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REVIEW ARTICLE

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Antibody-mediated rejection after kidney transplantation in children; therapy challenges and future potential treatments

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[Correction added on 22 April 2022 , after first online publication: CSAL funding statement has been added.]

Abstract

Antibody-mediated rejection (AMR) remains one of the most critical problems in renal transplantation, with a significant impact on patient and graft survival. In the United States, no treatment has received FDA approval jet. Studies about treatments of AMR remain controversial, limited by the absence of a gold standard and the difficulty in creating large, multi-center studies. These limitations emerge even more in pediatric transplantation because of the limited number of pediatric studies and the occasional use of some therapies with unknown and poorly documented side effects. The lack of recommendations and the unsharp definition of different forms of AMR contribute to the challenging management of the therapy by pediatric nephrologists. In an attempt to help clinicians involved in the care of renal transplanted children affected by an AMR, we rely on the latest recommendations of the Transplantation Society (TTS) for the classification and treatment of AMR to describe treatments available today and potential new treatments with a particular focus on the pediatric population.

KEYWORDS
antibody-mediated rejection, immunotherapy, pediatric kidney transplantation

1 | INTRODUCTION

Despite the improved quality of maintenance immunosuppression, the occurrence of antibody-mediated rejection (AMR) after kidney transplantation remains the first cause of graft failure.[1] Current treatment options have not demonstrated their efficiency in clinical trials. Indeed, no treatment has yet received FDA approval in the US.

Studies comparing AMR treatments have many limitations; the use of different AMR definitions and the lack of a recognized gold standard in AMR treatment make clinical trials difficult to compare. Placebo-controlled studies are often unethical due to the higher risk of graft loss without treatment. Furthermore, most studies compare multiple simultaneous treatments without randomization and with a small number of patients, making it difficult to assess the impact of every single treatment. AMR treatment in children and adults is challenging, and the number of available RCT including children is even scarcer. Therefore, most pediatric clinical protocols result from adult experiments. However, children differ from adults, and protocols must be critically adapted to the single situation. Furthermore, rational use of potent immunosuppressants is a priority in pediatric transplantation.

Due to the inability of the recent literature to define common approaches and comparable results, a recent meeting of experts of the Transplantation Society[1] (TTS) expressed a common phenotypical classification of AMR, based on the available literature and experts' opinions, and tried to propose a standard of care (SOC) for its treatment in adults.

In this literature review, considering the recommendations of the TTS and the experience today available on the pediatric population, we

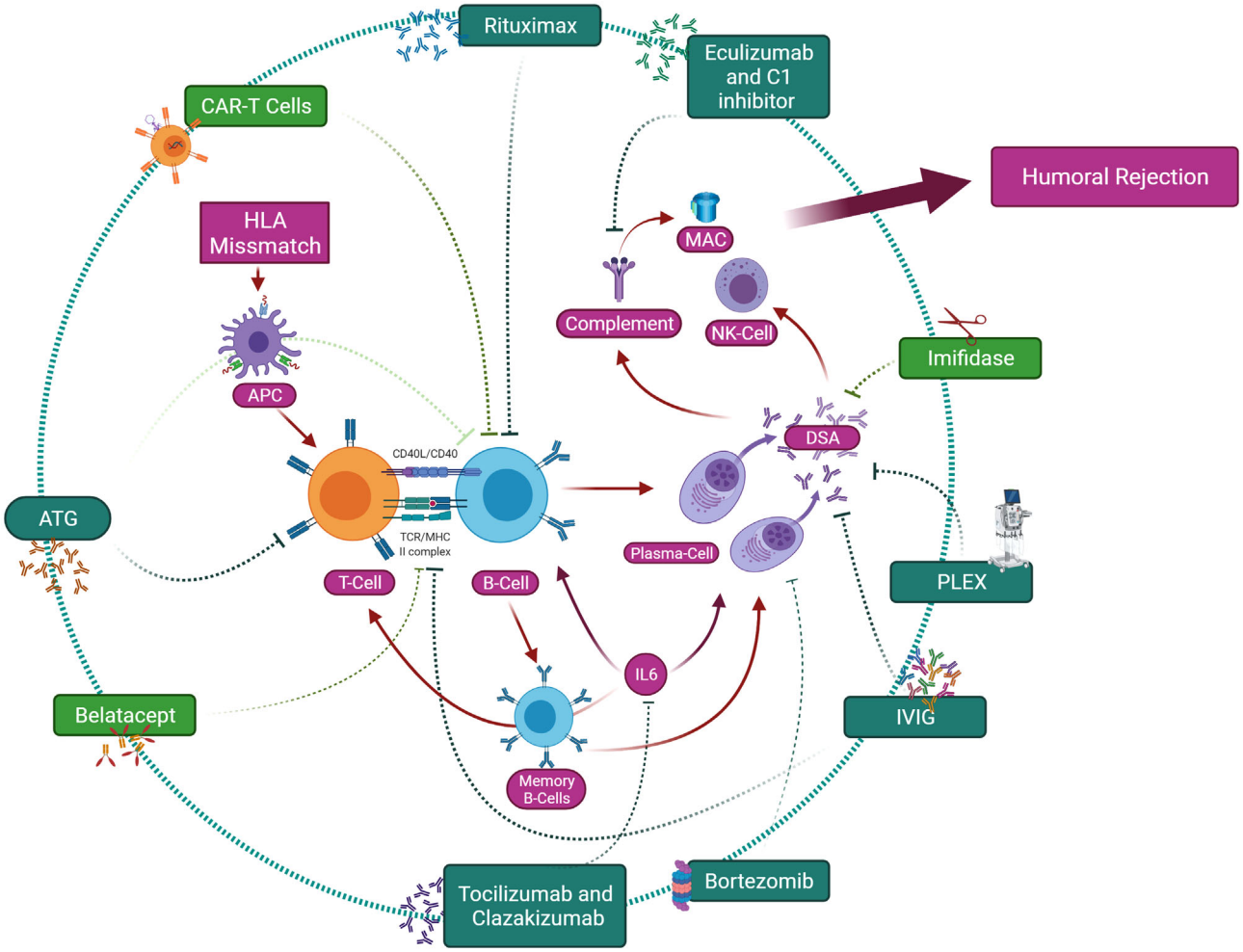

FIGURE 1 Site of action of drugs described in our review, mainly targeting T- and B-cells, plasma cells, and their effectors: DSA, complement, and Membrane Attack Complex (MAC)

propose a description of current available AMR treatments. At first, we will present conventional, adjuvant, and rescue treatments frequently used for AMR in children. We will briefly refer to experimental therapies currently under investigation and hopefully available soon (see Figures 1 and 2). Most of the evidence used to justify treatments used for AMR in children is based on adult studies. Therefore, a clear separation of pediatric and adult studies was not possible. For clarity, pediatric clinical trials, or studies including at least a small proportion of children, have been highlighted in Table 1 with an asterisk.

