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REVIEW ARTICLE

Drug-Induced Urolithiasis in Pediatric Patients

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Abstract
Drug-induced nephrolithiasis is a rare condition in children. The involved drugs may be divided into two different categories according to the mechanism involved in calculi formation. The first one includes poorly soluble drugs that favor the crystallization and calculi formation. The second category includes drugs that enhance calculi formation through their metabolic effects. The diagnosis of these specific calculi depends on a detailed medical history, associated comorbidities and the patient's history of drug consumption. There are several risk factors associated with drug-induced stones, such as high dose of consumed drugs and long duration of treatment. Moreover, there are some specific risk factors, including urinary pH and the amount of fluid consumed by children. There are limited data regarding pediatric lithogenic drugs, and hence, our aim was to perform a comprehensive review of the literature to summarize these drugs and identify the possible mechanisms involved in calculi formation and discuss the management and preventive measures for these calculi.

Key Points

Drug-induced urinary stone formation in the pediatric population is rare.

Knowledge of these stones is of great clinical importance as they may be missed, resulting in major health consequences.

Ceftriaxone, furosemide and topiramate are the most common drugs inducing stone formation in children.

1 Introduction

Urolithiasis is a common urological disorder with a higher prevalence in adults than in the pediatric population; however, pediatric urolithiasis is an evolving field of interest due to the dramatic increase in its incidence (up to five-fold) over the past 2 decades, with the subsequent increase in its associated morbidity and management costs [1, 2]. The Rochester Epidemiology Project database showed that there was a 4% annual increase in pediatric kidney stones from 1984 to 2008, which was more pronounced in older children, between 12 and 17 years old [3]. Moreover, a population-based study between 1997 and 2012 in South Carolina reported a 16% annual increase in the incidence of renal stones, particularly in young female patients between 10 and 24 years old [4]. Furthermore, pediatric nephrolithiasis is also associated with a high risk of recurrence, reaching up to 50% within 3 years from the first episode of nephrolithiasis [5]. The reason behind this increased prevalence remains elusive because of the lack of studies and may be multifactorial. The increased use and sensitivity of radiological studies (like computed tomography) may be associated with more diagnoses of stone disease in children [3, 6]. Furthermore, the metabolic abnormalities resulting from the increasing rates of pediatric obesity over the last few decades may play a role [7]; however, supporting evidence is not strong in the pediatric population [3]. Unhealthy diets among children and adolescents are another factor that may contribute to the rising incidence of pediatric urolithiasis, for example, reduced water intake, increase sodium consumption, and sugary drinks. These unhealthy dietary habits may result in urine supersaturation with calcium, oxalate and phosphate and predispose individuals to urinary stone formation [8].

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The rising incidence of pediatric nephrolithiasis has also been associated with a shift in its etiology from infectious to metabolic factors [2, 9, 10]. This etiological shift was confirmed by the higher number of urine metabolic abnormalities in children ≤ 10 years old compared to those > 10 years old [11]. In some cases, nephrolithiasis was linked to the use of specific drugs or medications. Drug-induced nephrolithiasis accounts for 1–2% of all kidney stones [12]. There are scarce data about pediatric lithogenic drugs in the literature in this setting; we aimed to perform a review to analyze the available literature data about these drugs.

2 Pediatrics Age Definition

The pediatric age limit in this review was determined based on the American Academy of Pediatrics' statement. This statement defines pediatric patients as any patient starting from birth to 21 years old [13].

3 Methodology

In this narrative literature review, an extensive search of the Medline database was performed by two of our authors (A.E. and A.Z.) to identify the articles discussing the lithogenic effect of commonly used drugs in the pediatric population. We included only articles published in English, without any time restrictions. A combination of the following keywords was used: "pediatric," "children," "child," "calculi," "urinary calculi," "nephrolithiasis," "urolithiasis," "stones," "calculus," "medications," "drugs," "ceftriaxone," "topiramate," "allopurinol," "silica," "silicate," "furosemide," "zonisamide," "vitamins," "antibacterial," "diuretics," "antiepileptic," and "sulphonamides." Furthermore, a manual search of the references of the identified articles was performed to identify all reports of interest.

4 Drug-Induced Nephrolithiasis Mechanisms

Generally, stone formation starts with the supersaturation of specific pathological or physiological ions in the urine, resulting in the formation of a nidus that represents the nucleus for the urolithiasis. This is followed by crystallization or formation of more crystals in the urine that allows the aggregation and growth of the stone. Urine supersaturation can be affected by several factors, including the total urine volume, stone-forming ions concentration, concentration of the inhibitors and promoters of crystallization, and the urinary pH [14].

Drug-induced nephrolithiasis can be classified based on its pathophysiology into (1) drug-containing nephrolithiasis, where the urine becomes supersaturated with the drug itself or one of its metabolites, and thus the drug or its metabolites are a component of the stone; and (2) metabolically drug-induced nephrolithiasis, where the drug or its metabolites cause metabolic changes in the urine contributing to stone formation, but the drug is not a component of the stone. This type of drug-induced renal stone is more challenging to diagnose, as these stones have a similar composition to common calculi, and diagnosis is mainly based on careful history taking [12]. Table 1 shows a summary of the pathophysiology and treatment options for different lithogenic drugs.

5 Lithogenic Drugs

5.1 Drug-Containing Nephrolithiasis

Table 2 shows a summary of the published reports on drug-containing nephrolithiasis.

5.1.1 Sulphonamides

Sulphonamides are a group of compounds that have been recognized for their antimicrobial effect since the late 1930s [15]; however, their use has decreased overtime due to the associated side effects and the production of new antibacterial drugs [16]. Lately, they have emerged again for the treatment of toxoplasmosis, especially in patients suffering from human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) [16].

Sulphonamide-induced urolithiasis has been documented in the literature starting as early as 1939 [17]. Since then, multiple reports have been published [15, 18, 19]; however, the lithogenic effect of these compounds in the pediatric population has been demonstrated only in five patients [16, 20–22]. This may be explained by the scarcity of toxoplasmosis and HIV/AIDS in children [16]. Sulphadiazine was the most commonly reported drug in this group, and it was associated with crystalluria in two patients [20, 22] and bilateral urolithiasis in another two patients [16]. On the other hand, Erturk et al. [21] reported drug-induced urolithiasis in a 19-year-old girl while using sulfasalazine for treatment of juvenile rheumatoid arthritis. It is noteworthy to mention that the urine analysis of the two patients with crystalluria showed sulphonamide crystals [20, 22]; in addition, in patients with stones, stone analysis showed a sulphonamide component in the stone, supporting the lithogenic effect of sulphonamides [16, 21].

5.1.1.1 Pathophysiology Sulphonamides are absorbed immediately after any route of administration, then part of the drug goes through acetylation in the liver, followed by its excretion (free and acetylated) by the kidney [15].

Table 1 Summary of the pathophysiology and treatment of different lithogenic drugs

Drug	Risk factors	Pathophysiology	Treatment
Sulphonamides	Large doses Acidic urine Dehydration Underlying tubular disease Long duration	Sulphadiazine and its acetyl derivative are characterized by their relatively low solubility in acidic urine, raising the risk of precipitation and urolithiasis	Sodium bicarbonate to keep urinary pH > 7.5 (alkalinization of urine) Hydration Discontinuation or replacement of sulphonamides Surgical intervention if indicated
Ceftriaxone	Positive family history of stones High dosages (> 100 mg/kg/day) Rapid infusion (< 30 min) Dehydration	Mechanism is not completely understood; however, ceftriaxone-induced stones are believed to occur as a result of its ability to form insoluble salts with calcium in 1:1 molar ratio	Discontinuation or replacement of ceftriaxone Acidification of urine Citrate Surgical intervention if indicated
Triamterene	High dosages (>100 mg/day) Low urinary pH (< 6.0) Family history of uric acid stones	The main mechanism of triamterene-induced urolithiasis is related to its high excretion in urine and its low urinary solubility	Often pass spontaneously as they are small Surgical intervention if indicated
Felbamate	High dose Concurrent use of lithogenic drugs Deteriorated renal function	Mechanism is unknown	Discontinuation or lowering the dose of drug Hydration Surgical intervention if indicated
Silica	Silica-containing milk thickener	Mechanism is unknown; however, increased absorption of silica may play a role	Spontaneous passage after drug discontinuation Surgical intervention if indicated
Indinavir	Urinary pH above 5.0 Dehydration Large doses Concomitant antiviral drugs such as acyclovir	Poor solubility at urinary pH > 5	Spontaneous resolution or passage of stone Discontinuation or replacement of indinavir Hydration Surgical intervention should be avoided in these patients because of the risk of infection
Antibacterial (co-trimoxazole and ceftazidime)	High dose Long duration Low diuresis Change in urinary pH	Loss of *Oxalobacter formigenes* (as it is sensitive to co-trimoxazole and ceftazidime) may lead to increased hyperoxaluria	Discontinuation or replacement Surgical intervention if indicated
Furosemide	Low birth weight Congestive heart failure Oxygen ventilation Gestational age High calcium intake Total parenteral nutrition High dose	Multifactorial mechanism; however, inhibition of tubular calcium re-absorption causing hypercalciuria may play the main role in furosemide-associated nephrocalcinosis	Discontinuation and replacement of furosemide Surgical intervention if indicated
Acetazolamide	Preterm infants High dose Long duration Past history of stones	The most important lithogenic factors in patients treated with acetazolamide are the hypocitraturia, increased urinary pH, and hypercalciuria	Hydration Discontinuation or replacement of acetazolamide Surgical intervention if indicated
Topiramate	Non-ambulatory patients Ketogenic diet	Increase of bicarbonate and calcium urinary excretion, and citrate re-absorption causing hypocitraturia, hypercalciuria, and elevated urinary pH	Potassium citrate Careful metabolic follow-up of patients to avoid stone formation Surgical intervention if indicated

