Drugs (2015) 75:455–472
DOI 10.1007/s40265-015-0369-y

REVIEW ARTICLE

Antibody-Mediated Rejection in Pediatric Kidney Transplantation: Pathophysiology, Diagnosis, and Management

Yolanda W. Ng[1] · Manpreet Singh[2] · Minnie M. Sarwal[1]

Published online: 27 March 2015

Abstract Kidney transplant is the preferred treatment of pediatric end-stage renal disease. One of the most challenging aspects of pediatric kidney transplant is the prevention and treatment of antibody-mediated rejection (ABMR), which is one of the main causes of graft dysfunction and early graft loss. Most challenges are similar to those faced in adult kidney transplants; however, factors unique to the pediatric realm include naivety of the immune system and the small number of studies and randomized controlled trials available when considering pharmacological treatment options. Here, we present a case of ABMR in a pediatric patient and a review of the pathophysiology, diagnosis, and management of ABMR. ABMR in pediatric kidney transplant continues to be a frustrating condition to treat because (1) there still remain many unidentified potential antigens leading to ABMR, (2) children and adults are at different stages of their immune system development, and, thus, (3) the full pathophysiology of alloimmunity is still not completely understood, and (4) the efficacy and safety of treatment in adults may not be directly translated to children. As we continue to gain a better understanding towards the precise alloimmune mechanism that drives a particular ABMR, we can also improve pharmacotherapeutic choices. With continued research, they will become more precise in treating a particular mechanism versus using a broad scope of immunosuppression such as steroids. However, there is much more to be uncovered, such as identifying more non-human leukocyte antigens and their role in alloimmunity, determining the exact mechanism of adults achieving complete operational tolerance, and understanding the difference between pediatric and adult transplant recipients. Making strides towards a better understanding of these mechanisms will lead to continued efficacy and safety in treatment of pediatric ABMR.

Key Points

Antibody-mediated rejection (ABMR) continues to be a difficult-to-treat complication of kidney transplantation.

Non human leukocyte antigen (nHLA) antibodies should also be considered for recurrent episodes of ABMR.

Age-related differences in immunity and thus alloimmunity could contribute to variable responses to treatment.

1 Introduction

Kidney transplant is the preferred treatment of end-stage renal disease (ESRD) in pediatric patients. Despite the advancements in pediatric kidney transplant, challenges remain in the area of maintaining long-term stable graft function and avoiding rejection. One of these challenges is the prevention and treatment of antibody-mediated

✉ Yolanda W. Ng
yolanda.ng@ucsf.edu

[1] Division of Transplant Surgery, University of California San Francisco, S-1269, Medical Sciences Building, 513 Parnassus Ave, San Francisco, CA 94143, USA

[2] Division of Transplant Nephrology, University of California San Francisco, 400 Parnassus Ave, San Francisco, CA 94143, USA

rejection (ABMR), which continues to be the largest risk factor for graft dysfunction and loss [1–3]. ABMR occurs when there is deterioration in graft function associated with the development of alloreactive antibodies or donor-specific antibodies (DSAs) and characteristic histological changes on biopsy. For the most part, the challenges that exist in the pediatric population are similar to the adult population in that sensitization, development of de novo DSAs, and non-adherence to post-transplant immunosuppression regimens pose risks towards the development of ABMR. Additional challenges that exist in the pediatric population are associated with the naivety of their immune system and the fact that they will most likely require more than one graft in their lifetime. Preventive measures such as adequate and timely monitoring of alloantibodies and adequate maintenance immunosuppression are taken; however, even with strict adherence, the development of ABMR still persists as we lack sufficiently sensitive non-invasive monitoring tools to accurately measure the alloimmune response and subtle graft inflammation [4].

Though this review focuses on the management of ABMR in the pediatric population, the majority of our treatment experience comes from the management of ABMR in adult populations. This review does not focus on the variations in the immune response based on age, as they in themselves do not directly impact the management of ABMR, but it is important to mention some salient differences in the maturation of the immune response over time. Immaturity of the newborn immune system leads to a 'physiological immunodeficiency' that encompasses all arms of the host response as reflected by the increased susceptibility of young children to infections by both viral and bacterial pathogens. Differences in innate immunity involve variations in toll-like receptor-dependent [5], and dendritic cell immune function in infancy [6–8], and androgen and estrogen alterations in puberty affect Th1/Th2 balance [9–12]. The humoral immune system remains relatively underdeveloped [13], with the neonate initially being almost entirely dependent upon passively acquired maternal antibody. Age-specific variations in the immune response can continue to play a role in late childhood, as the capacity of mononuclear cells to synthesize interleukin (IL)-12 is still below adult levels at 12 years of age [14, 15]. The inherent Epstein–Barr virus (EBV) and cytomegalovirus (CMV) seronegativity in most children at time of transplant makes them more susceptible to post-transplant CMV infection, and disease is deleterious to graft function and rejection [16]. This also contributes to an increased risk of post-transplant lymphoproliferative disorder (PTLD) in the younger population [17], specifically when the burden of immunosuppression increases due to the treatment of T-cell-mediated rejection and ABMR. Immunosuppression protocols have now been tailored towards the pediatric populations to extend the use of antiviral agents [16] and to minimize the use of maintenance steroids [16, 18], which reduce the risk of viral replication and bone and cardiovascular morbidity.

We also present an illustrative case of ABMR in a pediatric patient in order to highlight the complexities of the pathogenesis, diagnosis, and current treatment options for ABMR of the kidney transplant in the pediatric population.

2 Literature Search Methods

Literature review was performed in PubMed using the following terms alone or in combination: pediatric, transplant, transplantation, renal, antibody mediated rejection, treatment. In addition, a search of the National Institutes of Health clinical trial database was performed for pharmaceuticals mentioned in this review.

Illustrative Case

A 7-year-old female with ESRD secondary to polycystic kidney disease received a living unrelated renal transplant in October 2010. At 1 month post-transplant, she experienced an episode of renal artery torsion and thrombosis that resulted in loss of the graft and thus immediate transplant nephrectomy followed by a wean to complete withdrawal of all her immunosuppression over a 6-month period. She was maintained on dialysis until receiving a deceased donor renal transplant in January 2014. Prior to this transplant, her calculated panel reactive antibodies was 99 %. She received all her standard pediatric vaccinations on time (with the exception of live vaccines, which were not given as she was immunocompromised), with her last being an influenza vaccine 14 months prior to transplant. Crossmatch done at the time of transplant showed negative T- and B-cell cross-matches (flow cytometry) with weak DSAs to human leukocyte antigen (HLA)-DQ8 [mean fluorescence intensity (MFI) 1961] from serum in November 2013. Due to the MFI meeting our center's criteria for being weakly positive, she did not receive prophylactic plasmapheresis prior to transplant. At transplant, she received standard induction of anti-thymocyte globulin (6 mg/kg), mycophenolate mofetil (MMF; 600 mg/m^2 × two doses), and methylprednisolone (MP; 10 mg/kg). Immediately post-transplant, she was started on standard triple immunosuppression of MMF, MP (later switched to prednisone with a taper), and tacrolimus (started post-operative day 2). Her creatinine on discharge from the hospital was 0.38 mg/

