Antibody-mediated rejection after lung transplantation

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Abstract: Antibody-mediated rejection (AMR) has been identified as a significant form of acute allograft dysfunction in lung transplantation. The development of consensus diagnostic criteria has created a uniform definition of AMR; however, significant limitations of these criteria have been identified. Treatment modalities for AMR have been adapted from other areas of medicine and data on the effectiveness of these therapies in AMR are limited. AMR is often refractory to these therapies, and graft failure and death are common. AMR is associated with increased rates of chronic lung allograft dysfunction (CLAD) and poor long-term survival. In this review, we discuss the history of AMR and describe known mechanisms, application of the consensus diagnostic criteria, data for current treatment strategies, and long-term outcomes. In addition, we highlight current gaps in knowledge, ongoing research, and future directions to address these gaps. Promising diagnostic techniques are actively being investigated that may allow for early detection and treatment of AMR. We conclude that further investigation is required to identify and define chronic and subclinical AMR, and head-to-head comparisons of currently used treatment protocols are necessary to identify an optimal treatment approach. Gaps in knowledge regarding the epidemiology, mechanisms, diagnosis, and treatment of AMR continue to exist and future research should focus on these aspects.

Keywords: Lung transplantation; graft rejection; allograft tolerance; acute lung injury; complement component; complement C4d; diagnostic techniques and procedures; plasmapheresis; intravenous immunoglobulins (IVIG); rituximab; eculizumab; outcome assessment

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Introduction

Lung transplantation is the ultimate treatment for selected patients with end-stage lung disease. While advances in surgical technique have improved early survival, long term outcomes remain disappointing, and the median survival after transplantation in the most recent era is 6.5 years (1). Chronic lung allograft dysfunction (CLAD) is the leading cause of death beyond the first year after lung transplantation and has emerged as the main barrier to better long-term outcomes (1). Antibody-mediated rejection (AMR) has been increasingly recognized after lung transplantation and has been consistently identified as a significant cause of morbidity, CLAD, and graft failure (2-7). Here, we present a review of our current understanding of AMR and discuss ongoing research and future directions to further our understanding of AMR and improve the management of this serious complication after lung transplantation.

History

Our understanding of AMR in lung transplantation was historically limited to hyperacute rejection, which
occurs when preformed donor-specific antibodies (DSA) bind to mismatched human leukocyte antigens (HLA) (8,9). Patients developed significant and often fatal graft failure intra-operatively or in the immediate postoperative period with hemorrhagic pulmonary edema and diffuse pulmonary infiltrates on imaging studies (8,10,11). Severe graft dysfunction occurred in spite of intensive immunosuppression targeting T-cell proliferation and activity, which suggested a role for humoral immunity in precipitating this response. Typically, these patients were found to have DSA and a positive direct lymphocytotoxicity crossmatch. Further investigation found that allosensitization was associated with worse survival after transplantation unless the reactive HLA were avoided in a prospective donor (8-10,12,13). Case reports of hyperacute rejection suggested the need for standardization of pre-transplant crossmatching (6,8). Although hyperacute rejection has become rare in the current era because of improved HLA antibody detection assays, it illustrates that HLA antibodies can cause fulminant graft failure and that the capillary endothelium is the focal point of injury.

Over time, cases occurring later after transplantation were recognized and our understanding of acute AMR began to evolve. Badesch and colleagues presented a case series of 5 patients with pulmonary capillaritis ranging from 3 weeks to months after transplant (14). In this series, all patients presented with alveolar hemorrhage and graft failure with temporary improvement in graft function with intensification of immunosuppression and activity, which suggested a role for humoral immunity in precipitating this response. Typically, these patients were found to have DSA and a positive direct lymphocytotoxicity crossmatch. Further investigation found that allosensitization was associated with worse survival after transplantation unless the reactive HLA were avoided in a prospective donor (8-10,12,13). Case reports of hyperacute rejection suggested the need for standardization of pre-transplant crossmatching (6,8). Although hyperacute rejection has become rare in the current era because of improved HLA antibody detection assays, it illustrates that HLA antibodies can cause fulminant graft failure and that the capillary endothelium is the focal point of injury.