1.1 | AMR classification

Besides the diagnosis of AMR, based on the 2017 revised Banff criteria,[2] the consensus of the TTS proposed a phenotypical classification of AMR into three forms (see Figure 3): (i) *early post-transplant AMR*: characterized by a rapid and aggressive onset in the first 30 days post-transplantation and developed from preexisting donor-specific Antibodies (DSA); (ii) *late post-transplant AMR*: developed from preexisting DSA but manifested after 30 days post-transplantation, often presenting a more subclinical evolution with a delayed impact on the graft function and appearing years later; and (iii) *late AMR*: developed from de-novo DSA, generally developed more than 30 days after transplantation, and also with a less acute onset than *early post-transplant* form. *Late AMR* emerges in the context of inadequate immunosuppression, usually associated with patient nonadherence,[3] a clinician-driven decrease of immunosuppression, or because of significant fluctuations of Calcineurin inhibitors (CNI) blood levels, often related to genetic polymorphism of CNI enzymatic metabolism.[4,5] The distinction between late post-transplant AMR and late AMR is crucial as de-novo DSA (DnDSA) have greater specificity for the graft, explaining the worse outcome and the higher resistance to treatments.[6–8] Children are more likely to form de novo antibodies in the first two years post-transplantation than adults, making this period even more critical for children.[9] At the same time, this form is frequent among adolescents because of the poor treatment compliance and explains AMR's bad long-time prognosis in this group of age.[10] The consensus specified that morphological signs of chronicity, such as transplant glomerulopathy,

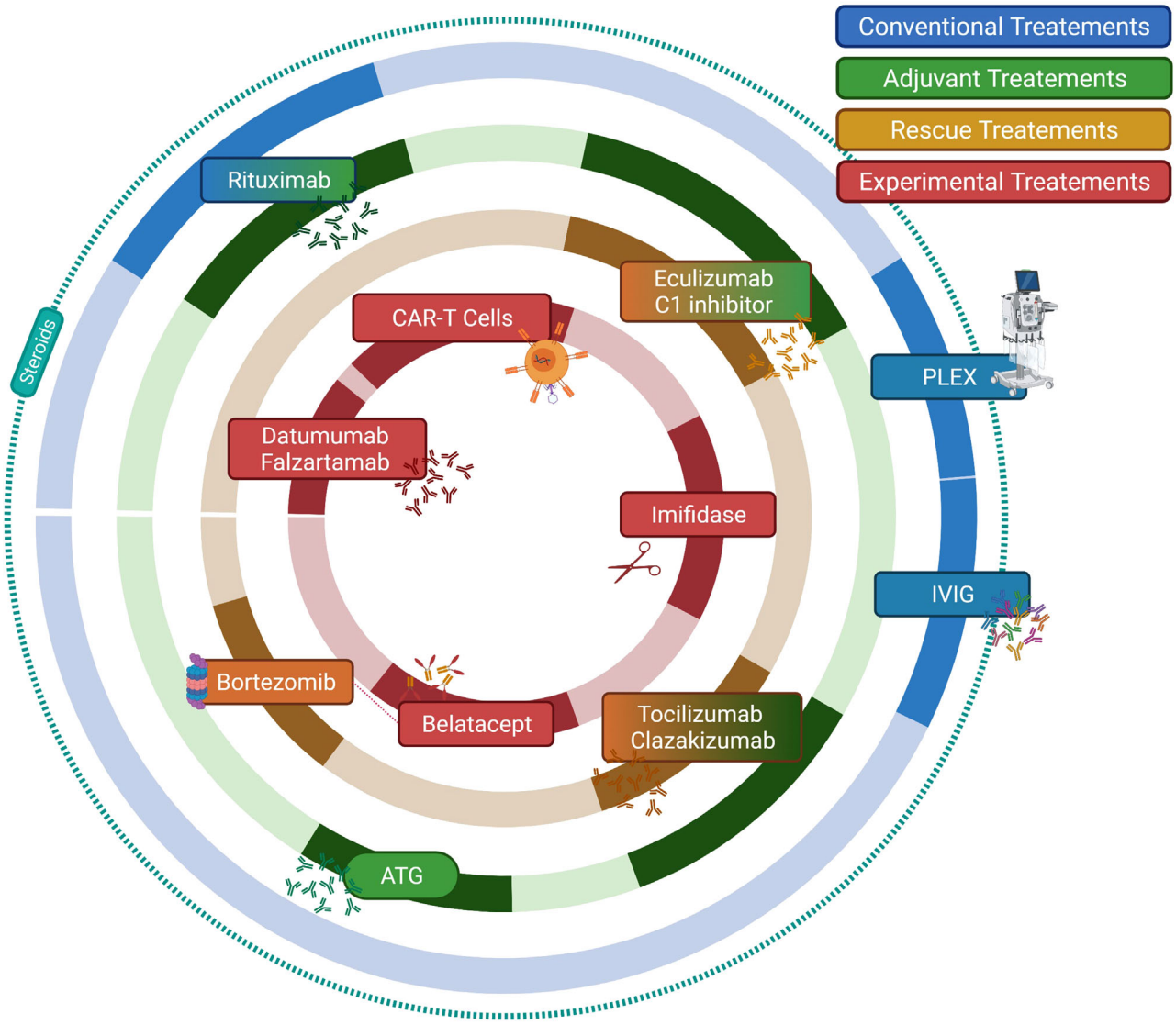

FIGURE 2 Suggested classification of the cited drugs with differentiation between conventional and adjuvant therapies, rescue treatments mainly used in refractory cases, and experimental treatments not routinely used jet and reserved to research protocols

