Brigham and Women's Hospital
Founding Member, Mass General Brigham

Late Loss of the Kidney Transplant

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Clinical Director, Kidney/Pancreas Transplant Program
Clinical focus: Onco-nephrology in transplant patients

DISCLOSURES

Clinical Trials activities :

- Alpine, Phase I/IIa Povetacicept in Primary IgA nephropathy, Membranous nephropathy
- Otsuka, Phase III Sibeprenlimab in Primary IgA nephropathy
- Alexion, atypical HUS global registry
- Natera, The Prospera Kidney Transplant ACTIVE Rejection Assessment registry (ProActive) study
- Novartis, Phase III Iprtacopan in adult atypical hemolytic uremic syndrome (aHUS) patients who are naïve to complement inhibitor therapy
-

How Late is “Late” Loss ?

Graft loss **1 year** after transplantation

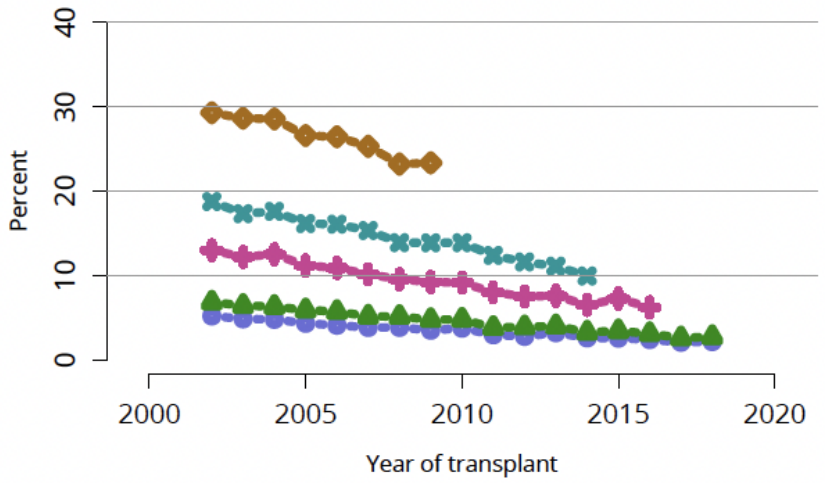
Intrinsic - “Graft Loss **without** Patient Death”

Extrinsic* - “Graft Loss **from** Patient Death”

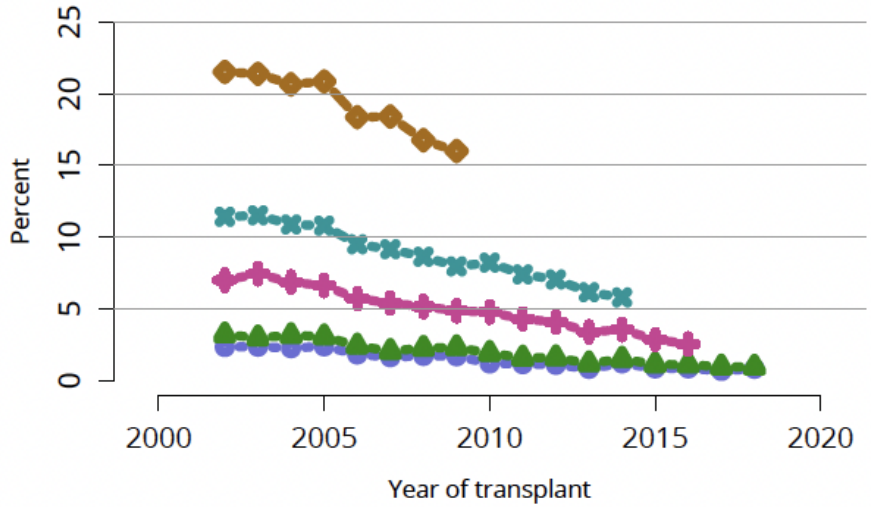
**Medical Complications in Late Post Transplantation will be discussed in a separate talk*

Most Allografts Fail “Late”

Deceased Donor, Death Censored



Living Donor, Death Censored

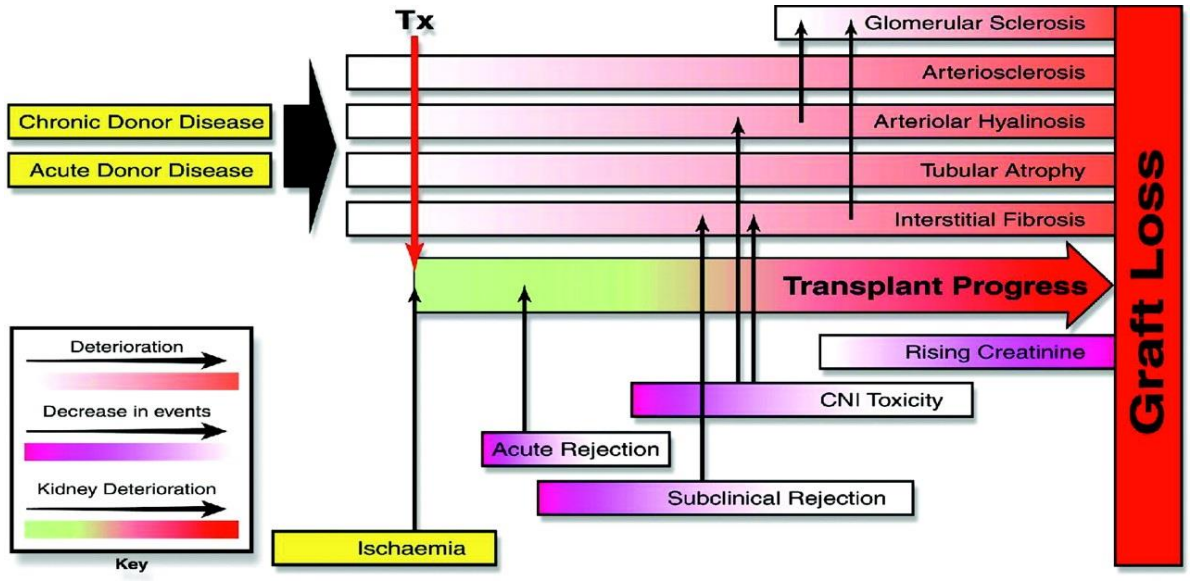


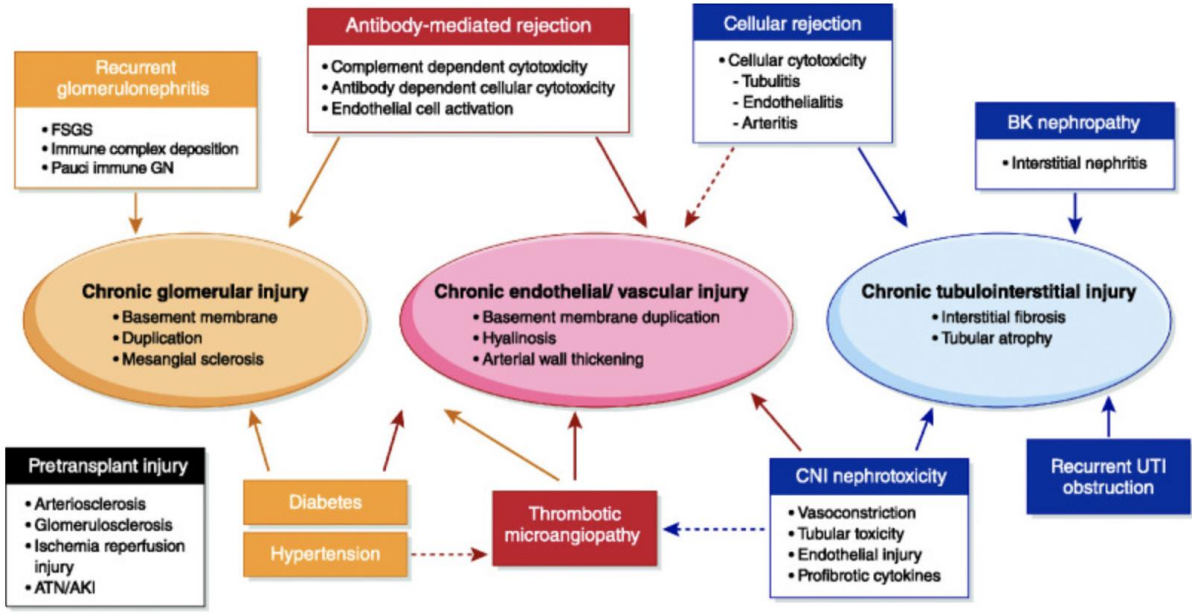
Allograft Survival Rate, All-Cause

At **1-year** post-transplant:	Over 95%
At **10-year** post-transplant:	50% of deceased donor grafts
	70% of living donor kidney grafts

Gaston et al., AJT 2018
Schold et al., AM J Trans 2020
USRDS 2015 Annual Data Report
OPTN/SRTR 2019 Kidney Annual Report

Allografts fail from multiple reasons





Chapman et al., JASN 2005
Langewisch et al., CJASN 2021
Viglietti et al, JASN , 2018; 29: 606-619

Allografts fail from multiple reasons

Pre-Transplant		Peri-Transplant	Post-Transplant	
Donor Factors	Recipient Factors		Non-immunologic	Immunologic
Donor Type	Age	HLA Matching	Death	Acute rejection
Donor Age	Underlying cause	Ischemia time	Infection	Chronic rejection
Cause of Death	Prior sensitization	Surgical complication	CNI Toxicity	Non-adherance
Donor disease	Vascular disease	Blood Type	Primary/De novo disease recurrence	
Nephron mass	Cardiac function	Size mismatch	Urologic issues	
	Genetics conditions		HTN	
	Primary disease		DM	

Chapman et al., JASN 2005
Langewisch et al., CJASN 2021
Viglietti et al, JASN , 2018; 29: 606-619

Question #1

The Kidney Donor Profile Index (KDPI) is a numerical measure that combines ten donor factors, including clinical parameters and demographics, to summarize into a single number the quality of deceased donor kidneys relative to other recovered kidneys. Which of the following is NOT a variable for KDPI.

A. Age
B. Race
C. Creatinine
D. HCV Status
E. Hx of Smoking

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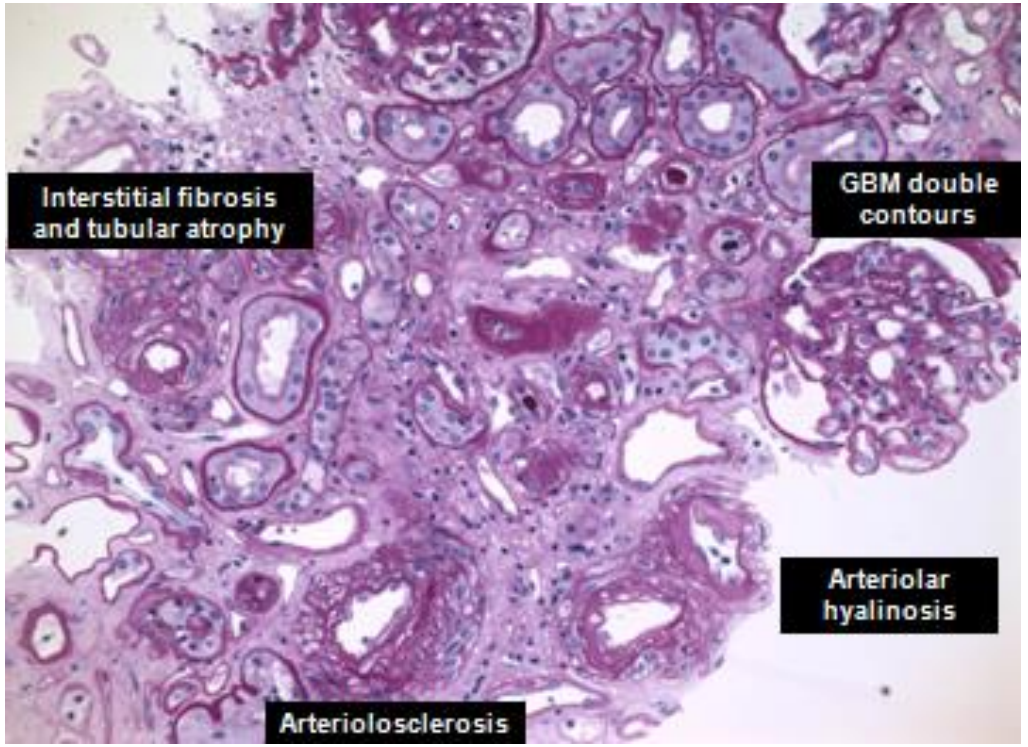
“Chronic Rejection,” Historical Perspective

[Banff, Canada on August, 1991]



“Chronic Allograft Nephropathy”

Question #2

What is the leading histopathological finding on for-cause biopsies performed after 1 year of transplantation?

A. Calcineurin Inhibitor Toxicity
B. BK Virus Nephropathy
C. Antibody-mediated rejection
D. Recurrence of original disease
E. T-cell mediated rejection

Question #2

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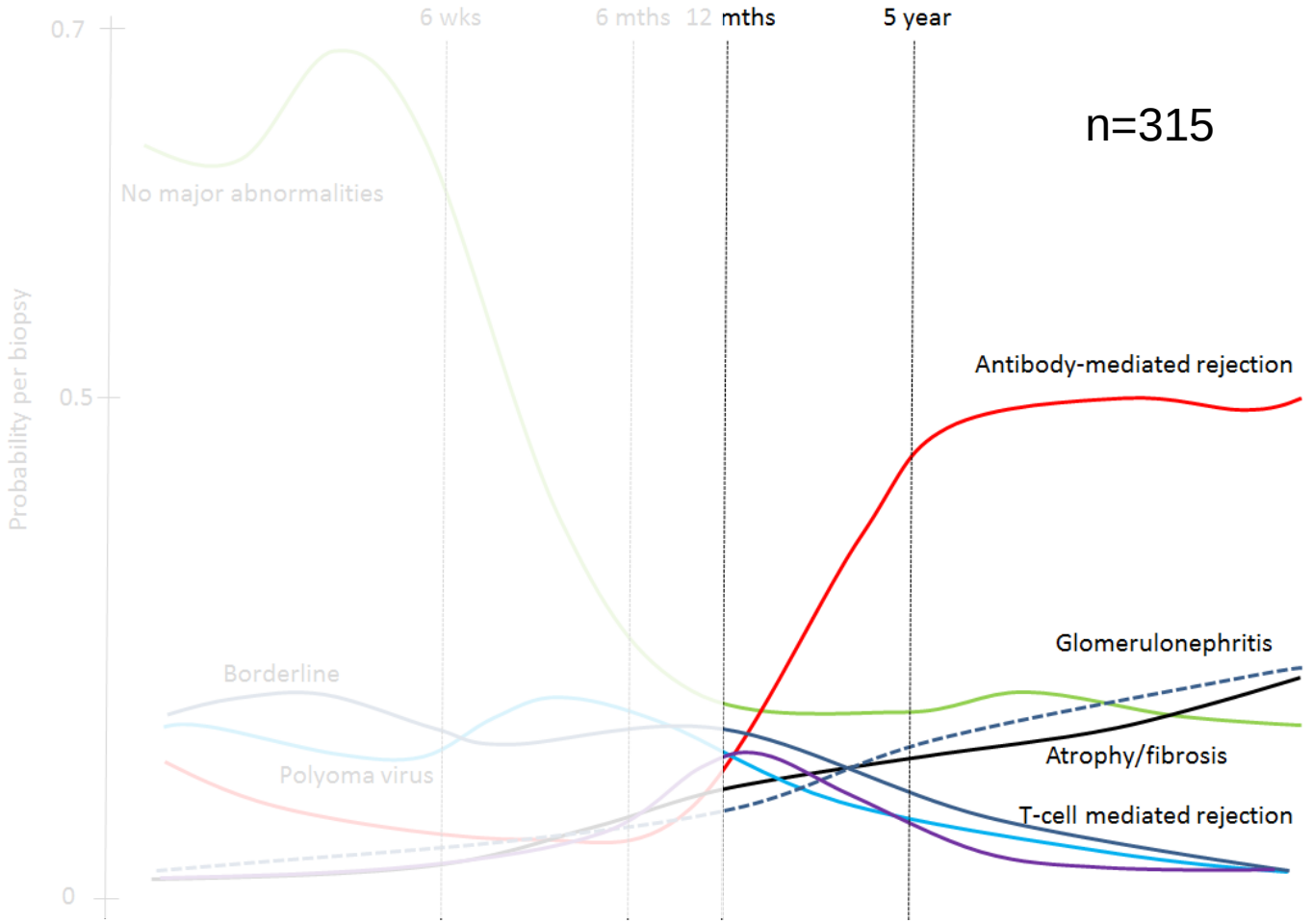
ABMR is a leading histopathological finding after 1 year



