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Insights in pediatric nephrology

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Insights in pediatric nephrology

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Editorial: Insights in pediatric nephrology

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Editorial on the Research Topic
Insights in pediatric nephrology

The field of pediatric nephrology continues to evolve, marked by both significant advancements and ongoing challenges. This collection of articles, assembled under the research topic "*Insights in Pediatric Nephrology*", highlights emerging discoveries, innovative approaches, and evolving perspectives that are shaping the future of kidney care in children. Below is an overview of the thematic content of the collection, highlighting significant findings and emerging trends that are poised to shape the future of pediatric nephrology.

Two articles reported on the treatment of primary hyperoxaluria type 1 (PH1) with Lumasiran, an RNA interference (RNAi) therapeutic agent that reduces the hepatic production of oxalate by targeting glyoxylate metabolism (Frishberg et al., Taroni et al.). PH1 is a rare autosomal recessive inborn disorder in glyoxylate metabolism that is particularly devastating in young children as it results in kidney failure due to kidney stones and nephrocalcinosis which then leads to systemic oxalosis with the deposition of calcium oxalate crystals throughout the body. Frishberg et al. reported on the efficacy and safety of 30 months of Lumasiran treatment in 18 patients under 6 years of age enrolled in the phase 3 ILLUMINATE-B trial (Frishberg et al.). Lumasiran was found to be remarkably effective with a sustained reduction in urine oxalate of approximately 70% and demonstrated stable renal function, improvements in medullary nephrocalcinosis, and a low rate of kidney stone events. In addition, there were no serious adverse events related to Lumasiran use. Taroni et al. described a fascinating report on Lumasiran initiated at 10 days of age in a newborn prenatally diagnosed with PH1, as an older sibling also presented with PH1 at 2 months of age, and later required a liver and kidney transplant (Taroni et al.). Despite the early initiation of therapy, the child developed nephrocalcinosis and nephrolithiasis with elevated urine oxalate levels. It took approximately 9 months for urinary oxalate levels to normalize. At the 20-month follow-up, renal function and urine oxalate levels were normal, with improved nephrocalcinosis and no evidence of systemic oxalosis. These studies demonstrate the remarkable impact that biological drugs have had on rare pediatric diseases.

Two articles reported on the clinical utility of radiological imaging in assessing hemolytic uremic syndrome (HUS) and vesicoureteral reflux, respectively (Rink et al.,

Zhu et al.). Hemolytic uremic syndrome is an important cause of acute kidney injury in children, frequently requiring acute dialysis and sometimes resulting in CKD. It can be difficult to predict whether a child with HUS will have a severe clinical course requiring dialysis. Rink et al. retrospectively evaluated whether renal sonograms provide clinically meaningful information and predict the need for acute dialysis in 30 children with HUS (Rink et al.). The authors found that both increased kidney size and elevated resistive indices were predictive of the need for acute dialysis. Increased kidney size was the most predictive factor, with a kidney size >130% compared to mean values being associated with a 67% likelihood of needing dialysis, while a combination of a kidney size >130% and a resistive index >1.0 was associated with a 73% likelihood of needing dialysis. Interestingly, no children with a kidney size <130% required dialysis. These results suggest that renal sonography may be clinically useful for predicting the need for dialysis in children with HUS. Zhu et al. retrospectively evaluated renal damage using both Dimercaptosuccinic acid (DMSA) renal scintigraphy and Technetium-99m-Ethylenedicysteine (99mTc-EC) dynamic renal scintigraphy in 226 children diagnosed with primary vesicoureteral reflux (Zhu et al.). They demonstrated that scintigraphic abnormalities were common and that split renal function was much lower in kidneys that had reflux.

Two review articles were included, one discussing sodium glucose co-transporter 2 inhibitors and the other discussing renal abscesses in children (Portalatin et al., Sun et al.). Portalatin et al. discussed the growing interest in SGLT2 inhibitors as renoprotective agents in pediatric nephrology (Portalatin et al.). Originally developed for glycemic control in adults with type 2 diabetes, these agents have shown substantial renal and cardiovascular benefits in major chronic kidney disease (CKD) trials in adults, independent of glycemic status. Proposed mechanisms underlying the renal benefits include the restoration of tubulo-glomerular feedback, the reduction of intraglomerular pressure, the attenuation of inflammatory and fibrotic signaling, and the stabilization of podocyte and mesangial cell function. Although pediatric data remain limited, extrapolation from adult studies suggests a strong rationale for the use of SGLT2 inhibitors in select children and adolescents with proteinuric CKD and progressive glomerular diseases (e.g., IgA nephropathy, FSGS, and Alport syndrome). The authors advocated for disease-specific pediatric trials and provided interim recommendations for the cautious use of these agents in adolescents, emphasizing the importance of closely monitoring renal function and volume status. Sun et al. reviewed pediatric renal abscesses and reported on 12 cases (Sun et al.). Patients present with non-specific symptoms, such as fever and abdominal pain, and typically require an abdominal CT scan or magnetic resonance urography for diagnosis. Abscesses are typically less than 3 cm and respond to antibiotics, eliminating the need for surgery.

Finally, the European Society for Paediatric Nephrology (ESPN) conducted a multi-institutional cross-sectional analysis to evaluate the organization, workforce, and delivery of pediatric nephrology care in 48 European countries (Ehrich et al.). Despite progress in establishing specialized centers, transplant programs, and dialysis services, wide disparities persist. Over 50% of countries experience shortages of pediatric nephrologists, dialysis nurses, and clinical support staff. Common challenges include limited access to dialysis, inadequate transplant services for younger children, and a lack of multidisciplinary teams. ESPN calls for initiatives to standardize care, optimize training, and reduce inequities across regions. Their findings underscore the need for coordinated policies and investments to ensure equitable access to quality pediatric kidney care across Europe.

In conclusion, we congratulate the authors on their invaluable contributions to the field of pediatric nephrology. Their research and insights not only advance our understanding of complex kidney-related disorders in children but also highlight innovative therapeutic strategies and systemic improvements necessary to enhance patient care. Despite these significant strides, much work remains to be done to further advance the care of children with kidney disease. Continued research, collaboration, and investment are essential to addressing the existing challenges and disparities in pediatric nephrology, ensuring that all children have access to the highest quality of care. We look forward to future developments and the ongoing commitment of the pediatric nephrology community to improving outcomes for young patients worldwide.

Author contributions

MM: Writing – original draft, Writing – review & editing. AS-U: Writing – original draft, Writing – review & editing. VK: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Thrombotic microangiopathy in pediatric multisystem inflammatory syndrome associated with COVID-19: a case series

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Introduction: This report provides insight into three distinct pediatric cases exhibiting a nexus between multisystem inflammatory syndrome in children (MIS-C) and thrombotic microangiopathy (TMA) triggered by COVID-19. The aim is to underscore the range of clinical presentations and the essentiality of early interventions.
Case presentations: This report presents three cases aged 10 months, 7 years, and 3 years with persistent fever, diarrhea, nausea, and vomiting. The first case, a 10-month-old girl, demonstrated acute kidney injury (AKI) and microangiopathic hemolytic anemia (MAHA) following a COVID-19 infection. Despite initial negative SARS-CoV-2 RT-PCR results, her condition escalated rapidly, presenting increased levels of LDH (peaking at 4,200 U/L) and requiring renal replacement therapy (RRT) to manage deteriorating renal function. Interventions with eculizumab and anakinra led to marked improvements, with a stable follow-up of 13 months post-hospitalization. The second case involved a 7-year-old girl who developed symptoms of MIS-C, hemolytic uremic syndrome (HUS), and posterior reversible encephalopathy syndrome (PRES) post-exposure to COVID-19, evidenced by heightened LDH levels (3,522 U/L at peak). After a precarious period of deteriorating kidney function and exacerbated hypertension, she responded positively to treatments, inclusive of IVIG, steroid therapies, and eculizumab, with a favorable 6-month follow-up showcasing stable laboratory results. The third case discusses a 3-year-old boy, without any medical history, manifesting HUS symptoms and COVID-19 infection. He exhibited increased LDH levels (peaking at 3,946 U/L) alongside elevated creatinine, marking renal impairment. He responded well to hemodialysis, IVIG, and steroid therapy, showcasing substantial recovery by the 19th day of hospitalization, which marked his discharge with a tapering steroid regimen.
Conclusion: This case series underscores that MIS-C-associated TMA is a significant complication in pediatric COVID-19. Our findings illuminate the potential for treatment success but simultaneously emphasize the need for a more comprehensive understanding of the underlying pathophysiology.

KEYWORDS

COVID-19, multisystem inflammatory syndrome, thrombotic microangiopathy, IVIG, anakinra, eculizimab

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, commonly known as coronavirus disease 2019 (COVID-19), primarily affects the respiratory system and can cause acute respiratory distress syndrome in severe cases, particularly among older individuals with comorbidities (1–3). However, children generally experience milder symptoms or are even asymptomatic when infected with SARS-CoV-2 (2–4).

Multisystem inflammatory syndrome in children (MIS-C) has emerged as a significant cause of hospitalization in children associated with SARS-CoV-2 infection. MIS-C is characterized by fever, inflammation, and organ dysfunction, often occurring several weeks after a COVID-19 infection (4–7). It has been observed that MIS-C is frequently accompanied by acute kidney injury (AKI), with reported incidence ranging from 10% to 60% of cases (5, 8, 9).

Thrombotic microangiopathy (TMA) is a potential complication of COVID-19-related hyperinflammatory syndrome and is reported in adults and the pediatric population. Complement activation, specifically the alternative pathway, has been implicated in the pathogenesis of TMA in the context of SARS-CoV-2 infection (10). Several studies have highlighted the occurrence of TMA in pediatric patients with MIS-C and SARS-CoV-2 infection (11–15). Recognizing and promptly treating TMA in children with MIS-C and SARS-CoV-2 infection is essential, as it can be associated with significant morbidity and mortality. Herein, we presented three patients diagnosed with MIS-C and TMA related to COVID-19.

Case reports

Case 1

The first patient was a 10-month-old girl with no previous medical history or family history of illness. She was admitted to the hospital with a 1-day history of diarrhea, vomiting, and a 3-day history of fever. Upon admission, her vital signs were as follows: fever of 38.7°C, heart rate of 140 bpm, blood pressure of 95/55 mm Hg, respiratory rate of 30 bpm, and oxygen saturation (SpO2) of 98% on room air. Physical examination revealed abdominal tenderness but was otherwise normal.

Initial laboratory results showed signs of inflammation, including elevated levels of C-reactive protein (CRP) at 147 mg/L (normal <5 mg/L) and hyperferritinemia at 1,075 ng/ml. The patient also had an increased white blood cell count of 20,490 per mm^3 and high D-dimer, LDH, AST, and ALT levels. Additionally, she had a low platelet count of 48,000 per mm^3. Electrolytes and renal function were normal. Urinalysis revealed 2+ proteinuria. Urine and blood cultures were negative, and there was no evidence of an active infection or neoplasia. Bone marrow examination did not show hemophagocytosis or leukemic infiltration.

The SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) test from a nasopharyngeal swab returned negative; the COVID-19 serology test was positive for IgG (>250 UA/ml) and negative for IgM. Echocardiography showed normal findings, while abdominal ultrasound revealed colitis findings and increased renal parenchymal echogenicity. The patient was diagnosed with MIS-C and treated with intravenous immunoglobulin (IVIG) at 2 g/kg/day and methylprednisolone at 10 mg/kg/day for a 3-day therapy. She continued with a maintenance dose of prednisolone at 2 mg/kg daily. Empiric broad-spectrum antibiotics were also initiated.

On the fourth day of her illness, the patient experienced a decrease in urine output, edema, anemia, thrombocytopenia, and acute kidney injury (AKI). Laboratory results showed a high creatinine level (1.8 mg/dl), low haptoglobin level, reticulocytosis (8%), and an LDH level of 4,200 U/L. The direct Coombs test was negative, and a peripheral blood smear examination revealed schistocytes. ADAMTS-13 activity and levels were within the normal range, while complement analysis showed decreased complement 3 levels. On the fifth day of hospitalization, she was transferred to the pediatric intensive care unit (PICU) for renal replacement therapy, including peritoneal dialysis. It was suspected that the patient developed microangiopathic hemolytic anemia (MAHA) due to MIS-C, as no other explanation could be found. MAHA associated with MIS-C, the patient received eculizumab treatment to reduce microangiopathic frequency. Her symptoms began to improve, with a decrease in ferritin levels, normalization of LDH levels, and stabilization of platelet and hemoglobin levels. The patient was transferred to the nephrology wards on hospital day 15 and while on stable under peritoneal dialysis. The urine output increased, and peritoneal dialysis was stopped. However, despite improved kidney function, the patient continued to have persistently high levels of ferritin and LDH and a declining platelet count. Anakinra was added to the treatment regimen after the second dose of eculizumab (on the 22nd day of hospitalization). Platelet levels increased, and ferritin levels decreased during the first week of anakinra treatment. In the outpatient follow-up, anakinra was eventually stopped after 2 months. Steroid therapy was discontinued at the end of the fourth month. The patient has since been doing well, with a follow-up period of 13 months.

Case 2

The second patient was a 7-year-old girl admitted to the hospital with complaints of nausea, vomiting, bloody diarrhea, and fever, which had been present for 2 days. She reported swimming in polluted lake water 1 week before the onset of symptoms.

On examination, the patient appeared ill but not in distress. She was febrile, with a blood pressure of 110/70 mmHg, a pulse rate of 85 bpm, a respiratory rate of 26 bpm, and an oxygen saturation of 98%.

Investigations revealed impaired renal function (BUN 70 mg/dl, serum creatinine 1.4 mg/dl), elevated LDH (3,522 U/L), ferritin (1,776 ng/ml), CRP levels (104 mg/dl), and decreased haptoglobin, hemoglobin, and platelet levels (<0.29 g/L, 7.5 g/dl, 16,000/μl, respectively). Peripheral blood smear examination showed the presence of schistocytes, indicating hemolysis. Complement evaluation revealed normal ADAMTS13 activity but decreased serum C3 level. The occult blood test was positive, and

PCR for SARS-CoV-2 infection was negative, but COVID-19 total antibody testing was positive for IgG (>250 UA/ml). The stool PCR for Shiga toxin was negative.

During the follow-up period, the patient's urine output decreased, and her kidney function deteriorated, with an increased creatinine level reaching 4.5 mg/dl, accompanied by worsened blood pressure control. Hemodialysis was initiated, but the patient continued to have persistent fever and elevated CRP and ferritin levels. MIS-C and hemolytic uremic syndrome (HUS) diagnoses were considered due to persistent MAHA, thrombocytopenia, decreased haptoglobin levels, increased inflammation markers, and positive COVID-19 antibodies. IVIG and pulse steroid therapy (10 mg/kg/day for 3 days) was initiated then oral prednisolone treatment was started at 2 mg/kg/day.

On the 8th day of hospitalization, the patient developed seizures, loss of consciousness, facial palsy, and hypertension. She was transferred to the PICU for the neurologic complication and hypertension. Brain MRI findings were consistent with posterior reversible encephalopathy syndrome (PRES), and no signs of papilledema were observed during the eye consultation. Electroencephalography (EEG) did not show epileptiform activity. Eculizumab treatment was administered, followed by two plasmapheresis sessions. The patient was transferred to the nephrology clinic and the second dose of eculizumab was given 1 week later. Hypertension was managed with antihypertensive medications (amlodipine, furosemide, captopril, propranolol), and hemodialysis treatments were continued. Acute phase reactants showed improvement following IVIG and steroid treatments. Kidney function improved, and hemodialysis was discontinued on the 20th day of hospitalization. The patient was discharged with amlodipine and steroids on the 26th day of hospitalization. Laboratory values at discharge showed serum creatinine of 0.78 mg/dl, LDH of 482 U/L, ferritin of 1,370 ng/ml, hemoglobin of 9.6 g/dl, and platelet count of 519,000/μl. Prednisolone treatment was prescribed at 10 mg (0.4 mg/kg) every other day and continued with a tapering regimen before discontinuation. The patient remained clinically stable with favorable laboratory results during a 6-month follow-up.

Case 3

A 3-year-old male patient complained of bloody diarrhea, vomiting, fever, and decreased urine output for 1 week. He had no known medical conditions and no previous hospitalizations. His parents had no consanguinity and no family history of kidney disease.

During the physical examination upon admission to the hospital, the patient had a high fever of 38.1°C. His blood pressure was 110/70 mmHg, heart rate was 140 beats per minute, respiratory rate was 28 breaths per minute, and oxygen saturation was 99%. Edema was noted in his eyelids and scrotum.

Initial laboratory results at admission revealed hyponatremia (sodium: 128 mg/dl), elevated blood urea nitrogen (BUN: 52 mg/dl), increased creatinine (Cr: 4.03 mg/dl), elevated lactate dehydrogenase (LDH: 3,946 U/L), elevated ferritin (1,468 ng/ml), hemoglobin (Hb: 10.8 g/dl), thrombocytopenia (platelets: 43,000/μl), and elevated d-dimer (>10,000 ng/ml). C3 was low, while C4 was within the normal range. ADAMTS13 activity (84%) fell within the normal reference range (40%–130%). The patient tested positive for COVID-19 through PCR and total antibody (23.5 U/ml) testing. Peripheral blood smear analysis revealed the presence of schistocytes and other signs of hemolysis. Shiga toxin-mediated HUS was ruled out by the absence of Shiga toxin in the stool PCR.

Abdominal ultrasound showed small bowel loops enlargement, minimal pelvis-free fluid, and grade 2 increased echogenicity in the renal parenchyma. Hemodialysis was initiated after 12 h of anuria since hospitalization. Along with renal failure, the patient's thrombocytopenia, anemia, and elevated levels of AST, ALT, LDH, ferritin, and d-dimer led to a diagnosis of MIS-C and hemolytic uremic syndrome.

IVIG treatment (2 g/kg) was administered on the first day of hospitalization. On the sixth day, the patient exhibited an upward gaze in his eyes. He was transferred to PICU for the management of seizure. The seizure resolved spontaneously and did not recur. EEG and cranial MRI results were normal. Pulse steroid therapy was initiated on the sixth day at a dose of 15 mg/kg/day due to a lack of improvement in laboratory findings and worsening clinic conditions. Pulse steroid therapy was given for 3 days, followed by continued steroid treatment at 2 mg/kg. The patient improved clinical and laboratory findings with IVIG, steroids, and supportive therapies. Renal function and urine output improved, and hemodialysis treatment was discontinued on the 12th day of hospitalization.

At discharge, blood tests showed BUN of 41 mg/dl, Cr of 0.64 mg/dl, LDH of 580 U/L, ferritin of 968 ng/ml, CRP of 0.6 mg/dl, Hb of 8.1 g/dl, and platelets of 213,000/μl. The patient was discharged on the 19th day of hospitalization with a tapering steroid therapy regimen, requiring no other post-discharge care. Steroid therapy was gradually tapered and discontinued over 8 weeks. **Table 1** summarizes the patient's clinical laboratory -treatment and outcome.

Discussion

Herein, we presented three cases highlighting the association between MIS-C and TMA in the context of COVID-19 infection. We discern distinctive yet interconnected features that shed light on the evolving understanding of MIS-C associated with COVID-19. Patient one, a 10-month-old infant, manifested a severe course of the syndrome, characterized by significant laboratory abnormalities, renal involvement requiring dialysis, and a lengthy recovery period marked by integrating various therapeutic approaches, including eculizumab and anakinra. Patient two, a 7-year-old with an exposure history to polluted lake water, experienced both renal and neurological complications, illustrating the multi-faceted nature of MIS-C. Notably, this case demonstrated the occurrence of PRES, a rare but significant neurological manifestation. The third patient, a 3-year-old male, portrayed the MIS-C's severe renal and

TABLE 1 Summary of the patient's clinical laboratory -treatment and outcome.

	Case 1	Case 2	Case 3
Age	10-month-old girl	7-year-old girl	3-year-old boy
Symptoms	Diarrhea, vomiting, fever, abdominal pain	Nausea, vomiting, bloody diarrhea, fever	Bloody diarrhea, vomiting, fever, decreased urine output
SARS-CoV-2 PCR	Negative	Negative	Positive
COVID-19 serology	Positive IgG (>250 UA/ml)	Positive IgG (>250 UA/ml)	Positive IgG (23.5 U/ml)
Laboratory findings (admission)			
Hg (g/dl)	11.4	7.5	10.8
Thrombocyte/µl	48,000	16,000	43,000
Leukocyte/mm^3	20,490	14,700	12,600
CRP (mg/L) (5 < N)	147	104	68
D-dimer (ng/ml)	>10,000	8,620	>10,000
Fibrinogen (mg/dl) ($n > 250$)	99	178	185
Ferritin (µg/L)	1,075	1,776	1,468
LDH (U/L)	1,526	3,522	3,946
Creatinine (mg/dl)	0.49	1.4	4
Complement C3 g/L ($N > 0.8$)	0.59	0.72	0.64
Treatment (day of hospitalization)	IVIG (day of 2) Pulse methylprednisolone (day of 3–6) Peritoneal dialysis (days of 5–18) Eculizumab (day of 5) Anakinra (day of 22–2 months) Oral steroid (day of 7–4 month)	Hemodialysis (day of 2–20) IVIG (day of 3) Pulse methylprednisolone (day of 4–7) Oral steroid (day of 8–26)	Hemodialysis (day of 1–12) IVIG (day of 1) Pulse methylprednisolone (day of 6–9) Oral steroid (day of 9–2 months)
Recovery or noteworthy notes-	Renal recovery (day of 18) Peritoneal dialysis was discontinued Exacerbation of MIS-C (day of 22) Hematologic response Improvement of MIS-C (day of 29)	Seizure (day of 8) PRES Plasmapheresis (day of 8–9) Eculizumab (day of 10, and 17) Hematologic response (day of 17)	Seizure (day of 6)
Current status	Recovery (follow-up period of 13 months)	Recovery (follow-up period of 4 months)	Recovery (day of 20)

hematological manifestations, warranting timely interventions such as hemodialysis and pulse steroid therapy.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, commonly known as COVID-19, primarily affects the respiratory system but can also lead to multisystem involvement in some cases, particularly in children. MIS-C has emerged as a significant cause of hospitalization in children with SARS-CoV-2 infection (1–3). According to the Center for Disease Control and Prevention (CDC), MIS-C presents with persistent fever >38.5°C, rash, conjunctivitis, peripheral edema, severe abdominal pain, and diarrhea. Notably, severe illness requiring hospitalization for clinical symptoms and evidence of COVID-19 exposure within 4 weeks are important factors not present in other case definitions (4, 16, 17).

One of the notable complications of MIS-C is the development of TMA, which involves endothelial dysfunction, microthrombi formation, and multiorgan involvement, including the kidneys (4–7). TMA diagnosis was supported by schistocytes in peripheral blood smears, indicating ongoing hemolysis and laboratory findings such as elevated LDH and decreased haptoglobin levels. Significantly, ADAMTS-13 activity, typically reduced in thrombotic thrombocytopenic purpura, was within the normal range in these cases, distinguishing them from primary TTP. However, complement analysis revealed decreased complement 3 levels in all cases, suggesting complement dysregulation and potential involvement of the alternative pathway in the pathogenesis of TMA.

The pathogenesis of TMA in the context of MIS-C and COVID-19 is not yet fully understood. However, several mechanisms have been proposed based on the existing literature. It has been suggested that the dysregulated immune response triggered by SARS-CoV-2 infection leads to an excessive release of pro-inflammatory cytokines and activation of the complement system. Complement dysregulation, particularly involving the alternative pathway, has been implicated in the development of TMA in MIS-C (4–6). In MIS-C-associated TMA, endothelial cell dysfunction, platelet activation, and the formation of microthrombi in the microvasculature contribute to tissue damage and organ dysfunction. This microangiopathic process can affect various organs, including the kidneys, leading to AKI and renal dysfunction. The underlying endothelial injury and thrombotic microangiopathy in the renal vasculature can result in proteinuria, hematuria, and decreased glomerular filtration rate (7, 8).

Several studies have reported cases of TMA in children with MIS-C and SARS-CoV-2 infection. For example, a study by Diorio et al. (13) described seven children with MIS-C and TMA. These patients exhibited features of TMA, including microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and evidence of endothelial injury. They also demonstrated evidence of complement activation, with low complement levels and increased levels of complement activation products.

The exact mechanisms underlying complement dysregulation and TMA in the context of SARS-CoV-2 infection are not fully understood. However, it has been proposed that the virus can directly activate the complement system, leading to excessive complement activation and subsequent endothelial damage and

thrombosis. Genetic factors and host immune responses may also influence the development of complement-mediated TMA in these patients (11, 12, 16, 18).

Recognizing and promptly treating TMA in children with MIS-C and SARS-CoV-2 infection is important, as it can be associated with significant morbidity and mortality. Treatment strategies may include supportive care, immunomodulatory therapies (such as corticosteroids and intravenous immunoglobulin), and complement-targeted therapies (such as eculizumab) (10, 18).

The primary goal of treatment is to control the inflammatory response, prevent further endothelial damage, and mitigate thrombotic complications. Immunomodulatory therapies play a key role in the management of MIS-C and TMA. IVIG is often the first-line therapy in MIS-C due to its anti-inflammatory and immunomodulatory effects. IVIG has been shown to improve clinical outcomes and reduce the risk of coronary artery abnormalities in MIS-C (1, 2, 9). In addition to IVIG, corticosteroids are frequently used to manage MIS-C-associated TMA. Steroids have potent anti-inflammatory properties and can modulate the immune response, thereby reducing endothelial damage and thrombotic complications. The optimal dosing and duration of steroid therapy in MIS-C and TMA remain areas of ongoing investigation (2, 9). Complement inhibitors, such as eculizumab, have shown promise in treating TMA associated with MIS-C and COVID-19. Eculizumab targets the complement cascade, explicitly inhibiting C5, and has successfully managed TMA in other contexts, such as atypical hemolytic uremic syndrome. However, further research is needed to determine the optimal timing, dosing, and duration of eculizumab therapy in MIS-C-associated TMA (10, 11).

There hasn't been a study that directly compares how patients with mild symptoms, monitored with or without immunomodulatory treatments, fare. This means there isn't a one-size-fits-all treatment approach yet. Patients with increasing inflammation markers or high BNP and troponin levels should be hospitalized and watched closely. Given the risks, like cardiac-related complications in patients with high D-dimer and cardiac markers, it seems wise to consider immunomodulatory treatments. If a patient shows severe, potentially life-threatening signs, starting these treatments immediately without waiting for a full diagnosis is best. The Best Available Treatment Study (BATS), a global research effort, found no significant difference in recovery from MIS-C among groups treated with just IVIG, corticosteroids, or a combination of both. It's worth noting that the BATS included a wider range of MIS-C patients, many of whom were less severely ill. Because of this, a stronger initial treatment might be needed for very ill patients to address cardiac problems quickly. Some other treatments, like anakinra and tocilizumab, have been tested, but we don't have solid evidence yet on their effectiveness. Some hospitals have used anakinra for MIS-C patients who didn't improve with the usual steroid or IVIG treatments (18, 19).

In the first case, the patient presented with fever, gastrointestinal symptoms, and signs of inflammation. Despite a negative SARS-CoV-2 PCR test, the serology test showed positive IgG antibodies, indicating previous infection. The patient fulfilled the diagnostic criteria for MIS-C and was treated with IVIG and methylprednisolone. However, on the fourth day of illness, the patient developed features of TMA, including AKI, thrombocytopenia, and MAHA. Treatment with eculizumab for two doses and anakinra improved clinical symptoms and laboratory abnormalities.

Similarly, the second and third cases presented with symptoms consistent with MIS-C and were found to have laboratory evidence of TMA. The patients exhibited hemolysis, thrombocytopenia, AKI features, elevated inflammatory markers, and positive COVID-19 antibody testing. Treatment with IVIG and steroids was initiated, but in the second case, the patient developed PRES and required eculizumab and plasmapheresis for management. Both patients showed clinical improvement and resolution of kidney injury.

Long-term follow-up is crucial for patients with MIS-C-associated TMA to assess renal recovery, monitor for late complications, and optimize overall outcomes. Ongoing research efforts are needed to elucidate the underlying pathophysiological mechanisms, refine diagnostic criteria, and establish evidence-based guidelines for managing MIS-C-associated TMA. Both patients improved after two doses of eculizumab. Eculizumab was discontinued.

In conclusion, this study provides evidence that MIS-C-associated TMA is a significant complication in children with COVID-19 infection, and appropriate treatment approaches can help improve clinical outcomes. Further research is needed to understand the pathophysiological mechanisms better, refine diagnostic criteria, and establish evidence-based guidelines for managing MIS-C-associated TMA. Additionally, long-term follow-up studies are necessary to assess these patients' long-term outcomes and potential late complications.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HN: Data curation, Formal Analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review and editing. HÖ: Methodology, Writing – review and editing. BB: Data curation, Writing – review and editing. DT: Data curation, Formal Analysis, Investigation, Writing – review and editing. EE: Data curation, Formal Analysis, Writing – review and editing. GT: Data

curation, Visualization, Writing – original draft, Writing – review & editing. ÖA: Data curation, Investigation, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case Report: effect of lumasiran treatment in a late preterm baby with antenatal diagnosis of primary hyperoxaluria type 1

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Background: Primary hyperoxaluria type 1 (PH1) is a rare disease with autosomal recessive transmission, characterized by increased urinary excretion of oxalate, resulting in chronic kidney disease secondary to recurrent urolithiasis, nephrocalcinosis, and accumulation of oxalate in various organs and tissues (systemic oxalosis). Since 2020, an innovative pharmacological approach, namely, lumasiran, has been added to the therapeutic armamentarium (dialysis and liver-kidney transplantation). The purpose of this paper is to describe the effect of lumasiran initiated at 10 days of life in a newborn with prenatally diagnosed PH1. A female fetus was prenatally diagnosed with hyperoxaluria type 1, based on family history and genetic testing. Her brother had the onset of the disease at 2 months of age and underwent liver and kidney transplantation at 13 months and 8 years of age, respectively. The baby was born late preterm at 36 weeks + 4 days of gestation via spontaneous labor, and lumasiran for compassionate use was started on the tenth day of life. At 20 months of age, the baby showed normal urinary oxalate values and kidney function, while the plasma oxalate level was under the threshold of oversaturation. There were no signs of systemic oxalosis.
Conclusions: Early use of lumasiran in young infants, who do not yet show signs of the disease, represents a therapeutic challenge for the pediatric nephrologist. The ability of the drug to act on the hepatocyte of the newborn and the most appropriate dosage to be used in these very young babies have yet to be clarified.

KEYWORDS
late preterm, lumasiran, newborn, prenatal diagnosis, primary hyperoxaluria type 1

Introduction

Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive inherited disease characterized by increased supersaturation of oxalate, resulting in chronic kidney disease and the need for replacement therapy, secondary to recurrent urolithiasis and nephrocalcinosis, and accumulation of oxalate in various organs and tissues (systemic oxalosis) (1). The median age at onset of the disease is 5.5 years, but the disease can be diagnosed at any age, from birth to the sixth decade of life (2).

PH1 is caused by mutations in the AGXT gene, which codes for the liver enzyme L-alanine glyoxylate aminotransferase (AGT). When AGT activity is absent or reduced, there is an accumulation of glyoxylate that is converted by hepatic lactate

dehydrogenase (LDH) to oxalate, the overproduction of which results in hyperoxaluria and hyperoxalemia (3–8).

Until 2020, the mainstays of therapy for PH1 were conservative therapy, dialysis, and liver-kidney transplantation. Currently, an innovative pharmacological approach based on the use of siRNA, such as lumasiran and nedosiran, has been added to the therapeutic armamentarium. Nedosiran inhibits the production of L-lactate dehydrogenase A (LDHA), which is essential for the cytosolic conversion of glyoxylate into oxalate. Lumasiran is designed to silence the gene that encodes the enzyme glycolate oxidase, which catalyzes the conversion of glycolate into glyoxylate (9). The ILLUMINATE A, B, and C studies have provided interesting evidence regarding the efficacy and safety of lumasiran. Data relating to the efficacy of lumasiran in the pediatric cohort are supported by the ILLUMINATE B trial in which 18 patients aged between 3 months and 6 years were enrolled. Therefore, experience of the use of lumasiran in newborns is limited to date (10–12).

The purpose of this paper is to describe the effect of lumasiran initiated very early in life in a newborn with prenatally diagnosed PH1.

Case description

A female fetus was prenatally diagnosed with hyperoxaluria type 1 based on family history and genetic testing.

Her brother, currently 9 years old, had the onset of disease at 2 months of age with a presentation of kidney damage and nephrocalcinosis, followed by genetic testing for PH1, which showed a compound heterozygous mutation of the AGXT gene (c.466G>A-p. (Gly156Arg)-c.943-1G>T), which was resistant to pyridoxine. At 13 months of life, the proband's sibling had a CKD stage 3 estimated by the Schwartz formula, and isolated liver transplantation was performed. GFR showed a slow decrease in the following years, reaching a value of 15 ml/min/1.73 m^2 at 7 years of age. Therefore, hemodialysis was started and the child underwent a kidney transplant from a living donor (his father) at the age of 8 years.

Given the family history, an indication was made to perform amniocentesis, which confirmed that the fetus had the same mutation as the brother. Fetal ultrasound scans and amniotic fluid were normal, with a regular course of pregnancy.

The girl was born via spontaneous labor at 36 weeks + 4 days of gestation with an adequate birth weight (2,615 grams). Hyperidratation by intravenous fluids (glucosaline solution, 70 ml/kg) and complementary breastfeeding were started, preventing weight loss of more than 5% of birth weight. Intravenous fluid administration was stopped on day 7 of life when the infant reached birth weight after a weight loss of 3% of birth weight. Then a fluid intake of 1.5 L/m^2 was given to maintain high hydration by breastfeeding and complementary breastfeeding.

At 72 h of life, urinary oxalate levels were 318 mMol/Mol creatinine (normal range <300 mMol/Mol creatinine) with normal kidney function (creatinine 0.8 mg/dl). At 7 days of age, urinary oxalate levels were 1,200 mMol/Mol and the plasma oxalate level was 68 µMol/L, with a normal range being <4 µMol/L. Serum creatinine on day 7 was 0.68 mg/dl.

Lumasiran was initiated for compassionate use on the tenth day of life, according to the product's prescribing information. Lumasiran was administered according to the following schedule: 3 mg/kg once monthly until 10 kg and then at a dose of 6 mg/kg every 3 months. The baby also continued to receive hyperhydration with complementary breastfeeding, and from the first month of life alkalizing therapy with potassium citrate. Urinary oxalate concentrations started to reduce at day 21 (11 days after the first dose of lumasiran) and reached normal value at 9 months. Plasma oxalate levels were 10 uMol/L under the value of oversaturation at 6 months (20 uMol/L) (9).

At 7 days of age, the first ultrasound scan of the kidneys and urinary tract was performed, which showed well-differentiated kidneys with normal echogenicity.

The baby underwent serial ultrasound scans showing nephrocalcinosis at 3 months of age, and then, at 9 months of age, concomitantly with acute pyelonephritis, two hyperechogenic images with slight posterior acoustic shadowing of 6 and 5 mm, respectively, at the left lower renal pole, and a stone of about 6 mm in the premural tract of the right ureter, with modest dilation of the upstream ureter in the pelvic tract (5 mm) (Figure 1).

The patient was then placed on tamsulosin 0.2 mg daily with ureteral stone expulsion 3 days after starting the medication without symptoms. Tamsulosin therapy was recommended by our pediatric urologist team and prescribed off-label after parental consent. The stone composition was 60% calcium oxalate dihydrate and 40% calcium oxalate monohydrate.

Urinary and plasma oxalate levels were monitored over time and are shown in Figures 2, 3, respectively.

At 12 and 20 months of age, the child showed growth according to the birth percentile.

At 20 months of age, the baby showed normal urinary oxalate values and kidney function, while the plasma oxalate level was 6 uMol/L. GFR matured normally during the first year of life and the infant presented a normal renal function from birth to the last follow-up. No signs of systemic oxalosis were observed.

The ultrasound scan at 12 and 20 months showed improvement in nephrocalcinosis and persistence of the two left kidney stones, unchanged from the previous examination. The baby showed no signs of systemic oxalosis at 20 months of age.

No adverse effect associated with the use of lumasiran was observed during the treatment.

Discussion

The patient described in this case report is, to the best of our knowledge, the only patient born before 37 weeks of gestation who underwent treatment with lumasiran.