Mechanisms of AMR were initially elucidated by investigations in transplantation of other solid organs, especially in kidney transplantation (16,17). This work has shown hyperacute, acute, and chronic forms of AMR in which activation of allospecific B-cells and plasma cells leads to formation of DSA that bind to HLA on the endothelium of vessels within the allograft (6,16,18,19). Antibody binding leads to complement dependent and independent recruitment of immune cells leading to graft dysfunction and tissue injury (6,16,18-20).

DSA were first identified in renal transplant recipients in the 1960s and were postulated to be the underlying cause for immediate graft failure. Subsequent investigation confirmed that the presence of preformed antibodies in recipient sera was associated with a high rate of graft failure. These failures led to the use of a crossmatch of the recipients serum with donor cells and assays to identify DSA (21-23). Since that time, highly sensitive and specific solid phase assays for the identification of HLA antibodies have been developed (6,16,24). Recipients may have pre-existing HLA antibodies (as a result of prior sensitizing events such as blood transfusion, pregnancy, or previous organ transplantation) or may develop HLA antibodies de novo after transplantation (6,9,11,12,17). Recipients may have antibodies to MHC class I antigens (HLA-A, HLA-B, or HLA-C) which are present on all nucleated cells, or to MHC class II antigens (HLA-DQ, HLA-DR, HLA-DP) which are present on antigen presenting cells (APCs) (25). Notably, pro-inflammatory cytokines have been shown to induce the expression of class II HLA on pulmonary endothelial cells (26,27). Recipients may also develop antibodies to non-HLA antigens (allo- or auto-antigens); however, no highly sensitive assays have been developed to detect such antibodies to date (5,25,28).

Complement-binding DSA are associated with worse
outcomes in kidney and heart transplant recipients, and preliminary work echoes these findings in lung transplantation (3,29,30). DSA bind antigens on donor endothelial cells with activation of the classical complement cascade and formation of the membrane attack complex (MAC). The MAC causes endothelial cell injury with exposure of the basement membrane and activation of the coagulation cascade leading to thrombosis and infarction. Moreover, complement factors 3a and 5a (C3a and C5a) are chemokines that attract immune cells to the allograft propagating inflammation and graft injury (11,15,31). Importantly, not all DSA bind and activate complement, and DSA-associated complement-independent mechanisms of allograft injury have been studied in vitro and in vivo models of solid organ transplantation (6,16,31-36). Proposed mechanisms include activation of signaling cascades that lead to endothelial and smooth muscle cell proliferation, release of inflammatory cytokines and chemokines, and von Willebrand factor (vWF) and P-selectin mediated platelet activation (6,11,31-36). These findings not only implicate DSA in complement-independent mechanisms of AMR, but also suggest a role for DSA in chronic allograft rejection (6,11,31,36,37).

Recent work by Li and colleagues has shown that the immunopathology of AMR may be different in lung allografts compared to allografts of other solid organs (38). This group utilized a mouse lung retransplantation model and found that tolerant pulmonary allografts developed bronchus-associated lymphoid tissue (BALT) (38). Suppression of FoxP3+ regulatory T-cells in this model led to the absence of BALT formation and development of AMR (38). These findings suggest that regulatory T-cells residing in BALT of pulmonary allografts suppress B-cell activation locally and that antigen presentation can occur within the allograft (38). These findings are contrary to models of AMR in other solid organ transplants where humoral responses are regulated peripherally (38). This is further echoed by the differences noted in the diagnosis, management, and outcomes of AMR in lung allografts as compared to other solid organ transplants (3-6,31,39,40).