dL [estimated glomerular filtration rate (eGFR) based on modified Schwartz; $k = 0.41$ was 98 ml/min/1.73 m^2]. Her 1-month polyoma virus screen was positive for BK viruria, and her MMF was decreased. At 2 months post-transplant, she had 6730 copies of BK detected by polymerase chain reaction in her blood and a rise in her creatinine to 0.68 mg/dL (eGFR 54 ml/min/1.73 m^2). Her biopsy showed SV40-positive (polyoma) cells and diffuse C4d tubulointerstitial capillary positivity concerning for acute ABMR along with borderline cellular rejection (g0, ptc0, cd4+, t1, i1 by Banff). She also had positive DSAs: HLA-A2 (MFI = 1693), HLA-B62 (MFI = 11,335), HLA-DR53 (MFI = 13,281), and HLA-DQ8 (MFI = 14,657) (Tables 1, 2). She received eight treatments of plasmapheresis with 1.5× volume plasma exchange (divided into two courses of four sessions each) and intravenous immunoglobulin (IVIG; two courses of 2 g/kg/course divided over three treatments). Her MMF was decreased to 150 mg/m^2 to allow clearance of polyoma virus, which decreased from 178,000 copies to <1000 copies in her blood in 1 month. During this month, her creatinine continued to rise to 0.80 mg/dL (eGFR 45 ml/min/1.73 m^2) and since her BK had cleared, her MMF had increased. She also received 750 mg/m^2 of rituximab (divided in two doses, 2 weeks apart) and started on a course of monthly eculizumab (600 mg/dose). Given that she received eculizumab, she was vaccinated with the meningococcal vaccine. She was started on ciprofloxacin for 2 weeks and transitioned to daily penicillin prophylaxis to continue for the duration of her eculizumab. After 2 months, she had a repeat biopsy that showed acute cellular rejection, type I and acute ABMR with patchy glomerulitis appreciated in <25 % of the glomeruli (g1, ptc2, c4d neg by Banff). Her DSAs showed some improvement, with HLA-A2 no longer detected, HLA-B62 (MFI = 1689), HLA-DR4 (MFI = 1,155), HLA-DR53 (MFI = 10,218), and HLA-DQ8 (MFI = 4992), and her creatinine had also improved to 0.55 mg/dl (eGFR = 72 ml/min/1.73 m^2). She continued to receive monthly IVIG treatments (2 g/kg/month divided over three treatments) along with monthly eculizumab (600 mg/dose) as well as a steroid pulse (10 mg/kg intravenous Solu-Medrol® for three doses) for cellular rejection. Her lymphocyte subsets have continued to show adequate suppression of her B-cell population. Over the 3 months since her last biopsy, she has continued to show improvement, with a new creatinine baseline of 0.45 mg/dl (eGFR 90 ml/min/1.73 m^2). Her DSAs also continue to downtrend with HLA-B62 no longer detected, HLA-DR4 (MFI = 1149), HLA-DR53 (MFI = 9125), and HLA-DQ8 (MFI = 3684).

3 Pathophysiology

ABMR, also known as humoral rejection, involves T cells, B cells, antibody formation, and the activation of complement. It can be classified into three groups: hyperacute (onset: seconds to days), acute [onset: days (early) to years (late)], or chronic (onset: months to years). Regardless of its classification, it involves the presence of alloantibodies directed towards antigens originating from the donor allograft, e.g., DSAs. They can be pre-formed or have formed de novo post-transplant. Pre-formed alloreactive antibodies lead to sensitization [19], which plays a large role in ABMR. Factors most relevant in pediatrics that contribute to sensitization include blood transfusions, prior transplants, and infections (bacterial and viral). Pregnancy is also a risk factor; however, it is less relevant in pediatrics. Risk factors that lead to formation of de novo antibodies include infection, usually concurrent with a decrease in immunosuppression, and non-adherence with the post-transplant immunosuppression regimen. These factors increase the risk for development of ABMR. Recently, it has been demonstrated that a previous episode of cell-mediated rejection predisposes to formation of de novo antibodies in unsensitized patients [20].

Presence of an allograft, in the absence of adequate immunosuppression, will permit for activation of a humoral-mediated response via antibodies directly binding to the allograft antigen or by alloantigen presentation by circulating antigen-presenting cells (APCs). Germinal centers have been found within the kidney [21] where APCs can present antigen and activate CD4+ effector T cells. CD4+ T cells interact with B cells via binding of their T-cell receptor to major histocompatibility complex (MHC)-I. Co-stimulatory signals are delivered via CTLA4 (CD152) or CD28 and CD40L on the T cells to the B7 (CD80/86) complex and CD40 on B cells. These co-stimulatory signals (CD28-B7 complex and CD40L-CD40) are required for IL-2-induced proliferation and differentiation of B cells into memory B cells and plasma cells, which secrete the DSAs (Fig. 1). Lack of the CD28 signal results in cell death. The CTLA4-B7 signal results in down-regulation of T-cell activity. Once the humoral response is activated, this leads to cellular infiltrates within the kidney and its vasculature, activation of complement, and graft destruction. If there is complement fixation, there is complement end product (C4d) deposition. A complement-independent mechanism of ABMR also exists as evidenced by a lack of C4d deposition in patients with ABMR [14]; however, it is the presence of complement-activating antibodies that is predictive of graft loss [22]. It is thought that the renal endothelial tissue can also directly activate T cells and thus B cells for antibody production.

Table 1 Summary of HLA types for recipient and donors

	HLA types								
	A	*B*	Bw	Cw	DR	DRw	DQB	DP	DPA
Recipient	11	13	4	7	15	51	5		
	33	44		10	16				
Donor 1	24	44	4	5	13	51	6	04:01	
	68	51		15	15		7	05:01	
Donor 2	2	13	4	10	4	53	8	04:01	01:30
	2	62	6	4	16	51	5	2:01/141:0	01:03

HLA human leukocyte antigen

Table 2 Summary results of donor-specific antibody levels reported as mean fluorescence intensity

Date	DSA levels (MFI)					Comments
	DR4	DQ8	DR53	B62	A2	
19 Nov 2013		1961				Prior to transplant
21 Mar 2014		14657	13281	11335	1693	2 mo after transplant
1 May 2014	3152	10666	14133	4422	1309	1 mo after last plasmapheresis tx
2 Jun 2014	2229	11627	14283	1985	1350	2 mo after last plasmapheresis tx
31 Jul 2014	1155	4993	10218	1689		4 mo after last plasmapheresis tx
27 Aug 2014	1149	3684	9125			5 mo after last plasmapheresis tx

Laboratory MFI categories at our institution are defined as follows: strong >8500, moderate 2000–8499, weak 1000–1999. Antibody testing was performed by solid phase methods that detect IgG antibodies

DSA donar specific antibody, *HLA* human leukocyte antigen, *MFI* mean fluorescence intensity, *mo* months, *Tx* treatment

