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# Apheresis treatment approaches for ANCA-associated vasculitis in children - synthesis of clinical data and case-based expert strategies

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## Abstract

# Background

ANCA-associated vasculitis (AAV) is rare in children, and evidence guiding therapeutic apheresis (TA) is almost exclusively derived from adult studies. We evaluated TA use and renal outcomes in a multicenter pediatric cohort and assessed current clinical practice in a nationwide survey of pediatric nephrologists. We hypothesized that TA would not provide substantial long-term renal benefit beyond contemporary induction therapy.

# Methods

Clinical outcomes of pediatric patients with renal involvement in AAV treated at four major German centers over 12 years were retrospectively analyzed, comparing patients who received TA with those who did not. Current clinical practice was assessed through an online case-based survey within the Society of German Pediatric Nephrology.

# Results

Nineteen patients were included (57.9% microscopic polyangiitis, 42.1% granulomatosis with polyangiitis), with a median age at diagnosis of 14.2 years. Six (31.6%) underwent TA. Median eGFR at diagnosis tended to be lower with TA (45 vs. 63 ml/min/1.73 m²), without reaching statistical significance. Renal function improved in both groups, reaching median eGFRs of 80 and 96 ml/min/1.73 m² at 36 months, respectively. Among surveyed German pediatric nephrology experts, 80–93% reported that they would use TA during treatment, particularly for severe or organ-threatening disease.

# Conclusions

Clinical outcome data did not demonstrate a clear renal benefit of TA in pediatric AAV, whereas the expert survey indicates that TA remains widely used for organ-threatening disease.

## Introduction

ANCA (Anti-neutrophil cytoplasmic antibody)-associated vasculitides (AAV) are systemic autoimmune diseases affecting small and medium size vessels. AAVs are rare diseases, especially among the pediatric population. Incidence varies between 0,5 and 6,39 per million children per year [1].

The 2012 Chapel Hill Consensus Conference nomenclature distinguishes the following three different entities of AAV: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Classification criteria for clinical or epidemiologic studies were

established in 2022 by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR), although the utility of these criteria in the pediatric population has yet to be finally evaluated [2, 3]. For GPA, pediatric-specific classification criteria, established at the 2008 Ankara Consensus Conference, remain available and have shown comparable classification performance in children and adolescents [4]. In contrast, no pediatric-specific classification criteria have been established for MPA or EGPA.

Treatment involves induction therapy, initiated as soon as the diagnosis is suspected, particularly in cases of severe kidney or lung involvement. It is followed by long-term maintenance therapy. Induction therapy includes glucocorticoids (GC) in combination with rituximab (RTX) or cyclophosphamide (CYC). In patients with severe disease, therapeutic apheresis (TA) - plasma exchange (PE) or immunoadsorption (IA) - may be used during induction to facilitate rapid removal of circulating ANCA-antibodies.

However, the role of TA has been the subject of ongoing debate. In 2007, the MEPEX trial reported short-term renal recovery and reduced risk of end-stage kidney disease at 12 months in adults with severe AAV after treatment including PE [5]. It thereby supported its use in those cases for many years. In 2020, the larger PEXIVAS trial critically reevaluated the efficacy of PE showing that PE in addition to standard induction therapy did not significantly reduce mortality or progression to end-stage kidney disease in adults with severe AAV [6]. Consequently, German, European, and American rheumatology and nephrology societies have revised their guidelines, now largely advising against the routine application of PE in AAV [7–10], (see Table 1). PE may be used in patients with severe kidney involvement. Statements regarding the use of IA do not exist in the current guidelines. However, the effectiveness of IA and PE in ANCA antibody removal is comparable and AAV patients with severe kidney involvement may benefit from IA [11, 12].

Table 1

**Comparison of treatment guidelines for AAV**. Overview of treatment recommendations from major medical societies as well as the most current recommendation for children regarding induction therapy, maintenance therapy, and the use of PE. *Avacopan: The U.S. Food and Drug Administration and European Medicines Agency recommend revoking the marketing authorization. American College of Rheumatology (ACR), azathioprine (AZA), Childhood Arthritis and Rheumatology Research Alliance (CARRA), cyclophosphamide (CYC), Deutsche Gesellschaft für Rheumatologie (DGRh), European Alliance of Associations for Rheumatology (EULAR), glucocorticoids (GC), Kidney Disease: Improving Global Outcomes (KDIGO), leflunomide (LEF), mycophenolate mofetil (MMF), methotrexate (MTX), and rituximab (RTX)

