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Pediatric Renal Anemia: Mechanisms, Clinical Impact And Evolving Strategies For Management In Chronic Kidney Disease

Ochilova Gulsora Shamsitdinovna – Department of Pediatrics[1], Chirchiq Branch of Tashkent State Medical University, Chirchiq, Uzbekistan.
Habibulloyeva Bibiroziya Rakhmatullozoda – Department of Propaedeutics of Childhood Diseases, Tashkent State Medical University.

Abstract.
Relevance. Pediatric chronic kidney disease (CKD) is increasingly recognized as a global health priority due to its early onset, rapid progression, and long-term complications. Among these, anemia represents one of the most frequent and clinically significant disorders, contributing to cardiovascular remodeling, neurocognitive delay, growth retardation, and reduced quality of life. Despite advances in nephrology, diagnosis and management of CKD-associated anemia in children remain challenging because of multifactorial pathogenesis and variability in therapeutic response.
Objective. To evaluate the pathophysiological mechanisms, prevalence patterns, clinical burden, and current evidence-based therapeutic approaches to anemia in pediatric chronic kidney disease, with emphasis on personalized and preventive strategies.
Materials and Methods. A structured review was conducted using PubMed, Scopus, Web of Science, Google Scholar, and national electronic databases. Keywords included "pediatric chronic kidney disease," "renal anemia," "erythropoietin deficiency," "iron therapy," "erythropoiesis-stimulating agents," and "prevention." A total of 162 publications from 2015–2024 were initially screened; 41 high-quality articles, guidelines (KDIGO, ERA-EDTA, ISN), and meta-analyses were included in the final review.
Results. The prevalence of anemia rises proportionally with CKD progression and reaches 75–90% in stages III–V. Key pathogenetic mechanisms include impaired erythropoietin synthesis, functional and absolute iron deficiency, chronic inflammation, uremic toxins, and disordered hepcidin regulation. Anemia severity correlates with left ventricular hypertrophy, reduced glomerular filtration rate, and growth delay. Current therapeutic approaches—oral and intravenous iron formulations, erythropoiesis-stimulating agents, vitamin D optimization, and anti-inflammatory therapy—are effective but not uniformly applied in pediatric practice. New-generation agents such as HIF-prolyl hydroxylase inhibitors (roxadustat, vadadustat) demonstrate promise, improving erythropoiesis while modulating iron metabolism.
Conclusion. Anemia is a critical component of the hemato-renal axis in pediatric CKD, directly influencing morbidity, progression of renal failure, and overall life quality. Early detection, individualized correction of iron status, rational use of ESAs, and incorporation of emerging therapies can significantly reduce complications. A comprehensive, personalized, and stage-specific management strategy should be considered essential in modern pediatric nephrology.
Keywords: pediatric chronic kidney disease, renal anemia, erythropoietin deficiency, iron metabolism, erythropoiesis-stimulating agents, HIF-PH inhibitors.

Introduction. Chronic kidney disease (CKD) in children is recognized today as one of the most serious non-communicable disorders affecting the growing organism. According to the International Society of Nephrology (ISN), CKD develops in 1 out of 1,000–3,000 children, yet its real prevalence is presumed to be much higher due to the asymptomatic early course and late diagnosis. Despite differences in etiology between children and adults, pediatric CKD demonstrates similarly rapid progression, early functional impairment, and a high burden of systemic complications.

Among the metabolic and hematologic abnormalities associated with CKD, renal anemia is considered one of the earliest and most clinically significant. In children, anemia develops earlier, progresses faster, and has a more pronounced effect on systemic homeostasis compared with adults. This is primarily explained by age-related sensitivity of erythropoiesis to hypoxia, higher iron requirements for growth, and immaturity of

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compensatory mechanisms. Numerous studies indicate that anemia in pediatric CKD is not only a laboratory finding but a key mediator of cardiovascular remodeling, impaired physical development, cognitive dysfunction, and reduced exercise tolerance. Moreover, the severity of anemia correlates with decreased glomerular filtration rate, left ventricular hypertrophy, and increased risks of hospitalization.

The pathogenesis of anemia in CKD is multifactorial. The central mechanism is insufficient production of renal erythropoietin, which begins to decline even at CKD stages II–III. Additional contributors include functional and absolute iron deficiency, chronic inflammation, elevated hepcidin levels, oxidative stress, metabolic acidosis, and accumulation of uremic toxins suppressing bone marrow erythropoiesis. Frequent infectious episodes and nutritional deficiencies exacerbate the condition. Thus, anemia in pediatric CKD represents a complex disorder requiring comprehensive clinical evaluation and individualized correction.

Despite significant progress in nephrology, achieving stable target hemoglobin levels in children remains a challenge. Inadequate dosing of erythropoiesis-stimulating agents (ESAs), poor adherence to oral iron therapy, inflammation-related hyporesponsiveness, and variability of iron absorption complicate treatment. New pharmacological options, such as hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), offer promising alternatives by stimulating endogenous erythropoietin production while improving iron mobilization and reducing hepcidin levels. These drugs are currently being integrated into international guidelines as potential future standards for pediatric CKD-related anemia.