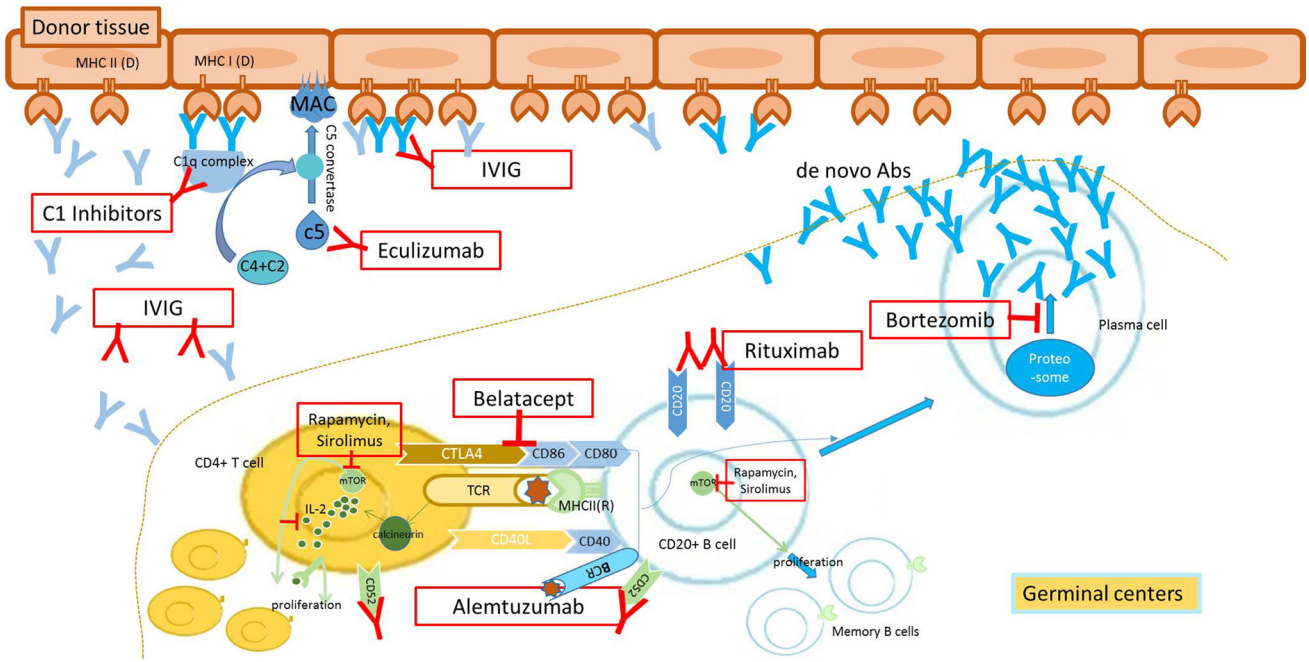

Fig. 1 Humoral immune pathway and targets of pharmacological treatments used in antibody-mediated rejection. *Abs* antibodies, *BCR* B-cell receptor, *CTLA* cytotoxic T-lymphocyte-associated protein, *IL* interleukin, *IVIG* intravenous immunoglobulin, *MAC* membrane attack complex, *MHC* major histocompatibility complex, *mTOR* mammalian target of rapamycin, *TCR* T-cell receptor

Conventionally, the most relevant DSAs were those formed against HLA; however, it is now known that non-HLA (nHLA) antibodies are also important in the context of ABMR. However, current routine testing for DSAs is rudimentary and only tests for HLA at six loci. Unfortunately, in the case presented, she had both pre-formed and de novo HLA antibodies and due to the weakly positive nature of her pre-formed DSAs at only one HLA locus, removal by plasmapheresis was waived. In hindsight, this weakly positive result was indeed significant, but in addition, her prompt onset of rejection may have been due to other pre-formed DSAs and/or non-HLA antibodies since she developed her second episode of rejection within 2 months of transplant.

3.1 Human Leukocyte Antigen (HLA) Antibodies

DSAs that contribute to ABMR have specificity for HLA. Currently, the HLA antibodies for which we test are directed towards MHC class I (HLA-A, B, C) and MHC class II (HLA-DR, DP, DQ).

3.2 Non-HLA Antibodies

The importance of nHLA antibodies in alloimmunity became evident when antibodies against endothelial antigens were identified as the culprit in hyperacute rejection [23–27] and the unexpected occurrence of rejection in HLA-matched donors and recipients [28]. In an ABO incompatible transplant, the ABO blood group antigens are the most common causes of rejection; however, in ABO-compatible transplants, other nHLA antigens and antibodies have been implicated. They include collagen type IV and VI, vimentin, myosin, protein kinase C zeta (PKCζ), MHC I-related chain A (MICA) [29], angiotensin II type I receptor (AT1R) [30], endothelial-1 type A receptors [30], and anti-endothelial antibodies (AECA) [16]. While HLA and ABO antibodies are most implicated in acute ABMR, it is postulated that nHLA antibodies currently may play a larger role in chronic ABMR [31]. AT1R antibodies have been associated with chronic ABMR [32]. AECA and MICA have been found to be up-regulated in patients who are undergoing renal transplant rejection [33]. In addition, MICA antibodies have been associated with an increased frequency of graft loss, especially if found in conjunction with anti-HLA antibodies [34, 35]. Endothelial-1 type A receptor (ETAR) antibodies were also studied in renal transplant patients and although there was no clear association with acute rejection, it was associated with poorer graft function as defined by higher serum creatinine levels when compared with patients who were anti-ETAR negative. However, an increased incidence of acute rejection was not observed on biopsy, therefore the significance of the presence of these antibodies in an ABMR is not clear, but it is possible they are associated with chronic ABMR. We have shown that nHLA antibodies such as those formed against PKCζ [36] and angiotensinogen [32] can play a critical role in steroid-resistant rejection and the hypertension of chronic kidney disease. With improved strategies to prevent hyperacute rejection, the association with nHLA antibodies and rejection has shifted towards a more chronic process; however, they still continue to play a role in acute rejection. A recent study by our group identified novel antigenic targets [endoglin, epidermal growth factor (EGF)-like repeats and discoidin I-like domains 3, intercellular adhesion molecule 4, and FMS-like tyrosine kinase-3 ligand], which were relevant to the development of acute ABMR as evidenced by a positive endothelial positive cross-match [37]. In addition, upregulation of nHLA proteins in acute rejection in transplant [38] have been described; it would be important to know whether these proteins serve as alloantigens.

3.3 Age

The age of the recipient may affect the development of ABMR. B-cell subsets change with age, thus affecting the B-cell repertoire and level of antibody production. It has been shown that the pediatric B-cell repertoire contains more naïve cells than memory B cells, while the memory compartment dominates in the adult B cell repertoire as evidenced by less immunoglobulin D in adults. The naivety in pediatrics is due to the lack of exposure to many antigens, including EBV and CMV, and has advantages and disadvantages. They may either be able to induce a level of tolerance if they still possess an intact thymus or create an entire subset of memory cells that are reactive to the newly transplanted organ. In contrast, adults have fewer B cells to respond to new antigens, but have a larger memory cell population [39–42], thus increasing their chance of being sensitized but decreasing their ability to form new antibodies against new antigens, which may explain the ability of some adult transplant patients to achieve operational tolerance. Age also affects de novo antibody formation. Pediatric patients are more likely to form de novo antibodies within the first 2 years of transplant [3] compared with adults who have a rate of de novo antibody formation ranging from 1 to 10 years, with a majority in the 5–10 years range [22, 43]. However, the incidence of de novo antibody formation in the pediatric population has been shown by one study to be around 6 % [3], whereas in the adult population it can be up to 30 %. This variation in timing and incidence may underlie the immune mechanism at play (memory vs. new), and it may be advantageous to be mindful of the nature of the origin of the antibodies when choosing an agent for treatment.

