

ISHLT CONSENSUS REPORT

# Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation



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## KEYWORDS:

lung transplantation;  
rejection;  
HLA antibodies;  
allograft dysfunction

Antibody-mediated rejection (AMR) is a recognized cause of allograft dysfunction in lung transplant recipients. Unlike AMR in other solid-organ transplant recipients, there are no standardized diagnostic criteria or an agreed-upon definition. Hence, a working group was created by the International Society for Heart and Lung Transplantation with the aim of determining criteria for pulmonary AMR and establishing a definition. Diagnostic criteria and a working consensus definition were established. Key diagnostic criteria include the presence of antibodies directed toward donor human leukocyte antigens and characteristic lung histology with or without evidence of complement 4d within the graft. Exclusion of other causes of allograft dysfunction increases confidence in the diagnosis but is not essential. Pulmonary AMR may be clinical (allograft dysfunction which can be asymptomatic) or sub-clinical (normal allograft function). This consensus definition will have clinical, therapeutic and research implications.

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Donor-specific anti-human leukocyte antigen (HLA) antibodies (DSA), are known to contribute to antibody-mediated

rejection (AMR) in solid-organ transplantation.<sup>1,2</sup> The best-characterized donor antigens are HLA, which are further divided, based on their structure and function, into HLA Class I and Class II. The presence of DSA at the time of transplant or detected de novo post-transplant is well described in renal transplantation, where it has been associated with compromised

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renal allograft survival.<sup>3-6</sup> De novo DSA and an increase in DSA titers, perhaps via an anamnestic response, have also been associated with lung allograft dysfunction, occasionally in asymptomatic patients.<sup>1,7,8</sup> However, there is no agreed-upon definition for pulmonary AMR in the literature.

AMR is a complex pathologic, serologic and clinical process that is well recognized in kidney and heart allografts but ill-defined in lung transplantation. A process of immune activation, whereby allospecific B-cells and plasma cells produce antibodies directed against donor lung antigens, is central to the concept of pulmonary AMR. The antigen-antibody complex results in an amplified immune response, via both complement-dependent and independent pathways, which results in lung tissue pathology and graft dysfunction to a variable degree. Complement is a multifunctional system of receptors, regulators and effector molecules that may amplify both innate and adaptive immunity contributing to the pathogenesis of AMR.<sup>9</sup>

To date, individual transplant centers have defined AMR uniquely, making it difficult to interpret studies and to compare strategies and outcomes between centers. A standardized definition is therefore required to: facilitate interpretation of the available literature; diagnose specific cases; develop treatment options; and inform research via identification of risk factors, incidence, prevalence, clinical course and prognosis. Most importantly, an agreed-upon definition with a universal nomenclature facilitates the conversation between user groups to improve collection of outcome data and allows comparison of treatment regimens and, ultimately, the creation and standardization of therapeutic guidelines, as recently described for the bronchiolitis obliterans syndrome (BOS).<sup>10</sup>

The primary aim was to reach a consensus on a formal working definition of pulmonary AMR. Secondary goals were to propose phenotypes of pulmonary AMR and identify knowledge gaps on topics related to pulmonary AMR to direct clinical evaluation and future research.

## Immunology of AMR

The major immunologic advances in the past decade in AMR in solid-organ transplantation have been implementation of sensitive and specific solid-phase assays for identification of DSA, improved understanding of the pathogenic effect of alloantibodies, and integration of molecular transcripts to better define the spectrum of graft injury mediated by alloantibody.<sup>11-13</sup> More recently, the use of molecular transcripts has demonstrated that microvascular inflammation without C4d staining may be an indicator of AMR in both kidney and cardiac allografts.<sup>14</sup>

DSA have been associated with acute allograft rejection in kidney, heart and lung allografts.<sup>2,11,15</sup> Importantly, DSA have also been associated with chronic allograft rejection, as manifested by transplant glomerulopathy in kidney recipients, cardiac allograft vasculopathy in heart recipients and obliterative bronchiolitis (OB) in lung transplant recipients.<sup>3,8,15,16</sup>

