

# Nephrolithiasis in a portuguese pediatric population

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## ABSTRACT

**Introduction and Aims:** Nephrolithiasis incidence in children has increased considerably. It is associated with substantial morbidity, recurrence and increased adulthood cardiovascular risk and chronic kidney disease. A thorough investigation is essential, as rare forms of urolithiasis have increased risk of renal failure. We aim to determine the epidemiology and outcomes of a pediatric population with nephrolithiasis presented in a nephrology unit of a tertiary centre.

**Methods:** Retrospective study of the records of all children (<18 years) with nephrolithiasis diagnosis between 2008-17. Clinical features, etiology, recurrence, treatment, and outcomes were evaluated and compared throughout the study period through two equal periods (2008-12 versus 2013-17).

**Results:** We identified 80 cases: isolated nephrolithiasis (86%) and associated with nephrocalcinosis (14%). Mean follow-up was 36 months (14–120). Median age at presentation was 8.6 years [3 months – 17 years]: 21% < 2 years-old and 46% ≥ 10 years. The annual ratio of referrals for nephrolithiasis increased on average 1.2% per year [0.3-11.8%]. Multiple etiological factors were present in 34%. A metabolic abnormality was identified in 54%: hypocitraturia (34%), hypercalcuria (24%), hyperoxaluria (15%), hyperuricosuria (15%) and cystinuria (1%), without age predominance ( $p=0.2$ ). Urinary tract infection (24%) was the next most significant etiology and was more frequent below 2 years of age ( $p=0.001$ ) and associated with struvite calculi ( $p=0.033$ ). Median age at diagnosis was significantly lower in the study's first half (5 vs 10 years;  $p=0.019$ ) and an infectious etiology was more frequent ( $p=0.043$ ). In a logistic-regression analysis, a family history of nephrolithiasis was associated with a metabolic cause ( $p<0.01$ ). Sixty-three percent became stone free and 24% had recurrence.

**Discussion:** Nephrolithiasis new referrals gradually increased throughout the study period. The most common etiology was metabolic, which is usually responsible for nephrolithiasis appearance and its recurrence, emphasizing the need for a complete evaluation.

**Keywords:** nephrolithiasis, kidney stone, children, Portuguese, metabolic disease, obesity

## INTRODUCTION

Urolithiasis incidence in children has increased considerably over the last few decades and is associated with substantial morbidity and recurrence. An estimated prevalence of 1-5% is reported in the United States of America and it is responsible for 1 in 1,000 pediatric hospital admissions, with a slight male predominance<sup>1-4</sup>. Recent epidemiological studies have

suggested an increased incidence of kidney stone disease in all age groups, particularly in children<sup>4-6</sup>. The etiology of pediatric urolithiasis is generally undetermined and this rising incidence has been endorsed by many reasons, such as metabolic, anatomical, dietary and environmental risk factors<sup>7-12</sup>. While in pediatric patients infection was considered the primary cause of urolithiasis<sup>13,14</sup>, the etiologic pattern in younger patients has changed from mainly infectious to

metabolic causes<sup>13-16</sup>. Anatomical abnormalities, such as ureteropelvic junction obstruction or vesicoureteral reflux, are associated with infection and urinary stasis, thus enhancing stone formation<sup>17-19</sup>. Over the past decades, metabolic disorders have been recognized in 33–95% of pediatric patients. Several studies have demonstrated the implication of metabolic risk factors – such as hypercalciuria, cystinuria and hyperoxaluria – in children with urolithiasis etiology<sup>20-24</sup>. Influences of some environmental features have to be considered, such as family diet patterns and the higher risk of lithiasis among stone-former relatives. Indeed, an increased consumption of salty fast food and high-protein diets has been associated with an increase in urolithiasis. On the other hand, it is well documented that hypercalciuria is significantly disturbed by dietary factors<sup>25</sup>: boosted by excessive calcium, sodium and animal protein intake and diminished by potassium and citrate (high in fruit and vegetables) ingestion<sup>26</sup>. It would appear that the eating of animal protein predisposes to the development of hyperuricemia, thereby creating an acid load, which increases the urinary excretion of calcium and uric acid and reduced citrate<sup>27</sup>. Chocolate contributes to an enlarged stone-forming risk due to its oxalate content<sup>28</sup>. Ingesting a diet high in fruit and vegetables, moderate in low-fat dairy products and low in salt and animal protein has been associated with reduced stone-formation risk<sup>29,30</sup>. Low urinary volume may be the most important risk factor for stone formation in healthy individuals and no child with urinary flow rate higher than 1.6 ml/kg/h is at risk of stone formation<sup>31</sup>. Finally, an increase in stone disease has also been attributed to other factors, such as an increasingly sedentary lifestyle, the global rise in obesity, global warming and climate changes<sup>32</sup>. An association between increasing body mass index (BMI) and increasing urinary excretion of sodium, calcium, uric acid, and citrate has been reported<sup>33</sup>.

