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Review

Non-HLA Antibodies in Kidney Transplantation: Pathogenesis, Clinical Impact, and Management Approaches

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Abstract: Antibody-mediated rejection is a critical factor in acute and chronic allograft rejection, with Human Leukocyte Antigen as the primary target of the humoral immune response in kidney transplants. In addition to HLA antibodies, non-HLA Abs also play a significant role in AMR. These non-HLA Abs, which can target either autoantigens or alloantigens, may be present pre-transplantation or develop post-transplant. They are associated with various types of allograft injury. The major non-HLA Abs include those directed against the angiotensin II type 1 receptor, endothelin type A receptor, and MICA, as well as other antigens such as vimentin, collagens, and anti-endothelial cell antibodies. Factors such as ischemia, reperfusion injury, and calcineurin inhibitor toxicity can trigger the pathogenic activity of these Abs. The mechanisms underlying non-HLA Ab production are not yet fully understood but are thought to involve endothelial injury and the exposure of neoantigens. Research indicates that these non-HLA Abs can cause graft injury through both complement-dependent and complement-independent pathways. However, detecting non-HLA Abs remains a challenge due to the lack of reliable diagnostic tools. Current treatment strategies for managing the effects of pathogenic non-HLA Abs include intravenous immunoglobulin, plasmapheresis, rituximab, and bortezomib. Early identification of high-risk patients and timely intervention are crucial to preventing graft failure. This review examines the development, mechanisms, and clinical significance of non-HLA Abs in kidney transplantation, highlighting the need for improved diagnostic methods and tailored therapeutic approaches.

Keywords: non-HLA; non-HLA antibodies; AMR; kidney transplantation

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1. Introduction

Antibody-mediated rejection (AMR) plays a significant role in both acute and chronic allograft rejection (AR) in kidney transplantation (KT). While the primary targets of the humoral immune response in renal allografts are human leukocyte antigens (HLAs), emerging studies also implicate antibodies against non-HLAs in AMR, affecting graft outcomes [1,2]. Non-HLA antibodies (Abs) may target autoantigens or alloantigens, either pre-existing before transplantation or developing de novo post-transplant [3]. Unlike HLA-DSAs, which have well-established diagnostic and therapeutic guidelines, non-HLA Abs remain less understood, and their clinical implications are not fully elucidated. The major non-HLA Abs associated with AMR include angiotensin II type 1 receptor antibody (AT1R-Ab), endothelin type A receptor antibody (ETAR), MHC class I chain-related antigen A antibody (MICA-Ab), vimentin antibody (AVA), tubulin antibody (anti-Ka1 tubulin), collagen antibodies (anti-Col), anti-endothelial cell antibodies (AECAs), anti-heat shock protein antibodies, and antiphospholipid antibodies [4,5]. These antibodies contribute to endothelial

damage, inflammation, and fibrosis, thereby accelerating graft dysfunction and failure. Recent studies have demonstrated that the activation of these non-HLA Abs is often triggered by acute rejection episodes, ischemia–reperfusion injury, hypoperfusion, calcineurin inhibitor toxicity, infections, or recurrent diseases [6,7]. Furthermore, their presence has been linked to increased risk of graft loss, even in patients without detectable HLA-DSAs. Despite these findings, routine screening for non-HLA Abs is not yet standard practice in clinical transplantation, and treatment strategies remain empirical rather than evidence-based [8–10].

While the understanding of the role of non-HLA Abs in graft survival continues to grow, a comprehensive overview remains lacking. This review aims to explore the development, mechanisms of action, clinical significance, and potential therapeutic strategies for non-HLA Abs in the context of KT.

The present review is the result of a comprehensive systematic web search across various databases, including PubMed, Google Scholar, Europe PMC, and ScienceDirect. We aimed to compile a thorough assessment of pertinent literature using search terms such as "non-HLA antibodies", "non-HLA Abs in kidney transplantation", and "detection techniques available for non-HLA antibodies" in various combinations. It is important to note that the literature cited in this review encompasses a global perspective and is not confined to any specific geographic region, with a focus on kidney transplantation. A total of 51 studies were included in this review article. By addressing the gaps in knowledge and highlighting emerging research, this review seeks to contribute to improved patient outcomes and inform future clinical guidelines.