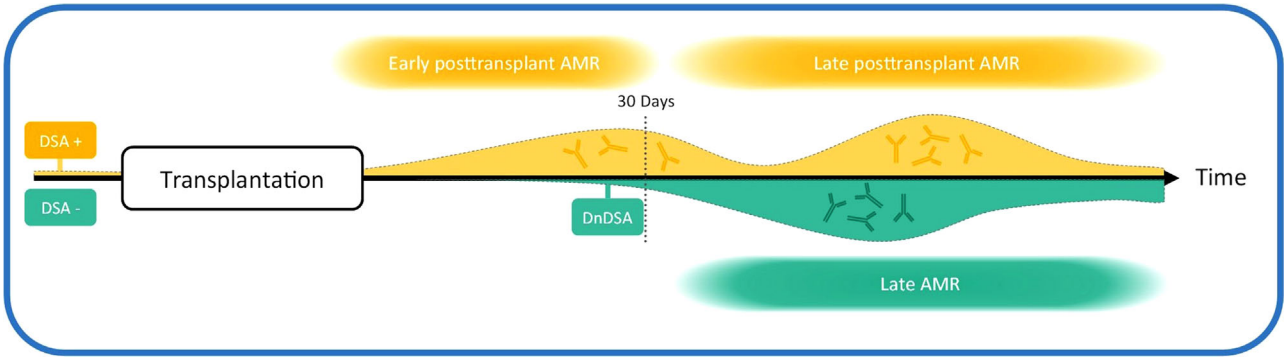

FIGURE 3 Classification of the three phenotypical forms of AMR; divided in early posttransplant AMR and late posttransplant AMR presenting pretransplant ADS and late AMR, only form developed from DnDSA

TABLE 1 Summary table of studies included in the present review

Reference (year)	Study type	Intervention	Control	*n*	Population	AMR form	Follow up	Outcome	Conclusions
A. Shaha, Transplantation (2004)	Descriptive (retrospective)	PLEX + IVIG + ATG	Transplanted patients without AMR	7:60	Adults	Acute C4d+ AMR (Early posttransplant AMR)	12 months	Creatinine level	Similar levels at 1 year
C. Lefaucheur, Am J Transplant (2009)	Non blinded, non-randomized control trial	High-dose IVIg alone	PLEX/IVIG/Ritux	12:12	Adults	Early onset C4d+ AMR	36 months	Graft survival	50% vs. 91.7% ($p = .02$)
G. A. Böhmig, Am J Transplant (2007)	RCT	IA ± Steroids	No treatment ± steroids + rescue IA after 3 Weeks	5:5	Adults	Severe C4d+ AMR	18 weeks	Graft Survival	100% vs 20% ($p = .048$)
F. Moreso, Am J Transplant (2018)	MC, prospective, placebo controlled, double-blind RCT	IVIG/Ritux	Placebo	13:12	Adults	Chronic AMR	12 months	eGFR	No difference ($p = .475$)
R. Redfield, Human immunology (2016)	Descriptive (retrospective)	Steroids/IVIG ± Ritux or ATG	No treatment	108:15	Adults	Chronic AMR	4.3 years (median)	Graft Survival	Steroids/IVIG superior to no treatment ($p < .001$). Steroids/IVIG ± RITUX or ATG superior to Steroids/IVIG but not statistically significant.
C. Lefaucheur, Lancet, (2013)	Descriptive Perspective population-based study	A: Steroids/ IVIG + Ritux or ATG B: Steroids/ PLEX/IVIG/ Ritux	Steroids/IVIG	29:22:13	Adults	Vascular AMR	72 months	Graft lost	A: HR .4 ($p = .1$) B: HR .16 ($p = .01$)
[a]Y. Cihan, Pediatr Nephrol. (2017)	Descriptive (retrospective)	ATG (1.5 mg/kg × 5 days)	None	9	Children	Refractive chronic AMR unresponsive to Steroids/IVIG/ Ritux/increase of immunosuppression ± Bortezomib	9 months	eGFR	Increased from 40 ml/min/1.73 m^2 to 62 ml/min/1.73 m^2 ($p = .039$)

(Continues)

TABLE 1 (Continued)

Reference (year)	Study type	Intervention	Control	*n*	Population	AMR form	Follow up	Outcome	Conclusions
[a]V. Zarkhin, Am J Transplant (2008)	Prospective RCT	Ritux/Steroids ± ATG	Steroids ± ATG	10:10	Children and young adults (2 to 23y)	Acute C4d+ AMR	12 months	eGFR and biopsy rejection score	eGFR improvement at 1 year ($p = .026$) Reduction of the rejection score at 1 month ($p = .0003$) and 6 months ($p < .0001$)
RITUX-ERAH B. Sautenet, Transplantation (2016)	MC, double-blind, placebo controlled, RCT	PLEX/IVIG/ Steroids + Ritux at day 5 or later rescue doses	PLEX/IVIG/ Steroids + Placebo at day 5	27:11	Adults	Acute early AMR	12 months	Graft loss and eGFR	Similar eGFR improvement in both groups and similar levels of proteinuria ($p = .744$)
RITUX-ERAH extension E. Bailly, Transplant International (2020)	MC, double-blind, placebo controlled, RCT	PLEX/IVIG/ Steroids + Ritux at day 5	PLEX/IVIG/ Steroids + Placebo at day 5	27:11	Adults	Acute early AMR	84 months	Death-censored graft survival and eGFR	No benefit for graft survival ($p = .91$) and renal function ($p = .33$)
[a]K. Gulleroglu, Transplant International (2020)	Descriptive, (retrospective)	Rituximab	Patients without Rituximab	18:60	Children and young adults (5–22 year)	–	3 years (mean)	Infection and hospitalization rate	Infection rate: 38% vs. 18% ($p < .05$) Hospitalization rate: 22% vs. 16% ($p < .05$)
E. K. Tan, Transplantation (2019)	Observational/ Descriptive (retrospective)	Eculizumab ± PLEX	None	15	Adults	Early AMR (Early posttransplant AMR)	13 months (median)	eGFR	Increased from 21 to 34 ml/min at 1 week ($p = .001$) and to 52 ml/min at 13 months
[a]E. Román-Ortiz and S. Mendizabal, Nephrology Dialysis Transplantation (2015)	Descriptive (prospective)	Eculizumab	None	4	Children	Acute AMR refractory to PLEX/IVIG/Steroid	32 months	Graft survival	75% Graft survival at 32 months. 50% with persistent DSA at the end of follow up.