| **Comparison of treatment guidelines for AAV** | | | |
|---|---|---|---|
| **Guideline** | **Induction therapy** | **Maintenance therapy** | **Statement on PE** |
| **ACR 2021** | **active/severe**: GC + RTX (or CYC) **active/non-severe**: GC + MTX (or RTX, CYC, AZA, MMF, without co-medication) | RTX recommended over MTX or AZA; least recommended MMF or LEF | recommendation against routine use in active glomerulonephritis or alveolar hemorrhage; may be considered in GPA or MPA with anti-glomerular basement membrane disease |
| **EULAR 2022** | **organ-/life-threatening**: RTX + GC or CYC + GC **not organ-/life-threatening**: RTX + GC (alternative: MTX + GC or MMF + GC) instead of GC Avacopan* possible | continuation or switch to RTX (or AZA or MTX) for 24–28 months; GC reduction, stop Avacopan* | PE may be considered to induce remission in GPA or MPA with serum creatinine > 300 µmol/L due to active glomerulonephritis; routine use in alveolar hemorrhage not recommended |
| **CARRA 2022 (GPA/MPA)** | RTX + GC or CYC + GC | RTX, AZA or MTX; reduction of GC over 6–12 months | PE use at the discretion of the physician |
| **KDIGO 2024** | RTX + GC or CYC + GC (instead of GC Avacopan* possible) or RTX + GC + CYC | continuation of RTX or switch to AZA; GC reduction | consider in patients with creatinine > 3.4 mg/dl (> 300 µmol/L), dialysis or rapidly increasing creatinine, or diffuse alveolar hemorrhage with hypoxemia |
| **DGRh 2024** | **organ-/life-threatening**: RTX + GC or CYC + GC **not organ-/life-threatening**: RTX + GC or MTX + GC (alternative: MMF + GC) instead of GC Avacopan* possible | continuation or switch to RTX (or AZA or MTX) for 36–48 months (alternative: MMF, LEF) | additive combination with GC and CYC or RTX for selected patients with active glomerulonephritis (creatinine > 300 µmol/L), not standard; routine use in alveolar hemorrhage not recommended |

Importantly, these recommendations are based exclusively on adult populations, and their applicability to pediatric patients remains uncertain. In 2022, the pediatric AAV working group published consensus-based treatment plans representing the most current recommendations for disease management in children and adolescents [13]. Notably, TA was not addressed in these guidelines, reflecting both the lack of pediatric data and the uncertainty regarding its potential benefit in this population.

This multicenter study aims to characterize the clinical presentation, disease classification, treatment strategies, and outcomes of a German pediatric cohort with AAV and renal involvement, with particular emphasis on the use and impact of TA in contemporary clinical practice. Additionally, we assessed current clinical practice using a nationwide survey of pediatric nephrologists. We hypothesized that TA does not provide a substantial long-term renal benefit compared to contemporary induction therapy in pediatric patients with AAV.

## Materials and Methods

# Multicenter pediatric AAV cohort

We performed a multicenter retrospective cohort study in collaboration with the pediatric nephrology departments of four tertiary care centers in Berlin, Hamburg, Hannover, and Cologne. All patients diagnosed with AAV and renal involvement between January 2012 and December 2024 were eligible for inclusion. The study protocol was approved by the Ethics Committee of the Charité Berlin (EA1/104/23).

Patient identification was performed differently across study sites. The differing approaches were necessary due to variations in documentation systems across sites (paper records, electronic files, and different hospital information systems). In Cologne and Berlin, eligible patients were identified through a systematic search of the digital hospital information system using the terms “vasculitis” and/or “ANCA”. In Hamburg and Hannover, patients were identified by the local senior physician through individual chart review of paper-based or electronic medical records according to predefined criteria.

Patients meeting the following criteria were included:

1. 1. A confirmed diagnosis of AAV with kidney involvement at the time of diagnoses or during follow-up. Kidney involvement was defined by reduced kidney function (estimated glomerular filtration rate (eGFR) < 90 ml/min/1.73m²) or proteinuria (urine protein-creatinine ratio > 200 mg/g creatinine) or both.
2. 2. Age at diagnosis between 0 and 18 years.

Epidemiological characteristics such as gender, age of onset and age at diagnosis were collected from patients’ initial clinical records. Clinical data, such as type of AAV, manifestation, biopsy site, or administered medication, were collected from medical records. Biochemical data including serum creatinine and urine protein-creatinine ratio as well as anthropometric measurements (weight and height) were recorded at specific timepoints (tp) when available: the initial presentation (tp0), 2–4 weeks (tp1), 2–4 months (tp2), 6 months (tp3), 1 year (tp4), 2 years (tp5) and 3 years (tp6) (see Fig. 2). Estimated eGFR was calculated using the bedside Schwartz formula [14]. Outcome measures were eGFR and proteinuria at the timepoints of follow-up.