Sellarés et al, *American Journal of Transplantation 2012*

Dignostic Criteria for AMR/MVI

(1) histologic evidence of AMR activity/chronicity

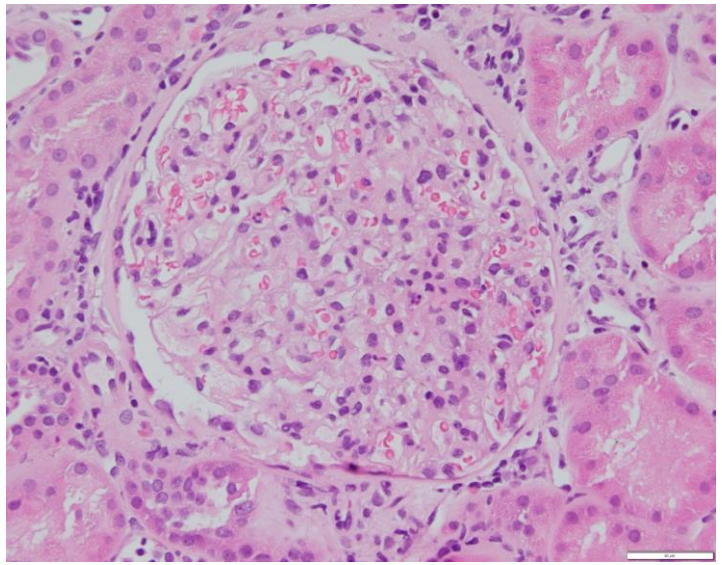
(2) evidence of antibody interaction with the donor endothelium

(3) serologic evidence of donor-specific antibodies (DSA).

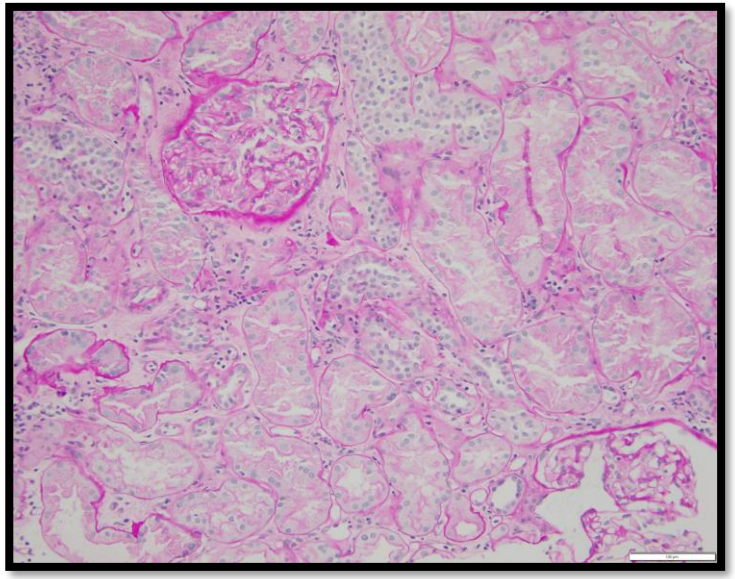
Histopathological finidings of AMR/MVI

g+ptc (MVI)>=2

Glomerulitis (g)

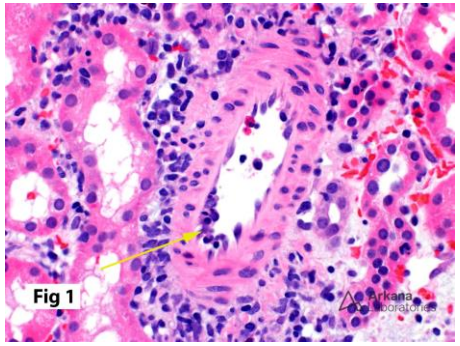


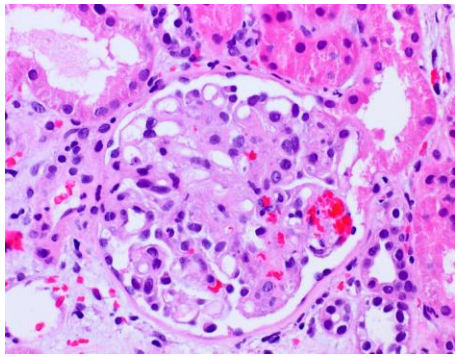
Peritubular Capillaritis (ptc)



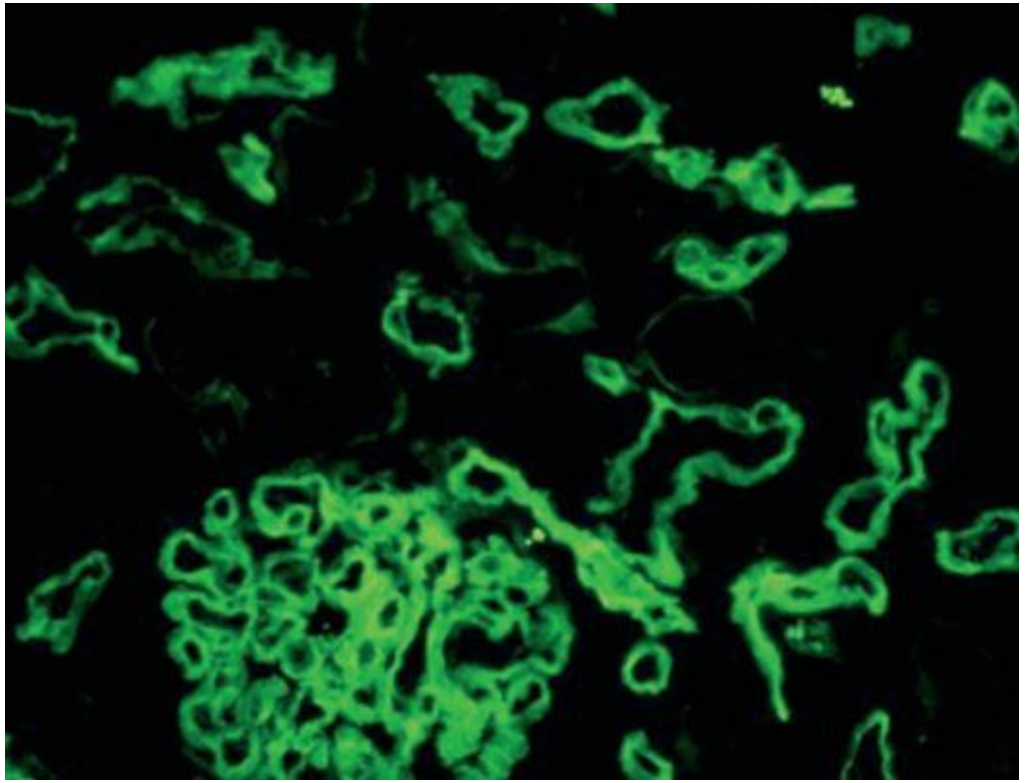
Courtesy of BWH Renal Pathology Team

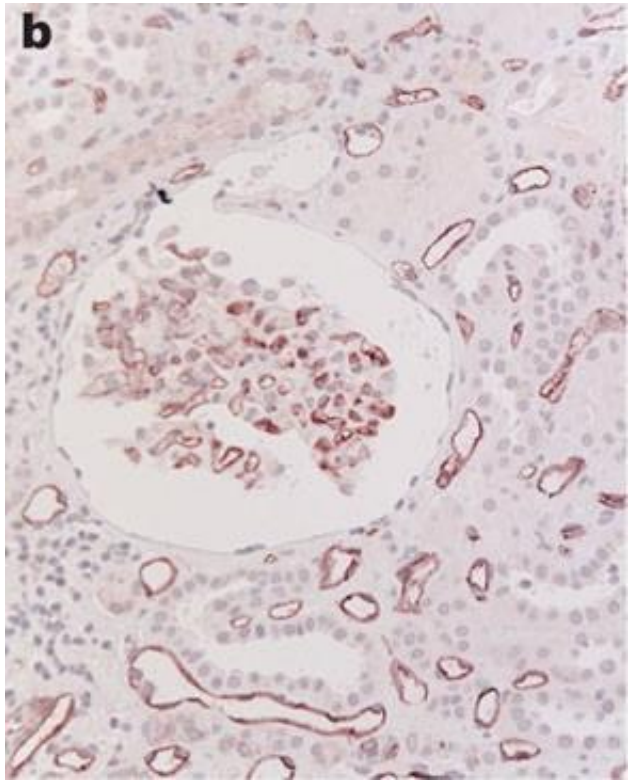
v>0 or TMA also considered as a diagnostic criteria





Evidence of Antibody interaction – Linear C4d deposition

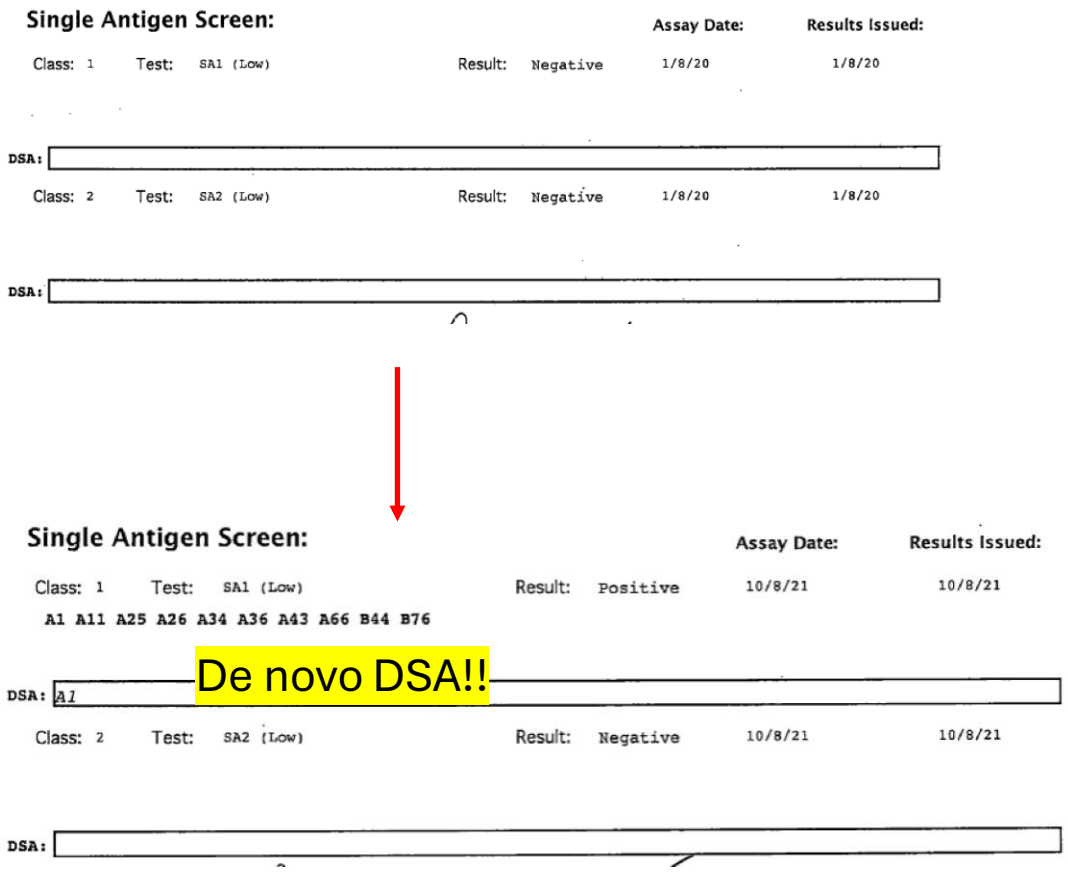




[Colvin et al Nat Rev Immunol 2005]

Serologic evidence of Donor-Specific Antibody

*refer to lectures from Drs. Yeung and Gulera regarding antibody screening



Presence of Non-HLA Abs such as

Anti-ABO Ab

MICA-Ab

Angiotensin II receptor Type 1-Ab

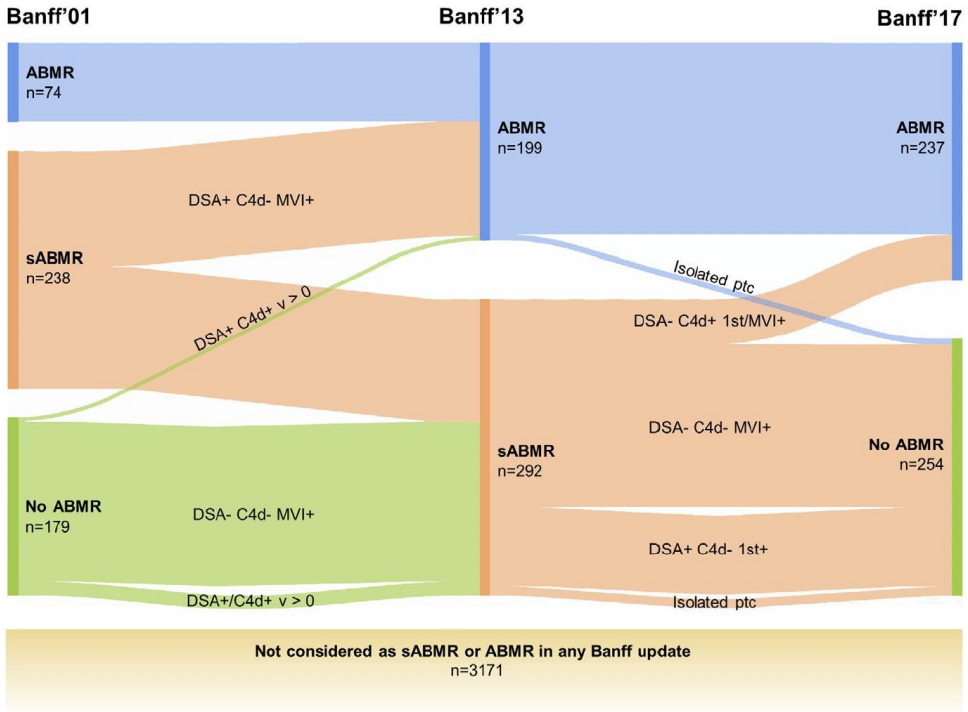
Endothelin Receptor-1 Type A-Ab

Also qualifies as the DSA criteria

“ABMR” is a spectrum of heterogeneous clinic-pathologic diagnosis that continuously evolves