(Continues)

TABLE 1 (Continued)

Reference (year)	Study type	Intervention	Control	*n*	Population	AMR form	Follow up	Outcome	Conclusions
G. Ghirardo, Pediatric Transplantation (2013)	Descriptive (prospective)	Eculizumab	None	1	Hyperimmune 17-yr-old male	Early post-transplant AMR refractory to Steroids/IVIG/45× PLEX	2 years	Biopsy proven rejection and eGFR	Complete resolution after 4× Doses of Eculizumab
D. Viglietti, Am J Transplant (2015)	Prospective, single-arm study	C1 inhibitor (C1-INH) + IVIG	None	6	Adults	Acute AMR refractory to SOC	6 months	eGFR	Improvement of eGFR in all patients ($p = .0277$)
[a]J. Choi, Am J Transplant (2017)	Descriptive (prospective)	Tocilizumab	None	36	32 adults and four children	Chronic AMR refractory to IVIG/Ritux ± PLEX	8 years	Graft survival, eGFR and DSA levels	80% of Graft survival at 6 years. Reduction of DSA levels and stable eGFR at 2 years.
[a]S. Kizilbash, Pediatric Transplantation (2017)	Descriptive (retrospective)	Bortezomib (± Ritux/IVIG/PLEX)	None	33	Children	C4d+ AMR	15 months (median)	Graft survival and eGFR	88% graft survival at 1 year. 61% improved or stabilized eGFR at 3 months and 36% at 12 months
M. J. Everly, Transplantation (2008)	Descriptive (prospective)	Bortezomib	None	6	Adults	Mixed AMR and TCMR	5 months	AMR Histology, DSA and eGFR	Histological reversal of AMR, Reduction of DSA levels, improved eGFR
F. Eskandary, J Am Soc Nephrol. (2018)	Randomized, placebo-controlled trial	Bortezomib (2× cycles of four doses each)	Placebo	21:23	Adults	Late AMR (Preformed and DnDSA)	24 months	eGFR decline, graft survival	No difference in eGFR decline ($p = .86$) and graft survival ($p = .12$)

(Continues)

TABLE 1 (Continued)

Reference (year)	Study type	Intervention	Control	*n*	Population	AMR form	Follow up	Outcome	Conclusions
[a] J. Waiser, Nephrol Dial Transplant (2012)	Non-randomized historical control trial	Bortezomib + PLEX/IVIG ± Steroids	Historical control: Rituximab + PLEX / IVIG ± Steroids	10:9	Adults and children	Acute AMR	18 months	eGFR and graft survival	Graft survival: 60% vs. 11% ($p = .071$). eGFR: 31.1 vs. 12.3 ml/min, ($p = .028$).
D. Jain, Am J Transplant (2020)	Descriptive (prospective)	Bortezomib and Belatacept + PLEX/IVIG	None	6	Adults	Severe early AMR	30 months	Graft survival and DSA levels	Resolution of AMR and sustained disappearance of circulating DSA
K. Doberer, J Am Soc Nephrol. (2021)	Phase 2 randomized pilot trial	Clazakizumab	Placebo	20	Adults	Late AMR	40 weeks	A: Safety B: eGFR decline, histological regection-score and DSA level	A: need for careful patient selection and monitoring B: Decreased DSA, lower rejection score, improvement of eGFR decline compared to placebo
IMAGINE study	Randomized, placebo-controlled trial	Clazakizumab	Placebo	350	Adults	Chronic AMR	5.5 years	All causes of allograft loss	Recruiting
Felzartamab study (G. Böhmig and F. Eskandary)	Randomized, placebo-controlled trial	Felzartamab	Placebo	20	Adults	Late AMR	12 months	Incidence of adverse events, eGFR and Graft loss	Recruiting
D. Kumar Transplantation (2021)	Non-randomized self-controlled trial	Belatacept	Tacrolimus	19	Adults	Chronic AMR	29 months (median)	Graft and patient survivals, eGFR	Stabilization in renal function after switch from Tacrolimus to Belatacept

Note: We decided to present only the primary results of cited studies, and in some cases, relevant aspects cited in this review. Studies describing desensitizing protocols have not been included in the table

[a] Studies including children.

peritubular capillary basement membrane multilayering, or arteriolar intima fibrosis, must be seen as an indicator of the AMR duration rather than considered as a different rejection entity.

1.2 | AMR in childhood

The incidence of AMR in children is unclear, and it may vary considerably between different countries. In a retrospective study assessing 58 kidney transplanted children with a follow-up between 1 and 5 years, Twombley et al.[11] estimated AMR incidence in children to approximately 5%.

Yolanda et al.[12] underlined the crucial difference between adults and pediatric recipients lies in the immaturity of the immune system and its variability with age. For example, the capacity of mononuclear cells to synthesize interleukin 2 (IL2) is lower compared to adults at least until 12 years of age,[13] entailing a lower stimulation of T cells proliferation following an exposition to alloantigen and possibly contributing to a better graft survival rate in children of <10 years of age compared to older transplanted patients.[14] The lower exposure to viral infection, with a lower rate of CMV and EBV seropositivity, increases the risks associated with a primo-infection and the risk of presenting post-transplant lymphoproliferative disease (PTLD). At the same time, one-third of children have a positive BK bacteriuria,[14] and the increased immunosuppression used in AMR could increase the risk of BK nephropathy.[15]

In children, the lower exposure to sensitizing agents, such as multiple blood transfusions, during previous transplantation or pregnancy could increase the role of non-anti-HLA antibody (nHLA) mediated rejection, possibly contributing to an increased risk of graft deterioration,[16] eventually with more undetected chronic subclinical AMR.[17] Moreover, more prolonged use of immunosuppression and the choice of more potent immunosuppressive Drugs for AMR treatment increase the long-term risk of infections and malignancy. For these reasons, adults' protocols must be critically adapted to the single situation, and rational use of potent immunosuppressants is a priority in pediatric transplantation.