Although DSA have been shown to appear before loss of lung function and are predictive of poor outcomes, controversy continues regarding: whether antibodies detected

solely by highly sensitive techniques are clinically relevant; how to monitor post-transplant; and when to implement antibody-removal therapies in the absence of clinical dysfunction.<sup>1,7,8</sup> Notably, DSA level and function should not be assessed by the mean fluorescent intensity (MFI) of the single antigen bead (SAB) assay, because the MFI does not represent the titer of circulating HLA antibody. It is the titer, not the MFI *per se*, that is indicative of antibody load. Furthermore, the presence of strongly binding antibodies may be underestimated due to inhibition by IgM or the C1 component of complement in undiluted sera.<sup>13,17</sup> The clinical relevance of DSA may depend on immunoglobulin G (IgG) subclass. Complement-fixing IgG (IgG1/IgG3) may be more damaging than non-complement-fixing IgG (IgG2/IgG4). However, IgG2 and IgG4 antibodies may also exert damaging effects by mechanisms other than complement activation. Modification of the SAB assay to detect complement binding (C1q assay) has provided a new tool for possible risk stratification of transplant recipients who exhibit DSA.<sup>18</sup> In cardiac transplantation, correlations have been demonstrated between C1q-positive antibodies and early AMR, and in renal transplants the presence of complement-binding DSA has been associated with a more severe graft injury phenotype and a significant risk for graft failure.<sup>15,19</sup> Similarly, in lung transplant recipients, the presence of Class II, C1q-binding antibody has been associated with allograft injury and high-grade acute cellular rejection (ACR).<sup>20</sup> Furthermore, although the presence of capillary C4d staining in alveolar tissue may support the presence of an antibody-mediated process, other etiologies, including procurement injury (e.g., acute alveolar injury after ischemia/reperfusion), high-grade ACR and infection, need to be considered in the differential diagnosis.<sup>20</sup> Extensive individual experience with protocol C4d staining of lung, heart, liver and kidney transplant biopsies improves the ability to discriminate confounding variables. Positive lung C4d staining in high-grade rejection may in fact represent mixed ACR and AMR rather than artifact.

The presence of high natural killer (NK) transcripts in many AMR renal biopsies supports the concept of the role of NK cells in mediating allograft injury. NK cells in the vascular lumen recognize antibody on the cell surface through their Fc-receptor, CD16, leading to increased interferon-gamma (IFN- $\gamma$ ) production. The inflammatory effects of IFN- $\gamma$  are manifested by increased major histocompatibility complex (MHC) expression on endothelial cells and activation of monocytes.<sup>3,11</sup> Furthermore, in the presence of DSA that activate complement (IgG1/IgG3), the inflammatory response includes both activated NK and monocytes. With non-complement-binding DSA (IgG2/IgG4), the inflammatory response is limited to monocyte infiltration.<sup>3</sup> Thus, graft injury in the presence of complement-binding DSA, especially of the IgG3 subtype, is induced by the cytotoxic effects of complement-activating antibody and by the induction of cellular effector mechanisms mediated by activated NK cells and monocytes.

In summary, there are now improved techniques available for determining DSA specificity, level and function. Using these refined assays we can better detect DSA, improve risk stratification, and intervene earlier with the hope of improving long-term allograft survival.