Table 1 (continued)

Drug	Risk factors	Pathophysiology	Treatment
Zonisamide	Increased number of antiepileptic drugs used Past history of stones Ketogenic diet	Increase of bicarbonate and calcium urinary excretion, and citrate re-absorption causing hypocitraturia, hypercalciuria, and elevated urinary pH	Hydration Discontinuation of zonisamide Surgical intervention if indicated
Allopurinol	Glucocorticoid therapy Chemotherapy induction (hyperuricemia and tumor lysis syndrome) Lesch-Nyhan syndrome	It inhibits the conversion of xanthine to uric acid, thus increasing the urinary excretion of xanthine, which is characterized by its low urinary solubility. Furthermore, the increased urinary level of oxypurinol (a metabolite of allopurinol) may predispose patients to stone formation	Forced hydration Dose adjustment Surgical intervention if indicated
Vitamins	Long duration High doses	Vitamin intoxication	Discontinuation Hydration Surgical intervention if indicated

They are capable of producing renal damage through different mechanisms, including crystallization and obstruction or to a lesser extent through interstitial nephritis and toxic acute tubular necrosis [16]. The process of crystallization is related to the urinary pH and the solubility of sulphonamides. Sulphadiazine and its acetyl derivative are characterized by their relatively low solubility in acidic urine, raising the risk of precipitation and urolithiasis [23]. Several risk factors (large doses, acidic urine, dehydration, and underlying tubular diseases) may favor sulphonamide urolithiasis in the pediatric population [16]. Sulphonamide-induced stones usually show the presence of acetylated derivatives (*N*-acetylsulfadiazine or acetylsulfapyridine) in their composition [16, 21].

5.1.1.2 Treatment and Prevention This lithogenic effect of sulphonamides can be reduced by using sodium bicarbonate to alkalinize urine to maintain urinary pH > 7.5, ensuring proper hydration, and using the minimal effective dose [16]. The management of this type of stone usually includes discontinuation or replacement of sulphonamides, proper hydration, and urine alkalization; however, in the pediatric population, stenting, shockwave lithotripsy (SWL) and urethral dilatation have been indicated [16, 20–22].

5.1.2 Ceftriaxone

Ceftriaxone is a third-generation cephalosporin and is characterized by its broad spectrum, high safety profile and long plasma half-life, rendering it among the commonly used antibacterial drugs during the childhood period for the treatment of different bacterial infections [24]. Ceftriaxone has been known for its biliary side effects, including biliary sludge and pseudolithiasis since the late 1980s [25]. In 1988, Schaad et al. [26] reported the first case of ceftriaxone-induced nephrolithiasis in one child out of 37 children. Soon after that, several authors reported crystalluria [27, 28], hypercalciuria [29, 30] and urolithiasis [31–45] in children following ceftriaxone use. It is considered the most common lithogenic antibacterial drug in the pediatric population, with an incidence ranging from 0.6% [45] to 8.3% [31]. A systematic review of 161 Chinese patients analyzing the age distribution of patients with ceftriaxone-induced urolithiasis showed that 21.1%, 19.3%, and 19.3% of those patients were < 3, 3–6, and 7–17 years old, respectively (overall 59.7% for the pediatric population from 0 to 17 years old), compared to 40.3% in the adult population, demonstrating a predominance of this side effect in pediatric patients [46].

5.1.2.1 Pathophysiology Ceftriaxone is mainly excreted in the urine (33–67%), and the remaining parts are excreted un-metabolized in the bile and finally in feces. It is charac-

terized by a plasma half-life of 5.8–8.7 h, plasma clearance of 0.58–1.45 L/h, and renal clearance of 0.32–0.73 L/h [31]. Being an anion, it is capable of forming an insoluble salt with calcium in a 1:1 molar ratio, resulting in precipitation of this salt once its solubility is exceeded. This may be the underlying mechanism for its biliary side effects [29]; however, the mechanism of ceftriaxone-induced nephrolithiasis is not yet completely understood [31].

In this setting, several authors have tried to investigate the pathophysiological mechanism for ceftriaxone-associated renal side effects [24, 46]. Zhang et al. [46] demonstrated in their animal study that the rats that were administered ceftriaxone and calcium showed a significantly lower volume of 24-h urine, with a significant increase in serum creatinine and blood urea nitrogen levels, suggesting that calcium chloride is important for stone formation. This is in contrast to Avci et al. [33], who reported unchanged calcium excretion in children treated with ceftriaxone. Moreover, Chatchen et al. [24] microscopically examined a Madin-Darby canine model (a model of distal renal tubular cells) in the presence and absence of ceftriaxone crystals for 48 h, demonstrating that heat stress response and heat shock protein 70 play an important role in the process of crystalline nephropathy and post-ceftriaxone acute renal injury.

Several risk factors for ceftriaxone-induced nephrolithiasis have been discussed in the literature, including a positive family history of stones, high dosage (> 100 mg/kg/day), rapid infusion rates (< 30 min), and dehydration [27]. Furthermore, Cong et al. [47] used an in vitro crystallization model to illustrate that ceftriaxone-induced crystallization was significantly decreased by lowering the urinary pH or increasing the urinary citrate level. In this setting, the dosage of ceftriaxone ranged from 50 to 100 mg/kg/day in the included studies, while the ceftriaxone-induced stone developed after 2 [28] to 16 [41] days. In the current review, only two studies reported the urine pH (7.32 and 5–6.5) after ceftriaxone treatment [35, 37] and four studies reported the calcium/creatinine ratio, ranging from 0.098–0.356 [29, 31, 33, 42].

Ceftriaxone-induced stones usually show ceftriaxone as their main component, and they are normally radiolucent; thus they are not diagnosed with plain X-rays, unless other calcium salts are found in their composition. They are characterized by their small size, loose texture and sand-like appearance, and they are usually asymptomatic and discovered on ultrasound examination [35]. However, in the current review, only six studies (30%) reported the stone analysis showing the presence of ceftriaxone and thus establishing the relationship between ceftriaxone administration and urolithiasis or crystalluria [32, 34, 35, 37, 39, 41].

5.1.2.2 Prevention and Treatment According to the study of Zhang et al. [46], citrate is capable of preventing the urinary biochemical changes resulting from ceftriaxone use and thus reducing its lithogenic effect. Ceftriaxone-induced nephrolithiasis and biliary pseudolithiasis are usually reversible and can disappear after 5–21 and 2–63 days, respectively [27, 44]. The current review demonstrated that most of the cases were treated by replacement or discontinuation of ceftriaxone and hydration (Table 2); however, some patients required surgical intervention like double J (DJ) stenting and ureteroscopy, and only one patient required an open surgical intervention, due to failure of DJ stenting and the development of deep and quick breathing with arrhythmia [35].

