Antibody-Mediated Rejection Present and Future

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Disclosure

Nothing to disclose

Objectives

- Examine the evolving understanding of the pathophysiology of Antibody-Mediated Rejection (ABMR).
- Evaluate current diagnostic techniques for AMR, including histopathology, DSA detection, and molecular testing.
- Explore existing treatment options, ranging from traditional therapies to new biologics.
- Pinpoint significant challenges and potential opportunities in managing ABMR to enhance long-term graft survival.

Introdcution

Antibody-mediated rejection (ABMR) was first formally described as a clinicopathological diagnosis in the Banff 97 classification.

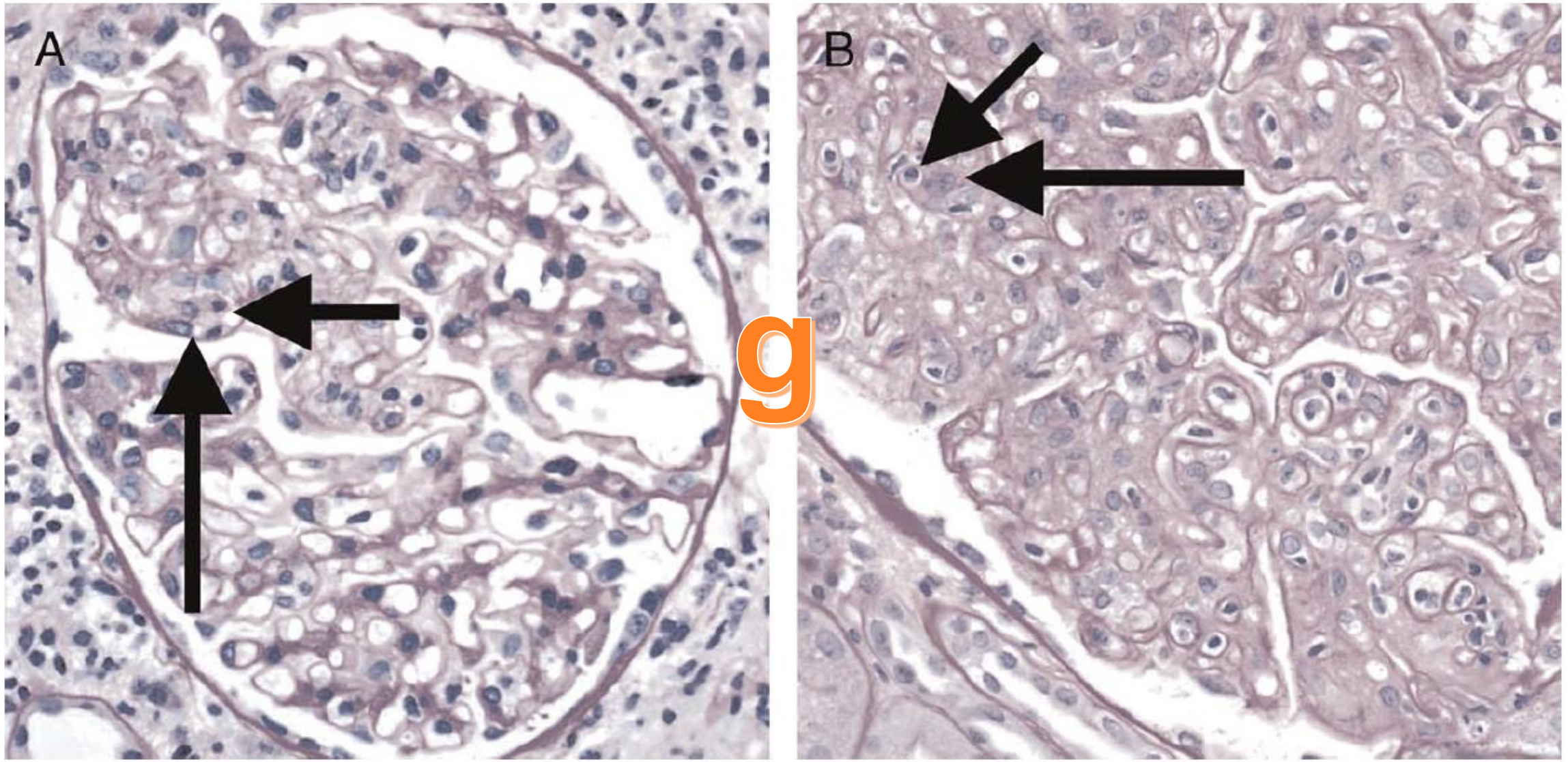
ABMR has emerged as the leading cause of late graft loss in kidney transplant recipients.

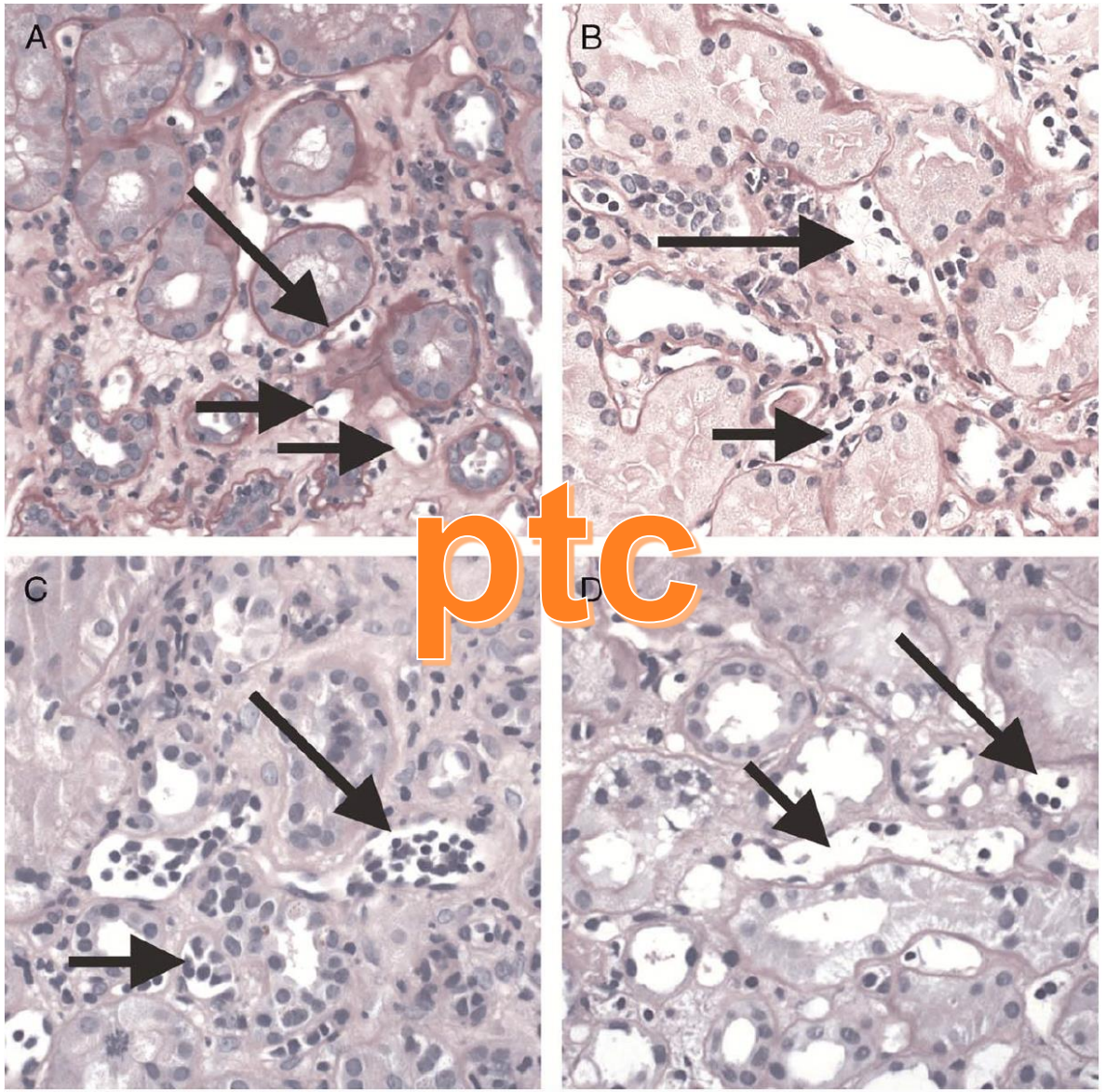
Chronic active ABMR (caABMR), defined by transplant glomerulopathy, evidence of antibody-antigen interactions, and serologic evidence of donor-specific antibodies (DSAs), is the most important cause of late graft failure.