Considering the increasing prevalence of CKD and the substantial impact of anemia on long-term outcomes, there is a pressing need for deeper analysis of the mechanisms, prevalence patterns, diagnostic criteria, and therapeutic approaches specifically tailored for the pediatric population. Early identification and individualized treatment of renal anemia play a key role in slowing CKD progression, reducing cardiovascular risks, and improving quality of life in affected children.

Materials And Methods/ This structured review was conducted in accordance with the principles of evidence-based medicine and PRISMA analytical standards, ensuring transparency, reproducibility, and scientific reliability of the obtained results.

Literature Search Strategy. A comprehensive search was performed across leading international scientific databases, including: PubMed/MEDLINE, Scopus, Web of Science Core Collection, Google Scholar, Cochrane Library

Additionally, national and regional electronic repositories (CyberLeninka, eLibrary, UzMedArchive) were screened to include materials relevant to local epidemiological features and clinical practices in Central Asia.

Search keywords and their combinations included: **“**pediatric chronic kidney disease,” “renal anemia,” “erythropoietin deficiency,” “iron deficiency in CKD,” “ESAs in children,” “hepcidin regulation,” “HIF-PH inhibitors,” “CKD complications in children,” “treatment,” “prevention,” and “outcomes.” Boolean operators (“AND,” “OR”) and filters for publication date (2015–2024), full-text availability, and pediatric population were applied.

Inclusion criteria:

- Studies involving children aged **0–18 years** with confirmed CKD (stages I–V).
- Articles reporting prevalence, pathogenesis, diagnostic methods, or treatment of anemia in CKD.
- Randomized controlled trials, cohort studies, case-control studies, clinical guidelines, and systematic reviews.
- Publications in English or Russian.

Exclusion criteria:

- Adult-only studies.
- Non-original publications (editorials, letters, commentaries).
- Studies lacking reliable methodological quality or clear diagnostic criteria for CKD or anemia.
- Duplicated data and pre-2015 publications, unless highly relevant.

Data Extraction and Analysis. For each selected study, the following parameters were extracted: CKD stage distribution, Prevalence and severity of anemia, Hemoglobin and ferritin thresholds, Erythropoietin concentration and iron metabolism markers, Diagnostic algorithms, Treatment modalities (oral/IV iron, ESAs, HIF-PH inhibitors), Clinical outcomes and complication rates

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To summarize findings, a comparative analytical framework was applied. Quantitative indicators were synthesized narratively due to heterogeneity in study designs. Evidence strength was evaluated according to GRADE criteria.

Results. Analysis of the 41 high-quality studies included in the final review revealed a consistent pattern demonstrating that anemia is one of the earliest and most burdensome complications of pediatric chronic kidney disease (CKD). Global epidemiological data from 2015–2024 indicate a steady increase in CKD prevalence among children, with anemia frequently emerging at early disease stages. Among children with CKD stages III–V, 75–90% exhibited hemoglobin levels below age-specific norms, a prevalence approaching that observed in adult populations. The synthesis of pathophysiological data confirmed that impaired renal erythropoietin synthesis is the primary and earliest mechanism of anemia development in pediatric CKD; however, additional factors—including absolute and functional iron deficiency, elevated hepcidin levels, chronic inflammation, oxidative stress, metabolic acidosis, and uremic toxin accumulation—significantly aggravate anemia severity. Findings across multiple studies demonstrated strong clinical correlations: children with hemoglobin levels below 10 g/dL exhibited a 45–60% rate of left ventricular hypertrophy based on echocardiographic data, while reduced hemoglobin levels were consistently associated with growth retardation, decreased exercise tolerance, and neurocognitive deficits. Iron deficiency was identified in approximately 70% of children with advanced CKD, and hyporesponsiveness to erythropoiesis-stimulating agents (ESAs) was most commonly associated with inflammation-driven hepcidin elevation and functional iron sequestration.

Evaluation of therapeutic strategies revealed that oral iron supplementation was effective in only 38–42% of pediatric patients, primarily due to poor gastrointestinal absorption and low adherence. In contrast, intravenous iron demonstrated nearly double the improvement in hemoglobin correction, emphasizing its importance in moderate-to-severe anemia. ESAs remained the cornerstone of anemia treatment, successfully increasing hemoglobin in most children; however, treatment individualization was often required due to variable responsiveness. Recently introduced hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), such as roxadustat and vadadustat, showed promising physiological effects by stimulating endogenous erythropoietin production, lowering hepcidin levels, and improving iron mobilization—although pediatric data remain limited. Across nearly all studies, timely identification of infection sources, individualized assessment of iron status, optimization of vitamin D levels, and stage-specific adjustment of ESA dosing were identified as critical determinants of therapeutic success.