The efficacy of lumasiran in the pediatric cohort was demonstrated in the ILLUMINATE B trial (12), which enrolled 18 patients aged <6 years (range 3–72 months). Therefore, data on the use of this drug in newborns are currently limited, and systematic clinical studies could be useful to evaluate its effects

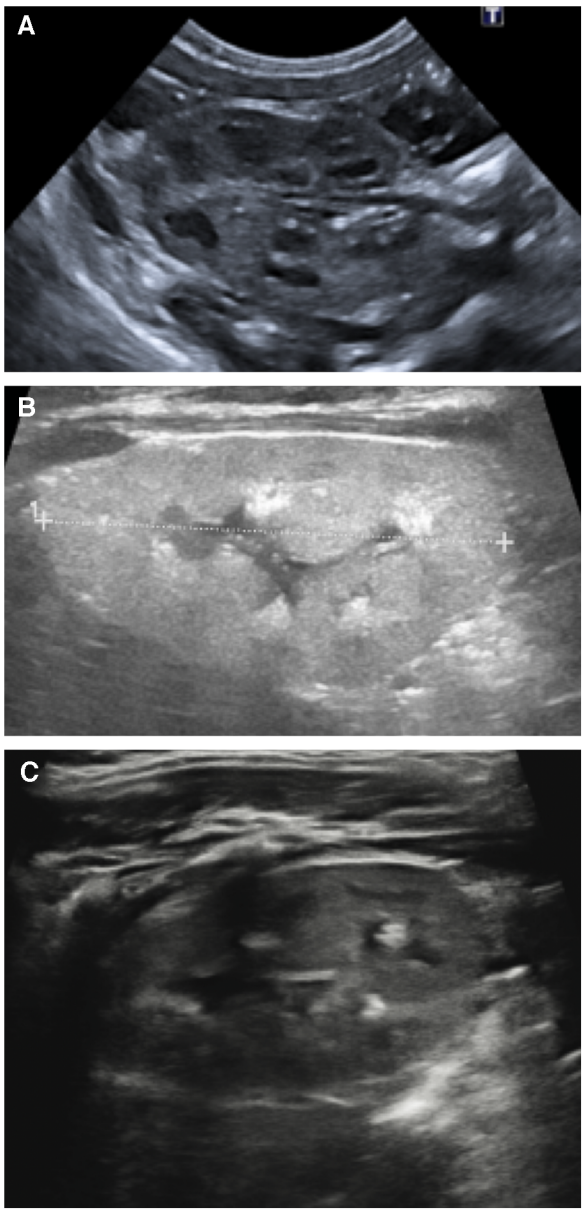

FIGURE 1
(A) Ultrasound scan at birth; (B) ultrasound scan at 3 months of age; and (C) ultrasound scan at 9 months of age.

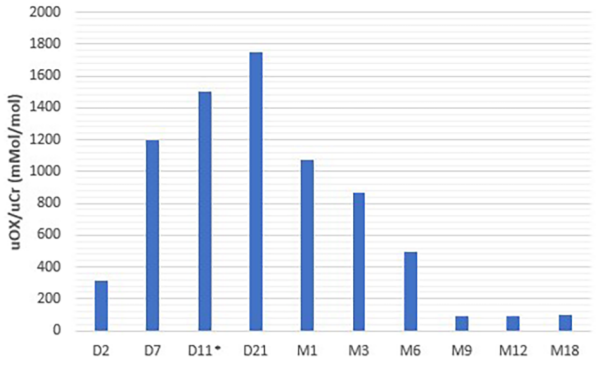

FIGURE 2
Urinary oxalate levels.

and pharmacokinetics in the early stages of life. The experience regarding the use of lumasiran in the early stages of life was described by Mèaux et al. (13) who reported three cases of young patients with PH1. The first patient had a similar history to the patient reported here since she received a prenatal diagnosis based on family history and started treatment at 9 days of age, combining hyperhydration and potassium citrate. Again, the ultrasound examination, which was normal at birth, showed worsening around 2 months of age with the appearance of nephrocalcinosis. In this case, ultrasound worsening was related to persistently elevated urinary oxalate levels in the first 2 months of life, so the dose of lumasiran was increased to lower oxalate concentrations. At 10 months of age, nephrocalcinosis improved and kidney function was normal. In the other two cases described by Mèaux et al. (13), the patients started treatment at around 3 months of age, and both had nephrocalcinosis with normal kidney function. After 9 and 5 months of treatment, nephrocalcinosis improved.

The case described here has features very similar to those of the infants described by Mèaux et al. (13). In particular, the history and timing of diagnosis and initiation of treatment are similar to those of the infant described by them. In our case, it was possible to start treatment no earlier than the tenth day of life because approval for the use of lumasiran was sought from the Ethics Committee (lumasiran was not yet available in the market at the time, but available for compassionate use according to the Ministerial Decree September 7, 2017).

The uOxalate/uCreatinine ratio was used to evaluate urinary oxalate excretion in our patient, as well as in young patients described by other authors (13). Low GFR is associated with low urinary creatinine excretion in the first months of life, so urine oxalate/creatinine ratio could not be a reliable measure of oxalate excretion in early age. However, some evidence could support the use of the ratio also in infants (14).

A study conducted by Sonntag et al. on premature infants in the first weeks of life compared the oxalate/creatinine ratio with oxalate excretion in 24-h urine collection. The authors concluded

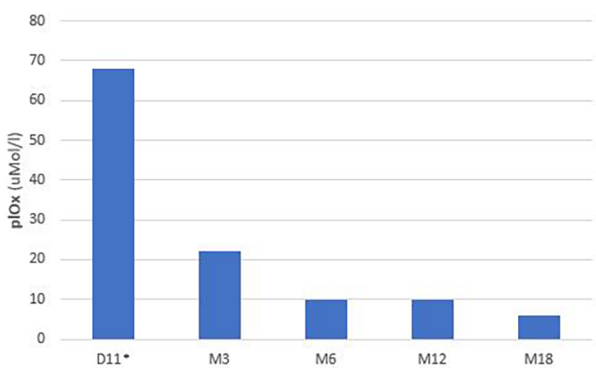

FIGURE 3
Plasma oxalate levels.

that the oxalate/creatinine ratio in spot urine samples is suitable for screening for hyperoxaluria. Moreover in the ILLUMINATE B trial, the oxalate/creatinine ratio was used during the first year of life to evaluate urinary oxalate excretion.

Our data, in agreement with those of Mèaux et al. (13), demonstrate that the reduction in urinary oxalate is not immediate after treatment initiation, but has a window period of at least 15 days in which oxalate levels are persistently high, which may have resulted in oxalate deposition in the kidneys with subsequent development of nephrocalcinosis and urolithiasis.

Renal outcome is very difficult to predict in PH1. A specific genotype–phenotype correlation is difficult to obtain in patients with PH1 because environmental factors and modifier genes may play an important role in the clinical manifestations of the disease (15).

A retrospective study of 932 patients with PH1 included in the Oxal-Europe registry analyzed the impact of genotype, nephrocalcinosis, urolithiasis, and urinary oxalate excretion on renal function. Homozygosity for AGXT null variants and nephrocalcinosis were the strongest determinants for kidney failure in PH1 (16).

The case reported here presented early nephrocalcinosis, despite tempestive diagnosis and treatment. Nephrocalcinosis improved during the first year of life but a longer follow-up will be necessary to evaluate the medium-long-term effects of early therapy with lumasiran.

Conclusion

To the best of our knowledge, the case reported here describes the first late preterm baby treated with lumasiran at birth, with a 20-month follow-up. The use of lumasiran appears to be safe in this type of patient. To date, early treatment of newborns with antenatal diagnosis of PH1 represents a therapeutic challenge for pediatric nephrologists.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

FT: Writing – original draft, Conceptualization, Data curation, Investigation. AB: Investigation, Writing – review & editing. MG: Investigation, Writing – original draft. FR: Data curation, Writing – original draft. GAM: Supervision, Writing – review & editing. GM: Supervision, Writing – review & editing.

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Conflict of interest

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Bone health in children with primary hyperoxaluria type 1 following liver and kidney transplantation

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Background: Primary hyperoxaluria type 1 is characterized by hepatic oxalate overproduction, leading to nephrocalcinosis, kidney stones, kidney failure and systemic oxalosis, including oxalate osteopathy. Combined liver-kidney transplantation (CLKT) and kidney after liver transplantation (KALT) were established therapeutic options to stop the devastating consequences of oxalate bone disease.
Methods: We describe a retrospective cohort of 10 children with PH1who were referred to our hospital from different countries for combined transplantation. Demographic and clinical data were collected and symptoms of bone disease, conventional radiological examinations, plasma oxalate levels and other determinants of calcium-phosphate metabolism were compared pre and post transplantation.
Results: Ten patients (7 male, median age 5.8 years, median follow-up time 8.1 years) were included in this study. Seven patients were diagnosed with infantile oxalosis and 9 patients received an intensified dialysis regime prior to transplantation. In one patient the transplanted kidney never achieved primary function and the boy remained on HD. All other patients remained without graft failure and retained stable kidney and liver function. Prior to transplantation, seven patients suffered from severe skeletal pain and three children presented with 1–3 series of pathological fractures. Pathological fractures did no longer occur in children who underwent successful CLKT or KALT. Plasma oxalate levels dropped within 6 months following Tx. Determinants of calcium-phosphorus metabolism did not differ significantly in comparison to other HD children. Seven of ten children showed a restricted growth at the time of transplantation and presented a moderate catch-up-growth at the time of last follow-up.
Conclusions: Patients with PH1 suffer from severe consequences of a disturbed bone metabolism. However, bone health and growth can partially improve following CLKT/KALT.

KEYWORDS

bone health, PH1, osteopathy, children, kidney transplantation, liver transplantation

Abbreviations
PH1, primary hyperoxaluria type 1; CLKT, combined liver-kidney transplantation; KALT, kidney after liver transplantation; ESRD, end-stage renal disease; HD, hemodialysis; PD, peritoneal dialysis; RTx, renal transplantation; LTx, liver transplantation; GFR, glomerular filtration rate.

Introduction

Primary hyperoxaluria type 1 (PH1), a rare metabolic disorder of the hepatic glyoxylate metabolism, leads to endogenous overproduction and accumulation of oxalate in the body (1–5). Crystal deposition in the kidneys results in nephrolithiasis and nephrocalcinosis and finally causes renal failure. Once eGFR drops, oxalate crystals deposit throughout the body resulting in a multi-systemic disease and might lead to severe bone disease (5–9), anemia secondary to bone marrow replacement (6, 8), hypothyroidism (6, 8–10), retinopathy (11) and vascular disorders (6, 8). Oxalate accumulation is even more pronounced in young children with end stage renal disease (ESRD), making especially these patients at risk to develop systemic oxalosis and leading to a very high morbidity and mortality risk in this age group (3, 5, 12). Bone disease has a major impact on the patients' well-being since it leads to severe bone pain, growth retardation and bone deformities and consecutively to pathological fractures (5, 9). Therefore, early detection of this progressive disease is crucial and early treatment might improve long-term outcome.

Before the EMA and FDA approval of the oxalate production lowering agent lumasiran in 2020, liver transplantation, combined liver and kidney transplantation (CLKT) or kidney after liver transplantation (KALT) were the only established curative options to relieve patients from the devastating consequences of systemic oxalosis (13, 14). While the hepatic oxalate production normalizes after liver transplantation (LTx), it still takes several months before the body oxalate pool drops and ESRD patients who received LTx prior to renal transplantation (RTx) still require an intensified hemodialysis protocol to achieve plasma oxalate levels below a saturation level of 30 µmol/L (13). Only after RTx and normalization of kidney function, plasma oxalate levels drop. However, nobody could foresee whether correction of the body oxalate balance alone could reverse or improve already existing consequences of bone disease and how long it takes before patients achieve a normal bone metabolism. In this retrospective study, we describe a cohort of ten children and adolescents with oxalosis and severe bone disease who underwent CLKT or KALT in our center and present a follow up of the bone improvement within the years following transplantation.

Patients and methods

Ten children and adolescents with genetically confirmed diagnosis of PH1 who received CLKT/KALT between 1998 and 2021 in the University Hospital of Essen were included in this retrospective analysis. Patients came from different European, Asian and African countries (Libya, Hungary, Sri Lanka, Greece, Israel and Germany) and were referred to our center exclusively for CLKT/KALT. They underwent more or less intensified dialysis modes prior to transplantation.

Data of all patients were collected from medical records and included patients and family history, clinical lab chemistry, genetic testing as well as additional important examinations such as abdominal/renal ultrasound. All bone Xrays were taken as needed and recorded from the Picture Archiving and Communication system at our center. Mode and duration of dialysis prior to arrival and/or transplantation at our center was also recorded when available from foreign patient's records. Clinical lab chemistry data were compared with a cohort of age-matched non PH1-patients undergoing hemodialysis in our hospital. Since all data were collected retrospectively and did not follow a specific protocol or schedule of bone health assessment, bone pain was determined unsystematically from indirect markers such as patient's history, local swelling, sensitivity to touching and local irritation. All patients' records were screened for bone specific comments or unforeseeable radiologic examinations. Follow-up data included patients and grafts outcomes and all complicatons, oxalosis and non-oxalosis related. The glomerular filtration rate (GFR) has been estimated according to the Schwartz formula. Post-transplant catch-up growth is presented as change in body height Standard Deviation Score (SDS).

This study was approved by the ethics committee at the University of Duisburg-Essen [protocol number 15-6259-BO] and all patients gave their written consent to publish health related data and pictures taken for medical purposes.

Statistical analysis was performed using GraphPad Prism© (version 5.01 for Windows, GraphPad Software, San Diego, California, USA). Normally distributed data are presented as mean ± standard deviation and non-normally distributed data as median and range. A p-value of <0.05 was considered significant.

Results

Data from 10 children have been included in this study (7 male, median age 5.8 years, range 0.4–17.8 years) with a median follow-up time of 8.1 years (range 3–17 years). *AGXT*-gene mutations have been reported in ten children: 7 patients with homozygous *AGXT*-gene mutations, one patient with 2 heterozygous mutations, and 2 patients with not further differentiated *AGXT*-gene mutations (Table 1). Seven children were diagnosed with infantile oxalosis. None of our patients received lumasiran at any time. Four children received CKLT (mean age at CKLT 12.6 ± 3.9 years) and 6 KALT (mean age at LTx 1.4 ± 0.9 years and RTx 2.2 ± 1.1 years; Table 1). In 4 patients split liver segments were from living related donors and all other livers were from deceased donors. Nine children underwent an intensified hemodialysis regimen with 5–6 HD sessions for 4–6 h/day per week prior to RTx and daily peritoneal dialysis treatment. One kidney was living donated and 9 kidneys were from deceased donors. In one patient, the transplanted kidney did not show primary function and the boy remained on HD for the following 3 months until renal graft function normalized. Another patient never showed primary kidney function after transplantation and the boy (patient 10, Table 1) is still on hemodialysis. All other patients remained without graft failure and retained stable kidney and liver function with observation times exceeding 10 years (Table 1).

TABLE 1 Outcomes of CLKT/KALT in 10 patients with confirmed diagnosis of PH1.

#	*AGXT*-Gene Mutation	Infantile oxalosis	Initial mode of dialysis	Age at CLKT (years)	Liver survival (months)	Kidney survival (months)	Patient survival (months)/Time of last follow up	Bone pain /fractures prior/ post-Tx
1	Not further differentiated	–	–	17.8	84	84	84	–
2	Exon 4; homozygous p.Gly170Arg	+	PD/HD	11.8	195	195	195	+/fractures
3	Exon 4; homozygous p.Gly170Arg	–	PD/HD	8.1	139	139	139	+/fractures
4	Not further differentiated	–	HD	12.6	145	145	145	–
#				Age at KALT (years)	Liver survival (months)	Kidney survival (months)	Patient survival (months)	
5	Exon 4; p.Gly170Arg and Exon 8; p.Ile279Thr	+	PD/HD	Liver 1.7; kidney 3.1	>169	>152	>169	+
6	Exon 4; homozygous p.Gly170Arg	+	PD/HD	Liver 1.9; kidney 2.4	>75	>68	>75	+
7	Exon 4; homozygous p.Gly170Arg	+	PD/HD	Liver 0.4 kidney 1.4	>100	>88	>100	(+)
8	Homozygous p.Ile244Thr	+	PD/HD	Liver 0.7; kidney 1.1	>180	>168	>180	(+)
9	Homozygous c.956C > T	+	PD/HD	Liver 0.8; kidney 1.4	>104	>96	>104	(+)
10	Exon 10; homozygous pVal324Glyfs*7	+	PD/HD	Liver 2.9; kidney 3.9	>36	HD, no primary function	>36	+/fractures

PD Peritoneal dialysis; HD, Hemodialysis; + = patient suffers from severe bone pain (e.g. swelling, sensitive to touch, local irritation); (+) severe bone pain is not directly described.

All 10 patients had various radiological signs of osteodystrophy. Five patients suffered from severe skeletal pain and 3 children presented with 1–3 series of pathological fractures of the hip, femoral neck or upper arm prior to transplantation (Table 1 and Figure 1). Furthermore, two patients were unable to walk and needed a wheelchair.

Plasma oxalate levels dropped from 115 ± 40 µmol/L to 12 ± 8 µmol/L within 6 months following Tx (Table 2). When stratified by mode of transplantation (Table 3), children undergoing CLKT tend to show lower plasma oxalate levels 6 and 12 months after transplantation when compared to children undergoing KALT (6 ± 2 vs.17 ± 12 µmol/L after 6 months). However, this fails to reach statistical significance ($p = 0.11$). Determinants of calcium-phosphorus metabolism (PTH, 25-hydroxy vitamine D, calcium, phosphorus and alkaline phosphatase) did not differ significantly between PH1 patients and other children treated with HD following Tx and normalized after renal transplantation (Table 2). Seven of ten children showed a restricted growth at the time of transplantation (−1.1 ± 0.4 SDS) and presented a moderate catch-up-growth at the time of last follow-up (−0.8 ± 0.2 SDS).

Discussion

Among the three known types of primary hyperoxaluria, PH1—PH3, infantile PH1 is the most common and aggressive one which shows rapid progression to ESRD within the first few years of life (12, 15). Before new RNA interference-based therapeutic options (RNAi) became available in 2020, which target the reduction of liver oxalate production (16), CLKT or KALT was preferentially performed in patients with severe forms of PH1 who did not benefit from or respond to vitamin B6 therapy (13, 14). Although liver transplantation corrects the underlying metabolic disorder, the harm by the already existing body oxalate pool is devastating and besides renal failure, patients suffer extremely from bone disease and skeletal disorders (5–7, 9). While several studies describe the bone morphological and skeletal changes in patients with PH1 (5–7, 9), only few reports focus on the long term follow up of patients who successfully underwent CLKT or KALT (13, 15, 17). We have previously reported a favorable surgical outcome in pediatric PH1 patients undergoing CLKT or KALT (13) and provide new evidence that these patients partially recover from bone disease. Especially, bone pain disappeared in all patients within 18 months following Tx and they showed a moderate catch-up growth and bone re-calcification. Plasma oxalate levels dropped under the saturation level within 6 months and further electrolyte disturbances were not different from other patients who underwent HD and renal transplantation for other reasons. Our results are in good agreement with other studies showing that patients show at least a moderate catch-up-growth within the observation period (17).

Our paper tries to address two important facts of PH1 bone disease: First, it is a description of the current subjective and objective bone markers of a rare metabolic disorder, such as occurrence of bone pain, amount and quality of pathological fractures and disturbances of the electrolyte and vitamin-D-

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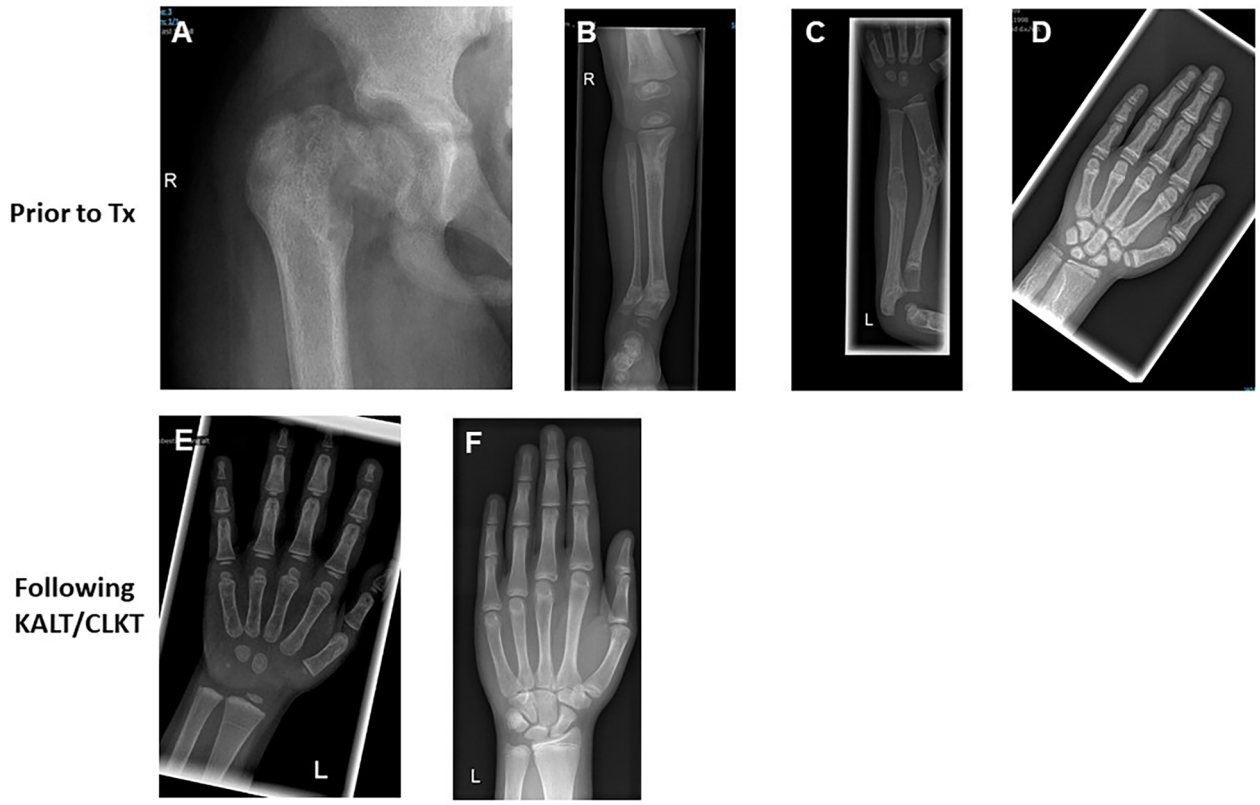

FIGURE 1
Skeletal changes in patients with PH1 prior and post CLKT and KALT. (A) ♀, 10 years, HD + PD; reduced bone calcification; osteopenic diaphysis; femoral head slipped to caudal (e.g., pathologic fracture of the femoral neck; older fatigue fractures). (B) ♂, 2 years, HD, uncompleted fracture of the right medial tibia in an area of increased sclerosis. (C) ♂, 5 years, HD, condition after KALT (no kidney function); constant dystrophy and increased sclerosis of radius and ulna with zigzag of the bone; several older fractures. (D) ♀, 11 years, HD + PD; increasing spotted decalcification of the sceletal system. (E) ♀, 2.7 years, condition after KALT 12 months before; calcification only slightly decreased. (F) ♂, 16 years, condition after CLKT; only slight bone sclerosis; no signs of renal osteopathy.

TABLE 2 Time course of eGFR, plasma oxalate, blood chemistry and SDS height of patients with PH1.

	Prior to CLKT/KALT ($n = 10$)	6 months ($n = 10$)	12 months ($n = 10$)	18 months ($n = 10$)	24 months ($n = 10$)	30 months ($n = 10$)
eGFR (ml/min/1.73 m^2)	Treated with dialysis	81 ± 12	75 ± 12	83 ± 9	80 ± 6	80 ± 6
Bone pain (n)	7	5	3	2	–	–
Height (SDS)	−1.1 ± 0.4	−1.1 ± 0.5	−1.1 ± 0.3	−0.9 ± 0.4	−0.8 ± 0.3	−0.8 ± 0.2
Plasma oxalate (µmol/L)	115 ± 40	12 ± 10	11 ± 8	nm	nm	nm
PTH (pg/ml)	258 ± 12	160 ± 110	55 ± 15	65 ± 15	60 ± 14	82 ± 1
25-hydroxy-vitamine D (ng/ml)	28 ± 10	30 ± 8	22 ± 4	25 ± 12	24 ± 7	29 ± 6
Calcium (mmol/L)	2.3 ± 0.2	2.0 ± 0.4	2.0 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.4
Phosphorus (mmol/L)	3.4 ± 2.2	2.1 ± 0.9	1.8 ± 0.2	1.8 ± 0.8	1.9 ± 1.1	1.5 ± 0.3
AP (U/L)	538 ± 210	236 ± 73	229 ± 58	199 ± 48	210 ± 30	214 ± 15

Nm, not measured; eGFR, estimated glomerular filtration rate; AP, alkaline phosphatase; PTH, Parathyroid hormone; SDS, Standard deviation score.

related metabolism. Pathological fractures occurred in all age groups and seemed to be independent from the length of ESRD or time spent on dialysis. However, the changes were more predominant in young children who did not receive an intensified HD protocol from the beginning, e.g., patient # 10, who came as fugitive and had received CAPD instead of HD for a longer period. We have recently demonstrated that only an intensified HD protocol is capable to reduce plasma oxalate levels significantly (1) and might therefore reduce the effects caused by the disturbed bone metabolism (12, 18). However, there is no clear evidence in the literature whether severity of bone disease is linked to individual plasma oxalate levels or the

TABLE 3 Plasma oxalate levels (μmol/L) prior and post transplantation, stratified by transplantation mode (CLKT or KALT).

Patient # (CLKT)	Prior to transplantation ($n = 4$)	6 months ($n = 4$)	12 months ($n = 4$)
1	116	7	6
2	156	8	7
3	187	5	5
4	89	4	5
Mean ± SD	137 ± 43	6 ± 2	6 ± 1
Patient # (KALT)	**Prior to transplantation ($n = 6$)**	**6 months ($n = 6$)**	**12 months ($n = 6$)**
5	145	20	18
6	89	12	14
7	89	25	30
8	89	8	12
9	56	3	8
10	130	35	7
Mean ± SD	98 ± 30	17 ± 12	15 ± 8

accumulated body oxalate pool (6, 15). Secondly, and this is new and important in this retrospective analysis, many changes were at least partially reversible regardless of the age of onset and we describe an approximate time course following CLKT and KALT. Although patients will probably never gain a normal catch-up-growth or complete bone repair, our study might add important information to provide a quantitative severity score in the future. However, it is very challenging to diagnose bone metabolism and link the outcome to certain metabolic parameters (18). Analysis of the previous few pediatric descriptions are important and necessary, but are more of historic value and have to be reevaluated in the near future when long-term studies of PH1 patients undergoing newer therapeutic strategies are available (12, 15–18). So far, it remains only speculative whether new therapeutics have the potential to fully replace liver transplantation in the future. In our opinion, this is highly dependent on the already existing individual damage of systemic oxalosis, the age of onset of renal failure and probably the underlying genotype. We are currently treating a one year old girl from Sri Lanka who was diagnosed with infantile oxalosis at the age of 2 months. The patient carries a very pathogenic loss of function mutation in Exon 1 of the *AGXT* gene (p.Lys21Glnfs*156), receives an intensified HD and PD treatment and is treated with lumasiran from her third months of life. She is now one year old and only poorly responding to the new therapy with oxalate levels remaining very high. In this case, it is hard to imagine that only renal transplantation is sufficient to improve the girl's outcome.

Our study has several limitations, primarily caused by its small size and descriptive and retrospective character. Furthermore, our study has a selection bias since we mainly report patients who were exclusively transferred to our center for the option of CLKT or KALT and underwent more or less intensified dialysis protocols in their countries of origin. Unfortunately, we did not follow a specific protocol or schedule of bone health assessment in our study and bone pain was determined unsystematically and not assessed qualitatively from indirect markers such as patient's history, local swelling, sensitivity to touching and local irritation. However, all patients' records were screened for bone specific comments or unforeseeable radiologic examinations. The skeletal status pre and post-transplantaton was derived from Xray analysis only when needed and bone mineral density was not measured (5). The epidemiology of bone impairment is difficult to assess, and it remains unclear whether certain levels of plasma oxalate or urine oxalate excretion are linked to the severity of bone disease. Xrays are only indirect, surrogate markers and do not allow exact interpretation of the bone mineralization or level of osteodystrophy. However, osteosclerosis, decalcification and calcification prior and post transplantation can be assessed satisfactorily by conventional Xrays and might therefore be sufficient to evaluate the stability of the bone.

In conclusion, patients diagnosed with PH1 suffer from severe consequences of systemic oxalosis and show a disturbed bone metabolism. Following successful CLKT or KALT, changes of bone morphology are partially reversible and patients suffer less from bone pain and show at least a moderate catch-up growth within a couple of years. Future prospective studies are necessary to evaluate whether modern therapies like lumasiran make liver transplantation or CLKT obsolete and have an impact on the severity of bone disease.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics committee of the University of Duisburg-Essen. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by- product of routine care or industry. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

RB: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Project administration,

Supervision, Writing – original draft. LP: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. AB: Conceptualization, Data curation, Formal Analysis, Methodology, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 30-month analysis of the phase 3 ILLUMINATE-B trial

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Background: Primary hyperoxaluria type 1 (PH1) is a genetic disorder resulting in overproduction of hepatic oxalate, potentially leading to recurrent kidney stones, nephrocalcinosis, chronic kidney disease, and kidney failure. Lumasiran, the first RNA interference therapeutic approved for infants and young children, is a liver-directed treatment that reduces hepatic oxalate production. Lumasiran demonstrated sustained efficacy with an acceptable safety profile over 12 months in infants and young children (age <6 years) with PH1 in ILLUMINATE-B (clinicaltrials.gov: NCT03905694), an ongoing, Phase 3, multinational, open-label, single-arm study.
Methods: Here, we report interim efficacy and safety findings from ILLUMINATE-B following 30 months of lumasiran treatment. Eligible patients had an estimated glomerular filtration rate (eGFR) >45 ml/min/1.73 m^2 if ≥12 months old or normal serum creatinine if <12 months old, and a urinary oxalate to creatinine ratio (UOx:Cr) greater than the upper limit of normal. All 18 patients enrolled in ILLUMINATE-B completed the 6-month primary analysis period, entered an extension period of up to 54 months, and continue to participate in the study.
Results: At Month 30, mean percent change from baseline in spot UOx:Cr was −76%, and mean percent change in plasma oxalate was −42%. eGFR remained stable through Month 30. In 14 patients (86%) with nephrocalcinosis at baseline, nephrocalcinosis grade improved at Month 24 in 12; no patient worsened. In the 4 patients without baseline nephrocalcinosis, nephrocalcinosis was absent at Month 24. Kidney stone event rates were ≤0.25 per person-year through Month 30. Mild, transient injection site reactions were the most common lumasiran-related adverse events (17% of patients).

Abbreviations
AEs, adverse events; BSA, body surface area; eGFR, estimated glomerular filtration rate; GalNAc, triantennary N-acetylgalactosamine; GO, glycolate oxidase; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantitation; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; RNAi, RNA interference; SEM, standard error of the mean; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

Conclusion: In infants and young children with PH1, long-term lumasiran treatment resulted in sustained reductions in urinary and plasma oxalate that were sustained for 30 months, with an acceptable safety profile. Kidney function remained stable, low kidney stone event rates were observed through Month 30, and nephrocalcinosis grade improvements were observed through Month 24.

Clinical Trial Registration: https://clinicaltrials.gov, identifier NCT03905694.

KEYWORDS

kidney, liver, lumasiran, oxalate, pediatric, rare diseases, RNA interference, primary hyperoxaluria type 1

1 Introduction

Primary hyperoxaluria type 1 (PH1; OMIM #259900) is an autosomal recessive disease resulting from excess production of hepatic oxalate, potentially leading to kidney stones, nephrocalcinosis, and eventually chronic kidney disease, kidney failure, and deposition of calcium oxalate crystals in body organs, including bone, heart, and eyes (systemic oxalosis) (1–5). The phenotype is variable, with high mortality associated with infantile oxalosis (4, 6–8). Symptoms of PH1, as well as hyperhydration treatment, are associated with a substantial burden, negatively impacting quality of life (9, 10). Prompt diagnosis and treatment are critical to reduce oxalate production and mitigate the impact of excess oxalate on the kidneys and other organs (8).

Historically, treatment for PH1 has consisted mainly of supportive measures to delay or minimize oxalosis, and reactive measures to address ongoing oxalosis and associated damage (2, 11). Patients not on dialysis may be treated with hyperhydration and crystallization inhibitors, and pyridoxine (vitamin B6) may be administered. However, pyridoxine may only be effective in pyridoxine-responsive patients (e.g., those with the c.508 G>A [p.Gly170Arg] mutation (4, 12). Hemodialysis to reduce oxalate levels in the blood becomes essential as kidney function deteriorates, but it is often insufficient to prevent manifestations of systemic oxalosis (1, 13, 14). Replacement of the defective native liver carries significant risk of morbidity and mortality (1, 15).

Lumasiran, an RNA interference (RNAi) therapeutic (ie, one involving targeted inhibition of gene expression) that is directed to the liver (16), has been approved in the European Union "for the treatment of PH1 in all age groups" (17) and in the United States "for the treatment of PH1 to lower urinary oxalate (UOx) and plasma oxalate (POx) in pediatric and adult patients" (18). Lumasiran consists of a double-stranded small interfering RNA that is covalently linked to triantennary N-acetylgalactosamine (GalNAc), allowing for targeted delivery to the liver (16, 19, 20). In PH1, glyoxylate levels are increased due to pathogenic variants in the *AGXT* gene and deficient activity of AGT, an enzyme that metabolizes glyoxylate to glycine (21). Lumasiran causes the mRNA-encoding glycolate oxidase (GO; OMIM #605023) to be degraded, hence reducing glyoxylate, a substrate for oxalate production (19).

The lumasiran clinical development program in PH1 comprises 5 clinical trials in which a total of 98 patients were enrolled, including people of different ages and degrees of PH1 severity (19). The Phase 3, single-arm ILLUMINATE-B study (NCT03905694) is being conducted to examine lumasiran's efficacy and safety in infants and young children (age <6 years) with PH1 and estimated glomerular filtration rate (eGFR) >45 ml/min/1.73 m^2 (22, 23). During the 6-month primary analysis period, lumasiran demonstrated clinically important reduction relative to baseline in spot urinary oxalate to creatinine ratio (UOx:Cr) by 72% (22). The most common treatment-related adverse events (AEs) were transient, mild injection site reactions (22). After 6 more months of treatment, during a long-term extension period, the efficacy and safety of lumasiran were maintained (23).

Here, we report efficacy and safety findings from ILLUMINATE-B following 30 months of lumasiran treatment.

2 Materials and methods

2.1 Study design and patients

ILLUMINATE-B is an ongoing, Phase 3, multinational, open-label, single-arm study. A primary analysis was conducted at 6 months; patients are now in an extension period of up to 54 months. The study design and eligibility criteria have been described previously (22, 23). Briefly, eligible patients had a genetically confirmed diagnosis of PH1, were <6 years old at study entry, had an eGFR >45 ml/min/1.73 m^2 if ≥12 months old or normal serum creatinine if <12 months old, and a UOx:Cr greater than the upper limit of normal (ULN) for age. Lumasiran was administered subcutaneously according to a dosing regimen based on body weight (Table 1). All patients received lumasiran as 3 loading doses, once monthly (at Day 1, at Month 1, and at Month 2) at a dose based on body weight category, then received lumasiran either once monthly (patients

TABLE 1 Dosing regimen of lumasiran.

Body weight	Loading dose	Maintenance dose (begin 1 month after the last loading dose)
<10 kg	6.0 mg/kg once monthly for 3 doses	3.0 mg/kg once monthly
10 kg to <20 kg	6.0 mg/kg once monthly for 3 doses	6.0 mg/kg once every 3 months (quarterly)
≥20 kg	3.0 mg/kg once monthly for 3 doses	3.0 mg/kg once every 3 months (quarterly)

weighing <10 kg) or once every 3 months (patients weighing ≥10 kg) at the maintenance dose, beginning at Month 3.

2.2 Details of ethics approval

The study protocol and amendments and informed consent form were reviewed and approved by Independent Ethics Committees/Institutional Review Boards prior to commencement of the study. This study was conducted in accordance with Good Clinical Practice as defined by the International Council on Harmonisation, the principles defined in the Declaration of Helsinki and its amendments, and all applicable national and international laws. Legal guardians provided informed consent and patients provided assent per local regulations and institutional standards.

2.3 Endpoints

The primary endpoint was percent change in spot UOx:Cr from baseline to Month 6, as described previously (22). Spot urine samples were used as an alternative to 24-hour UOx levels due to the inability of young children to comply with 24-hour urine collections (24–26). Secondary endpoints assessed in the extension period included absolute and percent change from baseline in UOx excretion, proportion of patients with UOx excretion less than or equal to the ULN and ≤1.5 × ULN for age, absolute and percent change from baseline in POx, and change from baseline in eGFR (23). The ULN for spot UOx:Cr is age-dependent and was based on Matos et al. (1999) (27) to account for an age-related decline that occurs in infants and young children. Exploratory endpoints included changes in nephrocalcinosis grade, kidney stone event rates, and plasma glycolate (23).

2.4 Assessments

Spot UOx and plasma glycolate were measured with validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays. Spot UOx was expressed relative to creatinine (spot UOx:Cr). POx was measured with a novel, validated LC-MS/MS assay (28). eGFR was calculated for patients ≥12 months old using the Schwartz Bedside formula (29); eGFR was not calculated for patients <12 months old as the Schwartz Bedside formula is not validated for that age group (29). Drug antibodies against lumasiran were evaluated in plasma using a validated enzyme-linked immunoassay.

Kidney stone events were adjudicated by the investigator. A kidney stone event was defined as an event that included ≥1 of the following: visit to healthcare provider because of a kidney stone, medication for renal colic, stone passage, or macroscopic hematuria due to a kidney stone.

Renal ultrasounds were performed at baseline and Months 6, 12, and 24 (but not Month 30) and read by a central radiologist. Changes from baseline in nephrocalcinosis grade were categorized as follows, accounting for both kidneys: no change (stable), improving (which was further categorized into improving and improving to complete resolution), worsening, and indeterminate (defined as 1 kidney improving and 1 worsening).