Banff 2022 Criteria AMR

Table 2. Criteria for diagnosis of active ABMR (all 3 criteria must be met).

Criteria 1	Histologic evidence of acute tissue injury, including 1 or more of the following: • Microvascular inflammation (g > 0 and/or ptc > 0), in the absence of recurrent or de novo glomerulonephritis • Intimal or transmural arteritis (v > 0) • Acute thrombotic microangiopathy, in the absence of any other cause • Acute tubular injury, in the absence of any other apparent cause
Criteria 2	Evidence of current/recent antibody interaction with vascular endothelium, including 1 or more of the following: • Linear C4d staining in peritubular capillaries or medullary vasa recta • At least moderate microvascular inflammation ([g + ptc] $\geq$ 2), in the absence of recurrent or de novo glomerulonephritis • Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated
Criteria 3	Serologic evidence of circulating donor-specific antibodies (DSA to HLA or other antigens); C4d staining or expression of validated transcripts/classifiers as noted above in criterion 2 may substitute for DSA


A
B
g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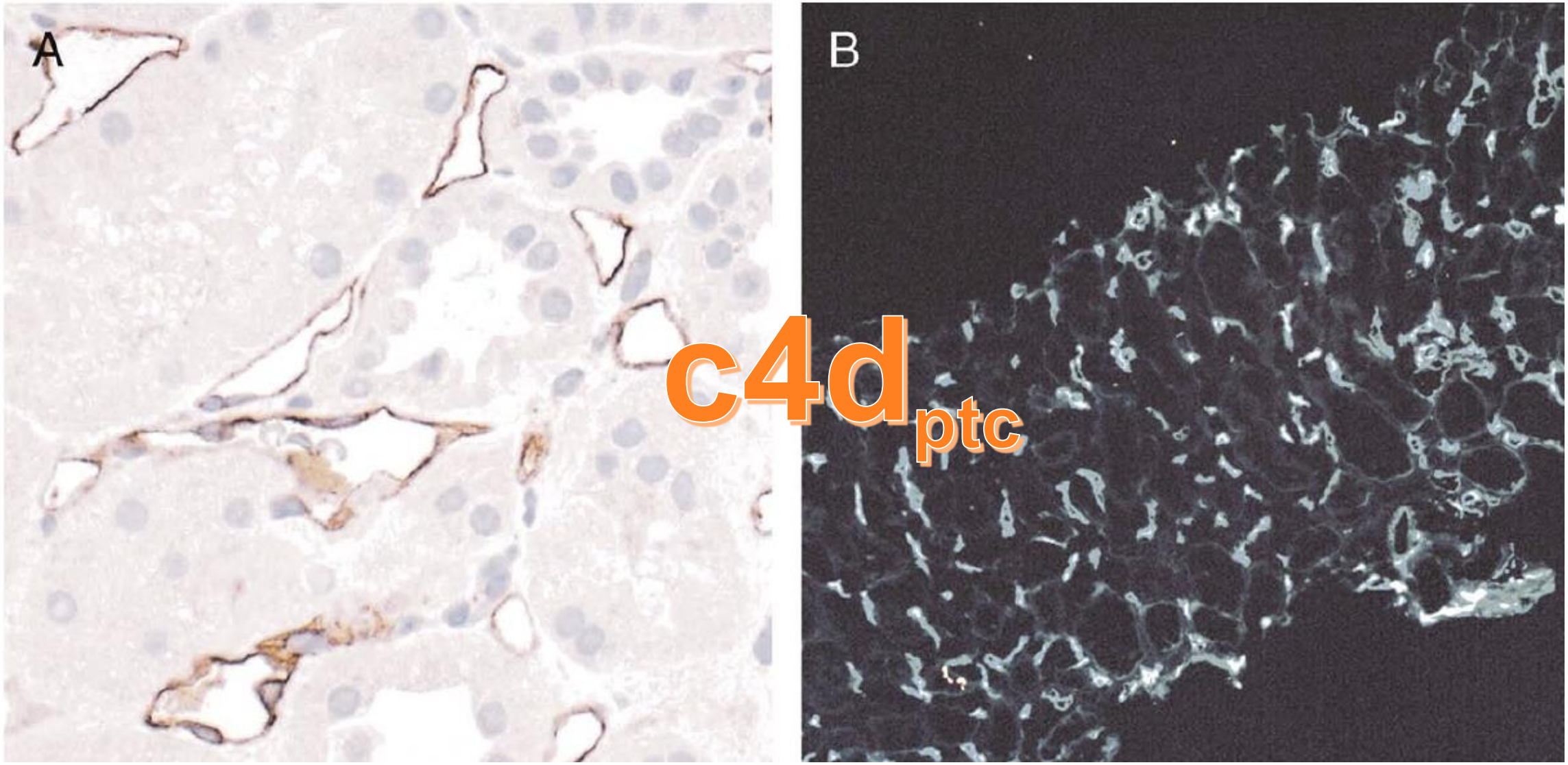

A
B
c4d ptc

The Spectrum of Kidney Transplant Rejection

Traditional View:

- The dichotomy of rejection: T-cell mediated rejection (TCMR) versus antibody-mediated rejection (ABMR).
- Guided the development of immunosuppressive therapies and the Banff classification over the past two years decades.

Emerging Insights:

- Heterogeneity in histology, serology, and prognosis.
- Role of donor-specific anti-HLA antibodies (DSA) and non-HLA mismatches.
- Innate allorecognition mechanisms, including monocyte and NK-cell driven rejection.

Challenges in Diagnosing ABMR

- **Histologic Lesions are Nonspecific:** glomerulitis and intimal arteritis overlap with other conditions (glomerulonephritis, TCMR).
- **HLA-DSA: despite advanced assays, 17–66% of ABMR cases lack detectable HLA-DSA.**
- **C4dptc:**
  - **Introduced in Banff '17** as a surrogate for HLA-DSA, but its specificity is debated.
  - **Not always linked to HLA-DSA** (due to DSA variability in antibody-endothelium interactions and complement activation).
  - **Seen in ABO-incompatible transplants** and some non-ABMR cases.
  - **Prognostic value is inconsistent** across studies.

