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RESEARCH LETTER

Clinical Factors and Adverse Kidney Outcomes in Children With Antineutrophil Cytoplasmic Antibody–Associated Glomerulonephritis

To the Editor:

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides are rare disorders in childhood with a variable clinical presentation. Given ANCA vasculitides' rarity, data informing clinical practice and treatment are mainly based on adult data. The purpose of this study was to characterize clinical characteristics of ANCA-associated glomerulonephritis (AAGN) in childhood to determine factors associated with adverse renal outcome and the requirement for kidney replacement therapy (KRT) across a global study population.

This was a retrospective cross-sectional international survey distributed through professional pediatric nephrology organizations from December 2019 to March 2020 intended to create a registry of children with AAGN to understand clinical practices. Through an online form, pediatric nephrologists entered demographic and clinical information on all children with AAGN in their center in de-identified fashion. All centers were required to obtain their own institutional ethics or governance approval. Inclusion criteria were patients under 20 years at presentation who were diagnosed with AAGN in 2000–2019 and had kidney involvement. Data elements that were collected included baseline demographic data, clinical features at presentation, treatment received (maintenance and induction), and data on 3 clinical outcomes: requirement for KRT, serum creatinine concentration (Scr), and death. Specifically, nephrologists were asked to report the peak Scr and any requirement for KRT in the first 3 months after presentation during the induction treatment period. Nephrologists were also asked to report on the need for KRT and vital status at last known follow-up. Further methodological details are in [Item S1](#).

Based on responses received from 114 different clinicians, 337 children from 41 different countries were included in the final analysis. Median duration between initial presentation and last known follow-up was 26 (IQR, 11–57) months. [Table S1](#) details baseline characteristics of included children. [Table S2](#) shows the organ involvement at presentation across different clinical phenotypes.

[Table 1](#) shows the most frequent induction and maintenance treatments used in the entire cohort. A total of 113 children (34%) received plasma exchange at induction. Sixteen deaths were reported in this cohort (5% mortality), with a mean age at death of 13.7 ± 5.7 years.

[Table 2](#) characterizes the clinical factors and treatment according to KRT requirements at initial presentation and at last known follow-up. We found a high prevalence of adverse renal outcomes, with 40% of children requiring KRT at last known follow-up, slightly higher than previously published data.^{1–4} Children who did (vs did not) require KRT at last known follow-up had a higher peak Scr

during the first 3 months after their initial presentation. There was a higher proportion of girls and a higher proportion of myeloperoxidase-ANCA positivity in children who required KRT at last known follow-up, compared to those who did not require KRT. We note that children who required KRT at last known follow-up were more likely to have received plasma exchange as induction treatment, but this may simply be because children with more severe kidney involvement at presentation were more likely to be treated with plasma exchange. We note that mycophenolate mofetil was used more commonly as maintenance treatment for children compared to azathioprine, which differs from suggestions in the adult literature.⁵

This study is unique, as it was conducted across 41 countries, giving a broad cross-sectional assessment of demographics and baseline characteristics of children affected by AAGN. Potential limitations of this study include an over-representation of children with severe renal outcomes, given the collection of data through a survey of pediatric nephrologists; but this is also a strength, as this study focuses on the subgroup of children with ANCA vasculitis who have kidney involvement. Data were only available at disease presentation and latest follow-up, which limits our ability to comment on kidney function over time. In addition, we did not collect data on histology, meaning that the diagnosis of AAGN was clinical rather than histological and we had limited ability to relate histology to clinical outcomes. We also do not have data on proteinuria at

Table 1. Main Combinations of Induction and Maintenance Treatment in Entire AAGN Cohort

Main Treatment Combinations	Value
Induction	
Steroids, ^a cyclophosphamide	100 (30%)
Steroids, ^a cyclophosphamide, PE (± IVIG)	56 (17%)
Steroids, ^a rituximab	25 (7%)
Steroids ^a	22 (7%)
Steroids, ^a cyclophosphamide, rituximab, PE (± IVIG)	21 (6%)
Steroids, ^a mycophenolate mofetil	13 (4%)
Other combinations	96 (28%)
None	4 (1%)
Maintenance	
Mycophenolate mofetil and steroids	100 (31%)
Azathioprine and steroids	49 (15%)
Cyclophosphamide and steroids	25 (8%)
Steroids	20 (6%)
Steroids and rituximab	19 (6%)
Azathioprine	17 (5%)
Mycophenolate mofetil	8 (2%)
Rituximab	8 (2%)
Other combinations	62 (19%)
None	15 (5%)

Induction therapy information was available from all 337 patients, maintenance treatment data from 327 patients. "Other combinations" refers to multiple different combinations used less commonly. Abbreviations: IVIG, intravenous immunoglobulin; PE, plasma exchange.

^aIntravenous or oral.

Table 2. Clinical Variables and the Requirement for KRT During the First 3 Months After Initial Presentation and Last Known Follow-up in 326 Children With AAGN

	Required KRT at Initial Presentation		Required KRT at Last Known Follow-up	
	Yes	No	Yes	No
No. of patients	119	207	132	194
Female sex	75%	69%	78%	68%
Age at presentation, y	12.1 ± 4.4	12.5 ± 5.4	11.9 ± 4.6	12.7 ± 5.3
MPO-ANCA	71%	64%	77%	60%
High-income GDP	61%	66%	58%	68%
Peak Scr during initial presentation, μmol/L	736 ± 345	173 ± 121	616 ± 333	218 ± 115
Organ involvement at presentation				
Respiratory tract	50%	42%	50%	41%
Ear, nose, and throat	12%	17%	10%	19%
Skin	13%	32%	17%	30%
Musculoskeletal	9%	24%	18%	19%
Neurological	16%	8%	18%	6%
Eye	5%	10%	7%	9%
Induction treatment				
IV steroids	95%	80%	92%	81%
Rituximab	29%	27%	25%	29%
IV cyclophosphamide	55%	57%	64%	56%
Plasma exchange	57%	19%	44%	26%
Maintenance treatment				
Azathioprine	22%	27%	24%	27%
Mycophenolate mofetil	46%	45%	43%	47%
Rituximab	17%	17%	14%	19%

Continuous variables given as mean ± SD. Follow-up on the need for KRT was not available on 11 children; therefore data on 326 children are presented in this table. Conversion factor for Scr μmol/L to mg/dL, ×0.0113. Abbreviations: GDP, gross domestic product; IV, intravenous; MPO, myeloperoxidase.

presentation, which is a further limitation. In conclusion, this large international cohort of children with AAGN demonstrates the high risk of chronic kidney disease and requirement for KRT in this population.

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Supplementary Material

Supplementary File (PDF)

Item S1; Tables S1-S2.

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