All children that present with urolithiasis warrant a thorough investigation because some rare forms of stone disease are associated with a different risk of renal failure<sup>34,35</sup>: adenine phosphoribosyltransferase deficiency, cystinuria, Dent disease, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, and primary hyperoxaluria. Although rarely obtained, a key part of the pediatric kidney stone check-up is the stone evaluation<sup>35</sup>. The urine chemistry is a crucial test, either from twenty-four hour collections or random urine samples in younger children.

The aim of this study was to characterize the epidemiology, clinical features, metabolic risk factors,

diagnosis, treatment and outcome of a pediatric population with stone disease evaluated at a tertiary centre nephrology unit. As secondary outcomes, we aim to determine recurrence risk factors and to assess if there were differences regarding epidemiology, etiology and clinical risk factors throughout the study period.

## ■ SUBJECTS AND METHODS

### ■ Study population

Retrospective review of medical records from all patients aged 0-18 years referred to the Pediatric Nephrology Ambulatory Department of a level III Hospital, from January 1<sup>st</sup>, 2008 to December 31<sup>st</sup>, 2017 with a nephrolithiasis diagnosis. Patients were divided into groups of equal period (2008-12 and 2013-17) and compared.

Clinical features, past medical conditions, renal lithiasis family history, etiology, treatment and outcomes were evaluated. Excessive dairy products, animal protein, oxalates, phytates and sodium were considered dietary errors, as was reduced water, fruit and vegetable intake. We defined obesity as a body mass index (BMI) superior to the 97th percentile and overweight between the 85th and 97th percentiles of BMI for age and gender of the World Health Organization charts.

Urolithiasis was always confirmed by ultrasonography. Voiding cystourethrography (VCUG) and isotopic renal scans (DMSA/MAG3 scan) were performed in selected cases: VCUG was performed in patients with recurrent urinary tract infection (UTI) and/or hydronephrosis; DMSA scan to identify renal scar and MAG3 scan if obstruction or hydronephrosis were suspected.

### ■ Workup

Blood serum with creatinine, urea nitrogen, uric acid, acid-base status, sodium, potassium, chlorine, magnesium, phosphorus and urine analysis were performed at the first medical appointment. Urine cultures were conducted if there were clinical and laboratory findings suggestive of UTI. In patients with UTI, metabolic assessment was performed after the infection was treated. A stone risk panel was executed on 24-hour urine samples. We considered hypercalciuria >4 mg/

kg/day, hyperoxaluria >0.5 mmol (45 mg)/1.73m<sup>2</sup>/day, hyperuricosuria >815mg/1.73m<sup>2</sup>/day, cystinuria >75mg/1.73m<sup>2</sup>/day, hypocitraturia <320 mg/1.73m<sup>2</sup>/day, hypomagnesuria <2 mmol/day. Lithogenic risk was defined as urinary calcium/citrate ratio >0.33<sup>16,31,36,37</sup>. Abnormal urinary excretion results were always confirmed in at least two samples.

Stone samples obtained by spontaneous passage, or open operation, were analysed by infrared spectroscopy analysis. The predominant component of the calculi was used to classify it.

**Statistical analysis**

The collected data was analysed by SPSS, 20<sup>th</sup> version software (SPSS, Chicago, IL) for Mac using Student’s T test, the Mann–Whitney U test, chi-square test, Fisher’s exact test and logistic regression analysis, with P values of <0.05 considered to be significant.

**Ethics**

The procedures were in accordance with the ethical standards of the committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 (revised in 2015).

**RESULTS**

We identified 80 cases in nine years of study: isolated nephrolithiasis (n=69, 86%) and associated with nephrocalcinosis (n=11, 14%). The annual ratio of referrals for nephrolithiasis increased on average 1.2% per year (2.3% requests in the first year – 11.8% the last year [Figure 1]). Mean follow-up was 36 months (14–120).

**Demographic characteristics**

Median age at presentation was 8 years [minimum 3 months-old – maximum 17 years-old] with a (3-14) interquartile range (Figure 1): 21% under 2 years old (n=17), 33% between 2-10 years (n=26) and 46% with more than 10 years old (n=37). Male predominance was observed (n=47, 59%).