## Mechanisms of AMR

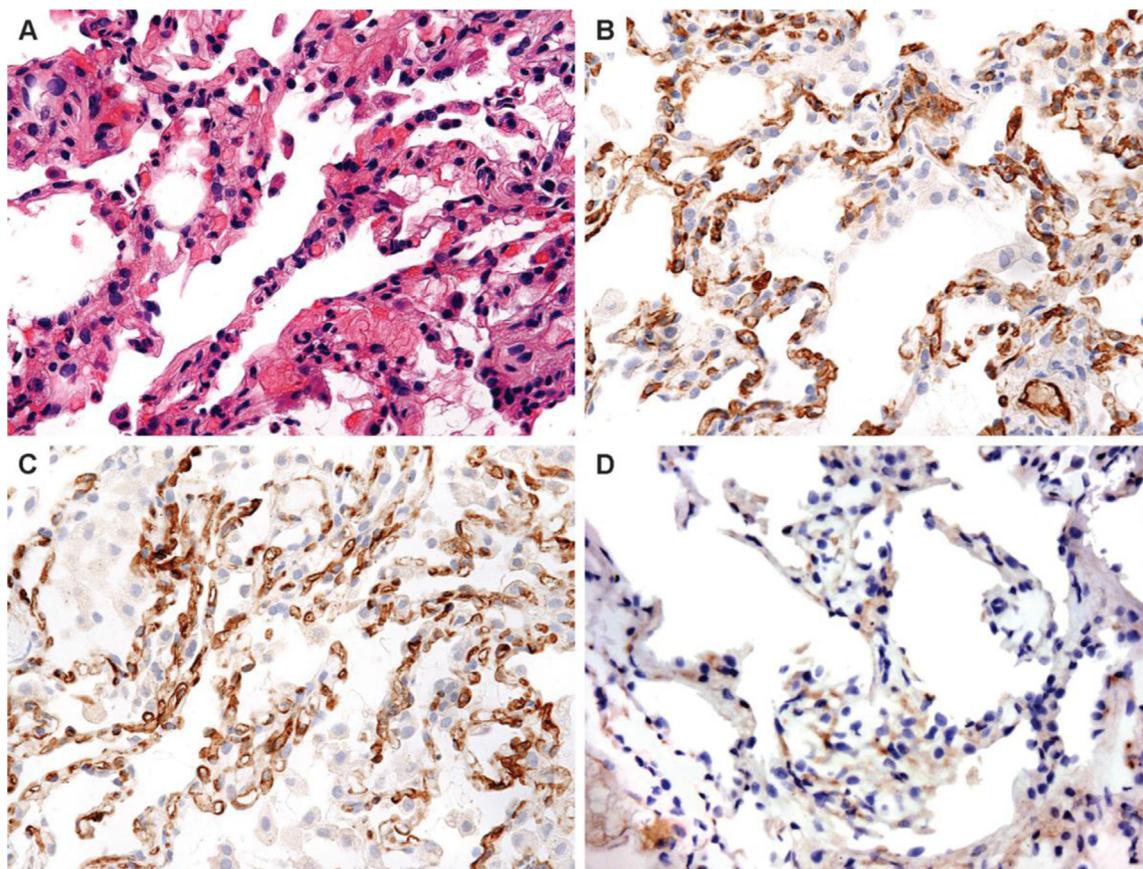
In the 1970s, early investigations into AMR demonstrated that antibodies with or without a cellular response could lead to a vasculopathy. Stronger evidence linking antibodies with allograft damage was provided in murine cardiac chronic rejection models by Russell et al,<sup>16</sup> who found, using Class I–mismatched strain combinations, that only recipients with complement-dependent cytotoxic antibodies developed a severe vasculopathy.<sup>16</sup>

Multiple investigations using both *in vitro* and *in vivo* studies have demonstrated that MHC ligation can lead to complement-dependent mechanisms with (classical and lectin pathways) and without (alternative pathway) C4d deposition that damage the allograft.<sup>21–23</sup> Furthermore, MHC ligation of endothelial cells with and without the help of integrin- $\beta$ 4 can lead to a vasculopathy through complement-independent mechanisms that include: (a) signaling cascades, such as FAK, SCR, PI3k, AKT, mTORC1 [(Raptor) GbL (mTOR)], S6k and S6RP, which cause endothelial/smooth muscle cells to proliferate and release inflammatory mediators; (b) exocytosis of granules containing von Willebrand factor (vWF) and P-selectin, which cause platelet activation and inflammation; (c) up-regulation of fibroblast-like growth factor receptor (FGFR)/FGF biology and its downstream MEK and ERK pathways leading to endothelial/smooth muscle cell proliferation; and (d) up-regulation of