The development of ABMR is affected by factors that include age, sensitization, infection, and level of immunosuppression at induction and maintenance. An additional risk is receiving an ABO-incompatible transplant; however, in the USA, ABO-incompatible transplants are not performed in the pediatric population.

4 Diagnosis

4.1 Clinical and Histological Diagnosis

Diagnosis of acute ABMR involves the presence of acute graft dysfunction, as represented by elevated creatinine and decreased GFR, which prompts a diagnostic biopsy of the allograft and serological testing for DSAs. Progression from acute to chronic is evident with development of proteinuria and hypertension with a slow decline in graft function. Histological evidence of acute and chronic ABMR in the kidney transplant is based on the presence of tissue damage, microvascular inflammation, and evidence of complement activity that fulfill the Banff criteria as well as serological evidence of DSAs. The Banff criteria for ABMR were first published in 2003 and recently updated in 2013 [44, 45]. Table 3 presents a summary of the Banff 2013 update. The most notable update is the addition of acute AMBR type 2, which now does not require the presence of C4d staining of the peritubular capillaries [45] if vascular and microvascular injury in the absence of C4d staining is present with serological evidence of DSAs and graft dysfunction [46]. Histological findings of transplant glomerulopathy and moderate inflammation with presence of plasma cells distinguishes a chronic process from an acute process.

4.2 Serological Diagnosis

Serological testing for DSAs are most commonly carried out using solid-phase detection methods with single antigen beads (SABs, Luminex) for anti-HLA antibodies. The use of Luminex beads has shifted from the use of the complement fixation assays such as the complement-dependent cytotoxicity (CDC) method to C1q and C3d assays. The CDC method is less sensitive and is being abandoned due to evidence that not all non-complement-fixing DSAs are insignificant. However, the C1q assay, in addition to being more sensitive than the CDC, may have value in that the presence of de novo antibodies that are C1q-positive HLA class I antibodies may be predictive of ABMR and the development of glomerulopathy and carry a poor prognosis [47, 48]. Most recently developed is the C3d complement-binding assay than may be more sensitive at predicting graft loss than the C1q assay [49].

The disadvantages of relying on these methods include that, in addition to the lack of consensus over the years in regards to the histological changes that make up ABMR and that DSA detection is only limited to six HLAs, it is also well established that once serum creatinine is elevated, injury to the kidney has already taken place. The treatment for ABMR was often foregone due to an absence of C4d staining; however, it is now evident that ABMR can be present without C4d deposition [33]. In addition, treating a rejection after a rise in creatinine becomes an attempt to reverse the rejection in order to salvage an already damaged graft. This is why the presence of DSAs in association with graft dysfunction also carries a poor prognosis for the graft [50]. In addition, protocol biopsies, conducted at set intervals post-transplant, have uncovered the phenomenon of subclinical rejection, which is detection of rejection on biopsy prior to the rise of creatinine and can occur in up to 10 % of kidney transplants [51, 52]. Although advances have been made in treating ABMR at an earlier time point and preventing it in sensitized patients via desensitization protocols, we can do better by targeting treatment towards preventing antibody formation and the onset of ABMR and thus preventing damage to the graft. However, with our current methods, early diagnosis of ABMR is difficult; thus, the discovery of biomarkers has become integral.

4.3 Molecular Diagnosis

Biomarkers, originating from blood or urine, can serve as molecular ‘signatures’ for rejection and are quickly being discovered. The ability to diagnose rejection at a molecular level from a blood or urine specimen is beneficial because it allows for non-invasive diagnosis and risk stratification of rejection without the traumatic biopsy of an organ that is already undergoing the trauma of rejection. Recently, studies have described patterns of gene expression [53, 54] and microarray analysis [55–57], urine proteomics [38], and a constitution of both molecular and clinical markers specific to acute rejection [58, 59] in solid organ transplants, including kidney transplants. Some of these studies [52, 59] have led to the development of the kidney Solid Organ Response Test [60], which can accurately diagnose acute kidney rejection with a peripheral blood sample. These developments confirm that a non-invasive molecular signature for ABMR in the kidney exists and, most importantly, can predate the rise in creatinine and histological changes [54]. In addition, genomic differences also exist in DSA-positive transplant patients who develop rejection compared with DSA-positive transplant patients who do not [61]. Once these are well developed, they will serve as valuable guides for immunomodulation and determining the effectiveness of treatment without having to re-biopsy post-treatment, and will allow for earlier initiation of

Table 3 Revised criteria from Banff 2013 classification of antibody-mediated rejection in renal allografts

	Acute/active ABMR (all three required)	Chronic/active ABMR (all three required)	C4d staining without ABMR (all three required)
Tissue injury	Evidence of acute tissue injury with 1 or more of 1. Microvascular inflammation ($g > 0$ and/or ptc > 0) 2. Acute TMA with no other cause 3. Acute tubular injury with no other cause	Evidence of chronic tissue injury with 1 or more of 1. Transplant glomerulopathy (cg > 0), if no evidence of chronic TMA 2. Severe peritubular capillary basement membrane multilayering by EM 3. New-onset arterial intimal fibrosis without any other causes	$g = 0$, ptc = 0, cg = 0 (by light and EM, if available), $v = 0$; no TMA, no ptc basement membrane multilayering, no acute tubular injury
Vascular endothelial injury/C4d staining	Evidence of current/recent antibody interaction with vascular endothelium with one or more of 1. Linear C4d staining in peritubular capillaries (C4d2+ by IF on frozen sections or C4d > 0 by IHC on paraffin sections) 2. Moderate microvascular inflammation (g + ptc) ≥ 2 3. Increased expression of thoroughly validated gene transcripts in the biopsy tissue consistent with endothelial injury	Evidence of current/recent antibody interaction with vascular endothelium with 1 or more of 1. Linear C4d staining in peritubular capillaries (C4d2+ by IF on frozen sections or C4d > 0 by IHC on paraffin sections) 2. Moderate microvascular inflammation (g + ptc) ≥ 2 3. Increased expression of thoroughly validated gene transcripts in the biopsy tissue consistent with endothelial injury	Linear C4d staining in peritubular capillaries (C4d2+ by IF on frozen sections or C4d > 0 by IHC on paraffin sections)
Serology/ other findings	Serologic evidence of DSAs (HLA or other antigens)	Serologic evidence of DSAs (HLA or other antigens)	No acute cell-mediated rejection (Banff type 1A or greater) or borderline changes [112, 115]

In addition, C4d-negative antibody-mediated rejection was also included in the definition of antibody-mediated rejection, then if there is presence of moderate microvascular injury and/or molecular evidence of endothelial injury in the absence of C4d staining [44, 45, 112–114]

ABMR antibody-mediated rejection, *cg* chronic glomerulopathy, *DSAs* donor-specific antibodies, *EM* electron microscopy, *g* glomerulitis, *HLA* human leukocyte antigen, *IF* immunofluorescence, *ptc* peritubular capillaritis, *TMA* thrombotic microangiopathy, *v* vasculitis

treatment for ABMR and serve as a tool for treatment decisions to avoid unnecessary exposure to aggressive immunosuppression. However, continued biomarker discovery is needed, especially in differentiating between cellular-mediated, ABMR, or mixed rejection. Thus, until a well-developed superior method of noninvasive diagnosis and/or prediction of transplant rejection can also differentiate acute versus chronic as well as ABMR versus cellular-mediated rejection, we continue to rely on our current methods of diagnosis.

