ANTIBODY MEDIATED RENAL TRANSPLANTATION REJECTION IN PEDIATRICS

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INTRODUCTION

- Despite all efforts, long-term renal allograft survival is limited to an average of 11 to 15 years .
- The cause of allograft failure is multifactorial. However, antibody-mediated rejection (ABMR) is the main factor contributing to progressive deterioration of allograft function and subsequent allograft loss.
- One of the key elements for the diagnosis of ABMR is the formation of donor-specific antibodies (DSAs).
- DSAs directed against mismatched human leukocyte antigens (HLA) class I and II attach to the endothelium,triggering complement activation via the classic pathway and inducing Fc gamma receptor–dependent effects on the activation of natural killer cells and macrophages.
- Membrane attack complex (MAC) activated by C1q is responsible for inflammation in the vascular endothelium, generating direct irreversible injury of the allograft .
- Histologic features, such as glomerulitis and peritubular capillaritis, as well as chronic glomerulopathy, indicate endothelial damage.
- In addition, microvascular injury stimulates platelet activation, resulting in the development of microthrombi.
- C4d is a specific correlate of complement cascade activation initiated by DSAs.
- As a degradation product of C4, C4d binds to endothelium.
- often rendering C4d deposits detectable in biopsy samples from allografts in patients with ABMR.
- Thus, C4d deposition in renal allografts is one diagnostic criterion for acute and chronic ABMR .
- Therapy for ABMR is one of the main challenges facing transplant medicine. Currently, no approved treatments for chronic ABMR exist .
- Plasmapheresis (PS) in combination with high-dose intravenous immunoglobulin (IVIG) has proved to be effective in several trials and is the current standard of care for acute ABMR .

INTRODUCTION

- (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.
- 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.
- 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.

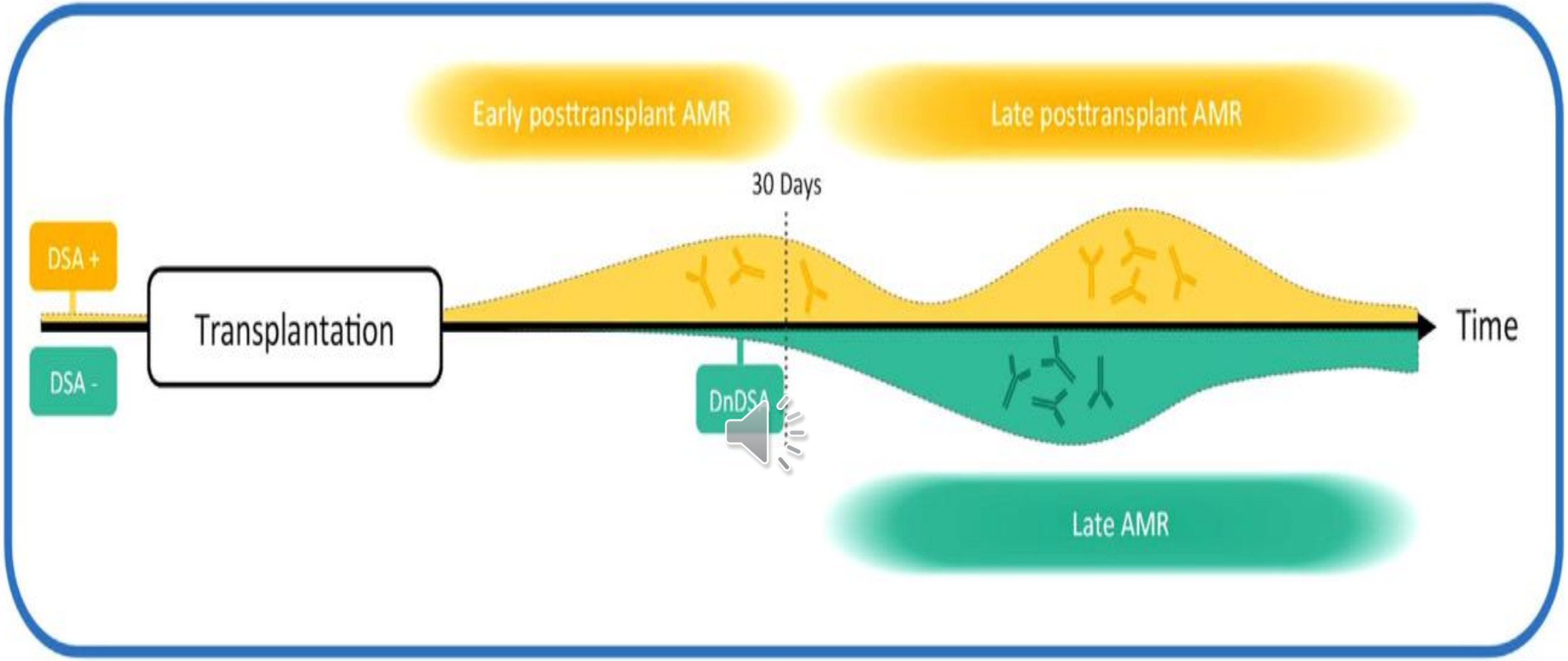

FIGURE 3 Classification of the three phenotypical forms of AMR; divided in early posttransplant AMR and late posttransplant AMR presenting pretransplant ADS and late AMR, only form developed from DnDSA

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.; 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.