5.1.3 Triamterene

Triamterene is a potassium-sparing diuretic that may cause nephrolithiasis in the adult population, due to its high urinary excretion and low urinary solubility [12]. Only one case report was found about this diuretic in the pediatric population, where a 21-year-old female patient was using it for a duration of 18 months to control her stone disease. The patient passed a ureteral calculus that was analyzed and showed 70% of the stone composition was made up of triamterene and triamterene metabolites. Triamterene stones are usually small and golden-mustard in color [48]. Furthermore, the main risk factors associated with triamterene-induced stones are low urinary pH and high drug doses [12].

5.1.4 Felbamate

Felbamate (FBM) is a lipophilic drug that is characterized by low water solubility. It is mainly excreted through the kidney (90%), with approximately 43–63% of it excreted unchanged [49]. FBM has a high safety profile, and was Food and Drug Administration (FDA) approved in 1993 for the treatment of refractory seizures and Lennox-Gastaut syndrome. The recommended dosages are 3600 mg/day for adults and 45 mg/kg/day for children. Most of the FBM-associated side effects occur with a relatively high dose of FBM [50]. Only three reports were found in the literature about the relation between FBM and urolithiasis in the pediatric population [49–51]. The pathophysiology of FBM-induced urinary stones is still vague; however, high doses, concurrent lithogenic drugs, and deteriorated renal function may represent risk factors for FBM urolithiasis [49].

Analysis of FBM-induced urinary stones showed that FBM and its metabolites constitute the main component of these stones [49–51]. FBM stones are radiolucent unless calcium salts are integrated in their formation, and they are characterized by the presence of FBM needle-like crystals ranging from 90 to > 1300 µm in size. Furthermore, they have a layered or flaky appearance and are easily fragmented with holmium laser lithotripsy [49, 50]. Treatment of this type of stone

Table 2 Summary of the studies reporting drug-containing nephrolithiasis

First author	No.	Age	Sex	Underlying disease	Drug	Dose or S. Conc.	Exposure period	Effect	Stone analysis	Treatment
Sulfonamides										
Catalano-Pons [16]	2	14 y	F	Toxoplasmic retinitis	Sulfadiazine	5 g/d	2 w	Bilateral urolithiasis	*N*-Acetylsulfadiazine	Bilateral stents Hydration Replacement
		15 y	M	Immunodeficiency and cerebral toxoplasmosis	Sulfadiazine	5 g/d	7 mo			Hydration Alkalization Replacement
Winterborn [20]	1	3 y	M	*Neisseria meningitis*	Sulphadiazine polytherapy	3000 mg/d	7 d	Anuria due to crystalluria	Acetylsulfadiazine crystals	Ureteral stents Hydration Discontinuation
Erturk [21]	1	19 y	F	Juvenile rheumatoid arthritis	Sulfasalazine	NR	NR	Bilateral renal stones	Acetylsulfapyridine	Left DJ stent Bilateral ESWL
Biorn [22]	1	4.8 y	M	Upper respiratory tract infection	Sulfadiazine	4 g	NR	Anuria due to crystalluria	Sulfonamide crystals	Dilatation and catheterization Hydration Discontinuation
Ceftriaxone										
Youssef [31]	60	6.9 y	F (40%)	Non-UTI infections	Ceftriaxone	80 mg/kg/d[c]	5 d[c]	5 (8.3%) renal stones 11 (18.1%) biliary sludge	NR	Conservative (follow-up)
	60	6.7 y	F (55%)	Non-UTI infections	Other AB	NR	NR	None	NR	None
Kimata [29]	43	2.7 y	F (53.5%)	Bacterial pneumonia	Ceftriaxone	91.1 ± 7.99 mg/kg/d[b]	6.07 ± 1.35 d[b]	5 (11.6%) hypercalciuria	NR	NR
	40	2.25 y	F (50%)		Amoxicillin	107 ± 11.8 mg/kg/d[b]	4.70 ± 1.11 d[b]	None	NR	NR
Lozanovski [32]	1	5 y	M	Pneumonia	Ceftriaxone	1 g/d	7 d	Urolithiasis	Ca+ ceftriaxonate	Forced hydration
Avci [33]	51	3.1 y	F (58.8%)	Infections	Ceftriaxone	50–100 mg/kg/d[c]	7.2 ± 1 d[b]; range (5–10)	4 (7.8%) nephrolithiasis	NR	Spontaneous
Li [34]	31	5.1 y	F (25.8%)	Post-ceftriaxone ARF	Ceftriaxone	86.7 mg/kg/d[b]	5.2 d[b]; range (3–7)	Bilateral mild HN (19.4%) Unilateral mild HN (35.5%) Ureteric stones (35.5%)	Ceftriaxone stones	Pharmacotherapy (29%) Bilateral stents (51.6%) Unilateral stent (16.1%) Temporary hemodialysis (3.2%)

Table 2 (continued)

First author	No.	Age	Sex	Underlying disease	Drug	Dose or S. Conc.	Exposure period	Effect	Stone analysis	Treatment
Shen [35]	15	4.76 y	F (20%)	Ceftriaxone acute kidney injury	Ceftriaxone	1 g/d[c]	5 d[c]	Multiple calculi	Ceftriaxone stones	DJ stent (60%) Ureteroscope (26.7%) Unilateral DJ + PCN (6.7%) Open surgery (6.7%)
Fesharakinia [36]	96	1.88 y	F (42.7%)	Infections	Ceftriaxone	50–100 mg/kg/d[c]	3.86 ± 1.34 d[ab]	6 (6.3%) nephrolithiasis	NR	Conservative (follow-up)
Azarfar [30]	84	3 y	F (45.2%)	Gastroenteritis	Ceftriaxone	50–75 mg/kg/d[c]	3 d[c]	44% hypercalciuria	NR	NR
					Other AB	NR	3 d[c]	28% hypercalciuria		
Cochat [37]	1	13 y	M	Meningococcal meningitis	Ceftriaxone	4 g/d	9 d	Bilateral urolithiasis	Ceftriaxone	NSAIDs Spasmolytics Hydration
Ustyol [38]	86	4.77 y	F (50%)	Infections	Ceftriaxone	100 mg/kg/d[c]	13.20 ± 5.89 d[b]	18 (20.9%) biliary sludge or lithiasis 1 (1.2%) nephrolithiasis	NR	Conservative (follow-up)
	68	4.53 y	F (48.5%)		Cefotaxime	15 mg/kg/d[c]	12.06 ± 4.49 d[b]	4 (5.9%) biliary sludge 1 (1.5%) nephrolithiasis	NR	Conservative (follow-up)
de Moor [39]	1	7 y	M	Acute bacterial meningitis	Ceftriaxone	3 g/d	4 d	Biliary sludge Nephrolithiasis	Ceftriaxone stone	Conservative (follow-up)
Prince [40]	1	14 y	M	Sinusitis + epidural abscess	Ceftriaxone polytherapy	4 g/d	8 d	Biliary pseudolithiasis Bilateral ureteral stones	NR	Replacement Bilateral stents
Acun [27]	35	4.08 y	F (47.2%)	Infections	Ceftriaxone	100 mg/kg/d[c]	9.6 ± 2.2 d[b]; range (5–14)	Biliary (14%) and urinary (3%) precipitation	NR	Discontinuation
Gargollo [41]	1	6 y	M	Septic arthritis	Ceftriaxone	85 mg/kg/d	16 d	Biliary and ureteric stones	Ceftriaxone + Ca^{+} phosphate	Discontinuation Oral hydration Analgesics
Tasic [42]	1	6 y	M	Acute pyelonephritis	Ceftriaxone	1 g/d	5 d	Biliary pseudolithiasis Nephrolithiasis	NR	Replacement Oral hydration
Mohkam [43]	248	NR	F (65%)	Pyelonephritis	Ceftriaxone	75 mg/kg/d[c]	9–10 d[c]	4 (1.4%) nephrolithiasis	NR	Oral hydration
Stojanovic [44]	1	3 y	M	Pneumonia	Ceftriaxone	100 mg/kg/d	6 d	Multiple urolithiasis	NR	Forced hydration Discontinuation

Table 2 (continued)

