toxins

MDPI

Review

Measurement and Clinical Interpretation of Uremic Solutes in Pediatric Chronic Kidney Disease: A Narrative Review

John Dotis [1,*], Maria Fourikou [1] and Athina Papadopoulou [2]

[1] Third Department of Pediatrics, Hippokration Hospital, Aristotle University of Thessaloniki, 54642 Thessaloniki, Greece; mfour@auth.gr
[2] First Department of Pediatrics, Hippokration Hospital, Aristotle University of Thessaloniki, 54642 Thessaloniki, Greece; athinapap80@yahoo.gr
* Correspondence: yandot@auth.gr; Tel.: +30-2310892486

Abstract

In pediatric chronic kidney disease (CKD), uremic solute measurements are interpreted during growth and maturation, when both exposure and clinically relevant outcomes may change. This narrative review examines indoxyl sulfate (IS), p-cresyl sulfate (pCS), and β2-microglobulin across CKD stages and treatment settings. Pediatric studies report solute-specific retention before dialysis. In the 4C cohort, total IS was associated with CKD progression and selected vascular measures, whereas corresponding adjusted associations were not established for pCS. A longitudinal pediatric study linked total IS with lower height velocity at ages 2–12 years. The association was small and requires independent replication with direct assessment of pubertal stage. Neurocognitive findings vary by metabolite and test. Hemodiafiltration findings depend on whether the endpoint is intradialytic removal or sustained predialysis concentration. Differences in sampling, measured fractions, and cohort membership limit comparisons with adult studies. The research priority is to determine whether repeated, standardized measurements add early prognostic information beyond established clinical markers and whether acting on that information improves growth, kidney health, or other outcomes relevant to children. Clinical thresholds and benefit from IS- or pCS-guided care have yet to be established.

Keywords: pediatric chronic kidney disease; uremic solutes; indoxyl sulfate; p-cresyl sulfate; protein-bound uremic toxins; hemodiafiltration; clinical utility

Key Contribution: This review distinguishes pediatric findings on early retention, vascular changes, growth, and neurodevelopment from evidence extrapolated from adults. It links the measurement of total and free solutes to a pediatric research pathway for validating early risk prediction and testing decisions informed by the result.

Check for updates

Received: 19 October 2026
Revised: 11 November 2026
Accepted: 14 November 2026
Published: 16 November 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

Assessment of chronic kidney disease (CKD) in children relies on estimated glomerular filtration rate (eGFR), proteinuria or albuminuria, blood pressure, and evaluation of complications [1,2]. Urea-based indices quantify delivered small-solute clearance during dialysis [3]. These measures capture selected aspects of kidney function and solute removal. The clinical question is whether direct solute measurement adds information that would change a decision [4].

Uremic retention solutes differ in source, binding, biological activity, and elimination. Indoxyl sulfate (IS) and p-cresyl sulfate (pCS) arise from microbial metabolism of dietary

substrates and host conjugation. Their concentrations reflect generation, tubular secretion, protein binding, and removal. Middle molecules such as β2-microglobulin have different clearance characteristics [5].

Pediatric studies have linked selected solutes to CKD progression, vascular phenotype, residual kidney function, and growth [6–10]. The timing of assessment matters: retention and vascular abnormalities can be observed before kidney failure, during periods of linear growth and neurodevelopment [6,10–12]. Children may also differ from adults in the distribution of kidney disease etiologies, the duration of exposure beginning early in life, and their dependence on adequate nutrition for growth [11,13,14]. A marker that captures kidney or vascular risk in adults may have a different role in children, where height velocity, acquisition of executive skills, and participation in school are important outcomes.

Existing reviews address cardiovascular associations, the gut–kidney axis, or emerging interventions [13,15,16]. This review examines what total and free solute measurements capture, how the same analytes have been studied in adults and children, and what evidence would justify their use in pediatric care. We focus on IS and pCS across non-dialysis CKD, dialysis, and transplantation and use β2-microglobulin as a prototype middle molecule. Particular attention is given to early risk assessment, linear growth, neurodevelopment, and nutritional safety.

2. Review Approach

This focused narrative review used iterative PubMed/MEDLINE searches from inception through 10 October 2026, before submission on 19 October 2026. Search concepts combined (child OR children OR pediatric OR adolescent), (chronic kidney disease OR dialysis OR kidney replacement therapy OR kidney transplantation), and (uremic toxins OR indoxyl sulfate OR p-cresyl sulfate OR protein-bound uremic toxins OR β2-microglobulin OR middle molecules). Focused searches added measurement, tubular secretion, protein binding, residual kidney function, progression, cardiovascular findings, growth, neurocognition, or interventions. Reference lists were checked. Embase, Scopus, and trial registries were not searched separately.

We prioritized pediatric CKD, dialysis, and transplant studies reporting relevant solute measurements, associations, or interventions, including healthy comparators and pediatric cohorts extending into young adulthood [17]. Adult and experimental reports provided comparative or mechanistic context. J.D. and A.P. collected and interpreted the literature, considering study design, population, analyte, fraction, assay, and sampling. We selected 10 pediatric reports for detailed tabulation, including two from the 4C study cohort. Iterative selection did not yield reliable screening counts; no PRISMA diagram, formal risk-of-bias assessment, or quantitative synthesis was undertaken. Targeted primary-source checks during revision supplemented the original search.

3. What Is Meant by Uremic Toxin Burden?

Uremic toxin burden encompasses solutes whose accumulation reflects reduced elimination, increased generation, or both. A retention solute is termed a toxin when evidence supports an adverse biological or biochemical effect. The evidence varies from experimental findings to clinical associations. An elevated concentration establishes retention; an association alone does not establish causality. This distinction matters in pediatric CKD, where evidence is predominantly observational [11,18–20].

Uremic solutes are commonly grouped into small water-soluble molecules, middle molecules, and protein-bound solutes. Removal also depends on distribution, native renal handling, and dialysis properties. Urea is readily accessible to diffusion-based dialysis; middle-molecule removal depends more on membrane permeability and convective trans-

port. Albumin binding limits the fraction of protein-bound solutes immediately available to cross a dialysis membrane, although dissociation replenishes the free pool. These categories explain handling rather than establish clinical importance [11,21,22]. Table 1 summarizes representative solutes.

Table 1. Representative uremic solutes: sources, handling, and evidence in children.

Class and Example (Origin; Binding)	Native Kidney Handling	Removal by Dialysis	Pediatric Measurements and Findings
Small water-soluble molecule: urea (hepatic nitrogen metabolism, unbound)	Filtered; partly reabsorbed	Readily removed by diffusion	Routinely measured for urea-based dialysis adequacy
Prototype middle molecule: β2M (host cell turnover, ~12 kDa)	Filtered, then taken up and catabolized by proximal tubular cells	Removal improves with high-flux membranes and HDF	Measured in CKD and dialysis; lower predialysis levels with HDF in one pediatric study
IS (microbial tryptophan metabolism and host oxidation and sulfation, albumin-bound)	Predominantly proximal tubular secretion	Free solute crosses the membrane. Protein binding limits overall removal.	Measured in CKD and dialysis; associated with progression in the 4C analysis
pCS (microbial tyrosine/phenylalanine fermentation and host sulfation, albumin-bound)	Predominantly proximal tubular secretion	Free solute crosses the membrane. Protein binding limits overall removal.	Measured in CKD and dialysis; no corresponding independent progression association in 4C

Sources: Rosner et al. [21]; Snauwaert et al. [8,11,17,20]; Holle et al. [7]. β2M, β2-microglobulin; CKD, chronic kidney disease; HDF, hemodiafiltration; HD, hemodialysis; IS, indoxyl sulfate; pCS, p-cresyl sulfate.

IS and pCS are representative gut-derived protein-bound solutes. Studies in pediatric cohorts have also measured indoleacetate, p-cresyl glucuronide, phenylacetylglutamine, and hippuric acid [8,11,20,23]. Their sources, binding, and clinical associations differ.

β2-microglobulin (β2M) is the noncovalently associated light-chain component of major histocompatibility complex class I (MHC I), released during cell-surface turnover. Filtration, uptake and catabolism by proximal tubular cells, and membrane-dependent dialysis removal distinguish its handling from that of IS and pCS [8,11,20,21].

Concentration is distinguished throughout from toxicity and from an actionable treatment target [24].

4. From Generation to Circulating Concentrations: Why eGFR Alone Is Insufficient

4.1. Generation: Diet, Microbial Metabolism, and Hepatic Processing

Urea arises from host nitrogen metabolism, and β2M is released during MHC I turnover [5,21]. IS and pCS generation involves dietary substrates, intestinal microbes, and host processing [25,26]. Microbial degradation of the aromatic amino acid tryptophan yields indole, which undergoes host oxidation and sulfation, principally in the liver, to form IS. Fermentation of tyrosine and phenylalanine yields p-cresol, which the host conjugates to pCS or p-cresyl glucuronide. Phenylacetylglutamine follows a separate route through microbial phenylacetate and host conjugation with glutamine [23–25,27]. Substrate availability influences microbial metabolism, but reported food intake alone cannot quantify production or exposure [18,28].

Pediatric observational findings link fiber intake with concentrations of selected solutes, although associations differ by metabolite and measured fraction [28,29]. These studies are discussed in Section 8.1. In adults, ex vivo bacterial generation did not ex-

plain stage-related differences in circulating protein-bound solutes [30]. A pediatric cross-sectional study of 126 participants across healthy control, CKD, hemodialysis, and transplant groups associated fecal genes involved in microbial trimethylamine production with plasma trimethylamine N-oxide (TMAO), after adjustment for eGFR and demographic variables [31]. Microbial gene abundance indicates metabolic potential, rather than a measured production rate.

4.2. Renal Elimination: Filtration and Tubular Secretion

Glomerular filtration of extensively protein-bound solutes is limited to the unbound component. Proximal tubular secretion also contributes, including blood-side uptake through organic anion transporters 1 and 3 (OAT1 and OAT3) and subsequent luminal transport [32]. Dissociation replenishes solute available for removal [33]. In a rat CKD model, probenecid reduced secretory clearance and altered circulating metabolite profiles without a detectable change in measured GFR [34]. Such experiments separate filtration from secretion but do not validate IS as a pediatric tubular-function test [35].