2.5 Statistical analysis

This analysis was conducted using data as of a cutoff date of April 29, 2022, after all active study patients had completed their Month 30 visit.

All efficacy analyses were conducted in the efficacy analysis set, defined as all patients who received any amount of lumasiran and had ≥1 valid spot UOx:Cr value at baseline and ≥1 valid spot UOx:Cr value from assessments at Month 3 to Month 6. Percent and absolute change in POx from baseline were additionally analyzed in the POx analysis set, which included only patients in the efficacy analysis set whose baseline POx was ≥1.5 times the lower limit of quantitation (LLOQ; 5.55 µmol/L). The kidney stone event rate was calculated as the total number of kidney stone events divided by the total patient exposure time (events per person-year). The 95% CI for the kidney stone event rate was obtained using a generalized linear model for a Poisson distribution unless the rate was 0, in which case the upper bound of the 95% CI was calculated using the exact Poisson method.

A pyridoxine-responsive (PR) genotype was defined as NM_000030.3(AGXT):c.508G>A (p.Gly170Arg) or NM_000030.3 (AGXT):c.454T>A (p.Phe152Ile), where N denotes nonsense and M denotes missense (30).

Cumulative safety data from the first dose of lumasiran through the data cutoff date are reported. Safety analyses were conducted in the safety analysis set, defined as all patients who received any amount of lumasiran. Duration of exposure to study drug was calculated using calendar months [duration of treatment (days)/30.44], whereas for study visits, 1 month was defined as 4 weeks (28 days).

All statistical analyses were performed using validated SAS statistical software, version 9.4.

3 Results

3.1 Patients

All 18 patients who enrolled in the study entered the extension and continue to participate. Baseline demographic and clinical characteristics are shown in Table 2.

3.2 Efficacy

Mean spot UOx:Cr decreased from 0.63 mmol/mmol at baseline to 0.11 mmol/mmol at Month 30; mean [standard error of the mean (SEM)] percent change from baseline was −75.8% (4.5%) (Figure 1; Table 3). Thirteen of 18 patients (72%) had spot UOx:Cr values ≤1.5 × ULN at Month 30, and 7 (39%) had spot UOx:Cr values ≤ ULN (Table 3). The percent change from

TABLE 2 Baseline demographic and clinical characteristics.

Characteristic	All treated (N = 18)
Age at consent, median (range), months	50.1 (3–72)
Age at diagnosis, median, months	16.3
Time from diagnosis to first dose date, median, months	23.5
Genotype,[a] n (%)	
PR/*	3 (17)
M/M or M/N	10 (56)
N/N	5 (28)
Pyridoxine use, n (%)	11 (61)
Spot UOx:Cr, median (range), mmol/mmol[b,c]	0.469 (0.166–1.708)
24-hour UOx corrected for BSA, mean (SEM), mmol/24 h/1.73 m^2	2.083 (0.3170)
POx, median (range), µmol/L[d]	11.5 (6.6–30.6)
eGFR, median (range), ml/min/1.73 m^2[e]	111 (65–174)
History of kidney stone events in past 12 months, n (%)	3 (17)
Presence of nephrocalcinosis at baseline, n (%)	14 (78)

[a]PR was defined as NM_000030.3(AGXT):c.508G>A (p.Gly170Arg) or NM_000030.3 (AGXT):c.454T>A (p.Phe152Ile). M and N were defined based on a publication by Mandrile et al. (30). The asterisk (*) denotes any genotype of PR, M, or N. M, missense; N, nonsense; PR, pyridoxine-responsive.
[b]1 mmol/mmol = 0.796 mg/mg.
[c]Age-related reference ranges in spot UOx:Cr: <1 year, 0.015–0.26 mmol/mmol; 1 to <5 years, 0.011–0.12 mmol/mmol; 5 to 12 years, 0.06–0.15 mmol/mmol (11, 31).
[d]ULN = 12.11 µmol/L for POx, as determined based on data from 75 healthy adults (22).
[e]eGFR was calculated based on the Schwartz Bedside formula (29) for patients ≥12 months, N = 16; eGFR was not calculated for 2 patients because their age at baseline was <12 months.
BSA, body surface area; eGFR, estimated glomerular filtration rate; POx, plasma oxalate; SEM, standard error of the mean; UOx:Cr, urinary oxalate:creatinine ratio.

baseline in 24-hour UOx was similar in the 4 patients who were able to provide samples (Table 3).

Mean POx decreased from 13.2 µmol/L at baseline to 6.3 µmol/L at Month 30 (ULN: 12.11 µmol/L); mean (SEM) percent change from baseline was −42.5% (6.0%) (Figure 2; Table 3). In patients with baseline POx ≥1.5 × LLOQ (N = 13), mean (SEM) POx decreased from 15.6 µmol/L at baseline to 6.4 µmol/L at Month 30; mean percent change from baseline was −53.0% (5.4%) (Table 3).

eGFR remained stable with a mean (SEM) of 112.8 (6.9) ml/min/1.73 m^2 at baseline and 112.5 (6.7) ml/min/1.73 m^2 at Month 30 (Figure 3; Table 3). Nephrocalcinosis was present at baseline in 14 of 18 patients. Among the 14 patients with nephrocalcinosis at baseline, nephrocalcinosis grade improved at Month 24 in 12 (86%), was indeterminate in 1 (7%), and remained stable in 1 (7%) (Figure 4). Two of the 14 patients improved to complete resolution (Figure 4). The 4 patients who had no nephrocalcinosis at baseline remained stable, with no nephrocalcinosis at Month 24. Kidney stone event rates were ≤0.25 per person-year through Month 30 (Figure 5).

Plasma glycolate initially increased, then plateaued, during the 6-month primary analysis period; thereafter, plasma glycolate declined slightly but remained elevated, as expected based on the mechanism of action of lumasiran (Figure 6).

Decisions regarding adjustments to hyperhydration and/or vitamin B6 regimens after Month 6 were left to the discretion of study investigators. Three of 13 patients on hyperhydration at

TABLE 3 Secondary efficacy endpoints.

	Lumasiran (N = 18)				
	Month 6	Month 12	Month 18	Month 24	Month 30
Change from baseline in spot UOx:Cr, mean (SEM)					
Absolute change from baseline, mmol/mmol[a]	−0.5 (0.1)	−0.5 (0.1)	−0.5 (0.1)	−0.5 (0.1)	−0.5 (0.1)
Percent change from baseline	−71.7 (3.4)	−71.9 (3.2)	−76.9 (3.9)	−75.4 (4.0)	−75.8 (4.5)
Patients with spot UOx:Cr, n (%)					
≤ULN[b]	1 (6)	2 (11)	3 (17)	3 (18)	7 (39)
≤1.5 × ULN[b]	9 (50)	10 (56)	11 (61)	7 (41)	13 (72)
Change from baseline corrected for BSA in 24-hour UOx, mean (SEM)[c]					
Absolute change from baseline mmol/24 h/1.73m^2	−1.4 (0.1)	−1.2 (0.3)	−1.5 (0.1)	−1.6 (0.1)	−1.5 (0.4)
Percent change from baseline	−68.4 (5.6)	−63.2 (7.2)	−75.2 (4.3)	−72.9 (3.4)	−73.5 (8.8)
Absolute change from baseline in POx, mean (SEM)[d]					
In efficacy analysis set	−5.0 (1.3)	−7.3 (1.5)	−7.1 (1.6)	−6.3 (1.8)	−6.9 (1.6)
In POx analysis set[e]	−6.5 (1.6)	−9.5 (1.7)	−9.5 (1.8)	−9.0 (1.9)	−9.2 (1.8)
Percent change from baseline in POx, mean (SEM)[d]					
In efficacy analysis set	−32.1 (6.7)	−47.1 (4.6)	−42.6 (6.4)	−33.9 (10.7)	−42.5 (6.0)
In POx analysis set[e]	−37.4 (8.8)	−56.4 (3.8)	−55.6 (4.7)	−51.0 (7.0)	−53.0 (5.4)
Change from baseline in eGFR, mean (SEM), ml/min/1.73 m^2[f]	−0.3 (3.8)	−1.5 (4.4)	−8.9 (3.6)	−3.2 (4.8)	−2.0 (4.7)

[a]One mmol/mmol = 0.796 mg/mg; 1 mmol/mmol = 1,000 mmol/mol.
[b]Age-dependent ULN (27).
[c]In patients with valid 24-hour UOx measurements; N = 2 at Month 6, N = 4 at Month 12, N = 2 at Month 18, N = 3 at Month 24, N = 4 at Month 30.
[d]ULN = 12.11 µmol/L for POx, as determined based on data from healthy adults (22).
[e]In patients with baseline POx ≥1.5 × LLOQ [5.55 µmol/L (N = 13); values below LLOQ were assigned a value of 5.55 µmol/L].
[f]eGFR (ml/min/1.73 m^2) was calculated based on the Schwartz Bedside formula (29) for patients ≥12 months old; N = 16 at Month 6, N = 16 at Month 12, N = 16 at Month 18, N = 16 at Month 24, N = 15 at Month 30.
BSA, body surface area; eGFR estimated glomerular filtration rate; LLOQ lower limit of quantitation; POx, plasma oxalate; SEM, standard error of the mean; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr urinary oxalate:creatinine ratio.

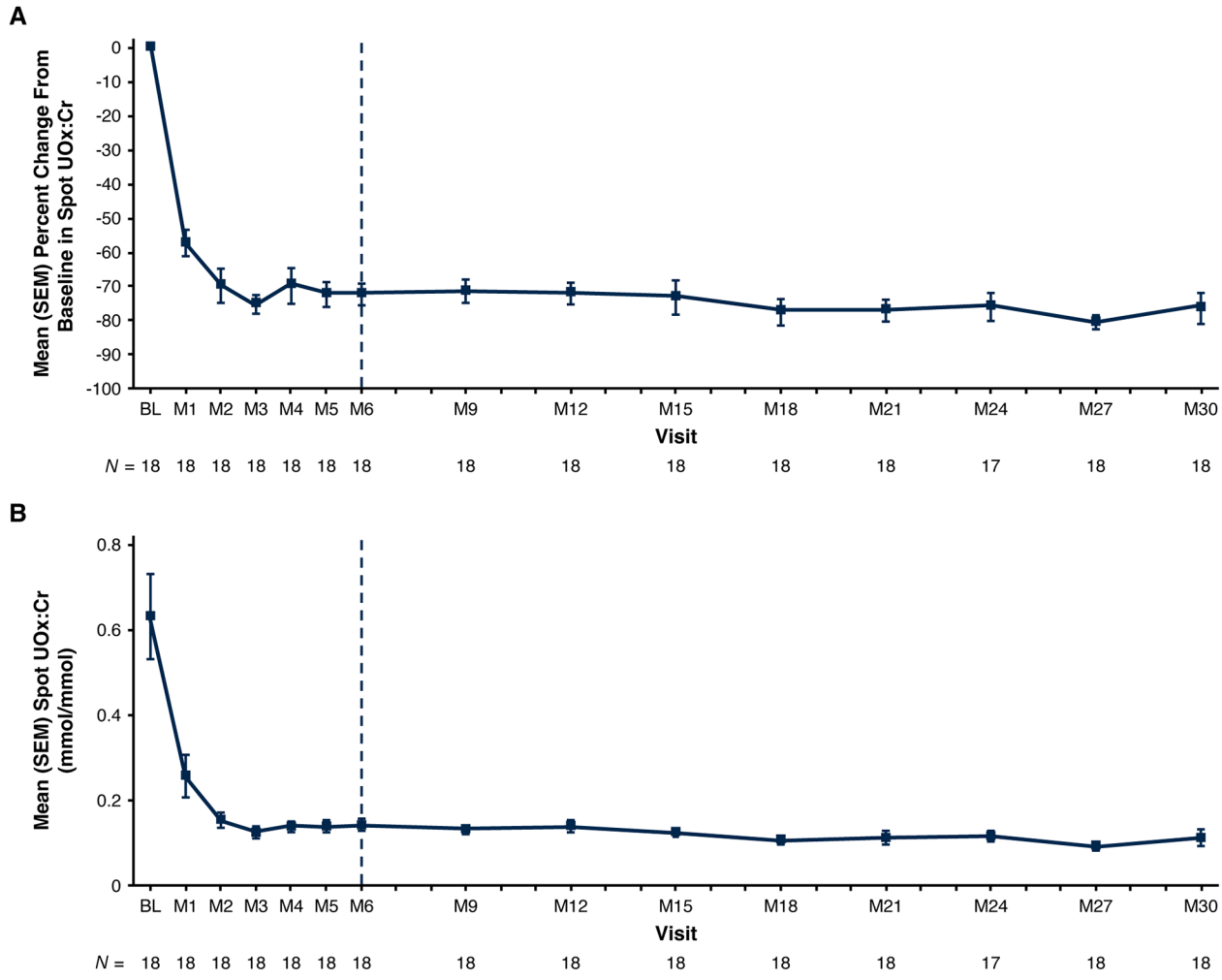

FIGURE 1
Mean (SEM) spot UOx:Cr. **(A)** Percent change from baseline at each visit and **(B)** actual values at each visit.[a] Baseline value represents the mean of all assessments collected prior to the first dose of lumasiran; 1 mmol/mmol = 0.796 mg/mg; 1 mmol/mmol = 1,000 mmol/mol. End of the primary analysis period is represented by the vertical dashed line. [a]The ULN for spot UOx:Cr is age-dependent (27). Age-related reference ranges in spot UOx:Cr: < 1 year, 0.015–0.26 mmol/mmol; 1 to <5 years, 0.011–0.12 mmol/mmol; 5 to 12 years, 0.06–0.15 mmol/mmol (11, 31). BL, baseline; M, month; SEM, standard error of the mean; ULN, upper limit of normal; UOx:Cr, urinary oxalate:creatinine ratio.

baseline decreased it during the extension period; no patients started hyperhydration during the study. After Month 6, 5 of 11 patients taking vitamin B6 at baseline stopped vitamin B6, 2 reduced their dose without stopping, and no patients started vitamin B6. There was no meaningful change in UOx:Cr ratios in patients who decreased or stopped hyperhydration or vitamin B6.

3.3 Safety

As of the cutoff date (April 29, 2022), median (range) exposure to lumasiran was 32.6 (27.5-35.3) months. Five (28%) patients had AEs deemed by the investigator to be related to lumasiran (Table 4). The most common lumasiran-related AEs were mild, transient injection site reactions [3 patients (17%)]; symptoms included erythema, discoloration, and pain at the injection site. One patient had a serious AE of viral infection (moderate in severity and considered unrelated to lumasiran), as reported previously (23).

There were no clinically relevant changes related to lumasiran in laboratory measures, vital signs, or electrocardiograms. One patient had an AE of blood bicarbonate decreased that was deemed by the investigator to be unrelated to lumasiran. At baseline, the patient had an eGFR of 134 ml/min/1.73 m^2 and a bicarbonate value of 19 mmol/L, and was on a stable dose of oral sodium bicarbonate for PH1. The AE of blood bicarbonate decreased was entered due to a bicarbonate of 18 mmol/L at Month 12; the dose of oral sodium bicarbonate was not changed.

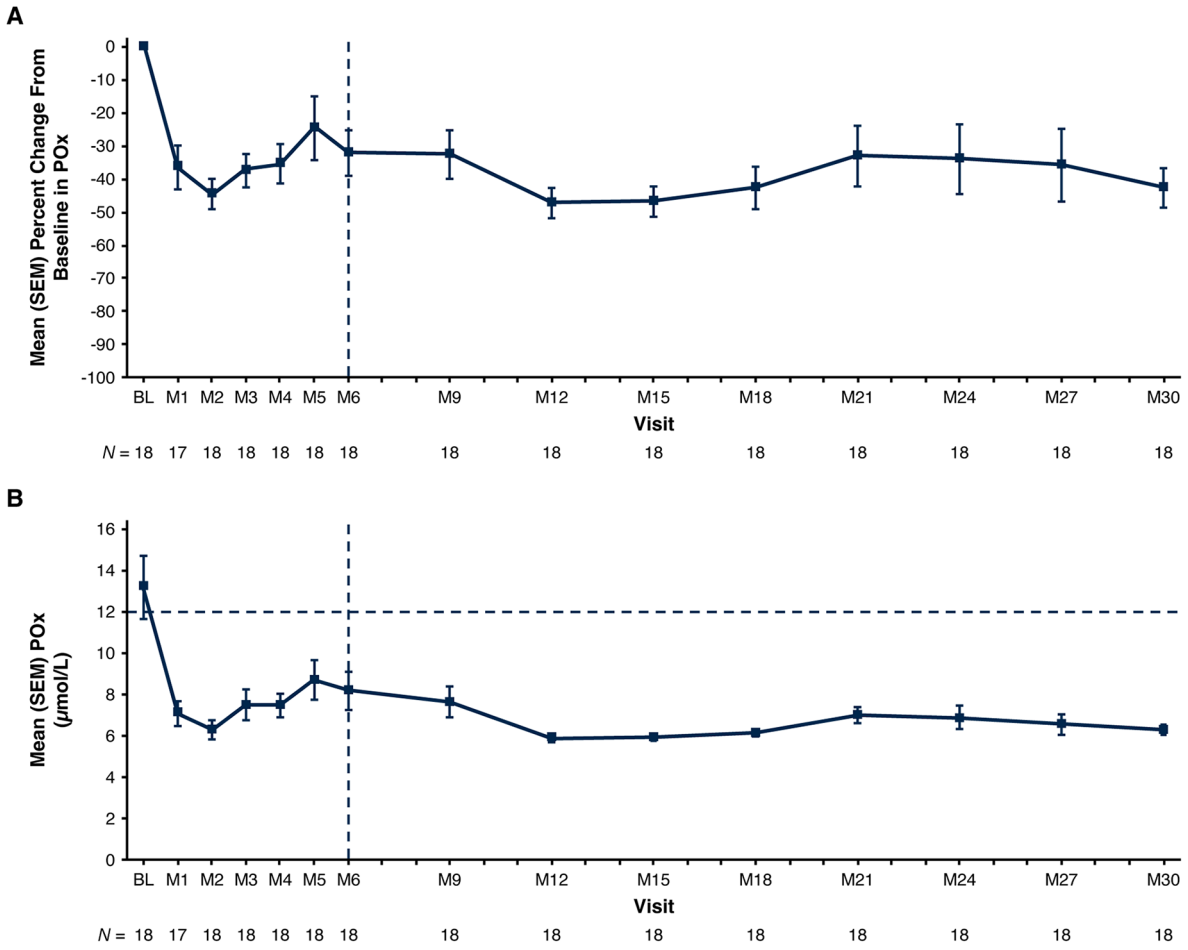

FIGURE 2
Mean (SEM) POx. (A) Percent change from baseline at each visit and (B) actual values at each visit. Baseline value represents the mean of all assessments collected prior to the first dose of lumasiran. The end of the primary analysis period is represented by the vertical dashed line. The ULN for POx, represented by the horizontal dashed line in panel B, is 12.11 µmol/L (determined based on data from 75 healthy adults) (22). The LLOQ is 5.55 µmol/L. Reductions in POx below the LLOQ were conservatively imputed as 5.55 µmol/L. BL, baseline; LLOQ, lower limit of quantitation; M, month; POx, plasma oxalate; SEM, standard error of the mean; ULN, upper limit of normal.

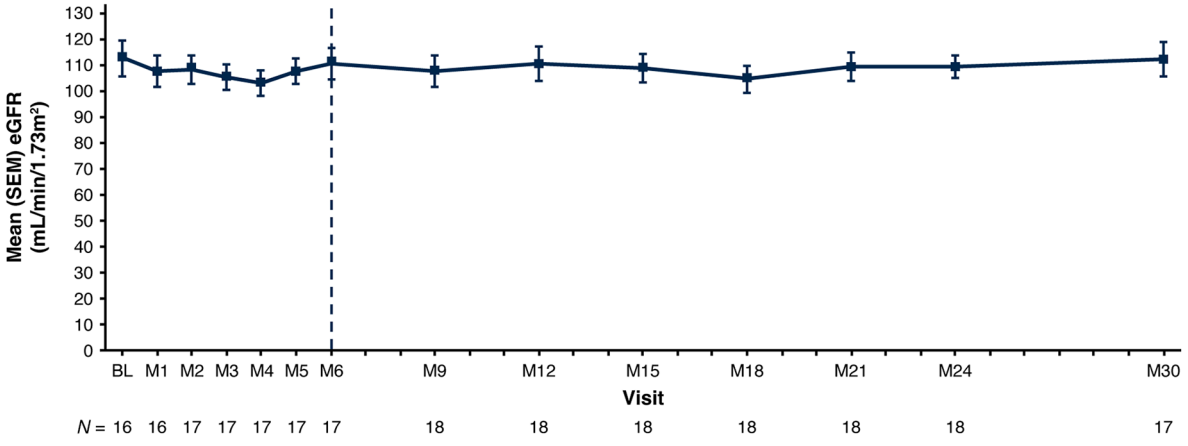

FIGURE 3
Mean (SEM) eGFR. Baseline is the last non-missing value collected prior to the first dose of lumasiran. The end of the primary analysis period is represented by the vertical dashed line. eGFR is calculated based on the Schwartz Bedside formula (29) in patients ≥12 months of age at the time of the assessment. BL, baseline; eGFR, estimated glomerular filtration rate; M, month; SEM, standard error of mean.

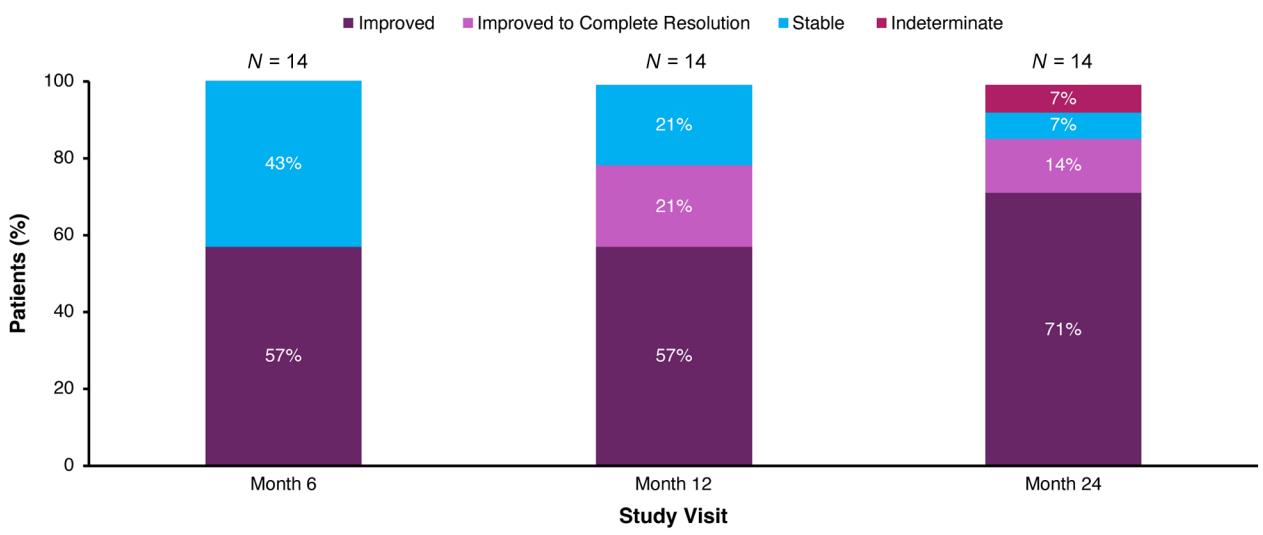

FIGURE 4
Change in medullary nephrocalcinosis grade in patients with nephrocalcinosis at baseline. Patients who had no nephrocalcinosis at baseline ($N = 4$) remained stable, with no nephrocalcinosis at Month 24; these patients are not depicted. Stable indicates grade same as baseline; improved indicates grade lower than baseline; and indeterminate indicates one side improved and the other side worsened. Renal ultrasound was not performed at Month 30.

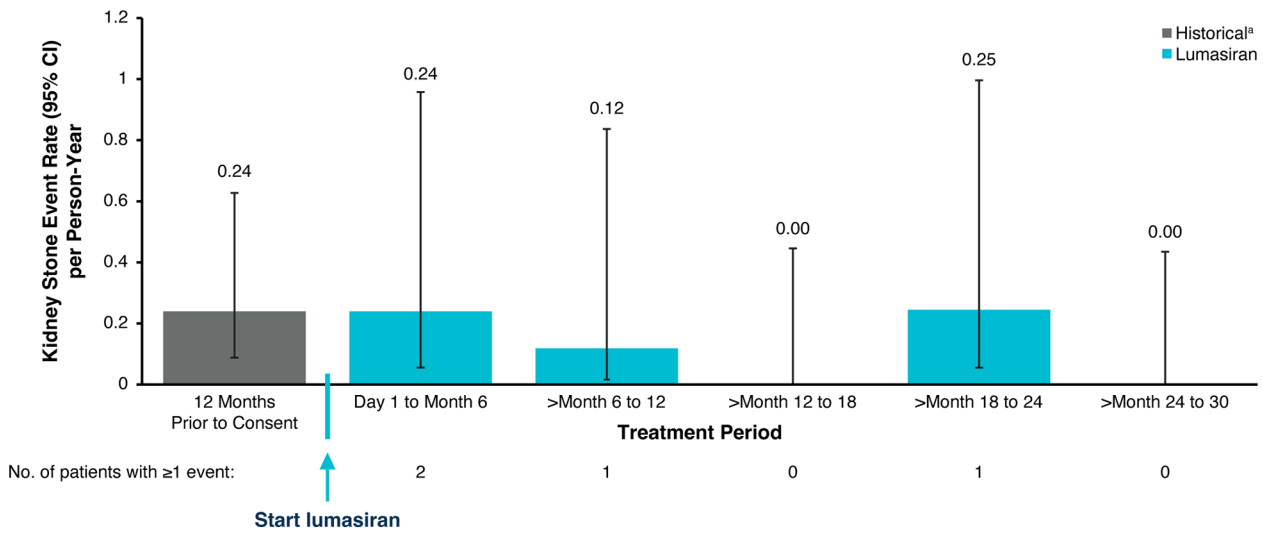

FIGURE 5
Kidney stone event rates. [a]Historical patient-reported history of kidney stone events. An annualized rate was not calculated for patients <6 months old. CI, confidence interval.

The AE was considered resolved after the bicarbonate value at Month 15 was 21 mmol/L. Plasma glycolate remained stably elevated. The patient received no treatment for the AE and remained on lumasiran.

Transient, low-titer (1:50) anti-drug antibodies were observed in 3 (17%) patients, with no observed impact on safety or efficacy. None of the patients tested positive for anti-drug antibodies at baseline.

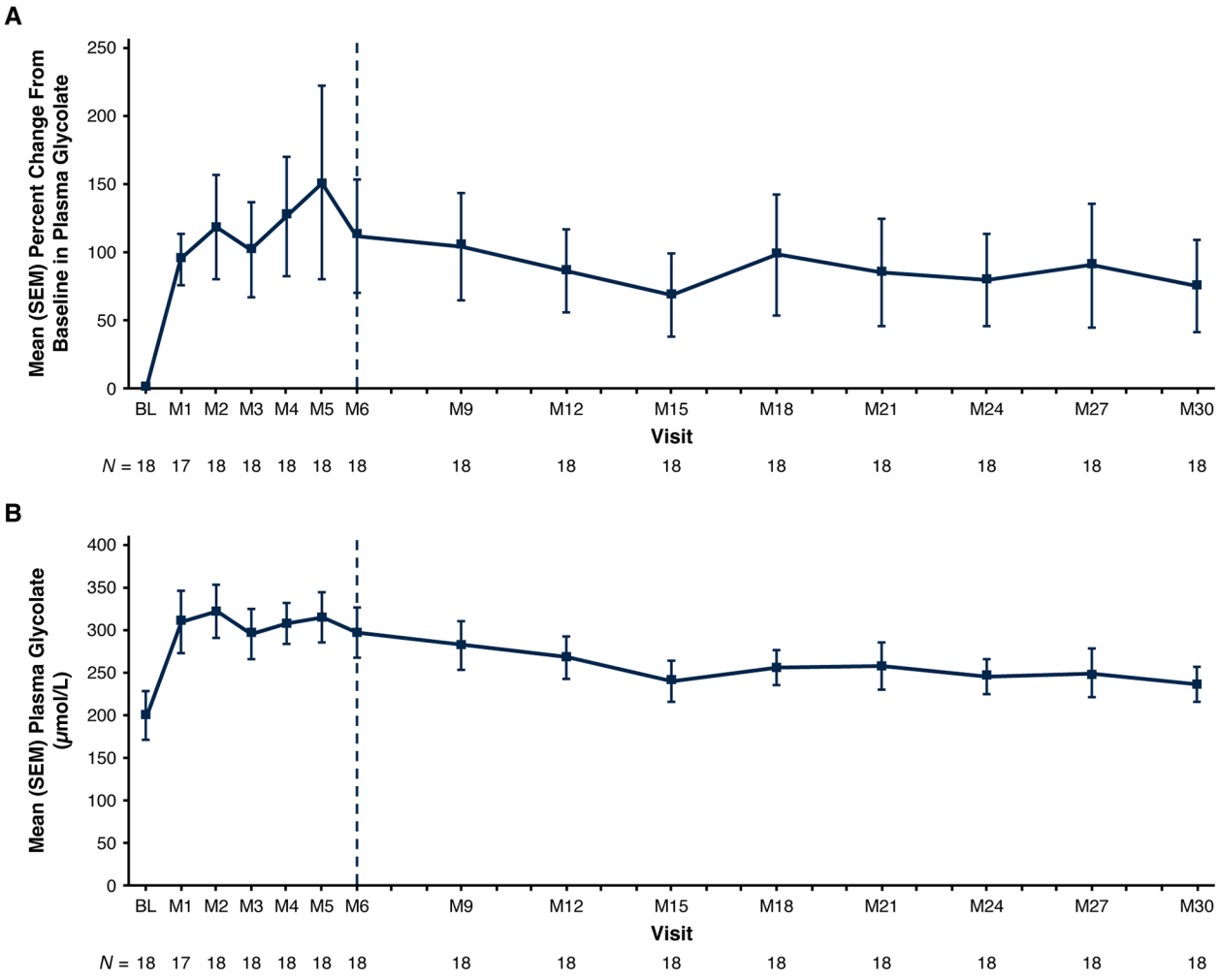

FIGURE 6
Mean (SEM) plasma glycolate. **(A)** Percent change from baseline at each visit and **(B)** actual values at each visit. Baseline value represents the mean of all assessments collected prior to the first dose of lumasiran. The end of the primary analysis period is represented by the vertical dashed line. BL, baseline; M, month; SEM, standard error of the mean.

TABLE 4 Safety profile of lumasiran.

	All treated (N = 18)
AEs	18 (100)
Treatment-related AEs[a]	5 (28)
AEs leading to treatment discontinuation	0
AEs leading to study withdrawal	0
Serious AEs	1 (6)[b]
Severe AEs	0
Death	0

[a]Treatment-related AEs included injection site reactions, transient blood bilirubin increase, and headache.
[b]One patient had a serious AE of viral infection (moderate in severity; considered unrelated to lumasiran by the investigator) during the 6-month primary analysis period, which was reported previously (22).
AE, adverse event.

4 Discussion

Lumasiran, the first approved treatment for PH1 (17, 18) and the first RNAi therapeutic to be studied and approved in infants and young children (22), is a disease-modifying therapy that addresses the source of hepatic oxalate overproduction in PH1 by substrate reduction leading to decreased hepatic oxalate synthesis (19). Long-term treatment with lumasiran was associated with sustained lowering of UOx excretion, stable renal function (eGFR), and improvements in medullary nephrocalcinosis in patients with PH1 who were <6 years of age and had an eGFR >45 ml/min/1.73 m^2 at baseline. Kidney stone event rates remained low. Plasma glycolate levels remained elevated, consistent with reduced hepatic glycolate

oxidase activity mediated by lumasiran; there are no known adverse consequences of elevated glycolate concentrations in blood (22, 23, 32).

Hyperhydration, or large daily fluid intake (proportionate to body size in children), may attenuate the effects of hyperoxaluria (9). However, hyperhydration requires a gastrostomy tube or nasogastric tube in some young children and negatively impacts quality of life; hence, adherence may be poor (9, 10, 33). In this study, hyperhydration status was recorded for all patients; 3 patients on hyperhydration decreased hyperhydration during the extension period, and none started it. Reducing the need for hyperhydration is likely to increase quality of life in patients with PH1 (10).

Vitamin B6 is recommended for patients with PH1 who have a vitamin B6–responsive genotype; it has been associated with a mean decrease in UOx of approximately 26% (34). In this study, 5 of 11 patients taking vitamin B6 at baseline stopped vitamin B6, 2 reduced their dose, and none started vitamin B6. Of the 5 patients who stopped taking vitamin B6, 3 had a pyridoxine-responsive genotype and 2 did not. This apparent reduction in the need for vitamin B6 with maintenance of UOx:Cr suppression strengthens the evidence for the efficacy of lumasiran.

Lumasiran demonstrated an acceptable safety profile; injection site reactions were the most commonly reported AE. There was only one serious AE (a viral infection) reported as of the Month 30 data cutoff, and it was not considered related to lumasiran. These findings suggest that RNAi therapy is safe for use in infants and small children. This is corroborated by recent case reports of lumasiran use in infants (35, 36) and young children (37).

Transient, low-titer (1:50) anti-drug antibodies were observed in 3 patients during the study. Similar findings of low-titer anti-drug antibodies in a minority of patients have been reported in other clinical studies of lumasiran, and, when assessed, no effect of anti-drug antibodies on lumasiran pharmacokinetics has been noted (22, 38–40). There was no observed impact of the anti-drug antibodies on efficacy or safety in this or other studies (22, 38, 40).

5 Conclusions

In infants and young children with PH1, lumasiran treatment resulted in reductions in UOx and POx that were maintained through Month 30. The safety profile of lumasiran was acceptable. Clinical assessments of kidney health were encouraging, including stable kidney function through Month 30 and improvement in nephrocalcinosis through Month 24. Kidney stone event rates were low through Month 30. The most common lumasiran-related AEs were mild, transient injection site reactions.

Data availability statement

Access to anonymized individual participant data that support these results is made available 12 months after study completion and not less than 12 months after the product and indication have been approved in the US and/or the EU. Requests for access to data can be submitted via the website http://www.vivli.org.

Ethics statement

The studies involving humans were approved by Independent Ethics Committees/Institutional Review Boards prior to commencement of the study. This study was conducted in accordance with Good Clinical Practice as defined by the International Council on Harmonisation, the principles defined in the Declaration of Helsinki and its amendments, and all applicable national and international laws. Legal guardians provided informed consent and patients provided assent per local regulations and institutional standards. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

YF: Conceptualization, Investigation, Methodology, Writing – review & editing. WH: Investigation, Writing – review & editing. HS-L: Investigation, Writing – review & editing. DS: Investigation, Writing – review & editing. MM: Investigation, Writing – review & editing. A-LS-L: Investigation, Writing – review & editing. JH: Investigation, Writing – review & editing. RW: Conceptualization, Data curation, Methodology, Writing – review & editing, Formal Analysis. JG: Conceptualization, Methodology, Writing – review & editing. DM: Conceptualization, Investigation, Methodology, Writing – review & editing.

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Conflict of interest

YF: consultancy fees from Alnylam Pharmaceuticals and membership in the safety review committee. WH: principal investigator for Alnylam Pharmaceuticals; travel and accommodation expenses from Alnylam Pharmaceuticals to attend an international investigators' meeting. HS-L: principal investigator for Alnylam Pharmaceuticals; travel and accommodation expenses from Alnylam Pharmaceuticals to attend international investigators' meetings. DJS: grants and other from Alnylam Pharmaceuticals and Dicerna Pharmaceuticals, and personal fees from Advicenne. MM: principal investigator for Alnylam Pharmaceuticals; served on advisory board for Novo Nordisk, Inc. ALS-L: consultancy fees from Alnylam Pharmaceuticals and Dicerna Pharmaceuticals, and principal investigator for research funded by OxThera. JH: consultancy fees from Alnylam Pharmaceuticals. RW and JMG: employees of and shareholders in Alnylam Pharmaceuticals; contributed to study design, data analysis, and (in partnership with all other authors) review and revision of the manuscript in accordance with the ethical principles of Good Publication Practice (GPP 2022) guidelines. DM: research funding, consultancy fees, and non-financial support from Alnylam Pharmaceuticals.