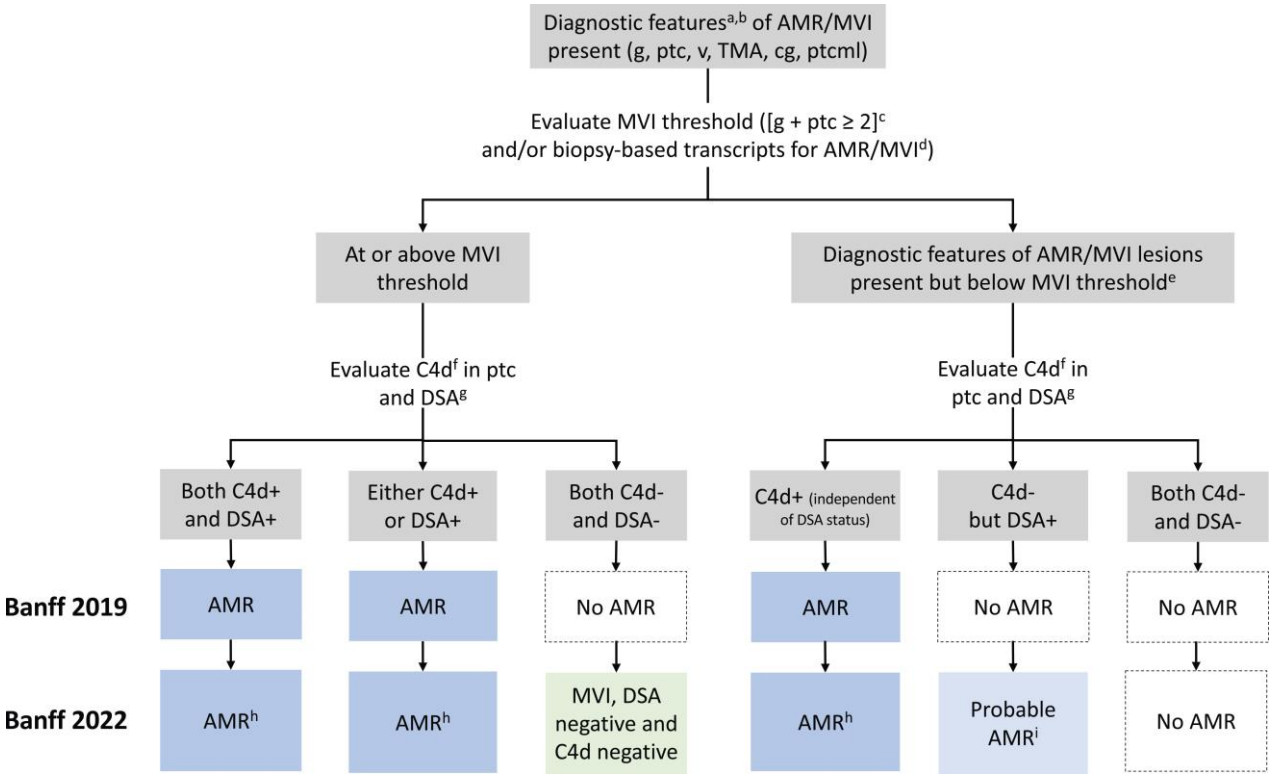
ABMR continuum

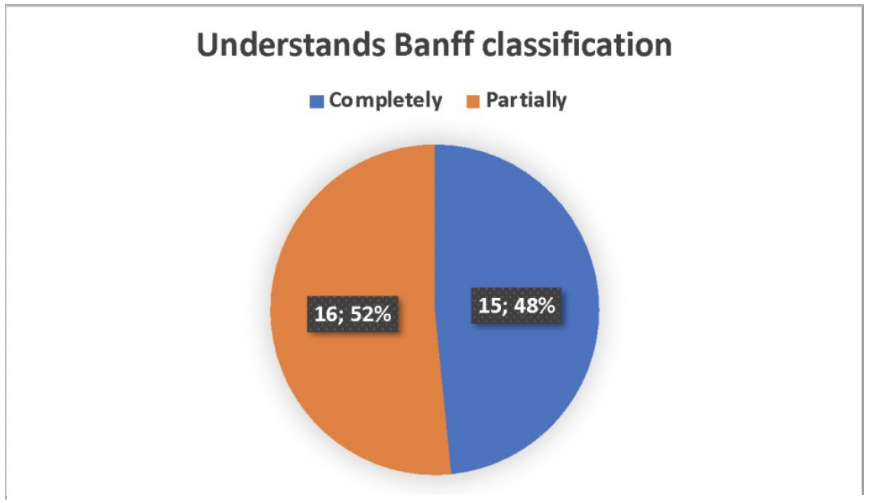
	Early acute ABMR (+XM)	Acute ABMR	Active (smoldering) ABMR	Chronic active ABMR
Clinical setting	Clinically apparent: AKI, <1 month post-transplant	Usually clinically apparent: AKI	Subclinical	Subclinical or clinically apparent: Progressive renal insufficiency, proteinuria, hypertension
Histology	ATN, thrombi, mild capillaritis, v lesions	ATN, thrombi, capillaritis, v lesions	Capillaritis only (g, ptc)	Capillaritis and TG, TA, or PTCBMML
C4d	Diffuse +	+	Negative, focal +, occasionally diffuse +	Negative, focal +, occasionally diffuse +
Serum DSA	High	High	Low, mid	Low, mid



Cornell Front in Immunol . 2021
Callemeyn et al., AJT. 2020

Banff 2022 Classification for Antibody-mediated rejection and microvascular inflammatory/injury (AMR/MVI)



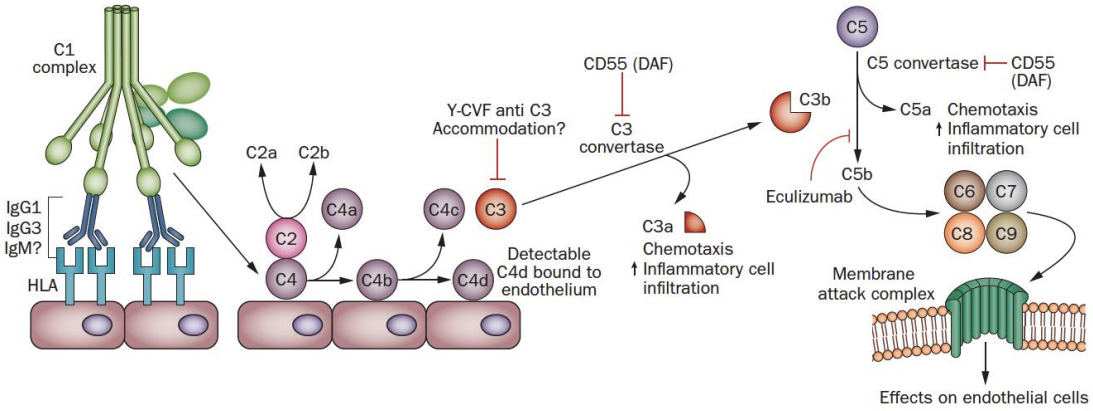


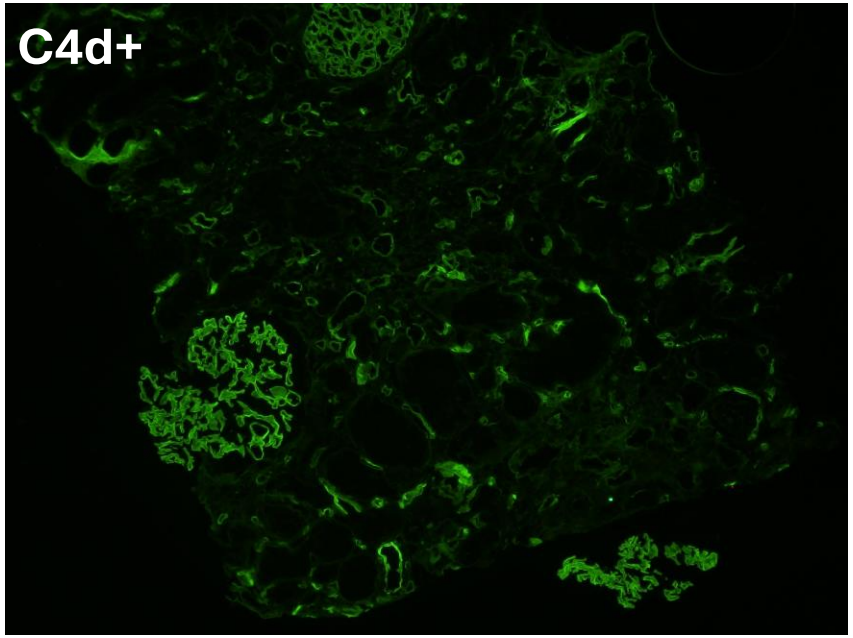
"The banff classification is changing too often" - From 2022,

Banff "Working" Group

[Nasesen et al., AJT 2024]

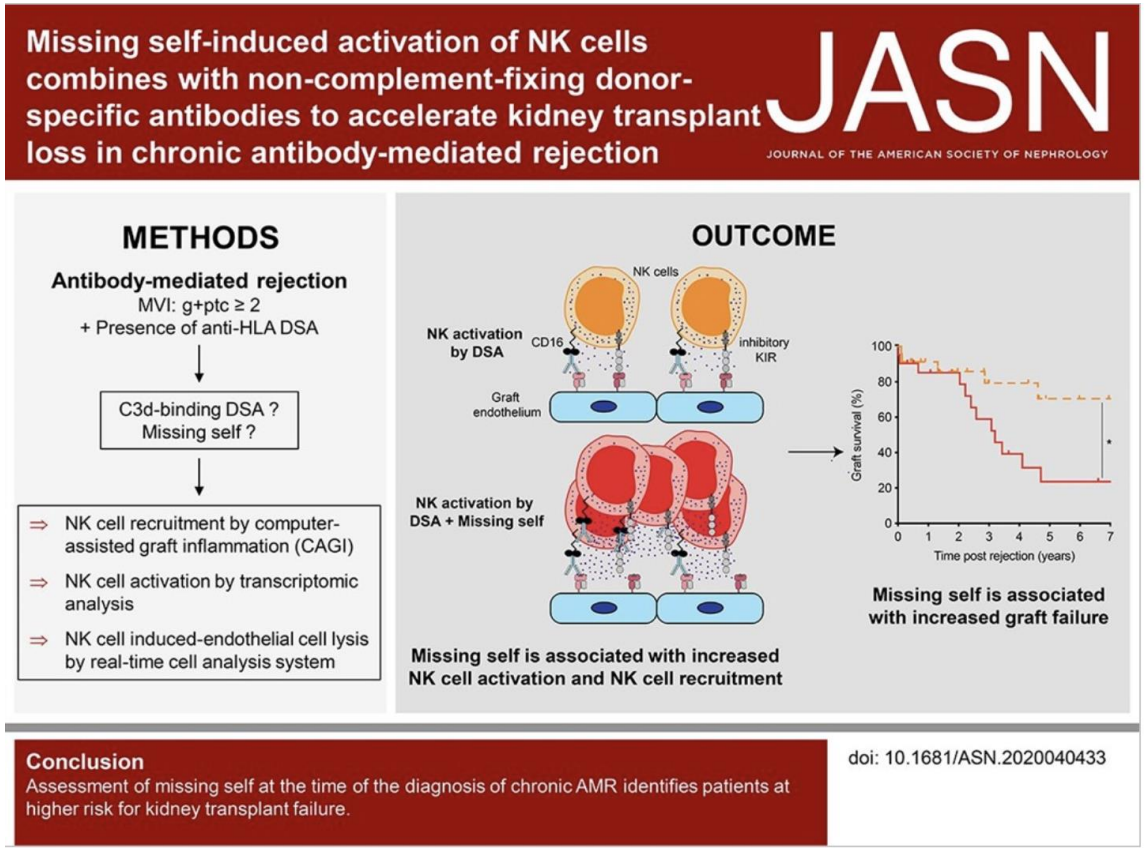
Mechanism: DSA+C4d+ AMR Role of complement (MAC)