Statistical analyses were performed using R (R Core Team, 2025, Vienna, Austria) and packages including gt, dplyr and ggplot2 [15–18]. Normality was assessed using the Shapiro-Wilk test. Statistical

significance was evaluated using the Kruskal-Wallis test. $P \leq 0.05$ was considered statistically significant. Artificial intelligence (AI) was used to assist with statistical programming, data analysis, and language editing. All AI-generated or AI-assisted content was reviewed and verified by the authors, who take full responsibility for the final content.

## Current clinical decision making in AAV

Three clinical case vignettes (Supplementary Material) were systematically developed to model key therapeutic decision points in pediatric AAV, each accompanied by identical questions regarding therapeutic management.

The vignettes were electronically distributed to pediatric nephrology experts via the mailing list of the German Society for Pediatric Nephrology. In addition, participation was actively encouraged during the annual meeting of the society. The survey was designed as an open questionnaire and was completed anonymously.

A total of 16 responses were received, including 15 pediatric nephrologists and one pediatric resident. For the purpose of analysis and to ensure comparability across responses, the resident response was excluded.

Responses were collected and statistical analyses were performed using R (R Core Team, 2025, Vienna, Austria) and package gt [15, 17].

## Results

# Multicenter pediatric AAV cohort

# Study population

Across the four German tertiary centers, 19 patients with AAV and renal involvement diagnosed between January 2012 and December 2024 were identified (Table 2). Nine patients were diagnosed in Berlin, four each in Hamburg and Hannover, and three in Cologne. Eleven patients (57.9%) were diagnosed with MPA and eight (42.1%) with GPA; no patient was diagnosed with EGPA.

Table 2

**Study population**. Demographic characteristics and clinical presentation in pediatric patients with AAV and renal involvement included in the multicenter cohort. Data are presented as median or absolute numbers and percentages. Values are n (%) or median (IQR). *As documented in the medical record.

| Variable | Total | TA | No TA |
|---|---|---|---|
| **Number of patients** | 19 (100%) | 6 (31.6%) | 13 (68.4%) |
| **Gender** | | | |
| – Female | 13 (68.4%) | 5 (83.3%) | 8 (61.5%) |
| – Male | 6 (31.6%) | 1 (16.7%) | 5 (38.5%) |
| **Age** | | | |
| – Age at onset (years) | 14.1 (11.9–15.8) | 13.1 (11.9–15.6) | 14.3 (12.1–15.7) |
| – Age at diagnosis (years) | 14.2 (12.5–16) | 13.7 (12.9–15.7) | 14.6 (12.2–15.9) |
| **Symptoms at presentation** | | | |
| – Deterioration of general condition | 18 (94.7%) | 6 (100%) | 12 (92.3%) |
| – Swollen/painful joints | 8 (42.1%) | 3 (50%) | 5 (38.5%) |
| – Tachycardia | 6 (31.6%) | 2 (33.3%) | 4 (30.8%) |
| – Persistent cough | 6 (31.6%) | 2 (33.3%) | 4 (30.8%) |
| – Hemoptysis | 5 (26.3%) | 5 (83.3%) | 0 (0%) |
| – Fever | 4 (21.1%) | 2 (33.3%) | 2 (15.4%) |
| – Conjunctivitis | 4 (21.1%) | 2 (33.3%) | 2 (15.4%) |
| – Abdominal pain | 4 (21.1%) | 1 (16.7%) | 3 (23.1%) |
| – Dyspnea | 3 (15.8%) | 3 (50%) | 0 (0%) |
| – Edema | 3 (15.8%) | 2 (33.3%) | 1 (7.7%) |
| – Persistent rhinitis | 3 (15.8%) | 1 (16.7%) | 2 (15.4%) |
| **Diagnosis*** | | | |
| – MPA | 11 (57.9%) | 4 (66.7%) | 7 (53.8%) |
| – GPA | 8 (42.1%) | 2 (33.3%) | 6 (46.2%) |
| **Positive serology at diagnosis** | | | |
| – MPO / pANCA only | 10 (52.6%) | 4 (66.7%) | 6 (46.2%) |
| – PR3 / cANCA only | 7 (36.8%) | 2 (33.3%) | 5 (38.5%) |

| Variable | Total | TA | No TA |
|---|---|---|---|
| – MPO and PR3 | 2 (10.5%) | 0 (0%) | 2 (15.4%) |
| **Localization of biopsy** | | | |
| – Kidney | 15 (78.9%) | 4 (66.7%) | 11 (84.6%) |
| – Nasal mucosa | 2 (10.5%) | 2 (33.3%) | 0 (0%) |
| – Lung | 1 (5.3%) | 0 (0%) | 1 (7.7%) |
| – Trachea | 1 (5.3%) | 1 (16.7%) | 0 (0%) |
| **Renal involvement at diagnosis** | | | |
| – Macrohematuria | 6 (31.6%) | 2 (33.3%) | 4 (30.8%) |
| – Microhematuria | 18 (94.7%) | 5 (83.3%) | 13 (100%) |
| – Proteinuria > 200 mg/g crea | 18 (94.7%) | 5 (83.3%) | 13 (100%) |
| – eGFR > 90 | 3 (15.8%) | 0 (0%) | 3 (23.1%) |
| – eGFR 60–90 | 6 (31.6%) | 2 (33.3%) | 4 (30.8%) |
| – eGFR 30–60 | 5 (26.3%) | 1 (16.7%) | 4 (30.8%) |
| – eGFR 15–30 | 2 (10.5%) | 2 (33.3%) | 1 (7.7%) |
| – eGFR < 15 | 3 (15.8%) | 1 (16.7%) | 1 (7.7%) |
| **Period of follow-up (months)** | 24 (12–36) | 12 (12–30) | 36 (12–36) |