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Ultrasound analysis of different forms of hemolytic uremic syndrome in children

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Background: Hemolytic uremic syndrome (HUS) is the most common cause of acute kidney injury in children. It is mainly caused by Shiga toxin-producing enterohemorrhagic *Escherichia coli* (EHEC; STEC-HUS) and is more rarely caused by uncontrolled complement activation (cHUS). Renal replacement therapy is frequently required and kidney function recovers in the majority of patients. Ultrasound (US) is the preferred imaging modality for the evaluation of any renal failure. The aim of this study is the evaluation of US diagnostics in both HUS types at disease onset and in the course of the disease.
Materials and methods: Clinical, laboratory, and US data from the digital patient records of children admitted as inpatients with a diagnosis of HUS were recruited for a monocentric, retrospective analysis. STEC-HUS and cHUS were diagnosed when, in addition to the laboratory constellation, EHEC infection and complement system activation were verified, respectively. US examinations were performed by pediatricians with certified pediatric US experience.
Results: In total, 30 children with STEC-HUS (13/25 male; median age of disease onset 2.9 years; most prevalent EHEC serotype was O157) and cHUS (2/5 male; median age of disease onset 5.4 years; 3/5 with proven pathogenic variation) were included. Renal replacement therapy proportions were comparable in the STEC-HUS and cHUS patients (64% vs. 60%). The resistance index (RI) was elevated at disease onset in the patients with STEC-HUS and cHUS (0.88 ± 0.10 vs. 0.77 ± 0.04, $p = 0.13$) and was similar in the STEC-HUS subcohorts divided based on dialysis requirement (yes: 0.86 ± 0.1; no: 0.88 ± 0.1; $p = 0.74$). Total kidney size at disease onset displayed a positive correlation with dialysis duration ($R = 0.53$, $p = 0.02$) and was elevated in both HUS types ($177\% \pm 56$ and $167\% \pm 53$). It was significantly higher in the STEC-HUS subcohort which required dialysis (200.7% vs. 145%, $p < .029$), and a regressor kidney size threshold value of 141% was indicated in the receiver operating characteristic analysis. A classification model using both US parameters sequentially might be of clinical use for predicting the need for dialysis in patients with STEC-HUS. The US parameters normalized over time.
Conclusion: The US parameters of RI and total kidney size are valuable for the assessment of HUS at disease onset and during therapy, and may be helpful in the assessment of whether dialysis is required in patients with STEC-HUS.

KEYWORDS

hemolytic uremic syndrome, acute kidney failure, complement activation, dialysis, ultrasound, renal size, resistance index, children

Introduction

Hemolytic uremic syndrome (HUS) is the most common cause of acute kidney failure in children under the age of 5 years, requiring dialysis. HUS is a thrombotic microangiopathy (TMA) that appears histologically and pathophysiologically as damage to endothelial cells, the subsequent activation of platelets, and, following thrombotic occlusion of small vessels, ultimately tissue damage. The three eponymous symptoms are intravascular hemolysis, thrombocytopenia, and acute kidney injury (AKI) and they are sensitive but not specific for the diagnosis of HUS as there are numerous differential diagnoses of TMA; these are mainly thrombotic thrombocytopenic purpura (TTP), numerous autoimmune diseases, disseminated intravascular coagulation (DIC), some medications, and infections (1–4).

HUS is typically categorized as caused by infection with Shiga toxin-producing enterohemorrhagic *Escherichia coli* (EHEC; 90% of all HUS cases, "STEC-HUS") or as complement-mediated HUS ("cHUS"), usually caused by uncontrolled complement activation, among other HUS forms (2, 4).

The released Shiga toxin in STEC-HUS causes endothelial cell damage. The most frequent age at onset of the disease is between 2 and 5 years and there is no gender difference. The most common EHEC serogroup is O157:H7 (somatic O antigen 157 and flagellar H antigen 7) (5–7). A massive HUS outbreak in Germany with over 800 HUS cases was caused by an *E. coli* serotype, O104:H4, which was distributed by contaminated sprouts, and predominantly affected adults (8, 9). The health authorities should be notified when STEC-HUS is detected.

Complement-mediated HUS is present in 5%–10% of all pediatric HUS cases with an incidence of 2 per 1,000,000. Uncontrolled activation of the alternative pathway of complement activation with the subsequent formation of C5b-9 complexes (membrane attack complex) that damages the endothelial cell surface in the kidneys and other organs represents the pathophysiological starting point for TMA (1, 10).

The majority of complement-mediated HUS cases result from heterozygous pathogenic variants in genes encoding for complement regulatory proteins factor H (CFH), factor I (CFI), factor B (CFB), and factor 3 (C3), or in the regulators membrane cofactor protein (MCP) and thrombomodulin (11). Particularly in the case of children, acquired antibodies against factor H, often combined with pathogenic changes in genes responsible for complement factor H-related proteins (CFHR), represent a further cause of complement-mediated HUS (1, 10, 12).

Among other HUS forms are the rare hereditary forms due to a pathogenic diacylglycerol kinase ε (DGKE) (13) or due to a cobalamin C deficiency (14). Acquired HUS is a rare complication of invasive infection with *Streptococcus pneumonia* (15) and there are secondary forms of HUS with underlying causes including allogeneic stem cell transplantation, various diseases such as systemic lupus erythematosus, and certain groups of drugs such as calcineurin inhibitors (16).

Impairment of renal function in STEC-associated HUS develops approximately 7–14 days after the onset of enteritic symptoms. The proportion of patients who need replacement therapy varies between 27% and 60% in different studies and kidney function recovers in the majority of the patients (3). The therapy in STEC-HUS is supportive and the proportion of STEC-HUS patients with permanent symptoms such as proteinuria, arterial hypertension, impaired average renal function, and extrarenal lasting symptoms amounts to approximately 30%. The acute mortality rate of STEC-HUS has been reduced to less than 5% and is mainly due to central nervous system (CNS) complications due to thrombotic microangiopathy (3, 6, 17). In contrast to complement-mediated HUS, STEC-HUS does not recur. The prognosis of complement-mediated HUS is significantly worse with higher mortality rates and more frequent progression to end-stage renal disease (ESRD) (17, 18). The prognosis improved significantly due to humanized monoclonal antibodies against complement protein C5 (eculizumab and ravalizumab) and they are therefore recommended as the first-line therapy for complement-mediated HUS (19, 20).

The laboratory constellation for microangiopathic hemolytic anemia with the presence of fragmentocytes, elevated lactate dehydrogenase (LDH) and bilirubin levels, reduced haptoglobin, a negative antiglobulin test, and frequently impaired renal function apply to all forms of HUS (2). A kidney biopsy is usually not necessary for the diagnosis of the primary forms of HUS (3). An ultrasound (US) is the preferred imaging modality for the initial evaluation of any renal failure and US information on renal morphology (size, echogenicity, and corticomedullary differentiation) and perfusion (Doppler US, flow velocity, and flow profile) supports the differentiation between acute and chronic kidney failure (21–23). US is a non-invasive technique and plays an important role in diagnostic support, therapy monitoring, and long-term follow-up in HUS (24–28).

The aim of our retrospective study was the analysis and evaluation of US diagnostics in STEC-HUS and complement-mediated HUS at the onset of the disease and during the clinical course.

Material and methods

Patient recruitment and data collection

Between 2017 and 2022, 45 children were admitted as inpatients with an initial diagnosis of HUS to the Department of Pediatric Nephrology at the Children's Hospital of the University of Duisburg-Essen, Germany. We consecutively recruited 30 of the 45 children (as shown in Figure 1) for retrospective analysis according to the following inclusion criteria. STEC-HUS was only diagnosed when there was microbiological evidence of *E. coli* infection, specifically stool cultures that were found to be positive for *E. coli* that produce Shiga toxin 2 (PCR and/or enzyme immunoassay) at the National EHEC Reference Center in Germany and/or through the detection of EHEC antibodies and when all three of the following main criteria are met: (1) thrombocytopenia, defined as a platelet count below 150,000/µl; (2) microangiopathic hemolytic anemia; and (3) acute kidney

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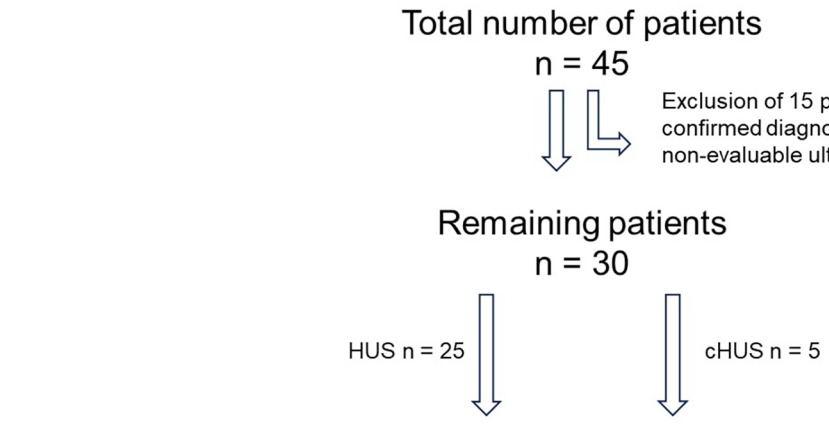

complete ultrasound at diagnosis	19/25	4/5
Ultrasound follow up 1-3 months	14/25	1/5
Ultrasound follow up 12 months	12/25	1/5
Ultrasound at all 3 timepoints	5/25	0/5

FIGURE 1
Selection algorithm for patients with HUS including ultrasound examination.

injury, defined as creatinine or cystatin c levels greater than 1.5 times the upper normal limit for that age. Complement-mediated HUS was diagnosed based on the laboratory parameters mentioned above, signs of complement system activation [including C3, C3d, C4, sC5b-9, activity of the classical (CH50) and alternative (APH50) complement pathways, and complement factor H antibody] and/or a genetic diagnosis confirmation of pathogenic variants in genes encoding for complement regulatory proteins, and, if necessary, by histopathological evidence of renal microangiopathy. Correspondingly, the exclusion criteria were defined as the absence of at least one of the aforementioned inclusion criteria and any potential clinical signs or any previous diagnoses that might cause a secondary form of HUS.

Clinical and laboratory data were collected from digital patient records. Implementation, type, and duration of a potential renal replacement therapy, supportive care, and potential therapeutic measures such as plasma exchange and drug-based complement blockade were also included in the analysis.

Standard ultrasound examination

As part of the routine clinical assessment and standard of care, all children with suspected impairment of renal function or suspected HUS underwent an abdominal ultrasound examination upon hospital admission. Standard US examination included an assessment of kidney size; parenchymal structure, including echogenicity and corticomedullary differentiation, kidney perfusion, including systolic and diastolic flow velocities; and renal resistance index (RI) analyzed by Doppler US technology. The kidney size was measured as the length (cm). The examination also included evaluation of liver size and structure, spleen size and structure, and presence of an ascites intestinal structure with signs of colitis such as a thickened intestinal wall and increased intestinal wall perfusion. The liver size was measured in the sternal line. The dimension of the spleen was determined below the left costal margin. All organ sizes are given as a percentage of the normal age- and height-related values (29).

For better comparability of kidney size, the measured lengths were standardized to normal kidney size for that age (30). The literature refers to the percentage of kidney size in comparison to the normal size (50th percentile kidney length) for the corresponding age and sex group, rather than the total kidney size. Enlarged kidneys were defined in the normal population as kidney lengths above the 97.5th percentile. This corresponds to a percentage kidney size in relation to the 50th percentile of 114.6% ± 1.8% (minimum 112%, maximum 121.2%). Based on this, kidney sizes greater than 120% of the age-based norm were considered enlarged for this study. RI values were compared with published normal values in children and adults (31, 32).

Ultrasound examinations were performed using an Aplio i800 (Canon Medical Systems Corporation, Otawara, Japan) with an i8CX1 transducer (PVI-475BT, single curved, 1.8–6.2 MHz) and an I18LX5 transducer (PLI-1205BX, linear, 5.0–18.0 MHz) and using a Zonare ZS3 (ZONARE Medical Systems, Mountain View, CA, USA) with a single curved C6-2 transducer and a linear L14-5 transducer. The pediatricians on duty with certified pediatric US experience performed all the US examinations.

All 30 patients underwent a US kidney perfusion analysis; however, only 23 of the 30 patients had a complete renal US examination including an assessment of the renal parenchyma and their kidney size. A follow-up US examination at the time of hospital discharge or in the following 2 weeks was performed in 15 of the 30 patients. A follow-up US examination 12 months after the initial diagnosis of HUS was performed in 13 of the 30 patients. A US examination at all three timepoints was performed in 6 of the 30 patients; this was due to the fact that the patients no longer presented to our clinic for follow-up.

Please refer to Figure 1 for a flowchart of the patients and available data for analysis and Table 1 for patient characteristics. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board at the University Hospital in Essen. As the analysis was retrospective and used only anonymized parameters obtained for routine clinical assessments, individual written consent was not required.

Statistical analyses

Statistical analyses were performed with SPSS (version 29) for Windows (IBM Corp, Armonk, NY, USA). Groups were compared by independent *t*-test or—in the case of multiple groups—using ANOVA with Dunnett's *post-hoc* analysis; Chi-square or Fisher's exact tests were used for comparisons between groups for categorical data. The significance levels were set at 0.05 unless stated otherwise.

For the calculation of a threshold value in relation to kidney size for the classification of the requirement for dialysis in patients with HUS, we first defined the regressor variable kidney size. This was defined as the quotient of the percentage deviation of the measured kidney size of the respective patient and the 50th percentile of the age-appropriate standard value (30). Our dependent variable was the binary variable dialysis requirement: yes vs. no.

We calculated different threshold values for the regressor variable, in which patients below the respective threshold value were classified as not requiring dialysis and patients with a value of at least this threshold value were classified as requiring dialysis. The resulting receiver operating characteristic (ROC) curve reflects the different specificities and sensitivities of the various thresholds used. The optimal threshold value was selected based on the maximum Youden index value (33). Balanced accuracy is indicated by the sensitivity and specificity means and reflects the importance of both values. The area

TABLE 1 Clinical and laboratory findings and treatment variables during inpatient treatment.

Number	Age at diagnosis (years)	Sex	HUS	Minimal eGFR (ml/min/1.73 m^2)	Maximum LDH (U/L)	Minimal thrombocytes (/nl)	Minimal hemoglobin (g/dl)	Dialysis (days)	Form of dialysis
1	2.4	M	STEC-HUS	15	2,902	255	6.8	17	PD
2	1.2	M	STEC-HUS	19	2,608	47	6.2	14	HD
3	0.8	M	STEC-HUS	20	1,586	81	5.5	0	
4	7.7	M	STEC-HUS	15	3,601	30	4.8	27	HD
5	6	F	STEC-HUS	17	2,777	93	5.8	26	HD
6	0.8	M	STEC-HUS	8	1,808	52	6.4	10	PD
7	2.5	F	STEC-HUS	9	1,361	83	6	5	PD
8	2.5	F	STEC-HUS	16	2,836	25	6	17	PD
9	3.1	M	STEC-HUS	12	3,065	61	4.7	4	PD
10	1.6	F	STEC-HUS	67	5,386	2	5.7	0	PD
11	1.2	F	STEC-HUS	12	2,578	56	6.3	24	PD
12	3.8	M	STEC-HUS	54	3,830	13	2.5	0	
13	1	M	STEC-HUS	12	2,467	89	7	15	PD
14	16.5	F	STEC-HUS	39	1,084	53	7.1	5	PD
15	12.8	F	STEC-HUS	9	2,455	20	5.6	6	PD
16	3.2	F	STEC-HUS	12	3,655	21	4.3	30	PD
17	0.9	F	STEC-HUS	6	959	310	5.3	0	
18	7.7	F	STEC-HUS	34	3,101	7	4.5	0	
19	2.9	M	STEC-HUS	12	4,039	29	5.1	8	PD
20	1.8	M	STEC-HUS	30	2,658	21	5.6	0	
21	2.9	M	STEC-HUS	25	1,903	63	6.5	0	
22	8.2	F	STEC-HUS	21	1,985	62	11.2	24	PD
23	14.5	F	STEC-HUS	40	1,058	48	5.8	0	
24	5.5	M	STEC-HUS	20	1,238	175	5.3	0	
25	7.6	M	cHUS	12	3,870	51	5.4	13	HD
26	11.1	F	cHUS	28	3,691	21	5.9	0	
27	3.1	F	cHUS	7	3,500	36	3.9	35	PD
28	3.8	M	cHUS	22	2,968	88	4	0	
29	5.4	F	cHUS	6	804	90	5.2	212	HD
30	2.5	M	STEC-HUS	11	3,458	70	6.8	32	PD

F, female; HD, hemodialysis; m, male; PD, peritoneal dialysis.

under the curve (AUC) of the ROC curve is a measure of the degree to which the kidney size is suitable as a classifier for the different threshold values (33).

Equivalently, we repeated the ROC analysis with the regressor RI value defined as the quotient of the percentage deviation of the measured RI values and the 50th percentile of the age-appropriate standard values (31).

In addition, we examined the classification capability of the two variables together using a decision tree and calculated thresholds for both of them. First, a classification was made using kidney size. Patients who were classified as requiring dialysis were then subdivided again using the RI value variable to improve the overall sensitivity and specificity compared to a classification based solely on kidney size or solely on RI value. The Gini index was used as the splitting index. For a detailed description, see Figure 4 and the corresponding caption.

For calculating the ROC in this analysis, we used R version 4.1.2 (2021-11-01) and the "roc" function of the R-package pROC. The decision tree was calculated via the "rpart" function of the R-package rpart.

Results

Patient characteristics

The STEC-HUS cohort included 25 children (aged 0.8–16.5 years, mean ± SD 4.8 ± 4.2 years, median 2.9 years). The distribution of sex was nearly balanced with 52% (13/25) male patients. The patients had normal weight (z-score mean ± SD, −0.4 ± 1.3, range −4.9 to 2.2) and body length (z-score mean ± SD, 0.4 ± 1.5, range −1.7 to 6.1). Their mean minimum platelet count was 70 ± 73/µl (range 2–310/µl), their mean minimum hemoglobin level was 5.8 ± 1.5 g/dl (range 2.5–11.2 g/dl), and their mean maximum LDH level was 2,576 ± 1,083 U/L (range 959–5,386 U/L). The Shiga toxin in the stool and/or EHEC was detected in all the STEC-HUS patients. The most prevalent EHEC serotype was O157 (36% of all cases), serotypes O126, O145, and O156 were each found in one patient (each correlating to 4% of all cases).

The cohort of complement-mediated HUS included five children (aged 2.2–10.2 years, mean ± SD 6.2 ± 3.2 years, median 5.4 years). The distribution of sex was nearly balanced with 40% (2/5) male patients. The patients had normal weight (z-score mean ± SD, −0.1 ± 1.1, range 1.1–1.5) and length (z-score mean ± SD, 0.2 ± 0.7, range −0.8 to 0.9). Their mean minimum platelet count was 57 ± 31/µl (range 21–90/µl), their mean minimum hemoglobin level was 4.9 ± 0.9 g/dl (range 3.9–5.9 g/dl), and their mean maximum LDH level was 2,967 ± 1,255 U/L (range 804–3,870 U/L). In three of the five patients (60%) with cHUS, the disease specific/causing pathogenic variants were known. One patient had a deletion leading to the loss of CFHR 1 and 3 causing CFH antibodies. Each patient had homozygous pathogenic variations in the CD46 gene, encoding for membrane cofactor protein, and in the C3 gene, encoding for complement protein C3. In the remaining two cHUS patients without genetic evidence, the diagnosis was confirmed by sustained complement activation and histopathological evidence of both chronic and acute thrombotic microangiopathy with arteriolar and glomerular involvement.

The individual data of the children with HUS are shown in Table 1.

The symptoms reported at hospital admission were similar in the patients with STEC-HUS and cHUS regarding seizures (16% vs. 20%) and macrohematuria (12% vs. 20%). However, diarrhea was reported more frequently in the STEC-HUS patients than in the cHUS patients (68% vs. 40%), but hematochezia was only reported in STEC-HUS patients (36%). Arterial hypertension was more frequent in cHUS than in STEC-HUS patients (40% vs. 8%) (Table 2).

A blood transfusion was performed in 63.3% of cases (60% in the STEC-HUS group and 80% in the cHUS group). Two patients (8%) with STEC-HUS received thrombocyte transfusions perioperatively with thrombocyte counts of 2 and 7/nl, respectively; no cHUS patient received a thrombocyte transfusion.

The complement factor C3 was reduced in 16.6% of cases (12% in the STEC-HUS group and 40% in the cHUS group).

Renal impairment

The mean estimated glomerular filtration rate (eGFR) at the initial presentation was 21.4 ± 15.1 ml/min/1.73 m^2 in the STEC-HUS patients and 14.7 ± 9.5 ml/min/1.73 m^2 in the complement-mediated HUS patients.

The proportion of patients that received renal replacement therapy was similar in STEC-HUS and cHUS patients (64% vs. 60%). While the median dialysis duration was similar (STEC-HUS 10 days vs. cHUS 13 days), the mean duration of dialysis was significantly longer in the cHUS patients with 49.6 days (range 0–212 days) compared to 10.5 days (range 0–32 days) for the STEC-HUS patients ($p \leq 0.001$). In one patient with cHUS, kidney function did not recover despite therapy with eculizumab and the patient received peritoneal dialysis for 7 months and subsequently underwent a successful kidney transplantation. Excluding this patient's mean dialysis duration in the cHUS group lowered the overall mean duration to a comparable 12 days. All the other patients showed

TABLE 2 Accompanying clinical symptoms in patients with STEC-HUS or cHUS at disease onset.

		STEC-HUS (25)	cHUS (5)
HT	No HT	23 (92%)	3 (60%)
	Reversible HT	2 (8%)	1 (20%)
	Irreversible HT	0 (8%)	1 (20%)
Seizure	Yes	4 (16%)	1 (20%)
	No	21 (84%)	4 (80%)
Diarrhea	Yes	17 (68%)	2 (40%)
	No	9 (36%)	3 (60%)
Macrohematuria	Yes	3 (12%)	1 (20%)
	No	22 (88%)	4 (80%)

HT, hypertension.

normalization of kidney function. In a subgroup analysis, patients with O157 serotype STEC-HUS ($n = 9$) had the lowest rate of dialysis at 55.5% (Table 3).

Dialysis was indicated in 63.3% of cases, hemodialysis was performed in 21.1%, and peritoneal dialysis in 78.9%.

Ultrasound parameters

US renal size

The total kidney size at disease onset for all patients with STEC-HUS represented as a percentage of the normal age-adjusted mean value was elevated (177.4% ± 56.2%, 95% CI: 150–204) and insignificantly higher than in the cHUS patients (167.0% ± 53.3%, 95% CI: 82–252, Figure 2A). In the subcohort of STEC-HUS patients who required renal replacement therapy, the total kidney size was significantly higher at 200.7% (±56%, 95% CI: 163%–238%) compared to the STEC-HUS cases who did not require dialysis at 145% (±40%, 95% CI: 112%–179%) (Figure 2B; $p < 0.029$; one-way ANOVA assessment). There were no outliers, according to inspection with a boxplot. Data was normally distributed for each group (Shapiro–Wilk test, $p > 0.05$) and there was homogeneity of variance (Levene's test, $p > 0.05$). While there was no correlation for the overall cohort between the kidney size at disease onset and the duration of dialysis ($R = 0.18$, $p = 0.39$), the subgroup analysis for the STEC-HUS patients revealed a positive correlation ($R = 0.53$, $p = 0.02$) for kidney size at disease onset and dialysis duration. The ROC analysis revealed a regressor kidney size threshold of 141% (1.41), for the need for dialysis in STEC-HUS patients. The corresponding sensitivity was 0.909, the specificity 0.625, and the balanced accuracy 0.767. This means that 76.7% of our patients ($N = 19$) were correctly classified. The corresponding ROC curve with an AUC of 0.8125 is shown in Supplementary Figure S1A.

The echogenicity of the renal parenchyma was increased in 76.9% of the patients (20/36) [STEC-HUS: 81.8% (18/22); cHUS 50% (2/4)].

The mean kidney size in the STEC-HUS group decreased at the time of discharge with a still slightly bigger size in the subcohort that required dialysis (146.8%; ±9.2%, 95% CI: 109–185 vs. 106.6%; ±39.1%, 95% CI: 58–155; $p = 0.14$) and it normalized in both STEC-HUS subcohorts after 1 year (98%; ±20.5%, 95% CI: 81–115 vs. 89.3%; ±15%, 95% CI: 64–115) (Figure 2B).

TABLE 3 Dialysis requirement and duration in patients with STEC-HUS or cHUS.

		STEC-HUS (16)	O157 STEC-HUS (9)	cHUS (5)
Dialysis (*n*)	Yes	10 (62.5%)	5 (55.5%)	4 (80%)
	No	6 (37.5)	4 (45.5%)	2 (20%)
Duration of dialysis (days)	Median	10	4.5	13
	Mean (standard deviation)	11.5 (11.1)	8.6 (11.7)	49.6 (85.3)
	Minimum	0	0,00	0
	Maximum	32	30,00	200
From of dialysis	HD	2 (20%)	0 (0%)	2 (50%)
	PD	8 (80%)	5 (100%)	2 (50%)
Chronic kidney failure	Yes	0 (0%)	0 (0%)	1 (20%)
	No	0 (0%)	0 (0%)	4 (80%)

Resistance index

The mean RI, an important ultrasound parameter for organ perfusion, was elevated at disease onset in the STEC-HUS (0.87 ± 0.10) and cHUS patients (0.78 ± 0.04) compared to normal values. However, the difference in mean RI values between the STEC-HUS and cHUS did not reach statistical significance ($p = 0.13$) even when taking into account the small cHUS cohort (Figures 2C, 3A). The RI values at the onset of the disease were also not significantly different in the children who received a blood transfusion (RI 0.88 ± 0.09 vs. 0.82 ± 0.10; $p = 0.20$). The RI values were comparable in the STEC-HUS subcohort that required dialysis compared to those who did not (0.86 ± 0.1 vs. 0.88 ± 0.1; $p = 0.74$) and these normalized at the time of discharge and remained within the normal range 1 year later (Figure 2D). The RI and dialysis duration in days showed no correlation ($R = 0.11$, $p = 0.65$).

The ROC analysis revealed a regressor RI value threshold of 1.098. The corresponding sensitivity was 0.333, the specificity 0.857, and the balanced accuracy 0.595, which was only slightly better than a random estimate. The corresponding ROC curve with an AUC of 0.5119 is shown in Supplementary Figure S1B.

Decision tree

For $n = 14$ patients, we calculated a threshold of 129.5% (1.295), for the variable kidney size and a threshold of 1.01 for the RI value. The corresponding sensitivity was 1.0, the specificity 0.7273, and the balanced accuracy 0.8636 (Figure 4).

Other US parameters

In individual cases, reduced renal microperfusion due to thrombotic microangiopathy had already been visualized using the superb microvascular imaging (SMI) mode. The atypically weaker tissue perfusion of the kidney compared to the overlying liver served as a comparison here (Figure 3B).

Liver size was only available in 56.6% of patients (17/30) and there was no age-adjusted hepatomegaly [measurement only in sternal line (STL)].

Spleen size was available in only 43.3% of patients (13/30) and no age-adjusted splenomegaly was observed.

Intestinal wall thickness was measured in only 50% of cases (44% in the STEC-HUS group and 80% in the cHUS group). It was increased in only 72.7% of the STEC-HUS patients (8/11 patients) and was measured up to 12 mm. The patients with enlarged intestinal walls all had diarrhea at the timepoint of the ultrasound. In the cHUS patients, it was increased to 4 mm in one patient.

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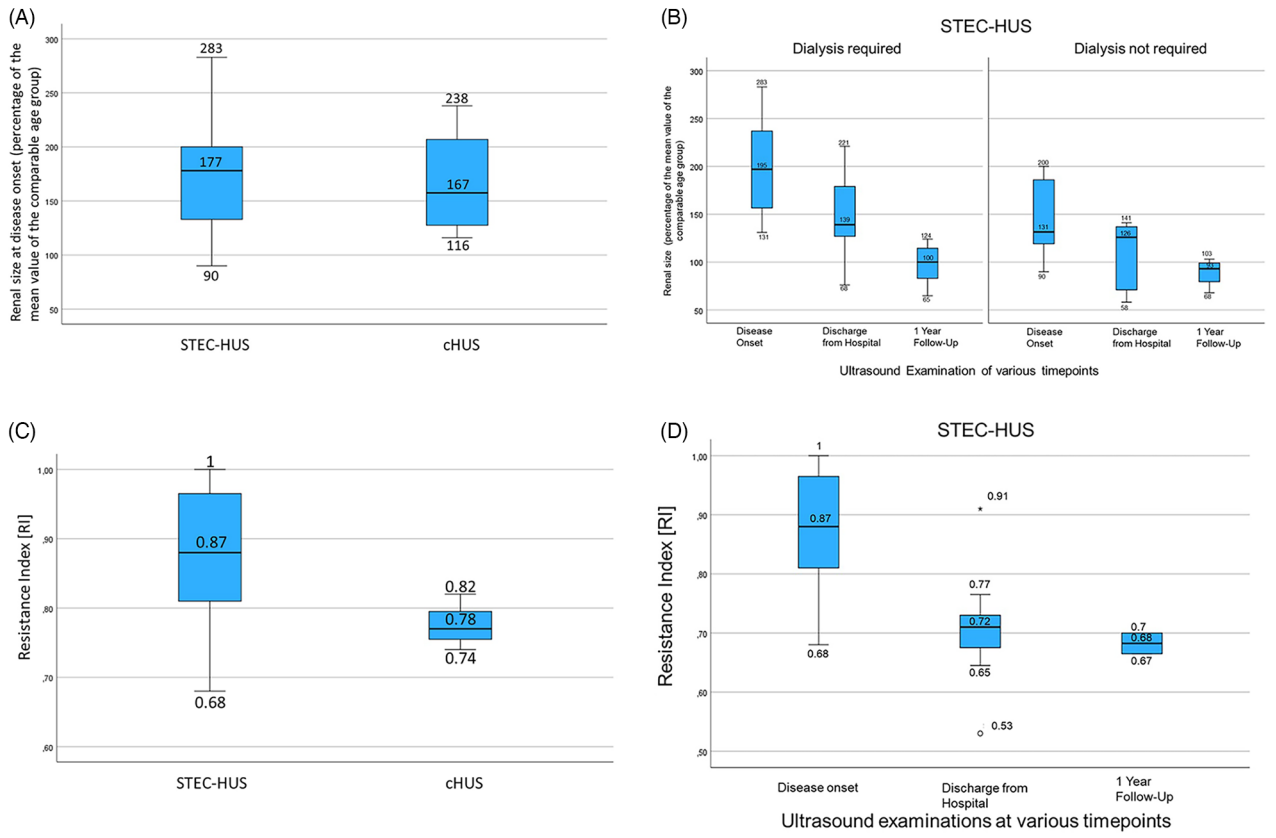

FIGURE 2
(A) A boxplot of age-adjusted kidney size in STEC-HUS and cHUS patients at disease onset. Both were significantly elevated compared to the normal range but not statistically significantly different from each other. (B) A boxplot of age-adjusted kidney size in STEC-HUS patients who required and did not require dialysis at disease onset, at the time of discharge, and at follow-up after 1 year shows significantly higher kidney sizes in STEC-HUS patients who required dialysis compared to those who did not. In both groups, kidney size returns to the age norm with clinical improvement. (C) A boxplot of RI in STEC-HUS and cHUS patients at disease onset shows lower RI values in the cHUS patients without demonstrable statistical significance due to the small sample size. (D) A boxplot of RI in the STEC-HUS patients at disease onset, recovery, and follow-up shows high values for RI at disease onset decreasing to the normal range in accordance with clinical improvement.

No patient displayed ascites or pleural effusion during the US examination (Table 4).

Discussion

We retrospectively analyzed a large cohort of children with STEC-HUS or complement-mediated HUS with a special focus on ultrasound diagnostics. We found prominent roles for RI at disease onset and total kidney size as indicators of the requirement for dialysis in acute kidney failure in STEC-HUS cases. We also demonstrated the normalization of various ultrasound parameters in the further course of the disease in line with the clinical improvement, as all but one case showed a normalization of renal function.

Study cohort

The predominant proportion of STEC-HUS in this cohort (83%), the most prevalent EHEC serotype being O157, and the genetic distribution of heterozygous pathogenic variants in cHUS all corresponded to published studies on HUS in childhood (5–7, 19). The median age of disease onset in patients with STEC-HUS was lower compared to those with cHUS (2.9 vs. 5.4 years) and there was an almost balanced sex distribution in both groups; both aspects are consistent with recent multicenter studies (7, 34). The proportion of diarrhea symptoms at the onset of the disease in the STEC-HUS patients was slightly lower than the published data (19) but it was still higher than in the cHUS group. This highlights the challenge that diarrhea at disease onset is not a specific sign of the presence of STEC-HUS and justifies the abandonment of the old classification of patients into either diarrhea- or non-diarrhea-associated HUS. Accordingly, as to be expected, C3 levels were higher in the cHUS cohort but less than half of the cases were in line with other studies (35), which makes it difficult to reliably identify a decisive role of the complement system in the early disease phase. In this and other studies (36, 37), temporary complement activation was present in some STEC-HUS cases, making the initial differentiation of HUS types even more difficult. The higher frequency of hypertension in cHUS is most likely due to

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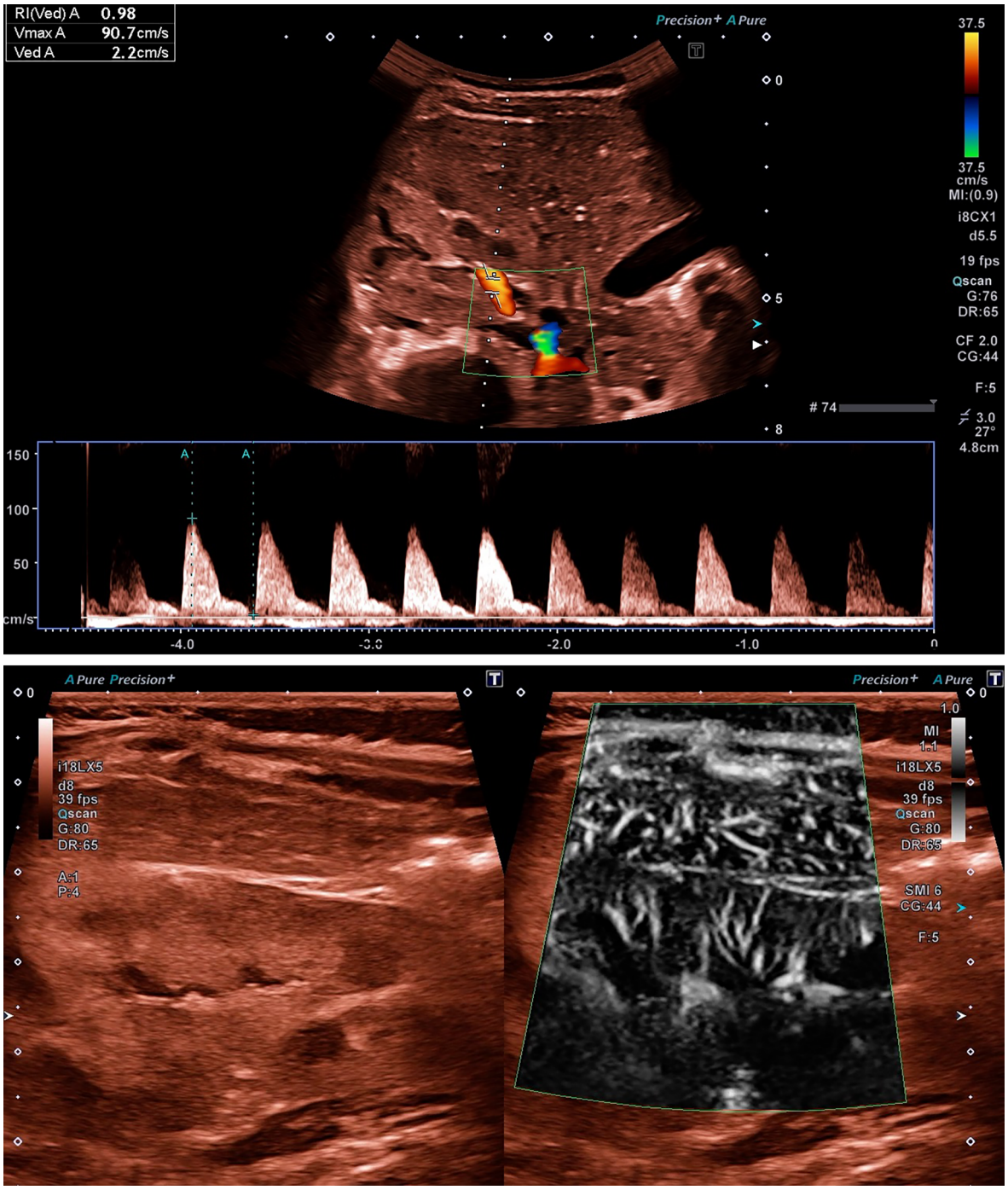

FIGURE 3
(A) Ultrasound examination of renal perfusion at disease onset with evidence of a significantly increased value for RI of 0.98 in a 10-month-old girl with STEC-HUS. **(B)** Reduced renal tissue perfusion in SMI mode, which is atypically even lower than the overlying hepatic tissue perfusion, in the same patient as in **(A)**. Video presentation in the Supplementary Material Video S1.

recurrent damage to the kidney tissue as part of the often wave-like course of cHUS (19). The proportion of children requiring renal replacement therapy for acute renal failure was in accordance with previous studies and was almost the same for both the STEC-HUS and cHUS groups with a frequency ranging between 60% and 68% (19, 38).

