



Acute rejection and post lung transplant surveillance

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Abstract

Purpose The purpose of this review is to summarize the current evidence on the evaluation and treatment of acute rejection after lung transplantation.

Results Despite significant progress in the field of transplant immunology, acute rejection remains a frequent complication after transplantation. Almost 30% of lung transplant recipients experience at least one episode of acute cellular rejection (ACR) during the first year after transplant. Acute cellular rejection, lymphocytic bronchiolitis, and antibody-mediated rejection (AMR) are all risk factors for the subsequent development of chronic lung allograft dysfunction (CLAD). Acute cellular rejection and lymphocytic bronchiolitis have well-defined histopathologic diagnostic criteria and grading. The diagnosis of antibody-mediated rejection after lung transplantation requires a multidisciplinary approach. Antibody-mediated rejection may cause acute allograft failure.

Conclusions Acute rejection is a risk factor for development of chronic rejection. Further investigations are required to better define risk factors, surveillance strategies, and optimal management strategies for acute allograft rejection.

Keywords Acute rejection in lung allograft · Acute cellular rejection · Antibody-mediated rejection

Introduction

Lung transplantation has rapidly evolved from an experimental treatment in the early 1980s to the standard of care for eligible patients with end-stage lung disease. There has been a tremendous increase in the number of lung transplants performed in the last 3 decades both internationally and in North America. As per the thirty-sixth International Society of Heart Lung Transplant (ISHLT) report published in October 2019, a total of 6,94,200 adult lung transplants and 4,128 adult heart–lung transplants were performed through June 2018 [1]. The significant advances in surgical techniques over the last two decades have led to marked improvements in perioperative and immediate postoperative outcomes in lung transplant recipients.

Despite advances, long-term survival remains disappointing. The most important cause of decreased survival is the development of chronic lung allograft dysfunction (CLAD). Bronchiolitis obliterans syndrome (BOS) is the prototypic form of CLAD. Around 50% of lung transplant recipients develop CLAD in 5 years post-transplant and the median 5-year survival post-transplant remains ~50–60% [1–3]. The scientific community in the last two decades has made considerable progress in understanding the risk factors and underlying pathobiology associated with increased risk of early and late graft failure. One of the most important risk factors for development of CLAD is acute graft rejection. Increase in severity and number of episodes of acute rejection is associated with increased risk of development of BOS and worse BOS free survival [4–9]. Multiple factors likely contribute to the high rates of rejection following lung transplantation, including increased susceptibility of the lung to injury and infection as well as constant environmental exposure [9]. This manuscript is a comprehensive review of the current literature pertaining to acute lung allograft rejection. The article details clinical and pathologic features of acute cellular rejection (ACR) and antibody-mediated rejection (AMR) after lung transplantation and discusses routine management and outcomes.

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Acute rejection

The incidence of acute rejection varies depending on the lung transplant population described and data source. According to the twenty-fourth ISHLT report, between January 2000 and June 2005 around 40–50% of recipients experienced acute rejection in the first-year post-transplant, and 45% of recipients experienced BOS in 5 years [10]. There has been a continued reduction in the incidence of acute rejection. The decrease in the incidence of acute rejection is mainly attributed to the foothold of induction therapy and maintenance immunosuppression. According to the recent ISHLT report of lung transplant recipients published in October 2019, 26.6% experienced at least one episode of acute rejection in the first-year post-transplant [1]. The Organ Procurement and Transplantation Network/Scientific Registry or Transplant Recipients report from 2016 notes a lower incidence of acute rejection at 17.1% in the first year post transplant [3]. Randomized controlled trials of different immunosuppressive regimens following lung transplantation describe higher rates of rejection. In a study of tacrolimus and cyclosporine, Hachem et al. reported that 44% of all patients had at least one episode of A1 rejection and 49% had at least one episode of A2 rejection [11]. In a study of mycophenolate versus everolimus in combination with cyclosporine, rates of acute rejection were 46% and 38% respectively in the first year after transplantation [12]. The difference in the incidence of acute rejection in these studies are likely due to differences in protocols and timing of transbronchial biopsies, patient populations, and criteria for treatment.