# Clinical presentation

Initial clinical manifestations prompting further diagnostic evaluation were heterogeneous. The most frequent presenting symptoms were deterioration of general condition (18/19) and swollen/painful joints (8/19). All five patients with symptoms indicating severe lung involvement like hemoptysis and dyspnea received TA. Other commonly reported symptoms included persistent cough, tachycardia and hemoptysis. Less frequent manifestations comprised conjunctivitis, rhinitis, fever, edema, abdominal pain or dyspnea.

## Applicability of the ACR/EULAR classification criteria

To assess the applicability of the ACR/EULAR classification criteria in pediatric patients, the criteria were applied retrospectively to all cases. In 15 of 19 patients, the classification criteria resulted in a single diagnosis concordant with the established diagnosis based on serology and histopathology, as given in the medical record. In four cases both GPA and MPA were possible according to the ACR/EULAR criteria.

Renal involvement was present in all patients at the time of diagnosis, therefore the clinical presentation was classified as potentially organ- or life-threatening according to current EULAR recommendations.

## Renal involvement

Renal involvement was characterized by a reduced eGFR in all patients (19/19) at diagnosis or during follow-up, proteinuria in 18 patients, and hematuria in 18 patients. The median eGFR at diagnosis was 54 ml/min/1.73 m² (IQR 31.75–85.5), the median proteinuria 0.8 g/g prot/crea (IQR 0.4–1.4). Among the 15 patients who underwent kidney biopsy, 12 showed pauci-immune glomerulonephritis.

Two patients required acute dialysis at the time of diagnosis and subsequently progressed to chronic dialysis dependence; one of these patients underwent kidney transplantation two years later. One additional patient became dialysis-dependent after six years of follow-up.

# Treatment

# Induction

An overview of individual treatment regimens is provided in Fig. 1, illustrating the heterogeneity of therapeutic approaches. All but one patient received intravenous pulse methylprednisolone (IVMP) as part of induction therapy. CYC was administered immediately after diagnosis in three patients and at a later stage in one patient. RTX was used as first-line induction therapy in 13 patients, following CYC in one patient, and after insufficient initial response in another. Azathioprine (AZA) was used for induction therapy in one case.

# Therapeutic apheresis

Six patients (31.6%) underwent TA (four PE, one IA, and one both). Fresh frozen plasma was used as replacement fluid in all PE procedures, with 4–8 sessions performed. Reported adverse events included allergic reactions in one patient and severe hypertension in three patients.

# Maintenance

Maintenance therapy consisted predominantly of GC; one patient received Avacopan instead. Mycophenolate mofetil (MMF) in combination with GC was administered to 15 patients. RTX was used as maintenance therapy in two cases, while one patient received AZA as monotherapy at a later stage of disease. One patient required extracorporeal membrane oxygenation at the time of diagnosis.

# Relapses

During follow-up, relapse was documented in seven patients. Relapses were identified by rising PR3- or MPO-ANCA titers and/or recurrence or increase of proteinuria or hematuria. Treatment of relapse included GC, IVMP, RTX and MMF.

# Therapeutic apheresis and renal outcome

The impact of TA on renal function was assessed by evaluating changes in eGFR and proteinuria over the follow-up period (Fig. 2). Median eGFR at diagnosis tended to be lower in the TA group (45 ml/min/1.73 m²) compared with patients who did not receive TA (63 ml/min/1.73 m²). Renal function improved in both groups during follow-up. At the end of follow-up, median eGFR remained lower in the TA group (80 vs. 96 ml/min/1.73 m², p = 0.66); however, no statistically significant difference between groups was observed. No significant differences in proteinuria were detected between the TA and non-TA groups during follow-up. The median overall eGFR at 36 months was 95 ml/min/1.73 m² (IQR 65–104), the median proteinuria 0.2 g/g prot/crea (IQR 0.17–0.5).