First author	No.	Age	Sex	Underlying disease	Drug	Dose or S. Conc.	Exposure period	Effect	Stone analysis	Treatment
Akl [28]	1	2 y	M	Meningitis	Ceftriaxone poly-therapy	100 mg/kg/d	2 d	Ceftriaxone precipitation causing AUR	NR	Conservative (follow-up)
Schaad [26]	37	7.8 y[a]	F (50%)[a]	Infections	Ceftriaxone	89 mg/kg/d[a,b]	11 d[a,b]; range (4–33)	16 (43%) biliary pseudolithiasis 1 (3%) urolithiasis	NR	Discontinuation
Biner [45]	156	4.5 y	NR	Infections	Ceftriaxone	50–100 mg/kg/d[c]	7–10 d[c]	11 (7%) biliary sludge 16 (10%) biliary pseudolithiasis 1 (0.6%) nephro-lithiasis	NR	NR
Triamterene										
Watson [48]	1	21 y	F	Stone disease	Triamterene	NR	18 mo	Recurrent uro-lithiasis since she was 19	Ca^{+} oxalate Triamterene (70%)	NR
Felbamate										
Ghousheh [50]	4	12 y	F	Refractory seizures	Felbamate	129 mg/kg/d	≥ 4 y	Gravels in diaper + 2 bladder stones	Felbamate metabo-lite composition	Endoscopic stenting Reduction of dose
		16 y	F		Felbamate	80 mg/kg/d		2 left renal stones		
		21 y	F		Felbamate	169 mg/kg/d		Small bilateral renal stones		
		6 y	M		Felbamate	145 mg/kg/d		Bladder and right ureteral stone + stent encrustation		
Meier [51]	1	3 y	F	Accidental inges-tion	Felbamate	232 mg/kg	Single dose	Crystalluria	Felbamate crystals	Hydration Metoclopramide
Sparagana [49]	1	15 y	M	Lennox-Gastaut	Felbamate + TPM	102 mg/kg/d	6 y	Multiple bilateral renal stones + bladder stone	Felbamate in blad-der stone	Endoscopic stenting Cystolithotripsy Felbamate discon-tinuation Replacement of TPM "phenytoin"
Silica										
Ulinski [54]	1	5 mo	M	Gastro-esophageal reflux	Gelopectose, containing 5.5% colloidal silicate	NR	NR	Bilateral nephro-lithiasis	Silica	Replacement

Table 2 (continued)

First author	No.	Age	Sex	Underlying disease	Drug	Dose or S. Conc.	Exposure period	Effect	Stone analysis	Treatment
Indinavir										
van Rossum [55]	2	3 y	F	HIV-1/AIDS	Indinavir polytherapy	500 mg/m^3/8 h[c]	27 mo	Medullary calcifications	NR	Replacement "nelfinavir" Hydration
		4 y	F				36 mo	Renal calcifications		Vitamin C "15 mg/kg/6 h"
Noble [56]	2	17 y	M	HIV/AIDS	Indinavir	800 mg/8 h	12 mo	Right UPJ obstruction + crystalluria	Indinavir	Ureteral stent
		14 y	M			600 mg/8 h	NR	Right UPJ obstruction	NR	Intravenous hydration Analgesics

AB antibiotic, *ARF* acute renal failure, *AUR* acute urinary retention, *d* days(s), *DJ* double J, *ESWL* extracorporal shockwave lithotripsy, *F* female, *HIV/AID* human immunodeficiency virus/acquired immunodeficiency syndrome, *HN* hydronephrosis, *M* male, *mo* month, *NR* not reported, *NSAIDs* non-steroidal anti-inflammatory drugs, *PCN* percutaneous nephrostomy, *S. Conc.* serum concentration, *TPM* topiramate, *UPJ* ureteropelvic junction, *UTI* urinary tract infection, *w* weeks, *y* years

[a]Data of the infants with nephrocalcinosis and/or nephrolithiasis (or biliary stones) only not the entire cohort

[b]Mean dose/period ± standard deviation

[c]Same dose/period for all children

includes reduction of FBM dose or if possible discontinuation, endoscopic stenting and hydration (Table 2) [49–51].

5.1.5 Silica Stones

Silica is commonly mistaken in the literature for silicate; however, they are different. Silica (SiO_2) is the oxidized form of silicone, and it represents the most common element of the earth's crust, while silicate (SiO_4) is any tetrahydrated compound of silica, and it is also a main component of the earth's mantle and crusts [52]. Silica stones are extremely rare, and account for 0.1–0.2% of all urinary stones. They are most commonly documented in adult patients after long-term use of silica-containing antacid for treatment of peptic ulcers [53]. In the pediatric population, they have been associated with the use of silica-containing milk thickener (Gelopectose, containing 5.5% colloidal silicate) for the management of infants' gastro-esophageal reflux [54]. Only one study reported the development of silica stones in the pediatric population (Table 2) [54]. Most silica stones pass spontaneously after discontinuation of the drug; however, in the case of persistence, other treatment options are recommended (e.g., SWL or percutaneous nephrolithotomy) based on the stone characteristics [53].

5.1.6 Indinavir Stones

Indinavir is a strong HIV protease inhibitor that is frequently used together with nucleoside reverse transcriptase inhibitors in the management of HIV/AIDS in adults and pediatric populations [55]. Indinavir is characterized by its relatively poor solubility at pH > 5, which can result in its precipitation and crystallization [56]. Two reports in the literature showed urolithiasis in children infected by HIV after treatment with indinavir (Table 2) [55, 56]. HIV/AIDS is a rare condition in the pediatric population, and this may explain the rarity of indinavir-induced stones in children. Indinavir-induced stones are radiolucent on plain x-ray and computed tomography; on the contrary, they may be diagnosed using ultrasonographic imaging studies [56]. Intravenous antibiotics, discontinuation or replacement of indinavir, and hydration represent the mainstays for the management of these stones, as surgical intervention should be avoided, as it carries the risk of infection in this group of immunocompromised patients. Up to 83% may resolve or pass spontaneously [56].

5.2 Metabolically Drug-Induced Nephrolithiasis

Table 3 shows a summary of the published reports on metabolically drug-induced nephrolithiasis.

5.2.1 Other Antibacterial Drugs

Overall, multiple antibacterial drugs are associated with renal stone formation. Considering the large number of patients treated with these drugs, the rarity of such a condition suggests that other favoring factors (high doses, long duration, low diuresis, and urine pH) may play a role [12]. Tasian et al. showed that several classes of antibacterial drugs, such as sulfas, fluoroquinolones, cephalosporins, nitrofurantoin, and broad spectrum penicillins, may increase the risk of nephrolithiasis, especially in younger populations [57].

Cefotaxime is also a third-generation cephalosporin similar to ceftriaxone. Ustyol et al. [38] compared the rate of biliary pseudolithiasis and nephrolithiasis between children using ceftriaxone and cefotaxime in the management of acute bacterial infection, showing no significant difference between these drugs in regard to drug-induced nephrolithiasis (1.2% vs 1.5%, $p > 0.05$). This is the only report in the literature about cefotaxime-induced nephrolithiasis in the pediatric population, and further studies are required to confirm the lithogenic effect of this antibacterial drug.

Furthermore, Bohles et al. [58] demonstrated that co-trimoxazole and ceftazidime may be associated with increased risk of stone formation in children suffering from cystic fibrosis. This may be explained by the oxalate hemostasis caused by loss of the intestinal bacterium *Oxalobacter formigenes* (which is sensitive to co-trimoxazole and ceftazidime) causing an increased risk of hyperoxaluria and calcium oxalate stone formation [59]. Overall, there are several theories explaining the relationship between stone formation and different antibacterial drugs, such as the lower diversity of the gut microbiome in patients with nephrolithiasis, indicating that multiple organisms are integrated in the relationship between antibacterial drugs and nephrolithiasis, not only *O. formigenes* [57].

5.2.2 Furosemide

Furosemide is a loop diuretic commonly used in the pediatric population for the correction of fluid overload in both acute and chronic disorders [60]. In the current review, it has been employed mainly in preterm infants with low birth weight or those suffering from congestive heart failure [61–77]. In 1982, Hufnagle et al. [66] were the first to link renal calcifications in preterm infants with furosemide use, where, over a 4-year period, they found ten preterm infants showing nephrolithiasis (ranging from small stones to staghorn calculi) within 12–44 days of high-dose furosemide therapy (2–4 mg/kg). Based on this finding, several authors studied the risk factors associated with the development of nephrocalcinosis and/or nephrolithiasis in preterm infants, showing that duration of oxygen ventilation, gestational age, birth weight, high calcium intake, total parenteral nutrition, dexamethasone, furosemide, theophylline, aminoglycosides, dehydration, toxic gentamycin/vancomycin levels, and male sex are all significant predictors in preterm infants [69–72, 76, 78]. Furthermore, Gimpel et al. [76] found that a furosemide dose of > 10 mg/kg during the neonatal intensive care unit stay increased the risk of neonatal nephrocalcinosis by 48-fold. The incidence of furosemide-induced nephrocalcinosis in preterm infants ranges from 13.9% to 20% [75, 77]. On the other hand, Saarela et al. [75] studied the effect of prolonged furosemide therapy on full-term infants with congestive heart failure, reporting 13.9% nephrocalcinosis in patients using furosemide versus 0% nephrocalcinosis in the control group without furosemide therapy. Interestingly, Blickman et al. [73] reported the concurrent presence of nephrocalcinosis and cholelithiasis in four preterm infants with chronic lung disease after furosemide therapy for 28 days.