The risk of acute rejection is greatest in the first few months after transplant and decreases with time. Several risk factors have been implicated as contributing to the development of acute cellular rejection (Table 1). A higher degree of class I and class II human leucocyte antigen (HLA) mismatching between donor and recipient increases the risk of acute cellular rejection [13]. Genetic variants

in interleukin (IL)-10, CCL4L chemokine, and toll-like receptor4 (TLR 4) may influence risk of acute rejection [14, 15]. Lung transplant recipients who are younger (< 35 years) have a trend toward increased incidence of acute cellular rejection compared to lung transplant recipients aged 35–49 years [1]. While immunosuppression is clearly the key for ACR prevention, no consensus exists regarding the optimal maintenance immunosuppressive strategy. Most evidence originates from retrospective studies. In the ISHLT registry, the rate of acute rejection in the first year was highest among recipients on cyclosporine-based regimens and lowest among those on tacrolimus-based regimens [1]. However, a Cochrane systematic review of 413 lung transplant recipients showed no difference in acute rejection between patients treated with tacrolimus and cyclosporine [16]. As regards induction immunosuppression, a Cochrane meta-analysis identified six randomized controlled trials, and reported no clear benefit or harm with the use of different anti-T cell antibody agents (anti-thymocyte globulin, antilymphocyte globulin, interleukin-2 receptor antagonists, alemtuzumab, or muromonab-CD3) for induction versus no induction [17]. Another important risk factor is infections in the immediate post-transplant period; cytomegalovirus (CMV) infection and viral infections like respiratory syncytial virus, coronavirus, influenza, parainfluenza, and rhinovirus infections are common. The underlying hypothesis is that any infectious etiology can cause allograft epithelial injury and result in expression of the donor antigens, thus triggering allo-sensitization [18, 19].

Acute allograft rejection has been classically described based on the immunobiology and histopathologic features of T cell-dependent (cellular) allo-immunity against the donor antigens expressed in the lung allograft. The diagnosis of acute rejection is made based on the presence of perivascular and interstitial mononuclear infiltrate in lung tissue. The diagnosis is most often made based on transbronchial biopsies. At least five pieces of alveolated lung parenchyma are recommended for the assessment of acute rejection [4].

Table 1 Risk factors for acute cellular rejection and antibody mediated rejection

Acute cellular rejection	Antibody-mediated rejection
High degree of class I and class II HLA mismatching	Presence of donor specific antibodies to HLA antigens (DSAs) prior to transplant or at the time of transplant
Lack of induction therapy, e.g., ATG/anti-IL2 R, anti-CD52 therapy	Presence of allosensitization, e.g., multiparous women, previous transplantation, blood transfusions, implants or indwelling catheters, ECMO cannulation, blood transfusions, bone or vascular grafts
Younger age	History of acute cellular rejection
Immune predisposition ex. single nucleotide polymorphisms (SNPs), CCL4L gene variation	Infections, e.g., viral infection like RSV, coronavirus, influenza, parainfluenza, rhinovirus, CMV
Infections, e.g., viral infection like RSV, coronavirus, influenza, parainfluenza, rhinovirus, CMV	History of pseudomonas infection in cystic fibrosis patients

An ISHLT pathology working group published “The Working Formulation for the Classification of Pulmonary Allograft Rejection” in 1996 detailing the definition, grading, and histopathological reporting nomenclature of acute rejection which was subsequently revised in the 2007 update [4, 20]. According to these criteria, acute rejection may affect the vasculature and the small airways of the lung allograft. Consequently, rejection may manifest as ACR, involving small vessels or lymphocytic bronchiolitis (LB), involving the small airways [4]. The histologic grade of acute cellular rejection is dependent on the intensity of the mononuclear cell infiltrates and extension into the adjacent interstitium with grades ranging from A0 (no rejection) to A4 (severe acute rejection). Table 2 summarizes the grading criteria for acute cellular rejection. Table 3 summarizes the histologic features of acute cellular rejection.

Lung transplant recipients with acute rejection may be asymptomatic or may present with non-specific symptoms such as dyspnea, cough, sputum production, and low-grade fever [21]. High-grade rejection may be associated with respiratory distress. Symptoms may be more frequent in patients with grade A2 or higher rejection compared with those with grade A0 or A1 rejection [21]. Physical exam findings can be nonspecific as well; crackles may be heard or decreased breath sounds when a pleural effusion is present. The differential diagnosis includes infection.

