

Failed allograft = Graft is either no longer functioning at all or is working so poorly that meaningful functional **improvement is not possible and additional kidney replacement therapy is required.**

"Vulnerable transition period" High morbid/mortality (higher than native kidney failure)

Michelle A. Josephson, Kidney International (2023)

Chronic allograft failure

Outcomes

- **Mortality rates were significantly higher** in failing graft comparing with native kidney failure (adjusted for confounding), esp. first 2 years after RRT
- Causes of death: **cardiac** (36%) or **infectious** (17%)
- ***No difference*** among mode of RRT (HD = PD)

Risk factor for mortality

- ***Non-use of AVF****
- ***Malnutrition***, underweight, hypoalbuminemia, Elderly, woman
- ***Comorbidity***: CHF, PAD, stroke, DM
- Higher eGFR at dialysis (eGFR > 10 mL/min/1.73 m2): malnutrition?

Amarpali Brar, et al. Am J Nephrol 2017;45:180–186.
Gill JS, et al. Kidney Int. 2002 Nov;62(5):1875-83.
Perl J, et al. Clin J Am Soc Nephrol. 2011 Mar;6(3):582-90.

CKD management in failing graft

- **Relisting** for future transplant **(Pre-emptive KT = The best option)**
- Mode of dialysis: same survival rate between each mode
- Access evaluation: **at GFR < 20 ml/min/1.73 m^2**
- **Preserve** functional AV access
- Avoid further sensitization (blood transfusion)
- Complications of CKD: **More severe/earlier compared with native kidney**
- **Timing** of dialysis: **Based on clinical factors and symptoms** rather than on eGFR evaluation alone

Josephson MA, et al. Kidney Int. 2023 Dec;104(6):1076-1091.
Lubetzky M, et al. Am J Transplant. 2021 Sep;21(9):2937-2949.

Chronic allograft failure

NEPHROLOGY

DRAFT

ไตทำงานลดลงมากหรือเข้าสู่การล้างไต

Failing allograft = persistent irreversible eGFR < 20 mL/min/1.73 m2 and **RRT in 1 y** (เริ่มพิจารณาปรับลดยากดภูมิตามความเสี่ยง)

ในกรณีที่ eGFR < 10 ml/minute/1.73 m^2 ร่วมกับมีปัสสาวะมากกว่า 400 ml/day

วางแผนการปลูกถ่ายไตใหม่ใน 1 ปี

YES

พิจารณาให้ลดยากดภูมิต่ำสุดจนปลูกถ่ายไตใหม่

NO

พิจารณาลดยากดภูมิจนหยุดยาใน 3-6 เดือน

ยากลุ่ม CNI: ลดยาลงโดยมีระดับยา tacrolimus trough level 2 - 5 ng/mL หรือ cyclosporine trough level 25 - 75 ng/mL และค่อยๆลดยาจนหยุดยา โดยไม่ต้องติดตามระดับยาต่อ

ยากลุ่ม anti-metabolite drug: เริ่มลดยาลง 50%จากขนาดที่ได้รับอยู่เดิม และ หยุดยาหลังจากนั้น ให้ prednisolone ในขนาด 2.5-5mg/day

TTC 4th, kidney transplant immunosuppression CPG (draft)

Take home message

- Chronic allograft dysfunction from non-immune causes is common and caused by multiple etiologies due to improved efficacy of immunosuppression
- Many causes are preventable or treatable to delay chronic allograft dysfunction
- In failing graft, morbidities and mortality are higher than native CKD
- Special considerations from both nephrologist and transplant center are needed in this vulnerable setting