Ultrasound analysis

The typical laboratory constellation is indicative for the diagnosis of all forms of HUS; therefore, a kidney biopsy does not contribute to a decisive gain in clinical knowledge, and the risk of complications is significantly increased in

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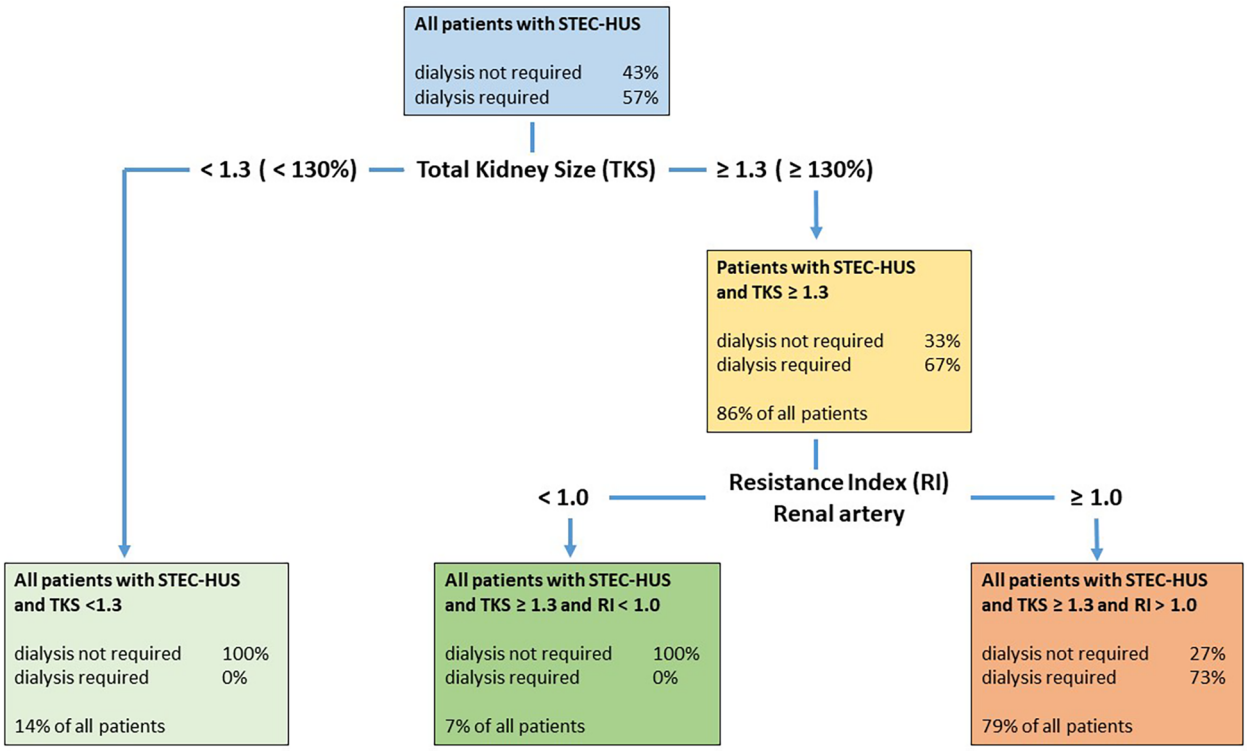

FIGURE 4
Decision tree with both classificatory variables, kidney size and RI, in patients with STEC-HUS. The decision tree first classifies the patients based on the kidney size variable and then based on the RI value variable. The algorithm used calculates suitable threshold values that optimize the classification using these variables. Patients with a total kidney size (TKS) ≥131% were classified as requiring dialysis, but only 67% actually required dialysis. Patients with an RI value ≥1.0 were classified as requiring dialysis; however, only 73% really required dialysis. This means that all patients requiring dialysis were recognized as such. However, some patients who did not require dialysis were also classified as requiring dialysis. This resulted in a sensitivity of 1.0 and a specificity of 0.7273.

TABLE 4 Other US findings in patients with STEC-HUS or cHUS.

		STEC-HUS		cHUS	
		Evaluable patients		Evaluable patients	
		n (%)		*n* (%)	
Echogenicity, *n* (%)	Very high	22 (88%)	12 (54%)	4 (80%)	2 (50%)
	High		6 (27%)		1 (25%)
	Normal		4 (18%)		1 (25%)
Liver (STL) (cm)	Median	13 (52%)	8	4 (80%)	9
	Mean (standard deviation)		8 (1.8)		9.3 (3)
Spleen (cm)	Median	10 (40%)	7	3 (60%)	8
	Mean (standard deviation)		8 (1.9)		8.3 (1.5)
Intestinal wall (mm)	Median	11 (44%)	6	4 (80%)	2
	Mean (standard deviation)		6.4 (3.7)		2.5 (1)

thrombocytopenia. However, the application of ultrasound as a non-invasive tool supports the confirmation of diagnosis and can influence the management of the treatment of HUS, which is evident in our analysis.

One key result of our data is the significantly increased total kidney size in children with both HUS forms at disease onset. The subgroup of children with STEC-HUS that required acute dialysis demonstrated significantly larger total kidney sizes at disease onset compared to those that did not. Although the few available publications on ultrasound examinations in HUS show an increase in renal size above the normal range, no further quantification of the extent of the increase in size was undertaken (26, 38, 39). Therefore, the importance of kidney size in estimating acute dialysis requirements in STEC-HUS has not yet been described in the literature. The relative value for kidney size of 141% shown in the ROC analysis can therefore serve as a guide for early decision-making regarding the need for dialysis in patients with STEC-HUS and dynamic acute renal failure. The

children with cHUS also showed similarly increased kidney sizes at disease onset. Further prospective studies in cHUS are required to evaluate whether kidney size is also more increased in children with cHUS who require acute dialysis as the small number of cHUS cases in our study was not sufficient for reliable analysis.

Another key result of our data is the role of significantly increased RI values, as a marker of the ratio between systolic peak flow velocity and end-diastolic flow velocity in the renal artery. In both the STEC-HUS and cHUS groups, we found an increased RI value in the renal artery compared to normal values, in particular as an expression of reduced end-diastolic flow velocity caused by thrombotic renal microangiopathy. The RI values in STEC-HUS patients at disease onset were comparable in the subcohorts (i.e., those who did or did not require dialysis) and therefore were not reliable for predicting dialysis indication alone, as was also demonstrated in the ROC analysis. The study by Reising et al. (38) confirms our study results in relation to elevated RI values in an adult cohort and, additionally, demonstrated higher RI values in STEC-HUS patients compared to cHUS patients at disease onset, which might be due to the different pathophysiologies, resulting in a more undulating clinical course in cHUS compared to the peak-like course in STEC-HUS. However, considering the small cHUS cohort in our study, our data did not demonstrate statistically significant numerical differences in elevated RI values in the STEC-HUS group compared to the cHUS group. In general, the RI values in all adult subcohorts with HUS are lower compared to our data in children, which is explained by the physiologically lower RI values in healthy adults compared to children (31, 38). While the RI value in adults was statistically significantly higher in patients with STEC-HUS who required dialysis compared to patients who did not, our data showed no significant differences in our cohort of children with HUS and, overall, significantly higher RI values (38).

A classification model using both US parameters (total kidney size and RI) sequentially might be of clinical use for predicting dialysis requirements in patients with STEC-HUS with high sensitivity and specificity. As part of a decision tree, all children with STEC-HUS who require dialysis can be recognized from a relative kidney size above 130% due to the high sensitivity, however, specificity is low. Therefore, an additional RI measurement is required in this subgroup in the next step and RI values display a high specificity to distinguish between dialysis-dependent ($RI > 1.0$) or non-dependent HUS ($RI < 1.0$) (Figure 4).

Total kidney size and RI of the renal artery decreased significantly at the time of discharge and normalized at follow-up after 1 year in line with the clinical improvement. All but one case showed a normalization of renal function. The subgroup of patients with STEC-HUS who required dialysis at disease onset still displayed increased kidney size at the time of discharge, emphasizing its suitability for progress monitoring.

Nearly all of our patients with STEC-HUS and cHUS demonstrated increased renal cortical echogenicity at disease onset, similar to previous results (26, 28), but without correlation with dialysis, GFR, or uremic acid.

The significant increase in RI is more specific for the presence of HUS as opposed to other causes of acute renal failure, as demonstrated in Reising's data (38). In contrast, increased kidney size is not specific for HUS as increased size and cortical echogenicity are also hallmarks of other forms of acute kidney injury just as decreased kidney sizes with reduced corticomedullary differentiation are typical for chronic kidney failure (23). Extrarenal ultrasound abnormalities such as hepatosplenomegaly, ascites, or thickening of the intestinal wall were common in the STEC-HUS patients and can be helpful in assessing further organ involvement and fluid balance.

Renal ultrasound as a non-invasive technique is an indispensable and valuable diagnostic tool to assess individual kidney involvement and the need for replacement therapy in STEC-HUS and cHUS patients but does not the reliable ability to distinguish between these different types. Ultrasound examination might be especially crucial in clinical cases when the diagnosis of HUS and the pathophysiological variant might be pending. New emerging US technologies such as SMI, which enables detailed tissue perfusion with pinpoint accuracy, have the potential to expand the possibilities for diagnostics and therapy control in HUS and in acute renal failure in general (40).

Limitations

The main limitation of this study is its retrospective design. The other main limitation is the small number of patients with complement-mediated HUS. Thus, the analysis of and conclusions drawn from this subcohort were significantly more limited compared to the larger cohort of children with STEC-HUS. A further disadvantage with regard to the decision tree also results from the small number of observations ($n = 14$). This meant that we were unable to divide our data into training and test datasets. It was, therefore, not possible to calculate the expected out-of-sample performance of our decision tree. The sensitivity, specificity, and balanced accuracy refer exclusively to the training data. An evaluation of the tree is possible through further data collection and subsequent testing of the tree. Another relevant limitation is the fact that in a considerable number of patients, clinical data at the time of discharge and in particular for the 1-year follow-up could not be obtained due to retrospective data collection and loss of follow-up. Therefore, analysis regarding the use of ultrasound in the clinical course is limited. In addition, most of the ultrasound examinations at disease onset were performed in emergency settings by different pediatricians with different ultrasound devices. Although only children with adequate US images were included, image quality was variable and not all parameters collected in this study were documented in every US examination. However, the present cohort of children with HUS included a significant number of patients with an outstanding US examination compared to previous clinical studies.

Conclusion

Increases in the US parameters of total kidney size, RI, and renal cortical echogenicity were present at disease onset in both HUS forms and normalized in the clinical course in line with the clinical improvement. In particular, kidney size at disease onset appears to be larger in patients with STEC-HUS who required dialysis compared to patients who did not. Therefore, total kidney size in relation to the normal value may be useful in the clinical assessment of HUS at disease onset together with RI. Future prospective studies are required to assess the diagnostic capability of emerging ultrasound technologies in evaluating different forms of HUS in children and predicting the severity of AKI and need for dialysis.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ Supplementary Material.

Ethics statement

The studies involving humans were approved by the ethics committee of the University Hospital of Essen. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because retrospective analysis and complete anonymization of the data including images.

Author contributions

LR: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. IF: Data curation, Formal Analysis, Writing – original draft. MK: Data curation, Writing – original draft. LS: Formal Analysis, Methodology, Software, Validation, Writing – original draft. LP: Formal Analysis, Methodology, Project administration, Resources, Supervision, Writing – original draft. MC: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft.

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Conflict of interest

MC received payments for lectures from Canon Medical Systems.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2024.1433812/full#supplementary-material

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Achievements, priorities and strategies in pediatric nephrology in Europe: need for unifying approaches or acceptance of differences?

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Background: There is a lack of information on the current healthcare systems for children with kidney diseases across Europe. The aim of this study was to explore the different national approaches to the organization and delivery of pediatric nephrology services within Europe.

Methods: In 2020, the European society for Paediatric Nephrology (ESPN) conducted a cross-sectional survey to identify the existing pediatric nephrology healthcare systems in 48 European countries covering a population of more than 200 million children.

Results: The reported three most important priorities in the care of children with kidney diseases were better training of staff, more incentives for physicians to reduce staff shortages, and more hospital beds. Positive achievements in the field of pediatric nephrology included the establishment of new specialized pediatric nephrology centers, facilities for pediatric dialysis and transplant units in 18, 16, and 12 countries, respectively. The most common problems included no access to any type of dialysis (12), inadequate transplant programs for all ages of children (12), lack of well-trained physicians and dialysis nurses (12), inadequate reimbursement of hospitals for expensive therapies (10), and lack of multidisciplinary care by psychologists, dieticians, physiotherapists, social workers and vocational counsellors (6). Twenty-five of 48 countries (52%) expected to have a shortage of pediatric nephrologists in the year 2025, 63% of clinical nurses and 56% of dialysis nurses. All three groups of health care professionals were expected to be lacking in 38% of countries. Prenatal assessment and postnatal management of renal malformations by a multidisciplinary team including obstetricians, geneticists, pediatricians, and pediatric surgeons was available in one third of countries.

Conclusions: Our study shows that there are still very marked differences in pediatric health care systems across the European countries and highlights the need need for appropriate services for children with kidney disease in all European countries.

KEYWORDS

European child healthcare services, nephrology, achievements, needs, workforce, prevention, rehabilitation

1 Introduction

From the perspective of understanding how to improve child healthcare service systems (CHCSS), Europe's pediatric community is aware of the diversity of provision of pediatric healthcare offered in 53 different countries (1–3). However, Europe has lacked a comprehensive understanding of how this diversity affects health outcomes. Neither the pediatric workforce resources nor the training capacities and needs in pediatrics were fully understood. Differences in the delivery of pediatric nephrology care are reported for European countries since the 1990ies (4–6). However, the underlying "root-cause-effect-outcome relationships"—which are the basis of today's needs and wishes of pediatric nephrologists and their patients—are still non transparent for many countries. After the fall of the Berlin wall in 1990, general health care services changed in several East European countries from the former Soviet Union system to a Western orientated structure to fill their obvious gaps. Following the 2008 financial crisis, many East European countries started discussing changes in existing health care systems essentially as part of cost containment (7, 8). There is no information available on whether this has led to an improvement in healthcare in these countries Indeed, concern have been raised about persistent inequalities in the health status of children and adolescents with acute and chronic kidney diseases (CKD) in Europe (1, 9). This is further complicated by the gap between public health research and clinical research, and the lack of quality of statistical data on the subject (10). Compared to adults, children make up only 3% of the total CKD population and are therefore not considered a priority for a country's healthcare system (11). However, many kidney diseases and conditions in adults are inherited and manifestin early life. Using the mother and child health life course model, one would assume that investing in services for children would pay off in adulthood (12).

The European Society for Paediatric Nephrology (ESPN) is a nearly 60-year-old association aiming to strengthen the individual efforts of all European pediatric nephrologists (13). Three surveys conducted by ESPN aimed to identify the existing pediatric nephrology healthcare systems in 48 European countries covering a population of more than 200 million children (4–6). Based on the analyses of these surveys, ESPN aims to improve future services by understanding disparities and translating research into practice, with a focus on "learning across borders and making a difference".

The first part of this article highlights the range of country profiles on national healthcare systems and policies, i.e., not only in terms of successes and failures in pediatric nephrology, but also in terms of priorities of care needs and highly specialized workforce provision in Europe in 2020. As complete and accurate official data on the logistical structures and organizational networks of pediatric nephrology centers were not available in many countries, the answers to our questions had to be based on the long-term experience of national ESPN members who are health system leaders in their countries and have consulted with their staff. The second part of this paper identifies challenges in the prenatal, preventive, rehabilitative and palliative care of children with kidney disease in order to improve the conceptualization, recommendations and standardization of multidisciplinary renal care for European children. The aim of this work is to explore the different national approaches to the organization and delivery of pediatric nephrology services and to provide a basis for comparative analysis.

2 Materials and methods

2.1 Study design

This is a cross-sectional survey designed to assess organization of European pediatric nephrology, the achievements and failures of healthcare services, needs and desires of pediatricians, workforce planning in these highly specialized centers, and multidisciplinary care in pediatric nephrology.

2.2 Questionnaire

A survey with twelve questions assessed the organization of renal care in children. All participants were asked to answer multiple-choice and open-ended questions. The questions about ESPN policy addressed workforce planning, health care delivery systems, organization of inpatient care for children with kidney disease, and multidisciplinary care including prenatal diagnosis, preventive treatment and rehabilitative and palliative therapy. The authors selected a leading pediatric nephrologist from each of 48 of the 53 European countries and asked them to represent their country and complete the questionnaire after consulting with colleagues where appropriate. All 48 participants were members of ESPN, either presidents of national pediatric nephrology societies or senior pediatric nephrologists in highly specialized pediatric renal centers.

2.3 Participating countries

Representatives from Iceland in the west to Kazakhstan in the east and from Norway in the north to Malta in the south participated in the survey. Five of 53 European countries with a total population of fewer than 200.000 inhabitants were excluded from the study. In selecting the European countries for our study, we followed the definition of Europe in the World Health Organization (WHO) list. The WHO Regional Office for Europe (WHO/Europe) is one of the six WHO regional offices in the world responsible for the WHO European Region, which comprises 53 countries.

2.4 Data collection and storage

The survey was administered by e-mail communication and all the 48 invited experts agreed to participate in the study. All respondents were fluent in the English language. Data were

entered into the study database designed in Excel. Data completeness and accuracy assessment was conducted by JE at the coordinating site in Hanover. In the case of incomplete data, the respective survey participants were contacted and missing information collected. Part A of the survey asked for achievements and failures of national health care services for children with kidney diseases, workforce planning and ESPN policy (Table 1). Part B identifies challenges in the prenatal, preventive, rehabilitative and palliative care of children with kidney disease in order to improve the conceptualization, recommendations and standardization of multidisciplinary renal care for European children (Table 2).

2.5 Statistical considerations

Data collected by the questionnaire were analyzed using descriptive statistics. When evaluating the reported data, they were not viewed as statistical facts, but as assessments and opinions of experts on the actual situation, which made statistical analyses not seen as appropriate. Therefore, similar to political opinion polls, percentages or ratios are given that could come close to the truth. For the purpose of analysis, countries were divided into groups based on (a) population size, (b) gross domestic product (GDP)/gross national product (GNP) per capita (low, lower-middle, upper-middle, and high income), (c) political systems and (d) geographic region.

TABLE 1 Questions 1.

Achievements and failures of national child health care services forchildren with kidney diseases, workforce planning and ESPN policy.
A1. Please list the top three positive achievements, unsolved problems and unsuccessful changes in renal child health care services in the last 15 years that turned out to be that had been made in your national health care system to improve childhood renal health care in children.
A2. Please list the top three priorities of CKD entities requiring urgent changes of current treatment strategies in your country.
A3. Are you expecting to have a shortage of pediatric nephrologists, ward nurses, and dialysis nurses in 2025 in your country?
A4. What institutions are involved in training young pediatric nephrologists in your country?
A5. What are the incentives for young pediatricians in your country to become pediatric nephrologists?
A6. What does your national society expect from ESPN in the near future?

TABLE 2 Questions 2.

Challenges in the prenatal, preventive, rehabilitative and palliative care of children with kidney disease in order to improve the conceptualization, recommendations and standardization of multidisciplinary renal care for European children.
B1. If prenatal counselling is desired for planning future care pathways for foetuses to detect defects of the developing kidneys and urinary tract, who is part of the counselling team for parents: obstetricians, geneticists, pediatric nephrologists, pediatric surgeons, or if other specialists, please specify where the teams work and how the cooperate?
B2. Are vaccinations administered to children with CKD by general practitioners, primary care pediatricians, pediatric nephrologists, public health facilities, or if other, please specify who administers the vaccinations?
B3. Are there analogous nephrology passports for children with kidney disease?
B4. Are electronic passports available for all children?
B5. Is rehabilitative care (including psychosocial care, schooling, health education, physiotherapy, nutritional counselling) available for children with CKD and if yes is it organized and coordinated in your country within the hospital, outside the hospital, or if elsewhere, please explain by whom and where?
B6. How is palliative care for children with long-term kidney disease organized and coordinated in your country within the hospital, outside the hospital, or if elsewhere, please explain by whom and where?

3 Results

3.1 National priorities in European pediatric nephrology

Physicians from 45 countries responded to the questionnaire's open-ended question about the top three priorities in the care of long-term kidney patients that require urgent changes to current treatment strategies (Table 3). Forty-one countries each reported 1–3 priorities in relation to different needs to improve the management of services. Four countries (Croatia, Germany, Iceland and Norway) reported no need for change and 3 countries did not respond to the question. The most frequently reported priorities were better training of staff ($n = 7$), more incentives for physicians to reduce staff shortages ($n = 3$) and more hospital beds ($n = 1$), a coordinated national nephrology

TABLE 3 Selection of major findings concerning priorities, successes, challenges, failures and workforce planning in European pediatric nephrology.

1. Most important priorities
– better training of staff
– more incentives for physicians to reduce staff shortages
– more hospital beds
– others
2. Positive achievements in the field of pediatric nephrology
– newly built facilities for peritoneal and hemodialysis and pediatric transplant units
– multidisciplinary care
– improved diagnostic methods
– others
3. Unsolved challenges
– no access to any type of dialysis
– inadequate transplant programs for all ages of children
– lack of well-trained physicians and dialysis nurses
– inadequate reimbursement of hospitals for expensive therapies (10)
– others
4. Unsuccessful attempts
– access to kidney transplantation
– Insufficient improvement in the fields of peritoneal or hemodialysis
– others
5. Workforce planning
– expected shortage of pediatric nephrologists, clinical nurses and dialysis nurses in the year 2025
– all three groups of health care professionals were expected to be lacking in 38% of countries.
– others

program for CKD patients ($n = 1$) with a focus on establishing an adequate number of high-level pediatric nephrology centers ($n = 1$), better collaboration between pediatric and adult nephrology/urology ($n = 2$), earlier referral of patients by primary care pediatricians to pediatric nephrologists ($n = 3$), and an improvement in long-term follow-up of children with CKD ($n = 3$). Furthermore, a change in legislation with approval of drugs used in adult nephrology ($n = 1$), improvement of the transplant program ($n = 1$), need for national guidelines ($n = 1$), a national registry for children with CKD ($n = 1$), telemedicine and incentives for research at university hospitals ($n = 1$) among the issues reported. Reports from 6 countries called for an improvement in the national diagnostic abilities, e.g., access to genetic testing for rare diseases ($n = 5$), improved kidney pathology services ($n = 2$), screening tests for kidney diseases (1), biomarkers for prognosis of CKD ($n = 1$) and improved criteria for diagnosis of AKI ($n = 1$). New additions to the therapeutic arsenal for the treatment of childhood kidney and urinary tract diseases was reported by 12 countries, such as the use of novel biologics and immunosuppressants for nephrotic and nephritic syndromes ($n = 9$), intensive care ($n = 1$), multidisciplinary care ($n = 4$), dietary ($n = 1$) and rehabilitative care ($n = 1$), treatment of CKD stages 2–4 ($n = 2$) and long-term follow-up for congenital kidney disease ($n = 2$).Thirteen countries specified 9 reasons explaining the need for improvement in pediatric dialysis care. Four countries called for home hemodialysis, overnight hemodialysis ($n = 1$), hemodialysis for small patients, including vascular fistulas for very young children ($n = 1$), and modern technologies ($n = 4$), catheters ($n = 1$) and biocompatible solutions ($n = 1$) for peritoneal dialysis. Ten countries reported a need for further improvement in their pediatric kidney transplant (Ktx) programs, including all types of KTx ($n = 8$), living donation ($n = 1$) and infant KTx ($n = 1$).

3.2 National successes in European pediatric nephrology

Eighteen positive achievements in the field of pediatric nephrology were reported from 46 European countries to have taken place in recent years in their national healthcare systems (Table 3). Eighteen countries had established new specialized pediatric nephrology centers. Sixteen countries had built facilities for peritoneal and hemodialysis and 12 countries had opened pediatric transplant units in the past 15 years. Accreditation of pediatric nephrology as a pediatric medical subspecialty was newly established in three countries. Multidisciplinary care became routine in 5 countries, including a new transition program to adult nephrology in one country. A standardized training program was created in one country for pediatricians. The range of diagnostic methods and abilities had expanded in 3 countries. Five countries reported improved medical and dietary care for children (2). The treatment of HUS, urinary tract infections and stones was standardized in one country. Two countries established a functioning cross-border care program to compensate for their own deficits. The diagnosis of kidney disease was improved by new techniques in six countries, and one country reported an improvement in national kidney research programs. Cost free treatment was introduced in seven countries. Treatment guidelines for doctors were published in two countries and information brochures for patients and families were published in one country.

3.3 National challenges in European pediatric nephrology

Forty-two countries reported up to three unresolved problems in childhood kidney care in their national health system (Table 3). The three most common problems included no access to any type of dialysis ($n = 12$), inadequate transplant programs for all ages of children ($N = 12$) and lack of well-trained physicians and dialysis nurses ($n = 12$), inadequate reimbursement of hospitals for expensive therapies ($n = 10$), lack of multidisciplinary care by psychologists, dieticians, physiotherapists, social workers and vocational counsellors ($n = 6$). The lack of (a) genetic testing ($n = 5$), (b) electronic health records systems ($n = 2$), (c) histopathology services ($n = 2$), (d) research resources ($n = 2$), (e) national registries ($n = 1$), (f) highly specialized reference centres ($n = 2$) and (g) problems of local, national and international collaboration ($n = 1$) were reported. Six countries identified communication gaps in pediatric nephrology between primary, secondary, tertiary and quaternary renal care (6), which was responsible for various problems such as overburdened outpatient clinics in tertiary and quaternary care centres, delayedor late referral of critically ill children to dialysis facilities, and also bureaucratic overload of staff members. Less frequently mentioned challenges included the drain of workforce from Eastern to Western European countries ($n = 1$), national healthcare crises ($n = 1$), high numbers of immigrants in EU countries ($n = 1$) and the lack of nationally adapted guidelines ($n = 1$). Seven countries had limited access to novel and expensive drugs, and in four countries patients had difficulty accessing highly specialized pediatric nephrology centres.

3.4 National failures in European pediatric nephrology

Twenty-nine countries reported that there had been unsuccessful attempts in the last 15 years to fill different gapsin childhood kidney care services (Table 3). The most frequent failure turned out to be the in access to kidney transplantation in 16 countries ($n = 13$, all from East Europe). All these countries reported that they had unsuccessfully tried to adapt transplant care in the last 15 years to the needs of children with CKD. Insufficient improvement in the fields of peritoneal or hemodialysis was reported from 7 Eastern countries. The persistent lack of pediatric nephrology centres ($n = 2$) and workforce ($n = 7$) due to insufficient training of doctors and nurses ($n = 6$), high workload ($n = 1$), or loss of specialists to other countries ($n = 1$) was reported mostly from East Europe.

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Managerial failures were claimed to have blocked merging between tertiary or quaternary hospitals ($n = 3$), closer cooperation between primary, secondary and tertiary care ($n = 2$) or between different pediatric nephrology centres ($n = 3$) and establishing multidisciplinary teams ($n = 1$).

3.5 National workforce planning in European pediatric nephrology

Regarding workforce planning, 25 of 48 countries expected to have a shortage of pediatric nephrologistsin the year 2025, 30 countries of clinical nurses and 27 of dialysis nurses (Table 3). All three groups of health care professionals were expected to be lacking in 38% of countries. A lack of pediatric nephrologists was anticipated in 14 of 28 European Union countries (EU) and in 6 of 20 Non-EU countries. The numbers were 9 of all 12 countries with high GDP/GNP per capita and 13 of 32 countries with either low or middle-income. Likewise, 9 of 10 countries with more than 21 million inhabitants reported a shortage as compared to 9 of 25 countries with a population of 4–21 million inhabitants.

The main incentives for young pediatricians to choose a training in pediatric nephrology were career opportunities in 34 of 48 countries, research in 30 and reputation in 25 and salaries in only 3 countries. Altogether 98% of countries reported that academia and research in nephrology was a key motivator for choosing pediatric nephrology, however, one third of countries reported too few pediatricians involved in research in their country. This proportion was the same for EU and Non-EU countries. The question—if there were enough qualified candidates for leading positions in highly specialized pediatric nephrology centers—was answered with "no" in 19 countries.

The national and regional planning and allocation of pediatric nephrology services in tertiary and quaternary care children's hospitals was determined by the ministries of health alone in 14 countries, together with the universities in 8 countries or by the universities alone in 6 countries and, last but not least, by the initiative of individual pioneers of pediatric nephrology in 12 countries. In the UK, the national health system was responsible for coordination of care; in the Netherlands the health insurance companies played an additional role to all of the influencers listed.

Forty-three pediatric nephrologists from 48 European countries reported that pediatric nephrology centers should be closely linked to cardiology, neonatology, intensive care and pediatric surgery/urology in highly specialized pediatric centers. Only Denmark reported a desired close contact between pediatric and adult nephrology. Pediatric nephrology was not an accredited subspecialty in one third of countries. Unfortunately, there were not enough data reported on the guidelines for accreditation of pediatric nephrology centers and for training curricula of pediatric candidates. For 27 out of 48 countries the first of the chosen top three ESPN priorities was the development of European guidelines for workforce planning in national pediatric nephrology services, secondly the development of operational manuals for nephrology service systems ($n = 22$), and thirdly written recommendations for patient pathways in outpatient renal care ($n = 23$) and multidisciplinary children's hospital care ($n = 27$).

3.6 Antenatal, preventive, rehabilitative and palliative care services for children with kidney disease

When congenital anomalies of the kidneys and urinary tract (CAKUT) were suspected during prenatal assessment, one third of the countries reported that obstetricians, geneticists, pediatric nephrologists and pediatric surgeons formed a joint consultation team planning postnatal care. Only in five countries did the consultation team consist of obstetricians only and in 6 countries did it consist exclusively of pediatric nephrologists. Teams of two or three specialists were reported less frequently (Table 4). Seventeen percent of countries reported the need to improve preventive care through screening and genetic testing. The need to establish a national registry of the number of patients with severe kidney disease was reported in the open questions on the most important needs of national pediatric nephrology services.

In a third of countries, families were given special analogue medical passports for individual children with chronic kidney disease (CKD). Vaccinations for children with kidney disease were provided by general practitioners and different specialists. Twenty-eight countries offered a mixture of 11 different combinations of care givers. In one country the vaccines were exclusively given by pediatric nephrologists, in five countries only by general practitioners, in seven countries only by primary care pediatricians, and in seven countries only by public health facilities.

Rehabilitation, including psychosocial care, schooling, health education, physiotherapy and nutritional counselling for children with CKD, was organized and coordinated within tertiary and quaternary care children's hospitals in 15 countries and by external providers in 27 countries. Only four countries reported having special rehabilitation centers for children with kidney disease that also offer vacation dialysis. Twenty-nine percent of countries reported the need to improve rehabilitative care by supporting education and vocational training for adolescents and

TABLE 4 Number of countries offering one to four specialists in antenatal kidney care in 48 European countries.

	Number	Number	Numbers and percentages
Type of specialist	Alone	Part of a team	Both types per 48 countries
Pediatric nephrologist	6	35	41 (87%)
Obstetrician	5	29	34 (72%)
Geneticist	0	27	27 (57%)
Surgeon	0	23	23 (49%)
Total	11	Not appl.	Not appl.
One specialist/any type	11	Not appl.	23%
Two specialists	Not appl.	10	20%
Three specialists	Not appl.	11	23%
Four specialists	Not appl.	16	34%
Total	11	37	Not appl.

guiding the transition from pediatric to adult care. A quarter of countries reported the need to increase the availability of multidisciplinary teams for both inpatients and outpatients, particularly by recruiting more dieticians, psychologists and teachers. Finally, palliative care for children with severe adverse outcomes of AKI and CKD was organized and coordinated within tertiary care children's hospitals in 21 countries and through a combination of hospital and home care in 18 countries.

4 Discussion

Our study shows that, despite all the achievements of recent decades, there are still very significant differences in pediatric health care systems across Europe, and it highlights the need need for appropriate services for children with kidney disease in all European countries. The most common challenges included no access to any type of dialysis, the lack of kidney transplant programs for young children, well-trained physicians and dialysis nurses, adequate reimbursement of hospitals for expensive therapies, and multidisciplinary care by psychologists, dieticians, physiotherapists, social workers and vocational counsellors.

Putting the achievements and failures of the management of pediatric nephrology and their impact on health outcomes for European children with kidney diseases at the center of our survey was justified because of great diversity of healthcare and of needs and desires of pediatric nephrologists. What are the needs of young people with kidney diseases? What is the need of pediatric nephrologists for material and non-material things in a country? What is the outcome of different national strategies in pediatric nephrology? What is important, what has priority and what should politicians pay attention to? Unfortunately, the scientific literature answering these questions is scarce. The term "special healthcare" is often understood as a subjective national attitude. The late philosopher Harry Gordon Frankfurt took a different perspective on this question (14). He argued that caring for people—whether they belong to majority or minority groups—makes needs equally important. In the current paper we focussed on the various elements of competence required of pediatric nephrologists. One of the most worrying results of our survey was prospect of even fewer well-trained doctors and nurses working in the field of pediatric nephrology in the year 2025. It was therefore not surprising that one half of all reporting countries had sent an appeal to ESPN for the establishment of acollective action to develop European guidelines for workforce planning in national pediatric nephrology services, and to design operation manuals for service systems and planning pathways for renal outpatient care and multidisciplinary hospital care for kidney patients. A look at the structure of European governments showed us that interest in pediatric nephrology appears to be low in some countries. Weak points can be the fragmentation of responsibilities, which leads to a lack of uniformity, and the fact that ministries do not have a budget.

The different results concerning priorities, successes, challenges, failures and workforce planning in European pediatric nephrology cannot be discussed in detail here because of lack of published comprehensive national reports. Therefore, our article may become the basis for discussions on this issue. For instance, with respect to unsuccessful attempts, it would be interesting to know what was "managerial failure" due to regulations, leadership bias, cultural differences? Another important aspect is the role of cost-free care in 7 countries which must be explained by local experts. Moreover, several other aspects concerning roots of success, causes of failure and last but not least outcomes need to be clarified for each country.

There is a great diversity of pediatric workforce and education offered in European countries which appears to be based not so much on science but on historical factors (3). The range and quality care offered by pediatric nephrologists is endangered in those European countries reporting major deficits. In spite of an overall decrease of mortality in children under 14years of age in Europe there is a considerable concern about the fact that some countries had poorer outcomes irrespective of their Gross National Product (1). Future research should focus on the question whether this unacceptable variation could be improved by better organization of services.

Regular prenatal care matters for pregnant women. Women of childbearing age living with CKD or any type of organ transplantation should be informed on the potential risks and reported outcomes. Maternal and fetal outcomes have improved since the introduction of regular prenatal monitoring by obstetricians and nephrologists (15). Healthy pregnant women may benefit from ultrasound at certain time points to detect CAKUT (16). Pediatric nephrologists can make an important contribution to ethical decision making when they make recommendations to families about possible termination of a fetus with severe CAKUT (17). In less severe cases, they coordinate multidisciplinary postnatal management with pediatric surgeons, neonatologists, radiologists, and others (18). In our survey, one-third of European countries reported that prenatal consultation teams consist of obstetricians, geneticists, pediatric nephrologists, and pediatric surgeons. Ehrich et al. (3) reported that 42 out of 46 European countries had a medical passport for all children in which routine outpatient clinical examinations in childhood are documented. Theoretically, early documentation of kidney disease in these passports or in separate passports for children with CKD could contribute to a better long-term outcome for affected patients. However, the benefit of early detection tools such as urine sticks was less clear. Urine screening was performed in one-third of countries, and the age at screening ranged from 4 months to 6 years (19).

The current ESPN survey shows that vaccinations for children with kidney disease were provided either by family physicians, pediatricians, pediatric nephrologists, public health centers, or all of these. Half of the countries offered different combinations of vaccination centers. Immunizations of children with kidney disease are a mainstay of infection prevention. However, the individual vaccination calendar must be adapted to the specific needs and risks of kidney patients which requires the of pediatric nephrologists. Modern vaccines are generally well tolerated and permanent side effects are rare. Achieving immunity against vaccine-preventable viral and bacterial infections through early immunization prior to kidney transplantation is essential (20).

Vaccination data collection and linkage to immunization information systems are integral components of this management. To this end, paper and electronic medical records should allow interoperability with these systems, including the ability to download, upload, and synchronize a child's immunization data (18).

The tradition and scope of paediatric rehabilitation in Europe varies widely, ranging from physical, sensory, intellectual, psychological and social functioning in children with CKD and disabilities (19). While some countries, such as the German-speaking countries, have largely adopted the 1980s trend of establishing pediatric rehabilitation as a separate discipline, other countries consider rehabilitation to be the responsibility of hospitals or other existing health care providers. There is still some uncertainty as to which children and adolescents with kidney disease are eligible for rehabilitation. Some legislators regarded rehabilitation as a measure to "restore the ability to work" and thus excluded children by definition. Others differentiated between congenital and acquired diseases and only provided rehabilitation for the latter (21). Whether or not children and adolescents received appropriate rehabilitation services depended largely on national regulations and, to some extent, on the individual commitment of pediatricians and other health professionals. However, rehabilitation of children with CKD and children receiving kidney replacement therapy plays a crucial role in empowering children with the association of CKD and disability and preparing young patients for adult life and social integration (22, 23). Our survey found that rehabilitative care, including psychosocial care, schooling, health education, physiotherapy and nutritional counselling, for children with CKD was mainly organized and coordinated within hospitals or in combination with multidisciplinary caregivers from outside the hospital. Very few countries reported having special rehabilitation centers for children that also offer vacation dialysis. Our previous study (2) documented "the shortage of non-physician health workers in many countries, leading to suboptimal psychosocial and nutritional support and poorly planned transition programs from pediatric to adult renal care". Therefore, we propose the development of harmonized recommendations for the age-related rehabilitation of children with CKD according to the needs and wishes of European countries and young patients in particular.