Immune Infiltrates in Rejection

- It affects the **vascular, epithelial, and stromal compartments** of the allograft.
- The **Banff classification** describes the **spatial organization** of inflammation but **not immune cell composition.**
- **Heterogeneity of Immune Infiltrates in Rejection:**
  - Significant variability in immune cell composition **within the same rejection phenotype.**
  - **ABMR** may be dominated by **macrophages or T cells,** while **TCMR** shows a similar spectrum.
  - **B-cell and plasma cell-rich infiltrates are seen across ABMR and TCMR.**
- The binary **T cell vs. antibody-mediated rejection** classification may oversimplify the complexity of immune responses in kidney transplantation.

Inconsistent Treatment Responses

- **ABMR lacks standardized prevention & treatment:**
  - Therapies (antibody removal, complement inhibition, B-cell/plasma cell depletion) improve **short-term** but not **long-term** outcomes.
  - **Eculizumab** was effective only in **complement-binding HLA-DSA** cases.
  - Need for **predictive biomarkers** to guide treatment.
- **Rejection treatment remains unpredictable, highlighting the need for personalized therapy approaches.**

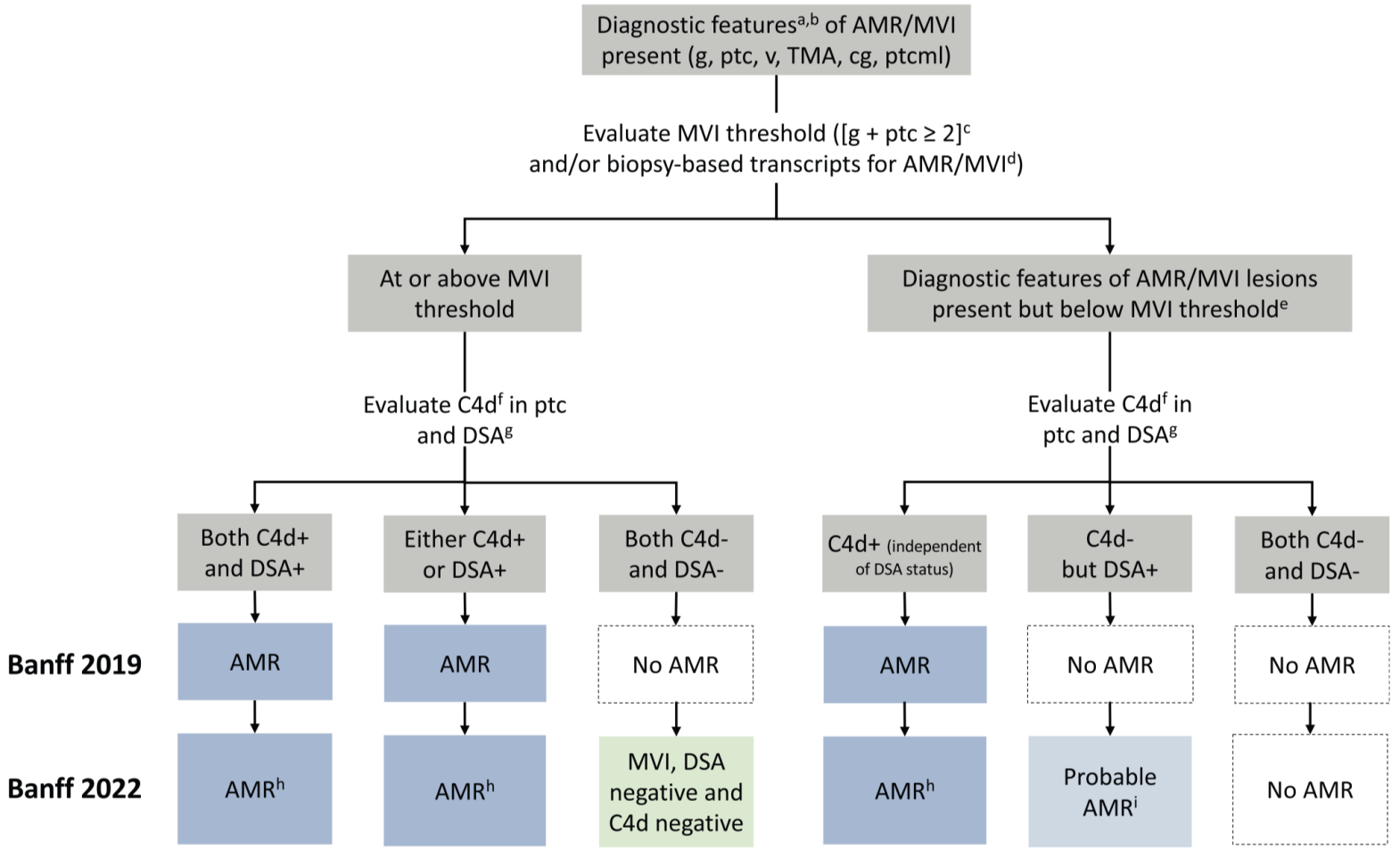
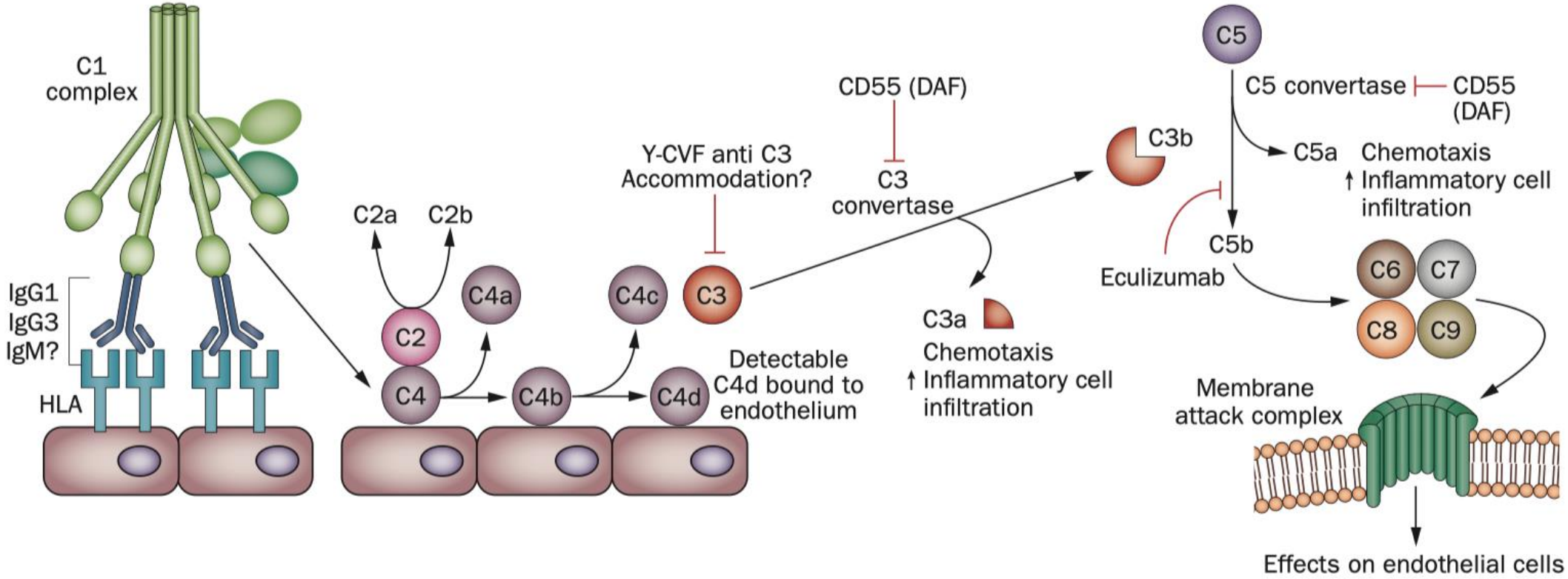


Figure 2. Flowchart of the Banff 2022 Classification for Category 2: Antibody-mediated rejection and microvascular inflammation/injury (AMR/MVI). This can be used as a companion for disease classification but does not modify the detailed Banff Classification for Category 2 AMR/MVI presented in Supplementary Table S1.



