assess the prospective association with graft function decline still needs to be delineated and would be an interesting one to address.

Finally, while we previously found no evidence for a cross-sectional association between plasma mercury and kidney function,[8] a potential prospective association cannot be excluded and likewise warrants further studies.

Camilo G. Sotomayor, MD, PhD, Daan J. Touw, PhD, and Stephan J.L. Bakker, MD, PhD, on behalf of the TransplantLines Investigators

Article Information

TransplantLines Investigators: A list of the members of this investigator group is provided in Sotomayor et al.[2]

Authors' Affiliations: Division of Nephrology, Department of Internal Medicine (CGS, SJLB), and Clinical Pharmacy and Pharmacology (DJT), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received September 22, 2022. Accepted September 27, 2022, after editorial review by an Associate Editor and a Deputy Editor.

 Published online July 8, 2022 with doi 10.1053/j.ajkd.2022.09.008

References

1. Yen J-S, Yen T-H. Chelation therapy for kidney transplant recipients with lead exposure. Letter. *Am J Kidney Dis*. Published online October 24, 2022. doi:10.1053/j.ajkd.2022.08.024
2. Sotomayor CG, Giubergia F, Groothof D, et al. Plasma lead concentration and risk of late kidney allograft failure: findings from the TransplantLines Biobank and Cohort Studies. *Am J Kidney Dis*. 2022;80(1):87-97.e1. doi:10.1053/j.ajkd.2021.10.009
3. Sommar JN, Hedmer M, Lundh T, et al. Investigation of lead concentrations in whole blood, plasma and urine as biomarkers for biological monitoring of lead exposure. *J Expo Sci Environ Epidemiol*. 2014;24(1):51-57. doi:10.1038/jes.2013.4
4. Lamadrid-Figueroa H, Téllez-Rojo MM, Hernández-Cadena L, et al. Biological markers of fetal lead exposure at each stage of pregnancy. *J Toxicol Environ Health A*. 2006;69(19):1781-1796. doi:10.1080/15287390600630195
5. Bergdahl IA, Vahter M, Counter SA, et al. Lead in plasma and whole blood from lead-exposed children. Environ Res 1999;80(1):25-33. doi:10.1006/enrs.1998.3880
6. Sotomayor CG, Groothof D, Vodegel JJ, et al. Plasma cadmium is associated with increased risk of long-term kidney graft failure. *Kidney Int*. 2021;99(5):1213-1224. doi:10.1016/j.kint.2020.08.027
7. Smith D, Hernández-Ávila M, Téllez-Rojo MM, et al. The relationship between lead in plasma and whole blood in women. *Environ Health Perspect*. 2002;110(3):263-268. doi:10.1289/ehp.02110263
8. Sotomayor CG, Gomes-Neto AW, Gans ROB, et al. Fish intake, circulating mercury and mortality in renal transplant recipients. *Nutrients*. 2018;10(10):1419. doi:10.3390/nu10101419

RESEARCH LETTERS

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)

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.
[a]Intravenous or oral.

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

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.

and we had limited ability to relate histology to clinical outcomes. We also do not have data on proteinuria at 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.