5 Treatment

Treatment for all types of ABMR target (1) the elimination of circulating allograft antibodies, (2) immunomodulation, and/or (3) the deactivation/inhibition of complement. The co-occurrence of DSAs and decreased graft function represents a poor prognosis for the graft, and abrupt removal of DSAs improves prognosis [43]; thus, removal of antibodies is often the first-line treatment of acute ABMR. However, removal alone is inadequate and thus arise the challenges in treating acute and chronic ABMR. These are the same challenges seen in the adult population and include resistance to steroid treatment and non-responsiveness to standard treatment, as evidenced by frequent repeat episodes. The main drawback to selecting therapy for pediatrics is that efficacy is based on adult studies and, as previously mentioned, age affects immune mechanisms and thus may dictate efficacy. Until recently, randomized controlled trials have been scarce, and treatment selection was often based on small single-center studies or case reports. Treatment strategy remains non-specific, especially in pediatrics. This is due to the lack of clinical trials and the limited number of studies on newer agents for pediatric use. The most available and widely used agents are broad-based immunosuppression, which is essentially analogous to throwing the kitchen sink at recurrent episodes (plasmapheresis, IVIG, steroids, and rituximab).

5.1 Acute and Sub-Acute

In pediatrics, studies involve new applications for old drugs or drugs that have been used to treat other inflammatory

diseases, and treatment has been tailored to try to better target different aspects of the antibody rejection pathway to achieve better outcomes. Here, we present a summary of the different modalities and drugs available, different combinations of treatments applied, and a summary of some, mostly adult and some pediatric, studies available for first-time and recurrent episodes of acute ABMR (Table 4).

5.1.1 Removal of Circulating Anti-Allograft Antibodies

Plasmapheresis or therapeutic plasma exchange (TPE) is the most common initial treatment for acute ABMR. This process requires a large centrally placed catheter and removes large molecular-weight proteins, including alloantibodies, from the blood. The patient's plasma is removed and replaced with either 5 % albumin or fresh frozen plasma (FFP) at different ratios. For the treatment of ABMR, FFP is used to replace lost protective antibodies and clotting factors, since many rounds are required for clearance of DSAs. In pediatrics, the most common ratio used (1.5 exchange) allows for removal and replacement of approximately 75 % of the plasma compartment and thus removal of a significant portion (~65 % per round) of DSAs; thus, multiple rounds are required [62, 63]. Most common side effects include hypotension due to volume depletion associated with plasma removal, especially in smaller patients, and hypocalcemia due to the use of citrate as an anticoagulant. Blood priming and co-administration of a calcium infusion as preventive measures facilitates this modality to be well tolerated by the pediatric population including smaller (<20 kg) children. The response rate for TPE is approximately 50 %. Thus, it is rarely used as monotherapy; however, when used in conjunction with IVIG, the success rate is 80–90 % for the treatment of acute ABMR [64, 65]. The use of TPE with chronic ABMR is variable; however, one adult study reports improvement in GFR with the use of up to 14 rounds of TPE when used in combination with IVIG [66].

Immunoadsorption is used mainly for preconditioning in the treatment of ABO-incompatible transplants and rarely in pediatrics. However, as these are not routinely conducted in the USA and immunoadsorption is not used, it is not discussed in depth in this review. Briefly, it is similar to plasmapheresis, but involves the use of a filter that specifically isolates anti-ABO antibodies. While plasmapheresis removes both IgG and IgM antibodies, immunoadsorption is more efficacious but removes only IgG antibodies.

5.1.2 Immunomodulators

Mechanisms of immunomodulation include B- and/or T-cell depletion, inhibition of cell signaling, and inhibition of complement. Current antibodies and biologics have been developed to target these points of the pathway and have been adapted to treat ABMR. Some are primarily only used in adults; however, some have been transitioned for use in pediatrics after clinical trials demonstrated efficacy and safety.

5.1.3 Cell Depletion

Rituximab, originally used to treat B-cell lymphomas, is a humanized chimeric anti-CD20 antibody that depletes mature antigen-presenting B cells from circulation and spares immature and terminally differentiated plasma cells. Its uses have extended to treating autoimmune disease as well as various pathologies for transplant, including kidney transplant rejection. A typical dose is 375 mg/m^2; however, one study reports using 650 mg/m^2 [67]. It has been shown to improve graft function when added to conventional therapy in treating acute ABMR in pediatrics [50, 68] and adults [69–71] via high percentage, and in some cases complete, depletion of circulating CD20+ B cells. A meta-analysis by Hychko et al. [72] favored the use of rituximab over alternative therapies [72]. It has also been successful when used for desensitization in conjunction with IVIG [46]. However, results with chronic ABMR [73] and some acute ABMR remain variable [50, 67]. The therapeutic effects can be attributed to the elimination of preconditioned B cells from circulation and reconstitution of the naïve B-cell subpopulation since pediatric ABMR patients who did not relapse after rituximab demonstrated a higher percentage of naïve B cells after repopulation [68], suggesting that the B-cell repertoire has been reprogrammed and has less propensity to form a pre-programmed immune response towards the alloantigen and thus re-achieve desensitization. Some use of rituximab is associated with increased incidences BK nephropathy [74] and other infections [72]; however, larger studies [71, 75] have suggested that there is no significant difference in infectious complications when compared with other treatments. However, in cancer studies, an increased incidence of interstitial pneumonitis has been observed when rituximab is added to the regimen [76]. This may be due to concomitant use with other chemotherapeutic agents known to have pulmonary toxicity, such as cyclophosphamide; however, this is also an agent used in some pediatric kidney patients and therefore should be taken into consideration. Due to these complications, and since other immunomodulatory therapies are available and may avoid this complication, it may be more advantageous to use an alternative such as the inhibition of complement when appropriate. Non-responders to rituximab who experience improvement with bortezomib or eculizumab may already have many terminally differentiated plasma cells, another reason to favor alternative treatment.

Table 4 Summary of treatment regimens for acute or chronic antibody-mediated rejection