Pediatric findings support compound-specific relationships with kidney function. In 65 children with CKD, eGFR correlated more closely with β2M than with several protein-bound solutes [20]. In 150 Chronic Kidney Disease in Children (CKiD) participants, all five measured gut-derived metabolites were inversely associated with eGFR, while differences between glomerular and non-glomerular disease persisted after accounting for eGFR [23]. Such differences cannot isolate tubular dysfunction from changes in generation, binding, or treatment. A circulating concentration integrates these processes and is not a specific measure of secretory clearance.

4.3. Protein Binding: Total and Free Concentration

Total concentration includes bound and unbound solute; free concentration denotes the absolute unbound concentration. Albumin concentration, affinity, site occupancy, and competing ligands affect their relationship [36]. Similar total values can therefore coexist with different free concentrations. Adult studies document altered binding [37]. Ex vivo serum and modified-albumin experiments implicate oxidation, carbamylation, and guanidinylation; experimental guanidinylation reduced IS binding [38,39]. Their independent contribution in pediatric CKD remains undetermined.

Binding differs between children receiving HD, those with non-dialysis CKD, and healthy controls [8]. Reversible dissociation during removal [40] limits the use of a fixed binding percentage. Section 5.1 distinguishes concentration, free fraction, and percentage binding.

4.4. Growth and Puberty as Potential Modifiers

Age, growth, body composition, dietary requirements, and microbiome development are plausible modifiers of solute generation and handling [13]. In 102 healthy children, urinary IS/creatinine declined with age; these findings do not establish plasma reference values in pediatric CKD [41]. In children receiving hemodialysis, increasing age was associated with selected protein-bound solute concentrations and binding [8]. The mechanisms were unresolved and cannot be attributed specifically to microbiome or transporter maturation.

Longitudinal pediatric data identify eGFR as a contributor to concentration variability [9]. Pubertal sex steroids affect growth, lean mass, nutrient needs, and creatinine generation, potentially confounding relationships between solutes, creatinine-based eGFR, and height velocity [10,42]. Nobus et al. describe sex-dependent mechanisms involving microbial metabolism, hepatic processing, protein binding, and tubular transport, based mainly on adult and experimental evidence [43]. Their quantitative effects on IS/pCS

kinetics in children with CKD remain insufficiently characterized. Recording pubertal maturation alongside height velocity and kidney function can help separate developmental effects from solute associations.

5. Measurement and Interpretation of Uremic Solutes in Children

5.1. Total and Free Concentrations: Analytical Methods and Comparability

Analytical reports need to distinguish total concentration, free concentration, free fraction (free/total), and percentage protein binding [100 × (total − free)/total]. A higher free fraction need not indicate a higher absolute free concentration. When both concentrations are studied, separate measurements avoid fixed binding assumptions [8,11,37]; whether both are necessary for a future clinical test depends on comparative validation.

Snauwaert et al. used reversed-phase HPLC with fluorescence or photodiode-array detection for protein-bound solutes in 50 healthy children and 57 children with non-dialysis CKD; β2M was measured by immunoassay [11]. In the pediatric HD study, total concentrations were measured after protein denaturation and free concentrations in ultrafiltrate from untreated plasma, using reversed-phase UPLC with analyte-specific detection [8]. HPLC and UPLC use comparable chromatographic principles; platform names alone do not establish agreement. An earlier pediatric dialysis study used liquid chromatography with fluorescence detection [44].

Holle et al. measured total serum IS and pCS centrally by reversed-phase liquid chromatography with fluorescence detection in the Cardiovascular Comorbidity in Children with CKD (4C) cohort [7]. Targeted CKiD analyses used LC–MS/MS at the two-year visit [23]. Validated LC–MS/MS can quantify low concentrations, particularly free IS/pCS [45,46], while optical detection can suffice for total concentrations. Method agreement requires paired specimens across the relevant range, with fraction, matrix, calibration, and preparation matched.

When comparing results, attention should be paid to the units used; mass and molar concentrations are readily converted using the analyte's molecular mass. Total concentration, free concentration, and free fraction remain distinct. Matrix and ultrafiltration conditions, including temperature, can affect binding [47]. The cited pediatric studies provide no paired comparison establishing a systematic HPLC–UPLC difference [8,11]. Clinical decision limits additionally require outcome-based validation (Section 9.2).

5.2. Sampling Timing, Clinical Context, and Within-Patient Variability

Published pediatric HD samples were obtained midweek before dialysis; non-dialysis samples were collected at outpatient visits [8]. Healthy comparator samples were obtained around minor surgery, with anesthesia timing varying by age [11]. These are study conditions, not evidence of optimal sampling.

Sampling design depends on the question: predialysis concentration, sessional removal, and interdialytic exposure are different endpoints. Recording treatment timing, modality, and residual clearance permits these effects to be assessed. Consistent timing can reduce variation in longitudinal comparisons; serial sampling may be needed to characterize kinetics. No optimal pediatric schedule has been established.

In non-dialysis CKD, contemporaneous eGFR, albumin, intercurrent illness, and treatment changes help interpret longitudinal variation [11].

In 62 children with non-dialysis CKD, 403 observations over up to two years yielded within-patient coefficients of variation of 37–67% for protein-bound solutes; eGFR explained part of this variation [9]. These are cohort estimates, not assay-imprecision estimates or validated reference-change limits. They support evaluating repeated measurements, but do not determine visit frequency. Adult HD variability persists despite consistent sampling

and cannot be directly transferred to children [48]. Figure 1 summarizes determinants and interpretation of IS/pCS concentrations.

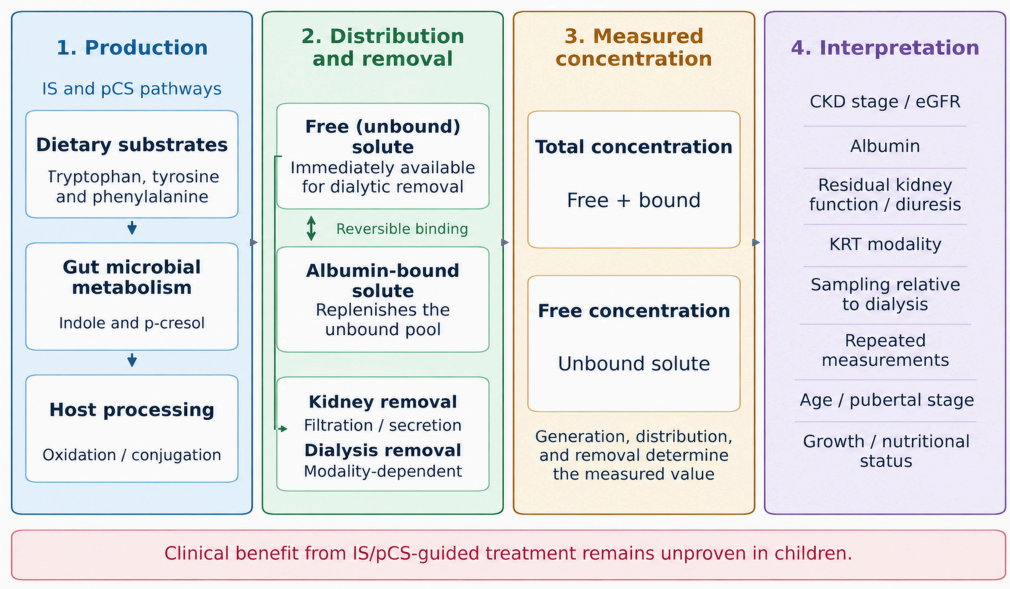


Figure 1. Generation, measurement, and interpretation of protein-bound uremic solutes. The diagram depicts IS and pCS pathways. Arrows indicate the connections between the depicted steps; the double-headed arrow denotes reversible binding to albumin. Panel colors distinguish the four labeled stages. Age, pubertal stage, growth, and nutritional status provide pediatric context for interpretation; their independent effects on solute kinetics remain uncertain. CKD, chronic kidney disease. eGFR, estimated glomerular filtration rate. IS, indoxyl sulfate. KRT, kidney replacement therapy. pCS, p-cresyl sulfate.

6. Pediatric Evidence Across CKD Stages and Dialysis Modalities

6.1. Non-Dialysis CKD

In 57 children with non-dialysis CKD and 50 healthy controls, total IS was already higher in the G1–G2 group. Total pCS and p-cresyl glucuronide were higher than controls in G4 and G5, while indoleacetate was higher in G3 and G5 [11]. These group differences in small stage subgroups establish early retention signals. The study did not assess whether those concentrations predict future complications. In 609 children in 4C (eGFR 10–60 mL/min/1.73 m^2), median total IS and pCS concentrations were 5.3 and 17.0 µmol/L, respectively [6].

In the related 4C analysis of 604 children (mean eGFR 27 ± 11 mL/min/1.73 m^2), log-transformed IS and pCS correlated inversely with eGFR ($r = -0.46$ and -0.43). Neither urinary protein/creatinine ratio nor albumin was independently associated with total IS in the baseline concentration model. pCS showed associations with age, albumin, residence, kidney disease category, and physical activity, among other variables [7]. Thus, similar relationships with eGFR do not imply identical determinants of IS and pCS. Outcome analyses from these overlapping 4C populations are considered in Sections 7.1 and 7.2.

6.2. Hemodialysis

Sampling within the dialysis cycle matters. In a multicenter study, midweek predialysis samples from 170 children on maintenance HD were compared with samples from 24 children with non-dialysis CKD stages 4–5. β2-microglobulin, p-cresyl glucuronide, hippuric acid, indole acetic acid, and IS were higher in the HD group; total pCS and 3-carboxy-4-

methyl-5-propyl-2-furanpropionic acid (CMPF) did not differ significantly. Differences in age and kidney diagnoses limit the cross-sectional comparison [8].