2. Mechanism of Non-HLA Antibody Production

The mechanisms underlying the production of non-HLA Abs are not yet fully understood. However, both autoantibodies and alloantibodies targeting non-HLA appear to share similar pathophysiological pathways [1]. Their production can be triggered by various mechanisms, including ischemia–reperfusion injury, surgical trauma, alloimmune responses, soluble antigens, extracellular vesicles, and apoptotic bodies. These factors lead to the exposure of organ-derived autoantigens, prompting an immune response. Inflammation further enhances antigen processing and proteolysis, while post-translational modifications, oxidative stress, and molecular mimicry by infectious agents can create neoantigens that the immune system recognizes as foreign [1,7,8]. The initial step in the development of non-HLA Abs involves endothelial injury, which leads to the exposure of neoantigens or cryptic antigens. Such injury may result from various factors, including acute kidney injury, chronic kidney disease, lupus nephritis, focal segmental glomerulosclerosis, diabetes, or preeclampsia [8]. Given their significant impact on transplant outcomes, understanding the mechanisms behind non-HLA Ab production is essential for developing targeted therapies to improve graft survival and patient prognosis.

3. Major Types of Non-HLA Antibodies in Kidney Transplantation

Unlike HLA antibodies, non-HLA Abs target a diverse range of endothelial, extracellular matrix, and intracellular proteins, leading to complex immunopathological mechanisms. Their pathogenicity varies, and their detection and clinical interpretation remain challenging. Here, we critically discuss the major types of non-HLA Abs, their mechanisms of action, and their potential clinical implications.

3.1. MHC Class I Chain-Related Antigen A Antibodies (MICA Abs)

MICA, a glycoprotein expressed on endothelial, epithelial, monocytic, and dendritic cells, has been implicated in graft rejection [10]. Antibodies targeting MICA were among

the first non-HLA Abs reported in KT. One of the earliest studies evaluating the role of anti-MICA Abs in KT was conducted by Zou et al. [11]. Subsequent research has consistently demonstrated that the presence of pre-transplant or post-transplant anti-MICA Abs is associated with AMR or T cell-mediated rejection, leading to impaired kidney graft function [8,12–15]. Preformed anti-MICA Abs can arise from classic sensitizing events such as pregnancy, blood transfusions, or a history of prior transplants. However, they can also develop in the absence of such sensitizing events, likely due to autoimmune mechanisms. A mismatch between donor and recipient MICA alleles can result in de novo anti-MICA donor-specific antibody (DSA) formation, independent of HLA [16]. Anti-MICA Abs are believed to act synergistically with anti-HLA Abs, thereby increasing the risk of AR. The graft injury mediated by anti-MICA Abs may involve two primary mechanisms: natural killer group 2, member D (NKG2D)-mediated cytotoxicity and complement-mediated cytotoxicity [8]. Higher levels of anti-MICA Abs pre-transplant are correlated with increased graft loss rates. De novo MICA-DSA formation post-transplant is linked to chronic allograft dysfunction and fibrosis.

3.2. Angiotensin II Type 1 Receptor Antibodies (AT1R Abs)

These were first described by Dragun et al. in 2005 [17]. Since then, several studies have investigated their impact on KT outcomes, making them one of the most studied non-HLA antibodies in kidney transplantation [17–19]. T1R Abs are associated with various rejection phenotypes, including AMR, and contribute to poor renal graft function and survival in both pre- and post-transplant recipients [18]. AT1R Abs belong to the IgG1 and IgG3 complement-fixing subclasses and are classified as autoantibodies. Their formation involves a sequential pathophysiological process, which overlaps with general autoantibody formation mechanisms [19]. These Abs are more likely to be detected in patients with hypertension and frequently co-exist with HLA DSA, further worsening rejection outcomes.

3.3. Anti-Endothelin A Receptor (Anti-ETAR) Antibodies

Anti-ETAR Abs contribute to endothelial injury and autoimmunity, playing a role in KT rejection. The ETAR is expressed on endothelial cells, smooth muscle cells, and immune cells, with genetic factors influencing its expression [18,20]. These IgG1 antibodies act as agonists, binding to ETAR and leading to downstream immune activation. Anti-ETAR Abs have been detected in up to 47.4% of KT recipients [4]. The presence of anti-ETAR Abs is linked to AMR, vascular rejection, and poorer graft function, particularly within the first-year post-transplant. When co-occurring with AT1R-Abs, these antibodies further exacerbate adverse graft outcomes [20]. Anti-ETAR Abs contribute to vascular remodeling, endothelial activation, and fibrosis, leading to chronic transplant vasculopathy.