**Clinical manifestations and diagnosis**

The International Society for Heart and Lung Transplantation (ISHLT) convened a working group in 2016 to create a uniform definition of AMR (6). The definition was largely based on experience in kidney and heart transplantation. According to this definition, a definite diagnosis of AMR requires the presence of allograft dysfunction, DSA, characteristic lung pathology, complement factor 4d (C4d) deposition on capillary endothelium, and the exclusion of alternate etiologies of graft dysfunction (6). The working group recognized potential shortcomings of these diagnostic criteria and proposed a qualitative assessment of the certainty of the diagnosis as being definite, probable, or possible based on the number of criteria met (6). Graft dysfunction associated with clinical AMR may range from fulminant respiratory failure to asymptomatic dysfunction identified on surveillance spirometry (6). Chronic AMR is a defined form of rejection in kidney transplantation and has been suggested in both heart and lung transplantation, but there is no specific definition in lung transplantation (16,17). Although investigations in lung transplantation have shown an association between DSA and CLAD, which most commonly presents as BOS, it is unclear if such cases represent chronic AMR as these are typically indistinguishable from cases that lack DSA (2-4,6,9,11,37,39,41). Furthermore, depletion of DSA has been associated with greater freedom from BOS (37). Roux and colleagues reviewed 206 transplanted patients and found that restrictive allograft syndrome (RAS) was only present in patients who had DSA and developed AMR, while BOS or mixed CLAD (BOS and RAS) were found in all groups of patients regardless of presence of DSA or AMR (5). It is appealing to consider whether RAS is a form of chronic AMR, but definitive data have been lacking to date. The ISHLT working group also recognized sub-clinical AMR as the detection of histologic criteria of AMR in the absence of graft dysfunction (6). Chronic and sub-clinical AMR remain poorly described in lung transplantation and further investigation is required to identify the significance of these diagnoses.

The presence of DSA is requisite for a diagnosis of AMR based on these criteria; however, only a minority of patients with DSA go on to develop AMR (11,16,42). Furthermore, detection of DSA can be missed due to phasic release or absence of the antigen on the screening assay (6). Highly sensitive solid phase assays for DSA provide mean fluorescence intensity (MFI) values which do not always accurately depict antibody strength (43). Specificity can be improved with assays for binding of complement factor 1q (C1q) but this may decrease sensitivity (43).

Multiple pathologic findings of AMR have been described in lung allografts including capillary
inflammation, endothelialitis, and acute lung injury (9,44,45). The earliest report of hyperacute AMR of a lung allograft noted the presence of acute lung injury with hyaline membrane formation along with alveolar edema and hemorrhage (8). Subsequent reports described pulmonary capillaritis and neutrophil infiltration as the hallmark findings of pulmonary AMR (46). However, further investigation has shown that neutrophils are just one of the many cell types that are part of the spectrum of microvascular inflammation and the absence of neutrophil infiltration or capillaritis should not rule out AMR (31,47,48). Neutrophilic capillaritis is nonspecific and has been associated with graft dysfunction in the absence of AMR (41,42,48). Furthermore, the presence of capillaritis may be obscured by severe acute lung injury. Acute lung injury may present as alveolar edema, alveolar hemorrhage, hyaline membrane formation with diffuse alveolar damage, fibrin deposition, intravascular platelet or fibrin thrombi, or arteriolar fibrinoid necrosis (2,47,49). These findings suggest that the histopathologic findings of AMR are nonspecific and underscore the need for a multidisciplinary approach to diagnosis.

Staining for complement split product C4d is the most controversial criterion for the diagnosis of AMR (50). Complement split products bind to endothelial cells non-covalently and are subsequently inactivated by membrane cofactor protein, decay accelerating factor, and CD59 (51). However, unlike other complement split products, C4d binds the endothelium covalently via a thioester bond (51). This covalent bond is stable, resistant to shedding, and allows C4d to be detected long after other complement split products have been inactivated (51). While C4d staining gained popularity in diagnosis of AMR in renal allografts and provides direct evidence of the immune-pathologic effect of antibodies, it has proven to be a challenging criterion in AMR of lung transplant recipients (5,6,11,44). C4d staining has been shown to be positive in pathology other than AMR such as ischemia-reperfusion injury, high grade ACR, and infection (5,6). Furthermore, C4d has been shown to be positive in only a minority of cases of AMR in lung transplant recipients, giving rise to “C4d-negative” AMR (2-4,52). It remains unclear if C4d-negative AMR represents a unique form of AMR due to complement-independent pathways or if this is related to limitations of staining or interpretation of specimens (52). Finally, Roden and colleagues found poor correlation between immunofluorescence and immunohistochemical testing for C4d, and poor inter-reader reliability among pathologists (50).

**Treatment**

Treatment options for AMR in lung transplantation have been adapted from other areas of medicine. Data supporting the use of individual interventions are sparse and no randomized clinical trials or head-to-head comparisons have been undertaken, making it difficult to draw conclusions about the efficacy of any single intervention (Table 1). Treatment regimens generally consist of multiple interventions and are individualized based on clinical course and response to other therapies.