Stegall, M., Chedid, M. & Cornell, L. The role of complement in antibody-mediated rejection in kidney transplantation. *Nat Rev Nephrol* **8**, 670–678 (2012).

Complement-Dependent AMR

Trigger: Donor-Specific Antibodies (DSA) interact with **C1q**.

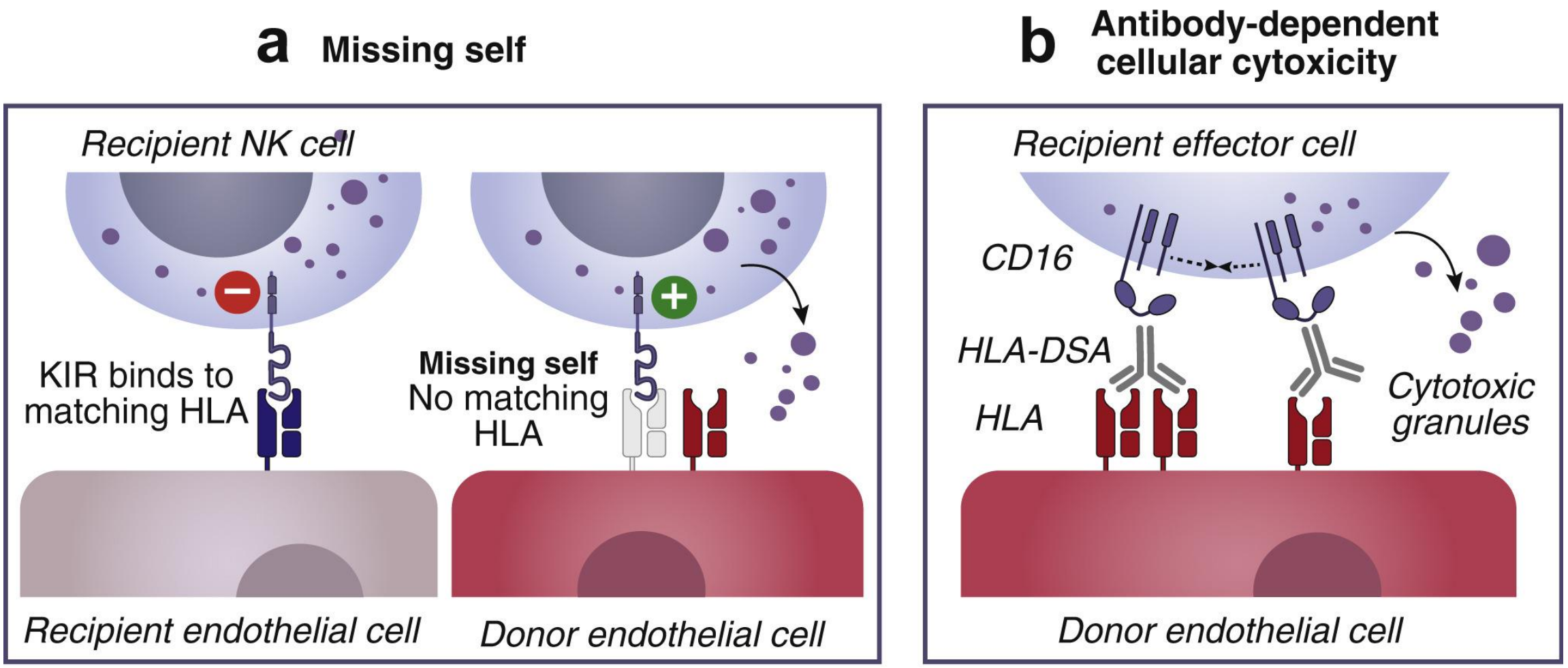
IgM/IgG3 is highly effective, while **IgG1 > IgG2/IgG4** in complement activation.

C1q Binding: Leads to **C4 cleavage (C4a, C4b) → C4d deposition**, marking AMR.

Loss of **complement inhibitors (CD55, CD59, CFH, CFI)** in stressed endothelium (Ischemic reperfusion) amplifies injury.

C4d deposition in peritubular capillaries (PTCs) is a diagnostic hallmark but not consistently predictive of complement activity.

Complement-dependent mechanisms dominate in Early AMR.



Allorecognition and the spectrum of kidney transplant rejection
Callemeyn, Jasper et al. Kidney International, Volume 101, Issue 4, 692 - 710

Complement-Independent Mechanisms in ABMR

Antibody-Dependent Cellular Cytotoxicity (ADCC) : DSA binds to Fcγ receptors (FcγR) on immune cells (NK cells, macrophages, B lymphocytes).

Missing Self: Loss of **HLA class I molecules** leads to **NK cell activation** and microvascular injury.

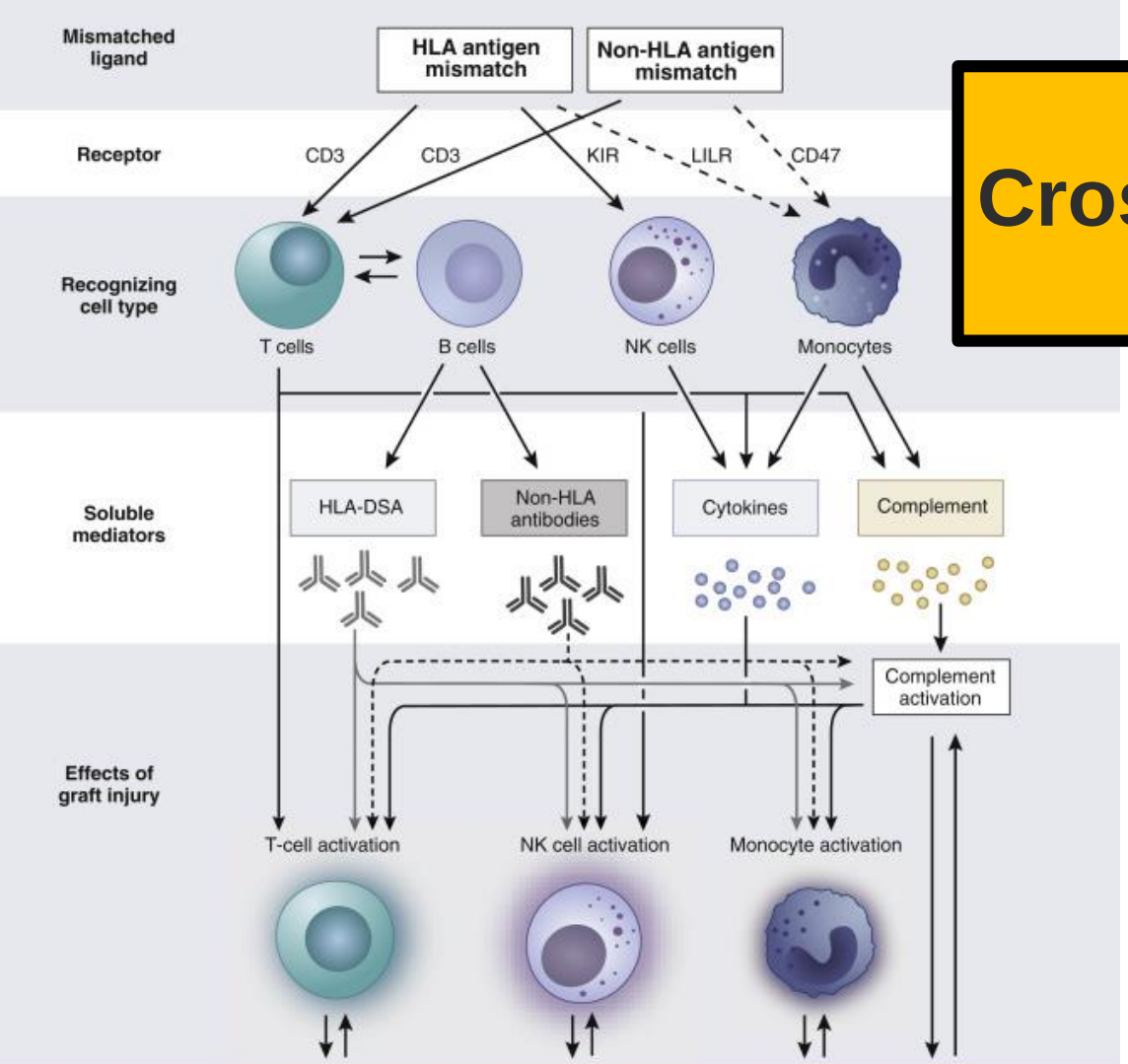
Some ABMR cases show **T-cell dominant activation.**