3.4. Anti-Perlecan/LG-3 Antibodies

Perlecan, a heparan sulfate proteoglycan found in vascular and epithelial basement membranes, contains the immunogenic LG3 domain. Increased levels of serum cathepsin L, LG3, and urinary LG3 correlate with vascular rejection in KT recipients, suggesting LG3 as both a biomarker and a contributor to vascular [21]. Endothelial dysfunction and apoptosis activate cathepsin L, which cleaves LG3 and releases immunogenic fragments, triggering anti-LG3 antibody production. These Abs, particularly IgG1 and IgG3, exacerbate ischemia–reperfusion injury, immune-mediated vascular rejection, and graft dysfunction [21,22]. Anti-LG3 Abs cause complement-dependent microvascular inflammation, vascular remodeling, and graft fibrosis. Their production requires T cells, and immunosuppressive treatment leads to decreased antibody levels [23].

3.5. Anti-Collagen Type IV, Type III, Type I, and Anti-Fibronectin Antibodies

Collagen type IV and fibronectin are crucial components of the glomerular basement membrane and can act as self-antigens following tissue injury. The presence of preformed or de novo Abs against these proteins increases the risk of transplant glomerulopathy. In affected patients, these Abs lead to T cell activation, with IFN-γ and IL-17 secretion increasing, while IL-10-producing T cells decrease [24]. This immune response contributes to the loss of peripheral tolerance. A study by Sehoon Park et al. found that anti-collagen type I and III Abs were associated with an increased risk of death-censored graft failure in AMR, highlighting their potential as diagnostic and prognostic biomarkers [25]. These autoantibodies are associated with chronic transplant glomerulopathy, a hallmark of chronic AMR. They contribute to progressive fibrosis, endothelial dysfunction, and microvascular inflammation, leading to long-term graft deterioration.

3.6. Anti-Agrin Antibodies

Agrin, a heparan sulfate proteoglycan, is a key component of glomerular basement membranes. Its C-terminal fragment (CAF) has been investigated as a potential biomarker for KT function [26].

CAF levels correlate with kidney function indicators such as creatinine and glomerular filtration rate (GFR), particularly early after transplantation. Elevated CAF is associated with delayed graft function, worsening proteinuria, and graft loss, which can be early indicators of chronic rejection Anti-agrin Abs are found in transplant glomerulopathy, a hallmark of chronic AMR, and may arise as autoantibodies following agrin overexpression [27,28].

3.7. Anti-Vimentin Antibodies

Vimentin, a type 3 intermediate filament protein, is found in multiple cell types, including endothelial and epithelial cells. While normally intracellular, it can relocate to the cell surface during endothelial injury, where it becomes an immunogenic autoantigen triggering anti-vimentin Abs [8].

Elevated anti-vimentin Abs correlate with graft failure, particularly in patients with anti-HLA DQ2 DSA. These Abs are linked to interstitial fibrosis, tubular atrophy (IFTA), and chronic AMR, where they activate the complement system [8,29]. They contribute to C4d deposition in peritubular capillaries, further exacerbating graft injury.

3.8. Anti-H-Y-Ab

The H-Y antigen, a minor histocompatibility antigen encoded by genes on the Y chromosome, is associated with 1 to 245 protein polymorphisms, including RPS4Y1, DDX3Y, UTY, and SMCY. These proteins exhibit strong immunogenic and specific properties. In KT with gender mismatches, female recipients of male donor grafts often develop alloantibodies targeting RPS4Y1 and DDX3Y antigens. These alloantibodies are linked to graft rejection and both short- and long-term graft failure [8]. These Abs are believed to mediate rejection via CD8+ T-cell responses, promoting chronic inflammation and graft dysfunction [30].