# Current clinical decision making in AAV

To assess current best clinical practice of AAV treatment we conveyed a multicenter case-based expert survey (full survey and case vignettes see Supplementary Material). The responses to selected questions are presented in Table 3a and 3b.

| A. | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| | **GPA, organ-threatening, moderate kidney involvement** | **MPA, organ-threatening, severe kidney involvement** | **GPA, organ-threatening, severe kidney involvement + alveolar hemorrhage** |
| **Which induction therapy would you primarily choose?** | | | |
| a. GC + RTX | 12 (80%) | 6 (40%) | 7 (46.7%) |
| b. GC + MMF + RTX | 2 (13.3%) | 4 (26.7%) | 2 (13.3%) |
| c. GC + CYC + RTX | 0 (0%) | 4 (26.7%) | 4 (26.7%) |
| d. GC + CYC | 0 (0%) | 1 (6.7%) | 1 (6.7%) |
| e. GC + MTX + RTX | 1 (6.7%) | 0 (0%) | 1 (6.7%) |
| **Which maintenance therapy would you prefer after remission induction?** | | | |
| a. RTX | 8 (53.3%) | 9 (60%) | 9 (60%) |
| b. MMF | 3 (20%) | 2 (13.3%) | 2 (13.3%) |
| c. AZA | 1 (6.7%) | 1 (6.7%) | 1 (6.7%) |
| d. Other | 3 (20%) | 3 (20%) | 3 (20%) |

| B. | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| | **GPA, organ-threatening, moderate kidney involvement** | **MPA, organ-threatening, severe kidney involvement** | **GPA, organ-threatening, severe kidney involvement + alveolar hemorrhage** |
| **Would you use therapeutic apheresis?** | | | |
| a. Yes, if renal function deteriorates during follow-up. | 9/15 (60%) | 3/15 (20%) | 5/15 (33.3%) |
| b. Yes, directly as part of induction therapy. | 2/15 (13.3%) | 9/15 (60%) | 9/15 (60%) |
| c. I would not use TA. | 3/15 (20%) | 2/15 (13.3%) | 1/15 (6.7%) |
| d. Yes, if renal function and proteinuria do not improve within one month. | 1/15 (6.7%) | 1/15 (6.7%) | 0 (0%) |
| **Which form of therapeutic apheresis would you use?** | | | |
| a. PE | 7/14 (50%) | 7/13 (53.8%) | 8/14 (57.1%) |
| b. IA | 7/14 (50%) | 6/13 (46.2%) | 6/14 (42.9%) |
| **Please explain why you chose PE** | | | |
| a. Greater institutional experience. | 2/7 (28.6%) | 2/7 (28.6%) | 2/8 (25%) |
| b. More scientific evidence. | 2/7 (28.6%) | 2/7 (28.6%) | 3/8 (37.5%) |
| c. Stop inflammation. | 2/7 (28.6%) | 2/7 (28.6%) | 2/8 (25%) |
| d. Previous reimbursement claim by the health insurance fund. | 1/7 (14.3%) | 1/7 (14.3%) | 1/8 (12.5%) |
| **Please explain why you chose IA** | | | |
| a. Fewer side effects. | 7/7 (100%) | 6/6 (100%) | 6/6 (100%) |

**Tables 3 and 3b**: **Case vignette-based expert survey.** Responses of 15 pediatric nephrology experts to therapeutic decision-making questions across three representative pediatric AAV case vignettes. **3a**. Pharmacological induction and maintenance therapy. **3b**. Use of TA. Values are shown as n (%). Only selected answers are displayed here, full survey with all possible answers see Supplementary Material.

# Induction and maintenance therapy

In milder disease presentation (case 1) all respondents would use a combination of GC and RTX as induction therapy. Two would add MMF and one methotrexate (MTX). None of the respondents would use CYC. However, in more severe cases (2 and 3) five would use CYC as induction therapy, either alone or in combination.

RTX was most frequently selected as maintenance therapy in all cases. Alternative approaches included MMF alone or RTX in combination with MMF, with or without complement blockade.

# Therapeutic apheresis

A substantial proportion of participants indicated that they would initiate TA either directly as part of induction therapy or in case of worsening or non-improving renal function during follow-up. In our survey, approximately half of the respondents selected IA as their preferred modality, with a slight decrease in preference with increasing disease severity. When IA was selected as the preferred modality, a lower rate of side effects was cited as the reason in all cases and replies.

## Discussion

We hypothesized that TA would not provide a substantial long-term renal benefit beyond contemporary induction therapy in pediatric patients with AAV. Our findings support this hypothesis, as we observed no significant differences in long-term renal outcomes between patients treated with and without TA. At the same time, our nationwide survey revealed that TA continues to be widely used by German pediatric nephrologists, particularly in organ-threatening disease. This discrepancy between limited pediatric evidence and current clinical practice likely reflects the absence of pediatric-specific prospective studies and the continued reliance on expert opinion when treating critically ill children.