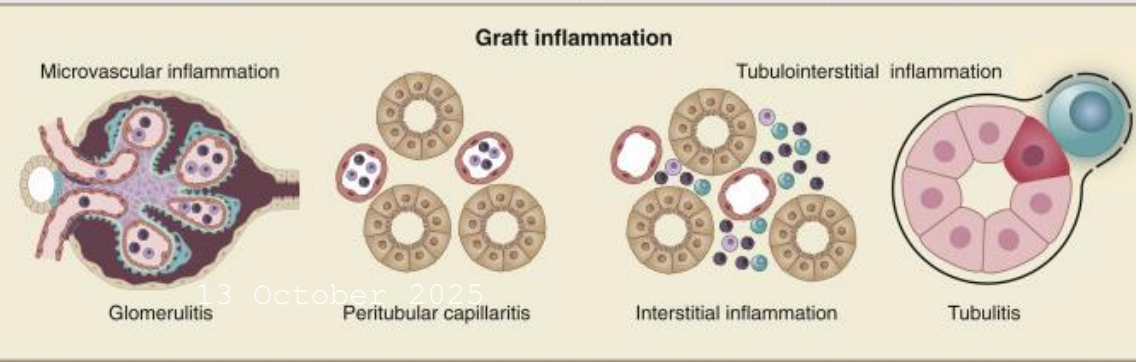
Direct Endothelial Activation: **Non-HLA antibodies** (e.g., anti-angiotensin receptor) can activate endothelial cells independently of complement.

Complement-independent pathways dominate in late AMR.

Require **alternative therapeutic targets beyond complement inhibitors** (e.g., targeting NK cells, FcγR blockade).

Crosstalk of allorecognition pathways





Allorecognition mechanisms have often been viewed as separate entities, yet multiple pieces of evidence suggest that these processes are interconnected.

Understanding these interwoven pathways can help refine therapeutic strategies targeting both humoral and cellular rejection mechanisms.

The traditional categorical approach is inadequate. Rejection types should be viewed on a spectrum that acknowledges multiple immune stimuli and diverse clinical presentations.

Allorecognition and the spectrum of kidney transplant rejection
Callemeyn, Jasper et al. Kidney International, Volume 101, Issue 4, 692 - 710

Early vs Late ABMR

Early ABMR:

- It occurs within 6 months post-transplant and is associated with pre-formed or de novo donor-specific antibodies (DSA).
- Abrupt acute AMR due to immunosuppressive withdrawal resembles early AMR.

Late ABMR:

- It Occurs >6 months post-transplant; primarily linked to de novo DSA development.

Key Features

Early ABMR:

- Strong complement activation (IgG3 and IgG1 subclasses dominate).
- C4d-positive
- Frequently linked to pre-existing DSA.
- Correlation with high mean fluorescence intensity (MFI) DSA.
- There is a higher risk of severe graft injury resulting in AKI.

Late ABMR:

- IgG subclass switch to non-complement-binding types.
- Less frequent complement activation may involve non-complement-binding antibodies (e.g., IgG2 and IgG4).
- Lower C4d positivity rates (~35-53%).
- Gradual injury progression.
- May present with chronic allograft injury (e.g., transplant glomerulopathy, peritubular capillary basement membrane