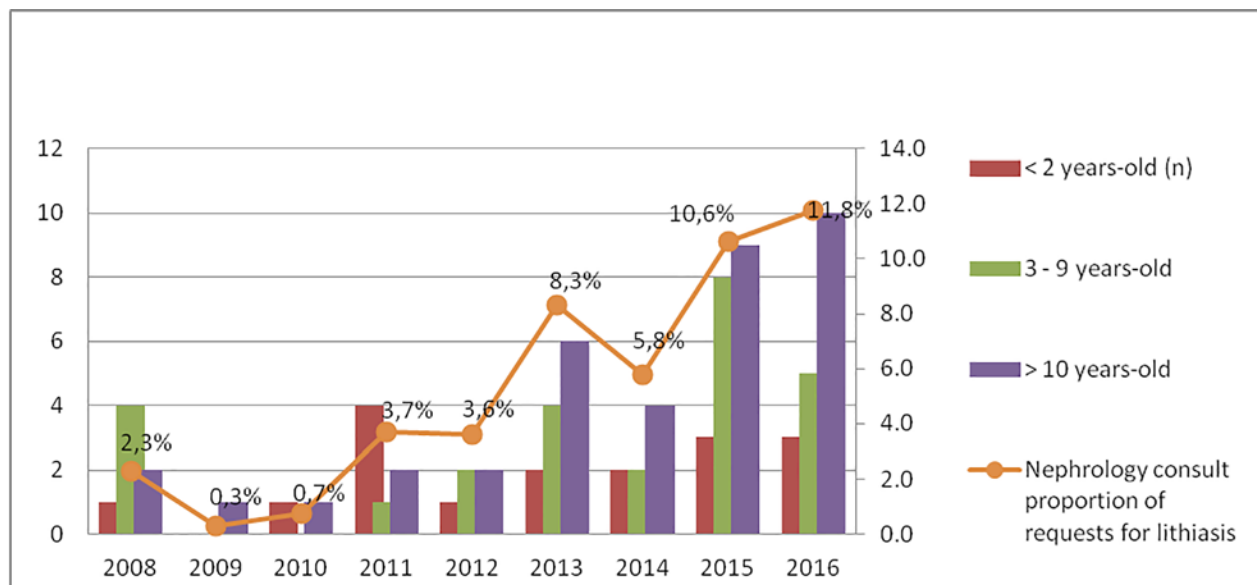
Regarding BMI, 4% (n=3) were under the 3<sup>rd</sup> percentile and 16% (n=13) above the 97<sup>th</sup> percentile (Table I). Figure 2 shows the BMI by year of study. We found no association between excessive weight and obesity (BMI > P85) and age above 10 years old (p=0.159).

**Presenting symptoms at diagnosis**

The most common presenting symptom was flank or abdominal pain (44%, n=35), followed by UTI (19%,

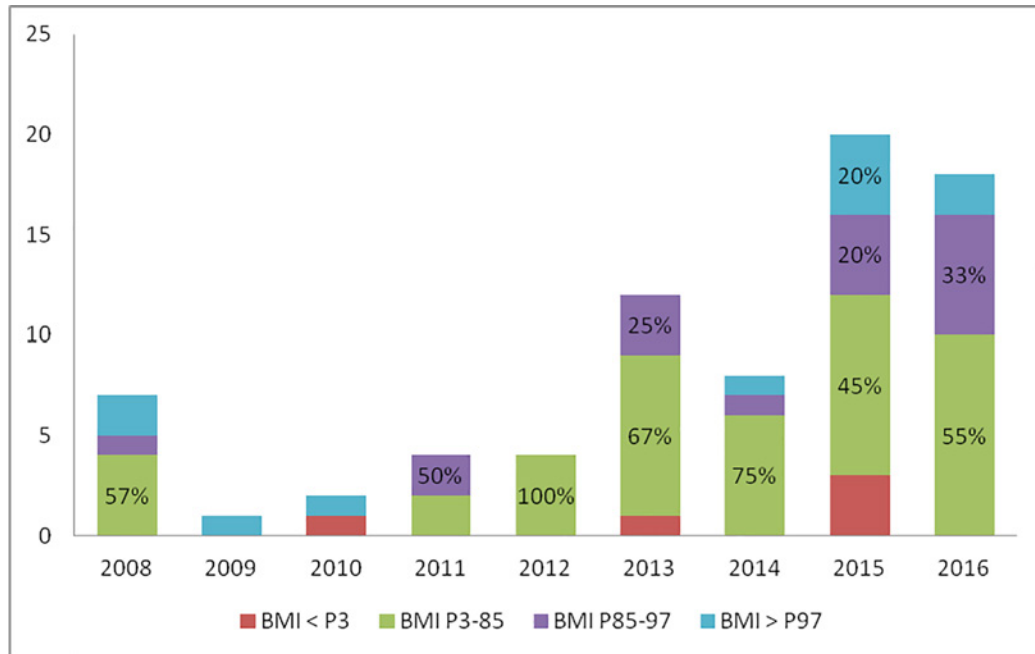
**Figure 1**

Patients distribution through 2008-2017 by age group at presentation. Annual referrals ratio for renal lithiasis, through the study period (orange line).