endothelial cell expression of chemokines, which recruit NK cells that express IFN- $\gamma$ –inducing cells to express more MHC Class I and II, generating further alloimmunity.<sup>3,21–31</sup> Alternatively, the Fc portion of antibodies can interact with leukocytes via Fc-receptors (FcR) initiating antibody-dependent cellular cytotoxicity (ADCC), opsonization and cytokine/chemokine expression, all of which exaggerate allograft damage.<sup>3,21–29</sup> Last, autoantibodies (e.g., vimentin, collagen V, perlecan,  $\alpha$ 1-tubulin, AT1R and MICA) can also cause significant allograft damage as well as amplify alloantibody damage.<sup>25,32,33</sup> In murine models, intrabronchial administration of anti-MHC Class I or II antibodies can upregulate autoimmunity, leading to OB.<sup>34,35</sup> Together, these studies showed that antibodies can lead to lung injury via multiple mechanisms, including complement-independent as well as complement-dependent direct damage. However, there are some antibodies (class- and titer-dependent) that may help with allograft accommodation.<sup>36</sup> Future studies should determine the balance of antibodies with regard to titer and class as well as molecular mechanisms that determine overall allograft outcomes.

## Pathology of AMR

The Pathology Council summarized the current understanding of the pathology of pulmonary AMR following



**Figure 1** (A) Transbronchial biopsy at high-power magnification showing no cellular rejection or neutrophilic margination (hematoxylin–eosin stain; original magnification  $\times 400$ ). (B) C4d staining showing diffuse, strong, linear staining of the interstitial alveolar capillaries ( $\times 400$ ). (C) Persistent C4d staining 6 weeks after study in (B) ( $\times 400$ ). (D) Absence of C4d staining 3 months after study in (B) ( $\times 400$ ).

consensus discussions at the annual scientific meeting of the International Society for Heart and Lung Transplantation (ISHLT) in 2012.<sup>37</sup> Histopathologic features, including neutrophil margination, neutrophil capillaritis and arteritis, are non-specific, as they may be seen in other forms of lung injury, as can organizing pneumonia. Immunohistochemistry for C4d, either by immunofluorescence (IF) or immunoperoxidase (IP) assays, may provide supportive evidence of AMR.

A survey of histopathologists was undertaken before the meeting. Based on the aforementioned criteria, histopathologic and immunohistochemical evidence of AMR was uncommon. It was agreed that the histopathologic features outlined in the 2013 report were still valid, and, based on current knowledge, need refining. However, the sensitivity of C4d staining was questioned in line with developments in the renal literature, where it is no longer an obligate criterion of AMR.

As there are only a small number of AMR cases that meet all the criteria (positive DSA, graft dysfunction, histopathologic features and C4d positivity), the experience of any individual pathologist must perforce be limited. Hence, cases of pulmonary AMR meeting these criteria are being gathered and scanned and made available online as digital whole slide images for group assessment. It has been proposed to gather a set of C4d-positive cases with enough material to be able to create a tissue microarray enabling the methods of different laboratories to be compared so we may confirm that the apparent lack of C4d-positive cases is not due to methodologic problems.<sup>38</sup> Currently, the majority of centers use IP on formalin-fixed tissue sections for C4d immunostaining (Figure 1), whereas others use IF on fresh tissue.

## Clinical diagnosis and monitoring

Diagnostic criteria for AMR in renal transplantation were proposed in 2003 by the Banff Working Group<sup>39</sup> and included the presence of circulating DSA, positive C4d peritubular capillary staining and other histopathologic changes. These criteria have been adopted and modified by

the lung transplant community to support a diagnosis of pulmonary AMR.<sup>37</sup> However, given the large physiologic reserve of the lung, reliance on graft dysfunction as a prerequisite for pulmonary AMR is likely to result in an under-appreciation of sub-clinical AMR that may be a precursor of chronic lung allograft dysfunction (CLAD).<sup>40</sup> Whether sub-clinical AMR represents a precursor to clinical AMR, and how often, is yet to be demonstrated, but it may depend on frequency of surveillance and efficacy of therapies.