Thank you for your attention

8th RENAL AND NUTRITION CONFERENCE

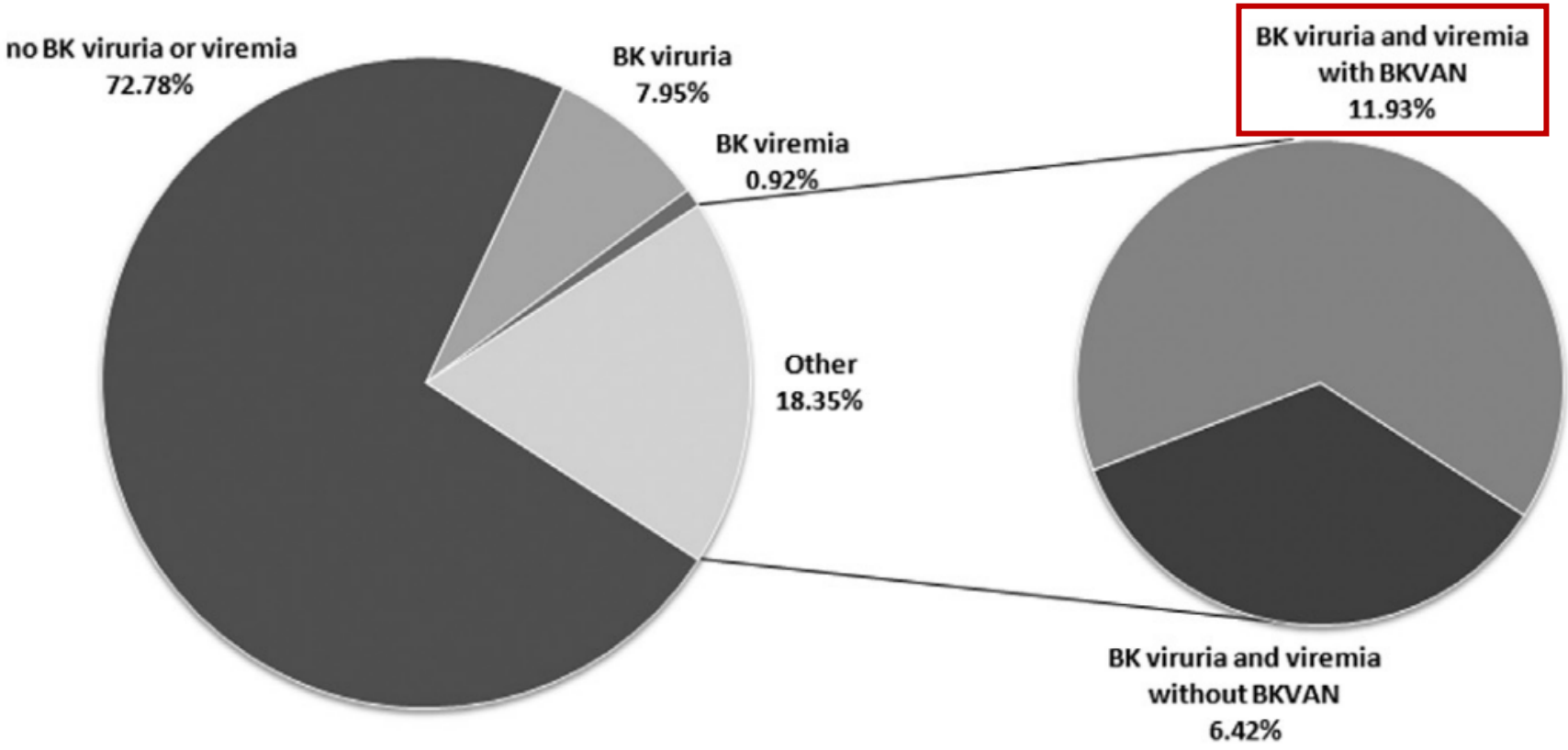
THE LEGEND OF NEPHROLOGY HEROES

16-18 มกราคม 2569

GRAND DIAMOND BALLROOM
IMPACT FORUM MUANG THONG THANI

BKPyVAN: Thai epidemiology

In 2 large transplant centers in Thailand 2011-2016 (796 KTRs)
BK viral load was poorly screened (52.5%). BKPyVAN was diagnosed 12% of total KTRs



Risk factors in both studies
- CDKT
- Prior CMV infection
- MMF > 1 g/d

BKPyVAN associated with
- High risk of rejection
- Allograft failure

Yooprasert P, Rotjanapan P. *Transplant Proc*. 2018;50(1):130-136.
Skulratanasak P, et al. Transplant Proc. 2018;50(4):1077-1079.