**Figure 2**

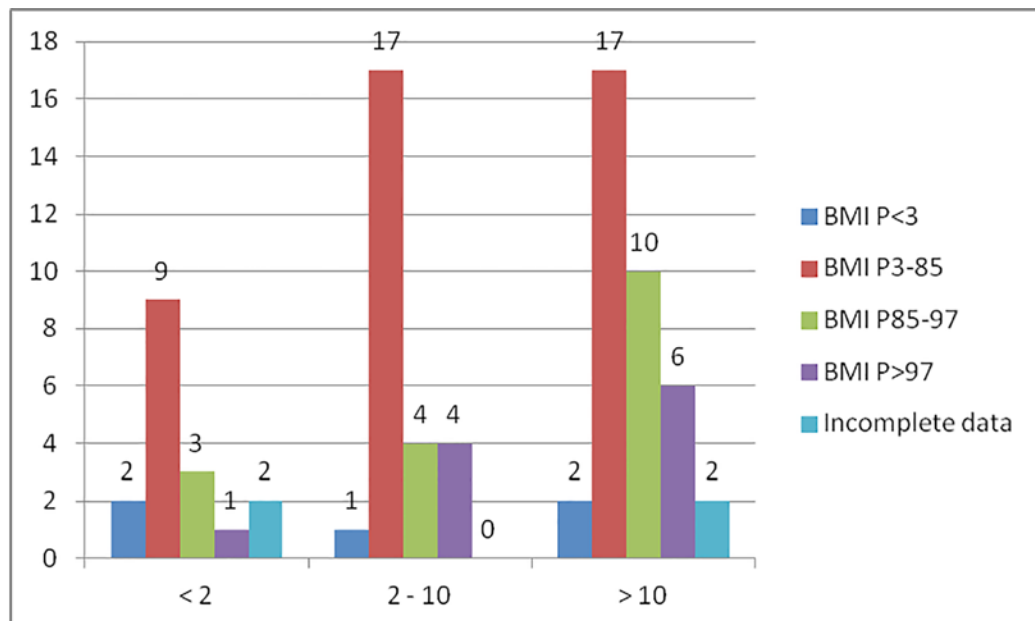
BMI distribution (%) through 2008-2017



\* Mann-Whitney U Test (p=0.653)

**Figure 3**

BMI distribution by age group (years-old)



BMI: Body mass index; P: percentile

**Table I**

Clinical history, calculi characteristics and etiology

Clinical history		n (%)
Dietary errors		33 (41)
Positive family history of stone disease		41 (51)
Presenting symptoms	Flank or abdominal pain and restlessness	35 (44)
	Urinary tract infection	15 (19)
	Spontaneous passage of stone	4 (5)
	Hematuria	3 (4)
	Enuresis / Urinary incontinence	3 (4)
	Nausea and vomiting	1 (1)
	Asymptomatic	19 (24)
Location of calculi	Upper tract	68 (85)
	Lower tract	7 (9)
	Both	5 (6)
	Bilateral	47 (59)
	Unilateral	33 (41)
Number of calculi	1	19 (24)
	> 1	61 (76)
Size of calculi	≤3 mm	34 (43)
	>3 mm	46 (57)
	Maximum	40 mm
Hydronephrosis		18 (23)
<b>Etiology</b>		
Metabolic abnormality		43 (54)
Urinary tract infection		20 (25)
Prematurity		10 (13)
Structural/functional (stasis)		8 (10)
Pharmacologic		8 (10)
Idiopathic		12 (14)

**Table II**

Metabolic etiology in the group with metabolic abnormalities (n=43)

Metabolic evaluation	n (%)
Isolated anomaly	24 (56)
Hypocitraturia	12 (28)
Hypercalcuria	7 (16)
Hyperoxaluria	3 (7)
Hyperuricosuria	1 (2)
Cystinuria	1 (2)
More than one anomaly	19 (44)
Hypercalcuria + hypocitraturia	6 (14)
Hypercalcuria + hyperuricosuria	2 (5)
Hypercalcuria + hyperoxaluria + hyperuricosuria	2 (5)
Hypercalcuria + hyperuricosuria + hyperphosphaturia	1 (2)
Hypercalcuria + Hypomagnesuria	1 (2)
Hypocitraturia + hyperoxaluria	2 (5)
Hypocitraturia + hyperuricosuria + hyperoxaluria	3 (7)
Hypocitraturia + hyperoxaluria + hypomagnesuria	1 (2)
Hypocitraturia + hyperuricosuria + hyperphosphaturia	1 (2)
Urinary calcium/citrate > 0.33	24 (57)

n=15) (Table I). Two patients had hypertension; one had chronic renal disease and the other an ureteropelvic junction syndrome. Four patients (5%) had spontaneous passage of stone (Table I).

In 24% (n=19) there were no symptoms and lithiasis was detected by ultrasound performed for syndromic diseases or structural malformations (11%, n=9), recurrent UTI evaluation (5%, n=4), prematurity follow-up (4%, n=3), tubulopathy investigation (3%, n=2) and inflammatory bowel disease (1%, n=1).

The upper urinary tract was the most commonly affected site (85%, n=68) (Table I).