5.2.2.1 Pathophysiology The plasma half-life of furosemide is markedly increased in preterm infants and neonates (33–100 min in adults vs 8–27 h in neonates). Glomerular filtration and tubular secretion are the main excretory pathways of furosemide [60]. Furosemide is capable of causing hypercalciuria in preterm infants through the inhibition of tubular calcium reabsorption [64]. In this setting, the stone composition in these preterm infants was available in only four reports (23.5%), showing calcium oxalate and/or calcium phosphate stones [62, 64, 66, 74]. However, this hypercalciuria cannot exclusively explain the furosemide-induced nephrocalcinosis and/or nephrolithiasis in this age group; thus the mechanism of this side effect is not completely understood and is considered a multifactorial process [79].

5.2.2.2 Prevention and Treatment Spontaneous resolution of nephrocalcinosis and/or nephrolithiasis occurs in up to 20–60% of preterm infants within 5–6 months after the discontinuation of furosemide [63, 70]. Discontinuation of furosemide therapy was the mainstay of management in the included studies; however, replacement with thiazide, pyelotomy, pyelolithotomy, and ureterolithotomy were indicated in some patients with persistent nephrolithiasis (Table 3) [61–77]. Using thiazide or potassium-sparing diuretics may reduce the risk of nephrocalcinosis and stone formation in this high-risk group, as they decrease calcium excretion [62, 63].

5.2.3 Other Diuretics

Acetazolamide and dorzolamide are carbonic anhydrase inhibitors that alkalinize urine through the reduction of bicarbonate reabsorption [64]. They are commonly used as an adjunct to other drugs in the treatment of refractory

Table 3 Summary of studies reporting metabolically drug-induced nephrolithiasis

First author	No.	Age	Sex	Underlying disease	Drug	Dose or S. Conc.	Exposure period	Effect	Stone analysis	Treatment
Furosemide/acetazolamide										
Ali [63]	3	2 y	M	Tetralogy of Fallot surgery	FUR	2 mg/kg/d	4 w	Renal pelvic stone 10 mm	NR	Hydration Discontinuation
		1.5 y	M	Glenn procedure	FUR	1–2 mg/kg/d	6 w	Renal pelvic stone 15 mm + left ureteral stone	NR	Hydration Discontinuation
		8 mo	M	Ventricular septal defect repair surgery	FUR	1 mg/kg/d	4 w	Renal pelvic stone 15 mm	NR	Hydration Discontinuation
Alpert [61]	1	33 d	F	Preterm + LBW	FUR	27.5 mg	9 d	Bilateral calcification	NR	Percutaneous nephrostomy Replacement "hydrochlorothiazide"
Alon [62]	5	5 mo	F	Trisomy 21 (CHF)	FUR	NR	14 mo	NC	Ca^+ oxalate	Discontinuation
		3 w	M	Noonan (CHF)	FUR	NR	4.25 mo	NC	Ca^+ oxalate	Discontinuation
		10 w	M	Trisomy 21 (CHF)	FUR	NR	9.5 mo	NC	Ca^+ oxalate	Discontinuation
		15 mo	F	Noonan (CHF)	FUR	NR	2 mo	NC	Ca^+ phosphate	Died
		2 w	M	Cardiac hypoplasia + Pulmonary artery stenosis	FUR	NR	40 mo	NC	Ca^+ phosphate	Died
Stafstrom [64]	7	32 d	M	Preterm + LBW + post-hemorrhagic hydrocephalus	FUR/ACZ	NR	7 d/8 d	Hypercalciuria + NC	Ca^+ oxalate	Spontaneous passage
		170 d	M		FUR/ACZ	NR	11 d/11 d	Hypercalciuria + NC	NR	Discontinuation Pyelotomy
		33 d	M		FUR/ACZ	NR	20 d/26 d	Hypercalciuria + NC	Ca^+ oxalate	Spontaneous passage
		87 d	M		FUR/ACZ	NR	42 d/42 d	Hypercalciuria + NC	NR	Spontaneous resolution
		67 d	M		FUR/ACZ	NR	36 d/90 d	Hypercalciuria + NC	NR	Discontinuation
		90 d	M		FUR/ACZ	NR	47 d/52 d	Hypercalciuria	NR	Discontinuation
		27 d	F		FUR/ACZ	NR	8 d/16 d	Hypercalciuria	NR	Discontinuation
Pope [65]	6	55.5 d	NR	Preterm + LBW	FUR	255 mg[b,c]	25.7 ± 10.7 d[c]; range (15–46)	NC (resolution)	NR	Discontinuation after 53 d
	7	55.7 d	NR	Preterm + LBW	FUR	195 mg[b,c]	39.4 ± 15.5 d[c]; range (21–66)	NC (non-resolution)	NR	Discontinuation after 14.9 d
Hufnagle [66]	10	NR	NR	Preterm + respiratory distress + PDA	FUR	2–4 mg/kg/d[d]	12–44 d[d]	NC + nephrolithiasis	Ca^+ oxalate Ca^+ phosphate	Addition of hydrochlorothiazide

Table 3 (continued)

First author	No.	Age	Sex	Underlying disease	Drug	Dose or S. Conc.	Exposure period	Effect	Stone analysis	Treatment
Noe [67]	1	29 WG	M	Preterm + bronchopulmonary dysplasia	FUR	2.5 mg/12 h	5 w	Bilateral nephrocalcinosis	NR	Replacement "hydrochlorothiazide"
Ezzedeen [68]	17	26.8 WG	F (47.1%)	Preterm + chronic lung disease	FUR + Ca^{+} + vitamin D + phosphorous	2.3 mg/kg/d[c]	40 ± 33 d[c]; range (4–137)	Renal calcifications	NR	NR
Short [69]	79	47 d[a]	F (61.9%)	Preterm infants	FUR (31.6%) + phosphorous + Ca^{+}	138.5 mg[a,c]	NR	21 (26.6%) NC (of which 71% were on FUR)	NR	NR
Mohamed [70]	97	32 WG	F (42.3%)	Preterm infants	FUR (20.6%)	NR	NR	14 (14.4%) NC (of which 50%, 57.1%, and 92.9% were on FUR, theophylline, and aminoglycosides)	NR	Conservative "follow-up" with complete resolution in 57.1%
					Theophylline (22.7%)	NR	NR		NR	
					Aminoglycosides (40.2%)	NR	NR		NR	
Chang [71]	102	80.5 d[a]	F (44%)	Preterm + LBW	FUR (5%) DXM (5%)	NR	NR	6 (6%) NC (FUR 33% vs 3% in the no NC group, and DXM 50% vs 2%)	NR	NR
Narendra [72]	101	72.8 d	NR	Preterm + LBW	FUR + DXM + surfactant + aminoglycosides	NR	NR	16 (16%) NC [of which FUR (56%), DXM (37%), aminoglycosides (69%), surfactant (94%)]	NR	NR
Blickman [73]	4	28 WG	M	Preterm + LBW + severe pulmonary dysplasia + intraventricular hemorrhage	FUR	NR	At least 28 d	Nephrolithiasis Cholelithiasis	NR	Discontinuation Surgery for gall bladder stone in one patient
		26.5 WG	F							
		28 WG	F							
		33 WG	M							
Gimpel [76]	55	26 WG	F (42%)	Preterm ± LBW	FUR	16 mg/kg[b,c]	NR	NC in 15 patients	NR	NR
		29 WG				0 mg/kg[b]	NR	No NC in 40 patients	NR	NR

Table 3 (continued)