“Proven” BKPyVAN criteria

Require DNAemia

TTC Guideline 2025 draft

ยืนยัน (proven)	ผลการตรวจทางพยาธิวิทยาชิ้นเนื้อไต -การเปลี่ยนแปลงรูปร่างของเซลล์ -ท่อไตอักเสบ (tubulitis) -ผังพืดที่ไต (interstitial fibrosis) หรือการฝ่อของหลอดไต (tubular atrophy) -พบหลักฐานการติดเชื้อจากการติด SV40 immunohistochemistry

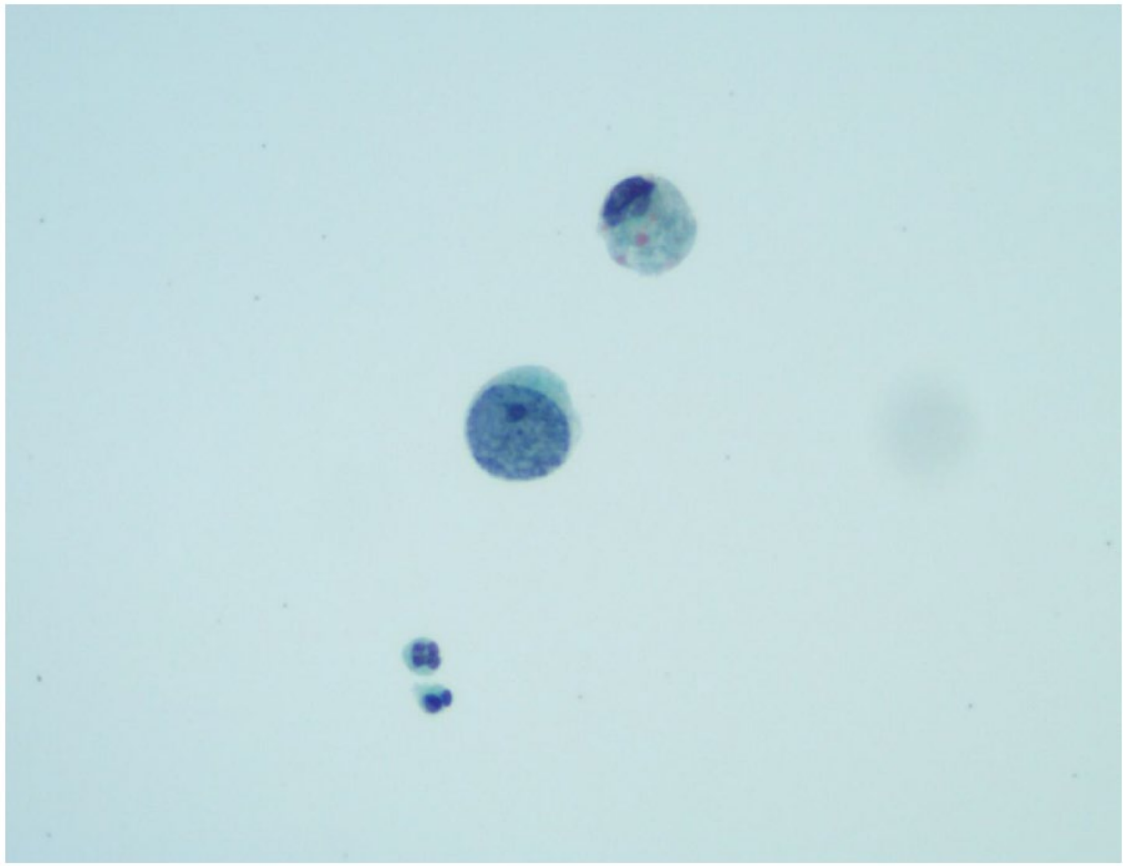
2nd International Consensus Guidelines 2024

Biopsy-proven BKPyV-nephropathy: detection of compatible cytopathic effects plus immunohistochemistry and a specific diagnostic test identifying BKPyV as opposed to JC polyomavirus (JCPyV).