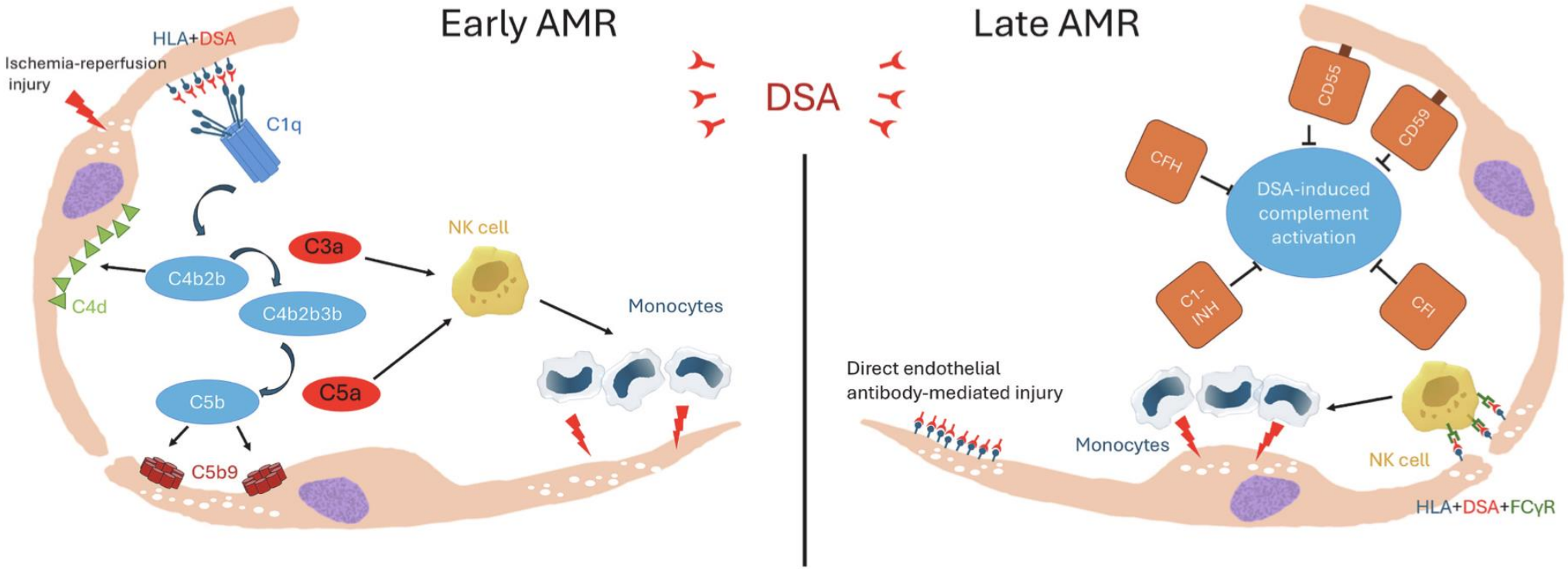


Fig. 1. Scheme of the different mechanisms likely to be leading the pathogenesis of microvascular inflammation (MVI) and endothelial injury in early and late AMR. In early AMR (left), classical complement pathway is primarily triggered by the interaction of C1q with HLA-DSA binding HLA molecules on endothelial surface. This phenomenon may be favored by loss of tissue complement regulators, induced by ischemia-reperfusion injury. C1q activation leads to C4d and C5b9 complex deposition on the surface endothelial cells, that are injured by direct complement activity. Moreover, final complement pathway releases anaphylatoxins C3a and C5a that attract and activate NK cells. These cells will then attract monocytes, that are the main cellular component of MVI. Il late AMR (right), DSA-induced complement activation is largely inhibited by upregulation of both cell-bounded and soluble complement regulators (including CD55, CD59, CFH, CFI and C1-INH). Direct interaction of NK cells with HLA-DSA complex through FCγ receptor leads to NK recruitment and activation, triggering the same pathway that leads to MVI. Moreover, DSA binding on endothelial HLA molecules may induce direct endothelial injury. All these mechanisms can be active, in different degree and even simultaneously, in AMR.

Early and late antibody-mediated rejection: Which game is the complement playing?, Transplantation Reviews, Volume 39, Issue 1,

Treatment Implications

Early ABMR:

- More responsive to complement-targeted therapies (e.g., eculizumab).
- Standard treatment includes plasmapheresis, IVIG, and rituximab.

Late ABMR:

- Reduced efficacy of complement-targeted therapies.
- Focus on mitigating chronic injury and addressing non-complement-mediated damage.

Role of Biomarkers in Antibody-Mediated Rejection

Conventional markers (**creatinine, eGFR**) lack sensitivity.

Biopsies are invasive, costly, and prone to errors.

Key Functions in ABMR

- **Early Detection** – Identify subclinical rejection before graft dysfunction.
- **Diagnosis & Differentiation** – Distinguish ABMR from TCMR.
- **Treatment Monitoring** – Assess therapy response.
- **Risk Stratification** – Predict long-term graft survival.

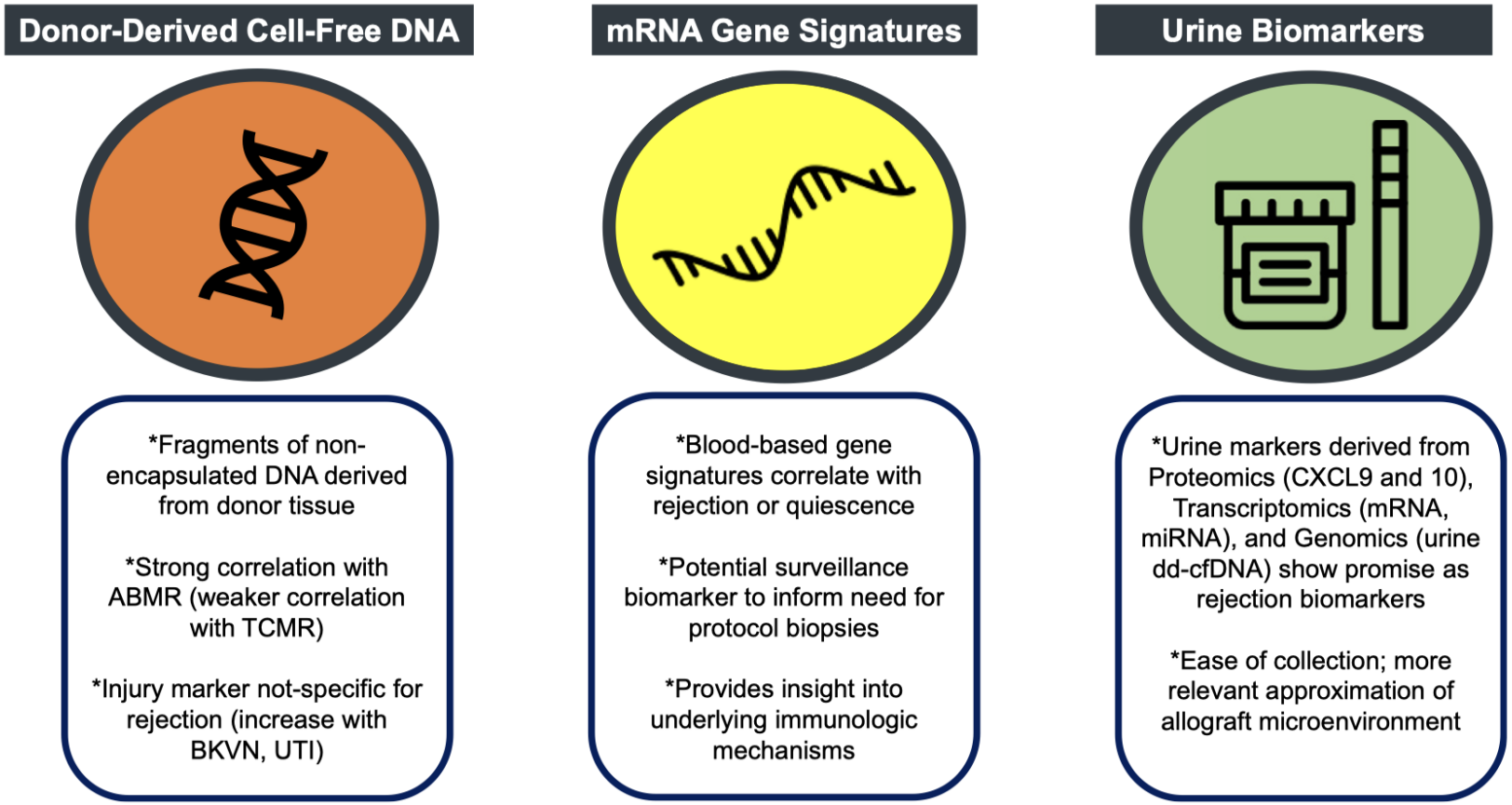


Figure 1. Noninvasive biomarkers of kidney transplant rejection. Abbreviations: ABMR, antibody-mediated rejection; BKVN, BK-polyoma virus nephropathy; dd-cfDNA, donor-derived cell-free DNA; mRNA, messenger RNA; miRNA, microRNA; TCMR, T-cell–mediated rejection; UTI, urinary tract infection.

Emerging Diagnostic Tools

Biomarkers of Rejection in Kidney Transplantation Westphal, Scott G. et al.American Journal of Kidney Diseases

HLA Donor-Specific Antibodies (DSA)

Presence of DSA correlates with a higher risk of ABMR.

Not all DSA-positive cases progress to ABMR.

Combining **DSA with dd-cfDNA** enhances diagnostic accuracy.

Useful for guiding biopsy decisions and therapeutic interventions.