2 | CONVENTIONAL TREATMENTS

Most of the treatments used in AMR today are based on adult desensitizing protocols designed to reduce the concentration of preexisting anti-HLA antibodies in high immunized patients (cPRA > 90%). Desensitization protocols are less frequent in children and are adapted from adults' protocols. An excellent review of desensitization strategies used on children has been published by Sharma et al.[18]; IVIG/Rituximab/PLEX are the most frequently used, but also, in this case, the number of RCTs is scarce. They also presented some protocols based on Bortezomib, Tocilizumab, Eculizumab, C1 esterase inhibition, IdeS, and Belatacept. Still, the use of those protocols remains primarily descriptive, and few comparative data are available today.

As described by the consensus,[1] no treatment demonstrated solid evidence of effectiveness on AMR. However, the consensus recommended using PLEX/Steroids/IVIG as the SOC for early post-transplant and late post-transplant AMR (with preexisting DSA) due to the low effectiveness on late AMR (with DnDSA). In this case, they proposed the optimization of the maintenance immunosuppression and encouraged the development of new strategies.

2.1 | Plasmapheresis and immunoadsorption

Plasmapheresis (PLEX) and immunoadsorption (IA) remove circulating DSA in the acute phase and have a well-documented short-term efficiency.[19,20] In 2006 Böhmig et al.[21] compared IA on five patients with acute C4d positive AMR with a control group of five patients receiving pulse steroids and ATG. Two weeks after randomization, an interim analysis showed 80% of graft loss in the control group against 20% in the group with IA. Therefore, the study was immediately interrupted, and based on similar observations, the use of PLEX or IA remains a non-questionable element in the treatment of acute AMR. Due to its higher availability, PLEX is generally preferred to IA in treating DSA induced AMR, reserving IA in the treatment of ABO-incompatible rejections and refractory AMR.

Protocols generally provide daily or every other day PLEX for three to five initial sessions associated with pulse corticoids.[22] Additional PLEX sessions are often performed until significant DSA mean fluorescence intensity (MFI) reduction. Nevertheless, evidence of outcome improvement in the long term remains limited. As Hemodialysis, the use of PLEX needs catheter insertion with related risks for infections and requires child compliance during therapy. Moreover, in small children, side effects such as hypotension, prolonged bleeding, and hypocalcemia have been frequently reported.[23] Until now, no valid alternative to PLEX has been found, and protocols with Rituximab/IVIG alone have been reserved to less aggressive forms of chronic AMR with unclear long-term benefits.[24]

2.2 | Polyclonal immunoglobulins (IVIG)

IVIG is widely used among children with an inflammatory disease and present a secure profile. Two approaches exist for IVIG use: (i) a substitutive strategy with the administration of low doses of IVIG to prevent hypogammaglobulinemia induced by PLEX; and (ii) an immunomodulatory strategy with the administration of high doses of IVIG to induce B-cell down-regulation and a scavenger effect on complement activation. Burton[22] published the results of a query from 28 American independent transplantation centers comparing the procedures used for AMR treatment. The results showed that most American centers used PLEX/IVIG as standard therapy with sporadic use of other adjuvant therapies. IVIG doses were either at substitutive doses of .1 or .15 g/kg after each PLEX session or at immunomodulating doses of 1–2 g/kg at the end of the PLEX cycle. Some centers used a combination of .1 g/kg substitutive doses after each PLEX session and one intermediate dose of .5 g/kg at the end of the session.

In a small RCT of 24 patients, Lefaucheur et al. demonstrated that using IVIG as monotherapy in patients with AMR had a significantly lower graft survival at 36 months than a combination of PLEX/IVIG/Rituximab (50% vs. 91.7%).[20] For this reason, the use of IVIG as monotherapy is generally not recommended. Moreso et al.[25] showed that the prolonged use of low doses of IVIG (.5 g/kg every 3 weeks) combined with Rituximab in chronic AMR did not improve eGFR, DSA level, and proteinuria compared to placebo after one year. For this reason, the use of IVIG as a chronic treatment is not recommended. It is helpful to note that anti-HLA detection is often misled after IVIG administration due to non-specific reactions of polyclonal immunoglobulins on Luminex® beads.

3 | ADJUVANT THERAPIES

3.1 | Anti-CD20 monoclonal antibody: Rituximab

Due to its efficient B-cell depletion, Rituximab has been successfully used in desensitization protocols and then introduced as an AMR treatment. Rituximab has a well-known profile in pediatrics as it is widely used for B cells NHL, CLL, rheumatic disease, and immunologic vasculitis. For this reason, Rituximab is often part of AMR's standard treatment in children, but available data on its efficacy is poor. As shown by Zarkhin et al.[26] in a pediatric RCT with 20 children affected by AMR, the short-term outcome seems to have improved after the treatment with Steroids/Rituximab ± anti-thymocyte globulin (ATG) compared to standard Steroids ± ATG, with a better creatinine evolution at 1 year and a lower acute rejection score at 1 and 6 months after randomization. These results have been reproduced in the RITUX-ERAH study, which failed to demonstrate Rituximab's efficiency in the long term, with no difference in graft and patient survival at 1 year[27] and 7 years.[28] Bailly et al. observed an increased incidence of tumors at 7 years in the group treated with Rituximab compared to those treated by Steroid/PLEX/IVIG. Even if this observation did not reach a statistical significance ($p = .154$), the risks and benefits must be carefully balanced when Rituximab is used in primary intention. Rituximab's use on children has been associated with an increased risk of severe infections (38% vs. 18% at 2 years) and a higher hospitalization rate (22% vs. 16% at 2 years).[29]

Rituximab is widely used as a first-line treatment for AMR in children. However, because of the insufficient evidence of its benefits, it may be more appropriate to consider Rituximab as adjuvant therapy for aggressive or refractory forms of AMR. Furthermore, it is essential to evaluate the expected benefits before implementing repeated doses of Rituximab. It is preferred to avoid B-cell and T-cell depleting agents' association due to the increased risk of severe infections.