Plasmapheresis and immunoadsorption

- Protocols generally provide daily or every other day PLEX for three to five initial sessions associated with pulse corticoids.
- 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.

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;
- (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.
- 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.

ADJUVANT THERAPIES
Anti-CD20 monoclonal antibody: Rituximab

- 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..
- 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.

Anti-thymocyte globulin

- ATG obtained from immunized rabbits (or horses) have been mainly employed as induction therapy and to treat T cells-mediate rejection
- 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.

Other potential adjuvant therapies and rescue treatments **Complement inhibitors: Eculizumab and C1-INH**

- Eculizumab is a monoclonal antibody targeting C5 on the complement alternative pathway 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.
- 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,
- Cases of Eculizumab accumulation have been described and monitoring of Eculizumab serum concentration is recommended.
- Moreover, complement deficiency has been associated with an increased risk of severe meningococcal, pneumococcal, and Hemophilus influenza infections.
- Therefore, it is recommended to complete children's meningococcal vaccination with amoxicillin prophylaxis until the immunization is protective

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.
- Clazakizumab, an engineered humanized immunoglobulin (IgG1) directly targeting Il-6, is an alternative to Tocilizumab.
- Children treated with Clazakizumab showed a slower decline of eGFR and an early reduction of DSA levels.

Proteasome inhibitor: Bortezomib

- Bortezomib is mainly used to treat multiple myeloma and refractory lymphoma and is known for its narrow therapeutic range.
- Bortezomib's efficacy must be proven in prospective RCT but seems superior to Rituximab on long-term graft survival.
- It can be safely considered for treating children presenting severe refractory AMR

Belatacept in chronic AMR

- Belatacept is a co-stimulation blocker (CTLA4-Ig) used for desensitization protocols 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.
- .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.

FUTURE POTENTIAL THERAPIES

- **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.

- 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.

Daratumumab and Felzartamab

- Daratumumab seemed to be effective in the anti-HLA reduction in both experimental models, with even better results than Belatacept Bortezomib's combination.
- 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.

Cyclophosphamide

- Cyclophosphamide is used for the treatment of antibodymediated diseases such as anti-neutrophil cytoplasmic antibody vasculitis or lupus nephritis.
- Previous anecdotal reports describe its use within a multimodal treatment regimen for the treatment of refractory rejections.

Splenectomy

- There are several case series of surgical splenectomy, splenic embolization, and splenic radiation being used as a salvage procedure for severe early AMR.
- It must be performed rapidly after the onset of early AMR to be effective.

Consensus treatment recommendations based on available evidence and expert opinion

Timing	DSA	Histology (Banff 2017)	Standard of care[a]	Consider adjunctive therapies
Early[a] Acute (<30 days posttransplant)	Preexisting DSA (or nonimmunologically naive)	Active AMR	Plasmapheresis (daily or alternative day × 6 based on DSA titer) (1C)[b] IVIG 100 mg/kg after each plasmapheresis treatment or IVIG 2 g/kg at end of plasmapheresis treatments (1C) Corticosteroids (EO)	Complement inhibitors (2B) Rituximab 375 mg/m^2 (2B) Splenectomy (3C)
Late (>30 days posttransplant)	Preexisting DSA	Active AMR	Plasmapheresis (daily or alternative day × 4–6 based on DSA titer) (2C)[b] IVIG 100 mg/kg after each plasmapheresis treatment or IVIG 2 g/kg at end of plasmapheresis treatments (2C) Corticosteroids (EO)	Rituximab 375 mg/m^2 (2B)
		Chronic AMR	Optimize baseline immunosuppression (eg, add steroids if on a steroid-free regimen) (1C)	IVIG (3C)
	De novo DSA	Active AMR	Optimize baseline immunosuppression (eg, add steroids if on a steroid-free regimen) (1C) Evaluate and manage nonadherence	Plasmapheresis and IVIG (3C) Rituximab (3C)
		Chronic AMR		IVIG (3C)

[a]For all cases, treatment of concomitant T-cell–mediated rejection (≥borderline) and optimizing immunosuppression is recommended. Optimizing immunosuppression includes the use of tacrolimus with goal trough of >5 and use of maintenance steroid equivalent to prednisone 5 mg daily.
[b]Fresh-frozen plasma to be used for replacement fluid for plasmapheresis if a biopsy was performed within 24–48 h. The codes for grades of evidence have been taken from KDIGO.[54,58]
AMR, antibody-mediated rejection; DSA, donor-specific antibody; EO, expert opinion; IVIG, intravenous immune globulins; KDIGO, Kidney Disease: Improving Global Outcomes.