Spirometry and radiographic imaging are often used as additional diagnostic modalities, but have low sensitivity and limited discriminatory value between ACR and other

causes of dyspnea. The sensitivity of a decrease in forced expiratory volume 1 s (FEV1) for detecting acute rejection grade 2 or higher is approximately 60% [22]. However, a decline in pulmonary function cannot differentiate between infection and rejection and stable pulmonary function does not rule out acute lung transplant rejection. Even so, spirometry remains a useful adjunct to clinical evaluation given its repeatable, inexpensive, and noninvasive nature. Spirometry is typically obtained at routine follow-up visits following lung transplantation and if dyspnea develops or worsens. Once post-operative function has stabilized, the variation in FEV1 and forced vital capacity (FVC) is less than 5%. Lung transplant recipients monitor their spirometry at home. A decline of 10% in spirometry values that persist for more than 2 days has been reported to indicate either rejection or infection [23].

Chest radiograph is typically obtained as a part of routine assessment and to assess the cause of new-onset dyspnea or cough in lung transplant recipients. Its main role is to identify diseases other than acute rejection. In early episodes of rejection (within the first three months), the chest radiograph may show perihilar opacities and interstitial edema with or without a pleural effusion [24]. The chest film is unchanged in approximately 80% of later episodes of rejection [24]. High-resolution chest tomography (HRCT) findings of acute lung transplant rejection include ground-glass opacities, septal thickening, volume loss, and pleural effusions. However, HRCT findings are neither sensitive nor specific and do not differentiate between infection and rejection [25].

Table 2 Pathologic grading of acute cellular rejection [4]

Acute rejection grade	Severity	Features
A0	None	No perivascular lymphocytic infiltrate, normal lung parenchyma
A1	Minimal	Scattered, infrequent small mononuclear perivascular infiltrate, no eosinophils
A2	Mild	More frequent perivascular infiltrate identified at low magnification, eosinophils may be present
A3	Moderate	Dense perivascular infiltrates, eosinophils and neutrophils common, pathognomic feature is extension into alveolar septae and airspaces
A4	Severe	Diffuse perivascular, interstitial and air-space infiltrates with pneumocyte damage, and features of acute lung injury

Table 3 Histologic features of acute cellular rejection [4]

Mononuclear infiltration	A0	A1	A2	A3	A4
Cell lineage	–	Lymphocyte	Lymphocyte, eosinophils	Lymphocytes, eosinophils, neutrophils	Lymphocytes, eosinophils, neutrophils
Perivascular	–	+	++	+++	++++
Sub endothelial	–	–	+	++	+++
Alveolar septum	–	–	–	+	++
Diffuse alveolar damage/necrosis	–	–	–	–	+

Acute rejection is a risk factor for BOS and hence early detection is important. The role of surveillance bronchoscopy for screening asymptomatic patients for acute rejection remains controversial. The performance of surveillance biopsies varies between lung transplant centers. A 2002 survey of lung transplant practices across North America revealed that 69% of the surveyed programs performed scheduled surveillance biopsies [26]. Of the centers that do perform surveillance bronchoscopy, the time intervals between bronchoscopies vary, but they are most commonly performed at 1, 3, 6, and 12 months post-transplant. Thirty percent of programs continue surveillance bronchoscopy until 2 years following transplantation. Thirty-one percent of programs perform bronchoscopy for clinical indications only. There is ongoing debate regarding the necessity of scheduled surveillance bronchoscopies. The argument in support of routine surveillance biopsies is that there is substantial prevalence of pathological evidence of rejection in asymptomatic lung transplant recipients. Retrospective evidence suggests that close to 25% surveillance biopsies demonstrate evidence of allograft rejection, with grade 2 or higher ACR noted in 16% of surveillance biopsies [27]. Surveillance bronchoscopies may also detect other clinically relevant diagnoses such as infection [27]. On the other hand, survival benefit of surveillance biopsies has not been clearly demonstrated. In a single-center study of patients monitored by surveillance bronchoscopy versus clinically indicated bronchoscopy, Valentine et al. found no differences in acute rejection, infection, or bronchiolitis obliterans free survival between the two groups [28]. Indeed, good long-term outcomes have been observed in patients managed without surveillance bronchoscopy protocols [29]. However, programs that do not perform routine surveillance bronchoscopy rely on low thresholds for allograft dysfunction and may ultimately perform an equivalent number of procedures. In a study by Tamm et al. that reported outcomes after the program stopped performing routine surveillance bronchoscopy, patients had an equal number of procedures whether they underwent surveillance bronchoscopies or only underwent clinically indicated procedures [29]. Individual transplant programs have developed protocols and practices based on their local resources for their patient population.