3.2 | Anti-thymocyte globulin

ATG obtained from immunized rabbits (or horses) have been mainly employed as induction therapy and to treat T cells-mediate rejection (TCMR) because of their specific ability to induce a strong depletion in T-cell lineage. Furthermore, regardless of their effect on T cells, a dose-dependent effect on B-cell lineage has been described.[30]

In a retrospective analysis on chronic AMR, Redfield et al.[31] noticed a positive trend on graft survival at 2 years in a group treated with IVIG/steroids + ATG or Rituximab compared to IVIG/steroids alone. However, this observation did not reach statistical significance, likely due to the low number of patients (12/123 patients received ATG and 37/123 received Rituximab). In a study on AMR with vascular rejection, Lefaucheur et al.[32] retrospectively compared the use of (i) Steroid/IVIG; (ii) Steroids/T-cell depleting drugs (Muromonab or ATG); and (iii) Steroids/PLEX/IVIG/Rituximab, showing similar results in groups treated with IVIG and ATG, but both were inferior to Steroids/PLEX/IVIG/Rituximab ($p = .01$). These results are plausibly influenced by the absence of PLEX in the first two groups but may suggest noninferiority of ATG to IVIG in vascular rejection. Cihan et al.[33] published a descriptive non-controlled study with the use of ATG as a rescue treatment in nine chronic AMR in children resistant Steroids/IVIG/Rituximab ± Bortezomib, showing a reversal of graft function degradation in six of the nine cases, with a clear improvement of the graft function in four of them at 9 months after ATG administration.

Even if the potential of ATG in AMR prevention is acquired and its use on AMR recommended from the KDIGO guidelines for adults, evidence of its employment in AMR is scarce, and the literature on the use of ATG as adjuvant therapy in children is almost inexistent. Prospective randomized studies, possibly comparing PLEX with and without ATG, are needed to validate its efficacy. Most centers do not use ATG as a standard treatment and reserve its use for AMR with a significant vascular component or concomitant TCMD. We did not find any elements recommending a different use of ATG on children compared to its use on adults. The main concern is the risk of long-term development of malignancy and severe infections; for this reason, a precautional use of repeated doses of ATG is needed.

3.3 | Other potential adjuvant therapies and rescue treatments

Due to frequent treatment failures with PLEX/IVIG/Rituximab, other options are investigated as alternative or adjuvant therapies. Most of them are used on expert's indication in refractory cases. Despite low evidence, the consensus of the TTS recommended using adjuvant therapies in refractory early post-transplant AMR. Their use in other forms of AMR is still controversial because of the absence of long-term outcome improvement and well-documented side effects.

3.3.1 | Complement inhibitors: Eculizumab and C1-INH

Eculizumab is a monoclonal antibody targeting C5 on the complement alternative pathway, blocking the attack complex and avoiding

complement cytotoxicity. It has been successfully used in desensitization protocols for patients with a positive crossmatch, reducing the risk of AMR from an expected rate of 41%–7.7% at 3 months.[34] Marks et al.[35] confirmed similar results in an RCT with Eculizumab versus SOC showing a potential beneficial effect of Eculizumab with a decreased incidence of AMR (Grade I to III) from 29% to 12% nine weeks after the transplantation of sensitized recipients ($p = .048$).

Among adjuvant therapies, the use of complement inhibitors (Eculizumab and C1-INH) on children increases because of a relatively safe profile. Results in the treatment of refractory AMR are promising,[36,37] Ghirardo[38] reported an interesting case of a sensitized 17-year-old boy presenting an early post-transplant AMR a month after his second transplantation. He was refractory to initial treatment of corticoids, 45 sessions of PLEX/IVIG (at substitutive doses of .2 g/kg), and two pre-transplantation doses of Rituximab (with a total depletion of B cells). For this reason, he was treated with four doses of 600 mg of Eculizumab with an interval of 14 days. A biopsy 10 days after the last dose showed an evident histological improvement of signs of rejection. He received eight supplementary monthly doses of Eculizumab with a complete AMR resolution in the protocol biopsy at 1 year, a normal creatinine and a lower DSA titer at 2 years.

A cheaper alternative is the C1-inhibitor (C1-INH), targeting the proximal part of the classical complement pathway. Data available on the use of C1-INH on AMR is limited to a few small trials showing encouraging trends but failing to show an improvement in graft survival compared to historical control.[39] A large RCT multicentric phase 3 trial sponsored by Bering is currently recruiting and will test the efficiency of C1-INH on acute refractory AMR.[40]

Cases of Eculizumab accumulation have been described and monitoring of Eculizumab serum concentration is recommended.[41] Moreover, complement deficiency has been associated with an increased risk of severe meningococcal, pneumococcal, and Hemophilus influenza infections.[42,43] Therefore, it is recommended to complete children's meningococcal vaccination with amoxicillin prophylaxis until the immunization is protective. The consensus insisted that the evidence for the use of complement inhibitors on AMR is poor and essentially based on case reports or small RCT. As for Rituximab, there is evidence of a short-term efficiency on early post-transplantation AMR; however, evidence on the long-term outcome is missing.

3.3.2 | IL6 inhibitors: Tocilizumab and clazakizumab

Tocilizumab is a monoclonal antibody working as a competitive inhibitor of the Il6-receptor, breaking the inflammatory cascade, reducing the recruitment of acute-phase proteins, and countering B-cell proliferation and plasma cells (PCs) differentiation. Choi et al.[44] proved that Anti-Il6 could reduce inflammation and antibody production in bone marrow and spleen. They used Tacilizumab on 36 chronic AMR patients, refractory to Steroids/PLEX/IVIG/Rituximab, and observed creatinine's stabilization and a reduction in DSA titer over a follow-up of 8 years. Graft survival was 80% at 6 years, similar to the evolution of general AMR. The lack of a control group limited a precise assessment of Tocilizumab's effect.

Clazakizumab, an engineered humanized immunoglobulin (IgG1) directly targeting Il-6, is an alternative to Tocilizumab. Doberer et al.[45] recently published a two-phase RCT using a protocol with repeated Clazakizumab injections along twelve weeks in 20 patients presenting late AMR. Children treated with Clazakizumab showed a slower decline of eGFR and an early reduction of DSA levels. In the second phase, control patients also received Clazakizumab, showing similar results. They reported nine major adverse events, with four serious infections characterized by a marked reduction of IgG levels and two diverticulitis, one of them necessitating open surgery because of perforation. Therefore, caution is recommended before using Clazakizumab with pre-existing gastrointestinal diseases (ex. inflammatory bowel diseases).

