



antibodies, a less neugistic effect [4,15].

### Non-HLA antibodies incidence and pathogenicity

non-HLA antibodies function as complement- and non-complementing antibodies and they may induce a large variety of allograft injuries, reflecting the complexity of their acute and chronic actions [17].

Complement-dependent and complement-independent mechanisms are not mutually exclusive [8,18]. For example, Anti-Vimentin Antibodies (AVA) seen to complement [19]. Similarly, ANCA Abs have been shown to be more efficient at complement activation and have been associated with C4d<sup>+</sup> AMR [2]. In contrast, 40%-50% of cases of severe sclerotic changes such as binoid necrosis are C4d-negative, implicating involvement of either non-complementing antibodies or other mediators, as noticed in cases of AMR in the presence of ANCA-Ab or ANCA that occurred in the evidence of complement activation [2, 20,21].

Besides, antibodies can induce lysis of target-cells, inhibit membrane bound antibodies through activation of natural-killer cells, a process called antibody-dependent cell mediated cytotoxicity [1,22]. Furthermore, non-HLA antibodies also contribute to short and long-term structural changes in the arterial wall or direct endothelial at promote clotting and narrowing [8].

Additionally, the capability of non-HLA antibodies to mediate allograft injury may depend on their specificity and affinity, density of the target antigen, and synergistic HLA antibodies [2]. It is likely that non-HLA antibodies can directly induce major graft damage since they react to rejection induced by these antibodies rather occur separately [23-37].

### Non-HLA Antibodies as Biomarkers of Injury

In the other hand, other studies claimed that non-HLA antibodies represent a marker for injury or moral activation rather than having independent pathogenic potential [2,11]. Therefore, in the near future, non-HLA antibodies may be used as biomarkers of ongoing immune response and herald the need for more suitable immunosuppression [8].

### Compartment specificity

non-HLA immune responses, including anti-ANCA antibodies, are detected against kidney compartment-specific antigens, indicating post-transplant recognition for renal pelvis and cortex specificity

Targets for Non-HLA Antibodies
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• Antibodies against G Protein-Coupled Receptors (GPCRs): AT1R (ETAR)
• Antiendothelial cell antibodies (AECAs)
• Anti endothelial precursor cell antibodies (AEPCA)
• LG3 (Perlecan)
•
•
• Antivimentin: <i>Intermediate Filaments – Vimentin (AVA)</i>

Clinical Relevance of Non-HLA antibodies	
Antibody	Clinical Relevance
Antivimentin (AVA)	tubular atrophy [27, 40-41].
histocompatibility complex class gene: A	transplantations: well matched for the HLA) [1,7,42,44]  * Contrary to expectations, patients with positive patients [1].
Anti-endothelial precursor cell antibodies  (AEPCA)	serum creatinine levels at 3 and 6 months post-Tx [45].
1 receptor (AT1R)	*Associated with a higher incidence of graft loss [1,28,49], cellular mediated) and malignant hypertension [7,27,29,46].  *Patients with both AT1R-Abs and HLA-DSA had greater incidence of allograft damage and graft loss [29,46-47].  *Patients with anti-AT1R Abs level >9 U/ml run a higher risk of graft failure independently of classical immunological risk factors [28].  *Patients with both anti-AT1R and DSA had lower graft survival than those with DSA alone [48].
Endothelin-1 type A receptor (ETAR)	*Associated with a higher incidence of graft loss and  *Vasculopathy or arteritis were observed in patients with
Duffy antibody (a chemokine receptor)	
Agrin antibody	*Associated with transplant glomerulopathy [7].
antibodies	glomerulopathy, a chronic lesion characterized by duplication of glomerular basement [27,50].
Antiendothelial cell antibodies (AECA)	[53].

**Table 3:** Clinical relevance of non-HLA antibodies.

### Non-HLA antibodies monitoring and graft failure prediction

Many of the late graft failures attributable to non-HLA effects

(antibodies against antigens expressed on umbilical vein endothelial cells), A or crossmatch techniques (antibodies against donor endothelial progenitors) (table 4) [3].

At present, use of both A and cytotoxicity assays in parallel for pre-transplant testing seems to allow a separation of anti-HLA from anti-non-HLA activities [14].

### **Current Treatment Modalities for Pathogenic Non-HLA Antibodies**

The presence of non-HLA antibodies are not an absolute contraindication to transplantation, but rather may suggest pre-emptive or ongoing tissue injury, and may be useful in identifying patients who should be treated either prior to transplantation or post-transplantation to avoid graft injury [2].

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21. Ming Y, Hu J, Luo Q, Ding X, Luo W, et al. (2015) Acute antibody-mediated