The demographic characteristics of our cohort, including age at diagnosis (14 years) and female predominance, are consistent with previously published pediatric AAV cohorts [19, 20]. Likewise, the predominance of MPA over GPA and the absence of EGPA reflects known epidemiologic patterns [21]. Notably, in EGPA, renal involvement is considerably less common than in other AAV subtypes [22]. Clinical presentation was heterogeneous and often non-specific, underscoring the diagnostic challenges in pediatric AAV.

Retrospective application of the ACR/EULAR classification criteria to this pediatric cohort showed good concordance with established diagnoses, based on serology and histopathology as given in the medical record, in most cases. However, multiple possible classifications occurred in a subset of patients. This observation is in line with previous observations that ACR/EULAR criteria work well in most pediatric cases, but, due to a lack of a classification sequence, lead to multiple simultaneous classifications [4, 23].

Therapeutic strategies varied considerably across centers, reflecting both evolving treatment paradigms and the absence of pediatric-specific randomized controlled trials. Most patients received GC in combination with RTX or CYC for induction therapy, in line with guideline recommendations extrapolated

from adult data. RTX was frequently used as first-line therapy, likely reflecting efforts to minimize CYC exposure and its long-term toxicity in children as recommended by the KDIGO guidelines [10]. Notably, MMF was used in a considerable proportion of patients despite not being recommended as first-line therapy by most international societies. Similar observations have been reported in other pediatric cohorts and may reflect broad clinical experience with MMF in pediatric nephrology and rheumatology [24]. Our case-based expert survey reflected these observations.

TA was employed in approximately one-third of patients. All Patients with more severe lung involvement, reflected by clinical symptoms, received TA. Additionally, in the TA group eGFR tended to be lower at presentation compared with those who did not receive TA. This is in line with current guideline recommendations that reserve TA for more severe clinical cases [10]. Consistent with these findings, experts in our case vignettes opted for use of TA either directly as part of induction therapy or in case of worsening or non-improving renal function during follow-up in 80–93% throughout the three cases.

Although renal function improved in both groups during follow-up, patients treated with TA remained at a lower median eGFR, and no significant long-term renal benefit of TA could be demonstrated.

Notably, despite the results of PEXIVAS and subsequent revisions of international guidelines recommending against routine TA use, TA was still administered in three patients after 2020 and chosen in the expert survey. This underscores the ongoing uncertainty surrounding the applicability of adult trial data to pediatric patients and highlights the influence of disease severity, clinician experience, and individual risk assessment in real-world decision-making. Thus, while TA may still be considered in selected clinical scenarios - such as rapidly progressive renal failure or severe extrarenal manifestations - our data suggests that TA is unlikely to reverse established renal damage once advanced glomerular injury has occurred. Moreover, TA-related adverse events, including allergic reactions and hemodynamic complications, were observed, emphasizing the procedural risks of extracorporeal therapies in pediatric patients.

Regarding the two different modalities - PE or IA - pediatric nephrology experts selected PE and IA with nearly equal frequency. PE was favored because of greater institutional experience, stronger scientific evidence, and a presumed more effective interruption of inflammation. Preference for IA was exclusively justified by a presumed lower rate of side effects in line with [28]. When addressing efficacy, the recent Cinevas study showed no difference in reduction of autoantibody levels comparing PE and IA in adult AAV patients [11]. This could support a preference for IA over PE in pediatric AAV. Yet current international AAV guidelines do not address IA as a therapeutic option.

Relapses occurred in a substantial proportion of patients during follow-up, reflecting the chronic and relapsing nature of pediatric AAV. Relapse management relied predominantly on glucocorticoids and RTX, consistent with current guidelines. This underscores the importance of long-term monitoring and individualized maintenance strategies to balance disease control against treatment-related toxicity.

Several limitations must be acknowledged, including the retrospective design, small patient number, and heterogeneity in treatment approaches across centers and time periods. These factors limit statistical power and preclude definitive conclusions regarding the efficacy of TA. Nevertheless, this multicenter cohort provides valuable real-world insights into contemporary management of pediatric AAV with renal involvement in Germany.

In conclusion, our multicenter cohort did not demonstrate evidence of a long-term renal benefit associated with the use of TA in pediatric AAV. Expert responses from case vignette surveys, however, demonstrate that clinicians still tend to use TA in selected patients with severe or organ-threatening disease. Early diagnosis and prompt initiation of effective immunosuppressive therapy remain critical to prevent irreversible organ damage. International collaborative registries are urgently needed to better define the role of TA and to establish evidence-based, pediatric-specific treatment algorithms.

# Declarations

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**Competing Interests:**

CT reports receiving travel support and/or honoraria for lectures from Ultragenyx, Sanofi, and Chiesi within the past three years. JT reports receiving an honorarium for a lecture from Diamed Medizintechnik GmbH. The remaining authors declare no competing interests.