Of the 170 HD participants, 101 had residual urine output and 69 were anuric. Greater 24-h urine volume, indexed to body surface area, correlated inversely with β2-microglobulin, p-cresyl glucuronide, hippuric acid, indole acetic acid, IS, and CMPF (Spearman r approximately −0.2 to −0.5), but not with total pCS. Urine volume did not directly measure each solute's renal clearance, and clinical outcomes were not assessed [8]. In a separate 20-child HD study, midweek predialysis pseudouridine and urea nitrogen related differently to body size, illustrating that urea does not represent every solute's behavior [49]. Comparisons should identify the analyte, measured fraction, sampling interval, and residual diuresis.

6.3. Peritoneal Dialysis and Comparison with Hemodialysis

Direct pediatric modality comparisons are small. In one single-center study, 16 children completed follow-up (11 on peritoneal dialysis [PD], five on HD); baseline pCS was higher in the PD group. Both solutes were elevated in the combined dialysis group relative to 16 children evaluated for microscopic hematuria. Nonrandom treatment assignment and the small groups prevent an inference that HD removes pCS more effectively [44].

A four-center study compared 23 children receiving automated PD: ten with measurable residual kidney function and 13 without. Although total Kt/V for urea was similar, plasma levels of 256 screened solutes in the group with residual function averaged 64% of the levels in the group without it; 59 were significantly lower after multiple-testing adjustment. This was not uniform: quantitatively assayed pCS was not lower in the residual-function group. The investigators used untargeted mass spectrometry for screening and isotope-dilution LC–MS/MS for IS and pCS. Their exploratory comparison with stored HD samples without residual function found widely varying PD-to-HD ratios across solutes; unmatched groups and distinct sampling schedules prevent attribution to modality [50].

Comparisons of PD and HD should account for measured residual clearance or urine output and specify the timing of sampling relative to treatment. A review of six pediatric studies found no conclusive evidence that either modality provides superior toxin clearance or cardiovascular outcomes [15].

6.4. Hemodiafiltration

In a nonrandomized HDF, Heart and Height (3H) comparison over 12 months, 37 participants received post-dilution hemodiafiltration (HDF), 42 high-flux HD, and 18 low-flux HD; ages ranged from 5 to 20 years. Predialysis β2M decreased with HDF and was lower than in either HD group at 12 months. No additional reduction in total or free predialysis concentrations of six protein-bound solutes was detected [17]. The result separates middle-molecule from protein-bound-solute behavior; it does not establish equivalence between modalities.

6.5. Kidney Transplantation

Pediatric transplant data include cross-sectional comparisons with dialysis and longitudinal metabolomic profiling. In a cross-sectional study, IS and pCS concentrations were lower in ten transplant recipients than in children receiving hemodialysis (n = 8) or peritoneal dialysis (n = 8), and did not differ significantly from those of 13 healthy controls. However, these were different children rather than measurements before and after transplantation in the same patients. Reduced gut microbial diversity also persisted in the transplant group [51].

In a longitudinal study of 23 pediatric transplant recipients, LC–MS/MS profiled 140 plasma metabolites. Several retention signals decreased after transplantation, and

the overall semiquantitative profile moved toward that of healthy children [52]. Relative changes in a multimetabolite profile do not establish absolute IS or pCS concentrations or demonstrate a solute-mediated improvement in graft or cardiovascular outcomes.

7. Associations with Clinical Outcomes: What Is Known and What Remains Unproven

7.1. CKD Progression

In the 4C study, total baseline serum IS and pCS were measured in 604 children with eGFR 10–60 mL/min/1.73 m^2. The renal-survival endpoint comprised a 50% decrease in eGFR, eGFR below 10 mL/min/1.73 m^2, or initiation of kidney replacement therapy. Over a median 2.2 years, 360 children (59.6%) reached this composite [7]; renal survival therefore does not denote avoidance of replacement therapy alone.

Both solutes were associated with shorter renal survival in unadjusted quartile comparisons. After adjustment for demographic, clinical, and laboratory covariates, the highest versus lowest IS quartile had a hazard ratio of 1.62 (95% confidence interval 1.12–2.35). The pCS association did not persist. Continuous IS was significant in a sensitivity analysis excluding 45 children with unusually high concentrations, while the main continuous analysis did not reach statistical significance [7].

This exploratory analysis used a single total concentration at baseline [7]. Residual confounding remains possible. Variation in binding could produce different free-solute associations; paired measurements against the same clinical model would test this. Adult secretory-clearance data provide mechanistic context [53]. Pediatric trials have not established whether lowering IS alters CKD progression.

7.2. Cardiovascular Phenotype

In the 4C cohort, total serum IS and pCS were measured in 609 children and examined in relation to carotid intima–media thickness (cIMT), central pulse-wave velocity (PWV), and left ventricular mass index (LVMI). In multivariable analyses, higher IS was associated with a higher cIMT standard-deviation score at baseline and with an increase in PWV standard-deviation score over 12 months. Corresponding independent associations were not established for pCS. Although LVMI was measured, it was not among the positive adjusted IS findings reported in this analysis [6].

The cIMT finding was cross-sectional and the PWV finding longitudinal, but both concerned surrogate markers. Kidney function and blood pressure remain potential sources of confounding. In 20 dialysis patients, lower β2M/homocysteine reduction measures accompanied cardiovascular abnormalities; the small observational comparison limits inference about the effects of increasing removal [54].

In 150 CKiD participants, p-cresol glucuronide and phenylacetylglutamine were inversely associated with LVMI z score, with neither association extending to categorical left ventricular hypertrophy [23]. The glucuronide is much less protein-bound than pCS, and phenylacetylglutamine is largely unbound [11,27]. These findings cannot be generalized to strongly albumin-bound solutes or taken as evidence of protection.

Two pediatric studies examined TMAO pathway metabolites in early CKD in relation to ambulatory blood pressure and vascular measurements [55,56]. Associations varied by metabolite and specimen type. Urine measurements characterize the urinary metabolite profile under the reported collection conditions. Plasma measurements address circulating exposure. Neither study established cardiovascular event prediction.

Adult results also vary: free pCS was associated with cardiovascular outcomes in CHOICE [57], whereas HEMO found no corresponding overall association for total IS or pCS [58]. Different cohorts and fractions prevent a direct comparison of predictive

performance. Neither result establishes the superiority of free pCS in children or excludes a free-fraction association when total pCS is unassociated.

7.3. Linear Growth

Linear growth is a pediatric outcome with a finite developmental window. In a prospective study of 81 children with CKD G1–G5D and 560 visits, a 10% higher concurrent total IS concentration was associated with a 0.002 SDS/year lower estimated height velocity in children aged 2–12 years, after adjustment for CKD stage, growth-hormone treatment, bicarbonate, and dietary protein intake [10]. The model estimate was small and its clinical significance is uncertain. No statistically significant association was identified in the pubertal age group. Unequal precision across age groups and variation in pubertal timing preclude concluding that the association differs by developmental stage without a direct test of interaction.

Growth-hormone resistance and altered insulin-like growth factor 1 signaling are established components of growth impairment in pediatric CKD [42]. Inflammation could connect solute retention to impaired growth-plate activity, but the available study did not establish this pathway or show that IS exposure preceded slowing of height velocity [10]. Acidosis, nutrition, CKD progression, treatment, and timing of the pubertal growth spurt can influence both exposure and outcome. Adult associations with vascular disease or survival do not test the growth-plate hypothesis.

The reported growth signal concerns total IS [10]. Whether free IS adds information requires paired measurements linked to height velocity and pubertal maturation. Any IS-lowering intervention would need to improve growth while preserving energy and protein intake.

7.4. Neurocognition and Other Outcomes

In a targeted analysis of 150 children in CKiD, the five measured gut-derived solutes, including IS and pCS, were inversely associated with eGFR. The investigators found no statistically significant association between the measured concentrations of these five solutes and the neurocognitive test scores analyzed [23]. The study did not assess whether paired measurements of free IS or pCS would improve prediction.

An untargeted study of 569 CKiD participants and 60 participants with CKD in the separate NiCK cohort identified signals involving phenylacetylglutamine, indoleacetylglutamine, and TMAO for parent-rated executive function [12]. Differences in analytes, samples, outcome instruments, and covariate adjustment limit direct comparison. The two reports share the CKiD source population. Separate CKiD metabolomics analyses also show variation with eGFR and proteinuria [59].

Pediatric neurodevelopment concerns skill acquisition, whereas adult screening often addresses impairment of acquired skills. An adult phenylacetylglutamine association [60] cannot establish a developmental effect. Inflammation and altered metabolism are plausible contributors [12,61]. Repeated age-standardized assessments could test temporality while accounting for CKD duration, blood pressure, anemia, and educational context.

In a study of 48 children across healthy control, CKD G3–G4, hemodialysis, and transplant groups, microbiome and tryptophan-metabolite differences accompanied inflammatory and immune-cell abnormalities. Complementary cell experiments supported biological plausibility, while the clinical comparisons could not assign inflammation to an individual solute [61]. Table 2 summarizes selected pediatric studies, their measurement conditions, and limitations.

Table 2. Selected pediatric studies measuring uremic solutes across CKD and dialysis settings.