Donor-Derived Cell-Free DNA (dd-cfDNA)

Fragments of DNA from donor cells released into the bloodstream due to allograft injury.

Higher levels correlate with ABMR severity.

Sensitive but not specific (also elevated in BK virus nephropathy, infection).

Key commercial assays include:

- **AlloSure (CareDx)**: Targeted Next-Generation Sequencing (NGS)
- **Prospera (Natera)**: Massively multiplexed PCR (over 13,000 SNPs)
- **TRAC (Eurofins-Viracor)**: NGS-based genome-wide analysis
- **VitaGraft (Oncocyte)**: Digital droplet PCR

surveillance and **monitoring treatment response.**

dd-cfDNA detects **ABMR** better than T-cell-mediated rejection (TCMR).

mRNA Gene Expression Signatures

Peripheral blood gene expression profiles (GEP) reflect immunologic activity.

Potential for detecting rejection and immune quiescence.

Not just injury markers but indicators of immune activation.

dd-cfDNA + mRNA signatures improve sensitivity for ABMR detection.

Examples:

- **TruGraf (Eurofins-Transplant Genomics):** Detects subclinical rejection.
- **Tutivia (Verici Dx):** Predicts rejection risk and graft loss.
- **Allomap Kidney (CareDx):** Surveillance biomarker for immune activity.

TABLE 4.

Consensus treatment recommendations based on available evidence and expert opinion

Timing	DSA	Histology (Banff 2017)	Standard of care[a]	Consider adjunctive therapies
Early[a] Acute (<30 days posttransplant)	Preexisting DSA (or nonimmunologically naive)	Active AMR	Plasmapheresis (daily or alternative day × 6 based on DSA titer) (1C)[b] IVIG 100 mg/kg after each plasmapheresis treatment or IVIG 2 g/kg at end of plasmapheresis treatments (1C) Corticosteroids (EO)	Complement inhibitors (2B) Rituximab 375 mg/m^2 (2B) Splenectomy (3C)
Late (>30 days posttransplant)	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)

[a]For all cases, treatment of concomitant T-cell–mediated rejection (≥borderline) and optimizing immunosuppression is recommended. Optimizing immunosuppression includes the use of tacrolimus with goal trough of >5 and use of maintenance steroid equivalent to prednisone 5 mg daily.
[b]Fresh-frozen plasma to be used for replacement fluid for plasmapheresis if a biopsy was performed within 24–48 h. The codes for grades of evidence have been taken from KDIGO.[54,56]
AMR, antibody-mediated rejection; DSA, donor-specific antibody; EO, expert opinion; IVIG, intravenous immune globulins; KDIGO, Kidney Disease: Improving Global Outcomes.

Recommended Treatment for Antibody-mediated Rejection After Kidney Transplantation: The 2019 Expert Consensus From the Transplantation Society Working Group. Transplantation 104(5):p 911-922, May 2020. | DOI: 10.1097/TP.0000000000003095

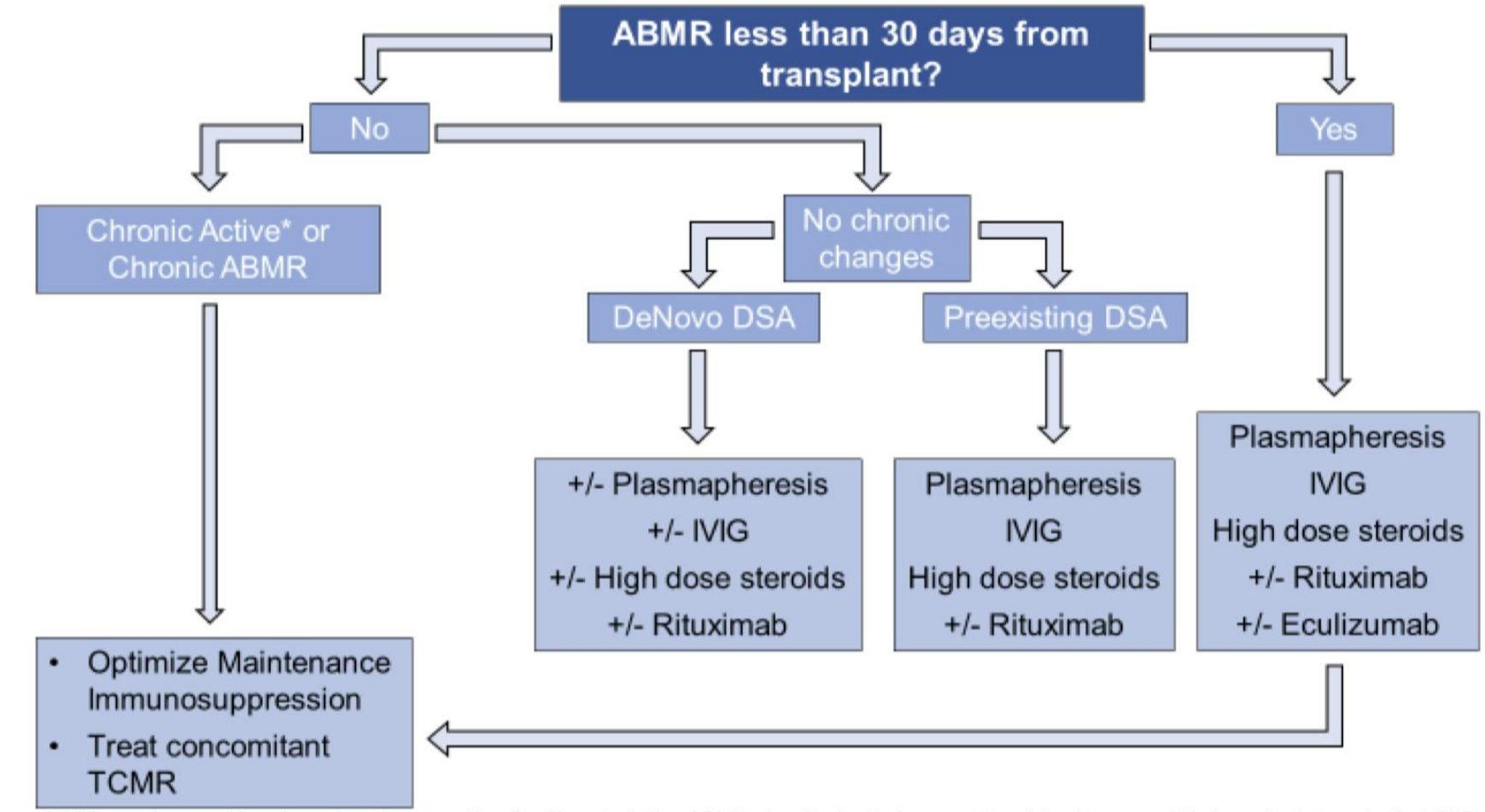


Figure 2. Algorithm for management of Antibody-Mediated Rejection.

Alasfar, S., Kodali, L., & Schinstock, C. A. (2023). Current Therapies in Kidney Transplant Rejection. *Journal of Clinical Medicine*, *12*(15), 4927. https://doi.org/10.3390/jcm12154927

Current Challenges in Chronic Active ABMR (caAMR)

Approximately 50% of transplanted kidneys fail within 8–11 years, with significant physical, emotional, and financial burdens

No FDA-approved treatments for acute or chronic AMR.

Current options (plasmapheresis, IVIG, steroids, ± rituximab) lack conclusive evidence.

Supportive care and baseline immunosuppression optimization are the only consensus strategies.