Treatment and study	Study type	*n*	Treatment regimen	Outcomes		
				Graft function	DSA response	Complications
Rituximab						
Becker et al. [69]	Pro	27	RTX 375 mg/m^2 single dose + IVMP ± ATG + PP	88 % graft survival at 24 months	N/A	Graft loss (*n* = 3) after 2 years due to CAN
Faguer et al. [70]	Pro	8	RTX 375 mg/m^2/week for 3–5 doses + PP + IVMP + ATG (*n* = 4) + OKT3 and IVIG (*n* = 1)	75 % graft survival at 10 months	DSA neg (*n* = 2), PRA improved (*n* = 2)	Septic shock (*n* = 2)/BKVAN (*n* = 3)/peritonitis (*n* = 1)/graft failure (*n* = 2)
Steinmetz et al. [116]	Ret, com	16	RTX 375 mg/m^2 single dose (*n* = 8) + conventional Rx vs. conventional Rx (*n* = 8)	B-cell depletion 100 % in RTX group, graft survival 100 % both groups at 3 months	N/A	BKAVN (*n* = 1)
Kaposztaz et al. [71]	Ret, com	54	RTX 375 mg/m^2 + PP (*n* = 26) vs. PP (28) ± IVIG (if low level)	Graft survival 90 % vs. 60 % at 2 years	N/A	Rate of infections similar in both groups at 6 months
Mulley et al. [117]	Pro	7	RTX 500 mg × 1 dose + PE + low-dose IVIG (0.1 gm/kg)	100 % graft and pt survival at 21 months	N/A	CMV viremia (*n* = 1), BKVAN (*n* = 1)
Zarkhin et al. [118][a]	RCT	20	RTX 375 mg/m^2 weekly × 4 weeks + ATG + steroids vs. ATG + steroids	B-cell depletion 100 % and improved graft function (higher CrCl) at 1 year in RTX group	N/A	Low-grade CMV and EBV and BK viremia (*n* = 1)
Vo et al. [46] (desensitization)	RCT	13	IVIG + PL (*n* = 7) vs. IVIG + RTX (*n* = 6)	Better graft function at 6 and 12 months in RTX group	DSA rebound with severe AMR 42.8 vs. 0 % in RTX group	BKVAN (*n* = 2) and graft loss (*n* = 2), TMA (*n* = 3) in PL group
Bortezomib						
Everly et al. [119]	CS	6	BOR 1.3 mg/m^2 × 4 doses ± IVMP/ATG/PP/IVIG	67 % graft and 100 % pt survival at 5 months (mean)	50 % reduction in DSA in all pts	Transient thrombocytopenia
Perry et al. [77]	Pro	2	BOR 1.3 mg/m^2 × 4 doses + PP + IVIG	100 % graft and pt survival at 12 months	Reduction in plasma cells and allospecificities after 1 week	None
Everly et al. [120]	Pro	5	BOR 1.3 mg/m^2 × 4 doses after other AMR Rx failure	100 % graft and pt survival at 6.9 months (median)	50 % reduction in DSA in all pts	Transient thrombocytopenia (*n* = 1)
Sberro-Soussan et al. [85]	CS	4	BOR 1.3 mg/m^2 × 4 doses	100 % graft and pt survival at 5 months	No change in DSA	

Table 4 continued

Treatment and study	Study type	*n*	Treatment regimen	Outcomes		
				Graft function	DSA response	Complications
Flechner et al. [121]	Pro	20	BOR 1.3 mg/m^2 × 4 doses, IVMP + PP × 4 sessions, IVIG (0.5 gm/kg) × 4 doses	85 % graft survival and 100 % pt survival at 10 months	DSA reduction in 55 %, undetectable in 2 pts	Graft failure (n = 2); transient thrombocytopenia
Walsh et al. [122]	Pro	2	BOR 1.3 mg/m^2 × 4 after each PP session and IVMP	100 % graft and pt survival	Reduction in DSA below detection threshold (n = 1)	Anemia (n = 1); peripheral neuropathy (n = 1); repeat dose (n = 1)
Waiser et al. [123]	CC (HC)	19	BOR 1.3 mg/m^2 × 4 doses, 6 PP and IVIG (30 g) + IVMP vs. RTX 500 mg × 1, PP and IVIG (30 g) + IVMP	Graft survival 60 % vs. 11 %, pt survival 100 % each group at 18 months	Reduction in DSA 5/10 vs. 4/7	Transient thrombocytopenia vs. leukopenia in RTX group
Nguyen et al. [67][a]	CS	4	BOR 1.3 mg/m^2 × 4 doses + IVMP + PP + RTX ± IVIG	Graft survival 75 % at 1 year	Reduction in DSA in all pts rebound months after treatment	
Eculizumab						
Locke et al. [103]	CR	1	ECU 600 mg + conventional Rx; PP + IVIG + RTX (375 mg/m^2) × 1 dose	Serum creatinine returned to baseline and remained stable at 4 months	N/A	Death from pulmonary hemorrhage and sepsis 4 months post-transplant with functioning graft
Lonze et al. [124]	CR	1	ECU 1200 mg × 1, then 600 mg weekly × 4 weeks and 1200 mg every 12 days × 3 doses	Stable serum creatinine at 6 months	N/A	UTI
Chandran et al. [125]	CR	1	ECU 1200 mg × 1, then 900 mg after 1 week × 1 + PP and IVIG	Stable serum creatinine at 4 months	N/A	
Noone et al. [126]	CR	1	ECU 900 mg × 1, then 600 mg after 1 week + IVIG + PP + RTX (375 mg/m^2) × 2 doses	Improved serum creatinine at 1 month	DSA remained detectable above threshold	Allograft loss due to BKVAN at 6 months
Stegall et al. [102]	CC (HC)	26	ECU 1200 mg at time of transplant, 600 mg on POD 1, then 600 mg weekly × 4 weeks. If DSA persistently high, 1200 mg week 5 and every 2 weeks	Incidence of ABMR 7.7 vs. 41.2 %. 100 % graft survival in ECU group vs. 96 % in control group		Burkitt's lymphoma 2.5 year after transplant (n = 1) in ECU group, died with functioning graft
Orandi et al. [104]	Ret	24	ECU 1,200 mg, then 900 mg next day with 600 mg after each PP, then 900 weekly × 4 does. 1,200 mg every 2 weeks until DSA reduced to give FCXM neg. Splenectomy alone (n = 14) vs. ECU alone (n = 5) vs. splenectomy + ECU (n = 5). All pts received IVIG + PP ± RTX	Graft survival 77.9 % vs. 30 % vs. 100 % at 1 year.	N/A	UTI (42.9, 40, 80 %); pneumonia (14.3, 0, 40 %); CMV viremia (14.3, 0, 20 %); sepsis (35.7, 40, 40 %), *Clostridium difficile* (0, 20, 60 %); skin/wound infection (35.7, 40, 60 %)

Table 4 continued

Treatment and study	Study type	*n*	Treatment regimen	Outcomes		
				Graft function	DSA response	Complications
Alemtuzumab						
Thomas et al. [94]	CR	1	ALE 30 mg × 2 doses + cytogam × 4 doses (8 g) after four sessions of PP	Improvement in serum creatinine at 2.5 months	N/A	Graft loss due to severe vascular rejection after 3 months
Csapo et al. [127]	CS	5	ALE total dose (55–93 mg) in 4–5 divided doses + IV MP ± IVIG, RTX	Improved serum creatinine at 2 weeks	N/A	Herpes Zoster (n = 1), idiopathic pneumonitis (n = 1)
Jirasiritham et al. [93]	CR	1	ALE 30 mg SC + IVIG + PP	Stable creatinine at 8 months	N/A	

ALE alemtuzumab, *ABMR* antibody-mediated rejection, *ATG* anti-thymocyte globulins, *BKVAN* BK virus-associated nephropathy, *BOR* bortezomib, *CAN* chronic allograft nephropathy, *CC* case–control, *CMV* cytomegalovirus, *CR* case report, *CrCl* creatinine clearance, *com* comparative, *CS* case series, *DSA* donor-specific antibody, *ECU* eculizumab, *HC* historical control, *IVIG* intravenous immunoglobulin, *IVMP* intravenous methylprednisolone, *N/A* not applicable, *OKT-3* muromonab-CD3, *PL* placebo, *POD* post-operative day, *PP* plasmapheresis, *pro* prospective, *pt(s)* patient(s), *RCT* randomized controlled trial, *ret* retrospective, *RTX* rituximab, *Rx* pharmacotherapy, *SC* subcutaneous, *TMA* thrombotic microangiopathy, *UTI* urinary tract infection