**Corticosteroids**

Corticosteroids inhibit the early steps of the acute inflammatory response by altering the transcription of numerous genes in leukocytes (53). These genes affect leukocyte maturation, differentiation, distribution, and trafficking (53). High-dose corticosteroids are utilized in treatment regimens for AMR across kidney, heart, and lung transplantation (4,16,54). Astor and colleagues presented a retrospective review of 40 patients of whom only 43% responded to steroid monotherapy (46). Steroid resistance was identified as a marker for AMR in early reports (14,46).

**Plasmapheresis**

Plasmapheresis separates and discards plasma from whole blood replacing it with fresh frozen plasma or albumin and, therefore, eliminates circulating antibodies. In addition to reducing DSA, plasmapheresis has been shown to decrease deposition of complement split products (15). While plasmapheresis depletes circulating antibody, it does not decrease antibody production and can result in a rebound increase in antibody production. Due to its ability to eliminate circulating antibody, plasmapheresis gained popularity for the treatment of AMR in kidney transplantation (55). Retrospective studies in AMR of lung allografts have found variable benefit with use of plasmapheresis (4,7,8,10,12,14,15,46,56). These results are challenging to interpret, as plasmapheresis is rarely used as monotherapy and plasmapheresis protocols differ among studies.

**Intravenous immunoglobulin (IVIG)**

IVIG has traditionally been used in the treatment of
immunodeficiency syndromes and passive immunity but also has applications in immune mediated conditions such as Guillan-Barré syndrome, immune thrombocytopenia (ITP), and myasthenia gravis. IVIG has become a standard part of protocols for treatment of AMR, but the precise mechanism of action is unclear (57). Proposed mechanisms include modulation of expression and function of the Fcγ receptor, inactivation of DSA, downregulation of B-cells, inhibition of complement cascade, reduction of MHC class II expression (57,58). IVIG may be used as monotherapy but is more commonly used in conjunction with plasmapheresis and/or corticosteroids (57,59). Dosing of IVIG has been variable with ranges from 100–2,000 mg/kg (4,57).

**Rituximab**

Rituximab is an anti-CD20 antibody that binds to pre-B-cells and mature B-lymphocytes in circulation, lymph nodes, and bone marrow and induces apoptosis and cell lysis (60). While rituximab depletes circulating B-cells, it has no known effect on plasma cells that may already be producing antibody. Rituximab has been studied in the treatment of B-cell neoplasms and autoimmune conditions (60). Rituximab plus IVIG was found to improve survival over IVIG alone in a protocol to preemptively treat DSA; however, groups were not randomized and no difference in rejection rates was found (37). Indeed, data for the treatment of AMR with rituximab are sparse.

**Proteasome inhibition**

Proteasomes degrade misfolded and ubiquitinated proteins. Bortezomib and carfilzomib bind and inhibit proteasomes in plasma cells allowing the accumulation of these proteins and leading to plasma cell apoptosis (61-63). Proteasome inhibitors have largely been studied in the treatment of multiple myeloma (61,62). Observational studies have shown that treatment with proteasome inhibitors in AMR depletes DSA and improves allograft function (61,62), but no head-to-head comparisons or clinical trials have been published to date.

**Complement inhibition**

Eculizumab is a monoclonal antibody that binds to C5 and inhibits formation of the MAC. Eculizumab has largely been studied in atypical hemolytic uremic syndrome. Case reports utilizing eculizumab as part of a multimodal treatment regimen for AMR have shown depletion of DSA and improvement in allograft function (10,64), but no head-to-head comparisons or clinical trials have been published to date.