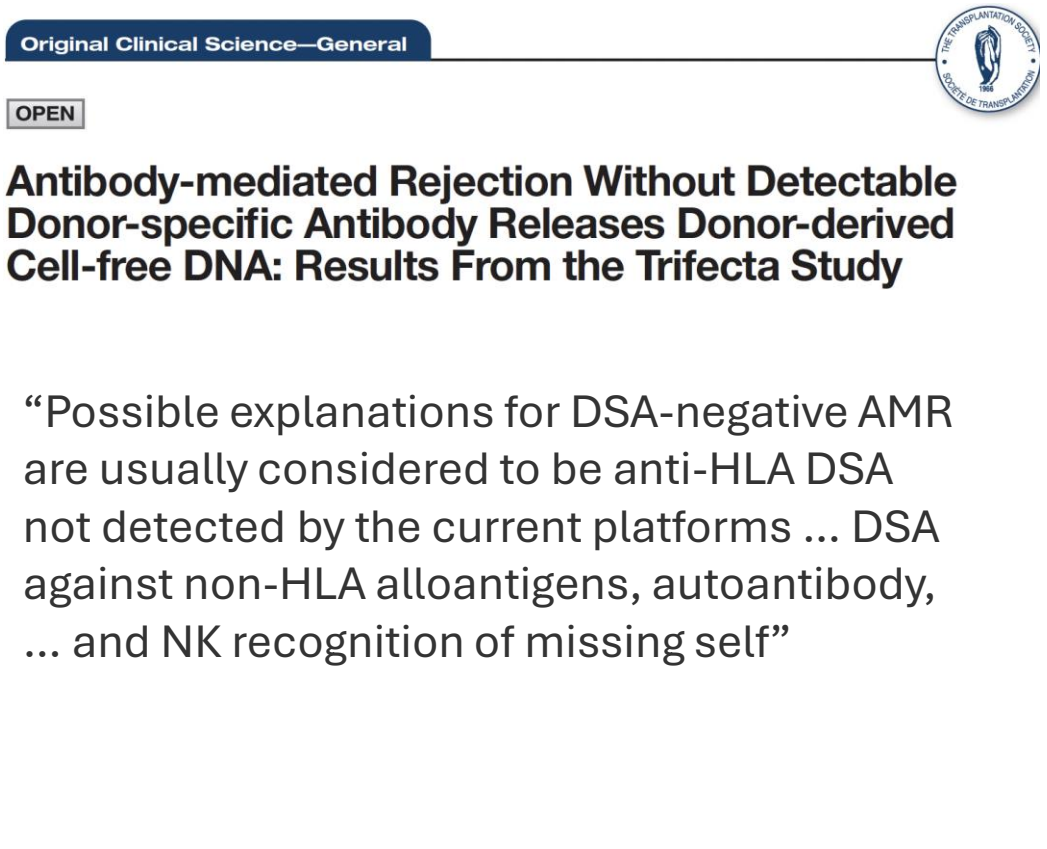




Stegall et al., Nat Review Nph 2012

Mechanism: AMR C4d- and/or DSA- NK Cells



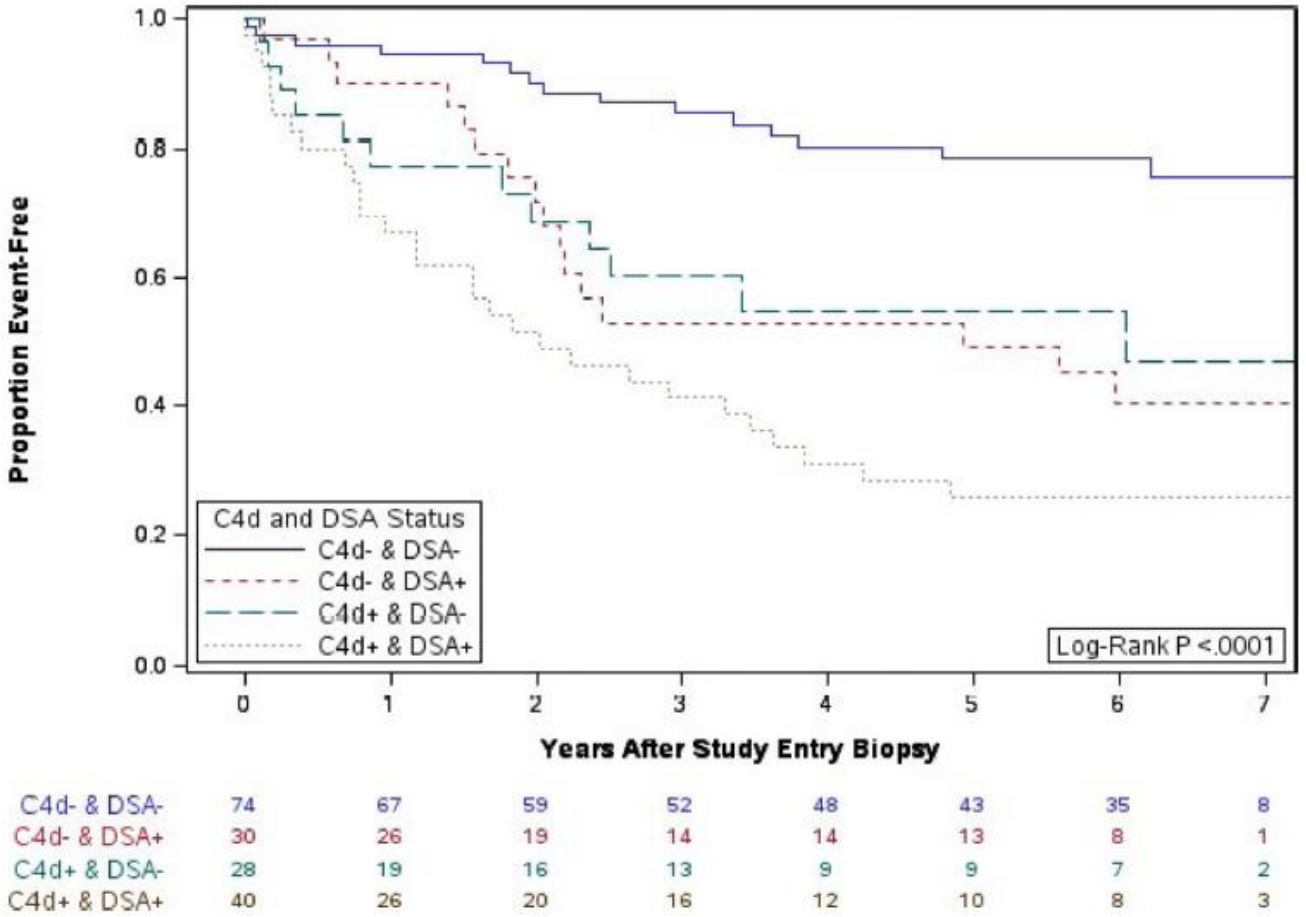


"Possible explanations for DSA-negative AMR are usually considered to be anti-HLA DSA not detected by the current platforms … DSA against non-HLA alloantigens, autoantibody, … and NK recognition of missing self"

[Schrezenmeier et al., NEJM 2024]

C4d and DSA are both strong prognostic variables

After index biopsy



C4d- & DSA-	74	67	59	52	48	43	35	8
C4d- & DSA+	30	26	19	14	14	13	8	1
C4d+ & DSA-	28	19	16	13	9	9	7	2
C4d+ & DSA+	40	26	20	16	12	10	8	3

Matas et al, *American Journal of Transplantation 2019; 19: 1432-1443*

Treatment of AMR, Consensus 2019

[Less likely to be asked on Board Exam..]

Plasma Pheresis (PLEX)/IVIG

Corticosteroid

+

Adjunctive Therapy

- Anti CD20 Ab
- IgG-degrading enzyme
- Proteosome Inhibitor
- Complement inhibitors
- Cyclophosphamide
- Antithymocyte Globulin
- Splenectomy

Treatment of AMR >30 days posttransplant

DSA	Histology (Banff 2017)	Standard of care[a]	Consider adjunctive therapies
Preexisting DSA	Active AMR	Plasmapheresis (daily or alternative day × 4–6 based on DSA titer) (2C)[b] IVIG 100 mg/kg after each plasmapheresis treatment or IVIG 2 g/kg at end of plasmapheresis treatments (2C) Corticosteroids (EO)	Rituximab 375 mg/m^2 (2B)
	Chronic AMR	Optimize baseline immunosuppression (eg, add steroids if on a steroid-free regimen) (1C)	IVIG (3C)
De novo DSA	Active AMR	Optimize baseline immunosuppression (eg, add steroids if on a steroid-free regimen) (1C) Evaluate and manage nonadherence	Plasmapheresis and IVIG (3C) Rituximab (3C)
	Chronic AMR		IVIG (3C)

Schinstock et al., Transplantation 2020

Emerging therapeutic target in AMR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

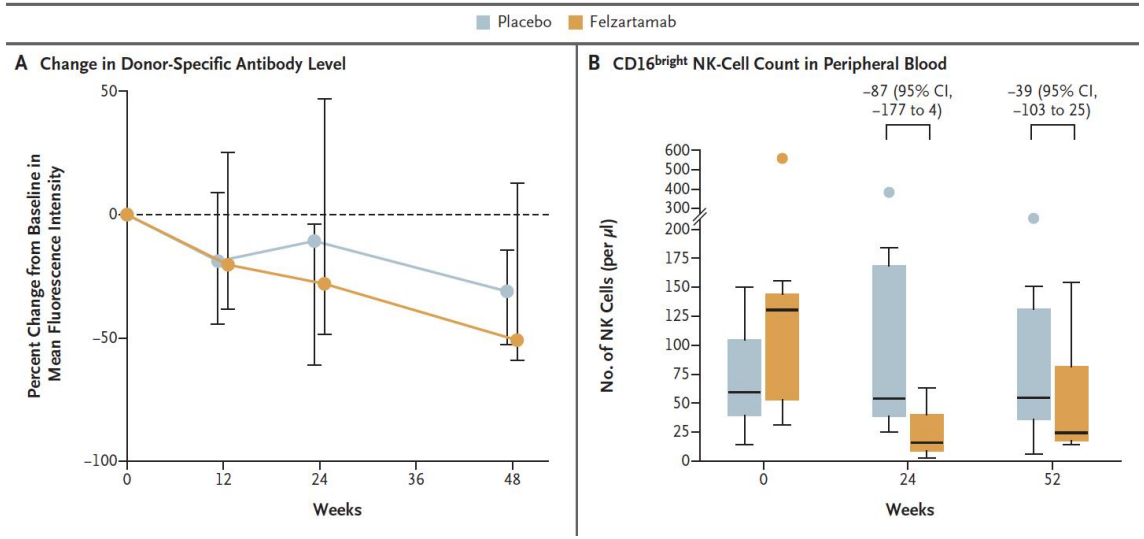
A Randomized Phase 2 Trial of Felzartamab in Antibody-Mediated Rejection

K.A. Mayer, E. Schrezenmeier, M. Diebold, P.F. Halloran, M. Schatzl, S. Schranz, S. Haindl, S. Kasbohm, A. Kainz, F. Eskandary, K. Doberer, U.D. Patel, J.S. Dudani, H. Regele, N. Kozakowski, J. Kläger, R. Boxhammer, K. Amann, E. Puchhammer-Stöckl, H. Vietzen, J. Beck, E. Schütz, A. Akifova, C. Firbas, H.N. Gilbert, B. Osmanodja, F. Halleck, B. Jilma, K. Budde, and G.A. Böhmig

ABSTRACT

BACKGROUND

Antibody-mediated rejection is a leading cause of kidney-transplant failure. The targeting of CD38 to inhibit graft injury caused by alloantibodies and natural killer (NK) cells may be a therapeutic option.



Question #3

A 26 year-old female with PMHx of ESRD status post deceased donor transplant in 2016 at age of 15, presenting for a follow up. Last known Creatinine was 1.1 (6-months prior). She takes Tacrolimus 4mg twice a day (Goal 6-8), Mycophenolate Mofetil 500mg Twice a day, which has not been changed for few years. After the clinic visit, her creatinine was found to be in 1.8 concern for late allograft dysfunction.
You proceed with the kidney allograft biopsy, which shows **chronic active AMR**

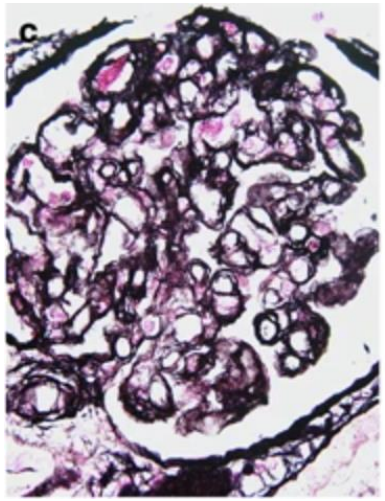
What is the leading cause of de-novo donor-specific antibody development as well as the poorest prognostic marker for the allograft survival

A. HLA mismatch
B. Medication Nonadherence
C. Previous T cell mediated rejection
D. T-cell mediated rejection

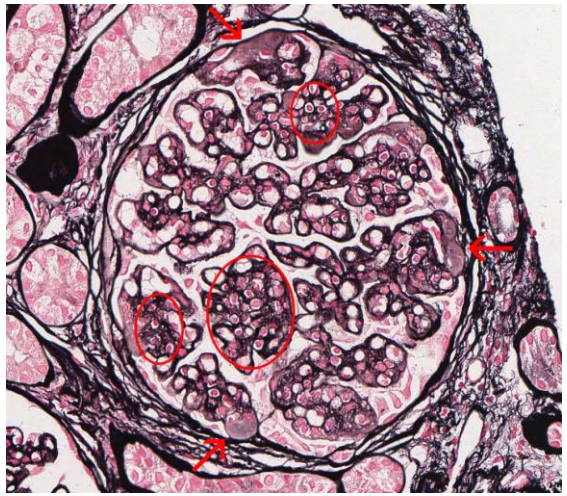
Chronic active AMR
Transplant Glomerulopathy

Reduplication/multi-lammination of GBM. Absence of immune deposits.
Poor Prognosis: HR: 3.7.
Consequence of long-term endothelial injury: Allo/auto-antibody, Hep C, NK cell, etc…

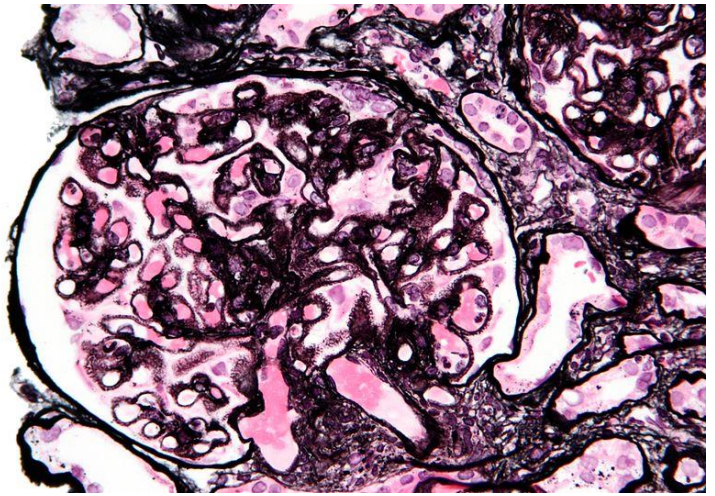
TG



MPGN: Double contour +Hypercelluarity

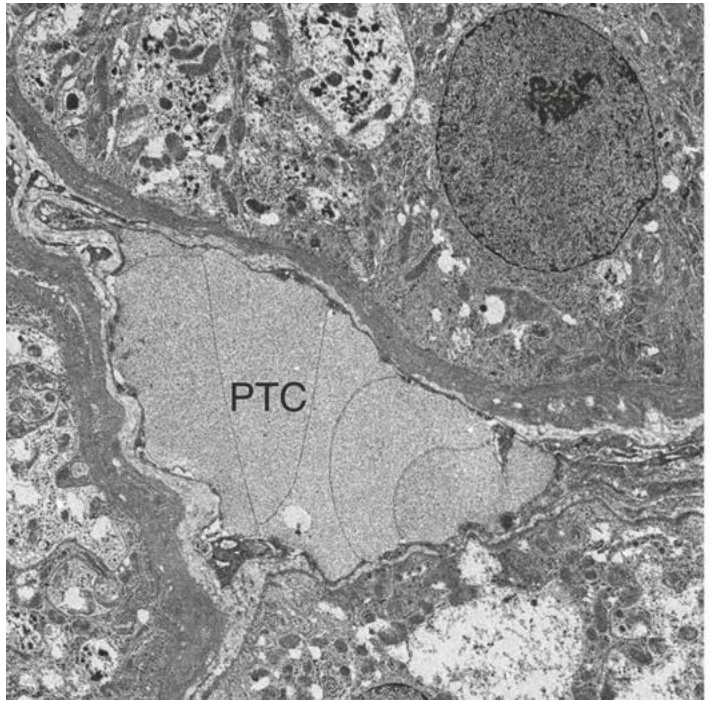


Membranous “Spikes”

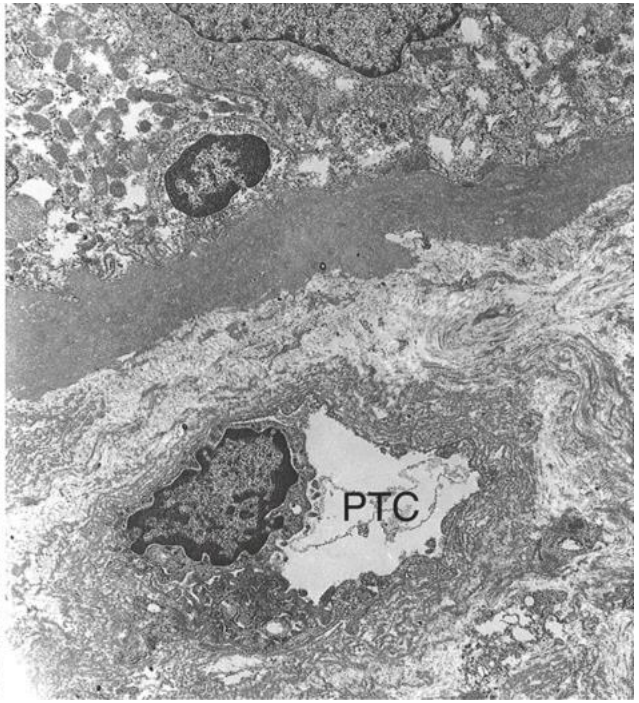


Chronic active AMR

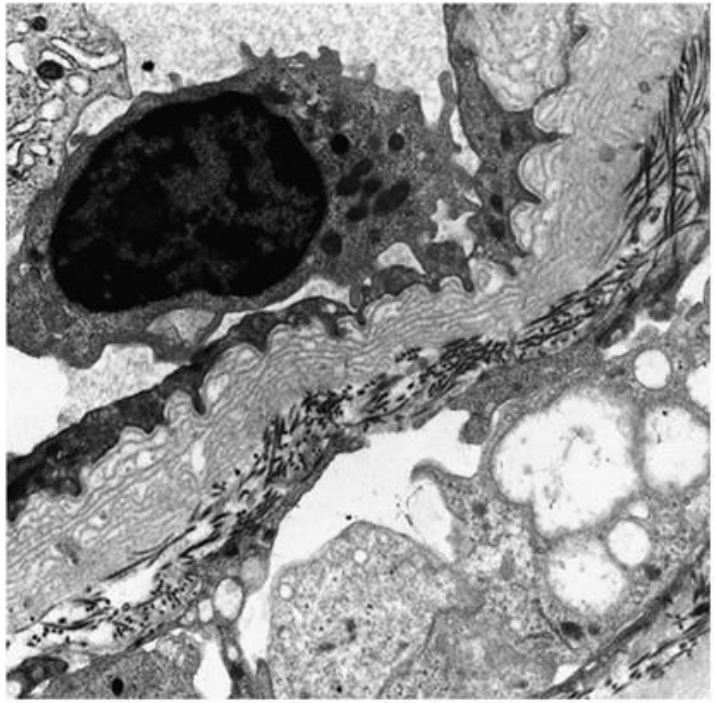
Peritubular basement membrane membrane multilayering