As regards treatment of ACR, in general, there is consensus that high-grade rejection (A2 or greater) requires treatment, most commonly with high dose steroids [19] (Fig. 1). However, there are no studies to define the optimal amount and duration of therapy. Most centers use a pulse dose steroid regimen, often methyl prednisone 10–15 mg/kg daily for 3 days followed by an oral taper. The rationale behind this is to decrease the risk of progression to higher grade ACR, which is likely to cause

graft dysfunction, and to mitigate the risk of subsequent development of BOS.

Follow-up bronchoscopy and transbronchial biopsies are generally indicated 3 to 6 weeks after an episode of ACR. If ACR was not treated, follow-up biopsy is indicated to exclude progression to higher grade ACR. Conversely, if ACR was treated, a follow-up biopsy is indicated to exclude persistent ACR or progression to higher grade ACR. If follow-up biopsy after initial treatment shows persistent rejection (14–28% of cases, in one study [30]), re-dosing steroids with the above schedule is most common. Some centers may adjust patients' baseline immunosuppression instead or in addition (i.e., switching tacrolimus to cyclosporine) [26]. There is no standardized regimen for treatment of persistent or refractory acute rejection. Early literature indicates a potential role of antithymocyte globulin, alemtuzumab, total lymphoid radiation, and extracorporeal photopheresis, but additional studies are warranted [31, 32].

There is less consensus regarding the significance and management of minimal rejection (A1), though majority of the investigation on this topic has favored treatment. Data suggest that even a single episode of minimal acute rejection, without recurrence or progression to a higher grade, is associated with earlier onset BOS [33, 34]. General recommendation is for augmentation of immunosuppression, though the specifics of steroid dosing are less well defined.