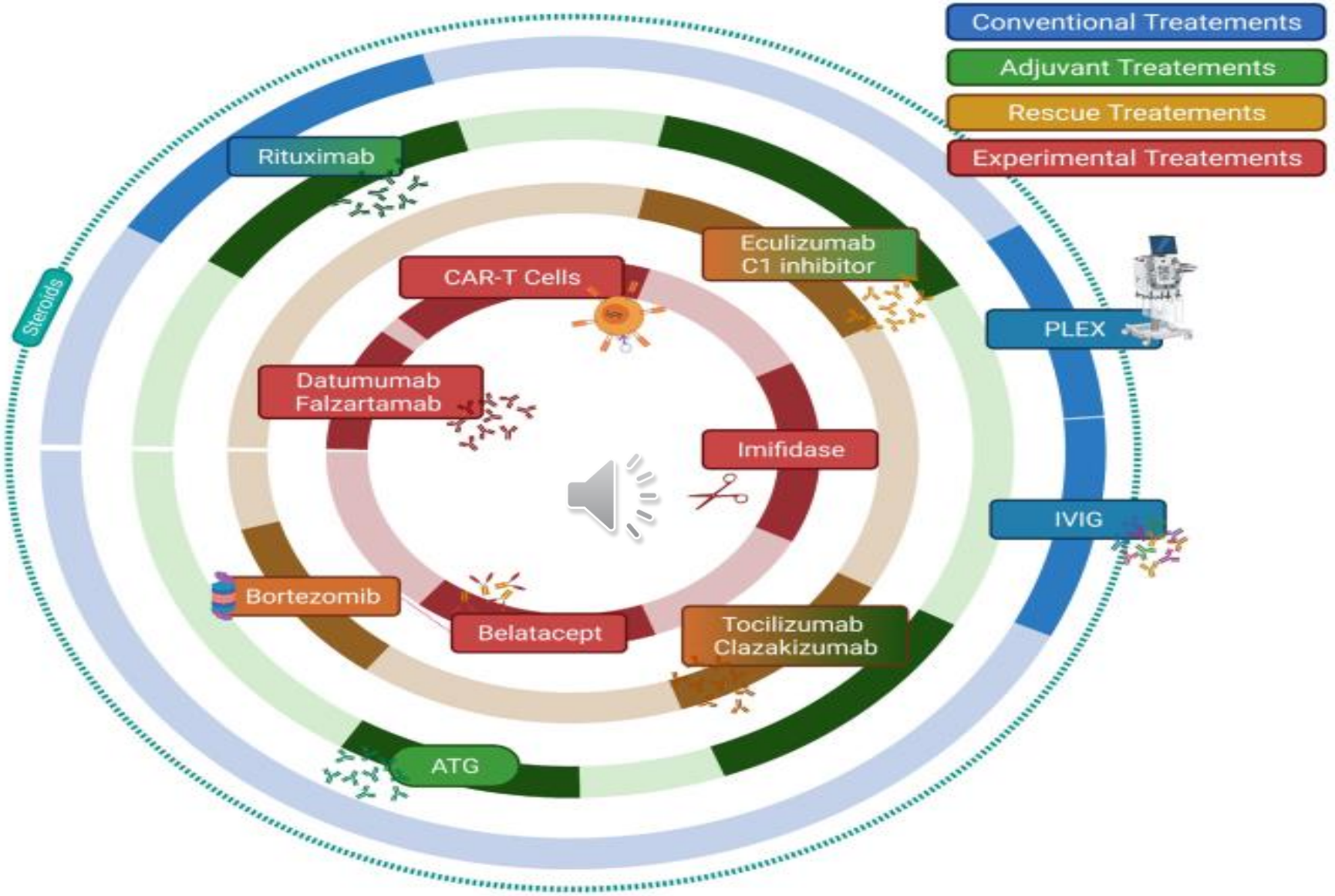

FIGURE 2 Suggested classification of the cited drugs with differentiation between conventional and adjuvant therapies, rescue treatments mainly used in refractory cases, and experimental treatments not routinely used jet and reserved to research protocols

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

CONCLUSION

- The use of adjuvant therapies often remains necessary for resistant and aggressive forms of AMR despite missing evidence and standardized protocols.