The main challenges in the diagnosis and grading of AMR in lung transplantation are the lack of specific diagnostic features and the variable relationship between DSA and the presence of graft damage and dysfunction. Confounding factors such as bronchopulmonary infection also need to be considered. Ultimately, a secure diagnosis of AMR mandates a multidisciplinary approach that integrates the clinical presentation with available immunologic and pathologic diagnostic tools.

## Definitions

Clinical AMR is associated with measurable allograft dysfunction, which can be asymptomatic. AMR may also be sub-clinical, with normal allograft function. Both clinical and sub-clinical AMR were further sub-categorized into 3 mutually exclusive possibilities (definite, probable and possible). These categories were based on the degree of certainty related to the presence or absence of a number of pathologic, serologic, clinical and immunologic criteria (Tables 1 and 2 and Figure 2).

## Diagnostic certainty

The degree of certainty of the diagnosis depends on the demonstration of whether multiple criteria are present or absent. Diagnostic confidence is increased in the presence of more positive criteria. "Definite AMR" has all criteria present and other possible causes excluded, noting that ACR and AMR may coexist. "Probable AMR" lacks 1 criterion or other possible causes have not been excluded, whereas "possible AMR" has 2 criteria missing. It is possible to

**Table 1** Definition and Diagnostic Certainty of Clinical Pulmonary Antibody-mediated Rejection

	Allograft dysfunction	Other causes excluded	Lung histology	Lung biopsy C4d	DSA
Definite	+	+	+	+	+
Probable <sup>a</sup>	+	+	+	-	+
Probable	+	+	+	+	-
Probable	+	+	-	+	+
Probable	+	-	+	+	+
Possible	+	+	+	-	-
Possible	+	+	-	-	+
Possible	+	+	-	+	-
Possible	+	-	+	+	-
Possible	+	-	+	-	+
Possible	+	-	-	+	+

DSA, donor-specific antibodies; +, item present; -, item absent or missing.

<sup>a</sup>There is building evidence that antibody-mediated rejection can be diagnosed confidently in the absence of positive C4d staining, hence this group is recognized separately.

**Table 2** Definition and Diagnostic Certainty of Sub-clinical Pulmonary Antibody-mediated Rejection

	Lung histology	Lung biopsy C4d	DSA
Definite	+	+	+
Probable	+	-	+
Probable	-	+	+
Probable	+	+	-
Possible	+	-	-
Possible	-	+	-
Possible	-	-	+

DSA, donor-specific antibodies; +, item present; -, item absent or missing.

move from one stage to another as further information is obtained and the degree of certainty increases. For example, an initial “possible AMR” can become “probable AMR” when the DSA result comes back positive or if, in another case, the virology results are negative. However, the panel agreed that the diagnosis of AMR is not excluded solely because there are coexisting entities present such as infection, ACR or CLAD. One sub-category of sub-clinical AMR describes patients who have an isolated finding of DSA without other manifestations of AMR. This recognizes the concept of AMR as a clinicopathologic spectrum that starts with DSA alone, as discussed at the 2011 ISHLT Cardiac AMR Consensus Conference, and is in synchrony with the conclusions of the 2003 National Conference to Assess Antibody Mediated Rejection in Solid Organ Transplantation, of which ISHLT was a contributing partner.<sup>41,42</sup>

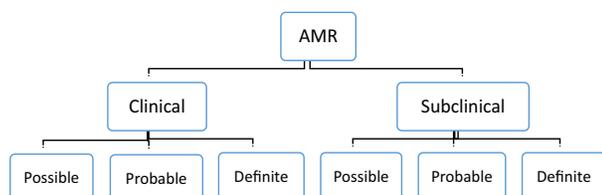
## Circulating DSA

Although the group agreed that circulating DSA (whether de novo or not) was the criterion most often seen with AMR, there may be situations in which DSA may not be detected due to phasic release, presence of a DSA not detected by contemporary testing platforms, or other limitations of the diagnostic test. Alternatively, DSA may be absorbed into the lung allograft.