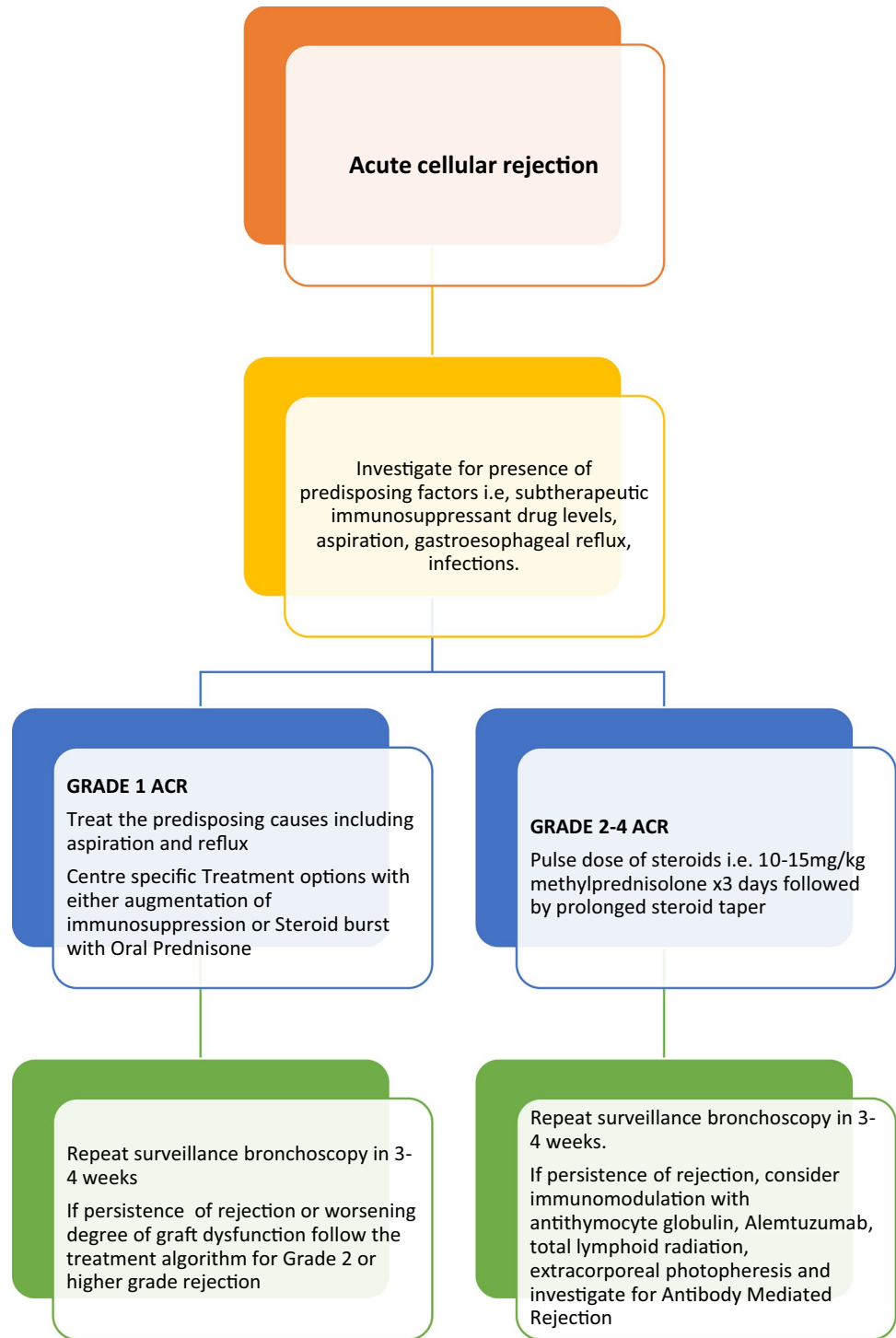
It is well established that even a singular episode of high-grade ACR is associated with increased mortality in lung transplant recipients [35]. Further, the presence of a single episode of high-grade ACR substantially increases the risk of subsequent high-grade ACR [36]. In patients who have recurrent high-grade ACR after treatment, data suggest earlier onset of BOS without any change to mortality [30]. Hence, the importance of prompt treatment, even of sub-clinical ACR, and the role for surveillance becomes clear.

Lymphocytic bronchiolitis

Lymphocytic bronchiolitis is characterized by airway inflammation without identifiable cause, such as coexisting infection. Lymphocytic bronchiolitis is graded as no airway inflammation (B0), low-grade small airway inflammation (B1R), and high-grade small airway inflammation (B2R) (Tables 4 and 5) [4]. Bronchiolar sampling and processing problems are common with transbronchial biopsies. An ungradable category (BX) exists for biopsies limited by sampling or processing problems.

Airway inflammation often accompanies acute rejection, particularly higher grades of ACR. Patients are oftentimes treated with bolus methyl prednisone for concomitant high-grade ACR. The treatment of isolated lymphocytic bronchiolitis is controversial. Lymphocytic bronchiolitis, independent of ACR, has been found to be a significant risk factor

Fig. 1 Management of acute cellular rejection



for both the development of BOS and death [37]. Notably, in a study of patients with lymphocytic bronchiolitis who had a decrease in lung function and were treated with bolus methylprednisolone, only 32% has an improvement in lung function to within 10% of baseline therapy [38]. Sixty-five percent developed BOS a mean 8 months after the episode of lymphocytic bronchiolitis. This illustrates the seriousness

of lymphocytic bronchiolitis and its refractoriness to steroid therapy.