### ■ Etiology

Multiple etiological factors were present in 34% (n=27) of patients. In 54% (n=43), urine evaluation revealed a metabolic disturbance (Tables II and III) and the majority (56%, n=24) had a single disturbance. Globally, the most common metabolic abnormalities were hypocitraturia (63%, n=27), followed by hypercalcuria (44%, n=19), hyperoxaluria (28%, n=12) and hyperuricosuria (28%, n=12). Lithogenic risk was present in 56% (n=24). No gender ( $p=0.759$ ) or age ( $p=0.719$ ) with statistically significant predominance was observed (Table III). In a logistic-regression analysis adjusted for age, sex, weight, dietary errors, type of calculi and recurrence of symptoms, a known family history of nephrolithiasis was associated with an increased risk for a metabolic cause (odds ratio = 6.86; 95% confidence interval, 1.663-28.302;  $p<0.001$ ).

UTI was the second most significant etiology (25%, n=20) and functional/structural urinary anomalies were also an important cause (10%, n=8). Children below 2 years of age were more likely to have UTI as a cause ( $p=0.001$ ), without gender predominance ( $p=0.238$ ) (Table IV). *Proteus mirabilis* was the most frequent agent identified.

Other identified causes included prematurity and medications, such as vitamin D and corticosteroids (Table I).

In 14% (n=11) none of the previously mentioned causes were identified and therefore were considered idiopathic. Recognized possible risk factors for these cases were low urinary volume (55%, n=6), other dietary errors (55%, n=6) and family history of urolithiasis (36%, n=4). In the majority of these (63%, n=7), lithiasis

reduction or disappearance was observed and only two had recurrence.

**Table III**

Univariate analysis in patients with metabolic disturbances.

		Metabolic diagnosis			
		Yes (n=43) n (%)	No (n=37) n (%)	p	
Gender	Female	19 (44)	15 (41)	0.759*	
	Male	24 (56)	22 (59)		
Age at diagnosis	< 10 years	22 (52)	21 (51)	0.719*	
	≥ 10 years	21 (49)	18 (49)		
Body mass index	BMI < p85	25 (58)	23 (62)	0.483*	
	BMI ≥ p85	18 (42)	14 (38)		
Dietary errors	Yes	22 (51)	10 (27)	0.032*	
	No	21 (49)	27 (73)		
Calculi	Solitary	8 (19)	11 (30)	0.118*	
	Multiple	35 (81)	26 (70)		
	Unilateral	16 (42)	17 (46)		0.372*
	Bilateral	25 (58)	20 (54)		
Recurrence	Yes	15 (35)	7 (19)	0.054*	
	No	28 (65)	30 (81)		
Family history of urolithiasis	Yes	30 (70)	12 (32)	0.001*	
	No	13 (30)	25 (68)		
Surgical treatment	Yes	11 (26)	12 (32)	0.595*	
	No	32 (74)	25 (68)		

\* Chi-Square Test

**Table IV**

Univariate analysis in patients with an infectious cause.

		Infectious diagnosis			
		Yes (n=20) n (%)	No (n=60) n (%)	p	
Gender	Female	6 (30)	27 (45)	0.238*	
	Male	14 (70)	33 (55)		
Age at diagnosis	< 2 years	10 (50)	7 (12)	0.001*	
	2-9 years	5 (25)	21 (35)		
	≥ 10 years	5 (25)	32 (53)		
Calculi	Solitary	4 (20)	15 (25)	0.649*	
	Multiple	16 (80)	45 (75)		
	Unilateral	7 (49)	24 (42)		0.120*
	Bilateral	9 (51)	33 (58)		
Recurrence	Yes	3 (15)	19 (32)	0.086*	
	No	17 (85)	41 (68)		
Family history of urolithiasis	Yes	8 (40)	33 (55)	0.249*	
	No	12 (60)	27 (45)		
Surgical treatment	Yes	12 (60)	11 (18)	<0.001*	
	No	8 (40)	49 (82)		

\* Chi-Square Test

## ■ Dietary errors and urinary output

Dietary errors were identified in 34% (n=27): excessive dairy products in 67% (n=18); reduced water intake in 48% (n=13); reduced fruit and vegetables in 33% (n=9); excessive phytate containing beverages in 19% (n=5), high intake of animal proteins in 15% (n=4); excessive salt 15% (n=4); excessive chocolate 7% (n=2). Patients with dietary errors had a more frequent familial history of kidney stone (p=0.017) and a metabolic abnormality (p=0.032) (Table III).

Of the 68 patients evaluated for urinary output, we found that 37% (n=25) had low urine output (<1 ml/kg/h).

## ■ Stone analysis

Stone analysis (Tables V and VI) was available for 28% (n=22) (stone size 3-40 mm), revealing a calcium carbonate oxalate and/or mineral calcium oxalate composition in more than half. The calcium carbonate composition was more frequently encountered in the female gender (p=0.044) and the struvite composition in children less than two years old (p=0.037). Struvite calculi were associated with infectious causes (p=0.033).