## AMR staging

AMR may be defined as either clinical or sub-clinical:

1. *Clinical AMR*: The presence of allograft dysfunction (defined as alterations in pulmonary physiology, gas exchange properties, radiologic features or deteriorating



**Figure 2** Classification of antibody-mediated rejection (AMR) according to presence (clinical) or absence (sub-clinical) of allograft dysfunction, and confidence of diagnosis.

functional performance) associated with AMR. Clinical AMR may be asymptomatic, such as a small but significant change in pulmonary physiology.

- (a) *Definite clinical AMR*: Allograft dysfunction in the presence of DSA plus positive histology suggestive of AMR and positive C4d staining. ACR and AMR can be concurrent, but other causes have been excluded.
- (b) *Probable clinical AMR*: Allograft dysfunction in the presence of 2 of the 3 following criteria: presence of DSA; positive histology suggestive of AMR; and positive C4d staining. A grading of probable AMR may be given to a recipient who has coexistent AMR with infection or ACR when all 3 diagnostic criteria are present.
- (c) *Possible clinical AMR*: Allograft dysfunction in the presence of 1 of 3 following criteria: presence of DSA; positive histology suggestive of AMR; and positive C4d staining. A grading of possible AMR may be given to a recipient who has coexistent AMR with infection or ACR when 2 diagnostic criteria are present.

It was agreed that idiopathic allograft dysfunction may, in some cases, be due to a form of AMR not yet characterized.

2. *Sub-clinical AMR*: Histologic criteria of AMR detected on surveillance transbronchial biopsies (with or without C4d and with or without the presence of DSA) in the absence of allograft dysfunction. An example of positive histology in this setting would be evidence of a neutrophilic capillaritis in the absence of pneumonia. When there is an isolated finding of DSA without other manifestations of AMR, such as histology, C4d staining or allograft dysfunction, heightened surveillance for allograft dysfunction is warranted.

## Clinical phenotypes of AMR

While acknowledging the presence of different clinical phenotypes of AMR, the group considered the enunciation of specific criteria for each phenotype beyond the scope of this consensus document. The group discussed the arbitrary nature of temporal divisions of AMR into hyperacute (occurring intra-operatively or within 24 hours of surgery), acute (often mimicking ACR) and chronic (potentially manifesting as an occult cause of CLAD). Group sentiment was that the important concept of chronic AMR deserves a separate in-depth evaluation as there was insufficient evidence at the time to evaluate causal links between persistent AMR and CLAD, irrespective of how appealing this hypothesis may be.

## Grading severity of AMR

Not only are there several phenotypes of AMR, there is a spectrum of severity of each phenotype, similar to ACR.

AMR histopathologic severity is based on changes that progress through morphologic alterations leading to acute lung injury with or without hyaline membranes. This is similar to the severity grading of ACR. Changes in graft function also define severity. The group did not come to a consensus regarding which graft function parameter and what degree of change determines AMR onset, severity, progression, improvement and resolution. It was agreed that severe pulmonary AMR may cause acute hypoxemic respiratory failure requiring oxygen replacement therapy and other supportive measures, ranging from non-invasive or invasive mechanical ventilation to extracorporeal life support.

## Pediatric AMR

AMR is increasingly recognized as a potential contributing factor to acute lung allograft dysfunction and the development of CLAD in pediatric lung transplant recipients (<18 years of age). Although the frequency is unknown in children, AMR has clearly been documented across all pediatric age groups from infancy to early adulthood.<sup>43–47</sup> In 2009, Astor and co-workers described the first case of pulmonary capillaritis in a young child after lung transplantation, with evidence of C4d deposition in the lung allograft, circulating DSA and severe allograft dysfunction.<sup>43</sup> Recently, it has been shown that DSA were more prevalent in patients with cystic fibrosis (CF), which is the major pediatric indication for lung transplantation.<sup>2</sup> Although histopathologic and immunophenotypic features of AMR are now considered part of diagnostic criteria for lung allograft rejection in pediatric lung transplantation, current diagnostic criteria are neither fully established nor universally accepted and there is no specific pediatric nomenclature.<sup>37,42,48,49</sup> Hence, adult diagnostic criteria for lung allograft rejection are often applied to pediatric patients, with recent confirmation that these criteria are consistent in children.<sup>45,50</sup> A limiting factor, particularly in neonates, is the inability to acquire sufficient tissue for histopathology, so the final determination is frequently left to the clinician.<sup>45,50</sup>