Study and Population	Solutes	Assay and Sampling	Principal Finding	Main Limitation
Snauwaert et al. [11], UToPaed. 50 controls and 57 children with CKD G1–G5	Selected small, middle, and protein-bound solutes	HPLC for protein-bound solutes; immunoassays for β2M; single samples	Retention patterns differed by solute and CKD stage	Cross-sectional design; small stage subgroups
Holle et al. [6,7]; 4C, 609/604 participants	Total IS and pCS	Total serum IS and pCS at baseline, measured centrally by reversed-phase LC with fluorescence detection	IS associated with selected vascular markers and the composite kidney endpoint; corresponding adjusted pCS findings were absent	Overlapping cohort; observational analyses; vascular surrogate markers
Snauwaert et al. [8]; 3H/UToPaed, 170 receiving HD	β2M and protein-bound solutes	Chromatography and β2M immunoassay; midweek predialysis	Residual urine volume correlated inversely with several solutes, but not total pCS	Cross-sectional; urine volume does not measure solute clearance
Snauwaert et al. [17]; 3H, 97 receiving HDF/HD	β2M and six protein-bound solutes	Chromatography and β2M immunoassay; midweek predialysis at baseline and 12 months	Lower β2M with HDF; no additional reduction in total or free protein-bound solutes	Treatment assignment was not randomized; biochemical endpoints
Ganesan et al. [50]; 23 children receiving PD	Metabolomic panel; targeted IS and pCS	LC–MS screening and targeted LC–MS/MS; plasma, dialysate, and timed urine	Residual kidney function associated with lower levels of many solutes, with exceptions including pCS	Small, cross-sectional groups
Snauwaert et al. [9]; UToPaed, 62 with CKD	Panel including protein-bound solutes	Repeated measurements over up to two years	Within-patient variability of protein-bound solutes was 37–67%	Longitudinal clinical variation; not a validated reference-change limit
Snauwaert et al. [10]; UToPaed, 81 with CKD G1–G5D	Selected solutes, including total IS	Serial blood samples approximately every three months	Higher IS associated with lower height velocity at ages 2–12 years	Observational association; limited age-group samples.
Ebrahimi et al. [23]; 150 CKiD participants	Five gut-derived metabolites	UHPLC–MS/MS; two-year study visit	Inverse associations with eGFR. No statistically significant association with the neurocognitive scores assessed.	Single-visit metabolite analysis; limited outcome scope
Lee et al. [12]; 569 CKiD participants and 60 with CKD in NiCK	Untargeted metabolomics: plasma in CKiD and serum in NiCK	Untargeted metabolomics in plasma (CKiD) and serum (NiCK). Neurocognitive assessments.	Selected metabolites associated with parent-rated executive function; findings differed by model and cohort	Observational analyses with multiple comparisons. CKiD source population shared with targeted analysis.

Abbreviations: β2M, β2-microglobulin. CKD, chronic kidney disease. HD, hemodialysis. HDF, hemodiafiltration. IS, indoxyl sulfate. pCS, p-cresyl sulfate. PD, peritoneal dialysis. HPLC, high-performance liquid chromatography. LC–MS, liquid chromatography–mass spectrometry. LC–MS/MS, liquid chromatography–tandem mass spectrometry.

Table 3 places laboratory and outcome findings for the same solutes side by side across kidney function and treatment settings. Table 4 identifies publications that draw on related populations.

Table 3. Adult and pediatric evidence on the same uremic solutes.

Setting or Outcome	Evidence in Children	Evidence in Adults	Interpretation for Pediatric Research
Healthy comparators	Total IS 0.056 ± 0.025 mg/dL, total pCS 0.244 ± 0.179 mg/dL, and β2M 1.74 ± 0.34 µg/mL (n = 50) [11].	Published comparator values summarized in the same report: total IS 0.053 ± 0.029 mg/dL, total pCS 0.190 ± 0.130 mg/dL, and β2M 1.90 ± 1.60 µg/mL [11].	Descriptive means ± SD from separate sources. These values cannot establish age effects or transferable reference intervals.
Non-dialysis CKD	IS and β2M were elevated in G1–G2 and pCS in G4–G5 versus pediatric controls [11]. Across G1–G2, G3, G4, and G5, median z scores were 1.9, 2.4, 17.8, 32.2 (IS) and 0.7, 2.1, 7.5, 7.8 (pCS) [11]. In 4C (eGFR 10–60), median total IS and pCS were 5.3 and 17.0 µmol/L [6].	In adults with G2, G3, G4, and G5 CKD, median total concentrations were 0.16, 0.23, 0.36, 0.79 mg/dL (IS) and 0.47, 0.95, 1.19, 3.29 mg/dL (pCS), respectively [37]. Adult IS also related inversely to eGFR in a separate non-dialysis subgroup [62].	Compare the same fraction and assay within eGFR strata and account for etiology, albumin, and maturation. No age effect can be isolated from these cohorts.
Maintenance dialysis	At 12 months in 3H, the high-flux HD group (n = 42) had median predialysis total IS and pCS of 2.06 and 2.18 mg/dL, respectively. Post-HDF lowered β2M without a detectable additional reduction in IS or pCS [17].	In one adult HD group, median predialysis total IS and pCS were 1.40 and 2.06 mg/dL, respectively [37]. In adult dialysis, low residual kidney function contributes to solute removal [63].	Compare the same time point, modality, fraction, and residual kidney function. Sessional removal and sustained exposure are separate endpoints.
Kidney and vascular outcomes	Higher total IS was associated with CKD progression and selected cIMT/PWV measures in 4C. Corresponding adjusted pCS associations were not established [6,7].	Adult reports linked IS to vascular disease or mortality and free pCS to cardiovascular outcomes. HEMO did not detect overall associations for total IS or pCS [57,58,62].	Pediatric vascular measures are surrogate outcomes. An analyte, fraction, and endpoint must be matched before attributing differences to age.
Growth and cognition	Total IS was associated with slightly slower height velocity at ages 2–12 years [10]. Targeted IS/pCS and broader metabolomic analyses address different neurocognitive questions [12,23].	Adult phenylacetylglutamine data address cognitive impairment [60]. Linear growth and acquisition of executive skills are childhood endpoints.	Follow age-standardized trajectories and test modification by maturation. Adult cognitive impairment cannot establish a developmental effect.

Adult and pediatric estimates are descriptive comparisons across studies. eGFR is expressed in mL/min/1.73 m^2. SD, standard deviation. cIMT, carotid intima–media thickness. PWV, pulse-wave velocity.

Table 4. Related study populations in the pediatric evidence.

Source Population	Related Reports and Sample Sizes	Overlap and Implication
4C	Holle [6] (609, vascular phenotype) and Holle [7] (604, progression). Bartels [64] used 4C to develop a different biomarker model and ESCAPE for external validation.	The IS/pCS reports use the same parent cohort. The exact intersection of the 609 and 604 is unavailable here. Kidney and vascular associations are related findings.
CKiD and NiCK	Ebrahimi [23] (150, targeted). Lee [12] (569 CKiD and 60 NiCK participants with CKD, untargeted). Lee [59] (longitudinal CKiD metabolomics).	Exact participant overlap among CKiD analyses is unavailable here. NiCK is a separate cohort and used a different specimen matrix. Interpret replication by matching analyte, cognitive domain, and model.
3H	Snauwaert [8] (170 HD, mixed 3H/UToPaed). Snauwaert [17] (97, biochemical comparison). Shroff [65] (190 enrolled, clinical HDF/HD study).	The biochemical analysis included 97 of the 133 children who completed one year in 3H [17,65]. The related reports do not provide independent replication or establish mediation. The exact intersection with the mixed HD sample is unreported.
UToPaed and related pediatric studies	Snauwaert [11] (57 CKD and 50 controls), [9] (62, variability), [10] (81, growth), and El Amouri [28] (61, fiber). Snauwaert [8] draws from UToPaed and 3H.	The 50 healthy comparators reported in [11] were reused in [8]. The exact overlap of CKD, growth, fiber, and variability samples is unavailable here. Treat the UToPaed analyses as related evidence.

Numbers refer to the reported analysis or study population. Overlap refers to shared participants when explicitly reported and otherwise to a shared source population. Reported sample sizes cannot be added to estimate independent participants.

8. Interventions to Reduce Production or Enhance Removal of Uremic Solutes

8.1. Diet and Dietary Fiber

Pediatric dietary evidence remains observational. In a two-year study of 61 children with CKD, each additional reported gram of daily fiber was associated with approximately 3.1% lower free IS and 2.5% lower free pCS [28]. No prescribed increase was tested; kidney function, food choices, and other confounders may contribute. An adult resistant-starch trial reduced free IS but does not establish pediatric efficacy [66].

Low fiber intake is reported in pediatric CKD [29]; Pediatric Renal Nutrition Taskforce recommendations acknowledge limited CKD-specific evidence [67]. Solute-directed dietary trials must preserve energy, protein, and micronutrient adequacy [14]. Lower concentrations alone do not justify compromising growth.

8.2. Probiotics and Microbiome-Directed Approaches

In an uncontrolled 12-week VSL#3 probiotic study, 16 of 20 children receiving chronic dialysis completed treatment: 11 on PD and five on HD. Neither IS nor pCS decreased significantly [44].

The small sample, uncontrolled design, and short follow-up preclude comparative efficacy claims. Future trials need defined preparations and doses, adherence and tolerability assessment, and clinical outcomes alongside concentrations.

8.3. Dialysis Prescription and Solute Removal

For protein-bound solutes, sessional removal need not reduce sustained exposure: dissociation, redistribution, and continued production affect subsequent concentrations [40]. Reduction ratios, dialysate recovery, and later predialysis values answer different questions [68]. Interpretation therefore depends on timing, fraction, dialysis prescription, and residual kidney function.

The post-HDF comparison found divergent β2M and protein-bound-solute responses at 12 months [17]. Favorable clinical associations in related 3H reports cannot be attributed to IS/pCS lowering without evidence of mediation [65].

In a randomized crossover trial with two four-week periods and 21 completers, prefilter HDF achieved higher total IS/pCS reduction ratios than post-filter HDF. Diastolic blood pressure was also higher and related to replacement volume and postdialysis sodium [69]. This sessional endpoint differs from sustained predialysis concentration. Longer or more frequent treatments may alter removal, but an optimal pediatric prescription for sustained IS/pCS reduction remains undefined [70].

8.4. Preservation of Residual Kidney Function

Adult data associate even very low residual kidney function with lower concentrations of selected solutes [63]. Pediatric HD and PD findings are likewise solute-specific [8,50]. These observations support assessing native clearance, but do not estimate the effect of an intervention preserving it.

In 401 children starting PD, kidney disease and higher ultrafiltration requirements were associated with loss of residual diuresis [71]. A single-center study associated greater glucose exposure and ultrafiltration with loss of residual function and diuretic use with preservation [72]. Pediatric PD guidance supports attention to volume management and serial urine measurements [73]. These data do not establish that prescription changes or diuretics improve outcomes through IS/pCS lowering.

8.5. Combined Strategies and Research Priorities

Combined interventions could address intestinal generation, residual kidney clearance, and dialytic removal in children with CKD. In adults, the SYNERGY synbiotic trial lowered pCS but did not meet its primary IS endpoint [74]. Pediatric benefit and tolerability require direct testing, including nutritional and treatment burden [3].

Table 5 separates treatment comparisons from observational associations and reports biochemical and clinical findings separately.