The ideal clinical model for palliative care of young patients with advanced kidney disease is currently unknown. Internationally, outpatient renal palliative care clinics have been described with positive results (24). In our exploratory survey, we report data from the perspective of European pediatric nephrologists. We identified gaps in palliative care for children with adverse outcomes of acute and long-term kidney disease. In half of the countries, palliative care was organized and coordinated within the children's hospital or through a combination of hospital and home care. There were no reports on the role of hospices. Further studies are needed to determine the appropriate model of palliative care in pediatric nephrology (24).

A major limitation of our study is its qualitative, rather than quantitative research due to the variable availability of hard data in study centres. When planning the survey, the organisers were aware of the fact that—even if available—institutes of medical statistics did not contain enough data on pediatric nephrology; or, for political reasons, official statistics might not always reflect the true medical data in some special European countries. This mostly East European problem had been discussed by one of us (JE) with Professor Martin McKee when he was research director of the European Observatory on Health Systems and Policies. Finally, our ESPN teams had come to the conclusion in the late 1990ies that all responding national pediatric nephrologists of ESPN surveys should be very well known to ESPN. In our present survey the responders represented altogether more than a cumulative 1000 years of experience in European pediatric nephrology. Moreover, all responders knew that their individual wish was respected if confidential news should not be published or if the origin of a country should not be identifiable. Each question included the option to answer either "I don't know" or "yes or no, or other". The percentage of "I don't know" responses to all questions given by all countries was less than 5%, indicating that the questions were well understood. When analyzing this percentage for 13 countries that were formerly part of the former USSR as republics, there were slightly more "I don't know" than indicated for the EU countries. Respondents also had the option of refusing to answer a particular question without giving a reason, but this option was very rarely used.

ESPN has taken action to close these gaps by joining forces and becoming a member of the European Kidney Health Alliance (EKHA). The EKHA is a common effort by stakeholders for the challenges of management of people with CKD in Europe through effective prevention and a more efficient care pathway. EKHA works on the principle that the issue of kidney health and disease must be considered at European level and that both the European Commission and European Parliament have vital roles to play in assisting national governments with these challenges.

5 Conclusions

This cross-sectional survey on the existing pediatric nephrology healthcare systems in 48 European countries showed many unmet needs. The most common problems included no access to any type of dialysis, inadequate transplant programs for all ages of children, lack of well-trained physicians and dialysis nurses, inadequate reimbursement of hospitals for expensive therapies, and lack of multidisciplinary care by psychologists, dieticians, physiotherapists, social workers and vocational counsellors. If pediatric nephrologists had too many priorities, they probably risked doing a little bit of everything, and with less success. Our study shows that there are still very marked differences in child health care systems across the European countries and that there is an urgent need to set up appropriate services for children with kidney disease in all European countries.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

DH: Methodology, Supervision, Writing – original draft, Writing – review & editing, Conceptualization, Formal Analysis, Investigation. JE: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Writing – original draft, Writing – review & editing. VT: Writing – original draft, Writing – review & editing. VE: Writing – original draft, Writing – review & editing. EP: Writing – original draft, Writing – review & editing. LP: Writing – original draft, Writing – review & editing. CS: Writing – original draft, Writing – review & editing. RT: Writing – original draft, Writing – review & editing. DS: Writing – original draft, Writing – review & editing. AS: Writing – original draft, Writing – review & editing. TM-S: Writing – original draft, Writing – review & editing. RF: Writing – original draft, Writing – review & editing. IK: Writing – original draft, Writing – review & editing. EL: Writing – original draft, Writing – review & editing. DP: Writing – original draft, Writing – review & editing. DR: Writing – original draft, Writing – review & editing. DM: Writing – original draft, Writing – review & editing. AE: Writing – original draft, Writing – review & editing. TS: Writing – original draft, Writing – review & editing. MF: Writing – original draft, Writing – review & editing. IV: Writing – original draft, Writing – review & editing. JK: Writing – original draft, Writing – review & editing. MT: Writing – original draft, Writing – review & editing. IR: Writing – original draft, Writing – review & editing. PH: Writing – original draft, Writing – review & editing. GR: Writing – original draft, Writing – review & editing. AA: Writing – original draft, Writing – review & editing. DL: Writing – original draft, Writing – review & editing. LP: Writing – original draft, Writing – review & editing. NN: Writing – original draft, Writing – review & editing. NB: Writing – original draft, Writing – review & editing. EJ: Writing – original draft, Writing – review & editing. AJ: Writing – original draft, Writing – review & editing. ON: Writing – original draft, Writing – review & editing. VS-C: Writing – original draft, Writing – review & editing. AC: Writing – original draft, Writing – review & editing. SP: Writing – original draft, Writing – review & editing. MO: Writing – original draft, Writing – review & editing. AB: Writing – original draft, Writing – review & editing. MT: Writing – original draft, Writing – review & editing. AT: Writing – original draft, Writing – review & editing. AL: Writing – original draft, Writing – review & editing. AT: Writing – original draft, Writing – review & editing. VS: Writing – original draft, Writing – review & editing. LP: Writing – original draft, Writing – review & editing. TL: Writing – original draft, Writing – review & editing. ME-H: Writing – original draft, Writing – review & editing. PB: Writing – original draft, Writing – review & editing. GS: Writing – original draft, Writing – review & editing. HA: Writing – original draft, Writing – review & editing. DI: Writing – original draft, Writing – review & editing. JD: Writing – original draft, Writing – review & editing. KK: Writing – original draft, Writing – review & editing.

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Sodium glucose co-transporter 2 inhibitors (SGLT2i) for pediatric kidney disease: the future is near

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The sodium glucose co-transporter 2 (SGLT2) functions in the proximal tubule to reabsorb the bulk of filtered glucose. SGLT2 inhibitors have been developed to promote renal glucose excretion to improve glycemic control in diabetes. Regulatory guidance mandated adequately powered studies to detect increased cardiovascular risk from emerging hypoglycemic medications. This led to recognition of remarkable improvement in cardiovascular and kidney outcomes with SGLT2 inhibition. Moreover, cardiovascular and kidney benefits extend beyond patients with diabetes. The dramatic kidney benefits of SGLT2 inhibitors documented in CKD in adult patients underscores the need for pediatric nephrologists to familiarize themselves with SGLT2 inhibitor therapies. This review explores the currently available body of knowledge regarding the kidney protective effects of SGLT2 inhibitors in adults and mechanisms thought to contribute to improved kidney outcomes. The limited data for SGLT2i treatment in pediatric kidney disease are reviewed and highlight the need for randomized controlled trials of this drug class in pediatric kidney patients as has been done for pediatric diabetes. Dosing patterns for SGLT2 inhibitors from other pediatric settings are reviewed as well as guidance for initiating SGLT2 inhibition in young adults remaining in pediatric nephrology care.

KEYWORDS

empagliflozin, dapagliflozin, canagliflozin, pediatric chronic kidney disease, SGLT2 inhibitors, chronic kidney disease, IgA nephropathy, proteinuria

Introduction/background

The preeminent twentieth century renal physiologist Homer Smith wrote,

> "Maintaining the composition of the blood in respect to other constituents devolves largely upon the kidneys. It is no exaggeration to say that the composition of the blood is determined not by what the mouth ingests but by what the kidneys keep;" (1, 2)

Glucose homeostasis is a prime example of Smith's observation. Glucose is freely filtered by the glomerulus into the tubule, and then completely reabsorbed from the ultrafiltrate by the end of the proximal tubule. This is achieved by the sodium glucose co-transporter 2 (SGLT2) in the luminal brush border of the S1 segment which

reabsorbs 90% of the filtered glucose. The rest of the glucose is reabsorbed by the sodium glucose transporter 1 (SGLT1) in the final portion of the proximal tubule (S3 segment) (3). The main action of the SGLT2 inhibitors is to enhance renal glucose excretion by inhibiting tubular glucose reabsorption. A crucial advance in the understanding of renal glucose handling was made by Joseph Von Mering in 1885 who showed that phlorizin, a compound that had been isolated from the bark of apple tree roots fifty years prior induced glucosuria and diuresis in dogs and humans (4). It is now understood that phlorizin produced glucosuria through inhibition of renal tubular SGLT2. Though identified before insulin, phlorizin was limited as a diabetes treatment because of its poor oral absorption and its effects to reduce intestinal glucose absorption that causes diarrhea through nonselective inhibition of SGLT1 which is prominently expressed in the gut lumen (5).

By the 1930s, phlorizin's action to block renal glucose reabsorption was localized to the proximal tubule (6, 7). The novel and far-reaching impact of the coupling of glucose transport with sodium transport was first identified in the intestinal brush border and subsequently in the proximal tubule, with sodium facilitating glucose movement up a concentration gradient (8–12). The intestinal Na+ glucose transporter is now recognized to be SGLT1 (13). Antibodies to SGLT1 identified a similar protein in the renal brush border which shared 59% sequence identity with SGLT1 (14, 15). This second renal Na+/glucose cotransporter, termed SGLT2, is located in the proximal tubule S1 segment, is blocked by phlorizin, and has now been shown to be the high-capacity mechanism of renal proximal tubular glucose reabsorption observed a century before (16).

The potential for inhibition of SGLT2 as a novel treatment for diabetes was substantiated in 1999 when the first orally-available SGLT2 inhibitor, T-1095, a synthetic phlorizin O-glycoside analog, lowered blood glucose and hemoglobin A1c in diabetic animal models by increasing urinary glucose excretion (17). Like phlorizin, however, T-1095 also inhibited SGLT1 and led to gastrointestinal disturbances (18). T-1095 and other first generation SGLT inhibitors were abandoned in favor of improved SGLT2 selectivity as well as longer metabolic stability achieved through a C- glycoside structure. One such C-glycoside SGLT2 inhibitor, dapagliflozin was shown to be 30 times more potent for SGLT2 inhibition than phlorizin and effective at once daily dosing (19). Bristol Myers Squibb soon reported SGLT2 inhibition with dapagliflozin as treatment in Type 2 diabetes patients. Improvement in postprandial glucose was noted by day 2 of 14 of dapagliflozin treatment and fasting serum glucose improved significantly by day 13 (20). Longer duration treatment (12 weeks) in patients with Type 2 DM resulted in a decline in hemoglobin A1c of 0.55%–0.9% (21). Healthy subjects administered dapagliflozin showed dose-dependent glucosuria but no decrease in serum glucose reflecting multiple pathways of glucose homeostasis (22).

In 2012, the European Medicines Agency (EMA) approved dapagliflozin for use in adults with type 2 diabetes, both as monotherapy and in combination with other anti-diabetic medications. In 2014, the US Food and Drug Administration (FDA) followed suit as well as approving another SGLT2 inhibitor, empagliflozin. Over the next couple of years, multiple SGLT2 inhibitors were approved for unaccompanied treatment of type 2 diabetes (canagliflozin and empagliflozin) as well as in combination with metformin. In 2018, Merck was approved for unaccompanied use of the SGLT2 inhibitor ertugliflozin as well as combined with metformin and also in combination with the DPP-4 inhibitor sitagliptin (23). In Jan 2023 bexagliflozin was approved for Type 2 DM treatment. Importantly, the first recognition of SGLT2 inhibition benefits beyond diabetes control was by the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME). The study reported that the addition of empagliflozin decreased cardiovascular death by 38% and all-cause mortality by 32%, compared to placebo (24).

By exploring the improved kidney outcomes with SGLT2 inhibition in adults and the limited data available for SGLT2 inhibition in children and youth with kidney disease, this review aims to highlight the need for robust and well-funded evaluation of SGLT2 inhibitors for treatment of kidney disease in pediatric patients. Moreover, the review aims to facilitate the use of SGLT2 inhibitors for young adults remaining in pediatric nephrology care, for whom SGLT2 inhibitors are presently available.

Efficacy in chronic kidney disease

Clinical trials indicate that SGLT2 inhibitors in adults have wide-ranging cardiovascular and kidney effects beyond their glucose lowering action. These benefits are also observed in individuals without diabetes mellitus. These effects were recognized due to the mandatory cardiovascular outcome trials required by the United States Food and Drug Administration and the European Medicines Agency for all new antidiabetic drugs which required inclusion of high-risk groups including those with renal impairment (25). The EMPA-REG OUTCOME trial published in 2015 showed that adults with type 2 diabetes and cardiovascular disease treated with empagliflozin had a lower rate of cardiovascular death, all-cause mortality, and hospitalization for heart failure when compared to placebo (24). Two years later, the CANVAS trial demonstrated that in patients with type 2 diabetes who were 30 years of age or older with a history of symptomatic cardiovascular disease or patients 50 years of age or older with at least two risk factors for cardiovascular disease, treatment with canagliflozin led to a decrease in the rate of the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (26). Notably, the CANVAS trial also found less progression of albuminuria and a decreased risk of the composite outcome of 40% reduction in eGFR, need for renal replacement therapy, or death from renal causes in persons who received canagliflozin, suggesting a role for SGLT2 inhibitors in kidney protection. Although the DECLARE-TIMI trial of dapagliflozin in patients 40 years of age or older with type 2 diabetes at risk for cardiovascular disease or established cardiovascular disease found no difference in the risk of major adverse cardiovascular events (MACE) compared to placebo, it found a decreased risk of heart failure hospitalization (27). Moreover, DECLARE-TIMI reported kidney protection with

SGLT2 inhibitors in secondary analysis with the risk halved for GFR drop of 40% to <60 ml/min/1.73 m^2 or ESRD or death from renal causes in dapagliflozin treated Type 2 diabetics.

Remarkably, the kidney protective effects were observed even in individuals without diabetes. The first of these observations came in the CREDENCE trial. Indeed, this study was terminated early due to efficacy. It was conducted in type 2 diabetes patients > 30 years of age, with an eGFR of 30-<90 ml per minute per 1.73 m^2 (CKD), a urinary albumin to creatinine ratio of >300–5,000 mg/g (macroalbuminuria), and already treated with renin-angiotensin system blockade. Canagliflozin-treated patients had a 30% decrease in relative risk of the composite outcome of end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular outcomes if treated with canagliflozin in just median 2.6 years follow up (28). Another trial, DAPA-CKD enrolled patients 18 years of age or older with an eGFR 25–75, a urine albumin to creatinine ration between 200 and 5,000 mg/g, and who were stable on maximum tolerated ACE inhibitor or ARB with type 2 diabetes (two thirds of patients) or without diabetes. Patients were randomized to dapagliflozin or placebo. Irrespective of the patient's type 2 diabetes status, dapagliflozin treatment led to a significantly decreased risk of the composite of decrease in eGFR of 50%, end-stage kidney disease, or death from renal or cardiovascular causes with hazard ratio 0.61 (95% CI: 0.51–0.72; $P < 0.002$) (29).

EMPA-KIDNEY enrolled patients 18 years of age or older with or without diabetes (of any type) who were randomized to empagliflozin or placebo. Patients with an eGFR between 20 and <45 were enrolled irrespective of albuminuria and patients with an eGFR between 45 and <90 who had a urine albumin to creatinine ratio of at least 200 mg/g. Treatment with empagliflozin led to a decreased risk of progression of kidney disease or death from cardiovascular causes with results consistent across eGFR subgroups and irrespective of diabetes diagnosis. Benefit was most pronounced in proteinuric patients with albumin to creatinine ration above 300 mg/gm (30). Notably, 1,669 patients in EMPA-KIDNEY had glomerular disease as the cause of their CKD: 817 IgA nephropathy, 195 FSGS, and 657 had other causes of glomerulonephritis. The primary outcome of kidney disease progression or cardiovascular death was decreased similarly across all main categories of cause of kidney disease (31). In addition, empagliflozin treatment for two years led to a ~50% reduction in decline in GFR without difference between primary kidney disease groups (diabetes, hypertension/renovascular, glomerular, and other/unknown).

While most of the published trials report better kidney outcomes with SGLT2i, this is not universal. The much smaller and shorter DIAMOND study was conducted in patients without diabetes and mean GFR 55–60 ml/min/1.73 m^2 with dapagliflozin for 6 weeks ($N = 53$). No change in proteinuria was observed and dapagliflozin treatment decreased GFR by 6.6 ml/min/1.73 m^2 which was reversed upon discontinuation of medication (32).

Reduction of proteinuria with SGLT2 inhibition has been observed repeatedly in diabetic kidney disease and likely contributes to the improved renal outcomes (33). In the CANVAS trials involving over 10,000 type 2 diabetic patients, progression of albuminuria was assessed as 30% increase in albuminuria or increase from normoalbuminuria to micro- or macroalbuminuria or microalbuminuria to macroalbuminuria. Among patients treated with canagliflozin for 3–4 years, remarkable improvement in proteinuria was observed: progression of albuminuria was decreased (hazards ratio 0.73; 95% CI: 0.67–0.79) (26). Conversely, regression of albuminuria (using the reverse definitions) was more common in canagliflozin-treated patients (Hazards ratio 1.7 (95% CI: 1.51–1.91). In the CREDENCE trial of canagliflozin in type 2 DM patients with macroalbuminuria and decreased GFR (30–90 ml/min/1.73 m^2), urine albumin to creatinine ratio was decreased by 31% in patients receiving canagliflozin (28). In the DELIGHT trial in patients with type 2 DM and albuminuria (30–3,500 mg/gm creatinine), patients treated with dapagliflozin for six months ($n = 140$) showed a 21% reduction in albuminuria vs. placebo-treated patients (34). The EMPA-Kidney trial, in whom patients had less albuminuria overall, with median albumin to creatinine ration 329 mg/gm, showed a 19% decrease in albuminuria in empagliflozin-treated patients (30). Even among diabetics with nephrotic range proteinuria (urine albumin to creatinine ratio ≥ 2,200 mg/gm), treatment with empagliflozin resulted in a hazard ratio of 2.30 (95% CI: 1.34–3.93) for at least a 30% decrease in proteinuria compared to placebo (35). Moreover, median predicted time to ESKD was increased from 5 to 10 years in the empagliflozin-treated.

Data for SGLT2 inhibitor reduction in non-diabetic kidney disease is less plentiful but emerging. Among Spanish adults with biopsy-proven glomerular disease ($n = 493$), SGLT2 inhibition resulted in a mean 48% proteinuria reduction at 1 year follow up, occurring less often in those with serum albumin < 3.5 g/L. As in diabetic disease those with ≥30% proteinuria reduction showed slower decline in GFR (36). Among Egyptian adults with varied glomerulonephritis ($N = 25$), treatment with empagliflozin decreased progression of proteinuria (Odds ratio 0.65; 95% CI: 0.55–0.72) (37).

Mechanisms of SGLT2 inhibitors in the kidney

Multiple studies including CREDENCE, DAPA-CKD, and EMPA-Kidney have demonstrated beneficial effects of SGLT2-inhibitors: lower risk of CKD progression, reduction of proteinuria, and lower risk of cardiovascular mortality. However, one must question, "How does this all happen?" Sodium glucose transporters located on the luminal side of the proximal tubule are responsible for nearly all glucose reabsorption. Diabetes upregulates the SGLT co-transporters, increasing glucose reabsorption.

Augmented tubuloglomerular feedback

An important mechanism for the kidney protective effect SGTL2-inhibitors involves tubuloglomerular feedback (TGF) whereby tubular flow and composition modulate arteriolar

vascular tone and thus the glomerular filtration. Under normal conditions, TGF acts to limit glomerular filtration when flow in the distal tubule is ample. Diabetes blunts tubuloglomerular feedback. Prevailing hyperglycemia upregulates proximal tubular sodium-glucose cotransporter and increases glucose, sodium, and chloride reabsorption. The ensuing reduction in sodium and chloride delivery to the distal nephron and macula densa results in decreased afferent arteriolar tone (vasodilatation) and increased glomerular perfusion and filtration (38). Support for this scenario is provided by studies in spontaneously diabetic mice ($Ins2^{+/Akita}$) that show single nephron GFR is two-fold higher than non-diabetic controls, (15.8 ± 6.8 nl/min vs. 4.9 ± 1.3 nl/min, control). Importantly, treatment with the SGLT2 inhibitor empagliflozin normalized the increased GFR in diabetic mice (8.0 ± 3.3 nl/min) (39). The underlying mechanism involves local vasoactive adenosine which acts on smooth muscle cells to induce vasoconstriction of the afferent arteriole, resulting in decreased glomerular blood flow (Figure 1). In another preclinical diabetes model, *in vivo* imaging was able to visualize afferent arteriolar vasoconstriction after SGLT2 inhibitor treatment and decrease in single nephron GFR (41). Moreover, SGLT2 inhibitors can act synergistically to reduce intraglomerular pressure and hyperfiltration by the concomitant efferent vasodilation by renin-angiotensin-aldosterone blockade (42).

Even in the absence of diabetes, SGLT2 inhibition offers kidney protection at least in part through tubulo-glomerular feedback. In the 5/6 nephrectomy rat model of chronic kidney disease in which diabetes does not feature, SGLT2 inhibition with empagliflozin ameliorated glomerular hypertrophy, glomerulosclerosis and interstitial fibrosis as effectively as inhibition of the renin angiotensin system with telmisartan (43). Moreover, preservation of creatinine clearance over time correlated directly with higher urinary adenosine levels (indicating improved TGF and afferent arteriolar vasoconstriction). Higher adenosine levels also correlated with minimization of interstitial fibrosis pointing to overall renal preservation.

Renal tubule effects

Proximal tubular cells are the exclusive site of glucose reabsorption from the glomerular ultrafiltrate. They are, therefore, dramatically impacted by persistent hyperglycemia on a cellular level. Histologically, the tubulointerstitial changes include proximal tubular cell basement membrane thickening, hyperplasia, and hypertrophy, eventually resulting in atrophy as diabetic disease progresses. Direct effects of high glucose levels result in activation of inflammatory and profibrotic effects in proximal tubular cells (PTCs). Thus, PTCs cultured in a high glucose environment showed increased expression of Toll-like receptor 4, increased nuclear DNA binding of transcription factors NF-κB and AP-1 as well as increased expression of collagen IV and secretion of IL-6—all of which were attenuated by SGLT2 inhibition with empagliflozin (44). The damaging

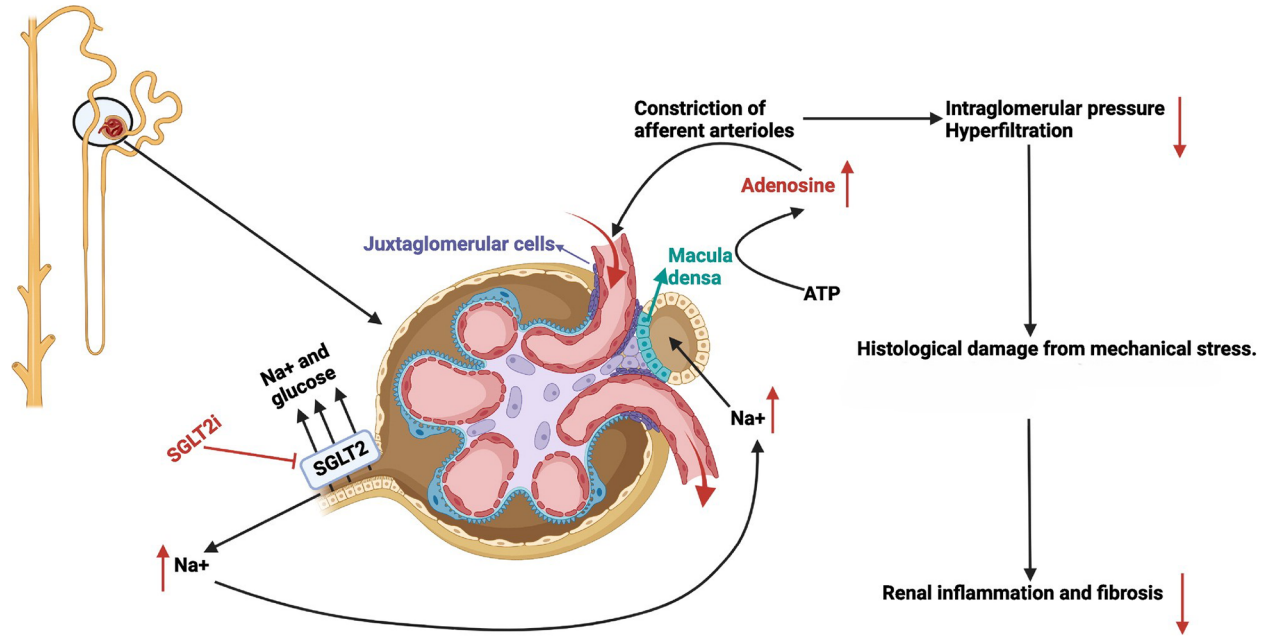

FIGURE 1
Mechanism of action of sodium glucose co-transporter 2 inhibitors through enhanced tubular glomerular feedback. With permission from Ref. (40, p. C664). A nephron is shown on the left with the glomerulus, juxtaglomerular apparatus, and early proximal tubule enlarged on the right. SGLT2 inhibitors (red text) block the reabsorption of Na+ and glucose in the proximal tubule leading to glucosuria and increased Na+ delivery to the distal tubule and macula densa. As a result, macula densa cells release ATP which is hydrolyzed locally to adenosine (red text). Adenosine acts on adjacent smooth muscle adenosine receptors to constrict the afferent arterioles. Decreased afferent arteriolar blood flow lowers intraglomerular pressure and decreases glomerular filtration, thus ameliorating proteinuria, podocyte derangement and loss, as well as downstream inflammation and renal fibrosis.

effects on proximal tubular cell growth and function have been linked to cytokine TGFβ, resulting from increased glucose exposure and intracellular influx (45). SGLT2 inhibitors moderate this destruction via blockade of glucose transporters (46). SGLT2 inhibitors may also mitigate transition from renal monocytes to inflammatory M1 macrophages which contribute to renal interstitial fibrosis (40). Among patients with diabetes inadequately controlled by metformin, SGLT2 inhibition reduced circulating biomarkers of inflammation and fibrosis compared to treatment with the insulin secretagogue glimepiride in 1–2 years follow up. Thus, plasma samples from canagliflozin treated patients showed lower levels of circulating TNF Receptor 1, IL-6, Matrix metalloproteinase 7, and fibronectin 1 despite identical hemoglobin A1c levels to glimepiride treated patients (47).

Kidney biopsies from teens and young adults with type 2 diabetes and healthy controls were interrogated with single cell transcriptional profiling (48). The renal biopsies were not performed for clinical reasons. Among patients with diabetes, some had been treated with SGLT2 inhibition allowing comparison to SGLT2i-untreated patients. As expected, a variety of transcripts along the renal tubule were differentially regulated by diabetes and SGLT2 inhibition identifying significant alterations in the mTORC1 pathway. Phosphorylation of ribosomal protein S6 (rpS6), a marker of mTORC1 signaling activation was detected in the proximal and distal tubules of the diabetic patients, indicating mTORC1 activation in SGLT2i untreated diabetics. Phosphorylated rpS6 staining was normalized in those treated with SGLT2 inhibitors. Thus, even before overt kidney disease is present, renal tubular cells in Type 2 DM show upregulation of mTORc1 that can be ameliorated by SGLT2 inhibition. As mTORc1 functions at a nexus of metabolic, growth, immune and fibrogenic signaling, the implications of its treatment extend beyond diabetic kidney disease with potential relevance for all progression of chronic kidney disease (49).

Impact on mesangial cells

Increased extracellular glucose concentration results in dysfunction of other renal cell lines. Mesangial cells are specialized pericytes which have a role in regulation of glomeruli circulation that ensures maintenance of constant blood flow. Diabetic nephropathy is marked by progressive mesangial expansion, nodular accumulation of mesangial matrix (Kimmelstiel Wilson nodules) and resultant capillary microaneurysms (50). Using *in vitro* studies, mesangial cells from diabetic rats showed loss of contractile response to angiotensin II, cell swelling, over-production of extracellular matrix, and apoptosis. The mesangial dysfunction resulted in induction of glomerular hyperfiltration and development of glomerular microaneurysms. Normalization of these effects was described with SGLT2 inhibitors indicating renoprotective effects on mesangial cells (51). Mesangial cells cultured with high glucose showed increased TGF beta and fibronectin that was normalized by treatment with canagliflozin (52). Interestingly, aside from mesangial cells, SGLT2 is also expressed in retinal pericytes that maybe involved in diabetic microaneurysm formation (51). It is therefore notable that the incidence of sight threatening retinopathy was significantly decreased in type 2 diabetic patients treated with SGLT2 inhibition compared to DPP4 inhibition, pioglitazone or sulfonylureas (53).

Impact on podocyte function

Podocytes are critical in maintaining the glomerular filtration barrier and proteinuria indicates their functional decline, common in all chronic kidney disease. In addition to improved glucose control and decreased blood pressure, SGLT2 inhibition significantly decreased podocyte shedding into the urine which was not seen in control treated patients (54). Mice with proteinuria induced by protein overload showed increased glomerular staining for SGLT2 which colocalized with nephrin confirming its podocyte location. Animals treated with dapagliflozin showed significant preservation of glomerular structure and amelioration of proteinuria to the same degree as ACEi treated animals (55).

Upregulation of SGLT2 expression in cultured human podocytes resulted in observed marked remodeling of the cytoskeleton caused by NF-κB activation. SGLT2 inhibition with dapagliflozin ameliorated cytoskeleton rearrangement and improved overall podocyte dysfunction (55). Ongoing research indicates that human and wild type mouse podocytes in culture express SGLT2. Podocyte damage in animal models of non-diabetic disease such as the Col4a3 knockout model of Alport Syndrome prone to lipotoxicity showed that empagliflozin was protective of lipotoxicity-induced podocyte apoptosis (56). Similar benefits were reported in podocytes from lupus prone mice and patients with lupus nephritis (57). Some of the impact of SGLT2 inhibition to various non-diabetic kidney disease may relate to the degree of SGLT2 expression in podocytes in various clinical settings. In one pilot trial of SGLT2 inhibition in FSGS, proteinuria did not decrease after eight weeks of treatment with dapagliflozin which the authors theorized might relate to podocyte downregulation of SGLT2 mRNA which they observed in a archival renal biopsies of FSGS (58).

Role in inflammation

The benefits of SGLT2 inhibition may reflect alterations in immune function (59). Reduction in IL-6 levels has been repeatedly observed in clinical trials of SGLT2 inhibitors. Given the importance of IL-6 to vascular pathophysiology, IL-6 reduction likely contributes to the cardiovascular and renal benefits of SGLT2 inhibition (60). In lupus prone MRL/*lpr* mice treated with empagliflozin for 20 weeks, dramatic improvement in serum creatinine, proteinuria, and renal histology was observed compared to untreated animals (57). Unexpectedly, empagliflozin treated mice also showed significantly lower IgG levels and anti dsDNA levels. In another study, some complement components were altered by SGLT2 inhibition. Thus, in rats with 5/6 nephrectomy the upregulation of C1q subunits A and C were normalized during treatment with

empagliflozin and was thought to contribute to renoprotection (43). Canagliflozin was recently shown to impair T cell function through diminished T cell receptor signaling, reduced activation, reduced proliferation, altered metabolism and decreased cytokine production (61). Dapagliflozin did not show these same effects and SGLT2 expression in T cells is not robust or absent, so Canagliflozin's effects in T cells is likely off-target, though not yet clarified. Calls have been made for the repurposing of canagliflozin for autoimmune diseases (62).

SGLT2 inhibition in specific kidney diseases

The large data sets available from CKD treatment trials with SGLT2i allow subsequent analysis of differential impact in various primary renal diseases. Together with trials conducted in more restricted groups of kidney diseases, assessment of the potential for benefit for SGLT2i in specific clinical entities is rapidly emerging.

IgA nephropathy

Because it is the most common chronic primary glomerular disease, IgA nephropathy (IgAN) contributes significantly to prevalent CKD (63). Therefore, available SGLT2i treatment data for IgAN is sufficient to draw conclusions regarding efficacy. The DAPA CKD trial enrolled 270 patients with IgAN who fulfilled its inclusion criteria of with GFR 25–75, urine albumin to creatinine ration 200–5,000 mg/g, stable dose of ACEI/ARB and no immunotherapy for 6 months before enrollment. They were randomized to dapagliflozin 10 mg daily or placebo. Dapagliflozin dramatically reduced (by ~75%) those patients reaching the composite renal endpoint of ESKD, 50% decrease in GFR or kidney disease-related death (Hazard ratio 0.24 [0.09, 0.65], $P = 0.002$ (64). Secondary analysis of the EMPA-KIDNEY trial included 870 IgAN patients with GFR 45–90, UAC >200 mg/g, with use of single ACEI/ARB required for all participants. Those taking prednisone ≥45 mg daily or IV immunosuppression in the preceding 3 months were excluded. Kidney disease progression (development of ESKD or GFR < 10 or 40% decrease in GFR) was again dramatically reduced in those IgAN patients receiving empagliflozin [Hazard ratio 0.67 (95% CI: 0.46–0.97)]. The decline in GFR over time was lessened by 30%–40% among the empagliflozin treated IgAN patients (31). Recently, a large observational European cohort of glomerulonephritis patients was published of whom all were on some dose of ACEI/ARB and all received SGLT2 inhibitors. The study included 203 patients with IgAN or IgAV who showed a 50% decrease in proteinuria after 12 months of SGLT2i treatment (36). This is a notable finding given that proteinuria reduction vs. persistence is a satisfactory surrogate marker for outcomes in IgAN (65). A smaller Chinese study shows that even in patients on maximal doses of ACEI/ARB, further proteinuria reduction (~25%) was seen in a short duration of SGLT2i treatment (6 months) (66). Thus, multiple sources of evidence align to indicate that SGLT2 inhibition greatly benefits patients with IgAN by reducing proteinuria and slowing decline in kidney function.

FSGS

FSGS is a glomerular disease which is often resistant to treatment and continues to constitute a common diagnosis leading to ESKD, especially in pediatric patients. Data from SGLT2i treatment of FSGS continue to accrue from adult studies. In an eight-week pilot trial of dapagliflozin in ten adult FSGS patients, all treated with ACEi/ARB, no decrease in proteinuria was observed (58). A prespecified analysis of the DAPA-CKD trial showed a promising Hazard ratio of 0.67 for biopsy-proven FSGS patients ($N = 104$) with regard to reaching ESKD or experiencing ≥40% drop in GFR, the kidney composite outcome. Unfortunately, the 95% confidence interval for the HR was 0.19–2.44 and so intersected the HR 1.0/Forest plot Line of no effect. The authors hypothesized that small sample size was obscuring dapagliflozin benefits in FSGS, but disease heterogeneity and/or low/no efficacy may have contributed as well (67). Among EMPA-KIDNEY patients with FSGS and a larger sample size ($N = 195$), empagliflozin did not appear to decrease the kidney progression outcome (ESKD or ≥40% GFR decrease). In fact, the Hazard ratio 1.35 (0.65–2.81) favored placebo over empagliflozin. Analyses of GFR slope for FSGS patients in EMPA-KIDNEY did appear to favor empagliflozin slightly over placebo, but in all subgroup analyses of FSGS, the 95% CI intersected the Forest plot line of no effect tempering enthusiasm for empagliflozin in FSGS (31). More promising results are seen in the large observational European cohort of glomerulonephritis patients described above, of whom all were on ACEI/ARB and all received SGLT2 inhibitors. 56% of primary FSGS patients ($N = 32$) and 83% of secondary FSGS ($N = 58$) showed a ≥30% reduction in proteinuria (36). The optimism for SLGT2 inhibitor treatment generally must remain cautious for FSGS treatment given currently available evidence, though disease heterogeneity of FSGS raises the possibility that some patients may benefit from SGLT2 inhibition.

Obesity related glomerulopathy (ORG)

ORG is a chronic kidney disease characterized by glomerular hyperfiltration and proteinuria which occurs in obese individuals (68). The incidence of ORG has increased at least 10-fold in the last several decades and occurs in pediatric patients as well (69, 70). Histologically, ORG is characterized by glomerulomegaly and podocyte hypertrophy. The glomerular enlargement effects the increase in GFR. Given that podocytes are terminally differentiated and do not proliferate, their number does not increase and their density declines in the enlarging glomerulus. Podocytes undergo increasing stress, fail and detach, leading to glomerulosclerosis.

Multiple components of the pathophysiology of ORG may be amenable to treatment with SGLT2i (71). The glomerular hyperfiltration of severe obesity entails prominent afferent arteriolar vasodilation, and as above, SGLT2 inhibition curbs afferent arteriolar vasodilation through natriuresis and increased tubuloglomerular feedback (72). Alterations in adipokines in obesity also contribute to renal damage. Leptin stimulates TGF beta overexpression. Resistin upregulates inflammatory cytokines such as TNF alpha, Il-6 and IL-12 contributing to low grade chronic inflammation. By contrast, adipose-derived adiponectin declines with worsening obesity, thus decreasing its normal renoprotection to injured podocytes (73). Dapagliflozin, empagliflozin, and canagliflozin have been shown to ameliorate these metabolic derangements, increasing circulating levels of adiponectin and decreasing leptin, TNF- alpha and IL-6 (74). Given that obesity worsens outcomes of other glomerular disease beyond ORG, it is noteworthy that a recent trial of SGLT2 inhibition in glomerulonephritis patients showed higher proteinuria reduction with SGLT2 inhibition in patients with increased BMI (36, 75).

Alport syndrome

Alport syndrome, or hereditary nephritis, is a chronic kidney disease frequently encountered in pediatric nephrology in which the glomerular basement membrane is impaired by mutations in the collagen IV genes COL4A3, COL4A4, and COL4A5 which also impair collagen containing structures in the ear and eye. Beginning with microscopic hematuria, AS progresses to albuminuria, overt proteinuria and then declining kidney function (76). Eighty percent of AS is caused by mutations in COL4A5 located on the X chromosome leading to worse outcomes in males. Fifty percent of males reach ESRD by age 25 whereas 40% of females reach ESRD by age 80 (77, 78). Treatment with ACEi reduces proteinuria and delays time to kidney failure and more so the higher the GFR at ACEi initiation, making timely nephroprotection imperative (79).