Most pediatric lung transplant physicians would consider active treatment in a patient with DSA, C4d deposition on immunohistochemistry, abnormal histopathology and substantial graft dysfunction. However, the treatment of a child with evidence of “sub-clinical” AMR remains controversial.

## Clinical outcomes and therapy

There are limited data in the published literature describing the management of AMR after lung transplantation (6 case series and 7 case reports), with 1 series outlining an antibody-depletion strategy in clinically stable lung transplant recipients who developed DSA.<sup>1,2,45,46,51–60</sup> Importantly, there have been no randomized, controlled trials and no head-to-head comparisons of different treatment regimens. Different studies have used different definitions, which makes it unclear whether all cases represent the same syndrome. Treatment has generally consisted of interventions that aim to deplete circulating antibodies, suppress

B-cells and mitigate further antibody-mediated allograft injury. However, it is difficult to make firm conclusions about the relative efficacy of any regimen because treatments have been individualized and are highly dependent on clinical course and response to other treatments. Despite these limitations, the published literature suggests that allograft failure due to AMR can be reversible, although outcomes are generally poor,<sup>52,53,56,59</sup> In fact, Witt et al reported that 15 of 21 patients hospitalized with severe allograft dysfunction due to AMR improved and were discharged from the hospital, whereas 6 died of refractory AMR.<sup>60</sup> However, 13 of 14 patients developed CLAD and 15 of 21 died during study follow-up.<sup>60</sup> Two other case series reported a 50% to 70% mortality rate after AMR.<sup>2,55</sup> Clearly, these results indicate that AMR can be refractory to aggressive therapy and may often lead to allograft failure and death. Given the aforementioned caveats, and the lack of an accepted clinical definition of lung AMR hitherto, reports in the literature detailing the outcomes of “clinical AMR” must be considered with caution. As a case in point, early reports suggested pulmonary capillaritis was a form of AMR distinct from ACR that was not associated with long-term adverse effects on allograft function.<sup>51,61</sup> We now know *de novo* DSA develop in 25% to 55% of lung transplant recipients and are associated with decreased survival and an increased incidence of BOS.<sup>44,62–66</sup> Furthermore, the persistence of DSA or autoantibodies correlates with poor outcomes.<sup>67</sup>

Once present, pulmonary AMR may stabilize, progress or improve. Improvement may be partial or complete. Suggested definitions for each of these terms are provided in what follows, the use of which in clinical trials of pulmonary AMR will allow direct comparison of outcomes:

1. *Complete response*: Return to baseline graft function if applicable, abolition of DSA titers and reversal of pathologic changes.
2. *Partial response*: Improvement in graft function if applicable, but not all parameters return to baseline.
3. *Stabilization*: No further clinical deterioration.
4. *No response*: Ongoing clinical deterioration and continued abnormal pathology. In the clinical arena it was agreed that a complete response was an infrequent event.

## The sensitized patient

The sensitized candidate presents unique challenges both pre- and post-transplant. To fully characterize the candidate, HLA antibodies should be screened by solid-phase assays with specificities determined by single antigen beads. These patients should have frequent updates (monthly to every 3 months) while on the waitlist and after sensitizing events such as transfusion of blood products and pregnancy. Waitlist protocols for desensitization have generally been based on kidney transplant candidate protocols and involve intravenous immunoglobulin (IVIg) and plasmapheresis with occasional addition of bortezomib and rituximab.<sup>68–72</sup> Notably, these interventions may reduce MFI without