Antibody-mediated rejection

Recent decades have shed light on the role of humoral immunity in lung allograft rejection, distinct from T cell-mediated

Table 4 Pathologic grading of lymphocytic bronchiolitis [4]

Grade	Severity	Features
B0	None	No evidence of bronchiolar inflammation
B1R	Low grade	Single-layer mononuclear cells in bronchiolar submucosa
B2R	High grade	Larger infiltrates of larger and activated lymphocytes in bronchiolar submucosa with potential involvement of eosinophils and plasmacytoid cells
X	Ungradable	No bronchial tissue available (can occur due to sampling problem, no clear small airways on transbronchial biopsy, or evidence of superimposed infection)

Table 5 Histologic features of lymphocytic bronchiolitis [4]

Mononuclear infiltration	B0—none	B1R—low grade	B2R—high grade	Bx—ungradable
Submucosal	–	+	++	Sampling artifact/infection
Intraepithelial	–	–	+	
Necrosis, exudates	–	–	+	

allograft rejection. Humoral immunity has been well characterized and commonly implicated in graft failure for heart and kidney transplants [13]. However, in lung transplant recipients, antibody-mediated rejection (AMR) has been less well understood and characterized.

The central concept of AMR is that allo-specific plasma cells produce antibodies targeted toward donor lung antigens, thereby creating and propagating a cycle of tissue injury and destruction. The sensitization of the recipient to allo-antigens can occur even before transplantation occurs. Individuals who have been pregnant, who have been exposed to blood transfusions, who have undergone previous transplant, or who have had infectious exposures all may have pre-formed antibodies to non-self-antigens [39]. In fact, literature cites that up to 10 to 15% of lung transplant recipients have some degree of pre-sensitization to allo-antigens [40]. Similarly, de novo donor specific antibodies (DSAs) can arise post transplantation, at rates ranging from 25 to 55% of all lung transplant patients [41].

Presence of preformed DSA to mismatched human leucocyte antigens between the donor and recipient leads to hyperacute rejection. Hyperacute rejection occurs within minutes to hours of transplantation and is marked by fulminant allograft dysfunction. The recipient's DSAs bind to the allograft endothelial cells and initiate a cascade of cell destruction and tissue necrosis [42]. Hyperacute rejection has become rare in recent years because of advances in HLA antibody detection methods.

Over the last decade, there has been growing experience with the diagnosis of pulmonary AMR at later time-points after transplantation, with multiple case series published [43, 44]. An important limitation of this early work was a lack of a widely accepted definition of pulmonary AMR. Presence of DSA is thought to be a crucial feature

in antibody-mediated rejection. However, because DSA has been observed in the absence of allograft dysfunction, and suspected AMR has been diagnosed in the absence of DSA, varying definitions of pulmonary AMR have been described.

In 2016, the ISHLT convened a working group to develop a consensus definition [41]. The issues the working group attempted to reconcile included the heterogeneity in the definition of AMR among institutions, the lingering lack of consensus on the histopathologic features of AMR, and the grading of AMR severity.

Ultimately, five unranked contributing characteristics of AMR were established:

1. Allograft dysfunction (defined as alterations in pulmonary physiology, gas exchange, radiologic features, or deteriorating functional performance)
2. Lung histology (acute lung injury pattern, alveolar interstitial neutrophilic margination, acute capillaritis)
3. Positive C4d staining on lung biopsy sample
4. Presence of DSA
5. Other causes excluded

The diagnostic certainty of AMR is further subcategorized as definite, probable, and possible based on the number of diagnostic features present in a given case, with greater number of features increasing diagnostic certainty. Of note, the group did not make the presence of DSA a *sine qua non* for AMR, as expert experience cited cases and causes where DSA may not be detected. Further, the allowance was made for sub-clinical AMR, in which allograft dysfunction was not (yet) observed but a diagnosis of AMR might still change management.

It is important to note, that unlike ACR, AMR has typically been associated with signs and symptoms or allograft

dysfunction and often results in allograft failure [44, 45]. Histologic findings in AMR are nonspecific patterns of lung injury including neutrophilic capillaritis, acute lung injury with or without diffuse alveolar damage, and arteritis [46]. Deposition of complement split product C4d on the capillary endothelium has been suggested as a marker of AMR in other organ transplants. However, C4d immunofluorescence staining on lung tissue is a less reliable test, because of high background from nonspecific binding, frequent focal staining, and presence of C4d deposition in infection and reperfusion injury [8]. The diagnosis of AMR requires multidisciplinary approach including input from the clinician, the pathologist, and the allogen laboratory director, unlike ACR which is a purely histologic diagnosis.