Matko Marlais, FRCPCH, Tanja Wlodkowski, PhD, Nikoleta Printza, MD, PhD, Dorothea Kronsteiner, PhD, Regina Krisam, PhD, Lukas Sauer, MSc, Marina Aksenova, PhD, Isa Ashoor, MD, Atif Awan, FRCPCH, Justine Bacchetta, MD, PhD, Ramnath Balasubramanian, MRCPCH, Biswanath Basu, MD, Zivile Bekassy, PhD, Olivia Boyer, MD, PhD, Eugene Yu-hin Chan, FHKAM(Paed), Dagmar Csaicsich, MD, Stéphane Decramer, MD, PhD, Eiske Dorresteijn, MD, Magdalena Drozynska-Duklas, MD, Loai Akram Eid, MD, Laura Espinosa, MD, Verónica Ferraris, MD, Hana Flögelová, MD, PhD, Jessica Forero-Delgadillo, MD, Alessandra Gianviti, MD, Valentina Gracchi, MD, Mercedes López González, MD, Matthias Hansen, MD, Motoshi Hattori, MD, PhD, Xu Hong, MM, Nakysa Hooman, MD, Dmytro Ivanov, MD, Hee Gyung Kang, MD, PhD, Vasiliki Karava, MD, Ina Kazyra, MD, PhD, Adrian Lungu, MD, Stephen Marks, MD MSc, Andrew Maxted, MBBS, Anna Moczulska, MD, PhD, Rebekka Müller, MD, Tatiana Nastausheva, MD, Mattia Parolin, MD, Carmine Pecoraro, MD, Iliana Principi, MD, Cheryl Sanchez-Kazi, MD, Seha Saygili, MD, Raphael Schild, MD, Mohan Shenoy, FRCPCH, Rajiv Sinha, MD, Ana Paula Spizzirri, MD, Maria Stack, MD, Maria Szczepanska, MD, Alexey Tsygin, MD, Julia Tzeng, MD, Vaidotas Urbonas, MD, PhD, Carlos Zapata, MD, Jakub Zieg, MD, PhD, Franz Schaefer, MD, PhD, Marina Vivarelli, MD, PhD, Kjell Tullus, MD, PhD

Supplementary Material

Supplementary File (PDF)

Item S1; Tables S1-S2.

Article Information

Authors' Affiliations: UCL Great Ormond Street Institute of Child Health, University College London, London, United Kingdom (MM, SM, KT); Division of Pediatric Nephrology, Heidelberg University Hospital, Heidelberg, Germany (TW, RM, FS); Paediatric Nephrology, 1st Department of Pediatrics, Hippokratio General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece (NP, VK); Institute of Medical Biometry, University of Heidelberg, Heidelberg, Germany (DK, RK, LS); Y. Veltischev Research and Clinical Institute for Pediatrics, Pirogov Russian National Research Medical University, Moscow, Russia (MA); Louisiana State University Health Sciences Center, New Orleans, Louisiana (IA); Children's Hospital Ireland at Temple Street, Dublin, Ireland (AA, MStack); Centre de Référence des Maladies Rénales Rares, Hôpital Femme Mère Enfant, Lyon, France (JB); Evelina London Children's Hospital, London, United Kingdom (RB); Department of Pediatrics, N. R. S. Medical College & Hospital, Kolkata, India (BB); Skane University Hospital Lund, Sweden (ZB); Pediatric Nephrology, MARHEA Reference Center, Imagine Institute, Paris University, Necker Hospital, APHP, Paris, France (OB); Paediatric Nephrology Centre, Hong Kong Children's Hospital, Hong Kong (EY-hC); Universitätsklinik für Kinder- und Jugendheilkunde, Medizinische Universität Wien, Vienna, Austria (DC); Pediatric Nephrology and Internal Medicine, CHU Purpan, Toulouse, France (SD); Erasmus MC-Sophia Childrens Hospital, Rotterdam, The Netherlands (ED); Department of Pediatrics, Nephrology and Hypertension, Medical University of Gdańsk, Gdańsk, Poland (MD-D); Pediatric Nephrology, Dubai Medical College & Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates (LAE); Paediatric Nephrology Department, University Hospital La Paz, Madrid, Spain (LE); Hospital Italiano de Buenos Aires, Buenos Aires, Argentina (VF); Department of Paediatrics, Faculty of Medicine, Palacky University, Faculty Hospital Olomouc, Olomouc, Czech Republic (HF); Servicio de Nefrología Pediátrica Fundación Valle del Lili, Universidad Icesi, Cali, Colombia (JF-D); Bambino Gesù Children's Hospital, Rome, Italy (AG, MV); University of Groningen, University Medical Center Groningen, Department of Pediatrics, Beatrix Children's Hospital, Groningen, The Netherlands (VG); Department of Pediatric Nephrology, University Hospital Vall d'Hebron, Barcelona, Spain (MLG); KfH Kidney Center for Children and Adolescents, Frankfurt, Germany (MHansen); Department of Pediatric Nephrology, Tokyo Women's Medical University, Tokyo, Japan (MHattori); Department of Rheumatology, Children's Hospital of Fudan University, National Children's Medical Center, Shanghai, China (XH); Aliasghar Children's Hospital, Department of Pediatrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran (NH); Shupyk National Medical Academy of Postgraduate Education, Kyiv, Ukraine (DI); Department of Pediatrics, Seoul National University College of Medicine, Seoul, South Korea (HGK); Belarus State Medical University, Minsk, Belarus (IK); Pediatric Nephrology, Fundeni Clinical Institute, Bucharest, Romania (AL); Nottingham Children's Hospital Renal and Urology Unit, Nottingham, United Kingdom (AMaxted); Jagiellonian University Medical College of Krakow, Krakow, Poland (AMoczulska); Voronezh State Medical University, Voronezh, Russia (TN); Pediatric Nephrology, Dialysis and Transplantation Unit, Woman's and Child's Health Department, University Hospital of Padova, Padova, Italy (MP); A.O.R.N. Santobono-Pausilipon-Annunziata, Naples, Italy (CP); Department of Nephrology, Hospital Pediátrico Humberto J Notti, Mendoza, Argentina (IP); Loma Linda University Children's Hospital, Loma Linda, California (CS-K); Cerrahpaşa Faculty of Medicine, Department of Pediatric Nephrology, Istanbul University-Cerrahpaşa, Istanbul, Turkey (SS); Division of Pediatric Nephrology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany (RSchild); Royal Manchester Children's Hospital, Manchester, United Kingdom (M Shenoy); Institute of Child Health, Kolkata, India (R Sinha); Nephrology Department, Hospital de Niños "Superiora Sor Maria Ludovica," La Plata, Argentina (APS); Department of Pediatrics, Faculty of Medical Science in Zabrze, Medical University of Silesia, Katowice, Poland (MSzczepanska, AT); National Medical Research Center for Children's Health, Moscow, Russia (AT); Valley Children's Healthcare, Madera, California (JT); Vilnius University Clinic for Children's Diseases, Vilnius, Lithuania (VU); Hospital Infantil Universitario "Rafael Henao Toro," Manizales, Colombia (CZ); and Department of Paediatrics, Second Medical Faculty, Motol University Hospital, Charles University, Prague, Czech Republic (JZ).