A recently started large multicentric RCT, the IMAGINE Trial,[46] expects to include 350 adult patients from living and deceased donors, testing Clazakizumab against placebo on chronic AMR. The two arms will be compared for time to allograft loss with a follow-up of up to 5.5 years.

3.3.3 | Proteasome inhibitor: Bortezomib

Bortezomib is a specific proteasome inhibitor, and it is the only available drug today that targets PCs. An extensive description of Bortezomib's mechanisms of action has been published by Ejaz et al.[47] Bortezomib is mainly used to treat multiple myeloma and refractory lymphoma and is known for its narrow therapeutic range. Most experiences on AMR are limited to case reports and retrospective studies showing some optimistic results with an improvement of eGFR and reduction of histological rejection signs.[48,49] In particular, Bortezomib has been described as efficient in acute refractory AMR in children.[11] Eskandary et al.[50] compared Bortezomib (two cycles of 4×1.3 mg/m^2 over two weeks) to placebo in an RCT on late AMR (with preformed and DnDSA), and showed a similar evolution of eGFR, DSA level, as well as graft and patient survival at 24 months. A rebound of DSA levels between 1 and 4 months after the treatment has been reported in the literature[49] and could explain the lack of long-term outcome improvement. Eskandary et al. observed more adverse events in the Bortezomib group, but the difference was not statistically significant. Adverse events prevented three patients from receiving the second cycle, emphasizing the problem of the narrow therapeutic range. Other studies specified that adverse events in children are generally minor side effects and mainly without life-threatening events.[48]

Bortezomib's efficacy must be proven in prospective RCT but seems superior to Rituximab on long-term graft survival.[51] It can be safely considered for treating children presenting severe refractory AMR.

3.3.4 | Belatacept in chronic AMR

Belatacept is a co-stimulation blocker (CTLA4-Ig) used for desensitization protocols[52] and maintenance immunosuppression on patients

with significant side effects of calcineurin inhibitors (CNI). Generally, it is not considered as an acute-phase treatment for AMR. Nevertheless, Kumar et al.[53] presented the results of a self-controlled prospective study involving 28 adult patients with chronic AMR treated with the conversion from Tacrolimus to Belatacept, showing stabilization of renal function and the reduction of microvascular inflammation and rejection-score at 6 and 12 months without additional rescue immunosuppression therapies. It is important to note that the use of Belatacept is often limited in children because of the frequent negative EBV status and the increased risk of PTLD development. Still, the conversion of Belatacept in chronic AMR patients might be a valid option for teenagers and older children with proven EBV seropositivity, possibly taking advantage of the better compliance associated with its monthly administration.

4 | FUTURE POTENTIAL THERAPIES

4.1 | Belatacept and Bortezomib in early posttransplant AMR

Jain et al.[54] published a remarkable mouse-to-human experiment combining an initial administration of Bortezomib followed by Belatacept's serial infusions in the context of early post-transplant AMR. This way, they combined Bortezomib's efficiency on PCs depletion and DSA titer reduction with Belatacept's stabilization potential, avoiding the generation of new PCs and, therefore, the rebound of DSA titer. They initially tested this procedure on immunized mice showing that therapy with Bortezomib and Belatacept (B/B) was efficient in depleting PCs and reducing DSA. Similar results were observed in induced AMR on immunized skin transplanted mice. Later, they tested the same protocol on six patients with severe early AMR refractory to Steroids/PLEX/IVIG. They observed a rapid reversal of AMR and the disappearance of DSA at 30 months. Only one patient returned to dialysis because of extensive damages of concomitant TCMR but did not present any DSA at the time of the kidney failure. These results are highly encouraging, and further validation is needed. As for the use of Belatacept in chronic AMR, its use in this context must be balanced for risk and expected benefit and should be considered only for EBV-seropositive patients.

4.2 | Imifidase (IdeS)

Imifidase is a high specific IgG degrading enzyme extrapolated from Streptococcus pyogenes. IdeS cleave IgGs between the human FC segment and the Fab region, inactivating the IgG and preventing complement- and antibody-dependent cytotoxicity. The cleavage of IgG is highly effective, leading to complete inactivation of IgGs in 2–6 h.[55,56] IdeS has been used in desensitization protocols with excellent results on preexisting DSA depletion. Unfortunately, a rebound of DSA levels is frequently observed after 7–14 days, and further dose administration is often impossible due to anti-IdeS antibody formation, increasing the risk of hypersensitivity reactions after the first or second administration.[55]

Jordan et al.[57] published an excellent two-phase study with an initial dose-finding study followed by two intervention cohorts (in the USA and Sweden) using IdeS in experimental desensitization protocols. Lonze et al.[56] published a similar protocol on seven high sensitized patients, using IdeS at induction. Both studies showed a rapid and complete IgG and DSA depletion, and all patients underwent transplantation. A significant number of patients presented early episodes of AMR due to DSA rebound, but all of them recovered to a stable kidney function after an extensive treatment of AMR. Jordan et al. observed different results in the American and Swedish cohorts, highlighting the importance of different dosages and protocols. Kjellman et al.[58] recently presented the data of a 3-year follow-up of a multicentric four-arms phase 2 study on Imifidase as desensitization protocol in high immunized patents. Those patients presented a death-censored allograft survival of 84% and overall patient survival of 90%. Kjellman et al. also observed that the MFI of dominant DSA decreased progressively after the initially expected rebound. Despite this, some patients developed severe AMR with an overall AMR incidence of 38%, underlining the need to define the optimal patient target and acceptable MFI thresholds. A phase 2 clinical study investigating the use of Imifidase in AMR is ongoing.[59]

It is helpful to consider that IdeS could neutralize concomitant treatments based on monoclonal or polyclonal antibodies, as IVIG or ATG. For this reason, horse ATG is preferred to rabbit ATG as they are not as cleaved by IdeS.