normal PTC



multilamellation of the basal lamina



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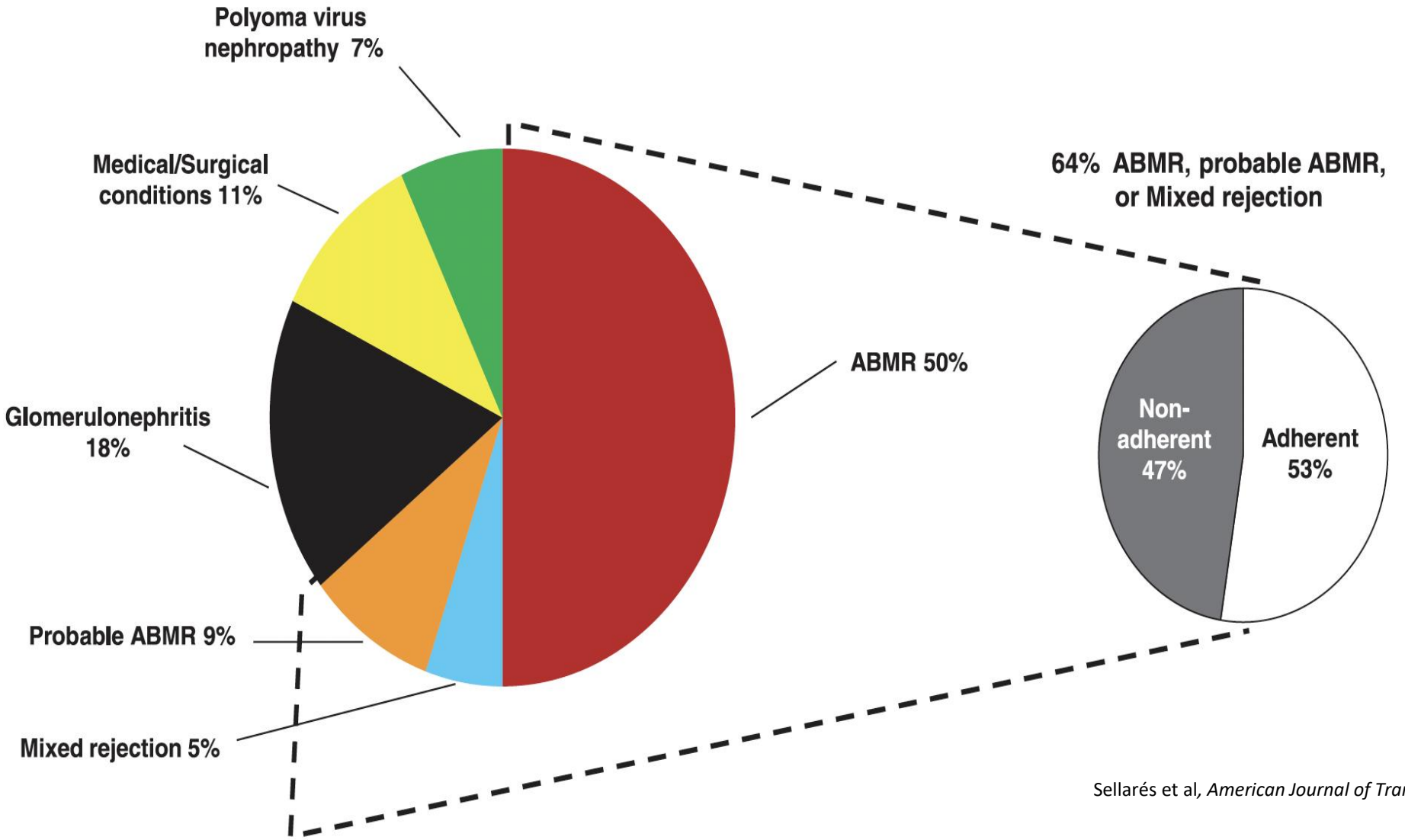
Attributed causes of graft failure



Sellarés et al, *American Journal of Transplantation 2012*

Case Study

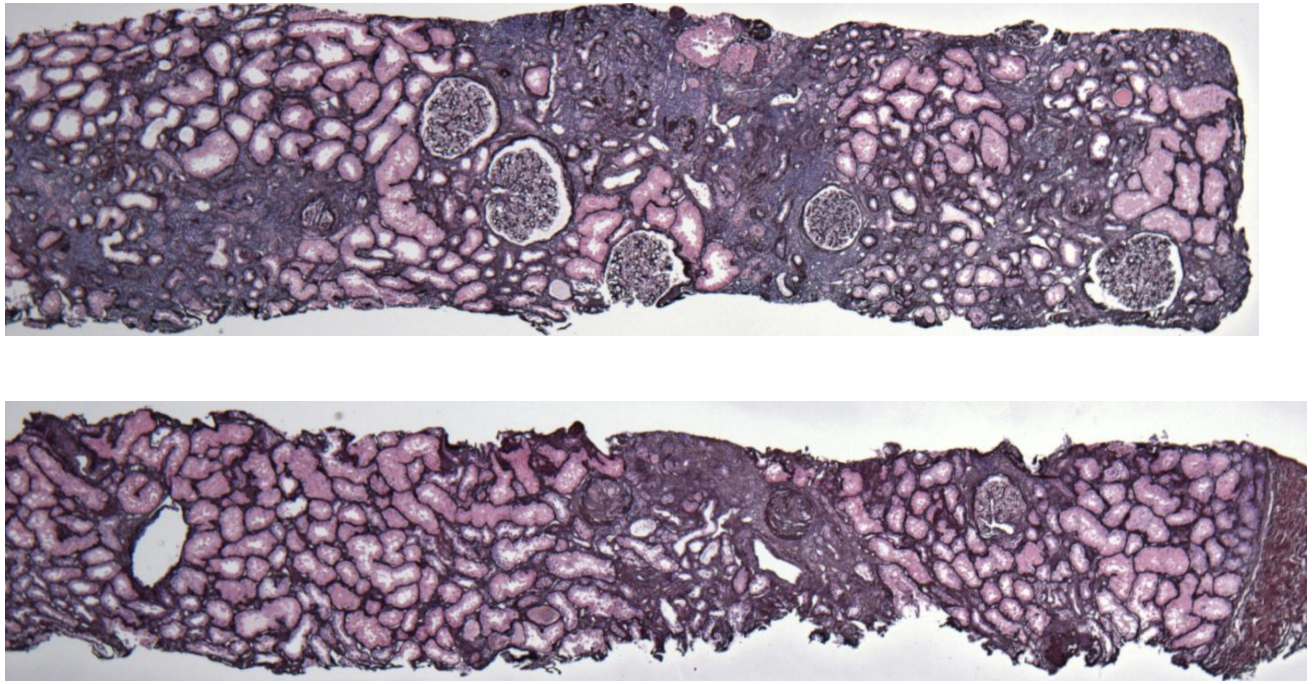
A 50 year-old woman originally from Jamaica with ESRD 2/2 collapsing glomerulopathy and immune-complex GN s/p DDKT (2016 April) complicated by slow graft function/prolonged delayed graft function (Cr 2.7 after 1 month).

Her immunosuppression is Tacrolimus 8mg BID (Goal 8-10), MMF 360mg QID, Prednisone 5mg QD
Biopsy Performed.

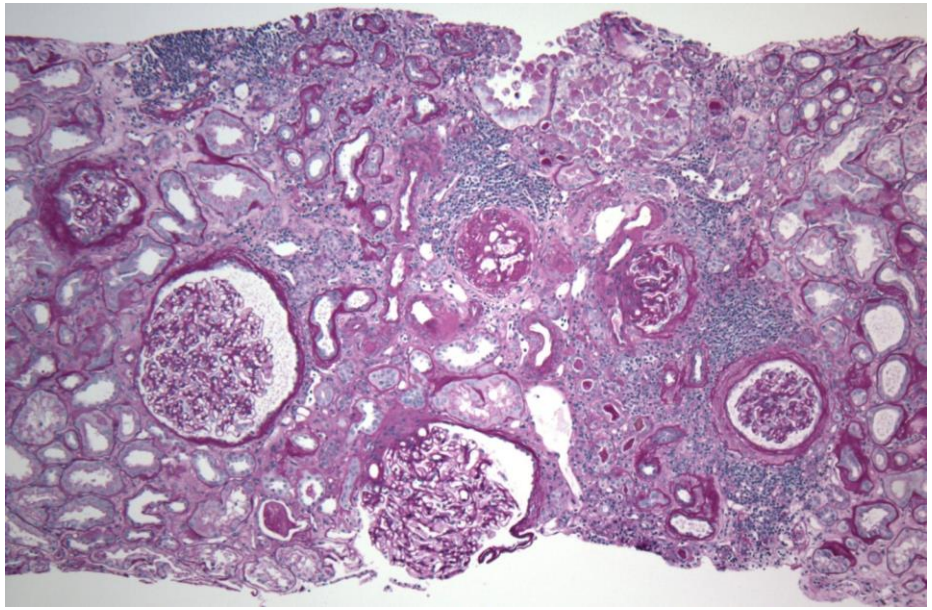
Donor Characteristics:
52 year Old, Male. Cardiac Arrest down time 2 minutes, CPR 40minutes
Height: 5’9” BMI:29
PMHx of Sarcoidosis, no HTN/DM
No IVDU, No Smoking
KDPI: 45%

Biopsy (2016) 40 Days post-transplantation

Jones' (Silver) Stain



PAS



Courtesy of BWH Renal Pathology Team

Biopsy report: 40 Days post-transplantation

ALLOGRAFT WITHOUT SIGNS OF ACTIVE REJECTION;
- THERE ARE NO SIGNS OF INTERSTITIAL INFLAMMATION, TUBULITIS, OR ENDOTHELIALITIS (i0 t0 v0)
- THERE ARE NO SIGNS OF ACTIVE GLOMERULITIS, PERITUBULAR CAPILLARITIS, AND THE STAINING FOR C4d IS NEGATIVE ALONG PERITUBULAR CAPILLARIES (g0 ptc0 C4d0)

MODERATELY ADVANCED CHRONIC CHANGES OF THE PARENCHYMA, MOST LIKELY REPRESENTING DONOR-RELATED DISEASE (SEE BELOW)

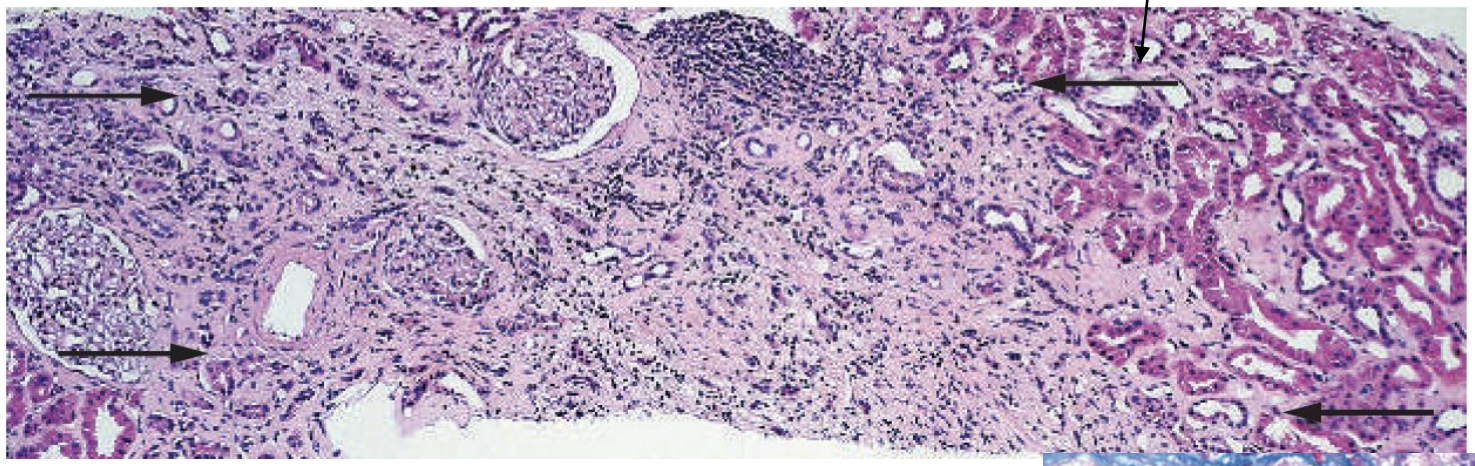
MILD DISTENTION OF THE TUBULES ASSOCIATED WITH MILD TUBULAR INJURY

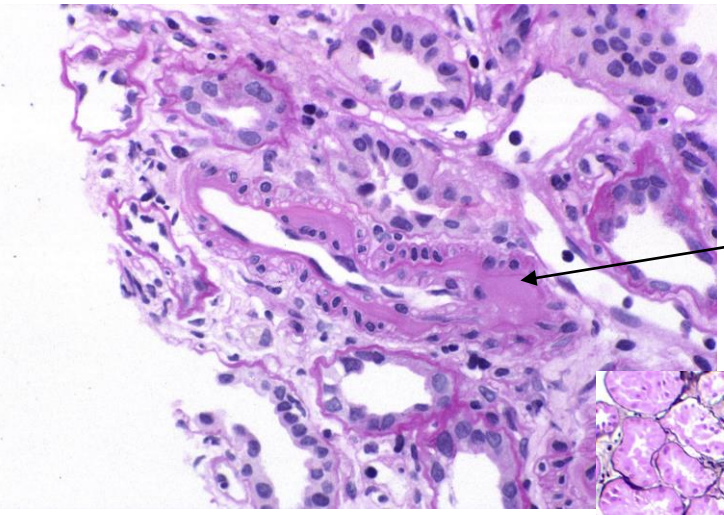
MODERATELY ADVANCED CHRONIC CHANGES OF THE PARENCHYMA, INCLUDING:
- FOCAL GLOBAL GLOMERULOSCLEROSIS AND SIGNS OF GLOMERULAR HYPOPERFUSION (42% OF GLOMERULI)
- MARKED GLOMERULAR HYPERTROPHY AND MODERATELY SEVERE THICKENING OF THE GLOMERULAR BASEMENT MEMBRANES
- FEW GLOMERULAR CAPILLARIES SHOW SIGNS OF ENDOTHELIAL INJURY AND CAPILLARY WALL REMODELING
- FOCAL TUBULAR ATROPHY AND INTERSTITIAL FIBROSIS (40-50% OF THE CORTEX)
- SEVERE ARTERIAL AND ARTERIOLAR SCLEROSIS (ci2 ct2 cv2 cg1 mm2 ah1)

CNI Toxicity (Acute and Chronic)