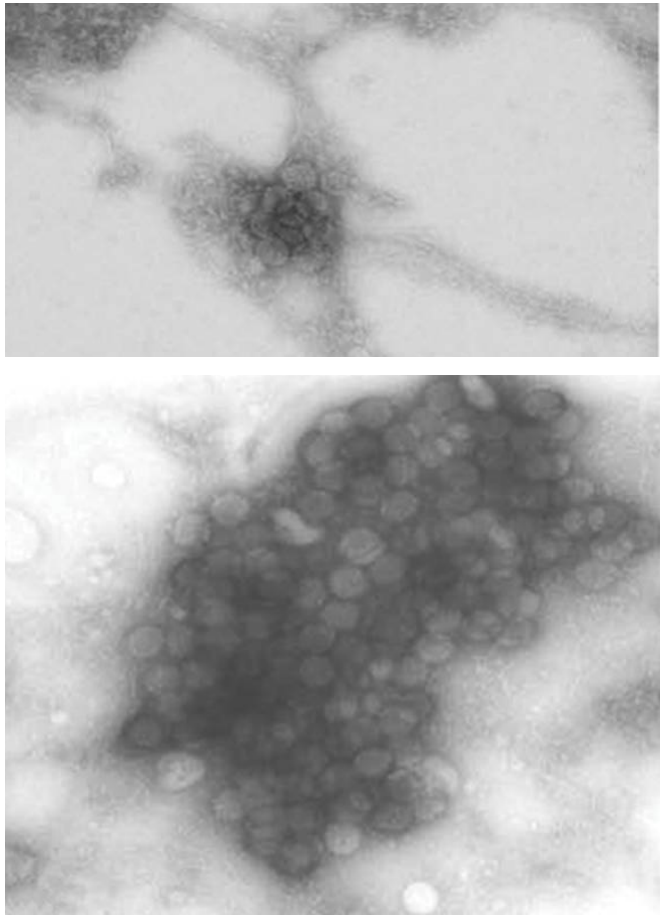
BKV Transplantation Associated Virus Infections Working Group consensus 2022

Proven BKPyVAN requires demonstration of active BKPyV replication within renal tissue by at least 1 of the following methods [10, 11, 13, 28, 29]: immunohistochemistry (IHC) staining reaction for SV40-T antigen or in situ hybridization (ISH) and demonstration of BKPyV DNAemia using a previ-

Urine exam of BKPyV viruria



Decoy cell: PAP stain showing enlarged nucleus and clumped chromatin mimicking uroepithelium atypia



Haufen: Three-dimensional cast-like polyomavirus aggregates rich in Tamm-Horsfall protein visible in EM

Kant S, Dasgupta A, Bagnasco S, Brennan DC. Viruses. 2022;14(8):1616.
Singh HK, Andreoni KA, Madden V, et al. J Am Soc Nephrol. 2009;20(2):416-427.

Features	CMV	BKPyV	Adenovirus
Incidence of graft infection	0.2%	5%	< 0.5%
Common organs	GI tract, lung, liver	Kidney	Lung, GI tract, disseminated
Viral inclusion			
Nucleus:			
- Homogenous ground glass	+/-	++	+++
- Halo	+++	+/-	+/-
- Granular clumped	-	++	+/-
Cytoplasmic	+	-	-
Cell tropism			
- Tubular epithelial cell	+++	+++	+++
- Endothelial cell	++	-	-
- Mononuclear cell	+	-	+/-
Parenchymal necrosis	+	-	+++
Interstitial hemorrhage	-	-	++
Granulomatous formation	+/-	+/-	++

Hantalom R, Jirajan B. Journal of the Nephrology Society of Thailand. 2016;22(2):4-12.
Geetha V, et al. J Cytol. 2012;29(2):133-134.
Storsley L, et al. J Am Soc Nephrol. 2011 Aug;22(8):1423-7.