Potential benefit of SGLT2 inhibition in AS has been proposed, utilizing SGLT2i-induced afferent arteriolar vasoconstriction to lessen glomerular pressure exerted through the diseased glomerular basement membrane (80). Very recently, results were published from an international observational study in Alport patients of SGLT2 inhibitor therapy added on to renin angiotensin inhibition in 112 AS patients, aged 38 ± 14 years (81). Allowing for the limited duration of the study, reduction in proteinuria is taken as a surrogate marker for reduced risk of progression. Baseline albuminuria of 1,797 ± 1,600 mg/g creatinine decreased to 1,197 ± 978 mg/g creatinine after 1–3 months of treatment ($P = 0.002$) and remained at essentially the same level in those followed to 4–8 months and 9–15 months. In patients followed for two years, the baseline albuminuria of 2,127 mg/g creatinine dropped to 1,903 ± 1,371 mg/g creatinine and was not significant, possibly due to low patient number ($N = 7$). Subgroup analysis of the ten pediatric patients (age 15 ± 3 years) showed stable blood pressure after 4 ± 5 months of SGLT2i therapy (BP 116 ± 13/72 ± 11 to 117 ± 13/71 ± 13 mm Hg). GFR decreased from 119 ± 32 ml/min/1.73 m^2 to 107 ± 36 ml/min/1.73 m^2. In the two patients with overt proteinuria, urine albuminuria decreased from 1,426 ± 1,247 mg/g creatinine to 641 ± 190.

A multicenter, randomized, double-blind, placebo-controlled trial of dapagliflozin in AS has recently been announced by the German Society of Pediatric Nephrology. The DOUBLE PROTECT Alport Trial will enroll pediatric patients (age 10–17 years) and young adults (18–39 years) who despite being on stable maximum dose RAS inhibitor have persistent albuminuria (>300 mg/g creatinine for children > 500 mg/g creatinine for adults). Importantly and differing from previous clinical trials of SGLT2 inhibition, DOUBLE PRO-TECT will enroll patients with mild CKD (Stage 1–2) but at high risk of CKD progression. Treatment to placebo randomization will be 2:1 and treatment will last 48 weeks with reevaluation 4 weeks after discontinuation. Open-label SGLT2i continuation after that will be offered in adults (82).

Lupus nephritis

Lupus nephritis patients were excluded from the large trials of SGLT2 inhibitors in chronic kidney disease (28, 29). Available data of SGLT2i use in Lupus has been sparse but is promising. Five adult SLE patients with eGFR 34–94 ml/min/1.73 m^2 experienced a 50% reduction in proteinuria after eight weeks treatment with empagliflozin 10 mg (83). Similarly, among nine adult patients with eGFR 60–126.8 ml/min/1.73 m^2, two months of SGLT2 inhibitor treatment resulted in significant decreases in proteinuria ranging from 29.6–96.3% (57). Database assessment of the U.S. Collaborative Network of the TriNetX clinical data platform identified $N = 3{,}550$ patients with SLE and type 2 DM. Those treated with SGLT2 inhibitors had significant reduced risk for lupus nephritis [adjusted hazard ratio (AHR) 0.55; 95% CI: 0.40–0.77], dialysis (AHR 029; 95% CI: 0.17–0.48), kidney transplant (AHR 0.14, 95% CI: 0.03–0.62), heart failure (AHR 0.65, 95% CI: 0.53–0.78) and all-cause mortality (AHR 0.35, 95% CI: 0.26–0.47) (84).

Autosomal dominant polycystic kidney disease (ADPKD)

Patients with ADPKD were also excluded from the large trials of SGLT2 inhibitors in chronic kidney disease (29, 30). SGLT2i effects of natriuresis and diuresis would be thought to lead to increased circulating vasopressin. Importantly, antagonism of vasopressin effect on the kidney by tolvaptan slows cyst growth, preserves kidney function and is FDA approved for kidney preservation in progressive ADPKD (85). Indeed, preclinical studies show an increase in urinary vasopressin during SGLT2i treatment (86). Nonetheless, the pleiotropic benefits of SGLT2 inhibitors could be hypothesized to outweigh the negative impact of vasopressin increase. Further consideration of SGLT2i kidney preservation in ADPKD has been advocated (87). Two recent

studies with dapagliflozin in ADPKD help address these issues (88, 89). Despite small numbers ($N = 7$ and $N = 10$, respectively) and short duration (102 ± 20 days and 20 months), both studies showed a significant increase in height adjusted total kidney volume during treatment, the most useful surrogate marker for kidney progression in ADPKD (90). Indeed, the latter study was able to demonstrate an increase in the rate of kidney growth during dapagliflozin treatment. These preliminary studies do not support the use of SGLT2 inhibition for kidney preservation in ADPKD at this time and may even sway clinicians to choose other hypoglycemic treatments in those patients with diabetes and ADPKD.

SGLT2 inhibitor use in the young

The dramatic kidney benefits of SGLT2 inhibitors documented in CKD in adult patients underscores the need for pediatric nephrologists to familiarize themselves with SGLT2 inhibitor therapies. SGLT2 inhibitors are EMA/FDA approved for use in adult CKD and are, therefore, available for patients older than 18 still under pediatric nephrology care. While health-care transition from pediatric to adult nephrology is a widespread goal, the reality of formal transition care may remain aspirational in many centers (91). The development of the "CKiD under 25" GFR estimating equations and calculator for children through to young adults attests to the reality that patients with CKD above the age of 18 may still be cared for by pediatric nephrologists (92). As such, young adults still under pediatric nephrology care require access to all therapeutic options to improve kidney outcomes, including SGLT2 inhibitors.

Pediatric diabetes

The long-term harm from type 2 diabetes in the pediatric population is magnified, because the younger a child is at diagnosis with T2DM, the higher incidence of diabetes complications even in young adulthood (93). While SGLT2 inhibitors have become widely used in adults, until 2019 with the advent of glucagon-like peptide-1 (GLP-1) receptor agonists such as liraglutide, the only approved treatments for pediatric patients/children with type 2 diabetes mellitus (T2DM) were insulin and metformin. GLP-1 receptor agonists, however, have several obstacles to their use in pediatric patients. They are injectable, cost-prohibitive, and often in short supply, in part because they are also used in the treatment of obesity. SGLT2 inhibition is now an option for T2DM treatment in pediatric patients. On June 20, 2023, the oral SGLT2 inhibitor empaglifozin was FDA approved for pediatric use down to the age of 10 years (94). Empagliflozin was shown to be safe and efficacious in the DINAMO study, a double-blind, placebo-controlled trial performed in 108 sites in 15 countries in 262 youths aged 10–17 years with type 2 diabetes mellitus (95). Fifty-two pediatric patients were treated with empaglifozin at doses of 10 and 25 mg and after 26 weeks showed a significant and clinically meaningful reduction in hemoglobin A1c not seen for linagliptin. Thus, mean decrease in HgbA1c was 0.84% for empagliflozin vs. placebo (range −1.50–−0.19; $P = 0.012$) whereas the linagliptan group's hemoglobin A1c decrease of 0.34 was not significant (range −0.99–+0.30; $P = 0.29$). There were no differences in the rate of severe hypoglycemia. Therefore, as an adjunct to metformin, empaglifozin represents another valuable treatment of type 2 diabetes, especially in pediatric patients who are often fearful of injections.

Data regarding safety and efficacy of SGLT2 inhibitor use in pediatric patients is gradually beginning to accrue, frequently from case reports and series. A twelve-year old with Prader-Willi Syndrome and insulin resistance while on growth hormone could not be successfully managed with a variety of insulin regimens or metformin or liraglutide. She achieved glycemic control when empagliflozin was combined with liraglutide (96). Among seventeen obese pediatric patients aged 10–17 years with type 2 diabetes weighing a mean of 107 kg, the pharmacokinetics and pharmacodynamics of identical dose canagliflozin did not differ from adults (97). The DAPADream study utilized add-on Dapagliflozin in thirty type 1 diabetes patients (age 12–20 years) which was a double-blinded, placebo-controlled crossover study after two unannounced meals in patients on DreaMed closed loop insulin management. Glucose time in range (TIR) was significantly improved during dapagliflozin treatment with a total insulin dose reduction of 22% but no increase in glucagon or hypoglycemia (98). Beta hydroxy butyrate levels were statistically increased in dapagliflozin- treated patients but remained in the normal range.

SGLT2 inhibitor dosing in the young

A recently published systematic review of pediatric use of dapagliflozin or empaglifozin reports three hundred and fifty-two patients with diabetes ($n = 189$), heart failure ($n = 38$), kidney disease ($n = 9$, discussed below), PK studies ($n = 84$), as well as glycogen storage disease-related illnesses and congenital neutropenia ($n = 32$) (99). The average age of these disease groups of SGLT2i-treated pediatric patients differs: diabetes patients were teens (mean age 14.7 ± 2.9, concurrent with the largest clinical trials enrolling age 10–17 years), the glycogen storage disease patients being the youngest including patients as young as 1 year (mean age 8.5 ± 5.1) and the heart failure/CKD group being between these (mean age 11.2 ± 6.1). For dapagliflozin, in diabetics the mean daily dose was 11.4 ± 3.7 mg/day (range 5–20) and lower for the younger heart failure/CKD patients, 6.9 ± 5.2 mg. The empagliflozin mean daily dose in the pediatric diabetes patients was 15.7 ± 7.4 mg (range 5–25 mg) compared to 0.44 ± 0.28 mg/kg (range 0.1–1.3 mg/kg) in the younger and smaller glycogen storage disease patients.

Pediatric glycogen storage disease

The experience with SGLT2i in children with Glycogen storage disease (GSD) provides insights which may be useful to translate the kidney benefits of SGLT2i to younger age groups. Besides

fasting hypoglycemia and hepatomegaly often detected in infancy, GSD type 1 can have nephromegaly, proteinuria and risk for FSGS as well as hypocitraturia and risk for nephrolithiasis (100). In GSD-1a, the enzyme glucose-6-phosphatase α catalytic subunit is impaired which catalyzes the last step of glucose release from glycogen stores leading to hepatic and renal glycogen accumulation and organomegaly. In GSD-1b, the translocase for glucose—6- phosphate is impaired so that glucose-6-phosphate is not delivered to the site of enzymatic glucose release. Clinically, GSD-1a and GSD-1b are similar except for the distinguishing hallmark of neutropenia, recurrent infections and inflammatory bowel disease in GSD-1b. The cause of the neutropenia and neutrophil dysfunction in GSD-1b was recently identified as excess levels of the glucose analog, 1,5-anhydroglucitol (1,5AG) which, like glucose 6-hosphate, requires movement by the same translocase for metabolism and elimination (101). Interestingly, SGLT2 inhibition with canagliflozin decreases urinary 1,5 AG reabsorption and increases its elimination (102). Accordingly, repurposing of empagliflozin in GSD-1b patients led to a marked decrease in 1,5 AG levels in blood, improvement in neutrophil dysfunction, and less hospitalization for infection (103–105). Even in GSD, an entity characterized by hypoglycemia, only 6.3% of patients treated with empagliflozin reported symptomatic or severe hypoglycemia (99). An international questionnaire to physicians regarding off-label empagliflozin treatment indicated 112 patients with GSD-1b being treated in 24 countries, with 80 patients aged < 18 years. Twenty patients (18%) developed level 3 hypoglycemia (<54 mg/dl) and 9 patients (8%) required hospitalization (105). This international questionnaire attests to the spread of off label SGLT2 inhibitor use for a rare pediatric disease as well as the acceptance of the associated risks in order to achieve a demonstrable improvement in health.

Pediatric kidney disease

As in adults, it is likely that SGLT2 inhibitors will benefit CKD progression in pediatric patients. However, it is important to recognize that diabetic nephropathy or hypertensive nephrosclerosis are uncommon in the pediatric age group. Moreover, SGLT2 inhibitor treatment for renal hypoplasia/dysplasia and congenital abnormalities of the kidneys and urinary tract, CAKUT, which are common causes of progressive kidney damage in children, may be complicated by the fact that polyuria is a prominent feature of these disorders. Therefore, the generalizability of SGLT2i benefits to all pediatric CKD may be limited. Nonetheless, efforts are underway to foster early pediatric inclusion in glomerular disease trials (106). Moreover, the publication of EMPA-KIDNEY trial data and sub analyses in 2023–2024 has occasioned calls for prompt testing of SGLT2 inhibitors in pediatric CKD as well (107). A single-center short-term trial of empagliflozin in patients with CKD aged 12–25 years is currently recruiting patients in the US (SGLT2I-IN-KIDS (NCT06430684). Importantly, Boehringer Ingelheim will be soon initiating a multi-center trial of empagliflozin in pediatric chronic kidney disease patients.

Currently available data for SGLT2 inhibitor use in pediatric kidney disease is very limited. Liu et al. initiated treatment with dapagliflozin in nine pediatric patients with proteinuric kidney disease with mean age 10.4 years (range 6.4–13.8 years) (108). The degree of proteinuria ranged 1.23–6.21 g/m^2 BSA at enrollment (mean 2.1). One patient had familial FSGS, five had Alport syndrome with mutations in *COL4A5* (four) and *COL4A3* (one), one had *PAX2* mutation, one *NUP150* mutation and nephrotic range proteinuria, and one a variant in *CLCN5* causing Dent Disease. The dosing of dapagliflozin utilized the threshold of 30 kg body weight: for weight above 30 kg, the dose was 10 mg daily; for body weight <30 kg, the dose was 5 mg daily. All patients received a stable dose of fosinopril. One patient was lost to follow up. All eight patients experienced a reduction in proteinuria (ending urine protein 0.55–4.28 g/m^2 BSA, mean 1.5) at twelve weeks ($P < 0.05$). The percentage decrease in proteinuria was 22.6% (95% CI: 8.3–36.9%). Mean serum albumin increased from 35.3 ± 6.7 g/L to 37.5 ± 7.9 g/L ($P < 0.05$). GFR declined minimally from mean 109.2 ± 32 ml/min/1.73 m^2 (range 63.3–163.6) to 103.8 ± 28.2 ml/min/1.73 m^2 (range 60.8–150.6). One patient had an episode of asymptomatic bacteriuria and no patient discontinued dapagliflozin during treatment. No hypoglycemia was reported.

Another small case series encompassing younger adults has been reported for SGLT2 inhibition added to RAS inhibition in glomerular disease in hopes of prompting large prospective intervention trials (109). Two patients in this series were aged 23 and 25 years. Both showed a dramatic decrease in proteinuria with SGLT2 inhibition. In the former (with FSGS), albuminuria decreased from 530 mg/gm creatinine to 192 mg/gm creatinine after 3 months, though his serum creatinine increased from 1.66 mg/dl to 2.24 mg/dl (GFR decrease from 57 to 40 ml/min/1.73 m^2). In the latter (with FSGS), albuminuria dropped from 4,900 to 805 mg/gram creatinine after 11 months with serum creatinine improving from 1.33 to 1.02 mg/dl attributed to recovery of nephrotic syndrome.

A larger, real-world series has recently been reported for dapagliflozin treatment in 22 pediatric patients ranging in age from 12.9–17.2 who had kidney disease and proteinuria (110). Patients had Alport syndrome ($n = 7$), medication resistant nephrotic syndrome/FSGS ($N = 7$), IgAN ($N = 5$), atypical HUS ($N = 2$) and CAKUT ($N = 1$). All were treated with RAS inhibition. Dapagliflozin dose ranged 5–10 mg per day with two thirds receiving 10 mg. After 8 months of treatment, eGFR decreased from 71.1 ml/min/1.73 m^2 at baseline to 65.5 ($P = 0.003$). Urine protein to creatinine ratio, however, did not decrease during dapagliflozin treatment (uPCR 0.6 mg/mg before treatment to 0.7 mg/mg). A decrease in proteinuria was also not seen for any of the disease subgroups.

The very recently reported trial of SGLT2 inhibition in Alport Syndrome ($N = 112$) included ten pediatric patients aged 15 ± 3 years (81). They were treated with dapagliflozin 10 mg daily ($N = 9$) and 5 mg daily in the youngest patient, aged 9. Blood pressure was stable and GFR decreased minimally, remaining above 100 ml/min/1.73 m^2. Two pediatric patients had overt proteinuria which improved with dapagliflozin, from urine

albuminuria 1,426 ± 1,247 mg/g creatinine to 641 ± 190 after 4 ± 5 months of treatment.

Taken together, these retrospective, pediatric case series in predominantly glomerular disorders show considerable variation in proteinuria reduction during SGLT2 inhibitor treatment but somewhat less improvement than some similar studies in adults. The Immunology Working Group of the European Renal Association and the Spanish Group for the Study of Glomerular Diseases reported more striking results for SGLT2 inhibition in adults with glomerulonephritis (36). Among a retrospective, observational cohort of four-hundred and ninety-three adult glomerulonephritis patients already on RAS inhibition, treatment with SGLT2 inhibition resulted in reductions of proteinuria of 35%, 41%, 45%, and 48% at 3,6,9 and 12 months of treatment. Those achieving >30% proteinuria reduction had a slower decline in GFR (−3.7 vs. −5.3 ml/min/1.73 m^2/year; $P = 0.001$). More proteinuria reduction correlated with higher BMI. Whether or not similar results to these will be seen in larger pediatric cohorts will require well designed and funded trials.

Practical considerations for the use of SGLT2 inhibitors

With the rapid advance of favorable clinical trial data regarding the use of SGLT2 inhibitors in adults with kidney disease, there is a reasonable expectation that their benefits would extend to patients under age 18. Their use, though, brings with it certain pragmatic considerations around "best practice" at the time of prescribing.

Selecting an SGLT2 inhibitor

There are currently five SGLT2i that are commercially available for clinical use—canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and bexagliflozin. Each has been studied in varying populations, with an emphasis on diabetic and then cardiovascular outcomes. While each agent boasts slightly different outcomes among their trials, similar effect sizes were observed. In three RCTs conducted with primary renal outcomes, all showed overwhelming efficacy with respect to improved eGFR slopes with all three trials ending early due to efficacy (28–30). Given the similar effect sizes for both cardiovascular and renal outcomes, the observed clinical benefits of SGLT2i use is likely a class effect. Within the current landscape of clinical practice, where insurers or payors often have medication formulary restrictions that have a significant impact on patients' ability to afford these agents, it is wise to select the agent with the lowest out-of-pocket cost. Pragmatically, this often results in a reliance on the electronic medical record to advise which agent falls into the highest formulary tier or for patients or office staff to communicate with insurers to assist with selection. Empaglifozin was approved in the US in 2023 for use in pediatric type 2 diabetic patients down to age 10 (94). Innovation in pediatric subspecialty medicine has historically been advanced through off label drug use, so the use of SGLT2 inhibitors in pediatric patients without diabetes is likely to follow a similar pattern. Whether pediatric approval for Type 2 diabetes will mean empaglifozin is easier to obtain for pediatric patients than other SGLT2 inhibitors remains to be seen.

Patient counseling with SGLT2 inhibitor initiation

At the time of prescribing, counseling should focus on the potential benefits emphasized in previous sections of this class of agents. Emphasis on the observed slowing of chronic kidney disease in clinical trials done among adults can be coupled with discussion of adjunct cardiovascular and diabetic benefits in appropriate patient populations. The possible adverse events, anticipated side effects should also be discussed, along with counseling regarding practical strategies to use to mitigate those risks.

It is important to discuss the risk of volume depletion due to the diuretic effect of SGLT inhibition. This discussion should include advice on monitoring for symptoms of orthostatic hypotension, with counseling on corrective action if experienced. Counseling at the time of prescribing can encourage optimal hydration habits and perhaps reduce discontinuance of the drug. It is also sensible to provide patients with a "sick plan" for appropriate therapy interruptions. The SGLT2i inhibitor can be held during periods of illness or perioperatively. Among appropriate populations, attention must also be given to discussing medication use during periods of fasting. Extreme caution must be advised for the use of SGLT2 in patients with pre-existing polyuria, polydipsia and/or salt wasting phenotypes of kidney disease such as renal hypoplasia, dysplasia or posterior urethral valves which are common causes of pediatric chronic kidney disease.

There has been an observed increased risk of genital mycotic infections (GMI)—vulvovaginitis, and balanitis. These are more common in women and those with any personal history of mycotic genital infections, with lowest incidence observed in circumcised men (111). Within early clinical trials, the rates of GMI ranged between approximately 5% and 10%. This was more than observed among those treated with placebo and resulted in the FDA recommending issuing a safety announcement around the prescribing of these agents. In the DINAMO study using empagliflozin in diabetic patients aged 10–17 years, a single hospitalization was reported, for skin candida infection –its site not identified as genitourinary—so its relationship to glucosuria cannot be ascertained (95). Nonetheless, when prescribing SGLT2 inhibitors, focused counseling regarding personal hygiene practices has been shown to reduce the likelihood of early infectious issues (112) and bears discussion during initial counseling.

Controversy exists as to whether the risk of urinary tract infections is increased among patients treated with SGLT2i, with both single studies as well as meta-analyses being contradictory. One recent meta-analysis showed that dapagliflozin at 10 mg daily increased the risk of UTI (Odd Ratio 1.29; 95% CI: 1.15–

1.46) but that dapagliflozin at 5 mg or 2.5 mg daily did not (113). An earlier, larger meta-analysis did not show a significant risk for UTI in SGLT2i- treated vs. untreated (Relative Risk 1.05; 95% CI: 0.98–1.12) (114). Because meta-analyses of trial data may be underpowered to detect adverse events and may exclude higher risk patients, analyses of large patient databases may be useful. In one such analysis of >200,000 patients in two cohorts, risk of severe UTI (hospitalization, sepsis, pyelonephritis) was not increased in patients treated with SGLT2i compared to other second line hypoglycemic agents (Hazard Ratios 0.98 and 0.72 for the two cohorts) (115). Such data is being carefully examined and marshalled in the renal and cardiac communities to provide reassurance to patients and physicians for the use of SLGT2 inhibitors and continuation after UTI so as not to deny their benefits unnecessarily (116, 117). It has been hypothesized that the bacterial growth-promoting effect of glucose in the urine caused by SGLT2 inhibition may be countered by the diuresis, acting to reduce bacterial load (118). The development of Escherichia coli septicemia in an elderly man with bladder outlet obstruction treated with dapagliflozin may be cautionary for the use of SGLT2i in pediatric patients with CKD associated with abnormalities of the urinary tract (119).

Monitoring and anticipated changes

Guidelines vary in their recommendation for serial laboratory monitoring following prescription of an SGLT2 inhibitor. Routine laboratory monitoring of creatinine after initiation of an SGLT2i is not strictly defined. It is our practice in adults to follow a basic metabolic panel at four to eight weeks, then at the next routine follow up visit. Within those who have not yet reached adulthood, other experts have recommended also monitoring hepatic function given ongoing maturation as well as for any early signals of genitourinary infections (120). After the initiation phase, clinicians should continue routine clinical monitoring of renal function according to their clinical judgement.

It is important to acknowledge that there is an expected rise in serum creatinine after initiation of therapy. This rise is hypothesized to relate to the induced intraglomerular hemodynamic changes that come with therapy initiation as mentioned previously. Among the large clinical trials done for each agent, the median drop on eGFR after SGLT2i initiation ranged between 3 and 6 ml/min per 1.73 m^2 (Figure 2). Like the decline in eGFR observed with initiation of ACEi/ARB, this acute decrement is balanced by favorable change eGFR slope over time. In a post-hoc analysis of the EMPA-REG Outcome trial a significant "dipping" of eGFR—defined as a decrement of ≥10 ml/min per 1.73 m^2—was observed in 28% of trial participants during weeks 2–4 after initiation, with 41% of patients seeing an eGFR decline of 0–10 ml/min per 1.73 m^2. These patients were older with longer duration of diabetes and less controlled hypertension. Among those with initial observed decline, some "recovery" of eGFR by week 12 was observed among all groups; further, "dippers" saw the same cardiovascular benefits as observed larger trial group (121).

In practice, our group generally accepts a serum creatinine rise of up to 25%–30%. Changes greater than that prompt a volume assessment and additional hydration counseling or concurrent medication adjustments where appropriate (i.e., diuretics). If concurrent modifiable contributors to serum creatinine rise are identified, adjustments with continued SGLT2i use often leads to

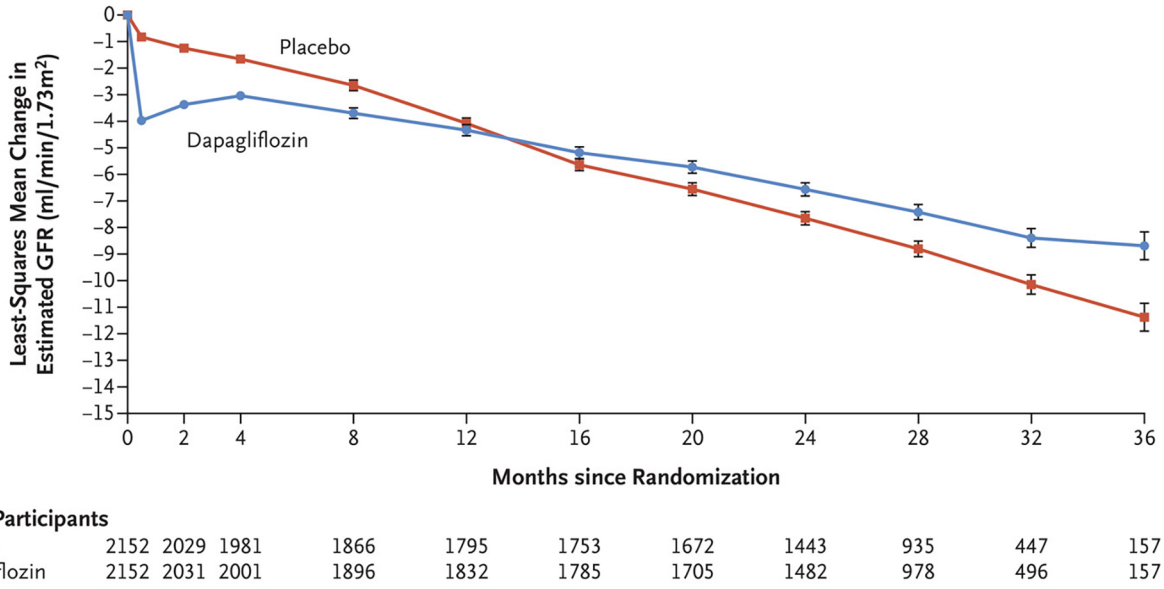

FIGURE 2
Change in estimated GFR (eGFR) from baseline in the DAPA-CKD trial. With permission from Ref. (29). The mean eGFR at baseline for the dapagliflozin group was 43.2 ml/min/1.73 m^2 and 43 ml/min/1.73 m^2 in the placebo group. Dapagliflozin treatment results in a prompt drop in eGFR but a slower decrease in eGFR over time, mitigating CKD progression.

reassurance with repeat labs in 2–4 weeks. If no obvious alternative cause can be identified, a medication hold with repeat laboratory studies after 2–4 weeks is reasonable. In our experience, there are a small number of patients who cannot continue. Published algorithms for surveillance of kidney function after initiation of SGLT2 inhibitor therapy offer similar guidance (122).

Consideration of the likelihood of some decrease in eGFR with SGLT2 inhibitor therapy raises the issue of the lower limit of kidney function below which SGLT2i are better avoided. Drug manufacturers and studies differ slightly in their guidance. For canagliflozin, the manufacturer discourages drug initiation in patients with eGFR less than 30 ml/min/1.73 m^2, though continuation of drug if eGFR falls to this level during therapy is allowed. For the makers of dapagliflozin and empagliflozin, the lowest GFR levels recommended for initiation of therapy are 25 and 20 ml/min/1.73 m^2 respectively. In adults, our practice uses these agents routinely in those with an eGFR above 25 ml/min/1.73 m^2 and with caution in those with an eGFR between 20 and 25 ml/min/1.73 m^2. Given the complexity of managing other burdens—physiologic, psychological, and logistical—we generally do not consider the addition of SGLT2i below an eGFR of 20-ml/min/1.73 m^2.

Conclusions

The discovery of the coupling of sodium and glucose absorption in the gut has been called "potentially the most important medical advance" in the 20th century as it informed oral rehydration therapy by which enteral glucose allowed sodium and water absorption and increased survival of diarrheal illness especially in resource limited environments (123–125). In the 21st century, the worldwide obesity epidemic means that diabetes, CKD, and heart disease together now contribute to mortality and functional decline more than diarrheal illness. SGLT2 inhibitors were developed to block the co-transport of sodium and glucose in the renal tubule to increase renal glucose excretion as a treatment for diabetes. In adults, SGLT2 inhibitors improve renal hemodynamics and prolong kidney function by increasing distal sodium delivery. Limited pediatric data have emerged indicating safety of SGLT2 inhibition and some reduction of proteinuria. The development of randomized, controlled trials in pediatric kidney disease are crucially needed to determine if SGLT2 kidney benefits observed in adults will translate to pediatric patients.

Author contributions

GP: Writing – original draft, Writing – review & editing. IH: Writing – original draft, Writing – review & editing. AB: Writing – original draft, Writing – review & editing. EG: Writing – original draft, Writing – review & editing. TH: Writing – original draft, Writing – review & editing, Conceptualization, Supervision.

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Functional assessment of renal damage in children with primary vesicoureteral reflux

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Objectives: To evaluate the renal function damage in children with primary vesicoureteral reflux (VUR).
Methods: A total of 226 children with VUR (65 cases with left, 39 with right, and 122 cases with bilateral VUR) were screened. Eighty-five urinary tract infection (UTI) cases, without urinary malformations, during the same period were collected as controls. Age at diagnosis, body weight, renal ultrasound, VUR grade, serum creatinine level, dimercaptosuccinic acid (DMSA) level, and effective renal plasma flow (ERPF) values were retrospectively analyzed.
Results: There were no significant differences in age at diagnosis between study groups. Total ERPF was significantly lower in the bilateral VUR group than in the control group. The ERPF in unilateral VUR was significantly lower than that in the contralateral or ipsilateral side in the control group ($P < 0.001$). The mean split renal function, as assessed by DMSA of VUR, was 28.00% and 29.12% on the left and right sides, respectively, both of which were lower than the control group's 40.27%. Renal damage was also correlated with a VUR grade ($P = 0.008$), a transverse diameter ($P = 0.002$), and pyelectasis ($P = 0.037$).
Conclusion: Split renal function was impaired in the reflux kidney. The total ERPF in the bilateral VUR group was lower than that in the unilateral VUR group. Renal damage was correlated with a VUR grade, a transverse diameter, and pyelectasis.

KEYWORDS

vesicoureteral reflux, children, renal function, dimercaptosuccinic acid, effective renal plasma flow

Introduction

Vesicoureteral reflux (VUR) is a congenital defect of the ureterovesical junction that leads to the retrograde passage of urine from the bladder towards the ureter and kidneys. The prevalence of VUR in children with febrile urinary tract infections (UTI) is approximately 30%, and this proportion is higher in neonates and small infants with UTI (1). VUR is one of the most common causes of UTI in children, and recurrent UTI may cause renal scarring and damage, as well as chronic kidney disease (CKD), including end-stage renal disease (ESRD) (2, 3). The formation of kidney scarring is positively correlated with reflux grade (4). VUR grade has a greater impact on renal function, but the extent of its impact has not been reported. Ultrasonography is an important imaging modality that has a positive correlation with renal function (5). Dimercaptosuccinic acid (DMSA) renal scintigraphy provides an accurate assessment of functional renal parenchyma (6). Dynamic renal scintigraphy provides an accurate assessment of split renal function in hydronephrosis (7). Technetium-99m-Ethylenedicysteine (^{99m}Tc-EC) dynamic renal scintigraphy is beneficial for evaluating split renal function in transplant kidneys and percutaneous nephrolithotomy (8–10).

^{99m}Tc-EC dynamic renal scintigraphy can predict the split renal function as an alternative to DMSA scintigraphy (11, 12).

This retrospective study aimed to evaluate the influence of VUR on renal function in children. In this study, we analyzed renal function by comparing kidney size, renal hypodysplasia, acquired renal scarring, and split renal function evaluated by nuclide imaging of the kidneys on both sides of the VUR and on the healthy side.

Patients and methods

Clinical data collection

This study was conducted as a retrospective chart review of pediatric patients evaluated at a single tertiary care center between January 2015 and December 2018. All children with febrile UTI or recurrent UTI were screened. Inclusion criteria is inpatient children, less than 14 years old. All patients finished voiding cystourethrography (VCUG), ultrasound, DMSA scanning and dynamic renal scintigraphy. Ultrasound, DMSA scanning and dynamic renal scintigraphy were performed within 3 months before or after VCUG procedure. Exclusion criteria is solitary kidney. The patients with missing DMSA scanning or dynamic renal scintigraphy data were also excluded. Patients with secondary VUR, including the posterior urethral valve, urethremphraxis, neurogenic bladder, duplex kidney, anal atresia, and tethered cord syndrome, were also excluded. Original records of all-grade VUR with UTI cases were reviewed. Children with UTI without urinary tract abnormalities during the same period were included as the control group. Urinary tract abnormalities in UTI cases were excluded by VCUG and ultrasound. Reflux on the left or right side was unilateral VUR, reflux on both left and right sides was bilateral VUR. Patient demographics (age at diagnosis, sex, and body weight), laboratory investigations (serum creatinine and serum cystatin C), imaging (ultrasound, scintigraphy, VUR grade), and clinical course were extracted. The ERPF values of split renal function were corrected by body surface area, which was calculated according to the following formula: body surface area = 0.035 × body weight (kg) + 0.1 m^2 (13).

Recurrent UTI

Recurrent UTIs were defined as at least three episodes of UTI in 12 months or at least two episodes in 6 months. All recurrent UTI cases had not received continuous antibiotic prophylaxis before VCUG.

VUR grade

All cases of VUR were identified using VCUG. VUR was diagnosed by a demonstration of urine reflux into the upper urinary tract by conventional VCUG. VUR was graded according to the International Reflux Study Group classification: mild (grade 1–2), moderate (3), and severe (4–5).

Renal parenchymal defects

Abnormal DMSA scan was defined as decreased uptake with loss of contours or cortical thinning, with distortion of parenchymal volume. All data files were re-evaluated at the coordinating center by the same nuclear medicine specialist using a workflow software (Philips, Amsterdam, Netherlands). Abnormal DMSA scan was characterized as focal (a single delimited area with decreased uptake), multifocal (more than one uptake defect), or generalized (a small kidney with generalized reduced tracer uptake).

Dynamic renal scintigraphy

Dynamic renal scintigraphy were performed within 3 months before or after VCUG procedure. Patients were given 10–20 ml/Kg of water orally 30–40 min before the procedure. Posterior dynamic acquisition was performed after intravenous injection of 3.7 MBq/kg of body weight of 99mTc-ethylene-dicysteinc (99mTc-EC) and 1 mg/kg of body weight of furosemide (with a maximum of 20 mg). Images were processed by an independent senior nuclear medicine physician by a homemade software programmed with workflow software (Philips, Amsterdam, Netherlands). Regions of interest were manually drawn on kidneys, heart and C-shaped perirenal background. Relative function was determined using the Patlak-Rutland method, or the Area Under the Curve method in studies in which the cardiac curve did not meet enough quality, according to international consensus recommendation. Drainage was quantitatively assessed by NORA (normalized residual activity), Renal Output efficiency and Tmax. The operator then classified the drainage as normal, borderline or poor (14).

Statistical analyses

Data are expressed as mean ± standard deviation. One-way way ANOVA, *t*-test, and Pearson χ^2 tests were used to test the measurement data of the two groups. For continuous variables, Spearman's rank correlation coefficient was used to compare two variables, and the Mann–Whitney *U*-test was used between groups. Correlation of renal function were evaluated by using linear mixed models. Statistical analyses were performed using the SPSS software ver. 19.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at two-tailed $P < 0.05$.

Ethical approval was obtained from the institutional ethics board of Xinhua Hospital, affiliated with the Shanghai Jiaotong University School of Medicine (Approval No. XHEC-D-2022-088).

Abbreviations

CKD, chronic kidney disease; DMSA, dimercaptosuccinic acid; ERPF, effective renal plasma flow; ESRD, end-stage renal disease; ^{99m}Tc-EC, Technetium-99m-Ethylenedicysteine; UTI, urinary tract infection; VCUG, voiding cystourethrography; VUR, primary vesicoureteral reflux.

Results

General information

In total, 226 children with VUR were screened. VUR was present in 348 kidneys, bilaterally in 122 cases, left-sided in 65 cases, and right-sided in 39 cases. The mean age at diagnosis in the bilateral VUR, unilateral VUR, and UTI control group was 21.65 ± 27.99 months, 28.35 ± 35.79 months, and 30.45 ± 31.72 months, respectively. The average age at diagnosis and body weight showed no significant differences among the groups. The male ratio was much higher in the VUR group than in the UTI control group ($P = 0.037$). Recurrent UTIs were more likely to occur in children with bilateral reflux ($P = 0.048$) (Table 1).