**Long-term outcomes**

Despite improvements in diagnosis, clinical outcomes after AMR remain poor (39). Astor and colleagues reported a case series of 40 patients who developed AMR and found 1- and 5-year survival to be near 80% and 40% respectively (46). Otani and colleagues presented a series of 9 patients who received therapy for AMR in which 5/9 initially improved with therapy, but 7/9 eventually developed CLAD and 6/9 (67%) died within 3 years of diagnosis of AMR (4). Witt and colleagues reported a series

| Treatment          | Mechanism                                                                 | References |
|--------------------|---------------------------------------------------------------------------|------------|
| Corticosteroids    | Alter transcription of genes in leukocytes                                | (4,14,16,46,53,54) |
| Plasmapheresis     | Elimination of circulating antibodies; decrease deposition of complement split products | (4,7,8,10,12,14,15,46,55,56) |
| Intravenous Immunoglobulin (IVIG) | Unclear; proposed mechanisms include modulation of Fcγ receptor, inactivation of DSA, downregulation of B-cells, inhibition of complement cascade, reduction of MHC class II expression | (4,57-59) |
| Rituximab          | Depletion of circulating B-cells                                           | (37,60)    |
| Proteasome Inhibition | Plasma cell apoptosis                                                     | (61-63)    |
| Complement Inhibition | Inhibition of formation of the membrane attack complex                   | (10,64)    |

AMR, antibody-mediated rejection; DSA, donor-specific antibodies.
of 21 patients who developed AMR of whom 6/21 died of refractory AMR, and all 15 who improved eventually developed CLAD (3). Overall, 15/21 (71%) patients died during the study period and the median survival after the diagnosis of AMR was 593 days (3). Aguilar and colleagues reported a series of 73 cases of AMR and found a 30-day mortality of 26% despite aggressive antibody depleting treatment (52). Indeed, multiple reports have shown that the inability to clear DSA and a diagnosis of AMR are associated with increased risk of CLAD (3,4). These reports suggest that although AMR may be a reversible cause of acute graft dysfunction, there is a high incidence of CLAD and poor long-term survival after AMR.

Sensitization prior to transplantation

The presence of HLA antibodies prior to transplantation has been associated with variable outcomes. While some reports found no difference in survival, acute rejection, or BOS, others have shown decreased survival, decreased rates of transplantation, prolonged waiting times, and increases in post-transplant ventilator days, acute rejection, AMR, and BOS (65-70). Notably, HLA class II antibodies have been associated with worse outcomes (3,52,68). Brugiere and colleagues found that patients with class II DSA had significantly higher mortality and significantly lower freedom from BOS (68). Descriptive studies by Witt et al. and Aguilar et al. also noted an association between HLA class II antibodies, especially HLA-DQ antibodies, and the development of AMR (3,52). Notably, pro-inflammatory cytokines have been shown to induce the expression of class II HLA on pulmonary endothelial cells (26,27). Together, these studies illustrate that endothelial cells are the focal point of antibody-mediated injury.

Desensitization protocols have been implemented for sensitized patients with variable success. Appel and colleagues treated 12/35 (34%) sensitized patients with peri-transplant IVIG and extracorporeal immunoadsorption (ECI) and found a significant decrease in acute rejection but no significant difference in survival or BOS (71). Snyder and colleagues treated 18/114 (16%) sensitized patients with a desensitization protocol including plasmapheresis, methylprednisolone, bortezomib, rituximab, and IVIG (72). Among the 9/18 (50%) treated patients who went on to receive a transplant, they found a significant decrease in HLA antibody with pretreatment MFI 5,000–10,000; however, they found no difference in PRA, cPRA, or post-transplant survival (72). Tinckam and colleagues treated 146 patients with known DSA or with PRA >30% with a desensitization protocol including perioperative plasma exchange, IVIG, anti-thymocyte globulin, and mycophenolic acid and compared them to 194 unsensitized controls (73). They found that treated, sensitized recipients had significantly lower rates of acute rejection compared with unsensitized controls and found no significant difference in spirometry or 1-year graft survival (73). Courtwright and colleagues reviewed 203 cases, 18 of whom had pretransplant DSA and were treated with peri-transplant plasmapheresis, and found that sensitized patients were more likely to require prolonged mechanical ventilation and to have AMR (74). They found no difference in mortality or CLAD-free survival between groups (74). While some centers have shown success, small sample size, varied protocols and immunosuppressive regimens, and heterogenous patient populations make it challenging to draw conclusions regarding the role and impact of desensitization protocols.