First author	No.	Age	Sex	Underlying disease	Drug	Dose or S. Conc.	Exposure period	Effect	Stone analysis	Treatment
Glasier [74]	2	25 WG	F	Preterm + PDA+ Respiratory distress	FUR	NR	5.5 mo	Left nephrolithiasis (passed to the ureter)	Ca^{+} oxalate	Discontinuation Ureterolithotomy
		26 WG	M	Preterm + PDA + hydrocephalus + bronchopulmonary dysplasia	FUR	NR	2 mo	Right nephrolithiasis	NR	Discontinuation
Saarela [75]	36	2.9 mo	F (55.6%)	CHF	FUR	1.9 mg/kg/d[ac]	2.1 mo[ac]; range (1.2–5.2)	5 (13.9%) NC	NR	Discontinuation (resolved in 3/5 patients with NC)
	36	3.4 mo	F (47.2%)	CHF	No FUR	NR	NR	No NC	NR	None
Downing [77]	117	NR	NR	Preterm + respiratory distress syndrome	FUR	NR	NR	20 (17%) NC	NR	Nephrolithotomy (10%) Discontinuation (50%) Death (20%)
Dorzolamide										
Carlsen [81]	1	17 y	M	Retinitis pigmentosa + perifoveal edema	Dorzolamide	NR	21 d	Nephrolithiasis	NR	Hydration Analgesics
Topiramate										
Ishikawa [86]	15	7 y	F (46.7%)	Refractory epilepsy + non-ambulatory	TPM	S. Conc. 16.6 µg/mL[c]	4–45 mo	Stones and calcifications (60%)	NR	NR
	11	9.8 y	F (45.6%)		No TPM	NR	NR	None (0%)		
Goyal [87]	22	18.1 y	F (45.5%)	Refractory epilepsy + disability	No AEDs	NR	NR	None	NR	NR
	23	21 y	F (52.2%)		Non-TPM AEDs	NR	NR	None	NR	NR
	24	21.3 y	F 54.2%)		TPM	7.9 mg/kg/d[c]	36.4± 21.3 mo[c]	13 (54.6%) nephrolithiasis	Ca^{+} phosphate Ca^{+} oxalate Struvite	Alkalinization Discontinuation (53.8%) Lithotripsy ± PCN (15.4%)
Mahmoud [88]	96	6.9 y	F (45.8%)	Epilepsy	TPM	NR	NR	5 (5.2%) nephrolithiasis	NR	NR
Corbin Bush [89]	41	9.2 y	F (51%)	Seizures	TPM	8.0 mg/kg/d[c]	27 ± 19 mo[c]; range (1–157)	2 (4.8%) nephrolithiasis	Ca^{+} phosphate	ESWL Ureteroscopy
Giannopoulou [90]	1	3 y	M	Complex focal seizures	TPM	6.5 mg/kg/d	18 mo	Large left renal stones	Ca^{+} phosphate	ESWL Open surgery

Table 3 (continued)

First author	No.	Age	Sex	Underlying disease	Drug	Dose or S. Conc.	Exposure period	Effect	Stone analysis	Treatment
Yam [91]	48	1.1–15.4 y	F (33.3%)	Epilepsy	TPM ± ketogenic diet	6 mg/kg/d[c]	8.3 y[c]; range (1.3–12)	2 (4.2%) nephrolithiasis	NR	Conservative "follow-up" Discontinuation (2.1%)
Barnett [92]	40	8.9 y	NR	Seizures	TPM polytherapy or monotherapy	Range: 2.2–21.4 mg/kg/d	Range 30–60 mo	4 (10%) nephrolithiasis or NC	NR	Discontinuation
Puri [93]	135	1 y	F (46%)	Refractory partial seizures	TPM polytherapy or monotherapy	30.2 mg/kg/d[c]	At least 1 y	18 (13.3%) nephrolithiasis	NR	NR
Zonisamide										
Go [96]	NR	10.7 y	NR	Epilepsy	ZNS + sulthiame	Therapeutic range	NR	Crystalluria	NR	NR
Miyamoto [99]	1	10 y	F	Refractory seizures	ZNS	600 mg/d	1 mo	Bilateral urolithiasis	NR	Discontinuation
Kubota [95]	3	13 y	M	Lennox-Gastaut	ZNS + ACZ	9 mg/kg/d	2 mo	Left urolithiasis	Ca^{+} phosphate	Hydration Discontinuation (ZNS and ACZ)
		7 y	M	Lennox-Gastaut	ZNS polytherapy	7 mg/kg/d	NR	2-cm anterior bladder wall sludge	Ca^{+} phosphate crystals	Hydration Discontinuation
		15 y	F	Focal epilepsy	ZNS polytherapy	5 mg/kg/d	NR	3-cm anterior bladder wall sludge	Ca^{+} oxalate	Discontinuation
Go [97]	278 [e]	12.3 y	F (39.2%)	Epilepsy	ZNS polytherapy containing ACZ	NR	NR	Crystalluria in 31.5%, 53.5%, 45.5% (treated with 2, 3, and > 3 drugs, respectively)	NR	NR
Go [98]	27	10.1 y	F (44.4%)	Refractory epilepsy	ZNS added	S. Conc. 17.4 g/mL[c]	1 mo[d]	Crystalluria significantly increase	NR	NR
	16	11.4 y	F (37.5%)		ZNS withdrawn	S. Conc. 13.6 g/mL[c]	NR	Crystalluria significantly decrease		
Ketogenic diet										
Paul [101]	17	NR	F (41%)	Refractory epilepsy	Ketogenic diet/ZNS	NR	28 ± 28/6 ± 6 mo[c]	Nephrolithiasis (4.5%)	NR	NR
	22	NR	F (32%)		Ketogenic diet/TPM	NR	26 ± 21/12 ± 18 mo[c]	Nephrolithiasis (17.6%)	NR	
	47	NR	F (53%)		Ketogenic diet	NR	23 ± 20 mo[c]	No nephrolithiasis	NR	

Table 3 (continued)

First author	No.	Age	Sex	Underlying disease	Drug	Dose or S. Conc.	Exposure period	Effect	Stone analysis	Treatment
Kossoff [104]	221	5.1 y	NR	Refractory epilepsy	Ketogenic diet	NR	22.1 ± 15 mo[c]	15 (6.8%) urolithiasis	Uric acid (40%) Ca^+ phosphate/oxalate (33.3%)	Hydration Alkalinization Lithotripsy (33.3%)
	80	4.8 y	NR		Ketogenic diet + ZNS or TPM	TPM = 8.4 mg/kg/d[ac]	Diet duration 10.4 ± 6.7 mo[c]	5 (6.3%) urolithiasis (all of them were on TPM)	NR	Hydration Alkalinization TPM discontinuation (60%)
Sampath [102]	195	3 y	F (53.8%)	Refractory epilepsy	Ketogenic diet + CAIs	NR	Median 7 mo	13 (6.7%) urolithiasis	Ca^+ phosphate Ca^+ oxalate Uric acid	NR
Choi [103]	1	5 y	F	Refractory epilepsy	Ketogenic diet	Non-lipid: lipid = 4:1	3 mo	Uretero pelvic junction urolithiasis	NR	Hydration
Allopurinol										
Shiozawa [106]	1	11 y	M	ALL	Allopurinol + chemotherapy	NR	23 d	Ureteral stones	Ca^+ phosphate	Forced hydration
Shields [107]	1	12 y	M	Lesch-Nyhan	Allopurinol	200 mg/d	10 y	Bilateral staghorn stones	Xanthine	Bilateral PCNL
Pais [108]	1	13 y	M	Lesch-Nyhan	Allopurinol	NR	NR	Bilateral urolithiasis	Xanthine	Failed ESWL Bilateral PCNL Oral hydration Potassium citrate
Sikora [109]	1	9 y	M	Lesch-Nyhan	Allopurinol	20–30 mg/kg/d	8 y	Bilateral staghorn stones	Xanthine	Analgesics + antibiotics Reduction of dose Surgery
LaRosa [110]	1	11 y	F	ALL	Allopurinol	400 mg/m^3/d	17 d	Acute renal failure due to bilateral nephrolithiasis	Xanthine	Died
Landgrebe [111]	1	8 y	M	Hyperuricosuria	Oxypurinol	20 mg/kg	4 mo	Urinary sludge and ureteric stone	Oxypurinol	Surgical removal
Greene [112]	1	16 y	M	Lesch-Nyhan	Allopurinol	50 mg/6 h	NR	Multiple small stones	Xanthine	Endoscopic removal
Brock [113]	2	17 y	M	Lesch-Nyhan	Allopurinol	300 mg/8 h	NR	Multiple large renal calculi	Oxypurinol	Pyelolithotomy
		16 y	M	Lesch-Nyhan	Allopurinol	200 mg/ 8 h	NR	Bilateral urolithiasis	Xanthine + oxypurinol	
Torres [114]	19	7 y	NR	Lesch-Nyhan	Allopurinol	NR	NR	3 (15.8%) nephrolithiasis	Xanthine	ESWL Dose adjustments
Potter [115]	1	11 y	M	ALL	Allopurinol + chemotherapy	NR	NR	Multiple small stones	Xanthine	Died