## ■ Evolution through the study period

By dividing the sample in two groups – patients followed between 2008-2012 and 2013-2017 – we found that median age at diagnosis was significantly different (p=0.019): 5 years-old in the first group and 10 years-old in the latter, meaning adolescents became more frequently affected in recent years. Although we observed a gradual increase in overweight/obesity ratio throughout the study period, it was not more frequent in 2013-2017 (p=0.653). In the 2008-2012 group, an infectious etiology was more frequent (p=0.043) (Table VII).

**Table V**

Stone analysis (n=25).

Stone analysis			
Components	n (%)	Major Component	n (%)
One	16 (64)	Hydrated calcium oxalate and/or mineral calcium oxalate	14 (56)
Two	5 (20)	Struvite	6 (24)
Three	1 (4)	Cystine	1 (4)
Inconclusive/not tested	3 (12)	Uric acid	1 (4)

**Table VI**

Calculi composition and risk factors

		Calculi composition					
		Calcium carbonate			Struvite		
		Yes n (%)	No n (%)	P	Yes n (%)	No n (%)	P
<b>Gender</b>	Female	6 (50)	0 (0)	0.044#	0 (0)	6 (43)	0.077*
	Male	6 (50)	7 (100)		5 (100)	8 (57)	
<b>Age at diagnosis</b>	< 10 years	7 (58)	6 (86)	0.216*	4 (80)	9 (64)	0.516*
	≥ 10 years	5 (42)	1 (14)		1 (20)	5 (38)	
	< 2 years	1 (8)	3 (43)	0.117#	3 (60)	1 (7)	0.037#
	≥ 2 years	11 (92)	4 (57)		2 (40)	13 (93)	
<b>Infections diagnosis</b>	Yes	5 (42)	5 (71)	0.210*	5 (100)	5 (36)	0.033#
	No	7 (58)	2 (29)		0 (0)	9 (64)	
<b>Body mass index</b>	BMI < p85	6 (50)	4 (57)	0.502*	2 (40)	8 (57)	0.800*
	BMI ≥ p85	6 (50)	3 (43)		3 (60)	6 (43)	
<b>Dietary errors</b>	Yes	3 (28)	3 (43)	0.409*	2 (40)	4 (29)	0.409*
	No	8 (72)	4 (57)		3 (60)	10 (71)	
<b>Calculi</b>	Solitary	3 (25)	3 (43)	0.419*	2 (40)	4 (29)	0.435*
	Multiple	9 (75)	4 (57)		3 (60)	10 (71)	
<b>Recurrence</b>	Yes	3 (25)	2 (29)	0.865*	1 (20)	4 (29)	0.709*
	No	9 (75)	5 (71)		4 (80)	10 (71)	
<b>Family history of urolithiasis</b>	Yes	5 (46)	4 (57)	0.858*	3 (60)	5 (39)	0.200*
	No	6 (54)	3(43)		2 (40)	8 (61)	
<b>Surgical treatment</b>	Yes	7 (58)	17 (29)	0.568*	4 (80)	8 (57)	0.363*
	No	5 (42)	41 (71)		1 (20)	6 (43)	

\* Chi-Square Test, # Fisher's Exact Test

**Table VII**

Groups comparison by years of study.

		Period of diagnosis		
		2008-2012 (n=22) n (%)	2013-2017 (n=58) n (%)	P
<b>Gender</b>	Female	6 (27)	27 (47)	0.118*
	Male	16 (73)	31 (53)	
<b>Age at diagnosis</b>	< 10 years	13 (62)	29 (50)	0.019*
	≥ 10 years	8 (38)	29 (50)	
<b>Infections diagnosis</b>	Yes	9 (41)	11 (19)	0.043*
	No	13 (59)	47 (81)	
<b>Metabolic diagnosis</b>	Yes	12 (55)	30 (52)	0.821*
	No	10 (45)	28 (48)	
<b>Body mass index</b>	BMI < p85	12 (55)	37 (64)	0.837*
	BMI ≥ p85	10 (45)	21 (36)	
<b>Dietary errors</b>	Yes	8 (36)	25 (43)	0.627*
	No	14 (64)	33 (57)	
<b>Calculi</b>	Solitary	4 (18)	15 (26)	0.471*
	Multiple	18 (82)	43 (74)	
<b>Recurrence</b>	Yes	7 (32)	15 (26)	0.968*
	No	15 (68)	43 (74)	
<b>Family history of urolithiasis</b>	Yes	12 (55)	29 (50)	0.832*
	No	10 (45)	29 (50)	
<b>Surgical treatment</b>	Yes	6 (27)	17 (29)	0.857*
	No	16 (73)	41 (71)	

\* Chi-Square Test

**■ Treatment**

The majority was conservatively treated (71%, n=57). Surgical treatment was performed in 29% (n=23); extracorporeal shock-wave lithotripsy (ESWL) in 14% (n=11) and, due to recurrence or failure of ESWL, 10% (n=8) underwent stent placement and 10% (n=8) open surgeries. The UTI cause was more likely to need surgical treatment (p<0.001) (Table IV).