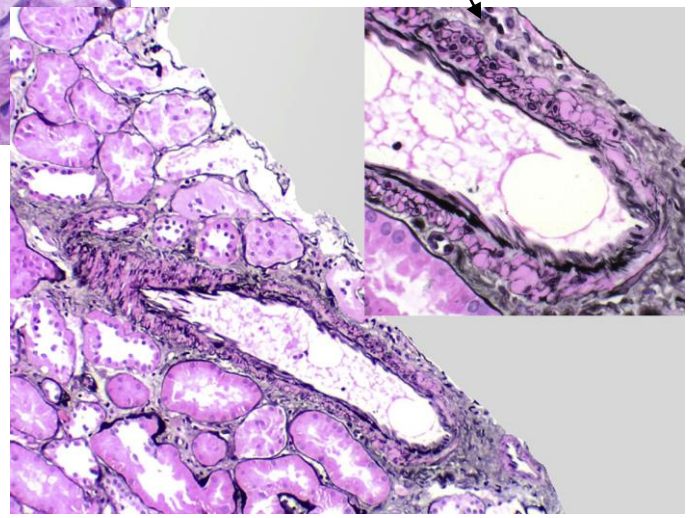
Risk Factors
↑Donor Age
↑Arteriosclerosis (@0time biopsy)
↑ *CYP3A5*3/*3a "slow metabolizer"*

Interstitial Fibrosis and Tubular Atrophy in a band-like "striped" pattern

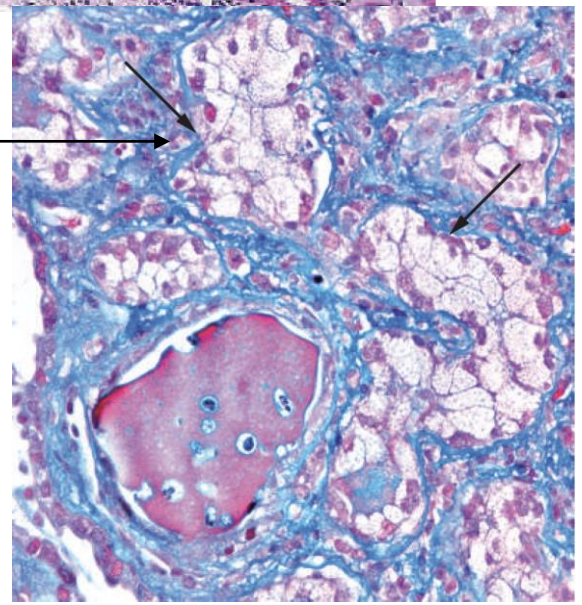




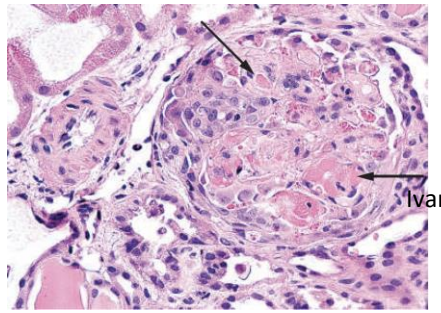
Nodular hyalinosis arteriolopathy



Isometric Vacuolization of Proximal Tubules (Acute)



Glom: Capillary swelling or shrinking, psuedo-thrombi ->FSGS/GGS



Ivanyi et al, Nature Clinical Practice Nephrology *2006; 2:398-402*
Lusco et al., AJKD 2017
Xia et al., Drug Des Devel Ther. 2018

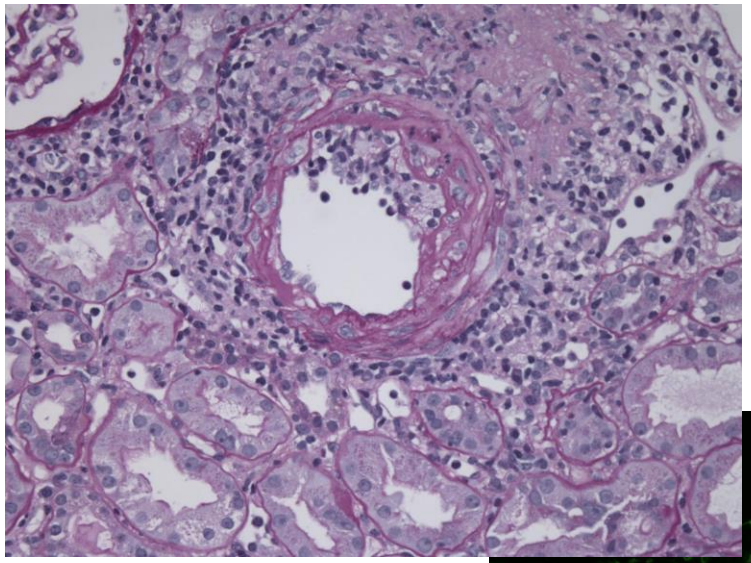
Case -Continued

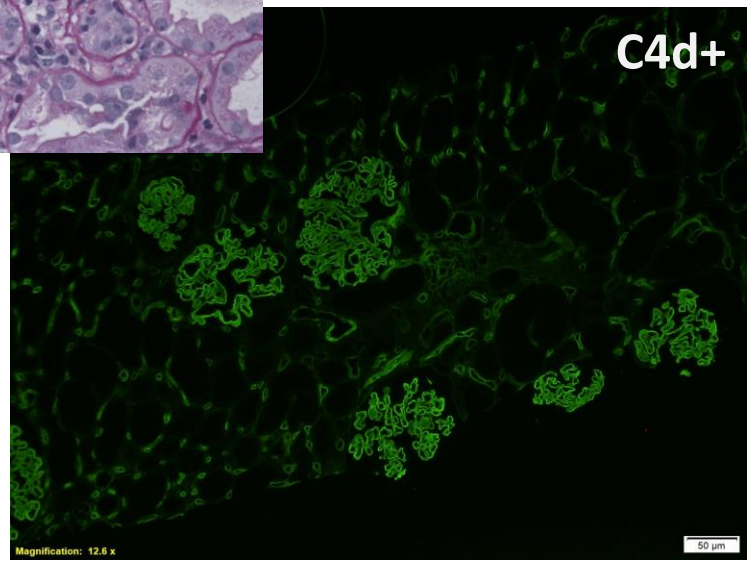
A 50 year-old woman originally from Jamaica with ESRD 2/2 collapsing glomerulopathy and immune-complex GN s/p DDKT (2016 April) complicated by slow Graft Function (Cr 2.7 after 1 month). Biopsy showed moderate degree of donor-related chronic changes and arteriolar sclerosis for which the immunosuppression was switched to CTLA4-Ig (Belatacept) with slow taper of Tacro (over the next 6 months). By September 2016 (5-month post tx) her Cr improved to 1.6.

One month later, she developed mild discomfort in the area of her transplanted kidney.
Her creatinine increased from 1.6->2.51->3.34. Biopsy was performed.

What do you think is happening?

Biopsy #2 (Oct 2016, 6-month Post Tx)





ACUTE VASCULAR ALLOGRAFT REJECTION, BANFF TYPE IIA-B, WITH MODERATE VASCULITIS AND SEVERE INTERSTITIAL INFLAMMATION AND TUBULITIS (t3 i3 v2)

ACUTE ANTIBODY-MEDIATED ALLOGRAFT REJECTION, WITH DIFFUSELY POSITIVE C4d STAIN IN PERITUBULAR CAPILLARIES BY IMMUNOFLUORESCENCE MICROSCOPY TECHNIQUE (g0 ptc1-2 c4d3 cg0-1)

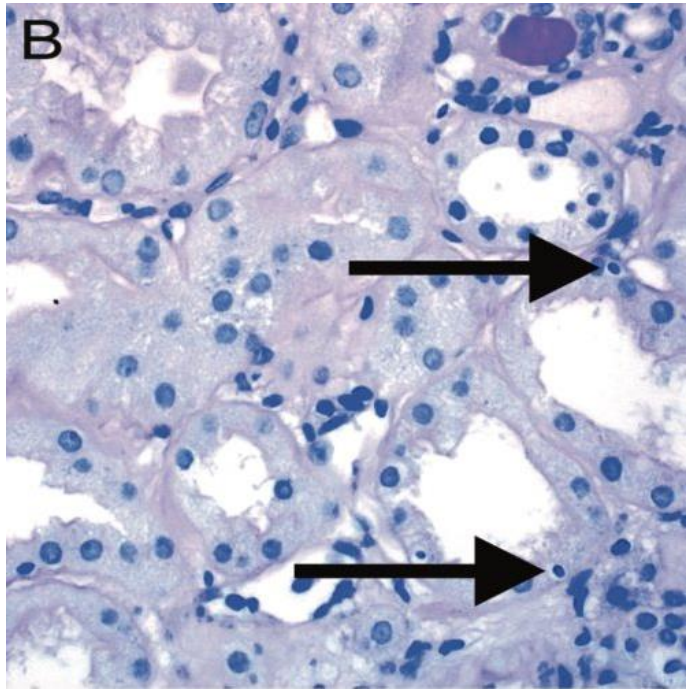
MILD CHRONIC CHANGES OF THE PARENCHYMA, INCLUDING:
- GLOBAL GLOMERULOSCLEROSIS (10% OF GLOMERULI)
- TUBULAR ATROPHY AND INTERSTITIAL FIBROSIS (20% OF CORTEX)
- NO SIGNIFICANT ARTERIAL AND ARTERIOLAR SCLEROSIS (cg0-1 mm0 ct1 ci1 cv0 ah0)

Courtesy of BWH Renal Pathology Team: Dr. Rennke and Dr. Weinstein

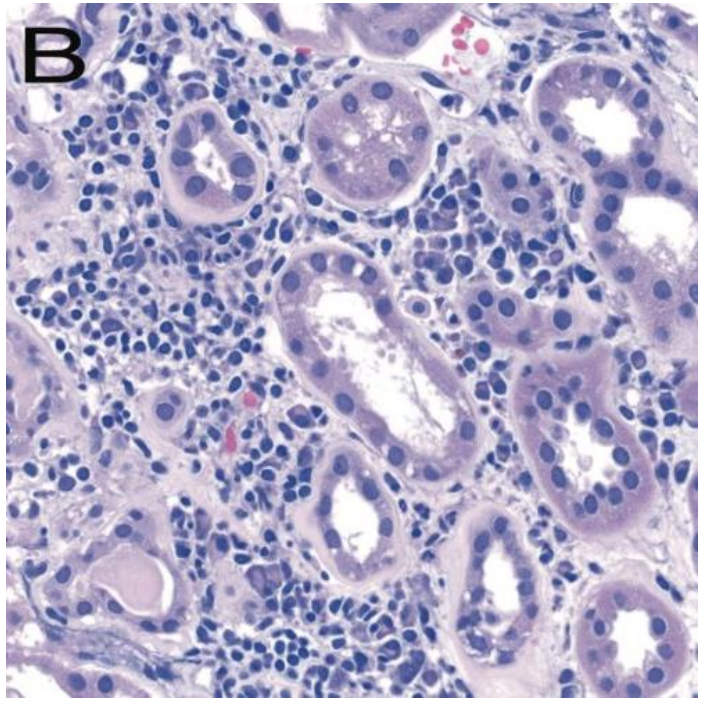
Acute T-Cell mediated rejection (TCMR)

**note this patient had mix of TCMR and AMR*

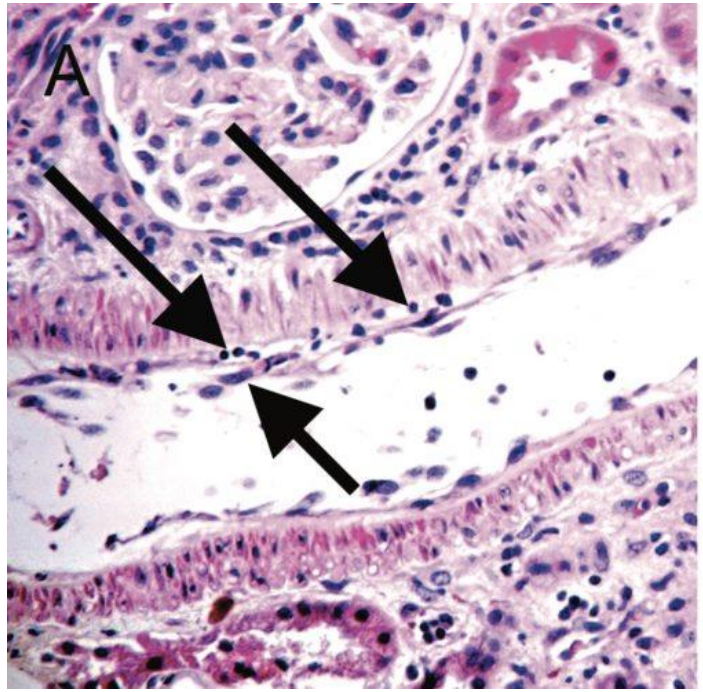
Tubulitis (t)



Interstitial inflammation (i)

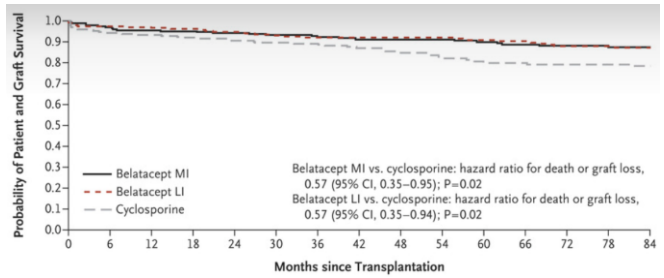


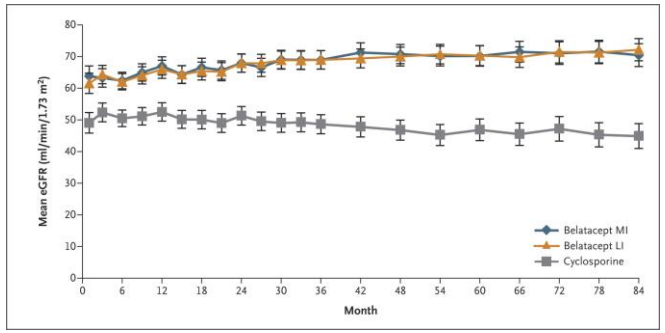
Intimal arteritis (v)

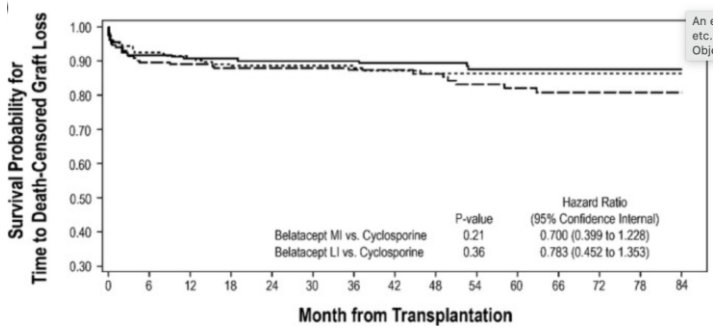


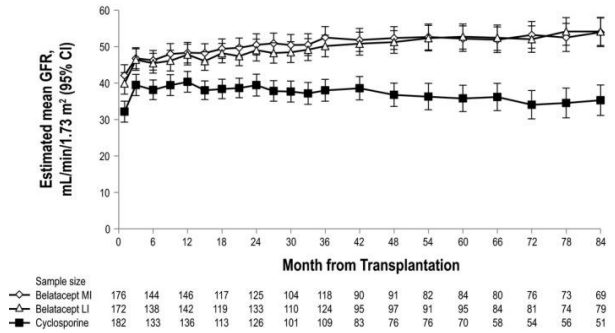
CTLA4-Ig (Belatacept) vs CNI (Cyclosporine)

BENEFIT (Standard Criteria Donor)	BENEFIT-EXT (Extended/High risk Criteria Donors)
Sustained, improved eGFR **Lower incidence of de-novo DSA development** **Improved metabolic and Cardiac profile** **Increased incidence of PTLD (EBV- recipient, <24mos)**	
Improved patient and allograft survival (composite) Increase episode of acute rejection	No difference in patient/allograft survival No difference in episode of acute rejection