**Ethics approval:**

The study protocol was approved by the Ethics Committee of the Charité Berlin (EA1/104/23).

**Consent to participate and to publish:**

Informed consent was obtained from all individuals or from legal guardians regarding analyzing and publishing their data.

**Data availability statement:**

The data underlying this article are not publicly available because they contain information that could compromise the privacy of research participants. De-identified data may be made available by the

corresponding author upon reasonable request and subject to approval by the participating institutions and applicable data protection regulations.

**Authors‘ contributions:**

Klara Brüning and Julia Thumfart designed the study and developed the survey. Klara Brüning collected and analyzed the data, carried out the survey, interpreted the results, and drafted the manuscript. Data collection was supported by Nele Kanzelmeyer, Sebastian Loos and Christina Taylan. Literature collection was supported by Laura Peters. Julia Thumfart supervised the study. All authors contributed to data interpretation, and critically revised the manuscript. All authors reviewed and approved the final manuscript.

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# Figures

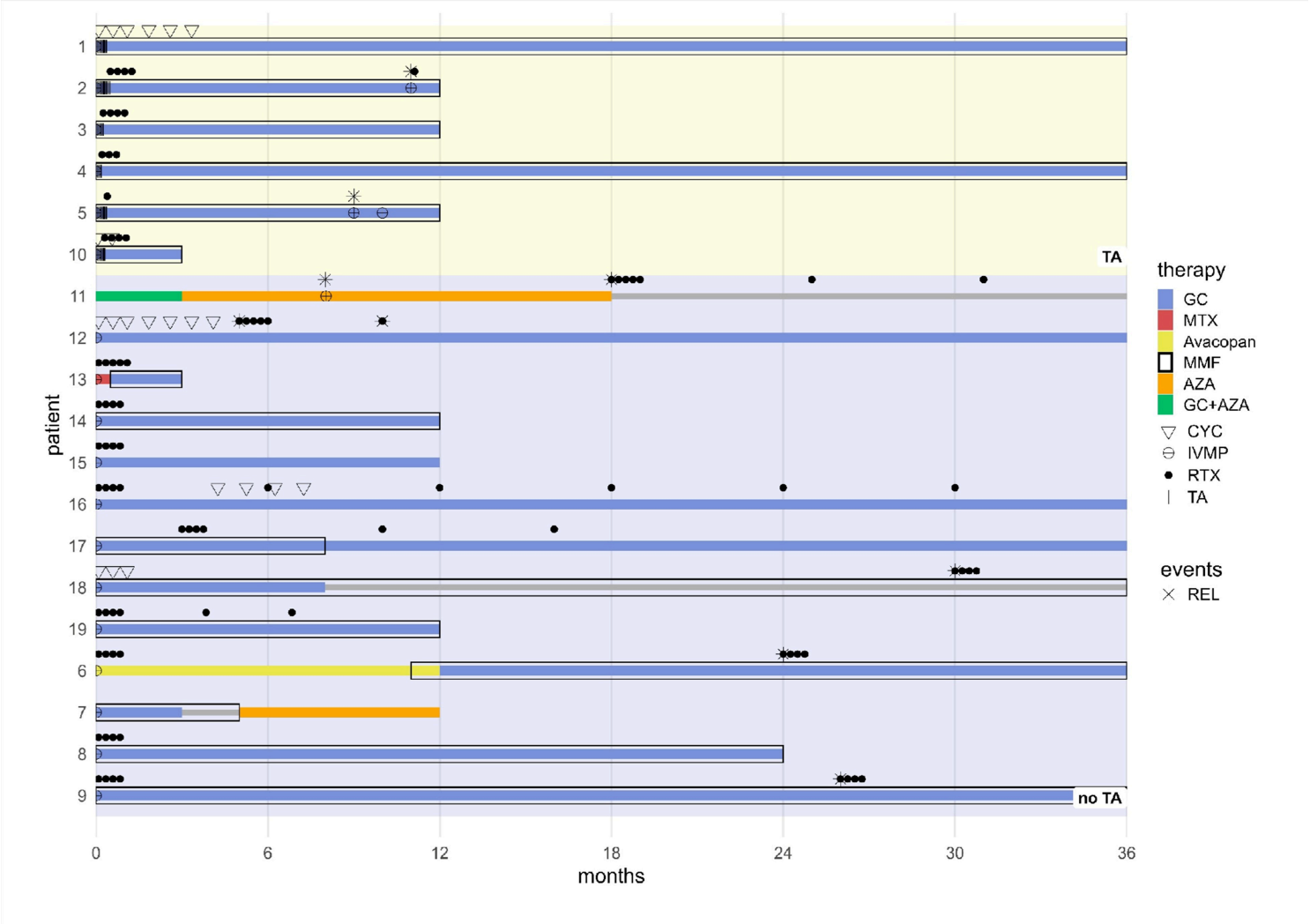
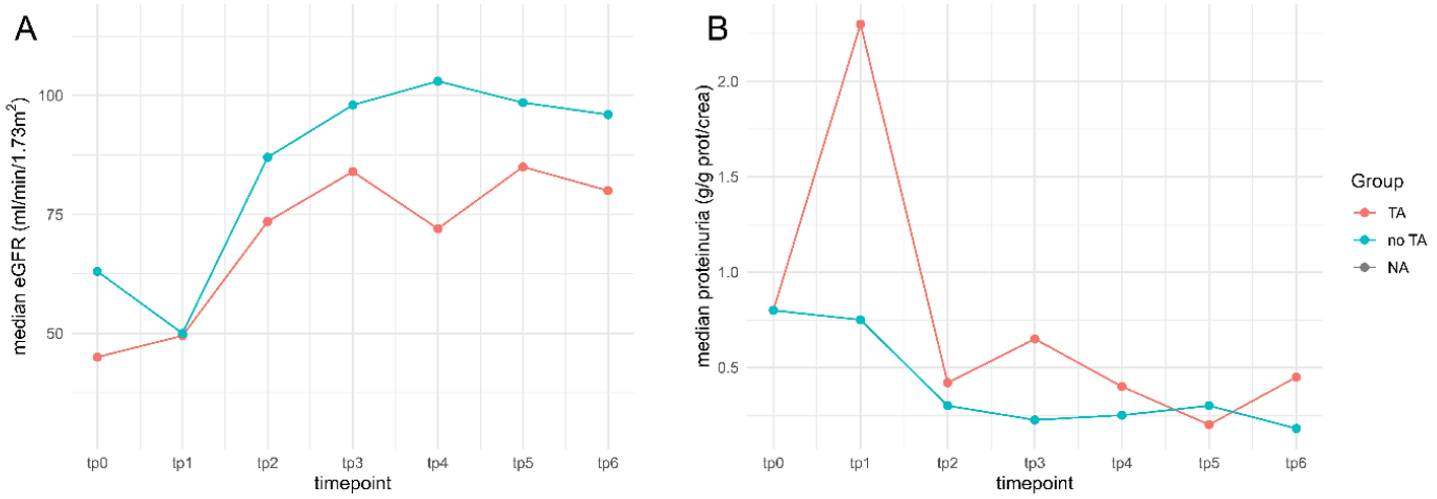