Table 3 (continued)

First author	No.	Age	Sex	Underlying disease	Drug	Dose or S. Conc.	Exposure period	Effect	Stone analysis	Treatment
Other drugs										
Chen [117]	1	9 y	M	None	Vitamin C supplement	3 g/d	6 y	Ureteral stone	Ca^+ oxalate (mono and dehydrate)	ESWL Discontinuation
Conti [118]	2	12 y	M	None	Vitamin D supplement	254,490 IU/d	1 mo	Nephrolithiasis	NR	Discontinuation
		15 y	M			212,000 IU/d	2 w	None		
Cranefield [122]	16	24–28 WG	M	Preterm + LBW	DXM long course (42 d)+ aminoglycosides	6.5 mg/kg[c]	42 d[c]	Ultrasound data available only for 18 infants, of which 15 (83%) showed nephrocalcinosis by discharge	NR	NR
	17				DXM short course (18 d)+ aminoglycosides	3.8 mg/kg[c]				

ACZ acetazolamide, *AEDs* antiepileptic drugs, *ALL* acute lymphoblastic leukemia, Ca^+ calcium, *CAIs* carbonic anhydrase inhibitors, *CHF* congestive heart failure, *d* day(s), *DXM* dexamethasone, *ESWL* extracorporal shockwave lithotripsy, *F* female, *FUR* furosemide, *LBW* low birth weight, *M* male, *mo* month, *NR* not reported, *NC* nephrocalcinosis, *PCN* percutaneous nephrostomy, *PCNL* percutaneous nephrolithotomy, *PDA* patent ductus arteriosus, *S. Conc.* serum concentration, *TPM* topiramate, *w* weeks, *WG* weeks of gestation, *y* years, *ZNS* zonisamide

[a]Data of the infants with nephrocalcinosis and/or nephrolithiasis (or biliary stones) only not the entire cohort

[b]Cumulative

[c]Mean dose/period ± standard deviation

[d]Same dose/period for all children

[e]Urine samples not patients

epilepsy [80], post-hemorrhagic hydrocephalus in preterm infants [64], or glaucoma [81]. These drugs are known for their lithogenic effects in adults [81, 82]; however, there is a lack of data about their effect in the pediatric population.

Stafstrom et al. [64] demonstrated that combination therapy of furosemide and acetazolamide in the management of preterm infants with post-hemorrhagic hydrocephalus may be associated with an increased risk of nephrocalcinosis and/or nephrolithiasis; thus, close monitoring of the urine calcium/creatinine ratio is recommended. On the other hand, Katayama et al. [80] reported stone passage in a 21-year-old patient after 6.5 years of 10 mg/kg/day acetazolamide polytherapy (sodium valproate, carbamazepine, and clonazepam) for management of refractory epilepsy. Carlsen et al. [81] reported the development of renal stone in a 17-year-old male patient suffering from retinitis pigmentosa and perifoveal edema after 2 years of dorzolamide therapy (Table 3).

5.2.4 Topiramate

Topiramate (TPM) is a sulfamate-substituted derivative of D-fructose monosaccharide that was approved by the FDA in the USA in 1996 as a monotherapy or for adjunctive management of partial seizures, refractory epilepsy, and migraine prophylaxis [83]. It has even extended its indications to include some off-label uses such as mood disorders, obesity, and smoking cessation [84]. Thus, TPM has become one of the most frequently prescribed drugs in the USA, ranking among the top 50 most prescribed drugs [85]. TPM has been long known for its lithogenic effect through the metabolic changes induced by this drug [86–93]. A systematic review published in 2013 showed that the overall annual incidence of symptomatic nephrolithiasis with TPM usage was 2.1% [94]; however, the incidence of nephrolithiasis in the pediatric population ranged from 4.2% to 60% (Table 3). It is worth mentioning that the high incidence of 60% may be explained by the presence of other risk factors for urolithiasis as this study was performed in non-ambulatory children, a population in which there are increases in bone resorption, which subsequently leads to hypercalcemia and hypercalciuria [86].

Two studies tried to determine the accurate incidence of TPM-induced urolithiasis in the pediatric population through comparing the incidence of urolithiasis between children with disability using TPM for management of refractory epilepsy versus a control group of similar children not using TPM. They showed similar results, with an incidence of urolithiasis significantly higher in the TPM group versus the no TPM group (60% vs 0% and 54.6% vs 0%) [86, 87]. Furthermore, an open-label extension study from two studies (phase 1 and phase 3) in 284 infants < 2 years old with refractory partial-onset seizures treated with TPM (only 135 infants completed the open-label extension study) was published in 2011 and showed that one of the treatment-emergent adverse events found was nephrolithiasis in 18 of the 135 patients (13.3%) [93].

5.2.4.1 Pathophysiology TPM has several mechanisms of action, including weak carbonic anhydrase inhibition (similar to acetazolamide) that increases bicarbonate excretion by the proximal tubules. Moreover, it leads to an increase in calcium excretion and citrate reabsorption. Interestingly, TPM may cause an increase in bicarbonate loss through the gastrointestinal tract (mostly due to diarrhea). These metabolic alterations cause metabolic acidosis, elevated urinary pH, hypocitraturia, and hypercalciuria and, subsequently, an increase in the risk of calcium stone formation [83, 86]. Dell'Orto et al. [94] demonstrated in their systematic review a significant tendency towards metabolic acidosis, where the circulating bicarbonate was significantly lower in TPM patients compared to control subjects; however, this finding was not significantly related to the dose of TPM. In this review, few studies reported the urinary pH and the calcium/creatinine ratio, and these ranged from 6.8–8.07 [86, 87] and 0.22–0.30 [87, 89], respectively. Generally, the relation between TPM administration and stone formation should be interpreted with caution, as stone composition was not analyzed in most of the patients reported in the literature and the causal relationship was based only on the duration between the stone event and the start of medication.

5.2.4.2 Prevention and Treatment Barnett et al. [92] recommended that all children undergoing TPM therapy should have a baseline evaluation including urinalysis, urinary calcium/creatinine ratio, serum electrolyte and urinary citrate/creatinine ratio, with follow-up of these tests at 6-month intervals. Furthermore, children who show a urine calcium/creatinine ratio > 0.21 should have renal ultrasonography follow-up every 6 months. Potassium citrate may also be used while on TPM therapy to reduce the risk of urolithiasis. The included studies showed that discontinuation may be difficult in some children; thus the main treatment options were endoscopic lithotripsy, SWL, and open surgeries (Table 3).

5.2.5 Zonisamide

Zonisamide (ZNS) is a carbonic anhydrase inhibitor similar to TPM; however, it is reported to be 100 times less potent as a carbonic anhydrase II inhibitor than acetazolamide [95]. It has been strongly associated with urolithiasis and crystalluria in the pediatric population (Table 3) [95–99]. Go [98] studied the metabolic effect of ZNS through examining the urine of 27 children 1 month after starting ZNS therapy and 1 month after its withdrawal, demonstrating

that urinary pH was not significantly changed with the addition or the withdrawal of ZNS; however, the degree of crystalluria was significantly increased after addition and significantly decreased after the withdrawal of ZNS therapy. Furthermore, Go [97] showed in another study that crystalluria during ZNS therapy was increased with the number of antiepileptic drugs used, where crystalluria was found in 31%, 53.3%, and 45.5% of 278 urine samples obtained from patients treated with two, three, and more than three drugs, respectively. Wroe [100] used the reports of four placebo-controlled, double-blind trials on ZNS treatment to identify the actual incidence of ZNS-induced urolithiasis among patients treated for epilepsy. At 3 months of ZNS, there was no symptomatic nephrolithiasis among the 498 patients on ZNS therapy; however, a follow-up at 24 months (open-label extension study) showed renal calculi in nine out of 626 patients (1.4%). Furthermore, the "all zonisamide" population database, that is a database including all the patients included in USA and European clinical trials, showed an incidence of 15 out of 1296 (1.2%) at 8.7 years follow-up [100].