Collectively, the synthesized findings confirm that anemia in pediatric CKD is not a secondary laboratory abnormality but a major factor influencing renal disease progression, cardiovascular remodeling, and overall quality of life. The strong proportional relationship between anemia severity and CKD stage underscores the need for early screening, personalized management strategies, and incorporation of emerging therapies to reduce morbidity and long-term complications in affected children.

Discussion. The findings of this review demonstrate that anemia remains one of the most clinically significant and prognostically important complications of pediatric chronic kidney disease (CKD), affecting both the course and the long-term outcomes of renal pathology. Numerous authors emphasize that anemia in children with CKD develops earlier and progresses more rapidly compared with adult patients due to age-specific characteristics of erythropoiesis and increased physiological iron requirements during growth. According to Warady et al. (2016), even mild declines in glomerular filtration rate lead to an early reduction in erythropoietin production, resulting in a measurable decrease in hemoglobin levels before overt renal insufficiency becomes clinically apparent.

Several studies (Atkinson et al., 2020; Shroff et al., 2017) highlight that chronic inflammation and hepcidin dysregulation play a central role in the development of functional iron deficiency, which is particularly prominent in pediatric patients due to repeated infections and nutritional instability. The elevated hepcidin levels inhibit intestinal absorption of iron and block its mobilization from storage sites, reducing the effectiveness of oral supplementation—a finding consistent with the results of Hamano et al. (2019), who demonstrated that 60–70% of children with CKD exhibit inadequate response to oral iron therapy.

Cardiovascular implications of renal anemia are well documented in the pediatric population. Mitsnefes et al. (2018) underscore that anemia is strongly associated with left ventricular hypertrophy, increased cardiac workload, and early structural remodeling. In our review, this correlation was consistently observed across

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several included studies, supporting the hypothesis that anemia is not merely a biochemical alteration but a key pathophysiological mediator of cardio-renal interactions.

Therapeutic approaches described in the literature confirm the central role of erythropoiesis-stimulating agents (ESAs). Hodson et al. (2021) report that individualized ESA regimens provide stable hemoglobin correction in most children, although inflammation-related hyporesponsiveness remains a challenge. KDIGO guidelines also emphasize that inadequate iron availability must be corrected before ESA dose escalation, supporting a personalized, stage-specific therapeutic algorithm.

Recent clinical trials involving HIF-prolyl hydroxylase inhibitors (HIF-PHIs) introduce a promising paradigm shift in anemia management. Chen et al. (2022) and Provenzano et al. (2021) demonstrate significant improvements in hemoglobin stability, iron mobilization, and decreased hepcidin levels with the use of roxadustat, even in patients previously hyporesponsive to ESAs. While pediatric data remain limited, preliminary findings suggest that these agents could become part of future therapeutic guidelines.

Several authors—including Rees et al. (2023)—highlight the need for integrated, multi-level management strategies combining iron optimization, infection control, inflammation management, nutritional support, and carefully titrated ESA therapy. Their work reinforces the conclusion that early detection and holistic treatment of anemia can slow CKD progression, reduce hospitalization rates, and substantially improve cognitive and physical development outcomes.

Overall, the evidence consistently supports that anemia in pediatric CKD is both a strong marker of disease severity and a modifiable therapeutic target. Improved screening algorithms, routine assessment of iron biomarkers (ferritin, TSAT), and timely implementation of individualized treatment strategies—including novel therapeutics—represent essential steps in reducing the systemic burden of CKD-related anemia in children.

Conclusion. This review highlights that anemia is not merely an accompanying laboratory abnormality but a critical component of the hemato-renal interaction in pediatric chronic kidney disease. The evidence consistently demonstrates that anemia develops early, progresses rapidly, and exerts profound effects on cardiovascular function, neurocognitive development, growth potential, and overall clinical outcomes in affected children. Its severity strongly correlates with advancing CKD stage, reduced erythropoietin production, impaired iron metabolism, chronic inflammation, and hepcidin dysregulation, making it a multifactorial condition that requires comprehensive clinical attention.

Effective management of renal anemia in the pediatric population demands an individualized, biologically grounded approach. Early identification of iron deficiency—both absolute and functional—along with timely correction of inflammatory triggers and adequate replenishment of iron stores remain central to successful therapy. Erythropoiesis-stimulating agents continue to represent the standard of care, though their optimal effectiveness depends on personalized dosing and concurrent correction of iron availability. Emerging pharmacological strategies such as HIF-prolyl hydroxylase inhibitors offer a promising future direction, with the potential to restore endogenous erythropoietin production, improve iron mobilization, and overcome inflammatory barriers to therapy.

Comprehensive management strategies that integrate routine hematologic monitoring, nutritional optimization, infection control, cardiovascular surveillance, and adherence to KDIGO and ISN guidelines can substantially reduce the burden of anemia and its complications. Ultimately, improving anemia management in pediatric CKD has the potential not only to slow renal disease progression but also to significantly enhance quality of life, physical development, and long-term survival prospects for affected children.

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