3.9. Anti-ARHGDIB Antibodies

ARHGDIB, an intracellular GTP-binding protein widely expressed in various tissues and involved in numerous cellular activities. Its expression in kidney grafts varies with normal and pathological states. In normal grafts, ARHGDIB shows weak expression in endothelial cells of interlobular arteries, peritubular capillaries, and glomerular capillaries. However, in acute tubular necrosis, its expression is robust in these cells and also present in podocytes and lymphocytes. A study of 4770 KT recipients revealed that pre-transplant anti-

ARHGDIB Abs significantly increase the risk of graft loss in deceased donor transplants, likely due to endothelial injury from ischemia–reperfusion [31]. Another study linked anti-ARHGDIB antibodies to reduced graft survival, especially in patients with anti-HLA DSA, though not with higher rejection rates. The ARHGDIB gene was over-expressed in AMR cases. Conversely, a separate study found elevated anti-ARHGDIB Abs in chronic AMR but no link to graft survival [8,30].

3.10. AntiPeroxisomal Trans-2-Enoyl-CoA Reductase (PECR Abs)

PECR is a peroxisomal NADPH-specific trans-2-enoyl-CoA reductase that reduces trans-2-enoyl-CoAs (chain lengths 6:1 to 16:1), with peak activity at 10:1 CoA. It plays a key role in fatty acid biosynthesis and is highly expressed in kidney, endothelial, and immune cells. Graft injuries can expose this intracellular protein, linking PECR to transplant glomerulopathy and biopsy-proven AMR in KT [8,32].

3.11. Anti-Protein Kinase C Zeta Type (PRKCZ Abs)

PRKCZ, a protein-kinase C involved in proliferation, apoptosis, cell survival, and inflammation, is overexpressed following ischemia–reperfusion injury in animal models. Sutherland et al. linked PRKCZ Abs to graft rejection and loss but concluded that insufficient data exist to confirm whether these Abs are causal or incidental [32].

Table 1 summarizes the major non-HLA antibodies, their target antigens, and their impact on graft survival.

Table 1. Different types of non-HLA antibodies and their role in kidney transplant rejection [6,8–33].

Antibody Type	Target Antigen	Expression Sites	Pathogenic Mechanisms	Clinical Impact
MICA Abs	MICA	Endothelial, epithelial, monocytes, dendritic cells	NKG2D-mediated cytotoxicity, complement activation	AMR, TCMR, increased AR risk
AT1R Abs	AT1R	Endothelial cells	Complement-fixing IgG1 & IgG3, endothelial activation	AMR, vascular rejection
Anti-ETAR Abs	ETAR	Endothelial and smooth muscle cells	Agonist activity on ETAR	AMR, vascular rejection, poor graft function
Anti-LG3 Abs	LG3 domain of Perlecan	Vascular basement membranes	Complement-dependent cytotoxicity	Microvascular inflammation, graft fibrosis
Anti-Collagen and Anti-Fibronectin Abs	Type I, III, IV Collagen, Fibronectin	Glomerular basement membrane	T cell activation, IFN-γ & IL-17 secretion	Transplant glomerulopathy, AMR
Anti-Agrin Abs	Agrin	Glomerular basement membrane	Autoantibody response	Chronic AMR, proteinuria, graft loss
Anti-Vimentin Abs	Vimentin	Endothelial, epithelial, immune cells	Complement activation (C4d deposition)	Chronic AMR, IFTA, graft failure
Anti-H-Y Abs	H-Y Antigen	Male donor kidney cells	Alloantibody-mediated rejection	Gender-mismatched transplant rejection

Table 1. *Cont.*

Antibody Type	Target Antigen	Expression Sites	Pathogenic Mechanisms	Clinical Impact
Anti-ARHGDIB Abs	ARHGDIB	Endothelial, immune cells	Endothelial injury, ischemia–reperfusion	Graft loss, AMR association
Anti-PECR Abs	ECR	Kidney, endothelial, immune cells	Exposure after graft injury	Transplant glomerulopathy, AMR
Anti-PRKCZ Abs	PRKCZ	Various tissues	Ischemia–reperfusion response	Potential role in graft rejection

Where, MICA Abs: MHC Class I Chain-Related Antigen A Antibodies; AT1R Abs: Angiotensin II Type 1 Receptor Antibodies; Anti-ETAR Abs: Anti-Endothelin A Receptor Antibodies, Anti-LG3 Abs: Anti-Perlecan/LG-3 Antibodies; Anti-Collagen and Anti-Fibronectin Abs: Anti-Collagen Type IV, Type III, Type I, and Anti-Fibronectin Antibodies; Anti-PECR Abs: Anti Peroxisomal Trans-2-Enoyl-CoA Reductase Antibodies, Anti-PRKCZ Abs: Anti-Protein Kinase C Zeta Type Antibodes; TCMR: T-Cell-Mediated Rejection, LG3: Laminin G-like domain 3; ARHGDIB: Rho GDP Dissociation Inhibitor Beta".