5.2.5.1 Pathophysiology The pathophysiology of ZNS-induced urolithiasis is similar to that of TPM, where it blocks normal bicarbonate reabsorption, resulting in primary alkalinization of urine and acidification of blood, followed by urine acidification as well. Furthermore, it provokes hypercalciuria through increases in sodium and calcium excretion. Eventually, the kidney tries to compensate for the resulting metabolic acidosis through the reabsorption of citrate, causing a further increase in the risk of urolithiasis [101]. Only one study reported analysis of ZNS-induced stones, showing that they are composed mainly of calcium oxalate and calcium phosphate [95].

5.2.5.2 Prevention and Treatment Most of the studies about ZNS-induced urolithiasis in children showed that hydration and discontinuation of ZNS are sufficient treatment for the developed crystalluria, urolithiasis and urinary bladder sludges [95, 99].

5.2.6 Ketogenic Diet

Despite not being a medication, we decided to add the ketogenic diet in this review as it is a major risk factor for nephrolithiasis in pediatric patients treated with antiepileptic drugs such as TPM and ZNS. The ketogenic diet is a high-fat, low-carbohydrate, and adequate-protein diet that has been used in the management of refractory epilepsy since 1921 [101]. This diet carries an increased risk of nephrolithiasis (3–10%) in pediatric patients treated for refractory epilepsy [102]. The ketogenic diet provokes urolithiasis through multiple mechanisms, including hypercalciuria, hypocitraturia, chronic acidosis, and dehydration. The metabolic acidosis resulting from the ketogenic diet increases the calcium excretion through reducing calcium reabsorption and increasing bone demineralization. Furthermore, this acidosis and metabolic changes may lower the urinary pH, reducing the uric acid solubility. Interestingly, the most important factor is dehydration, as the ketogenic diet interferes with the normal thirst mechanism. All these factors play an important role in the lithogenic effect of the ketogenic diet in children with refractory epilepsy [102, 103].

Paul et al. [101] compared three groups of children suffering from epilepsy, where 47 children who were treated only with ketogenic diet did not show any nephrolithiasis. On the other hand, nephrolithiasis was reported in 17.6% and 4.5% of children treated with the ketogenic diet + TPM and the ketogenic diet + ZNS, respectively. On the contrary, Kossoff et al. [104] reported no difference as regards the incidence of urolithiasis between epileptic children treated with the ketogenic diet alone and those treated with the ketogenic diet + ZNS or TPM (6.8% vs 6.3%, respectively). Hydration and alkalinization of urine represent the main preventive measures and treatment options for ketogenic diet–induced urinary stones [101–104]. Importantly, the ketogenic diet is associated with bleeding tendency in approximately one third of children treated for epilepsy. This may be explained by the presence of underlying bleeding-susceptibility factors together with the decreased platelet responsiveness induced by the ketogenic diet (due to changes in the lipid composition of the platelet membrane) [105]. This is clinically important, especially if children require extracorporal SWL for management of their stones. Table 3 shows a summary of the studies discussing antiepileptic drugs and urolithiasis.

5.2.7 Allopurinol

Allopurinol is a xanthine oxidase inhibitor that is commonly used in the treatment of gout, to control the hyperuricemia occurring as a part of Lesch-Nyhan syndrome (LNS), and to prevent tumor lysis syndrome in patients with acute lymphoblastic leukemia (ALL) before the induction of chemotherapy [106, 107]. Several reports demonstrated that allopurinol is associated with an increased risk of xanthine urolithiasis in children [106–115]. Table 3 summarizes all the reports of allopurinol-induced urolithiasis in the pediatric population discussed in the current review.

However, the incidence of urolithiasis in ALL patients is extremely rare; its incidence is increased during chemotherapy. Several factors may contribute to the increased risk, including glucocorticoid therapy, which may increase the risk of urolithiasis up to 48-fold during induction and 22-fold during continuation therapy [116]. Furthermore, ALL chemotherapy may be associated with hyperuricemia

and tumor lysis syndrome, which may increase the risk of urolithiasis in these patients [106]. Three case reports in the literature demonstrated the occurrence of urolithiasis in two 11-year-old boys and one girl taking allopurinol during the induction of chemotherapy for the management of ALL [106, 110, 115]. In one boy, the stone passed following treatment by forced hydration, and on analysis, it showed calcium phosphate composition [106]. The other boy and the girl died, and the autopsy analysis of the stones showed xanthine composition [110, 115].

LNS describes the presence of the triad consisting of hyperuricemia, central nervous system disorder, and familial inheritance, and it is characterized by a low incidence ranging from 1:100,000 to 1:300,000. The hyperuricemic component of this syndrome increases the risk of urolithiasis and gout [107]. Torres et al. [114] reported 15.8% urolithiasis after allopurinol therapy in children with LNS. Furthermore, several authors demonstrated that allopurinol therapy in children suffering from LNS was associated with multiple large stones [107–109, 113]. On the contrary, Greene et al. [112] reported the development of multiple small stones in a 16-year-old boy with LNS after allopurinol therapy.

5.2.7.1 Pathophysiology Allopurinol reduces uric acid production through inhibition of the xanthine oxidase enzyme, which is responsible for the conversion of xanthine to uric acid. In this setting, it increases the excretion of xanthine in urine. Xanthine is characterized by its low urine solubility; thus it may precipitate and increase the risk of urolithiasis [107, 110]. Moreover, the significant increase in the urinary level of oxypurinol, which is a metabolite of allopurinol, may predispose patients to the process of urolithiasis [107].

Allopurinol-induced urinary stones are usually composed of xanthine with/without oxypurinol [107–115]. Xanthine stones are typically radiolucent with Hounsfield units similar to the uric acid stones on computed tomography, and they occur more commonly in the upper urinary tract [108].

5.2.7.2 Prevention and Treatment Aggressive hydration, alkalinization, and adjustment of the allopurinol dosage represent the corner stone for the management of xanthine stones [108]. Potassium citrate may be used for urine alkalinization [109]; however, urinary pH should be carefully monitored during allopurinol therapy, as its increase above 7.0 increases the risk for calcium phosphate stone formation [108]. The allopurinol dosage should be strictly adjusted not to exceed 5 mg/kg/day in children and 100 mg/day in adults to allow the reduction of serum uric acid production without overproduction of xanthine, thus reducing the risk of urolithiasis [107]. If these measures fail, other treatment options may be used, including SWL, percutaneous nephrolithotomy, endoscopy and open surgery [106–115].

5.2.8 Vitamins

There are scarce data about the association between vitamin supplements and stone formation in the pediatric population. Urolithiasis was reported in one child who had a long history of vitamin C supplementation [117] and another child who had a 1-month history of vitamin D supplementation [118]. It is worth mentioning that the common risk factor between the two case reports was the very high dose consumption of vitamin supplements that led to vitamin intoxication (Table 3).

5.2.9 Others

Pozzi et al. [119] compared 191 pediatric patients who were capable of oral feeding versus 180 children who were on enteral nutrition to assess the incidence of urolithiasis among both groups. Interestingly, the oral feeding group showed no stones, while the enteral nutrition patients showed urolithiasis: 26 (14.4%); thus, the authors concluded that the use of enteral nutrition was significantly associated with stone formation ($p < 0.001$).

Moreover, methotrexate and prednisone are part of the chemotherapy used in different cancers. Some authors suggested that these drugs may increase the risk of stone formation in patients with ALL and kidney transplant patients [120, 121]. Dexamethasone and aminoglycosides have also been associated with increased risk of nephrocalcinosis in low-birth-weight infants [122].

6 Conclusion

Despite drug-induced nephrolithiasis being uncommon, it should be considered by physicians when dealing with children suffering from urinary tract calculi; otherwise an accurate diagnosis and the underlying cause will be missed, which may have harmful consequences. Careful evaluation with a detailed medical history including associated comorbidities and history of drug consumption is paramount for the diagnosis and management of this condition. Adequate knowledge of the potentially lithogenic drugs and follow-up of children receiving these drugs for a long duration, especially those with risk factors or a positive family history, can reduce the incidence of drug-induced urolithiasis.

Compliance with Ethical Standards

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