[a] Pediatric studies only

Bortezomib is a protease inhibitor that reduces antibody production from mature plasma cells via apoptosis and has been shown to effectively lower DSA levels [77]. Currently, it is only approved for use in multiple myeloma and mantle cell lymphoma; however, success in reduction of DSAs and treatment of ABMR for solid organ transplant has been demonstrated in large studies [78, 79]. Adult kidney transplant rejection studies have shown variable results for success when measured in terms of decreased DSAs, histological improvement, and/or improvement in graft function [80–85]. However, the cases that showed no response in graft function had improvements in DSA levels, but TPE was also used and follow-up was short, which may not have allowed enough time for reconstitution of DSAs. Subjects who maintained significantly low levels of DSAs were also given rituximab. Long-term improved graft function and DSA suppression is seen in cases where bortezomib is given after plasmapheresis, IVIG, rituximab, and steroids [67, 86], often due to minimal response to conventional treatment. A few small studies and case reports are available for pediatrics and report initial success for decrease in DSA when used at a dose of 1.3 mg/m^2/dose for four doses [87]; however, rebound occurred at 1 year. A larger case–control study in adults from Waiser et al. [123] had an 18-month follow-up and shows equal efficacy in DSA reduction compared with rituximab, but more patients in the bortezomib arm had better graft function. Another pediatric case showed a decrease in all alloantibodies as well as protective tetanus and measles antibodies at 1 year when given after rituximab [88]. A downfall is that plasma cells need to already be activated, and serious hematologic, neurologic, and gastrointestinal side effects are reported in adults with the use of multiple doses. Thus, it may be more effective as adjunct therapy or for desensitization for patients with pre-formed DSA versus monotherapy for AMR. It appears that DSA suppression is better when used in conjunction with rituximab. It may also be a good alternative for rituximab non-responders. It has not yet been studied, but could be considered as preventive therapy for recurrence in transplants for patients with primary diseases that are or may be antibody driven such as autoimmune diseases (lupus) and focal segmental glomerulosclerosis. Clinical trials to assess its efficacy for treatment of chronic ABMR and late ABMR [TRIBUTE (NCT02201576; Bortezomib in Rejection of Kidney Transplants) and BORTEJECT (NCT01873157; Bortezomib in Late Antibody-Mediated Kidney Transplant Rejection)] are underway.

Alemtuzumab is an anti-CD52 antibody that results in depletion of total T cells. It is typically used for induction and prevention of development of acute and hyperacute ABMR and has not been reported as a treatment for acute ABMR. In pediatric patients, studies highlight its effect

when used in induction, which results in greater prolonged depletion of CD4+ effector T cells over CD8+ T cells and an increase in the ratio of T-regulatory:effector cells at 3 months post-transplant. However at 1 year, this ratio returned to baseline, which the authors attributed to an initial increased depletion of effector memory cells and sparing of regulatory cells [89]. At the 2-year time point, 33 % of patients had developed DSAs. Other studies, including a pediatric study, describes a higher rate of rejection with alemtuzumab as induction therapy [90, 91]. Since it has a great effect in depleting effector T cells, but does not seem to prevent formation of an allo-specific T-cell effector population, it may be more effective as treatment for acute rejection and ABMR. Case studies exist that have demonstrated better efficacy in adults who were status post-living related donor transplants who had mixed ABMR and cellular rejection [92, 93] and one failed case of an adult who was status post his fourth deceased donor transplant with pure ABMR [94].

Splenectomy is the most aggressive form of treatment for all forms of antibody rejection. It effectively removes most of the peripheral reactive B cells and has been useful in the most extreme cases [95]. However, this is the least practical form of treatment for the pediatric population since it will predispose them for a longer period or a lifetime of a higher risk of infections.

5.1.4 Inhibition of Co-Stimulation

Belatacept is a biologic that is a fusion protein made from the extracellular portion of CTLA4 and a fragment of the Tc domain of IgG1. Thus, it selectively inhibits the co-stimulatory signal between T and B cells by binding to the CD86/CD80 (B7) complex. It is currently approved only for use in prevention of rejection. The Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial was a 3-year randomized prospective study in adults that investigated the use of belatacept compared with cyclosporine. The purpose of this trial was to find a comparable alternative to a calcineurin inhibitor (CNI), which is known to be nephrotoxic and to lead to long-term graft dysfunction. The results not only showed improvement in long-term graft function, but also, of those who developed rejection post-belatacept, none were antibody mediated, and there was a lower rate of DSA formation in the belatacept group [96]. However, the use of belatacept in children may be limited due to the incidence of PTLD in this study being higher in those who were EBV negative. This finding is consistent with other findings that EBV seronegativity is a large risk factor for development of PTLD [97, 98]. More pediatric patients than adults who receive kidney transplants have not seroconverted (up to 40 %) [97]. The manifestations of PTLD associated with the use of belatacept, especially central nervous system manifestations (>50 %), is quite severe, putting the pediatric population at high risk; however, treatment for PTLD is also improving [99]. Currently, there are no reports on the use of belatacept in children.

Abatacept is another biologic with the same target as belatacept that is currently used for autoimmune disorders. Theoretically, it could also be effective for treatment of ABMR; however, the side effect profile is not very favorable and, in addition to a higher risk of PTLD, other side effects reported include severe viral and bacterial infections, multiple sclerosis (MS), lymphoma, dyspnea, purpura, and transaminitis. The benefits of graft survival may need to be weighed against the risks.

5.1.5 Inhibiting Complement

IVIGs are pooled immunoglobulins that fix anti-allograft antibodies (HLA) to prevent complement activation at low dose (1 g/kg). Conventional initial treatment of acute ABMR is low-dose IVIG in conjunction with plasmapheresis and/or rituximab [50], which has been used successfully for the majority of acute ABMR cases. When used at a high dose (2 g/kg), in addition to the inhibition of lymphotoxicity, it has also been shown to decrease DSA levels [100, 101] and has also been successful when used in conjunction with TPE and/or rituximab. In addition to its use as treatment, high-dose IVIG is also a component of the desensitization protocol.

Eculizumab is a humanized antibody that inhibits the C5a component of the complement pathway. It acts on the common pathway and inhibits membrane attack complex deposition and thus tissue destruction. Originally approved for the treatment of paroxysmal nocturnal hemoglobinuria, it is now approved for the treatment of atypical hemolytic uremic syndrome (aHUS), where genetic defects in complement proteins lead to unregulated activation of complement and uncontrolled tissue destruction. It has also been used for the prevention of recurrence of aHUS in transplants. Small studies and case reports in adults and pediatrics [102–105], as well as our report in a young child, demonstrate the successful treatment of refractory ABMR [102–105]. There are also a couple of reports of failure [106]. Clinical trials are currently in progress to assess its efficacy versus IVIG and plasmapheresis and its safety for open-label use as treatment for ABMR (NCT01895127, NCT02113891). One of the major concerns with using eculizumab is the increased risk of infection by encapsulated organisms as noted by the black box warning about meningococcal infections, which have been reported despite appropriately receiving the vaccine prior to the drug. Aside from infectious side effects, eculizumab appears promising as an adjunct treatment in cases of severe recalcitrant ABMR.