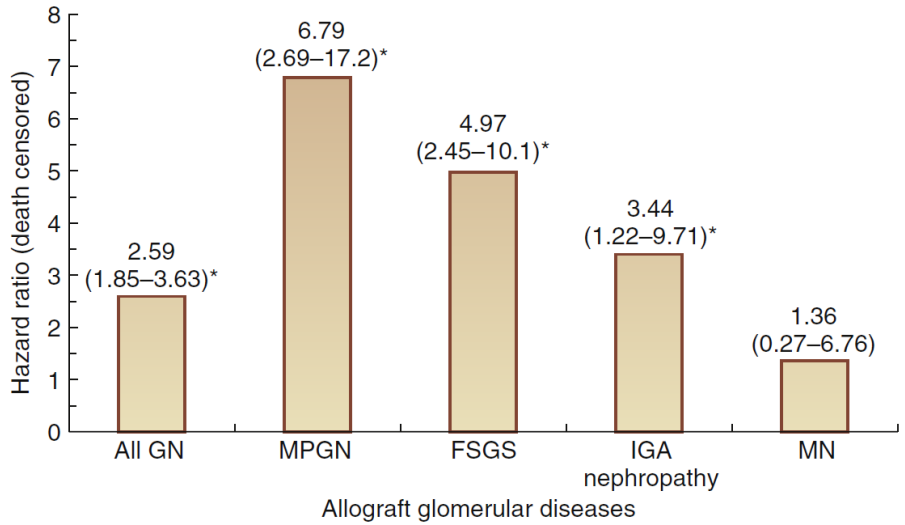
Adjunctive treatment for BKPyVAN

Drug	Example dosing regimen	Toxicities	Precautions and monitoring	Guideline supported[a]	Other considerations
Intravenous Immunoglobulin	300 mg/kg 3-weekly Note existing studies have used variable dosing regimens	Infusion reactions Anaphylaxis	IgG levels may be used to titrate dose	Yes [22][b] Equivocal [21]	A multicentre RCT assessing a human monoclonal VP1-specific IgG1 is ongoing (ClinicalTrials.gov identifier: NCT04294472)
Leflunomide	100 mg loading, then 40 mg daily	Bone marrow suppression Hepatotoxicity Haemolysis	Teratogenic with relevance to both males and females[c] Monitor FBC and LFT fortnightly for 6 months, then 8-weekly	No [22] Equivocal [20, 21]	Variable inter-patient metabolism
Fluoroquinolones	500 mg daily levofloxacin	Achilles tendonitis Gastrointestinal upset Rash	History of tendon damage related to quinolones	No [22] Equivocal [21]	Lack of efficacy demonstrated in two RCTs [49, 50]
Cidofovir	0.25–1 mg/kg at 1–3-week intervals. Increase dose depending on response and toxicity	Nephrotoxicity Anterior uveitis and other eye manifestations	Monitor renal function, proteinuria, and FBC at least 48 hours prior to each dose Regular eye examination e.g. fortnightly during treatment	No [22] Equivocal [21]	Consider concomitant administration with oral probenecid Avoid concomitant use with tenofovir due to increased risk of Fanconi syndrome

Al-Talib M, et al. Nephrol Dial Transplant. 2025 Apr 1;40(4):651-661.