The true incidence of pulmonary AMR is unknown. Recent studies that define AMR by the ISHLT consensus definition, report prevalence between 4.3 and 27% of lung transplant patients. The approximate time to diagnosis from transplant is between 120 and 258 days [45].

Treatment of suspected antibody-mediated rejection is, at the present time, focused on removing antibodies and depleting B cells responsible for producing antibodies. This is driven by the current understanding of the pathophysiology of AMR, rather by robust clinical trial data. In fact, there is both a paucity of randomized trials and standardization of regimens across institutions in treatment of AMR [47]. The key components of AMR treatment include plasmapheresis, intravenous immunoglobulin (IVIg), rituximab, and steroids. The limited studies that exist on the treatment of AMR use these components in combination (Fig. 2).

Hachem and colleagues compared outcomes in 65 patients diagnosed with AMR and treated with IVIg alone versus IVIg and rituximab [48]. They observed similar rates of DSA clearance between groups, but described lower mortality among patients whose DSA cleared. It was also observed that those treated with IVIg alone had a sooner onset of CLAD and higher mortality than those treated with combination IVIg + rituximab, though lack of randomization limits the generalizability of this conclusion.

Proteasome inhibitors (i.e., carfilzomib or bortezomib) which promote plasma cell apoptosis have been used in treatment of AMR. Ensor et al. described 14 patients with AMR who were treated with carfilzomib in addition to fixed schedule IVIg and plasmapheresis [49]. They observed a significant reduction of DSA levels as well as an improvement in spirometry suggesting reversal of allograft dysfunction associated with AMR. Among those who did not have a DSA level reduction (“non-responders”), progression to CLAD and mortality was significantly higher.

These studies suggest that DSA depletion is associated with favorable outcomes. Nevertheless, outcomes after AMR remain disappointing and the prognosis is poor with high rate of progression to CLAD. Additional randomized

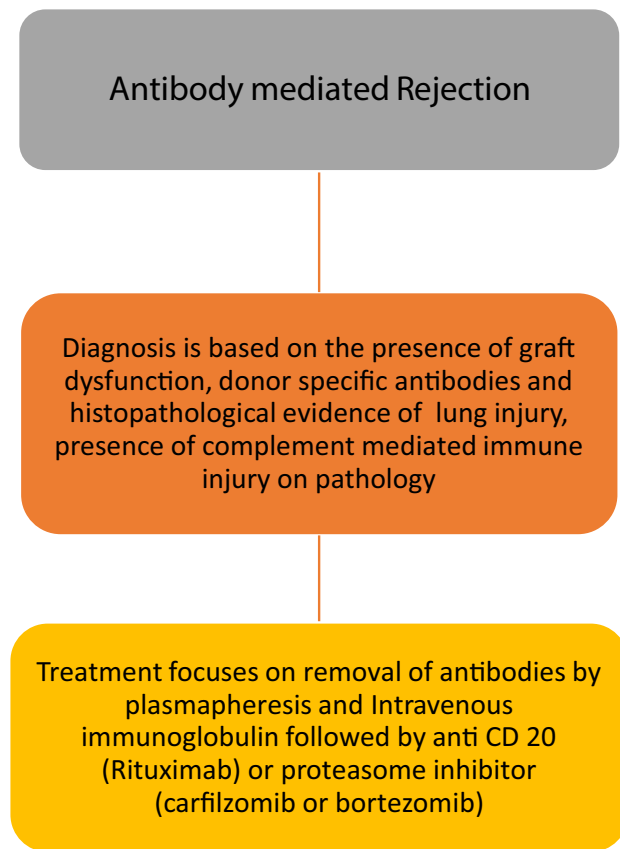


Fig. 2 Management of antibody mediated rejection

control trials with head-to-head comparison of treatments are necessary to identify the optimal management regimens. Multicenter collaboration is necessary.

Conclusions

Rejection remains a significant problem following lung transplantation. Acute cellular rejection, lymphocytic bronchiolitis, and AMR are all risk factors for the subsequent development of CLAD. Ongoing research is required to further identify risk factors, improve diagnostic tools, and optimize management strategies for allograft rejection.

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