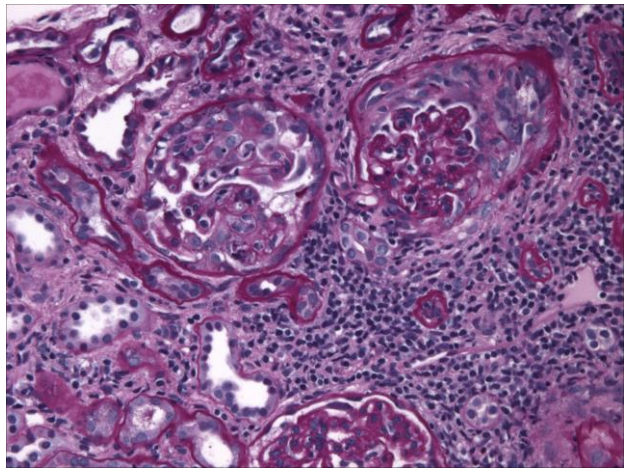


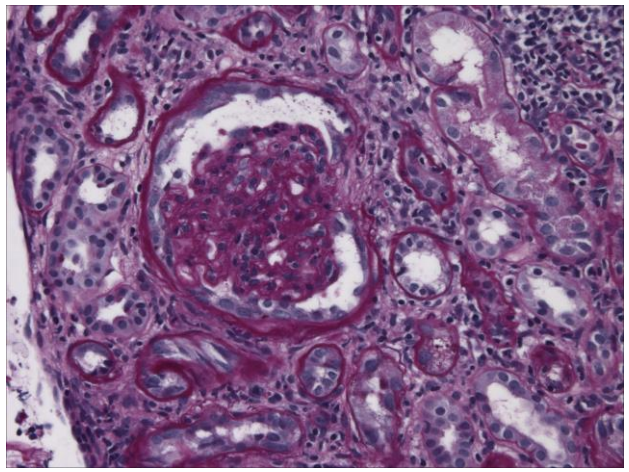


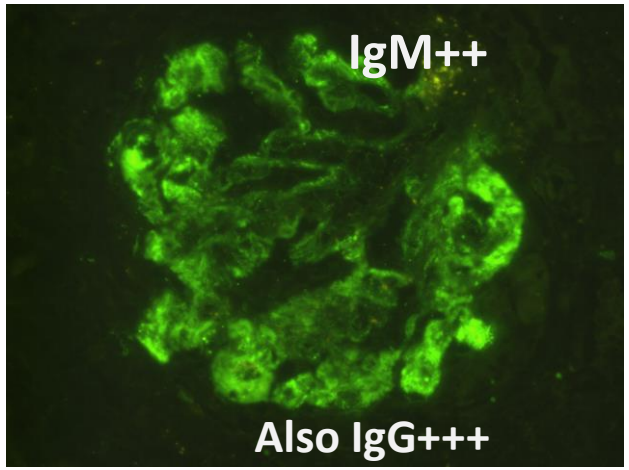


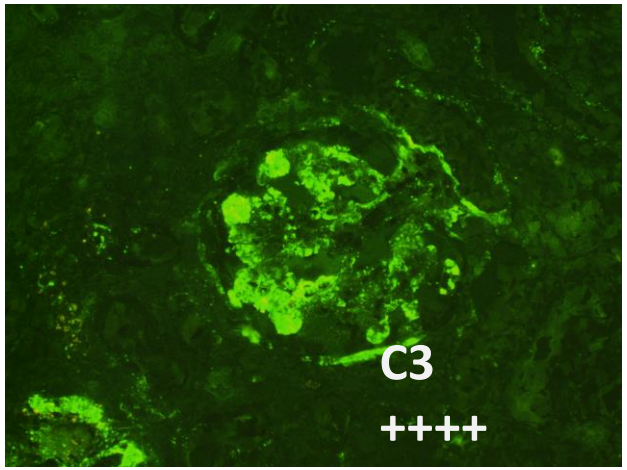
Durrbach et al., AJT 2016
Vincenti et al., NEJM 2016

Back to the case, review of Native Biopsy (Pre-transplant, 2005)









Courtesy of BWH Renal Pathology Team

- EXTENSIVE INJURY OF THE GLOMERULAR VISCERAL EPITHELIAL CELLS WITH FEATURES OF COLLAPSING GLOMERULOPATHY
- IMMUNE COMPLEX-MEDIATED GLOMERULONEPHRITIS, ACTIVE, WITH MESANGIAL, SUBEPITHELIAL, AND SUBENDOTHELIAL IgG DEPOSITS
- ARTERIAL AND ARTERIOLAR SCLEROSIS, MODERATE

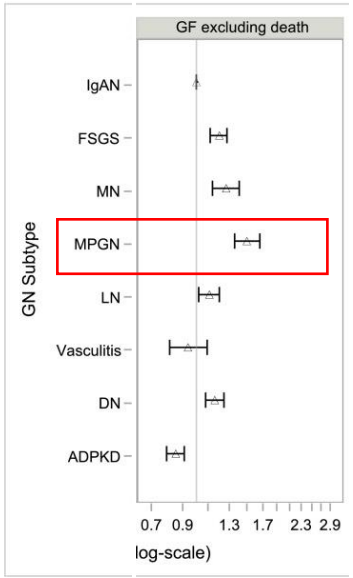
Allograft failure led by non-alloimmune related causes

Recurrent GN

Recurrent MPGN: the worst prognosis
Younger recipients ↑ risk of GN recurrence
Lack of consensus regarding the role of IS to prevent recurrence

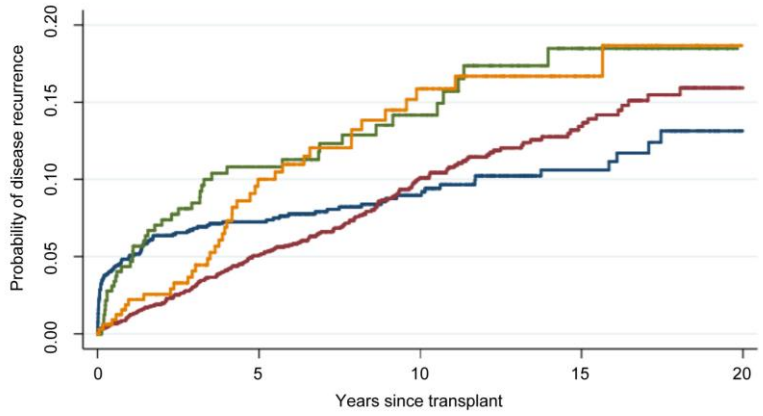
US Data (N=32,123)

Death-censored allograft lost

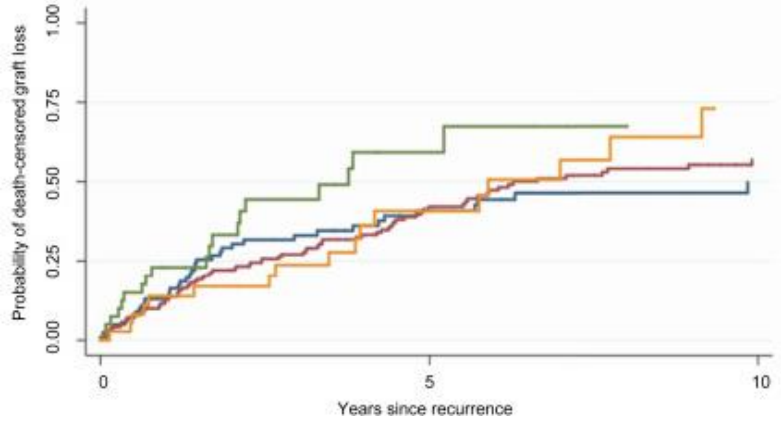


Australia/New Zealand Data (N=6597)

Disease recurrence



Death-censored allograft lost



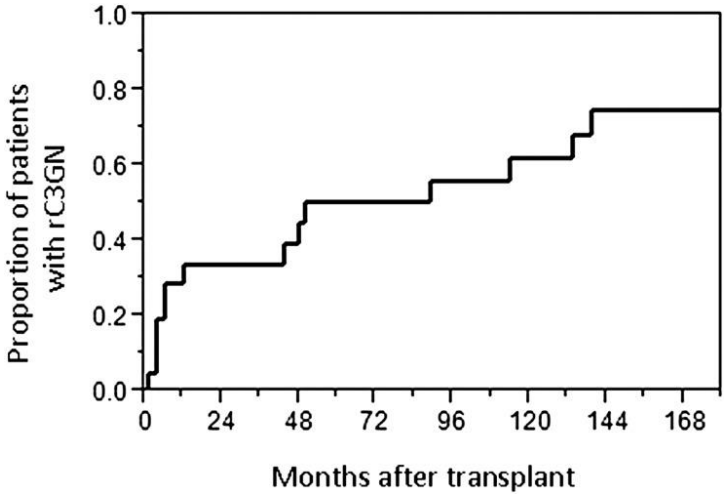
FSGS
IgA nephropathy
MPGN
Membranous GN

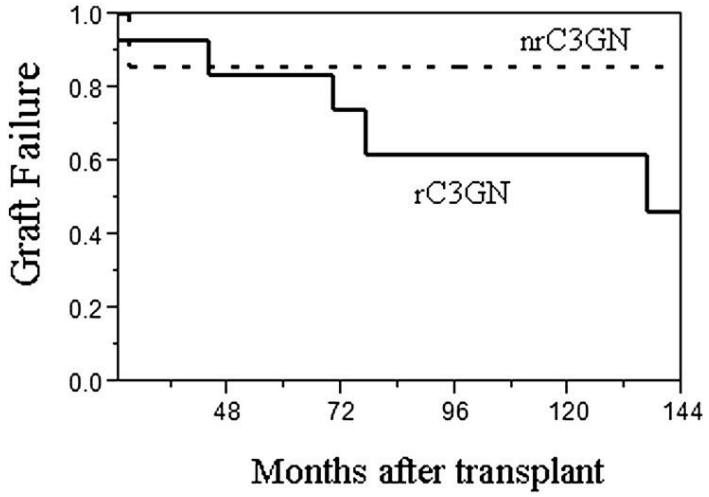
O'Shaughnessy et al., JASN 2017
Allen et al., KI 2017

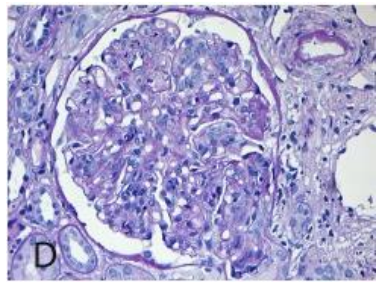
Recurrent GN, continued

MPGN is a "pattern" of injury not a disease/diagnosis.

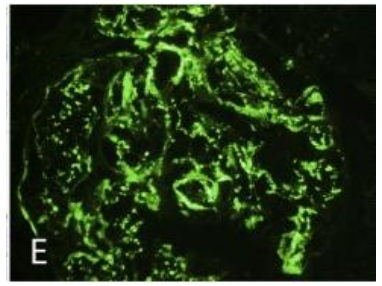
Example: C3GN recurs at a high rate (66.7%) Median Time: 28 months
Allograft loss 50% of patient with rC3GN (Median Time: 77 months post-Tx)



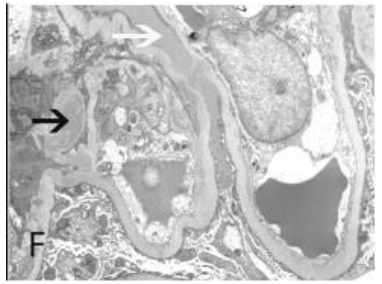




MPGN



C3



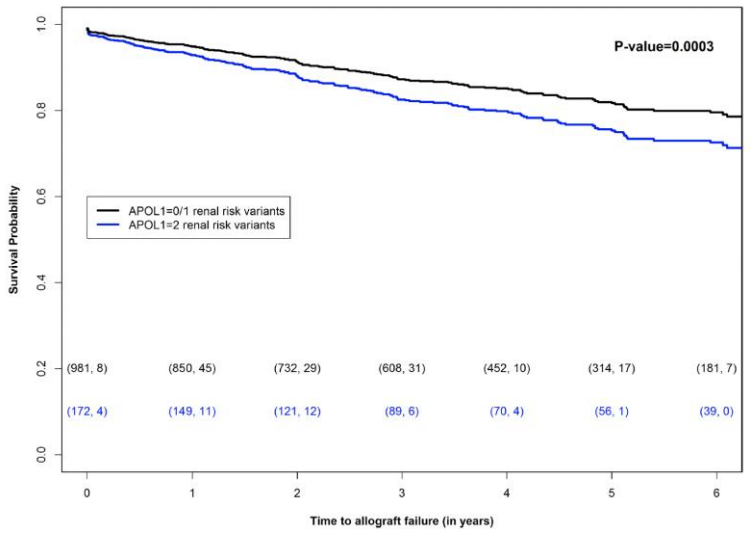
Subepithelial
Mesangial
Electron
Dense
Deposit

Genetical Predisposition – APOL1

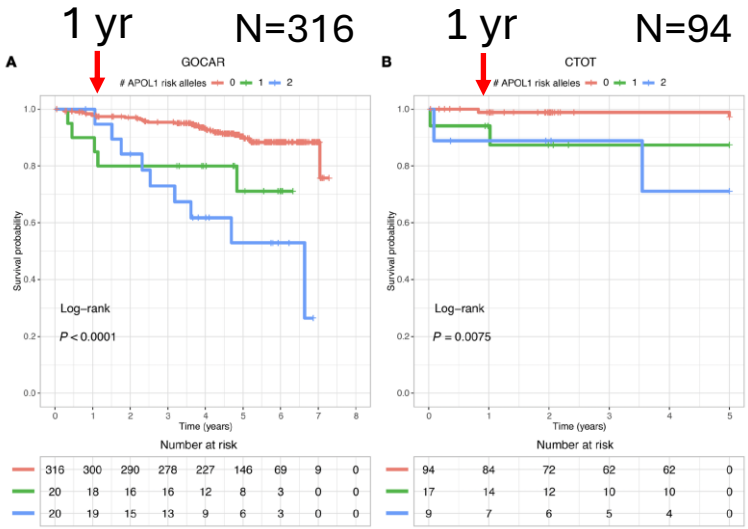
High risk APOL1 alleles in donors (HR: 1.6) and recipients (HR: 2.3) are associated with ↑risk of allograft lost

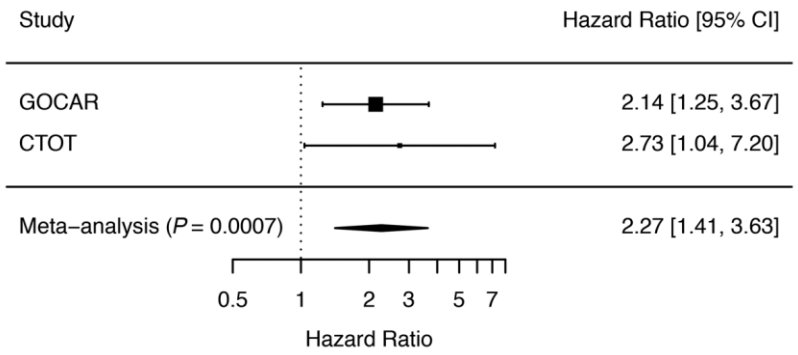
More to come..
APOL1 Long-term Kidney Transplantation Outcomes Network (May 2019 – May 2025)

Donor Status



Recipient status





Freedman et al., Transplantation 2016
Zhang et al., JCI 2021

BK Nephropathy (BKVN)