Rate of recurrence and graft loss

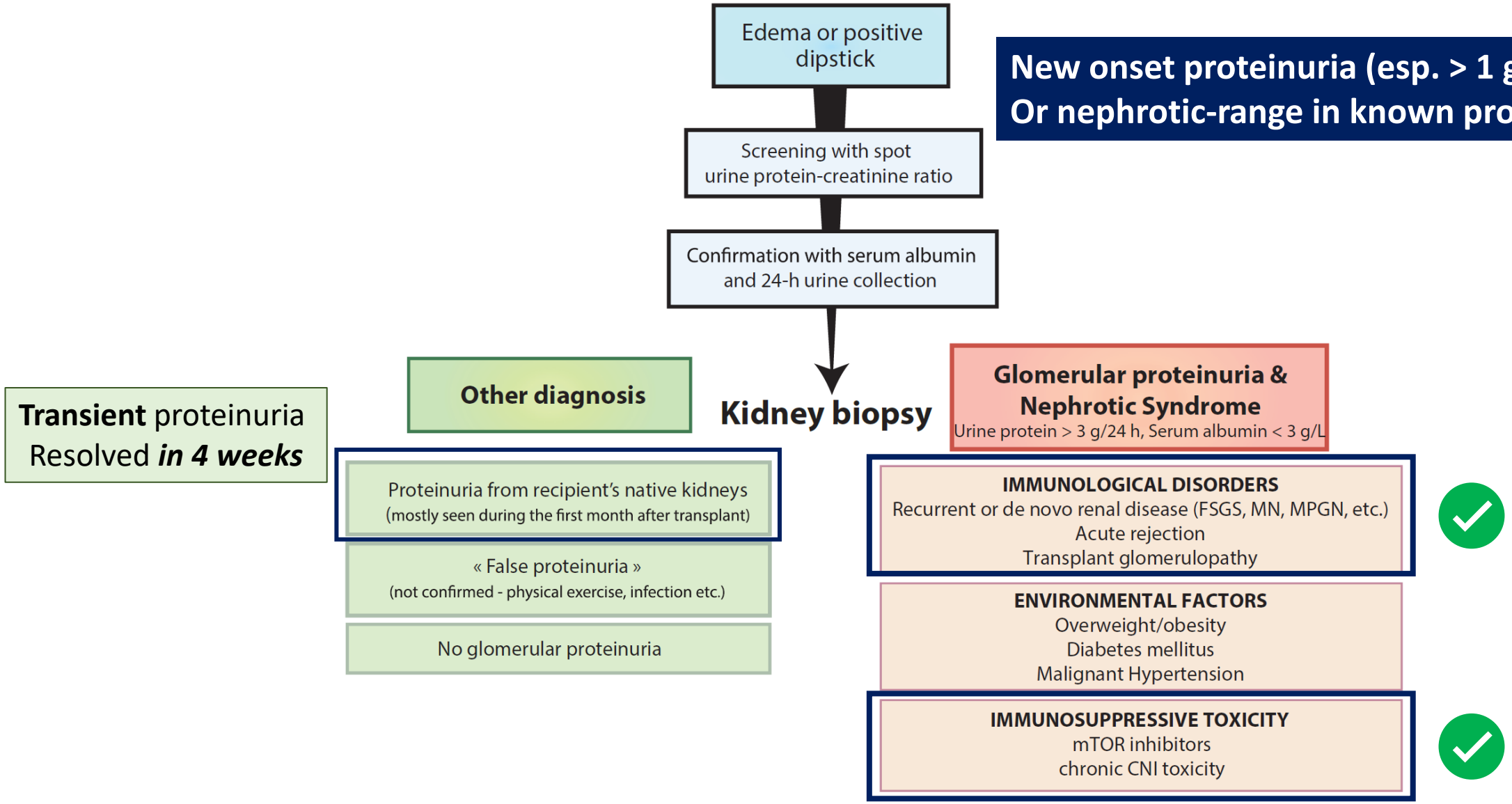
Type of glomerulonephritis	Clinical recurrence rate (% of recipients)	Rate of graft loss after 5–10 years (% of recipients)
FSGS	20–40	20
Membranous nephropathy	10–30	50
MPGN type I	20–33	High
MPGN type II	67–100	34–66
Anti-GBM nephritis	<5	Can occur
ANCA-positive crescentic glomerulonephritis	0–20	8
IgA nephropathy	7–30	3–16
Idiopathic D^- HUS	33–82	90