4. Mechanism of Injury

Non-HLA Abs contribute to allograft injury through both complement-dependent and complement-independent pathways, demonstrating the complex acute and chronic effects of these antibodies [34,35]. These processes collectively result in inflammation, fibrosis, and progressive graft dysfunction. Complement activation plays a key role in the pathogenicity of anti-HLA DSA on endothelial cells, promoting membrane attack complex (MAC) formation, chemokine release, and cellular activation. In contrast, AMR involving anti-endothelial cell antibodies (AECAs) often occurs without complement deposition (e.g., C4d or C3d), suggesting the involvement of complement-independent mechanisms. These mechanisms include antibody-dependent cellular cytotoxicity (ADCC), mediated by natural killer (NK) cells, and signaling pathways like PI3-kinase and Akt, which regulate endothelial cell survival, migration, and activation. IgG subclasses play distinct roles in complement activation and Fc receptor interactions, with IgG1 and IgG3 being more potent than IgG2 and IgG4. Certain Abs, such as anti-AT1R, can activate transcription factors and induce the release of pro-inflammatory cytokines. AECAs may also promote endothelial apoptosis and graft thrombosis, though their exact mechanisms remain poorly understood [3,36]. The presence of AECAs post-transplantation could reflect either an injury response or a consequence of the transplantation process itself. While new diagnostic tools are emerging, further studies are needed to determine the clinical significance of different non-HLA antibodies and improve strategies for rejection monitoring and prevention [6,37]. The summary of the injury mechanisms of the major types of non-HLA Abs is shown in Table 2.

Table 2. Non-HLA antibodies and their mechanisms of injury [3,6,31,34,36,37].

Non-HLA Antibodies	Autoantibody/Alloantibody	Mechanism of Injury
MICA Abs	Autoantibody and Alloantibody	Complement-dependent
AT1R Abs	Autoantibody	Complement-independent
Anti-ETAR Abs	Autoantibody	Complement-independent
Anti-perlecan Abs	Autoantibody	Complement-dependent
Anti-collagen types IV, III, I Abs	Autoantibody	Could be complement-dependent or involve antibody-mediated cellular cytotoxicity (ADCC).
Anti-Agrin Abs	Autoantibody	Could be complement-dependent or receptor blockade
Anti-vimentin Abs	Autoantibody	Complement-dependent
Anti-H-Y-Abs	Alloantibody	Complement-dependent
Anti-ARHGDIB Abs	Autoantibody	Complement-dependent
Anti-PEC Abs	Autoantibody	Complement-dependent
Anti-PRKCZ Abs	Autoantibody	Signaling disruption or immune-mediated cytotoxicity

5. Non-HLA Antibody Detection

Although many assays have been developed, routine screening for non-HLA antibodies has not yet been widely adopted in transplant medicine. Techniques such as endothelial crossmatching with flow cytometry (e.g., XM-ONE) have been utilized, alongside other methods like ELISA, high-density protein arrays, indirect immunofluorescence, and SEREX, for antibody detection [38]. Current diagnostic methods for detecting non-HLA Abs face technical challenges and yield inconsistent results, underscoring the need for more reliable and sensitive testing approaches [39]. Simultaneous detection of multiple Abs could enhance understanding of their role in graft rejection and help identify risk profiles. Effective detection methods include solid-phase assays targeting GPCRs, MICA, collagen-V, and vimentin, as well as immunofluorescence, ELISA, and flow crossmatch. Combining ELISA with cytotoxicity assays in pre-transplant testing offers the advantage of distinguishing anti-HLA activity from anti-non-HLA activity. Late graft failures attributable to non-HLA effects might be preventable by identifying recipients at higher risk of late graft loss before transplantation [37,38]. This early identification could enable the development of tailored immunosuppressive strategies. Specifically, the detection of anti-AT1R Abs has emerged as a significant complementary risk factor, with levels above 9 U/mL serving as an independent predictor of graft failure. Consequently, monitoring non-HLA Abs, such as anti-AT1R Abs, should accompany the assessment of HLA-DSA to effectively identify high-risk patients [5,7,20]. There are studies utilizing the XM-ONE assay to detect anti-endothelial cell antibodies (AECAs) in kidney transplantation. The findings indicate varying associations between AECAs and transplant outcomes. Breimer et al. (2009) found that pre-transplant AECA positivity was linked to a higher risk of rejection or impaired kidney function post-transplant [39]. In contrast, Soyöz et al. (2020) observed no detectable AECAs in post-transplant sera, even among patients with biopsy-confirmed rejection [40]. Zitzner et al. (2013) reported no correlation between XM-ONE results and biopsy-proven rejection or vasculopathy at one-year post-transplant [41]. Yu et al. (2020) suggested that AECAs and AT1R-Abs might independently contribute to worse post-transplant outcomes in low-risk patients [42]. Lastly, Philogene et al. (2017) found that AT1R-Abs may exacerbate microvascular injury in antibody-mediated rejection (ABMR), particularly in the presence of HLA-DSA [43]. The information published by Rosa et al. further supports the ongoing debate regarding the clinical significance of non-HLA antibodies and highlights the need for standardized methodologies in AECA detection [38]. Table 3 summarizes the key findings of various techniques for detecting non-HLA Abs in KT.