**■ Outcome**

During follow-up, 63% (n=50) of patients became stone free or diminished in size and 28% (n=22) had

**Table VIII**

Outcome

Outcome	n (%)
Stone free or diminished in size	50 (63)
Recurrence	22 (28)
Obstruction	9 (11)
Renal scarring	9 (11)
Acute renal lesion	2 (3)
Chronic kidney disease	1 (1)

recurrence (Table VIII). No association was found between recurrence and metabolic ( $p=0.054$ ) or infectious ( $p=0.087$ ) causes or dietary errors ( $p=0.927$ ). Complications were observed in 25% ( $n=20$ ): acute renal lesion in 3% ( $n=2$ ), obstruction in 11% ( $n=9$ ), renal scarring in 11% ( $n=9$ ) (Table VIII). One patient developed stage II chronic kidney disease (CKD) at the age of 13 years old, four years after the diagnosis of type 1 primary hyperoxaluria (AGXT homozygous mutation).

## DISCUSSION

### Incidence

Over the last decade an increasing incidence of kidney stone disease in children and adolescents has been reported, between 4 to 10% annually<sup>11,38-40</sup>.

This study is not a population-based study and our results might vary from the overall pediatric stone disease population in Portugal, but it may also reflect an increasing incidence in the general population, as we are one of five Portuguese tertiary pediatric centres. In this study, a gradual increase of 1.2% per year (on average) of the proportion of referrals for nephrolithiasis was observed [minimum 0.3% in 2009 – maximum 11.8% in 2017]. The higher incidence may be explained by various reasons, including dietary errors<sup>12,15,27-30</sup>, but we did not identify any significant cause in the study's second half group.

### Age

Most pediatric series note a significant number of adolescents with kidney stones<sup>36</sup>. In our group, 46% were over 10 years. We ascertained a higher median age of presentation (10 vs 5 years-old,  $p=0.019$ ) and a higher adolescents proportion in the 2013-2017 group. Tasian *et al.*<sup>38,39</sup> found a 52% higher annual incidence of nephrolithiasis among 15 to 19-year-old females than males the same age. Also, Dwyer ME's study<sup>40</sup> had 36% of patients aged 12 to 17 years old and showed a three-fold increased incidence in adolescents, while it remained stable in the younger age groups. However, the authors did not find a specific reason for this increase. In our population, we observed a decrease in infectious causes in the second half of the study ( $p=0.043$ ), which was in relation with younger ages (<2 years-old,  $p=0.001$ ).

### BMI and obesity

Also, although not statistically significant, we noticed an increase in the proportion of patients with excessive weight and obesity.

It has been hypothesized that the rising incidence of stone disease in pediatric populations is related to childhood obesity, but it still is not consensual, as shown by Dwyer *et al.*<sup>40</sup> and, more recently, by Issler *et al.*<sup>41</sup> an increased incidence with normal average BMI. We also did not set a significant correlation between BMI > P85 and age or BMI > P85 and the 2013-2017 group, although we noted a gradual increase of the ratio of patients above P85 for weight.

### Etiology

#### Metabolic

The majority (54%) had a metabolic disturbance that was significantly related to family history of nephrolithiasis ( $p=0.001$ ) and to dietary errors ( $p=0.032$ ). A single disturbance was identified in 56% of these patients. Overall, our most common metabolic disturbances were hypocitraturia (34%) and hypercalcuria (24%). Indeed, metabolic disturbances are the most recognized causes of nephrolithiasis worldwide. Between 33 to 56% pediatric patients have an identifiable underlying metabolic risk factor<sup>18,39</sup> and, in general, these are more likely in younger patients. The contribution of environmental factors, such as family diet patterns and dietary errors, are well recognized and our findings are in close accordance with previous studies<sup>27,29,42</sup>.

The relationship between metabolic disorders, dietary errors and family kidney stone history in our population probably reflect the family lifestyle pattern. On the other hand, we find that this higher risk is likely due to a combination of environmental exposures and genetic predisposition to calcium oxalate stone formation in families. Unlike the Sas DJ review<sup>5</sup>, our results did not show that metabolic causes were more prevalent in younger patients or in the more recent group.

Hypercalciuria and hypocitraturia are the most frequent metabolic causes of pediatric urolithiasis, reported between 7-66%<sup>39,41,44</sup> and 38-63%<sup>36,41,44</sup>, respectively. Moreover, Gürgöze *et al.*<sup>36</sup> identified hypocitraturia as the first metabolic cause (42%) compared to hypercalciuria (25%). Our findings are in agreement with these results (hypocitraturia 34%, hypercalciuria 24%).