Table 5. Pediatric evidence on approaches that may alter uremic solute exposure.

Approach	Pediatric Evidence	Biochemical Change	Clinical Outcomes	Main Qualification
Intervention: VSL#3 probiotic	Hyun et al. [44]; 16 children completed 12 weeks; uncontrolled study	No significant reduction in IS or pCS	No clinical efficacy established in this uncontrolled study	Small sample; no concurrent placebo group
Treatment comparison: post-HDF versus HD	Snauwaert et al. [17]; 3H, nonrandomized; 97 participants, 12 months	Lower predialysis β2M with HDF; no additional reduction in total or free protein-bound solutes	Clinical efficacy not evaluated in this solute analysis	β2M and protein-bound solutes behaved differently

Table 5. *Cont.*

Approach	Pediatric Evidence	Biochemical Change	Clinical Outcomes	Main Qualification
Intervention comparison: pre-HDF versus post-HDF	Agbas et al. [69]; randomized crossover; 21 completers	Greater sessional reduction ratios for total IS and pCS with pre-HDF; lower predialysis β2M	Long-term benefit unproven; diastolic blood pressure was higher with pre-HDF	Short treatment periods; blood pressure and sodium exposure matter
Observed treatment groups: HDF versus HD	Shroff et al. [65]; prospective, nonrandomized 3H study	The clinical findings were not linked to a measured change in IS or pCS	Favorable growth, vascular, and symptom associations; mediation by IS/pCS untested	Nonrandom allocation; shared 3H origin with solute analysis
Observational association: dietary fiber	El Amouri et al. [28]; UToPaed, 61 children with CKD	Higher intake associated with lower free IS and pCS; no prescribed increase was tested	Clinical effect of increasing fiber was not assessed	Any dietary strategy must preserve growth and nutritional adequacy
Observational association: residual kidney function	Snauwaert et al. [8]; HD, and Ganesan et al. [50]; PD	Residual function associated with lower concentrations of several, but not all, solutes	Clinical effect of a preservation intervention was not assessed	Urine volume does not directly measure each solute's clearance

See Table 4 for related cohorts. β2M, β2-microglobulin. CKD, chronic kidney disease. HD, hemodialysis. HDF, hemodiafiltration. IS, indoxyl sulfate. pCS, p-cresyl sulfate. PD, peritoneal dialysis.

9. Clinical Utility and Conditions for Implementation

9.1. Current Clinical Role

Early markers could identify risk while an effective intervention can still alter outcomes. Pediatric studies detect retention and vascular abnormalities before kidney failure [6,11,55,56], supporting prospective evaluation in non-dialysis CKD. The larger adult evidence base likewise does not establish routine IS/pCS-guided care or causal effects on major outcomes [1,5,57,58,62]. No current pediatric solute result defines an indication for dietary restriction, microbiome therapy, or a dialysis change.

The exploratory 4C analysis assessed model fit [7]. Future prediction studies need a clinically relevant outcome and horizon, selected before analysis, and comparison with established predictors such as eGFR, proteinuria, blood pressure, and etiology [2,75]. Growth and vascular outcomes require separate, age-appropriate definitions.

9.2. Requirements for Clinical Adoption

Clinical adoption requires a defined analyte, matrix, fraction, units, sampling conditions, and acceptable measurement error. Individual LC–MS/MS validations [45,46] do not establish interlaboratory agreement. Shared thresholds additionally require harmonized calibration, external quality assessment, and reproducible free-fraction handling.

Reference intervals describe a reference population; decision limits identify when an action is expected to help. Age-specific distributions [11,76], cohort quartiles [7], and variability estimates [9] can inform study design but do not establish decision limits. Initial models can assess continuous concentrations, nonlinearity, and absolute risk.

A candidate threshold needs a specified decision, outcome, and horizon. For research, a validated risk model might trigger earlier structured assessment of blood pressure, growth, and nutrition. Derivation requires calibration and comparison with a model excluding

the solute [64,77]; threshold selection also considers missed cases, false positives, extra visits, and family burden. Any concentration cut-off requires comparison with continuous modeling. Independent validation and net-benefit assessment [78] would precede an impact trial comparing marker-informed with guideline-based care. Until clinical benefit is demonstrated, no solute threshold defines a treatment change. Figure 2 summarizes these evidence gaps.

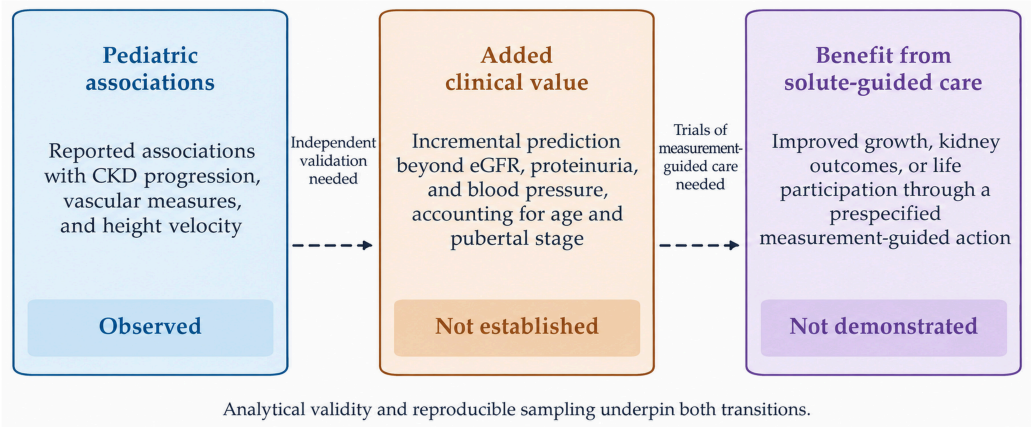


Figure 2. Evidence required for clinical use of emerging solute measurements in pediatric CKD. Reported associations are distinguished from unproven incremental predictive value and benefit from measurement-guided care. Dashed arrows indicate evidence required for each transition. CKD, chronic kidney disease. eGFR, estimated glomerular filtration rate.

10. Research Priorities

For early-risk prediction, recruit independent cohorts of children with CKD who have not initiated maintenance dialysis, including different diagnoses and stages of maturation. This refers to non-dialysis CKD, not sampling immediately before a dialysis session. Define the intended outcome and clinical decision first; select analytes, fractions, timing, and repeat frequency to test that question rather than reproduce existing protocols. Paired total/free measurements can test added value. Pubertal stage, height velocity, nutrition, albumin, and kidney function inform interpretation; dialysis-specific studies additionally need treatment timing and residual-clearance data [9].

Validate candidate markers against standard predictors for defined outcomes. The 4C IS signal requires independent replication and the differing pCS result supports analyte-specific hypotheses [7]. Section 9.2 outlines prediction and clinical-utility assessment.

Young people and caregivers prioritize fatigue, activity, daily restrictions, and growth [79]. Impaired growth affects self-esteem and participation [80]; SONG-Kids supports age-appropriate assessment of life participation [81,82]. These priorities can inform endpoints without implying a proven solute-specific effect.

Trials need a prespecified action and expected benefit, with assessment of inadequate intake, impaired growth, gastrointestinal symptoms, and treatment burden alongside biochemical and child-relevant outcomes [79–82].

11. Limitations of This Review

This focused narrative review used one bibliographic database and reference-list screening, with targeted primary-source checks during revision. It may have missed reports indexed elsewhere, unpublished studies, and registry records. Purposive selection and the absence of formal risk-of-bias appraisal may affect the synthesis. Differences in assays, sampling, kidney disease, and endpoints limit cross-study comparisons. Shared cohort

sources reduce the number of independent evidence streams (Table 4). Small samples and limited developmental measurements constrain inferences about growth, puberty, and neurocognition.

12. Conclusions

Selected solutes accumulate before kidney failure in children with CKD. Pediatric studies report associations with progression, vascular measures, and growth, with differing results across analytes and outcomes. The immediate priority is independent validation of repeated measurements for defined outcomes during childhood, including whether free concentrations add information to total concentrations and established clinical measures. IS- or pCS-guided treatment requires evidence that a specified action improves outcomes meaningful to children.

Author Contributions: Conceptualization, J.D.; literature collection and analysis, J.D. and A.P.; writing—original draft preparation, J.D.; writing—review and editing, M.F. and A.P.; visualization, J.D.; supervision, J.D. and A.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: The authors gratefully acknowledge all the researchers whose published work contributed to the conceptualization and development of this paper.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

3H	Hemodiafiltration, Heart and Height study
4C	Cardiovascular Comorbidity in Children with Chronic Kidney Disease study
AI	Artificial intelligence
β2M	β2-Microglobulin
CHOICE	Choices for Healthy Outcomes in Caring for End-Stage Renal Disease study
cIMT	Carotid intima–media thickness
CKD	Chronic kidney disease
CMPF	3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid
CKiD	Chronic Kidney Disease in Children study
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
HD	Hemodialysis
HDF	Hemodiafiltration
HEMO	Hemodialysis Study
HPLC	High-performance liquid chromatography
IS	Indoxyl sulfate
KDIGO	Kidney Disease: Improving Global Outcomes
KRT	Kidney replacement therapy
Kt/V	Urea clearance (K) × treatment time (t)/urea distribution volume (V)
LC–MS	Liquid chromatography–mass spectrometry
LC–MS/MS	Liquid chromatography–tandem mass spectrometry
LVMI	Left ventricular mass index
NiCK	Neurocognitive Assessment and Magnetic Resonance Imaging Analysis of Children and Young Adults with Chronic Kidney Disease study

OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
pCS	p-Cresyl sulfate
PD	Peritoneal dialysis
PWV	Pulse-wave velocity
SONG-Kids	Standardized Outcomes in Nephrology—Children and Adolescents
TMAO	Trimethylamine N-oxide
UHPLC–MS/MS	Ultra-high-performance liquid chromatography–tandem mass spectrometry
UPLC	Ultra-performance liquid chromatography
UToPaed	Uremic Toxins in Paediatrics