Table 3. Summary of the key findings of different techniques for detecting non-HLA antibodies in kidney transplantation [5,7,37–43].

Technique	Description	Key Findings	Strengths	Limitations
Solid-Phase Assays (ELISA, Luminex)	Detects specific non-HLA Abs (e.g., AT1R, ETAR, MICA) using antigen-coated beads or plates.	High levels of AT1R and MICA Abs have been linked to graft rejection and microvascular injury.	High-throughput, widely available, standardized.	May not account for donor-specific variations; limited to known antigens.
Flow Cytometry-Based Crossmatching	Uses donor endothelial cells as targets to detect non-HLA Abs.	Identifies AECAs, which have been linked to acute rejection in some cases.	High sensitivity provides cellular-level information.	Variability in IgG/IgM detection; difficult to standardize results.
XM-ONE Assay	Commercial flow cytometry-based test using endothelial precursor cells (EPCs).	Some studies associate AECAs with graft dysfunction, while others find no significant correlation.	Standardized commercial assay.	EPCs lack key endothelial markers (e.g., CD31, CD34), leading to uncertain clinical relevance.
Indirect Immunofluorescence (IIF)	Uses fluorescent-labeled antibodies to detect AECAs in serum.	Detects AECAs, but findings are inconsistent in predicting rejection.	Simple and widely available.	Lower sensitivity and specificity than flow cytometry.
Genetic Screening (Genome-Wide Analysis)	Identifies non-HLA mismatches linked to transplant rejection.	Some mismatches in transmembrane proteins were linked to increased graft loss.	Provides insight into patient–donor incompatibility.	Expensive, not widely used in clinical practice.
Multiplex Bead Assays (Luminex Panel)	Screens for multiple non-HLA Abs simultaneously.	Identified new rejection-associated antibodies (e.g., anti-vimentin, ARHGDIB).	High sensitivity, detects a broad range of antibodies.	Often lacks pre-transplant data, making causation difficult to establish.

6. Treatment Strategies for Pathogenic Non-HLA Antibodies

Non-HLA Abs are not an absolute contraindication for transplantation, but their presence may indicate prior or ongoing tissue injury. Identifying these Abs can help pinpoint patients who need treatment, either before or after transplantation, to prevent graft injury. Immunologic risk stratification, which includes assessing both HLA-DSA and non-HLA Abs, can provide a clearer understanding of sub-phenotypes associated with AMR or delayed graft function, allowing for timely initiation of targeted therapies. Early treatment is crucial for patients with increased immunologic risk and circulating non-HLA Abs [33,44]. Therapeutic approaches to reduce non-HLA Ab levels are similar to those used for HLA antibodies. Various therapeutic strategies have been developed to manage these antibodies, aiming to reduce AMR and improve long-term graft function. These strategies can be broadly categorized into pharmacological and non-pharmacological approaches. Pharmacological therapies, including intravenous immunoglobulin (IVIG), plasmapheresis, rituximab, bortezomib, eculizumab, and tocilizumab IVIG, modulate the immune response by inhibiting complement activation and reducing antibody production. It is frequently used in desensitization and post-transplant treatment, particularly in combination with plasmapheresis, whereas plasmapheresis (therapeutic plasma exchange, TPE) directly removes circulating DSAs from the bloodstream. It is effective in acute circumstances but requires combination with IVIG or other agents to prevent rebound antibody production [45,46]. Rituximab (anti-CD20 monoclonal antibody) depletes B cells, reducing antibody production. It is often used in desensitization and AMR management but has limited effects on plasma cells that produce existing antibodies [46,47]. Furthermore,