### Urinary tract infection

Infectious stones were found in 25% of our population and were more likely in patients under 2 years old ( $p=0.001$ ), consistent with the 22% rate and younger age (median age 4 years versus 5.2 years metabolic group) observed by Issler *et al.*<sup>40</sup>. We observed a decrease in infectious causes throughout the study ( $p=0.043$ ), which is in close accordance with the pediatric etiologic shift from predominantly infectious to metabolic causes<sup>15,16</sup>.

### Idiopathic

In 14% we found no etiology. In the group study by Issler *et al.*<sup>41</sup>, 44% had no metabolic or infectious stones. Within this group, 19% had a primary renal structural malformation and 17% were premature and/or exposed to prolonged immobilisation. In our population, 13% were born prematurely and 10% had structural malformations, probably explaining our low rate of idiopathic cases. Nevertheless, none had a kidney stone analysis performed, which would have been helpful for a diagnosis. Sáez-Torres *et al.*<sup>31</sup> suggested that low urinary volume might be the most important risk factor for stone formation in healthy individuals. Besides familial history and dietary errors, this was the most frequently recognized nephrolithiasis risk factor observed in this group (55%), although no statistically significant association was found. Indeed, in our entire sample, 37% had a low urinary volume.

### ■ Stone composition

In developed countries, calcium oxalate is the predominant stone constituent and the vast majority has mixed compositions<sup>41,42</sup>, similarly to our results. Moreover, bilateral stone disease was recognized in our population in 59%. In the Issler study group<sup>41</sup>, bilateral stones were found in 26% and were associated with metabolic causes. In our study, 58% of the population with metabolic disease had bilateral nephrolithiasis.

Furthermore, we found that struvite calculi were more frequent in children less than 2 years old ( $p=0.037$ ) and correlated with infectious causes ( $p=0.033$ ), regardless of gender. It may be explained by more common infections of the urinary tract in younger children and is in agreement with Kirejczyk JK findings<sup>44</sup>.

### ■ Outcome

Kidney stone disease has been associated with adulthood-increased risk of coronary heart disease,

CKD and hypertension<sup>45</sup> and therefore a correct investigation and management are of higher importance. In our cohort, no cases developed hypertension. However, before the nephrolithiasis diagnosis, two patients followed for nephro-urologic disease already presented hypertension and one CKD, representing an additional cardiovascular risk. One patient, with primary hyperoxaluria, progressed to CKD. In fact, inherited metabolic disorders such as primary hyperoxaluria are rare but important causes of CKD in children<sup>8</sup> emphasizing the importance of a thorough metabolic evaluation.

Moreover, as metabolic disorders are more common in children, the risk of recurrence is higher than in adults<sup>15,41,42,46,47</sup>. We observed a 28% recurrence rate, but no significant specific cause was set. Among Tasian *et al.* group<sup>38</sup>, 24% developed symptomatic recurrent stones over the follow-up, with 50% presenting symptomatic recurrence three years after the first episode. The author also observed that completing a 24-hour urine analysis was associated with a 60% decreased risk of recurrence, again enhancing the value of the metabolic investigation.

### ■ Limitations

The retrospective nature of this study is its primary limitation: first, complete metabolic work-up (magnesiumuria and phosphaturia) was not systematically performed but this fact was also pointed out by Issler *et al.*<sup>41</sup>; secondly, dietary intakes were estimated and not evaluated through a validated questionnaire.

Besides, this is not a population-based study and our results may vary from the overall pediatric Portuguese nephrolithiasis epidemiology.

Finally, genetic studies were sporadic, explaining why only one patient from the hyperoxaluria group had a genetic confirmation, and this might be relevant in positive family history cases with no other identified risk factor.

### ■ CONCLUSION

In conclusion, nephrolithiasis referrals' increased throughout the study period. Infectious causes predominate at younger ages and decreased throughout the study. Metabolic abnormalities were the most frequent cause. As they usually are responsible for

nephrolithiasis appearance, a complete screening in children is of crucial importance. To prevent recurrence, renal scarring and cardiovascular events, educating and promoting a healthy life style is a primary priority.

### ■ Contributions of all authors

Joana V. Andrade: Bibliographic research, study design, data collection, statistical analysis of the results, article script and critical revision.

Sofia Bota: Bibliographic research, study design, data collection, statistical analysis of the results, article script and critical revision.

Telma Francisco: Bibliographic research, study design, data collection, statistical analysis of the results, article script and critical revision.

Raquel Santos: Bibliographic research, study design, data collection, statistical analysis of the results, article script and critical revision.

Gisela Neto: Bibliographic research, study design, data collection, statistical analysis of the results, article script and critical revision.

Margarida Abranches: Bibliographic research, study design, data collection, statistical analysis of the results, article script and critical revision.

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