Address for Correspondence: Matko Marlais, FRCPCH, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London WC1N 3JH, UK. Email: m.marlais@ucl.ac.uk

Authors' Contributions: Designed the study, collected and collated data, conducted and reviewed analyses: MM, TW, NP, FS, MV, KT; devised the statistical analysis plan, conducted statistical analyses: DK, RK, LS; reviewed patients for inclusion, collected data: MA, IA, AA, JB, RB, BB, ZB, OB, EY-hC, DC, SD, ED, MD-D, LAE, LE, VF, HF, JF-D, AG, VG, MLG, MHansen, MHattori, XH, NH, DI, HGK, VK, IK, AL, SM, AMaxted, AMoczulska, RM, TN, MP, CP, IP, CS-K, SS, RSchild, MS, RSinha, APS, MStack, MSzczepanska, AT, JT, VU, CZ, JZ. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be

personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Support: This study has been supported by the European Rare Kidney Disease Network (ERKNet). ERKNet is co-funded by the European Union within the framework of the Third Health Programme "ERN-2016 - Framework Partnership Agreement 2017-2021." The funders had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgements: We are grateful to the European Society of Paediatric Nephrology (ESPN) and the International Paediatric Nephrology Association (IPNA) for their support in administering this study. We are grateful to all colleagues and pediatric nephrology centers contributing cases to this study.

Prior Presentation: Aspects of this work were presented in abstract form at the 53rd ESPN Annual Meeting held in Amsterdam, The Netherlands, in September 2021.

Peer Review: Received February 11, 2022. Evaluated by 2 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form May 18, 2022.