5.2 Chronic Antibody-Mediated Rejection

Chronic ABMR remains the most difficult to treat and has the poorest prognosis. The presence of transplant glomerulopathy on biopsy is diagnostic. The cause of chronic ABMR is not completely understood, but is strongly associated with de novo antibodies. Those who have low levels of DSA are also mildly C4d+; however, there are also some with undetectable DSA and C4d−. Some believe this is most likely due to persistently low levels of alloantibodies (anti-HLA and anti-nHLA). The treatment strategy is the same as for acute ABMR and most commonly consists of a combination of IVIG and rituximab [107], which has been shown to be somewhat successful in pediatrics; however, when not successful they are extremely difficult to treat. Bortezomib has also been shown to be successful in some recalcitrant cases. Overall, chronic ABMR remains difficult to treat. In extreme cases, as a last ditch approach, a splenectomy has been performed in adults.

No form of pharmacotherapy has been successful as monotherapy for acute or chronic ABMR; a combination of drugs that work in synergy is required. Most treatment regimens that are successful include TPE and IVIG. Currently, conventional therapy remains a combination of multiple rounds of TPE, followed by multiple rounds of IVIG and rituximab. Recalcitrant cases are treated successfully with either bortezomib or eculizumab. Prevention of ABMR via desensitization, and optimizing the induction and maintenance regimen is also an important factor. Studies for the most effective desensitization strategies include multiple rounds of IVIG with rituximab as the most commonly used regimen. Studies on eculizumab as desensitization are currently underway. However, in desensitizing a patient, in addition to clearing preformed alloantibodies, targets such as destruction of memory B cells and prior inhibition of proliferation would also be beneficial. The most commonly used induction protocols for pediatrics are either thymoglobulin or basiliximab, MMF, with or without MP. Large pediatric trials have shown that the steroid-free regimens are safe and have equal effects on DSA. Thus, even with the inclusion of steroids into induction and maintenance protocols, ABMR still develops [18, 50, 67, 108, 109]. Maintenance therapies are usually composed of a CNI such as tacrolimus and continuation of MMF.

6 Conclusions

ABMR continues to be detrimental towards graft survival. Because the age at transplantation is getting younger, improved graft survival is vital in the pediatric population since it is extremely likely that they will require more than one graft within their lifetime, such as the case of the patient presented. Unfortunately, she had lost her first graft due to mechanical complications, and difficulties encountered with her subsequent graft illustrates the difficulties

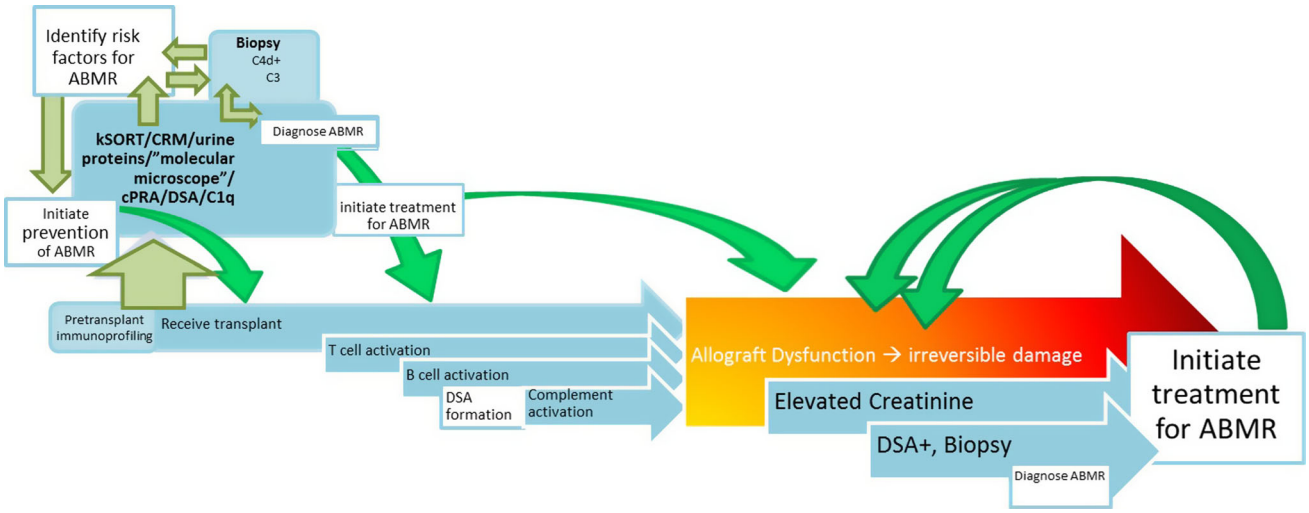

Fig. 2 Current treatment regimens in antibody-mediated rejection are mainly targeted at the removal of antibodies followed by suppression of cellular activity and inhibition of complement. They are typically initiated after allograft damage and elevation of creatinine. With continued improvement of diagnostic tools that are less invasive and have the potential to predict antibody-mediated rejection prior to elevated creatinine, we propose that this will improve prognosis of the graft by shifting the initiation of treatment to an early time point as well as shifting the target towards immunomodulation to prevent or decrease the formation of antibodies. *ABMR* antibody-mediated rejection, *cPRA* calculated panel reactive antibodies, *CRM* common rejection module, *DSA* donor-specific antibodies, *kSORT* kidney Solid Organ Response Test

we face in transplantation, such as sensitization, the naivety of the pediatric immune system and its capacity to respond to new antigen, infectious complications, the difficulties in treating ABMR, and the sequelae of difficult-to-treat ABMR. Thus, it is very important to increase the life of the first graft, prevent ABMR, and decrease the degree of sensitization to subsequent grafts.

Early formation of de novo antibodies leads to eventual graft loss [2], and pediatric patients are more likely than adults to form de novo antibodies within the first 2 years of transplant [3]. Prevention, early diagnosis, and predictive markers are key to improving graft survival. AMBR prevention lies in optimizing and emphasizing the importance of adherence to maintenance immunosuppression protocols. In treating the pediatric population, there are also special considerations such EBV and CMV status, which affect the choice of cell-depletion therapies and the use of steroids to avoid malignancy and infectious complications. Some protocols still include steroids; however, they have not been shown to affect DSA levels [3] or to be superior to other agents in treating [68] and preventing ABMR [18], and it would be beneficial to avoid them in the pediatric population.

Predictive strategies and earlier diagnosis may also lead to a shift from plasmapheresis, rituximab, and IVIG towards immunomodulators that inhibit T-/B-cell interaction to prevent antibody formation and possibly induce a peripheral immune compartment that may induce operational tolerance (Fig. 2). The immaturity of the pediatric immune system may make this more feasible. In patients who have mixed cellular rejection and ABMR, cell depletion and signal blockade therapies may also be more successful earlier in their course. The molecular signature for tolerance is currently being studied [110, 111] and may possibly be induced by specific immunomodulators, suggesting that there may be a potential for induction of operational tolerance, which would be the ultimate prevention of ABMR.

The continued research and discovery of nHLA alloantigens will help improve the DSA screening process while the tools for prediction and early diagnosis of ABMR become available. Together, they will hopefully change the focus of management of ABMR from treatment towards prevention and improved graft survival.

Acknowledgments The authors would like to thank Dr. Aris Oates for providing us with the case write up used in our review. Y. W. Ng, M Singh, and M. M. Sarwal declare no relevant conflicts of interest. No sources of funding were used to support the writing of this manuscript.

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