Total renal function in VUR

The serum creatinine values in unilateral VUR, bilateral VUR, and control groups were 25.19 ± 13.81 μmol/L, 26.72 ± 17.84 μmol/L, and 22.87 ± 10.90 μmol/L, respectively. The serum cystatin C values in unilateral VUR, bilateral VUR, and control groups were 0.54 ± 0.50 mg/L, 0.60 ± 0.57 mg/L, and 0.66 ± 0.37 mg/L, respectively. Serum creatinine and cystatin C levels were not significantly different between the groups ($P = 0.192$ and $P = 0.251$, respectively) (Table 1).

Total effective renal plasma flow (ERPF) values of unilateral VUR, bilateral VUR, and the control group were 219.74 ± 130.46 ml/min/m^2, 207.36 ± 110.81 ml/min/m^2, and 287.56 ± 76.16 ml/min/m^2, respectively. The total ERPF values in the unilateral VUR and bilateral VUR groups were significantly lower than those in the control group ($P < 0.001$ and $P < 0.001$, respectively). There was no significant difference in the total ERPF value between the unilateral and bilateral VUR groups ($P = 0.400$) (Figure 1).

Split renal function in VUR

Reflux occurred in 348 kidneys, and the 104 contralateral, unaffected-side kidneys included 65 left non-reflux kidneys and 39 right non-reflux kidneys. DMSA scans showed split renal function in unilateral reflux kidneys, contralateral unaffected-side kidneys, and ipsilateral side kidneys in the control group, which were 31.68% ± 25.94%, 42.02% ± 29.06%, and 40.00% ± 20.35%, respectively. Split renal function in unilateral reflux kidneys was much lower than that in ipsilateral kidneys in the control ($P < 0.001$) and contralateral unaffected kidneys ($P < 0.001$). Split renal function was not significantly different between the contralateral unaffected-side kidneys and ipsilateral side kidneys in the control group ($P = 0.518$) (Table 2).

The ERPF value of the split renal function in unilateral reflux kidneys and contralateral unaffected-side kidneys were 102.58 ± 70.04 ml/min/m^2 and 134.00 ± 81.51 ml/min/m^2, respectively. The ERPF values in reflux kidneys were much lower than those on the contralateral unaffected-side kidneys and the ipsilateral side kidneys in the control group ($P < 0.001$ and $P < 0.001$, respectively). In contrast, ERPF values in the contralateral kidney of reflux were not significantly different from those on the ipsilateral side in the control group ($P = 0.231$) (Table 2).

Impact on split renal function

The length diameters of the reflux kidneys and contralateral unaffected kidneys were 56.85 ± 25.01 mm and 58.61 ± 28.21 mm, respectively. Both length diameters in reflux and contralateral unaffected kidneys were much shorter than those in ipsilateral kidneys in the control group ($P < 0.001$ and 0.001, respectively). The transverse diameters of reflux and contralateral unaffected kidneys were 23.21 ± 10.85 mm and 23.51 ± 11.53 mm, respectively. Both transverse diameters in the reflux and contralateral un-reflux kidneys were much shorter than those in the ipsilateral kidney in the control group ($P < 0.001$ and 0.014, respectively). The pyelectasis of reflux and contralateral unaffected kidneys were 4.15 ± 6.34 mm and 1.06 ± 2.93 mm, respectively. Both pyelectasis in reflux kidneys were much larger than those in contralateral unaffected kidneys and ipsilateral kidneys in the control group ($P < 0.001$ and 0.001, respectively). There was no significant difference between the contralateral unaffected kidneys and ipsilateral kidneys in the control group ($P = 0.266$). The dilatation of ureters of reflux kidneys and contralateral unaffected kidneys were 1.14 ± 2.89 mm and 0.08 ± 0.78 mm, respectively. Both dilatation of ureters in reflux kidneys were much larger than those in contralateral unaffected kidneys and ipsilateral side kidneys in the control group

TABLE 1 Total renal function in VUR.

Variable	Unilateral VUR (n = 104 cases)	Bilaterally VUR (n = 122 cases)	UTI control (n = 85 cases)	F value	P value
Age at diagnosis (month)	28.35 ± 35.79	21.65 ± 27.99	30.45 ± 31.72	2.19	0.114
Body weight (Kg)	13.71 ± 9.38	12.27 ± 7.61	13.93 ± 8.80	1.273	0.281
Boys (n, %)	66, 63.46%	75, 61.48%	31, 36.47%	6.605	0.037
Creatinine (umol/L)	25.19 ± 13.81	26.72 ± 17.84	22.87 ± 10.90	1.659	0.192
Cystatin C (mg/L)	0.54 ± 0.50	0.60 ± 0.57	0.66 ± 0.37	1.388	0.251
Recurrent UTI (n, %)	67, 64.42%	92, 75.41%	51, 60.00%	6.09	0.048
Dynamic renal scintigraphy					
Total ERPF	219.74 ± 130.46	207.36 ± 110.81	287.56 ± 76.16	14.499	<0.001

VUR, Vesicoureteral reflux; UTI, Urinary tract infection; ERPF, effective renal plasma flow

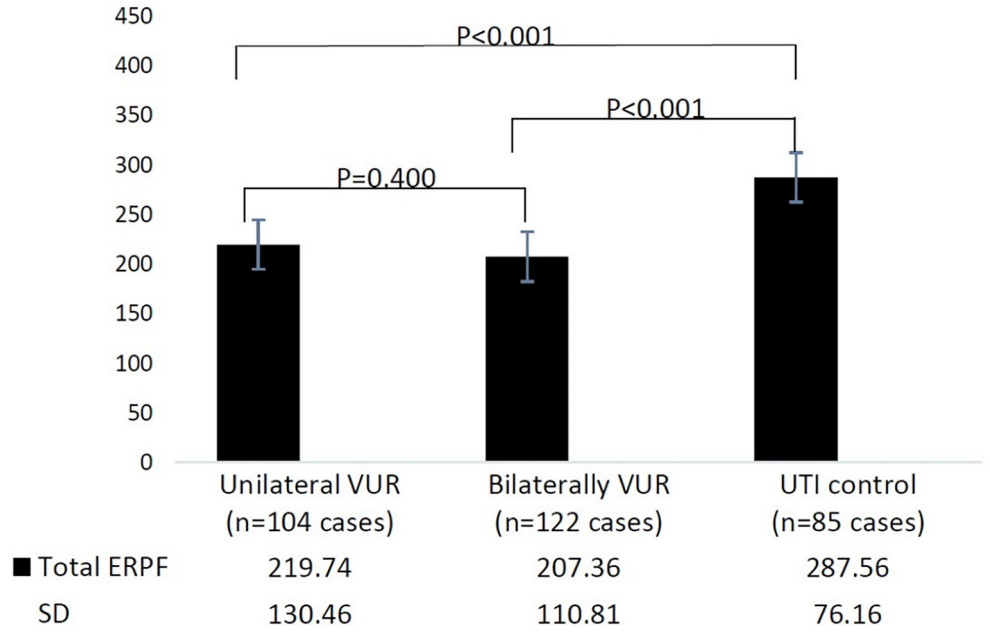

FIGURE 1
Total effective renal plasma flow (ERPF) in different groups. UTI, urinary tract infection; VUR, vesicoureteral reflux; ERPF, effective renal plasma flow.

TABLE 2 Split renal function in VUR and impact on split renal function.

Variable	Unilateral reflux kidneys (*n* = 348)	Contralateral un-affected kidneys (*n* = 104)	Ipsilateral side kidneys in control (*n* = 170)	*F* value	*P* value
Age at diagnosis (month)	23.65 ± 30.59	28.35 ± 35.79	30.45 ± 31.62	2.87	0.057
Body weight (Kg)	12.70 ± 8.18	13.71 ± 9.38	13.93 ± 8.77	1.411	0.245
Creatinine (umol/L)	26.26 ± 16.71	25.19 ± 13.81	22.87 ± 10.87	2.98	0.052
Cystatin C (mg/L)	0.58 ± 0.55	0.54 ± 0.50	0.66 ± 0.37	2.398	0.092
Recurrent UTI (*n*, %)	251, 72.12%	67, 64.42%	102, 60.00%	153.66	<0.001
VCUG					
VUR grade	3.49 ± 1.16	0	0	NA	NA
Ultrasound					
Length diameter (mm)	56.85 ± 25.01	58.61 ± 28.21	68.47 ± 13.36	14.837	<0.001
Transverse diameter (mm)	23.21 ± 10.85	23.51 ± 11.53	26.51 ± 5.17	6.818	0.001
Pyelectasis (mm)	4.15 ± 6.34	1.06 ± 2.93	0.37 ± 1.43	39.39	<0.001
Dilatation of ureters (mm)	1.14 ± 2.89	0.08 ± 0.78	0.04 ± 0.54	18.745	<0.001
DMSA					
Split renal function (%)	31.68 ± 25.94	42.02 ± 29.06	40.00 ± 20.35	10.246	<0.001
Abnormal DMSA scan					
Normal	65, 18.68%	63, 60.58%	54, 31.76%	77.218	<0.001
Focal	93, 26.72%	24, 23.08%	72, 42.35%		
Multifocal	95, 27.30%	3, 2.88%	36, 21.28%		
Generalized	49, 14.08%	0, 0.00%	2, 1.18%		
NA	46, 13.22%	14, 13.46%	6, 3.53%		
Dynamic renal scintigraphy					
ERPF	102.58 ± 70.04	134.00 ± 81.51	143.78 ± 40.06	25.8	<0.001

mm, millimeter; UTI, Urinary tract infection; VCUG, Voiding cystourethrography; VUR, Vesicoureteral reflux; DMSA, dimercaptosuccinic acid; ERPF, effective renal plasma flow; focal renal scarring: single delimited area with decreased uptake; multifocal renal scarring: more than one uptake defect; generalized renal scarring: a small kidney with generalized reduced tracer uptake; NA, no data.

($P < 0.001$ and <0.001, respectively). There was no significant difference between the contralateral unaffected kidneys and ipsilateral kidneys in the control group ($P = 0.896$) (Table 2).

Abnormal DMSA scan detected in the reflux, contralateral unaffected, and ipsilateral kidneys in the control group were 68.1%, 25.96%, and 64.81%, respectively. A small kidney with generalized reduced tracer uptake was more common in reflux kidneys ($P < 0.001$) (Table 2).

Using linear mixed models, we tested the following baseline variables for the prediction of renal damage: age at diagnosis, body weight, type of presentation, length diameter of the kidney, transverse diameters of the kidney, pyelectasis, dilatation of ureters, VUR grade, ERPF, febrile UTI, and recurrent UTI before inclusion. Renal damage was also correlated with a VUR grade ($P = 0.008$), a transverse diameter ($P = 0.002$), and pyelectasis ($P = 0.037$).

Discussion

VUR is a condition in which urine flows back from the bladder to the ureter or pelvis. VUR can be classified as primary or secondary according to its etiology. The enrolled cases in this study were all primary VUR cases, mainly caused by abnormal development of the vesicoureteral flap, which is closely related to genes (15). VCUG is the "gold standard" technique for detecting VUR. It provides high-resolution anatomical images of the renal parenchyma, calyx, pelvis, and bladder. The ureters and urethra can be partially visualized. VUR was divided into 1–5 grades according to the degree of urine reflux. Higher VUR grades had a greater probability of renal dysplasia or scarring formation and a greater chance of urinary tract infection (2). Recurrent urinary tract infections can easily cause renal scarring, proteinuria, hypertension, and other symptoms of reflux nephropathy. Severe reflux, bilateral reflux with renal scarring, hypertension, proteinuria, and decreased GFR are risk factors for the progression to CKD or ESRD (13). The early assessment of renal function in children with VUR is conducive to early intervention and improved prognosis.

This study included 104 children with unilateral VUR, and the mean age at diagnosis was not significantly different from that of the control group. The diameter of the reflux kidney was smaller than that of the control group, indicating that kidney development in the reflux kidney was significantly affected. The renal ERPF value in the reflux kidney was significantly lower than that in the contralateral unaffected and ipsilateral kidneys in the control group. Split renal function in reflux kidneys was significantly impaired. The split renal ERPF value of the bilateral reflux kidneys was lower than that of the same side in the control group, and the total ERPF value of the bilateral VUR was significantly lower than that of the control group. Patients with bilateral VUR have obvious renal impairment, which should be strengthened during long-term follow-up monitoring.

^{99m}Tc-DMSA is the gold standard for diagnosing renal scarring. It is commonly used to measure split-renal function. Split renal function is considered to range from 45% to 55% of the total uptake in healthy kidneys (16). It may be difficult to accurately evaluate lesions in bilateral VUR because the relative uptake remains stable. ^{99m}Tc-EC dynamic renal scintigraphy is beneficial for evaluating transplant kidney function (8). Following intravenous administration of ^{99m}Tc-EC, some (17%) of it is filtered in the glomeruli, while a major portion (50%) is secreted in the proximal part of the tubules by organic anion transporters (16). ERPF correlates with eGFR (17). ^{99m}Tc-EC was used to evaluate split renal function in hydronephrosis or UTI (18). The unilateral renal ERPF value of bilateral VUR was lower than that of the same side in the control group, and the total ERPF value of bilateral VUR was significantly lower than that of the control group.

The predictive factors for deterioration were recurrent febrile urinary tract infections, bilateral abnormalities, and reduced total glomerular filtration rate. Deteriorated renal status was more common in cases diagnosed prenatally than in those detected after urinary tract infection (19, 20). In this study, the predictive factors for renal function deterioration were analyzed. Abnormal DMSA scan ($P = 0.003$), VUR grade ($P = 0.008$), transverse diameter ($P = 0.002$), and pyelectasis ($P = 0.037$) were significantly correlated with renal function damage. Severe VUR was associated with impaired renal function (13). Renal parenchymal defects were observed in 87% of children at baseline, with a strong correlation with renal function, which is in accordance with several previous reports on congenital renal dysplasia (4, 6, 7, 21). VUR is often associated with recurrent urinary tract infections, which can lead to scarring and impaired kidney function. The average reflux was above grade 3, indicating moderate and severe reflux. Moderate and severe reflux are often accompanied by renal pelvis and ureteral dilation. Therefore, the degree of pyelectasis and ureteral dilation on the reflux side were higher than those in the control group.

The study screened 348 VUR kidneys at a tertiary center, and the outcomes were objectively measured by professional physicians. Nevertheless, owing to the retrospective design of the study, we cannot make a causal conclusion. Additionally, selection bias for a single-center study with measurement bias might not be excluded. It is possible that residual confounders, such as socioeconomic factors, which might introduce study bias. Due to the short term follow up and single-center study design, the generalization of our conclusions might be limited. Our findings warrant further study with the need for a well-designed, large-scale, long term follow up, prospective study.

In this retrospective study, we analyzed the effect on renal function in primary vesicoureteral reflux children. Split renal function in the reflux kidney was impaired. The total ERPF in the bilateral VUR group was lower than that in the unilateral VUR group. Renal damage was correlated with a VUR grade, a transverse diameter, and pyelectasis. Bilateral VUR with high VUR grade, more renal scarring and hydronephrosis requires attention to strengthen follow-up.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The Ethical Review is needed before using the dataset. Requests to access these datasets should be directed to liyufeng@xinhuamed.com.cn

Ethics statement

Ethical approval was obtained from the institutional ethics board of Xinhua Hospital, affiliated with the Shanghai Jiaotong University School of Medicine and it conforms to the provisions of the Declaration of Helsinki (Approval No. XHEC-D-2022-088). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because All patients enrolled in this study have signed the broad consent, which permits the researchers to engage in research use of patients' identifiable data during the hospitalization period and future follow-up without the requirement to obtain additional consents for the future storage, maintenance, or research usage, so long as the future activities are within the scope of the broad consent. The study protocol as well as the application form were fully reviewed and we have certified that this study does not raise any issues of patient risk or cause any harm to patients. We have also certified that the study was strictly in accordance with the Declaration of Helsinki and International Ethical Guidelines for Health-related Research Involving Humans.

Author contributions

YZ: Formal analysis, Writing – original draft, Writing – review & editing. YL: Formal analysis, Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. JJ: Writing – review & editing. JN: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Pediatric renal abscess: clinical analysis and literature review

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Background: Pediatric renal abscesses is a severe infectious disease with a long treatment period. Due to atypical symptoms, there is a risk of delayed diagnosis, missed diagnosis, and misdiagnosis. Inadequate or incomplete treatment can lead to prolonged hospital stays, even Irreversible kidney damage. This study aimed to analyze the clinical characteristics of pediatric renal abscesses, aiming for early diagnosis and timely, appropriate treatment.
Methods: A retrospective analysis was conducted on clinical manifestations, laboratory tests, imaging studies, and treatment data of 12 pediatric renal abscess cases treated in the Nephrology Department of our hospital from October 2018 to March 2023.
Results: Among the 12 cases, there were 3 males and 9 females, aged between 7 months to 12 years. All cases were from urban areas, with fever being the primary symptom (100%), accompanied in some by abdominal pain and urinary frequency/pain. Clinical symptoms were atypical, with 91% showing elevated white blood cell count(WBC), a significant rise in neutrophil percentage, C-reactive protein (CRP), and a marked increase in procalcitonin (100%). significant elevation of urinary white blood cells in 83.3% of cases. Both urine and blood cultures were negative. All 12 cases underwent abdominal CT or Magnetic Resonance Urography (MRU), showing abscesses, all less than 3 cm. Treatment included third-generation cephalosporins, with the addition of linezolid in cases where the initial treatment was ineffective. Hospital stays ranged from 10 to 21 days. Follow-up MRU showed the disappearance of abscesses.
Conclusion: Clinical symptoms of pediatric renal abscesses are atypical. Children with fever, accompanied by abdominal pain, and significant elevation in white blood cells, CRP, and PCT should be considered for renal abscess, and abdominal CT or MRU is recommended for early diagnosis. Conservative anti-infection treatment can yield good results for abscesses smaller than 3 cm.

KEYWORDS

renal, abscess, pediatric, management, review

Backgroud

Pediatric renal abscess is an acute localized purulent lesion of the renal parenchyma, which is very rare in children. Due to atypical symptoms, there is a risk of delayed diagnosis, missed diagnosis, and misdiagnosis. Inadequate or incomplete treatment can lead to prolonged hospital stays, even irreversible kidney damage,and endangering life. Compared with urinary tract infection, which is characterized by typical urinary tract irritation symptoms such as frequent urination, urgency, and painful urination, renal abscess has no specific clinical manifestations. Literature reports indicate that early diagnosis can be misidentified as respiratory infections, and even ultrasound may show

localized masses mistaken for tumors. The infection pathways of renal abscess primarily involve ascending urinary tract infection or hematogenous spread, with Escherichia coli being the most common pathogen, followed by Staphylococcus in some cases. Regarding treatment, literature mainly recommends conservative management. This study aimed to analyze the clinical characteristics of pediatric renal abscesses, aiming for early diagnosis and timely, appropriate treatment.

Materials and methods

General information

This study is a retrospective analysis. The study was approved by the Hospital's Medical Ethics Committee (approval number: EC2023-011). Guardians of the children involved in the study were fully informed, consented to the research, and signed informed consent forms. Clinical data of 12 pediatric patients with renal abscesses treated in the Pediatric Nephrology Department of our hospital from October 2018 to March 2023 were collected.

Methods

Clinical data of the pediatric patients were collected through the hospital's electronic medical record system. This included a range of information such as basic details (gender, age, living environment), clinical presentations, and laboratory tests (white blood cells, neutrophil percentage, C-reactive protein, calcitonin, erythrocyte sedimentation rate, serum creatinine, urine white blood cells, urine red blood cells, urine microprotein, urine culture, blood culture). Imaging studies like MRU, abdominal CT, urinary system ultrasound, and retrograde ureterography were also reviewed, along with treatment details. Patient outcomes were gathered through telephone follow-ups and outpatient medical record systems.

Statistical analysis

Descriptive analysis was employed. Quantitative data such as age, white blood cells, neutrophil ratio, and serum creatinine were represented using the median (M) and range.Results are presented as mean ± standard deviation for continuous variables.

Results

Basic information

Among the 12 pediatric patients, there were 3 males and 9 females; ages ranged from 7 months to 12 years (median age 6 ± 3.86 years), including 2 cases under 1 year old (Table 1). Residential Environment: All patients came from urban areas with parents having a college degree or higher education.

Clinical symptoms

All patients primarily presented with fever (100%), predominantly high fever (body temperature ≥39°C). The duration of illness before admission was 1–8 days (median course 4 ± 0.11 days), with no history of preceding infections. Five cases were accompanied by abdominal pain, two cases exhibited urinary frequency or urinary pain, one case had a right renal mass, three cases were transferred from the gastroenterology department, and one case from the surgery department. Only one child presented with renal percussion pain (Table 1).

Laboratory and imaging examinations

Renal ultrasound was performed on all patients upon admission, with only 4 cases (33.33%) showing renal abscesses. All 12 patients underwent abdominal CT or MRU, revealing abscesses (8 on the right side (66.67%), 2 bilateral (16.67%), and 2 on the left side (16.67%), all less than 3 cm in size). Three patients underwent Micturating Cystourethrography (MCU), of which 2 showed no reflux, and 1 exhibited bilateral grade 3 reflux (Table 1). Peripheral blood WBC ranged from (11.8 to 33) $\times 10^9$/L, neutrophil percentage (*N*) from 67 to 91%, CRP from 11 to 239 mg/L, and calcitonin from 0.49 to 15 ng/ml. Kidney function tests showed no abnormalities. Urinalysis indicated red blood cells (RBC) ranging from 4 to 26 per HP, white blood cells (WBC) from 0 to 528 per HP, and urinary red blood cells from 0 to 26 per HP. Both urine and blood cultures were negative (Table 2). Laboratory data showed that 91% of the children had elevated white blood cell counts, with a significant increase in the proportion of neutrophils. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were markedly elevated in 66% of the cases. Calcitonin levels were significantly increased in all cases (100%). Urinalysis revealed that 83.3% of the patients had a notable increase in urinary white blood cells. Hematuria was present in 50% of the cases, and the rate of positive urinary protein was 50% (Table 3).

Treatment

Upon admission, patients were treated with third-generation cephalosporin antibiotics. This treatment was effective in 7 cases, while 5 cases showed no response and were subsequently treated with linezolid. All patients received conservative treatment. The length of hospital stay ranged from 10 to 21 days. Within 2–10 days of treatment, the children's body temperature normalized. At 2 weeks to about 1 month post-discharge, a follow-up renal MRU in 8 cases showed the disappearance of renal abscesses (Figure 1). In 2 cases, abscesses completely resolved after continued medication for 2 months post-discharge. And the total duration of palliative antibiotic therapy was 14–60 days (median course 28 ± 7.30 days).In 1 case, the abscess size reduced after 4 months, and in 1 child, a small lesion was detected during a

TABLE 1 Clinical data and imaging, ultrasound, treatment, and outcomes of patients.

No.	Gender	Age (months)	Initial symptoms	MRU/CT findings	Urinary system ultrasound	MCU findings	hospital stay	Follow-up	Treatment
1	Female	7	Fever	Abscess in lower pole of right kidney	Bilateral renal cysts	Not done	21 days	3 weeks normal	Cefoperazone
2	Female	11	Fever	Abscess in upper pole of right kidney	No abnormalities	Not done	14 days	4 weeks normal	Ceftriaxone
3	Male	96	Fever, abdominal pain	Multiple patchy abnormal signals in both kidneys	No abnormalities	Not done	13 days	2 weeks normal	Cefoperazone
4	Male	144	Fever, abdominal pain	Multiple patchy abnormal signals on right side	Both kidneys enlarged	Not done	14 days	4 weeks normal	Cefoperazone
5	Female	52	Fever	Right kidney abscess	Right kidney low echo	No reflux	17 days	4 weeks normal	Cefoperazone, Linezolid
6	Female	63	Fever, abdominal pain	Infection with abscess in lower pole of right kidney	No abnormalities	Not done	10 days	3 weeks normal	Cefoperazone, Linezolid
7	Female	40	Fever, right renal mass	Right kidney abscess	Moderate echogenicity of right kidney	Not done	20 days	1 year: Reduced renal abscess	Cefoperazone, Linezolid
8	Female	120	Fever	Infection with abscess in right kidney	Upper pole of right kidney low echo	Not done	14 days	2 months normal	Cefoperazone, Linezolid
9	Male	84	Fever, urinary pain	Multiple patchy abnormal signals in both kidneys	Thickened bladder wall	Bilateral grade 3 reflux	10 days	4 weeks normal	Cefoperazone, Linezolid
10	Female	21	Fever, urinary frequency	Multiple enhancing lesions in left kidney	Enlarged left kidney	Not done	10 days	2 months normal	Cefotaxime, Cefoperazone
11	Female	105	Fever, abdominal pain, vomiting	Abscess in upper pole of right kidney	No abnormalities	No reflux	18 days	4 weeks normal	Cefotaxime
12	Female	115	Fever, abdominal pain	Abnormal signal in left kidney	Moderate echogenicity of left kidney	Not done	21 days	4 months: Reduced renal abscess	Cefoper

1-year follow-up ultrasound (with normal urinalysis). One child with reflux underwent surgical treatment and was normal at the 1-year follow-up (Table 1).

Discussion

Intra-abdominal abscesses are relatively rare in children, with renal abscesses being even rarer. A retrospective analysis study found that among approximately 200,000 pediatric emergency department visits, there were only 17 cases of renal abscesses. The incidence rate is about 0.007% (1). However, it is a severe infectious disease with a long treatment period and significant damage to renal parenchyma. Due to atypical symptoms, there is a risk of delayed diagnosis, missed diagnosis, and misdiagnosis. Inadequate or incomplete treatment can lead to prolonged hospital stays (2, 3). Literature review reveals no related guidelines; diagnosis and treatment are based on adult and small-sample data, with limited case information and no unified diagnostic and therapeutic strategies (4).

Children of all ages can be affected. An 11-year literature retrospective study found that the age of onset ranged from 1 month to 18 years, more common in girls (2, 4, 5), though some reports indicate a higher proportion in boys (6, 7). Our data show that the age of affected children in our group ranged from 7 months to 12 years (median age 6 ± 3.86 years), with a higher proportion in girls. This suggests that renal abscesses may not have a significant gender difference. Additionally, whether the incidence of renal abscesses is related to residential areas and living environments is unclear. Our group of children all came from urban areas, with parents having college-level education or higher, and living in good environmental conditions. This suggests that the occurrence of renal abscesses may not be related to living environments, but further accumulation of clinical data is needed for observation.

The clinical presentation of pediatric renal abscesses lacks specificity. Most cases present with fever as the main clinical manifestation, while some children experience back pain, abdominal pain, and abdominal masses (8, 9). Thus, patients are not initially admitted to nephrology or urology departments but are dispersed in other departments, such as initially being admitted to gastroenterology, general surgery, or other pediatric departments, diagnosed with "surgical diseases such as appendicitis, digestive system diseases, sepsis", etc. (2, 5, 10). Our data show that 3 cases were transferred from surgery, gastroenterology, and other pediatric departments, and even one child was only accurately diagnosed during a second hospitalization. All children in our study had fever, 5 with

TABLE 2 Laboratory data.

No.	WBC ($\times 10^9$/L)	Neutrophils (%)	CRP (mg/L)	Calcitonin (ng/ml)	ESR (mm/h)	Creatinine (μmol/L)	Urine WBC (/HP)	Urine RBC (/HP)	Urine tetra protein	Urine Culture	Blood Culture
1	11.8	76	68	14.29	36	23	25	4	Negative	–	-
2	24.9	67	11	0.49	34	21	528	4	Positive	–	-
3	13	71	0.6	1.59	12	63	2.7	8	Negative	–	-
4	13.9	90	222	8.2	97	80	14	4.8	Positive	–	-
5	15.9	75	89	0.62	88	47	0	–	Positive	–	-
6	20.9	81	107	4.5	39	59	136	7	Negative	–	-
7	12	60	0.07	0.6	32	23	6	–	Negative	–	-
8	19.6	19	129	0.5	78	59	11	–	Negative	–	-
9	25.8	84	45	0.6	20	45	196	26	Negative	–	-
10	33	69	86	11	30	32	9	2	Positive	–	-
11	10	79	107	0.6	18	-	6	2	Positive	–	-
12	16	91	239	15	46	-	12	0	Positive	–	-

WBC, white blood cell; CRP, C-reactive protein; RBC, red blood cell; ESR, erythrocyte sedimentation rate.

TABLE 3 Laboratory data overview.

Laboratory parameter	Number of cases ($n = 12$)	Percentage (%)
Elevated WBC	11	91
Elevated neutrophils	7	58
Elevated CRP	10	83
Elevated calcitonin	12	100
Elevated ESR	10	83
Elevated urine WBC	10	83
Elevated urine RBC	6	50
Positive urine protein	6	50
Negative urine culture	0	0
Negative blood culture	0	0

Elevated WBC > 10×10^9/L, Elevated CRP > 8 mg/L, Elevated calcitonin > 0.05 ng/ml, Elevated ESR > 20 mm/h, Elevated urine WBC > 5/HP, Elevated RBC > 3/HP.

accompanying abdominal pain and vomiting, only 2 with frequent urination and dysuria, and 1 child was hospitalized due to renal occupation.

In terms of laboratory data, our study found that the children's infection indicators were significantly elevated, such as peripheral blood white blood cell count, C-reactive protein, and procalcitonin, consistent with literature reports (4). Surprisingly, unlike acute pyelonephritis where urinary white blood cells are significantly higher than normal, we found that most children with renal abscesses had only a small amount of white blood cells in the urine, no pyuria, and a slight increase in urinary red blood cells. As literature reports, if the abscess does not break through the renal pelvis and calyces, and the pus does not enter the collecting system, obvious pyuria may not be present. Therefore, the presence and size of a renal abscess cannot be denied based on the degree of increase in urinary white blood cells and the presence or absence of pyuria (5, 7, 11).

Renal abscesses occur via different pathways, including ascending urinary tract and hematogenous infections, as well as inflammation spreading from adjacent organs. Ascending infections are often related to urogenital system malformations or recurrent urinary tract infections. The main pathogens are Gram-negative bacteria, predominantly Escherichia coli. Staphylococcal infections are the most common cause of hematogenous spread (12, 13). Lin Xiaoliang et al. reported a case of a child with a renal abscess where cultures were negative, and the pathogen was identified through metagenomic sequencing after ineffective treatment with third-generation cephalosporins. Urine and blood cultures in our group of children were all negative, which may be related to the abscesses being confined to the renal parenchyma and not breaking through the renal pelvis and calyces (7). Adult renal abscess patients often have underlying conditions such as diabetes, cirrhosis, female reproductive system infections, stress urinary incontinence, etc. (14, 15). It has been reported that children often have recurrent urinary tract infections, some of which are accompanied by urinary tract malformations (6) but children without underlying diseases can also develop renal abscesses (8). A Chinese study of 5 pediatric renal abscess cases found none with urogenital malformations, and 2 without recurrent urinary tract infections (16). Our group of children had no history of recurrent urinary tract infections, normal

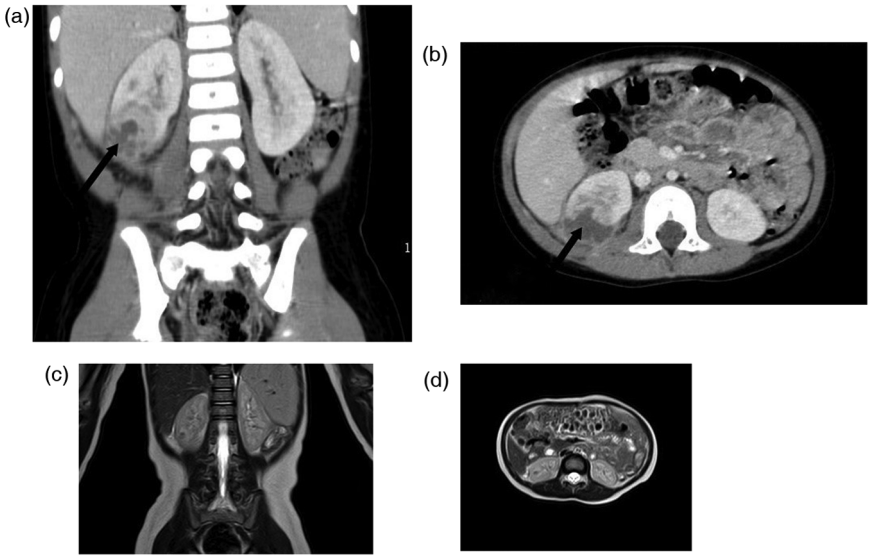

FIGURE 1
The changes of CT before treatment **(a,b)**, and MRU after about 1 month of treatment **(c,d)** in case five. **(a,b)** The abscesses in lower pole of the right kidney were measured as about 2.4 × 2.7 cm (arrow), **(c,d)** The abscesses was largely disappeared.

prenatal urinary system checks, and no history of urinary tract malformations or reflux. After infection control, cystourethrography was performed on 3 children, with one child found to have bilateral grade 3 reflux.

Due to the atypical clinical symptoms and lack of ultrasound, CT, and other imaging studies, it is difficult to make a definitive diagnosis based solely on clinical presentation and physical examination (13). Ultrasound, being simple to operate, radiation-free, non-invasive, affordable, and widely accepted by families, is often the first choice for initial examination. All 12 of our cases underwent ultrasound, but only 3 children showed abnormalities, suggesting that abscesses are hard to detect before abscess cavity formation and when the abscess is small, leading to missed diagnoses. After hospitalization, all children in our group completed CT or MRU scans. Due to the radiation of CT, children initially admitted to our department preferred magnetic resonance imaging, which showed good imaging results. Whether MRU will be preferred in the future requires further large-sample validation. Additionally, due to its simplicity, ultrasound can be used for clinical follow-up and assessment during the treatment of renal abscesses.

Based on acute pyelonephritis and previous literature reports of renal abscesses predominantly involving Gram-negative bacteria (2, 3, 5), treatment for our group of children upon admission initially involved third-generation cephalosporins. Since the children's blood and urine cultures were all negative, those whose temperature still fluctuated after 3–5 days of treatment were additionally treated with linezolid, achieving good results, with no similar reports in previous literature. Foreign literature reports the use of aminoglycoside antibiotics, which are almost never used in Chinese children (4, 12). There is still controversy regarding the treatment approach of conservative treatment vs. surgical intervention. Previous studies have shown that abscesses smaller than 3 cm can be treated with conservative anti-infection therapy, while those larger than 3 cm can be treated with percutaneous abscess puncture (2–4). A Chinese study showed significant therapeutic effects with conservative treatment for abscesses up to 4.7 cm in diameter (16). For cases 5 and 7, we initially considered abscess drainage. However, after adjusting antibiotics, the body temperature returned to normal, renal area tenderness was negative, and follow-up ultrasound showed the abscess had reduced in size. Therefore, abscess drainage was not performed, and conservative antibiotic treatment continued with good results, consistent with this study in our country.A Russian study retrospectively found that abscesses larger than 3 cm were treated with percutaneous abscess puncture and drainage (17). All 12 children in our group were treated conservatively, with a hospital stay of 10 days to 3 weeks and were discharged smoothly. 11 children were cured after 1–3 months of follow-up, the child with grade 3 reflux underwent surgical treatment for reflux, and 1 child showed a small abscess on ultrasound but had no clinical symptoms and normal urine routine.

This study highlights the atypical presentation and diagnostic challenges of pediatric renal abscesses. Fever, accompanied by non-specific abdominal or renal symptoms, should raise suspicion. The role of imaging, especially CT or MRU, is crucial in early diagnosis. Our findings suggest that conservative treatment with antibiotics is effective for small abscesses, while larger abscesses may require additional interventions.

Conclusion

In summary, pediatric renal abscesses, though rare, should be considered in children presenting with fever and abdominal or

renal symptoms. Early imaging and appropriate antibiotic treatment can lead to favorable outcomes, reducing the risk of complications.

This paper has some limitations: it is a single-center study with a small number of cases. Cultures were negative, and further metagenomic testing was not performed. Only some children underwent cystourethrography.

Author contributions

JS: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft. LS: Data curation, Formal analysis, Investigation, Resources, Writing – original draft. LY: Data curation, Investigation, Writing – original draft. YX: Conceptualization, Data curation, Investigation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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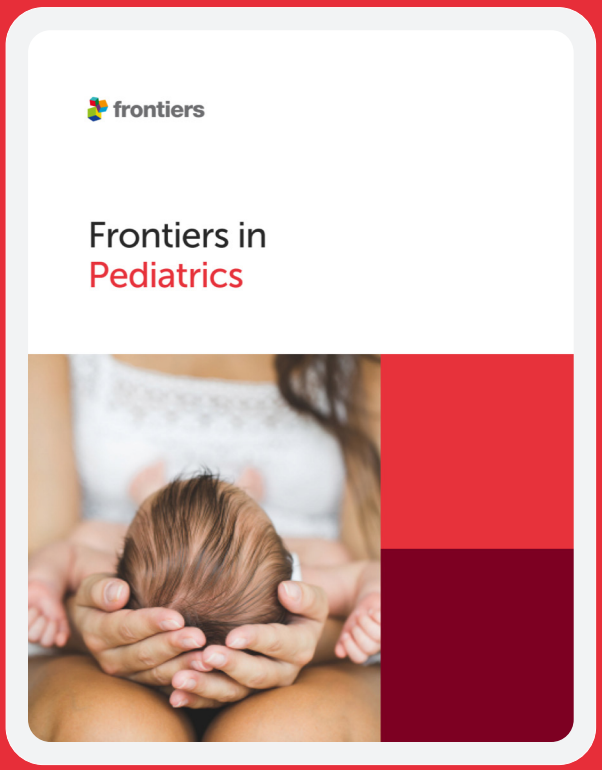

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