Gaps in knowledge and future directions

Despite the advances in diagnostic criteria and treatment modalities in AMR, significant gaps in knowledge remain. The true incidence of AMR remains unknown with prior reports describing widely variable incidence from 4% to greater than 50% (3,37,75,76). The previous lack of consensus diagnostic criteria and highly sensitive assays for DSA may explain this variability. However, the limitations of the current consensus diagnostic criteria present further challenges in defining the true incidence of AMR. In addition, chronic and subclinical AMR are ill-defined, and the impact of these potential forms of rejection on long-term outcomes remains unknown. The lack of highly sensitive assays for non-HLA antibodies further limits our understanding of AMR. While inability to clear DSA is associated with CLAD and poor survival, the associated mechanisms remain unclear, and protocols for prevention and treatment have yet to be developed. Long-term outcomes after AMR are poor and data for specific treatment protocols remain sparse. Large, multicenter, randomized clinical trials are necessary to better define the optimal treatment regimen. These studies need not be placebo controlled as equipoise exists for head-to-head comparisons of previously studied regimens. Furthermore, dosing studies are necessary to identify the optimal doses for treatment of AMR as current dosing strategies are based on the use of agents in other medical conditions.
Finally, as investigations of new diagnostic techniques and treatment strategies emerge, large, multicenter studies will be necessary to identify best-practices for implementation.

There are multiple areas of ongoing and future investigation in AMR including in the areas of mechanisms, diagnosis, and treatment. Li and colleagues developed a mouse lung re-transplantation model of AMR and found that tolerant allografts developed BALT and that depletion of regulatory T-cells led to AMR (38). They suggest a role for future investigation of the pathogenesis of AMR utilizing this model and the treatment of AMR by costimulatory blockade of T-cells and B-cells (38).

Given the limitations of the current consensus diagnostic criteria for AMR, alternative methods for diagnosis are actively being investigated including donor-derived cell-free DNA (ddcfDNA) and transcriptome analyses. The presence of injury in the allograft results in donor cell apoptosis and circulation of donor DNA in the serum of recipients (77-80). Assays have been developed that can quantify the amount of ddcfDNA in recipient serum (77-81). This technique involves sequencing DNA found in the serum of recipients and differentiating and quantifying donor DNA (77,81). These assays were found to have excellent sensitivity for acute rejection, but specificity is poor (77-81). Notably, Agbor-Enoh and colleagues found the sensitivity for AMR to be approaching 100%, but specificity was only 35%; however, when coupled with testing for DSA, specificity improved to 90% (82,83). In addition, they found that elevations in ddcfDNA preceded the clinical diagnosis of AMR by a median of 2.8 months (82). Measurement of cell-free DNA could serve as a noninvasive method to diagnose impending AMR; however, it is unclear if treatment of impending AMR will improve outcomes. The Early Detection and Treatment of AMR (eDATA) study proposes to identify patients who have elevated ddcfDNA and DSA and to initiate treatment prior to developing clinical AMR. This study is currently in progress and will compare outcomes with conventional diagnosis and treatment of clinical AMR (83).

Another area of active investigation is transcriptome analysis. Micro RNAs (miRNA) are short, noncoding RNA sequences that regulate gene expression. Transcriptome analysis can be performed on BAL cell pellets, peripheral blood mononuclear cells, and biopsy specimens (84-88). Early studies have shown that differential expression of miRNAs correlate with episodes of acute rejection and may even precede diagnosis of chronic rejection (84-88). While early data for antibody associated chronic rejection exists (84), transcriptome analysis has yet to be evaluated in the diagnosis of AMR.

Valenzuela and colleagues reviewed emerging therapies for AMR that inhibit antibody formation and antibody-mediated allograft injury by targeting CTLA4, IL-6 receptor, B-cell activating factor, C1, mTOR, and the Fc region of bound antibody (40). Future studies should evaluate the role of these alternate pathways of immune modulation in AMR.

**Conclusions**

AMR generally results in severe acute allograft dysfunction and is associated with increased risk of CLAD and poor survival. Despite development of consensus diagnostic criteria, treatment protocols have limited data and long-term outcomes remain poor. Promising diagnostic techniques are actively being investigated that may allow for early detection and treatment of AMR. Further research is required to identify and define chronic and subclinical AMR, and head-to-head comparisons of currently used treatment protocols are necessary to identify an optimal treatment approach. Gaps in knowledge regarding the epidemiology, mechanisms, diagnosis, and treatment of AMR persist and future research should focus on addressing these gaps.

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