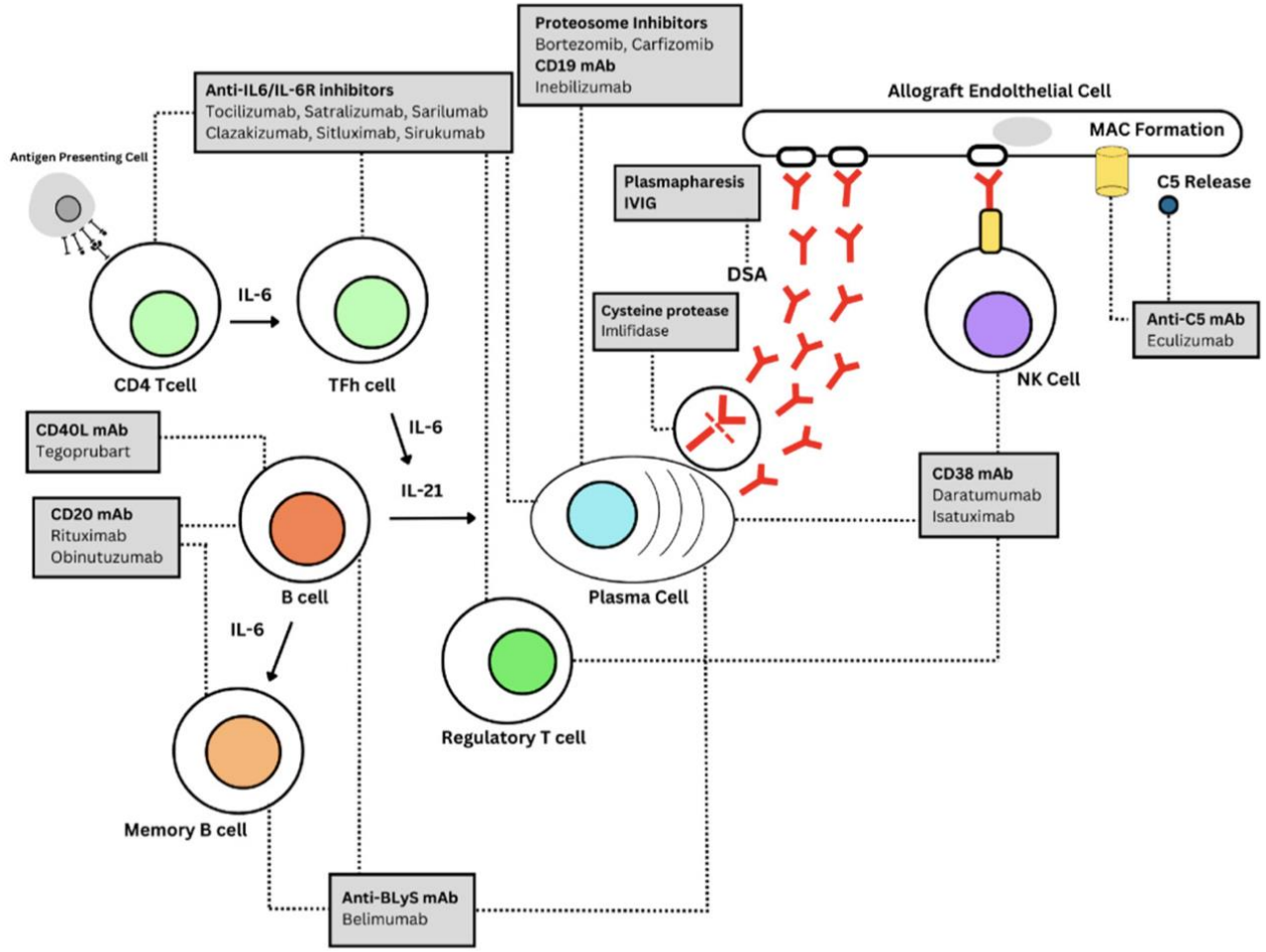


Figure 1. This figure shows the pathogenesis of AMR wherein an alloantibody reaction is presented by the antigen-presenting cell (APC) to the CD4 T-cell, which later matures to TFh helper cells amplifying B-cells through IL-6/21 activity. This leads to B-cell proliferation and differentiation, which in turn generates antibody-producing plasma cells. The binding of alloantibodies to the allograft endothelial cell induces natural killer (NK) cells (and macrophage) activation and triggers complement

Tocilizumab

IL-6 receptor inhibitor that prevents IL-6-mediated immune activation, reducing inflammation and DSA production.

Effective as a desensitization agent and for AMR treatment.

Several small studies suggest that tocilizumab reduces DSA titers, stabilizes renal function, and improves graft survival in chronic active AMR with no significant adverse events.

Potential adverse effects: infections, gastrointestinal perforation, elevated liver enzymes.

Clazakizumab

Clazakizumab is a high-affinity monoclonal antibody targeting IL-6, preventing AMR-related inflammatory responses.

A phase 2 study showed reduced DSA titers and graft inflammation.

A phase 3 trial (IMAGINE) was terminated early as analysis indicated that the study was unlikely to meet the primary efficacy outcome

Adverse effects: diverticulitis, pleural effusions, acute kidney injury.

Daratumumab

CD38 monoclonal antibody that depletes plasma cells, reducing alloantibody production.

Multiple case reports in kidney transplant patients show reductions in DSAs and improved graft function.

Risk of infusion-related reactions, hypogammaglobulinemia, and myelosuppression.

Felzartamab

CD38 monoclonal antibody that depletes plasma cells, reducing alloantibody production.

In phase 2, a double-blind, randomized, placebo-controlled trial, 22 patients underwent randomization (11 to receive felzartamab and 11 to receive placebo).

After week 24, resolution of morphologic antibody-mediated rejection was more frequent with Felzartamab (in 9 of 11 patients [82%]) than with placebo (in 2 of 10 patients [20%]), for a difference of 62 percentage points

Randomized Phase 2 Trial of Felzartamab in Antibody-Mediated Rejection. N Engl J Med. 2024 Jul 11;391(2):122-132. doi: 10.1056/NEJMoa2400763. Epub 2024 May 25. PMID: 38804514.

Imlifidase

IgG-cleaving enzyme rapidly reducing alloantibody levels, preventing complement activation.

Used in desensitization and AMR treatment trials.

Risk of antibody rebound and drug interactions with IgG-based therapies.

New CD-20 Agents

Ofatumumab:	A second-generation anti-CD20 monoclonal antibody.
	Case reports suggest efficacy in desensitization, but kidney transplant data are limited.
Obinutuzumab:	A glyco-engineered anti-CD20 antibody with enhanced B-cell depletion.
	Used in rituximab-resistant AMR cases.
Inebilizumab:	A CD19 monoclonal antibody targeting B-cells.
	Investigated for desensitization but lacks kidney transplant data.

Barriers to New Therapies:

Inconsistent diagnostic criteria

(e.g., evolving Banff classifications).

Small sample sizes, lack of control groups, and poor-quality endpoints hinder research.

Clinical trials face challenges such as slow recruitment and high costs.

The field requires disciplined, robust clinical research to address unmet needs.

Conclusion

- Understanding allorecognition pathways can help refine therapeutic strategies for both humoral and cellular rejection mechanisms.
- The advancement of novel biomarkers is key to offering personalized immunosuppressive strategies targeting multiple immune pathways.
- While several agents have shown promise, further randomized clinical trials are needed to establish