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.* **2024**, *105*, S117–S314. [CrossRef] [PubMed]
2. Furth, S.L.; Pierce, C.; Hui, W.F.; White, C.A.; Wong, C.S.; Schaefer, F.; Wühl, E.; Abraham, A.G.; Warady, B.A.; on behalf of the CKiD and ESCAPE Study Investigators. Estimating time to ESRD in children with CKD. *Am. J. Kidney Dis.* **2018**, *71*, 783–792. [CrossRef] [PubMed]
3. Paglialonga, F.; Patel, H.P. Adequacy of dialysis in children and adolescents: More than just Kt/V. *Pediatr. Nephrol.* **2026**. [CrossRef] [PubMed]
4. Sirich, T.L.; Funk, B.A.; Plummer, N.S.; Hostetter, T.H.; Meyer, T.W. Prominent accumulation in hemodialysis patients of solutes normally cleared by tubular secretion. *J. Am. Soc. Nephrol.* **2014**, *25*, 615–622. [CrossRef] [PubMed]
5. Glorieux, G.; Burtey, S.; Evenepoel, P.; Jankowski, J.; Koppe, L.; Masereeuw, R.; Vanholder, R. A guide to uraemic toxicity. *Nat. Rev. Nephrol.* **2026**, *22*, 50–68. [CrossRef] [PubMed]
6. Holle, J.; Querfeld, U.; Kirchner, M.; Anninos, A.; Okun, J.; Thurn-Valsassina, D.; Bayazit, A.; Niemirska, A.; Canpolat, N.; Bulut, I.K.; et al. Indoxyl sulfate associates with cardiovascular phenotype in children with chronic kidney disease. *Pediatr. Nephrol.* **2019**, *34*, 2571–2582. [CrossRef] [PubMed]
7. Holle, J.; Kirchner, M.; Okun, J.; Bayazit, A.K.; Obrycki, L.; Canpolat, N.; Bulut, I.K.; Azukaitis, K.; Duzova, A.; Ranchin, B.; et al. Serum indoxyl sulfate concentrations associate with progression of chronic kidney disease in children. *PLoS ONE* **2020**, *15*, e0240446. [CrossRef] [PubMed]
8. Snauwaert, E.; Holvoet, E.; Van Biesen, W.; Raes, A.; Glorieux, G.; Vande Walle, J.; Roels, S.; Vanholder, R.; Askiti, V.; Azukaitis, K.; et al. Uremic toxin concentrations are related to residual kidney function in the pediatric hemodialysis population. *Toxins* **2019**, *11*, 235. [CrossRef] [PubMed]
9. Snauwaert, E.; De Buyser, S.; Desloovere, A.; Van Biesen, W.; Raes, A.; Glorieux, G.; Collard, L.; Van Hoeck, K.; Van Dyck, M.; Godefroid, N.; et al. Assessment of within- and inter-patient variability of uremic toxin concentrations in children with CKD. *Toxins* **2024**, *16*, 349. [CrossRef] [PubMed]
10. Snauwaert, E.; De Buyser, S.; Van Biesen, W.; Raes, A.; Glorieux, G.; Collard, L.; Van Hoeck, K.; Van Dyck, M.; Godefroid, N.; Vande Walle, J.; et al. Indoxyl sulfate contributes to impaired height velocity in (pre)school children. *Kidney Int. Rep.* **2024**, *9*, 1674–1683. [CrossRef] [PubMed]
11. Snauwaert, E.; Van Biesen, W.; Raes, A.; Glorieux, G.; Van Bogaert, V.; Van Hoeck, K.; Coppens, M.; Roels, S.; Vande Walle, J.; Eloot, S. Concentrations of representative uraemic toxins in a healthy versus non-dialysis chronic kidney disease paediatric population. *Nephrol. Dial. Transplant.* **2018**, *33*, 978–986. [CrossRef] [PubMed]
12. Lee, A.M.; Xu, Y.; Hooper, S.R.; Abraham, A.G.; Hu, J.; Xiao, R.; Matheson, M.B.; Brunson, C.; Rhee, E.P.; Coresh, J.; et al. Circulating metabolomic associations with neurocognitive outcomes in pediatric CKD. *Clin. J. Am. Soc. Nephrol.* **2024**, *19*, 13–25. [CrossRef] [PubMed]
13. Holle, J.; Behrens, F.; Koppe, L. Pediatric and adult point of view on the gut-kidney axis in CKD. *Pediatr. Nephrol.* **2026**, *41*, 633–648. [CrossRef] [PubMed]
14. Shaw, V.; Polderman, N.; Renken-Terhaerdt, J.; Paglialonga, F.; Oosterveld, M.; Tuokkola, J.; Anderson, C.; Desloovere, A.; Greenbaum, L.; Haffner, D.; et al. Energy and protein requirements for children with CKD stages 2–5 and on dialysis: Clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *Pediatr. Nephrol.* **2020**, *35*, 519–531. [CrossRef] [PubMed]
15. Dalpathadu, H.; Salim, A.M.; Wade, A.; Greenway, S.C. A systematic review of uremic toxin concentrations and cardiovascular risk markers in pediatric chronic kidney disease. *Toxins* **2024**, *16*, 345. [CrossRef] [PubMed]
16. da Cunha, R.S.; Gregório, P.C.; Morais, A.C.C.; Barreto, F.C.; Stinghen, A.E.M. Targeting uremic toxins in chronic kidney disease: Current challenges and emerging therapeutic strategies. *Toxins* **2026**, *18*, 311. [CrossRef] [PubMed]

17. Snauwaert, E.; Van Biesen, W.; Raes, A.; Glorieux, G.; Vande Walle, J.; Roels, S.; Vanholder, R.; Askiti, V.; Azukaitis, K.; Bayazit, A.; et al. Haemodiafiltration does not lower protein-bound uraemic toxin levels compared with haemodialysis in a paediatric population. *Nephrol. Dial. Transplant.* **2020**, *35*, 648–656. [CrossRef] [PubMed]
18. Vanholder, R.; Pletinck, A.; Schepers, E.; Glorieux, G. Biochemical and clinical impact of organic uremic retention solutes: A comprehensive update. *Toxins* **2018**, *10*, 33. [CrossRef] [PubMed]
19. Vanholder, R.; Nigam, S.K.; Burtey, S.; Glorieux, G. What if not all metabolites from the uremic toxin generating pathways are toxic? A hypothesis. *Toxins* **2022**, *14*, 221. [CrossRef] [PubMed]
20. Snauwaert, E.; Van Biesen, W.; Raes, A.; Holvoet, E.; Glorieux, G.; Van Hoeck, K.; Van Dyck, M.; Godefroid, N.; Vanholder, R.; Roels, S.; et al. Accumulation of uraemic toxins is reflected only partially by estimated GFR in paediatric patients with chronic kidney disease. *Pediatr. Nephrol.* **2018**, *33*, 315–323. [CrossRef] [PubMed]
21. Rosner, M.H.; Reis, T.; Husain-Syed, F.; Vanholder, R.; Hutchison, C.; Stenvinkel, P.; Blankestijn, P.J.; Cozzolino, M.; Juillard, L.; Kashani, K.; et al. Classification of uremic toxins and their role in kidney failure. *Clin. J. Am. Soc. Nephrol.* **2021**, *16*, 1918–1928. [CrossRef] [PubMed]
22. Martinez, A.W.; Recht, N.S.; Hostetter, T.H.; Meyer, T.W. Removal of p-cresol sulfate by hemodialysis. *J. Am. Soc. Nephrol.* **2005**, *16*, 3430–3436. [CrossRef] [PubMed]
23. Ebrahimi, M.; Hooper, S.R.; Mitsnefes, M.M.; Vasan, R.S.; Kimmel, P.L.; Warady, B.A.; Furth, S.L.; Hartung, E.A.; Denburg, M.R.; Lee, A.M. Investigation of a targeted panel of gut microbiome-derived toxins in children with chronic kidney disease. *Pediatr. Nephrol.* **2025**, *40*, 1759–1770. [CrossRef] [PubMed]
24. Mair, R.D.; Sirich, T.L.; Plummer, N.S.; Meyer, T.W. Characteristics of colon-derived uremic solutes. *Clin. J. Am. Soc. Nephrol.* **2018**, *13*, 1398–1404. [CrossRef] [PubMed]
25. Aronov, P.A.; Luo, F.J.; Plummer, N.S.; Quan, Z.; Holmes, S.; Hostetter, T.H.; Meyer, T.W. Colonic contribution to uremic solutes. *J. Am. Soc. Nephrol.* **2011**, *22*, 1769–1776. [CrossRef] [PubMed]
26. Patel, K.P.; Luo, F.J.; Plummer, N.S.; Hostetter, T.H.; Meyer, T.W. The production of p-cresol sulfate and indoxyl sulfate in vegetarians versus omnivores. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 982–988. [CrossRef] [PubMed]
27. Poesen, R.; Claes, K.; Evenepoel, P.; de Loor, H.; Augustijns, P.; Kuypers, D.; Meijers, B. Microbiota-derived phenylacetylglutamine associates with overall mortality and cardiovascular disease in patients with CKD. *J. Am. Soc. Nephrol.* **2016**, *27*, 3479–3487. [CrossRef] [PubMed]
28. El Amouri, A.; Snauwaert, E.; Foulon, A.; Vande Moortel, C.; Van Dyck, M.; Van Hoeck, K.; Godefroid, N.; Glorieux, G.; Van Biesen, W.; Vande Walle, J.; et al. Dietary fibre intake is associated with serum levels of uraemic toxins in children with chronic kidney disease. *Toxins* **2021**, *13*, 225. [CrossRef] [PubMed]
29. El Amouri, A.; Snauwaert, E.; Foulon, A.; Vande Moortel, C.; Van Dyck, M.; Van Hoeck, K.; Godefroid, N.; Glorieux, G.; Van Biesen, W.; Vande Walle, J.; et al. Dietary fibre intake is low in paediatric chronic kidney disease patients but its impact on levels of gut-derived uraemic toxins remains uncertain. *Pediatr. Nephrol.* **2021**, *36*, 1589–1595. [CrossRef] [PubMed]
30. Gryp, T.; De Paepe, K.; Vanholder, R.; Kerckhof, F.-M.; Van Biesen, W.; Van de Wiele, T.; Verbeke, F.; Speeckaert, M.; Joossens, M.; Couttenye, M.M.; et al. Gut microbiota generation of protein-bound uremic toxins and related metabolites is not altered at different stages of chronic kidney disease. *Kidney Int.* **2020**, *97*, 1230–1242. [CrossRef] [PubMed]
31. Holle, J.; McParland, V.; Anandakumar, H.; Gerritzmann, F.; Behrens, F.; Schumacher, F.; Thumfart, J.; Eckardt, K.-U.; Kleuser, B.; Bartolomaeus, H.; et al. Gut dysbiosis contributes to TMAO accumulation in CKD. *Nephrol. Dial. Transplant.* **2024**, *39*, 1923–1926. [CrossRef] [PubMed]
32. Suchy-Dicey, A.M.; Laha, T.; Hoofnagle, A.; Newitt, R.; Sirich, T.L.; Meyer, T.W.; Thummel, K.E.; Yanez, N.D.; Himmelfarb, J.; Weiss, N.S.; et al. Tubular secretion in CKD. *J. Am. Soc. Nephrol.* **2016**, *27*, 2148–2155. [CrossRef] [PubMed]
33. Sirich, T.L.; Aronov, P.A.; Plummer, N.S.; Hostetter, T.H.; Meyer, T.W. Numerous protein-bound solutes are cleared by the kidney with high efficiency. *Kidney Int.* **2013**, *84*, 585–590. [CrossRef] [PubMed]
34. Bush, K.T.; Singh, P.; Nigam, S.K. Gut-derived uremic toxin handling in vivo requires OAT-mediated tubular secretion in chronic kidney disease. *JCI Insight* **2020**, *5*, e133817. [CrossRef] [PubMed]
35. Ahmed, S.; Chen, S.X.L.; Lucas, J.P.F.E.; Knoppert, S.N.; Harwood, R.; Faria, J.; Besseling, P.J.; Sparidans, R.W.; Broekhuizen, R.; Westphal, K.G.C.; et al. Indoxyl sulfate as a potential tubular function marker across kidney disease models. *Am. J. Physiol. Ren. Physiol.* **2025**, *329*, F160–F177. [CrossRef] [PubMed]
36. Devine, E.; Krieter, D.H.; Rüth, M.; Jankovski, J.; Lemke, H.D. Binding affinity and capacity for the uremic toxin indoxyl sulfate. *Toxins* **2014**, *6*, 416–429. [CrossRef] [PubMed]
37. Deltombe, O.; Van Biesen, W.; Glorieux, G.; Massy, Z.; Dhondt, A.; Eloot, S. Exploring protein binding of uremic toxins in patients with different stages of chronic kidney disease and during hemodialysis. *Toxins* **2015**, *7*, 3933–3946. [CrossRef] [PubMed]
38. Deltombe, O.; de Loor, H.; Glorieux, G.; Dhondt, A.; Van Biesen, W.; Meijers, B.; Eloot, S. Exploring binding characteristics and the related competition of different protein-bound uremic toxins. *Biochimie* **2017**, *139*, 20–26. [CrossRef] [PubMed]