changing the panel-reactive antibodies (PRA) and thus may not increase the donor pool. Furthermore, the vast majority of lung transplants are unscheduled, making the timing of waitlist desensitization problematic if antibody levels rebound. If the recipient is known to have a DSA, observational data suggest that peri-operative management with plasmapheresis, immunoabsorption, IVIg or rituximab may improve outcomes. The role of risk stratification based on virtual crossmatch versus cell-based crossmatch requires further study. After transplant, careful monitoring for DSA, AMR and ACR is warranted as single-center reports have indicated that pre-transplant HLA antibodies are associated with higher rates of ACR, BOS and primary graft dysfunction (PGD) and worse survival.<sup>62,73–75</sup> Before 2005, studies employing the complement-dependent cytotoxicity (CDC) method revealed variable effects of pre-sensitization on survival and BOS, but overall suggested that pre-sensitization was associated with an increased incidence of BOS. Subsequent studies using flow cytometry showed that the virtual crossmatch was effective at limiting early events and the development of BOS. More recent studies employing solid-phase assays have confirmed an association of pre-sensitization with an increased risk for BOS and poorer survival, whereas desensitization resulted in improved outcomes.<sup>76</sup> Notably, a United Network for Organ Sharing (UNOS) registry data analysis indicated no difference in survival in the recent era, suggesting sensitized candidates can be safely transplanted with careful attention to HLA antibodies.<sup>77</sup> Furthermore, a recent single-center study demonstrated the efficacy of peri-operative desensitization.<sup>78</sup>

### AMR research priorities summary

Research priorities are detailed in the [Supplementary material](http://www.jhltonline.org) (available online at <http://www.jhltonline.org>). Validation of the consensus definition is critical and this will include an understanding of potential confounding by other conditions. Analysis of the timing of testing for AMR and timing of AMR detection after transplantation should provide greater insights into the AMR phenotypes, such as hyperacute AMR, acute AMR, chronic AMR and even acute-on-chronic AMR. Criteria should be developed to define AMR resolution, recurrence and persistence. Immunotherapeutic trials should consider routine surveillance for AMR and incorporate AMR events into their assessment of outcomes, perhaps including freedom from AMR as part of a composite outcome (e.g., death, AMR and CLAD). The entity of chronic AMR requires additional study and development of a definition. Further studies should assess associations between antibody types and different CLAD phenotypes.

### Discussion

The consensus definitions are dynamic and will allow further modifications as new insights emerge. The limitations of this classification system include but are not necessarily limited to the following:

1. Criteria are based on limited data in the literature.
2. All centers may not be able to evaluate all criteria.
3. HLA assays, techniques and language are not standardized between laboratories.
4. Accuracy of histopathologic classification may be limited due to sampling error; lack of unique histopathologic features; between-observer variability in grading; and coexistence of other causes of allograft dysfunction, including graft preservation injury, acute cellular rejection, infection and other factors.
5. Severity has not been clearly defined, but it is agreed that severity may be confounded by concurrent diagnoses.
6. An evidence base to allow confidence in diagnosing chronic pulmonary AMR is yet to be developed.

The ISHLT Pulmonary AMR Working Group ([Appendix](#)) remains committed to ongoing collaboration that will lead to further efforts toward solving some if not all of the controversial areas just enumerated. In conclusion, the great challenge of lung transplantation is to maintain graft function long term. Perhaps with a better and more uniform understanding of pulmonary AMR, cohesive global efforts will lead to the development of effective strategies to prevent, diagnose and manage AMR, and thereby reduce its adverse consequences, particularly the development of CLAD.

### Disclosure statement

The authors have no conflicts of interest to disclose. We are grateful for the diligent reviews of the various councils and the primary oversight provided by the Standards and Guidelines Committee.

### Appendix

This multidisciplinary effort between the ISHLT Pulmonary Transplantation, Pathology, Pediatric and Basic Science Councils included the following co-chairs, leaders and task force members.

### ISHLT AMR Working Committee

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## Supplementary material

Supplementary materials associated with this article can be found in the online version at [www.jhltonline.org](http://www.jhltonline.org).

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