4.3 | CAR-T cells

The new frontier to oncologic treatments, CAR-T cells are bioengineered autologous leucocytes encoded using viral vectors to express chimeric antigen receptors, targeting specific tumor cells. Zhang et al.[60] described the case of a 57-year-old woman treated with CART-T cells for a relapsing follicular lymphoma. CAR-T cells were encoded to recognize cells expressing CD19, inducing a deep and sustained B-cell depletion, persisting in a follow-up of two years, and inducing the lymphoma remission. An analysis of the evolution of vaccinal titers showed stable values of Measles, Rubella, HIB, Mumps, Tetanus, and PCP antibodies throughout the two years follow-up. At the same time, the patient presented two Anti-HLA antibodies (B49 and A26) with stable MFI, concordant with the vaccinal antibody titer. The authors concluded that long-lived PCs (CD19-) might persist even after the complete depletion of naïve B cells, memory B cells, and short-lived PC (CD19+) and continue to produce antibodies able to maintain the immune response. CAR-T cells are attractive because of their high specificity and sustained effect, possibly avoiding the rebound observed in Rituximab and other treatments. Unfortunately, CAR-T cells targeting CD19+ seemed not effective on anti-HLAs reduction. New pharmacological targets like CD28, expressed on long-lived PCs and NK cells must be further studied.

4.4 | Daratumumab and Felzartamab

Kwun et al.[61] described an experience using Daratumumab, a monoclonal antibody targeting PCs (CD38+), as a desensitizing agent on height non-human primates, and one high sensitized 62-years-old patient on the waiting list for heart transplantation. Furthermore, they described its use to treat a refractory combined TCMR and AMR in a 32 years-old patient with combined heart-kidney transplantation. Daratumumab seemed to be effective in the anti-HLA reduction in both experimental models, with even better results than Belatacept-Bortezomib's combination. However, all non-human primates presented a rapid DSA rebound along with a profound T cell-mediated rejection. The first patients could be successfully transplanted after the desensitization protocol. The patient treated for AMR showed an initial improvement of kidney and heart function and a reduction of the acute histological lesions and PC-infiltrate. Unfortunately, the patient presented the recurrence of an acute PC-rich AMR and a rebound of DSA levels twenty weeks later.

Doberer et al.[62] published the experience of a 49-year-old kidney recipient presenting a chronic AMR and a newly diagnosed smoldering myeloma thirteen years after kidney transplantation. Considering the potential beneficial effect on both diagnoses, the patient was treated with nine cycles of Daratumumab for nine months. Efficient peripheral depletion of PCs and NKs was described, and DSA level became undetectable within 14 weeks. A biopsy at three months showed a decreased rejection score but signs of borderline rejection, an increased eGFR (29.8 vs. 27.7), and lower proteinuria (2000 vs. 2730 mg/g). The nine-month biopsy showed isolated transplant glomerulopathy (TG) without any signs of antibody interaction.

A recently designed phase 2 clinical trial will test Felzartamab, another monoclonal anti-CD38 antibody recently developed for treating multiple myeloma, against placebo on 20 patients with late AMR to assess its safety, tolerability, and efficacy.[63]

No experiment with IdeS, CAR-T cells, Daratumumab, or Falzartamab has been done so far on children, and the use of those drugs is still experimental. More trials will probably be available after validating those methods on adult recipients.

5 | NON-HLA ANTIBODIES AND CHRONIC AMR

The interest in non-HLA-associated AMR is strongly increasing. As explained in an excellent review of C. Lefaucheur et al.,[64] mainly inspired by the work of Dragun et al., there is strong evidence of significant involvement of non-HLA antibodies in AMR. They identified several endothelial and non-endothelial targets; in the foreground but among others: non-HLA anti-endothelial cell antibodies (AECAs)[65] possibly able to upregulate HLA class I,[66] and non-HLA AT1R associated with steroid-resistant rejections,[67] concerning adults[68] and children.[69] They also noticed how anti-AT1R, and other non-HLA antibodies, were frequently associated with chronic forms of AMR and might have a synergic effect with the HLA system.

The role of non-HLA antibodies has also been discussed by Kim et al.[70] in a recent review exploring immunologic mechanisms of chronic AMR and supporting the idea of complement-independent pathways. Kardol-Hoefnagel and Otten[71] summarize some promising findings using PLEX/IVIG, Rituximab, ATG on non-HLA antibody-associated AMR. Recent findings on non-HLA open the field to new treatments such as AT1R blockers,[72,73] Ides, and many others.

As said before, the role of non-HLA antibodies might be relevant in children as their lower exposure to sensitizing agents may increase their role in chronic AMR. Therefore, it is essential to include children in the protocol of future studies to identify potential treatment and specific limitations for this population.

6 | PREVENTION AND NONINVASIVE DIAGNOSIS OF AMR

Due to a higher risk of long-term immunologic complications related to life-long immunosuppression and a higher probability of multiple transplantations, the prevention of AMR is essential in children, especially in the absence of established treatment. Good organ matching, adequate immunosuppression, and the motivation of good compliance remain priorities in pediatric transplantation. At the same time, the recognition of early forms of AMR is essential, and many efforts have been made to find reliable non-invasive diagnostic procedures in children. Recently, algorithms based on urinary metabolic patterns have been developed as screening for indolent forms of AMR. These methods are becoming current and, in the future, should permit to avoid systematic biopsy in children. Guzzi et al.[74] recently published a systematic review on urinary biomarkers to predict AMR and TCMR, highlighting the promising results obtained by Tinel et al. using urinary CXC-Chemokine.[75] Of particular interest is also the work of Blydt-Hansen et al.,[76] who developed an algorithm from 133 urinary metabolite patterns with an excellent negative predictive value (.96), but a low positive predictive value (.40). They observed an overlapping of some key metabolites between AMR and TCMR. For this reason, a biopsy confirmation before treatment will still be necessary.

7 | CONCLUSION

The treatment of AMR in children and adults remains challenging; the literature, as well as the consensus of the TTS, fail to provide clear recommendations for its treatment. The use of adjuvant therapies often remains necessary for resistant and aggressive forms of AMR despite missing evidence and standardized protocols. With this review, we could not fill this gap. Still, while waiting for more substantial evidence, we highlighted that rational use of existing adjuvant therapies is possible and requires careful consideration of the patient's immunologic state and the evaluation of the treatment's expected benefits and harms.

This review highlights the need to proceed on two fronts: to validate existing treatments with larger RCT and to develop and validate new

methods with the inclusion of the pediatric population. Including children in acute and chronic AMR studies is essential to define high-risk patients and better target specific treatments. The phenotypical classification of AMR and the use of the SOC proposed by the consensus of the TSS are valuable tools and must be considered in the design of new clinical trials.

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