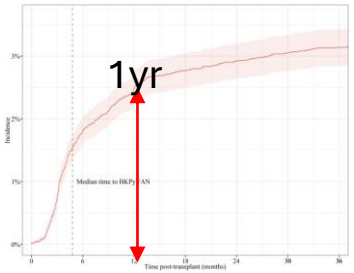
Most BKVN are detected < 1 year

BKVN carries poor prognostics (3-5 years from diagnosis)

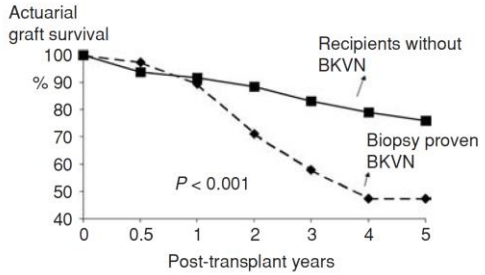
Plasma BK >10,000 copies/mL has 50% PPV for BKVN

Reduction of immunosuppression is a main treatment

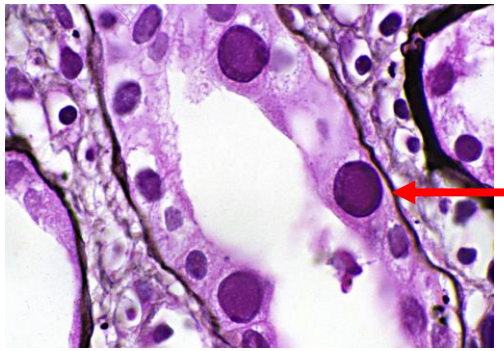
Incidence



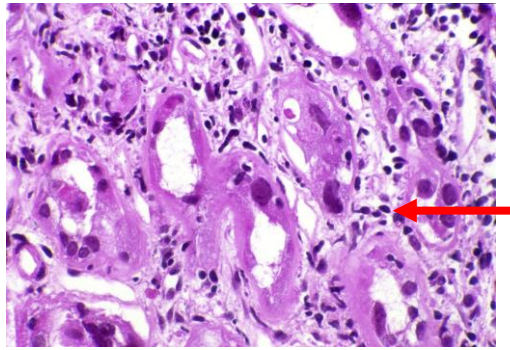
Graft Survival



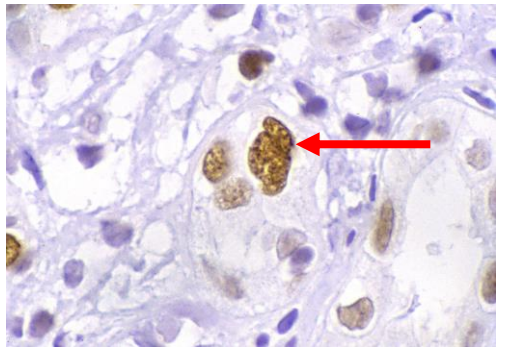
yr	w/o BKVN	W BKVN
1	92%	90%
3	83%	58%
5	76%	47%



Viral nuclear inclusion in Tubular epithelium



Interstitial infiltrates lymphocyte /plasma cells



SV40

AJKD Atlas of Renal Pathology: Polyomavirus Nephropathy
Gately et al., KI Reports, 2022
Vasudev et al., KI 2005
Hirsch et al., Transplantation 2005

Take home messages

ABMR: the leading cause of late allograft failure

ABMR Diagnostic Criteria: Allograft injury, C4d, DSA

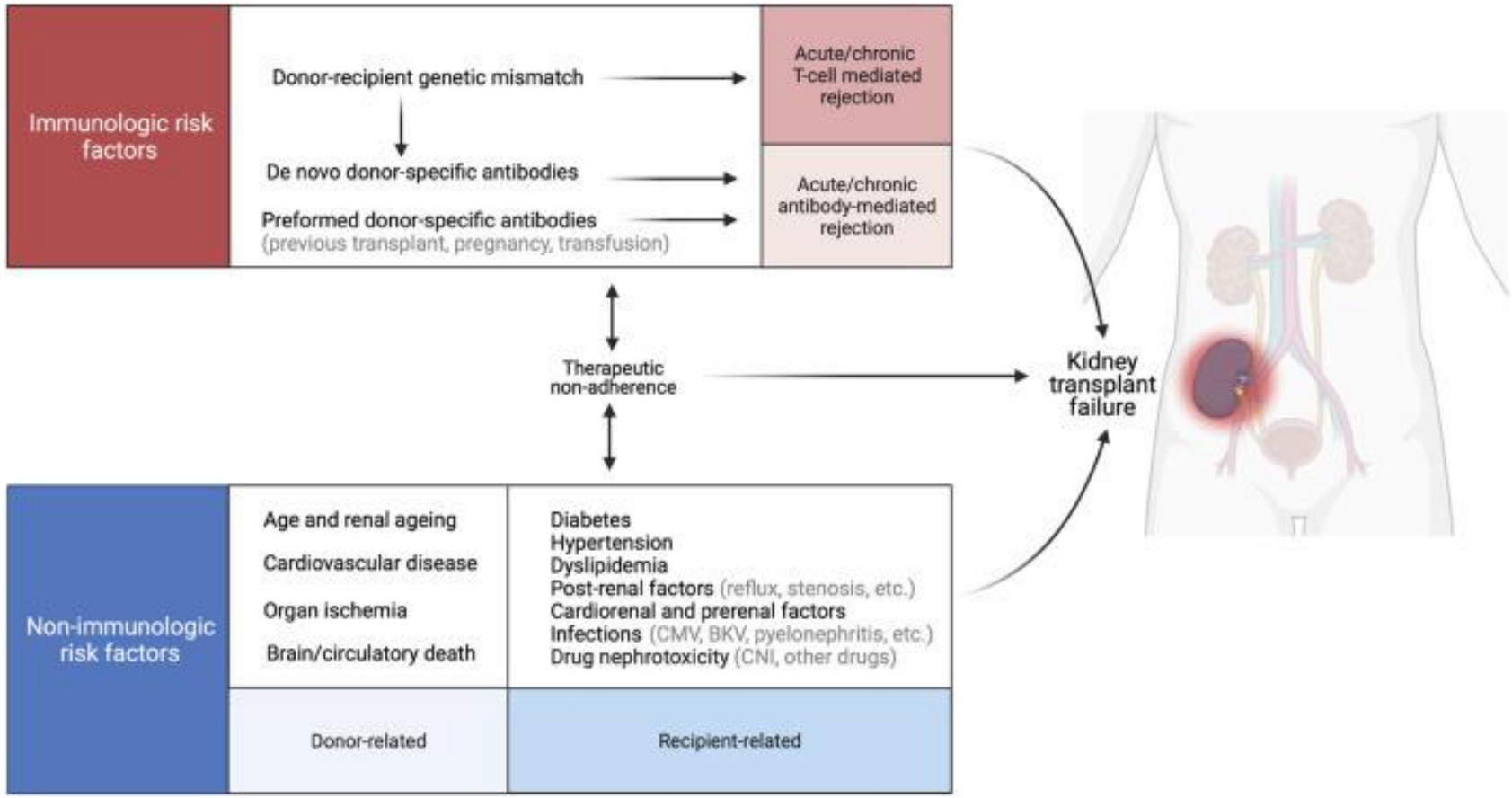
Belatacept: improved GFR, long-term allograft survival benefit in non-high-risk donor, less DSA formation, increased risk of PTLD (in EBV- recipient) and acute rejection <24 months period.

Transplant Glomerulopathy: Reduplication/multi-lammination of GBM w/o immune deposits.

Recurrent Disease: MPGN recurs early and aggressive than others. APOL recipients are at higher risk for earlier allograft failure.

BKVN: SV40, Viral nuclear inclusion in epithelium

Causes of late allograft loss



Selective References

Nankivell, B. J., Borrows, R. J., Fung, C. L.-S., O'Connell, P. J., Allen, R. D. M., & Chapman, J. R. (2003). The Natural History of Chronic Allograft Nephropathy. *New England Journal of Medicine*, *349*(24). https://doi.org/10.1056/nejmoa020009

Langewisch E, Mannon RB. Chronic Allograft Injury. Clin J Am Soc Nephrol. 2021 Nov;16(11):1723-1729. doi: 10.2215/CJN.15590920. Epub 2021 Apr 5. PMID: 33820759; PMCID: PMC8729407.

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Matas AJ, Fieberg A, Mannon RB, Leduc R, Grande J, Kasiske BL, Cecka M, Gaston R, Hunsicker L, Connett J, Cosio F, Gourishankar S, Rush D. Long-term follow-up of the DeKAF cross-sectional cohort study. Am J Transplant. 2019 May;19(5):1432-1443. doi: 10.1111/ajt.15204. Epub 2019 Jan 24. PMID: 30506642; PMCID: PMC7653899.

Wiebe C, Gibson IW, Blydt-Hansen TD, Pochinco D, Birk PE, Ho J, Karpinski M, Goldberg A, Storsley L, Rush DN, Nickerson PW. Rates and determinants of progression to graft failure in kidney allograft recipients with de novo donor-specific antibody. Am J Transplant. 2015 Nov;15(11):2921-30. doi: 10.1111/ajt.13347. Epub 2015 Jun 10. PMID: 26096305.

Schweitzer EJ, Matas AJ, Gillingham KJ, Payne WD, Gores PF, Dunn DL, Sutherland DE, Najarian JS. Causes of renal allograft loss. Progress in the 1980s, challenges for the 1990s. Ann Surg. 1991 Dec;214(6):679-88. doi: 10.1097/00000658-199112000-00007. PMID: 1741647; PMCID: PMC1358492. [Chronic Rejection]

Thank you

Continued

CATEGORY 1: Normal Biopsy Or Nonspecific Changes Requires exclusion of any diagnosis from the Banff Diagnostic Categories 2-4, 6 below.

CATEGORY 2: Antibody-mediated rejection and microvascular inflammation/injury (AMR/MVI)

Active AMR; All 3 criteria must be met for diagnosis

1. Active lesions* of AMR present, at least 1 of the following:

- Microvascular inflammation (g > 0 and/or ptc > 0), in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 1 alone is not sufficient and g must be ≥ 1
- Intimal or transmural arteritis (v > 0)
- Acute thrombotic microangiopathy, in the absence of any other cause

2. At least 1 or more of the following:

- Linear C4d staining in peritubular capillaries or medullary vasa recta (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
- At least moderate microvascular inflammation ([g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥1
- Biopsy-based transcript diagnostics for AMR/MVI above a defined threshold, if thoroughly validated for use as substitute for MVI and available

3. Evidence of circulating donor-specific antibodies (DSA to HLA or other antigens). If thorough testing for DSA (anti-HLA or other specificity) has not yet been performed, this should be done, following the STAR guidelines. Detection of non-HLA antibodies (including ABO antibodies in ABO-incompatible transplantation) can be used as serologic Banff criterion for diagnosis of AMR, if the testing protocols are sufficiently standardized and clinically validated for the appropriate clinical context. C4d staining as noted above in Criterion 2 may substitute for DSA.

*Can be observed in AMR and strengthen the diagnosis but not diagnostic in itself: acute tubular injury, in the absence of any other apparent cause

Continued

Chronic active AMR; all 3 criteria must be met for diagnosis

1. Chronic lesions* of AMR present, at least 1 of the following:
   - Transplant glomerulopathy (cg > 0) if no evidence of chronic TMA or chronic recurrent/de novo glomerulonephritis; includes changes evident by electron microscopy (EM) alone (cg1a)
   - Severe peritubular capillary basement membrane multilayering (requires EM)
2. Identical to criterion 2 for active AMR, above
3. Identical to criterion 3 for active AMR, above, including strong recommendation for DSA testing whenever criteria 1 and 2 are met.

*Other lesions can be observed in AMR and strengthen the diagnosis but are not diagnostic by themselves: arterial intimal fibrosis (cv) of new onset, excluding other causes; leukocytes within the sclerotic intima favour chronic AMR if there is no prior history of TCMR;

Chronic AMR; all 3 criteria must be met for diagnosis

1. cg > 0 and/or severe ptcml
2. Absence of criterion 2 as defined for active and chronic active AMR, above
3. Prior documented diagnosis of active or chronic active ABMR and/or documented prior (post-transplant) and/or current evidence of DSA (DSA as defined in above criterion 3 for active AMR)

C4d staining without evidence of rejection; all 4 features must be met for diagnosis[c]

1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
2. Criterion 1 for active or chronic active AMR not met
3. Negative biopsy-based transcript diagnostics for AMR/MVI as in criterion 2 for active and chronic active AMR
4. No acute or chronic active TCMR, or borderline changes

Continued

Microvascular inflammation/injury (MVI), DSA-negative and C4d-negative; all 3 criteria must be met for diagnosis

1. At least moderate microvascular inflammation ([g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥1
2. No linear C4d staining in peritubular capillaries (C4d0 or C4d1 by IF on frozen sections, or C4d = 0 by IHC on paraffin sections)
3. No serologic evidence of circulating donor-specific antibodies (DSA to HLA or other antigens, as defined in above criterion 3 for active AMR)

Probable AMR; all 4 criteria must be met for diagnosis

1. Identical to criterion 1 for active AMR, above
2. Criterion 1 for chronic active and chronic AMR not met
3. Absence of criterion 2 defined for active and chronic active AMR, above
4. Identical to criterion 3 for active AMR, above (but C4d must be negative)

C4d staining with acute tubular injury (ATI); all 3 criteria must be met for diagnosis

1. Acute tubular injury (ATI) is present
2. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
3. Criterion 1 for active or chronic active AMR not met

Clinical scenarios:

- Early posttransplant in crossmatch positive DSA sensitised patient -> “Probable AMR”
- ABO-incompatibility -> “Accommodation”
- DSA negative in conventional transplants -> “No AMR”

Continued

CATEGORY 3: Suspicious (Borderline) For Acute TCMR Foci of Banff Lesion Score t>0 AND Banff Lesions Score i=1 OR Foci of Banff Lesion Score t1 AND Banff Lesion Score i ≥ 2

CATEGORY 4: TCMR *Acute TCMR IA* Banff Lesion Score i ≥ 2 AND Banff Lesion Score t2

Acute TCMR IB Banff Lesion Score i ≥ 2 AND Banff Lesion Score t3

Acute TCMR IIA Banff Lesion Score v1 regardless of Banff Lesion Scores i or t

Acute TCMR IIB Banff Lesion Score v2 regardless of Banff Lesion Scores i or t

Acute TCMR III Banff Lesion Score v3 regardless of Banff Lesion Scores i or t

Chronic Active TCMR Grade IA Banff Lesion Score ti ≥ 2 AND Banff Lesion Score i-IFTA ≥ 2, other known causes of i-IFTA (eg, pyelonephritis, BK-virus nephritis etc.) ruled out

AND Banff Lesion Score t2

Chronic Active TCMR Grade IB Banff Lesion Score ti ≥ 2 AND Banff Lesion Score i-IFTA ≥ 2, other known causes of i-IFTA ruled out AND Banff Lesion Score t3

Chronic Active TCMR Grade II Arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima

Continued

CATEGORY 5: IFTA
Grade I (Mild) Banff Lesion Score ci1
OR Banff Lesion Score ct1
Grade II (Moderate) Banff Lesion Score ci2 OR Banff Lesion Score ct2
Grade III (Severe) Banff Lesion Score ci3 OR Banff Lesion Score ct3
CATEGORY 6: Other Changes Not Considered To Be Caused By Acute Or Chronic Rejection (Figure 20)
Polyomavirus Nephropathy, Posttransplant Lymphoproliferative Disorder, Calcineurin Inhibitor Toxicity, Acute Tubular Injury, Recurrent Disease, De Novo Glomerulopathy (Other Than TG), Pyelonephritis, Drug-Induced Interstitial Nephritis