39. Rueth, M.; Lemke, H.-D.; Preisinger, C.; Krieter, D.; Theelen, W.; Gajjala, P.; Devine, E.; Zidek, W.; Jankowski, J.; Jankowski, V. Guanidinylations of albumin decreased binding capacity of hydrophobic metabolites. *Acta Physiol.* **2015**, *215*, 13–23. [CrossRef] [PubMed]
40. Maheshwari, V.; Thijssen, S.; Tao, X.; Fuertinger, D.; Kappel, F.; Kotanko, P. A novel mathematical model of protein-bound uremic toxin kinetics during hemodialysis. *Sci. Rep.* **2017**, *7*, 10371. [CrossRef] [PubMed]
41. Akagawa, Y.; Akagawa, S.; Tsuji, S.; Kitawaki, T.; Ito, A.; Nakanishi, M.; Okada, T.; Yamanouchi, S.; Kaneko, K. Urinary indoxyl sulfate in children: Age-related decline and its association with Bacteroidota in the gut microbiota. *Biosci. Microbiota Food Health* **2026**, *45*, 197–203. [CrossRef] [PubMed]
42. Drube, J.; Wan, M.; Bonthuis, M.; Wühl, E.; Bacchetta, J.; Santos, F.; Grenda, R.; Edefonti, A.; Harambat, J.; Shroff, R.; et al. Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease. *Nat. Rev. Nephrol.* **2019**, *15*, 577–589. [CrossRef] [PubMed]
43. Nobus, O.; Carlier, A.; Mihăilă, S.M.; Dubois, V. Sex-Dependent Determinants of Uremic Toxicity in Chronic Kidney Disease. *Toxins* **2026**, *18*, 242. [CrossRef] [PubMed]
44. Hyun, H.S.; Paik, K.H.; Cho, H.Y. p-Cresyl sulfate and indoxyl sulfate in pediatric patients on chronic dialysis. *Korean J. Pediatr.* **2013**, *56*, 159–164. [CrossRef] [PubMed]
45. Ahmed, S.; Sparidans, R.W.; Lu, J.; Mihaila, S.M.; Gerritsen, K.G.F.; Masereeuw, R. A robust, accurate, sensitive LC–MS/MS method to measure indoxyl sulfate, validated for plasma and kidney cells. *Biomed. Chromatogr.* **2022**, *36*, e5307. [CrossRef] [PubMed]
46. Kobayashi, S.; Matsushita, K.; Kawasaki, K.; Seimiya, M. Clinical Quantitative Method Development of serum indoxyl sulfate (IS) assay using LC-MS/MS. *Biochem. Biophys. Rep.* **2025**, *44*, 102316. [CrossRef] [PubMed]
47. Deltombe, O.; Dhondt, A.; Van Biesen, W.; Glorieux, G.; Eloot, S. Effect of sample temperature, pH, and matrix on the percentage protein binding of protein-bound uraemic toxins. *Anal. Methods* **2017**, *9*, 1935–1940. [CrossRef]
48. Eloot, S.; Van Biesen, W.; Roels, S.; Delrue, W.; Schepers, E.; Dhondt, A.; Vanholder, R.; Glorieux, G. Spontaneous variability of pre-dialysis concentrations of uremic toxins over time in stable hemodialysis patients. *PLoS ONE* **2017**, *12*, e0186010. [CrossRef] [PubMed]
49. O'Brien, F.J.; Sirich, T.L.; Taussig, A.; Fung, E.; Ganesan, L.L.; Plummer, N.S.; Brakeman, P.; Sutherland, S.M.; Meyer, T.W. Plasma pseudouridine levels reflect body size in children on hemodialysis. *Pediatr. Nephrol.* **2020**, *35*, 305–312. [CrossRef] [PubMed]
50. Ganesan, L.L.; O'Brien, F.J.; Sirich, T.L.; Plummer, N.S.; Sheth, R.; Fajardo, C.; Brakeman, P.; Sutherland, S.M.; Meyer, T.W. Association of plasma uremic solute levels with residual kidney function in children on peritoneal dialysis. *Clin. J. Am. Soc. Nephrol.* **2021**, *16*, 1531–1538. [CrossRef] [PubMed]
51. Crespo-Salgado, J.; Vehaskari, V.M.; Stewart, T.; Ferris, M.; Zhang, Q.; Wang, G.; Blanchard, E.E.; Taylor, C.M.; Kallash, M.; Greenbaum, L.A.; et al. Intestinal microbiota in pediatric patients with end stage renal disease: A Midwest Pediatric Nephrology Consortium study. *Microbiome* **2016**, *4*, 50. [CrossRef] [PubMed]
52. Klawitter, J.; Kirkpatrick, B.E.; Shillingburg, R.; Klawitter, J.; Wheeler, G.; Shokati, T.; Cadnapaphornchai, M.A.; Galinkin, J.L.; Thurman, J.M.; Christians, U. Monitoring of allograft adaptation after kidney transplantation in pediatric patients by targeted plasma metabolomics. *Int. J. Mol. Sci.* **2025**, *26*, 9190. [CrossRef] [PubMed]
53. Chen, Y.; Zelnick, L.R.; Wang, K.; Hoofnagle, A.N.; Becker, J.O.; Hsu, C.-Y.; Feldman, H.I.; Mehta, R.C.; Lash, J.P.; Waikar, S.S.; et al. Kidney clearance of secretory solutes is associated with progression of CKD: The CRIC Study. *J. Am. Soc. Nephrol.* **2020**, *31*, 817–827. [CrossRef]
54. Özdemir, K.; Yilmaz, E.; Dincel, N.; Bozabali, S.; Apaydin, S.; Gun, Z.H.; Sozeri, B.; Mir, S. Association of clearance of middle- and large-molecular-weight substance with arterial stiffness and left ventricular mass in children receiving renal replacement therapy. *Minerva Pediatr.* **2017**, *69*, 495–502. [CrossRef] [PubMed]
55. Hsu, C.N.; Lu, P.C.; Lo, M.H.; Lin, I.C.; Chang-Chien, G.P.; Lin, S.; Tain, Y.L. Gut Microbiota-Dependent Trimethylamine N-Oxide Pathway Associated with Cardiovascular Risk in Children with Early-Stage Chronic Kidney Disease. *Int. J. Mol. Sci.* **2018**, *19*, 3699. [CrossRef] [PubMed]
56. Hsu, C.N.; Chang-Chien, G.P.; Lin, S.; Hou, C.Y.; Lu, P.C.; Tain, Y.L. Association of Trimethylamine, Trimethylamine N-oxide, and Dimethylamine with Cardiovascular Risk in Children with Chronic Kidney Disease. *J. Clin. Med.* **2020**, *9*, 336. [CrossRef] [PubMed]
57. Shafi, T.; Meyer, T.W.; Hostetter, T.H.; Melamed, M.L.; Parekh, R.S.; Hwang, S.; Banerjee, T.; Coresh, J.; Powe, N.R. Free levels of selected organic solutes and cardiovascular morbidity and mortality in hemodialysis patients: Results from the Retained Organic Solutes and Clinical Outcomes (ROSCO) investigators. *PLoS ONE* **2015**, *10*, e0126048. [CrossRef] [PubMed]
58. Shafi, T.; Sirich, T.L.; Meyer, T.W.; Hostetter, T.H.; Plummer, N.S.; Hwang, S.; Melamed, M.L.; Banerjee, T.; Coresh, J.; Powe, N.R. Results of the HEMO Study suggest that p-cresol sulfate and indoxyl sulfate are not associated with cardiovascular outcomes. *Kidney Int.* **2017**, *92*, 1484–1492. [CrossRef] [PubMed]