Overall, recurrent GN = worse allograft outcome
Worst outcome = MPGN, aHUS, FSGS

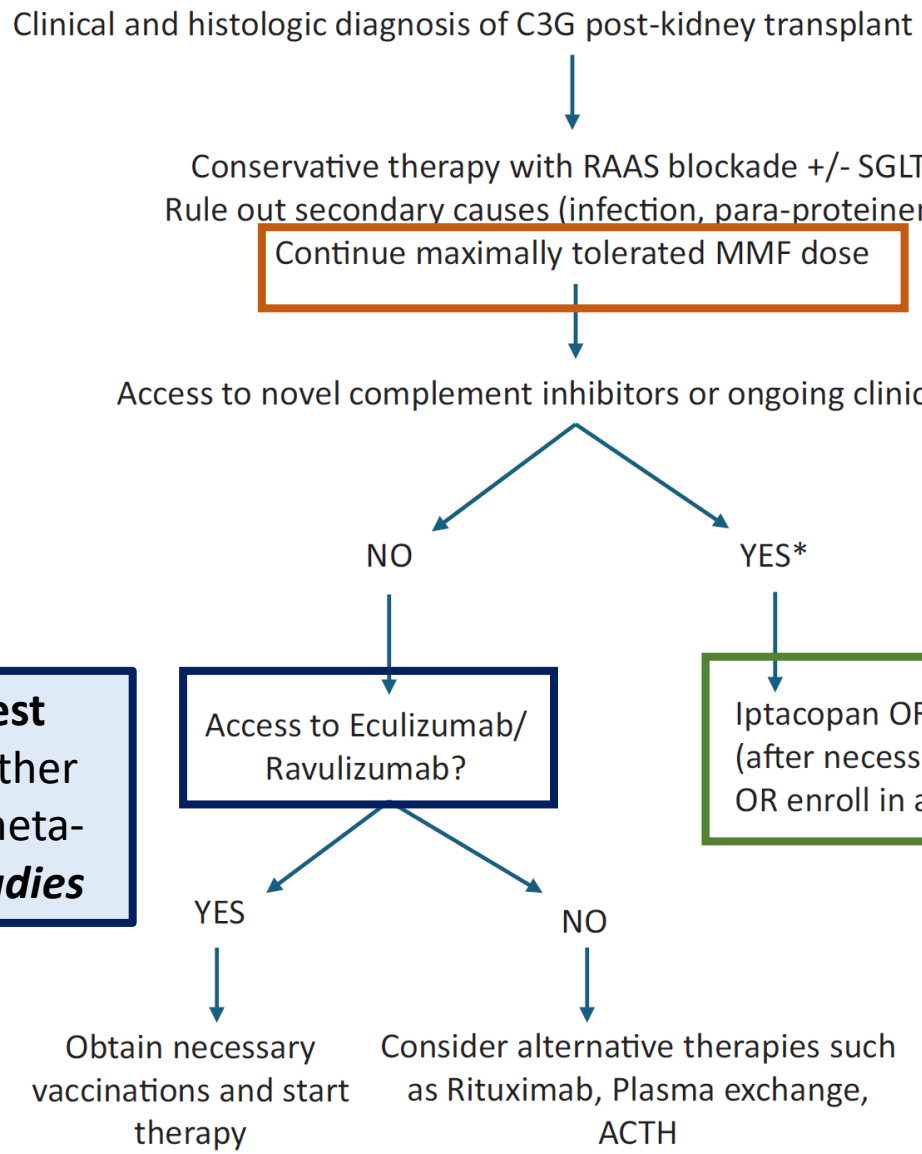
Ivanyi B. Nat Clin Pract Nephrol. 2008 Aug;4(8):446-57.
Cosio FG, Cattran DC. Kidney Int. 2017 Feb;91(2):304-314.

Proteinuria after transplant



Leon J, et al. Transplantation. 2019 Oct;103(10):1990-2002.

Proposed recurrent C3G treatment



MMF + steroids are effective treatment in ***native*** C3G

Eculizumab demonstrated **lowest graft loss** (esp. C3GN) among other treatment (rituximab, TPE) in meta-analysis from ***observational studies***

Iptacopan (factor B inhibitor) **Pegcetacoplan** (c3 inhibitor) have been proven for efficacy for C3G in ***phase II trials*** including recurrent diseases

Attieh RM, et al. Clin Kidney J. 2025 Apr 30;18(5):sfaf134.
Gonzalez Suarez ML, et al. Med Sci (Basel). 2020 Oct 21;8(4):44.
Nester CM, et al. Kidney Int Rep. 2024 Oct 28;10(2):432-446.

TRAS: diagnostic parameters

Parameters (for stenosis > 50%)	Sensitivity, Specificity	Comments
PSV of renal A > 250 cm/s	Sens 70%, Spec 96.8%	***False elevated*** in HT, early post-op, vessel tortuosity, inflammation
PSV renal A/iliac A > 2	Sense 80%, Spec 100%	False negative if iliac stenosis
Acceleration time ≥ 0.1 sec	Sense 100, Spec 96.7%	-
Resistance index < 0.65	Sense 50%, Spec 67.7%	Maybe high renal parenchymal disease

Overall sensitivity of 87% to 94% and a specificity of 86% to 100% in duplex ultrasound for hemodynamically significant TRAS

Gunawardena T, et al. Exp Clin Transplant. 2022 Dec;20(12):1049-1057.
Huimin Y, et al. Transplant Proc. 2025 Jun;57(5):777-783.
de Morais RH, et al. J Clin Ultrasound. 2003 Mar-Apr;31(3):135-41.