bortezomib, a proteasome inhibitor, targets plasma cells, reducing long-lived antibody production, and is effective in treating refractory AMR but is associated with side effects such as neuropathy, whereas eculizumab, a C5 complement inhibitor, prevents complement-mediated injury in AMR. Used in severe AMR cases, particularly in high-risk transplants, though its high cost limits widespread use. Tocilizumab, an IL-6 receptor blocker, reduces B cell activation and modulates the inflammatory response and is an emerging therapy with promising results in refractory AMR [48,49]. Further, extracorporeal photopheresis (ECP) and immune adsorption are also employed as non-pharmacological approaches [46,47]. Immune adsorption is another way to selectively remove antibodies without affecting other plasma components and is more specific than plasmapheresis, though it is less widely available [50] Additionally, angiotensin receptor blockers, such as losartan, have also been used to block AT1R-Ab-mediated rejection; however, chronic use may worsen outcomes by increasing AT1R expression. Additionally, bortezomib has shown promise in inhibiting the production of anti-LG3 auto-antibodies, potentially providing new therapeutic options to prevent auto-antibody production before transplantation [5,39,48,49,51]. Table 4 summarizes the key findings of different therapeutic strategies (both pharmacological and non-pharmacological) for non-HLA Ab elimination.

Table 4. Summary of the key findings of different therapeutic strategies [5,33,44–51].

Treatment	Mechanism	Indications	Efficacy	Limitations
Intravenous Immunoglobulin (IVIG)	Immunomodulation, complement inhibition	Desensitization, AMR	Moderate	High dose required
Plasmapheresis (**Therapeutic Plasma Exchange** (TPE))	Direct antibody removal	Acute AMR, desensitization	High	Rebound effect, requires adjunct therapy
Rituximab	B cell depletion	AMR, desensitization	Moderate	Limited effect on plasma cells
Bortezomib	Plasma cell depletion	Refractory AMR	High	Neuropathy risk
Eculizumab	Complement inhibition	Severe AMR, high-risk transplants	High	Expensive
Tocilizumab	IL-6 pathway inhibition	Refractory AMR	Moderate	Limited data
Desensitization	Pre-transplant DSA reduction	High DSA burden	Variable	Requires intensive monitoring
Photopheresis (ECP)	Immune modulation	Chronic rejection, refractory AMR	Moderate	Limited availability
Immune Adsorption	Specific antibody removal	AMR	Moderate	Not widely available

7. Conclusions

In summary, non-HLA Abs are a significant factor in both acute and chronic rejection following KT, contributing to graft injury and loss. These antibodies can target a variety of non-HLA, such as MICA and AT1R, and may develop either prior to transplantation or de novo after transplantation, triggered by factors like ischemia, infection, or immune responses. The presence of non-HLA Abs initiates complex pathogenic mechanisms, including complement activation, antibody-dependent cellular cytotoxicity, and signaling pathways that lead to endothelial damage and graft rejection. Although non-HLA Abs are not absolute contraindications for transplantation, their detection is crucial in iden-

tifying patients at higher immunological risk. Reliable diagnostic methods are essential for accurately identifying these antibodies, and their monitoring can guide personalized immunosuppressive strategies to prevent graft rejection and failure. Current treatment approaches, such as plasmapheresis, IVIG, rituximab, and other immunosuppressive therapies, aim to reduce antibody levels and mitigate graft damage. Further research is necessary to fully understand the mechanisms of non-HLA Abs and to enhance their detection and management in transplant recipients.

8. Future Perspectives

Looking ahead, the role of non-HLA Abs in KT is expected to evolve with the development of improved diagnostic tools, personalized treatment options, and enhanced patient outcomes. As research advances, non-HLA Abs will likely become increasingly important in the clinical management of transplant patients, providing new insights into graft survival and immunological risk factors.

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