59. Lee, A.M.; Xu, Y.; Hu, J.; Xiao, R.; Hooper, S.R.; Hartung, E.A.; Coresh, J.; Rhee, E.P.; Vasan, R.S.; Kimmel, P.L.; et al. Longitudinal plasma metabolome patterns and relation to kidney function and proteinuria in pediatric CKD. *Clin. J. Am. Soc. Nephrol.* **2024**, *19*, 837–850. [CrossRef] [PubMed]
60. Levassort, H.; Boucquemont, J.; Liabeuf, S.; Laville, S.M.; Lange, C.; Frimat, L.; Combe, C.; Fouque, D.; Laville, M.; Jacquelinet, C.; et al. Association of phenylacetylglutamine and cognitive impairment in CKD. *Kidney Int. Rep.* **2025**, *10*, 2720–2731. [CrossRef] [PubMed]
61. Holle, J.; Bartolomaeus, H.; Löber, U.; Behrens, F.; Bartolomaeus, T.U.P.; Anandakumar, H.; Wimmer, M.I.; Vu, D.L.; Kuhring, M.; Brüning, U.; et al. Inflammation in Children with CKD Linked to Gut Dysbiosis and Metabolite Imbalance. *J. Am. Soc. Nephrol.* **2022**, *33*, 2259–2275. [CrossRef] [PubMed]
62. Barreto, F.C.; Barreto, D.V.; Liabeuf, S.; Meert, N.; Glorieux, G.; Temmar, M.; Choukroun, G.; Vanholder, R.; Massy, Z.A.; European Uremic Toxin Work Group (EUTox). Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 1551–1558. [CrossRef] [PubMed]
63. Toth-Manikowski, S.M.; Sirich, T.L.; Meyer, T.W.; Hostetter, T.H.; Hwang, S.; Plummer, N.S.; Hai, X.; Coresh, J.; Powe, N.R.; Shafi, T. Contribution of 'clinically negligible' residual kidney function to clearance of uremic solutes. *Nephrol. Dial. Transplant.* **2020**, *35*, 846–853. [CrossRef] [PubMed]
64. Bartels, J.; Tabatabaeifar, M.; Kirchner, M.; Azukaitis, K.; Doyon, A.; Bayazit, A.; Düzova, A.; Canpolat, N.; Bulut, I.K.; Obrycki, L.; et al. GDF-15 and uEGF Independently Associate With CKD Progression in Children. *Kidney Int. Rep.* **2025**, *10*, 3369–3378. [CrossRef] [PubMed]
65. Shroff, R.; Smith, C.; Ranchin, B.; Bayazit, A.K.; Stefanidis, C.J.; Askiti, V.; Azukaitis, K.; Canpolat, N.; Ağbaş, A.; Aitkenhead, H.; et al. Effects of hemodiafiltration versus conventional hemodialysis in children with ESKD: The HDF, Heart and Height Study. *J. Am. Soc. Nephrol.* **2019**, *30*, 678–691. [CrossRef] [PubMed]
66. Sirich, T.L.; Plummer, N.S.; Gardner, C.D.; Hostetter, T.H.; Meyer, T.W. Effect of increasing dietary fiber on plasma levels of colon-derived solutes in hemodialysis patients. *Clin. J. Am. Soc. Nephrol.* **2014**, *9*, 1603–1610. [CrossRef] [PubMed]
67. Desloovere, A.; Polderman, N.; Renken-Terhaerdt, J.; Shaw, V.; Anderson, C.; Greenbaum, L.A.; Nelms, C.L.; Qizalbash, L.; Stabouli, S.; Tuokkola, J.; et al. The management of dietary fiber intake in children with chronic kidney disease: Clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *J. Ren. Nutr.* **2025**, *35*, 207–220. [CrossRef] [PubMed]
68. Eloot, S.; Van Biesen, W.; Dhondt, A.; Van de Wynkele, H.; Glorieux, G.; Verdonck, P.; Vanholder, R. Impact of hemodialysis duration on the removal of uremic retention solutes. *Kidney Int.* **2008**, *73*, 765–770. [CrossRef] [PubMed]
69. Agbas, A.; Canpolat, N.; Ranchin, B.; Schmitt, C.P.; Flammier, S.; Scwetlick, M.; Stronach, L.; Waters, K.; Saygili, S.; Snauwaert, E.; et al. A randomised cross-over trial of pre- and post-filter haemodiafiltration modalities in children on maintenance dialysis: Effects on solute removal and blood pressure. *Kidney Int.* **2026**, *in press*. [CrossRef] [PubMed]
70. Van Wesemael, P.; Eloot, S.; Raes, A.; Shroff, R.; Snauwaert, E. How dialysis frequency and duration impact uremic toxin and fluid removal: A pediatric perspective. *Pediatr. Nephrol.* **2025**, *40*, 1565–1578. [CrossRef] [PubMed]
71. Ha, I.-S.; Yap, H.K.; Munarriz, R.L.; Zambrano, P.H.; Flynn, J.T.; Bilge, I.; Szczepanska, M.; Lai, W.-M.; Antonio, Z.L.; Gulati, A.; et al. Risk factors for loss of residual renal function in children treated with chronic peritoneal dialysis. *Kidney Int.* **2015**, *88*, 605–613. [CrossRef] [PubMed]
72. Shen, Q.; Fang, X.; Zhai, Y.; Rao, J.; Chen, J.; Miao, Q.; Gong, Y.; Yu, M.; Zhou, Q.; Xu, H. Risk factors for loss of residual renal function in children with end-stage renal disease undergoing automatic peritoneal dialysis. *Perit. Dial. Int.* **2020**, *40*, 368–376. [CrossRef] [PubMed]
73. Warady, B.A.; Schaefer, F.; Bagga, A.; Cano, F.; McCulloch, M.; Yap, H.K.; Shroff, R. Prescribing peritoneal dialysis for high-quality care in children. *Perit. Dial. Int.* **2020**, *40*, 333–340. [CrossRef] [PubMed]
74. Rossi, M.; Johnson, D.W.; Morrison, M.; Pascoe, E.M.; Coombes, J.S.; Forbes, J.M.; Szeto, C.C.; McWhinney, B.C.; Ungerer, J.P.; Campbell, K.L. Synbiotics easing renal failure by improving gut microbiology (SYNERGY): A randomized trial. *Clin. J. Am. Soc. Nephrol.* **2016**, *11*, 223–231. [CrossRef] [PubMed]
75. Hlatky, M.A.; Greenland, P.; Arnett, D.K.; Ballantyne, C.M.; Criqui, M.H.; Elkind, M.S.V.; Go, A.S.; Harrell, F.E., Jr.; Hong, Y.; Howard, B.V.; et al. Criteria for evaluation of novel markers of cardiovascular risk: A scientific statement from the American Heart Association. *Circulation* **2009**, *119*, 2408–2416. [CrossRef] [PubMed]
76. Colantonio, D.A.; Kyriakopoulou, L.; Chan, M.K.; Daly, C.H.; Brinc, D.; Venner, A.A.; Pasic, M.D.; Armbruster, D.; Adeli, K. Closing the gaps in pediatric laboratory reference intervals: A CALIPER database of 40 biochemical markers in a healthy and multiethnic population of children. *Clin. Chem.* **2012**, *58*, 854–868. [CrossRef] [PubMed]
77. Steyerberg, E.W.; Vickers, A.J.; Cook, N.R.; Gerds, T.; Gonen, M.; Obuchowski, N.; Pencina, M.J.; Kattan, M.W. Assessing the performance of prediction models: A framework for traditional and novel measures. *Epidemiology* **2010**, *21*, 128–138. [CrossRef] [PubMed]
78. Vickers, A.J.; Elkin, E.B. Decision curve analysis: A novel method for evaluating prediction models. *Med. Decis. Mak.* **2006**, *26*, 565–574. [CrossRef] [PubMed]

79. Hanson, C.S.; Gutman, T.; Craig, J.C.; Bernays, S.; Raman, G.; Zhang, Y.; James, L.J.; Ralph, A.F.; Ju, A.; Manera, K.E.; et al. Identifying Important Outcomes for Young People With CKD and Their Caregivers: A Nominal Group Technique Study. *Am. J. Kidney Dis.* **2019**, *74*, 82–94. [CrossRef] [PubMed]
80. Wu, J.G.; Guha, C.; Hughes, A.; Torrisi, L.G.; Craig, J.C.; Sinha, A.; Dart, A.; Eddy, A.A.; Bockenhauer, D.; Yap, H.-K.; et al. Patient, Parental, and Health Professional Perspectives on Growth in Children With CKD. *Am. J. Kidney Dis.* **2025**, *85*, 14–24.e1. [CrossRef] [PubMed]
81. Hughes, A.; Matus Gonzalez, A.; van Zwieten, A.; Guha, C.; Carter, S.; Coghlan, D.; Dominello, A.; Recabarren Silva, J.; Craig, J.C.; Howell, M.; et al. Establishing a core outcome measure for life participation in children with chronic kidney disease: A Standardized Outcomes in Nephrology—Children and adolescents with chronic kidney disease (SONG-Kids) consensus workshop report. *Kidney Int.* **2026**, *109*, 273–282. [CrossRef] [PubMed]
82. Hanson, C.S.; Craig, J.C.; Logeman, C.; Sinha, A.; Dart, A.; Eddy, A.A.; Guha, C.; Gipson, D.S.; Bockenhauer, D.; Yap, H.-K.; et al. Establishing core outcome domains in pediatric kidney disease: Report of the Standardized Outcomes in Nephrology—Children and Adolescents (SONG-KIDS) consensus workshops. *Kidney Int.* **2020**, *98*, 553–565. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.