 Published online July 8, 2022 with doi 10.1053/j.ajkd.2022.05.013

References

1. Calatroni M, Consonni F, Allinovi M, et al. Prognostic factors and long-term outcome with ANCA-associated kidney vasculitis in childhood. *Clin J Am Soc Nephrol*. 2021;16(7):1043-1051. doi:10.2215/CJN.19181220
2. Özçelik G, Sönmez HE, Şahin S, et al. Clinical and histopathological prognostic factors affecting the renal outcomes in childhood ANCA-associated vasculitis. *Pediatr Nephrol*. 2019;34(5):847-854. doi:10.1007/s00467-018-4162-5
3. Morishita KA, Moorthy LN, Lubieniecka JM, et al. Early outcomes in children with antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol*. 2017;69(7):1470-1479. doi:10.1002/art.40112
4. Sacri A-S, Chambaraud T, Ranchin B, et al. Clinical characteristics and outcomes of childhood-onset ANCA-associated vasculitis: a French nationwide study. *Nephrol Dial Transplant*. 2015;30(Suppl 1):i104-i112. doi:10.1093/ndt/gfv011
5. Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA*. 2010;304(21):2381-2388. doi:10.1001/jama.2010.1658

Vitamin D and Parathyroid Hormone Levels in CKD

To the Editor:

Chronic kidney disease–bone mineral disorder (CKD-MBD) includes multiple interrelated abnormalities, including hypocalcemia, hyperphosphatemia, hypovitaminosis D, and elevated levels of fibroblast growth factor 23 (FGF-23) and parathyroid hormone (PTH).[1-3]

Calcitriol ($1,25(OH)_2D$), the activated form of vitamin D, is a central regulator of mineral metabolism. In CKD-MBD, metabolic abnormalities are augmented by $1,25(OH)_2D$ and 25-hydroxyvitamin D (25(OH)D) deficiency, resulting in secondary hyperparathyroidism. Multiple studies have demonstrated that maintaining 25(OH)D levels at ≥30 ng/mL is associated with lower PTH levels in early stages of CKD,[4-6] but efficacy in late-stage CKD is unclear. The most recent KDIGO guideline recommends that vitamin D deficiency in CKD patients be treated similarly as in the general population.[3]

The effects of calcium, phosphorus, vitamin D, and glomerular filtration rate (GFR) on PTH are profoundly interdependent. Currently available data clearly answer whether vitamin D supplementation benefits patients with advanced CKD. We therefore examined the relationships of serum calcium, 25(OH)D, phosphorus, and estimated GFR (eGFR) with PTH among a large national sample of patients evaluated during routine clinical practice.

The data were extracted from a set of adult patients who had GFR estimated at a Labcorp facility in the United States from November 2011 through June 2014; the earliest set of simultaneously obtained calcium, phosphorus, 25(OH)D, and PTH values was used (Item S1). Assay platforms were constant over the entire study. To eliminate primary hyperparathyroidism cases, individuals with elevated PTH levels were excluded if serum calcium exceeded 10.2 mg/dL. eGFR values were stratified using KDIGO criteria. 25(OH)D levels were categorized as adequate (>40 ng/mL), low (20-40 ng/mL), and depleted (<20 ng/mL). The research was approved by the Western–Copernicus Group Institutional Review Board, with informed consent waived for use of de-identified data. Analyses used SAS, version 9.4 (SAS Institute Inc).

Entry criteria were met by 153,611 individuals; 56.6% were female; mean age was 65.9 ± 14.0 years (Table 1).

Figure 1 illustrates the relationship between calcium and PTH, stratified by CKD stage and 25(OH)D level. At all levels of serum calcium in all eGFR categories, vitamin D levels ≥40 ng/mL (vs <20 ng/mL) were associated with 20%-40% lower PTH levels; patients with 25(OH)D levels 20-<40 ng/mL had intermediate PTH levels. PTH levels were greater at greater CKD stage, and patients in CKD stages 3-5 with 25(OH)D levels of ≥40 ng/mL had PTH levels comparable to 25(OH)D-depleted patients with more normal kidney function. Results were similar when we included patients with calcium levels up to 12 mg/dL (Fig S1).

Our findings illustrate the interdependencies of calcium, vitamin D, and eGFR in their association with PTH level in CKD. Two main points were apparent: 25(OH)D levels ≥40 ng/mL were associated with lower PTH among patients in every eGFR category at every level of serum