**Figure 1**

**Individual treatment courses in pediatric ANCA-associated vasculitis.** The plot depicts the timing and duration of induction and maintenance therapies for each patient during follow-up. Patients who received therapeutic apheresis (TA) are found in the upper (yellow) part of the plot, patients who did not receive TA are found in the lower (blue) part. Azathioprine (AZA), cyclophosphamide (CYC), Glucocorticoids (GC), methotrexate (MTX), mycophenolate mofetil (MMF), i.v. methylprednisolone (IVMP), relapse (REL), rituximab (RTX)




| | tp 0 | tp 1 | tp 2 | tp 3 | tp 4 | tp 5 | tp 6 |
|---|---|---|---|---|---|---|---|
| TA | **45** [29-88] | **49.5** [41.5-63.5] | **73.5** [58.5-90.75] | **84** [79-95] | **72** [62-88] | **85** [80-90] | **80** [72.5-87.5] |
| no TA | **63** [34-78] | **50** [34-90] | **87** [50-107] | **98** [36.25-118.5] | **103** [46.75-120] | **98.5** [74.5-111.25] | **96** [62.5-107.5] |
| p-value | 0.767 | 0.759 | 0.456 | 0.428 | 0.458 | 0.695 | 0.661 |

| | tp 0 | tp 1 | tp 2 | tp 3 | tp 4 | tp 5 | tp 6 |
|---|---|---|---|---|---|---|---|
| TA | **0.8** [0.6-0.86] | **2.3** [0.92-3.7] | **0.42** [0.11-0.85] | **0.65** [0.48-0.82] | **0.4** [0.33-0.43] | **0.2** [0.1-0.3] | **0.45** [0.43-0.48] |
| no TA | **0.8** [0.4-1.6] | **0.75** [0.55-2.35] | **0.3** [0.15-0.85] | **0.22** [0.08-0.7] | **0.25** [0.07-0.48] | **0.3** [0.05-0.4] | **0.18** [0.14-0.35] |
| p-value | 0.685 | 0.327 | 0.895 | 0.396 | 0.582 | 0.881 | 0.297 |

**Figure 2**

**Renal outcomes over time. (A)** Median [IQR] eGFR and **(B)** median proteinuria [IQR] at different follow-up timepoints

# Supplementary Files

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