Review Article

Imaging modalities and treatment of paediatric upper tract urolithiasis: A systematic review and update on behalf of the EAU urolithiasis guidelines panel

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Summary

Background
Prompt diagnosis and treatment of paediatric urolithiasis are required to avoid long term sequelae of renal damage.

Objective
To systematically review the literature regarding the diagnostic imaging modalities and treatment approaches for paediatric urolithiasis.

Study design
PubMed, Science Direct, Scopus and Web of Science were systematically searched from January 1980—January 2019. 76 full-text articles were included.

Results
Ultrasound and Kidney-Ureter-Bladder radiography are the baseline diagnostic examinations. Non-contrast Computed Tomography (CT) is the second line choice with high sensitivity (97—100%) and specificity (96—100%). Magnetic Resonance Urography accounts only for 2% of pediatric stone imaging studies. Expectant management for single, asymptomatic lower pole renal stones is an acceptable initial approach, especially in patients with non-struvite, non-cystine stones<7 mm. Limited studies exist on medical expulsive therapy as off-label treatment. Extracorporeal shock wave lithotripsy (SWL) is the first-line treatment with overall stone free rates (SFRs) of 70—90%, retreatment rates 4—50% and complication rates up to 15%. Semi-rigid ureteroscopy is effective with SFRs of 81—98%, retreatment rates of 6.3—10% and complication rates of 1.9—23%. Flexible ureteroscopy has shown SFRs of 76—100%, retreatment rates of 0—19% and complication rates of 0—28%. SFRs after first and second-look percutaneous nephrolithotomy (PNL) are 70.1—97.3% and 84.6—97.5%, respectively with an overall complication rate of 20%. Open surgery is seldom used, while laparoscopy is effective for stones refractory to SWL and PNL. Limited data exist for robot-assisted management.

Conclusions
In the initial assessment of paediatric urolithiasis, US is recommended as first imaging modality, while non-contrast CT is the second option. SWL is recommended as first line treatment for renal stones <20 mm and for ureteral stones<10 mm. Ureteroscopy is a feasible alternative both for ureteral stones not amenable to SWL as well as for renal stones <20 mm (using flexible). PNL is recommended for renal stones >20 mm.

Introduction

The true incidence of nephrolithiasis in children remains unclear due to the global lack of large epidemiologic studies. Data derived from nation-wide epidemiologic studies [1], studies performed in different counties worldwide [2—4], or large-scale databases [5,6] indicate that the incidence and prevalence of paediatric urinary stone disease has increased over the last decades. Although boys in the first decade of age are still more commonly affected [7] the greatest increase in incidence has been seen in older female adolescents [2,3,8].

Stone composition is similar in children compared to adults [9]. Calcium is the main component of urinary stones with 75—80% of stones composed predominantly from calcium oxalate, 5—10% from calcium phosphate while 10—20% are struvite stones, 5% are uric acid and 1—5% are cystine stones [10]. Compared to historical data, metabolic abnormalities responsible for stone formation are less commonly identified in children nowadays

[11—13]. Hypocitraturia, low urine volume and hypercalciuria predominate [11—13]. Age may affect the predominant metabolic abnormality with hypercalciuria and hypocitraturia being the most common disorder present in children ≤10 and >10 years old, respectively [13]. Genetic or systemic diseases (e.g. Cystinuria or Nephrocalcinosis) contributing to stone formation are rare in children accounting for less than 17% of the identifying causes [11—14]. The role of diet remains unclear in children although there is some evidence that children are drinking less water and taking greater daily amounts of sodium than is recommended [15—17].

Children with urinary stones can be asymptomatic or present with non-specific symptoms that necessitate a high index of suspicion for proper diagnosis [18]. Symptoms are age-dependent with infants presenting with crying, irritability and vomiting in 40% of the cases [19] while in older children flank pain, non-glomerular micro or gross-haematuria and recurrent urinary tract infections are more common [20,21]. Children can also present with recurrent urinary tract infections which can lead to imaging exams and eventually stone identification, while acute renal failure or urine retention due to urethral obstruction are rare events [22].

Paediatric stone disease has a high recurrence with reported rates after complete clearance as high as 55% at 5 years [23]. In order to reduce these high recurrence rates, a meticulous diagnostic approach and the utilization of the appropriate treatment modality are of utmost importance, including metabolic evaluation. First-line imaging techniques aim to minimize the radiation exposure while the application of minimally invasive endoscopic treatments especially with the miniaturization of instruments can achieve high stone free rates (SFRs) with minimal complications.

This systematic review was performed by the European Association of Urology (EAU) Urolthiasis Guideline Panel as part of its update for 2019 and aimed to provide a comprehensive update of the imaging and stone removal modalities in paediatric urolithiasis.

Materials and methods

Search strategy

A systematic review of the literature using PubMed, Science Direct, Scopus and Web of Science from January 1980 up to January 2019 was performed. Separate searches for each diagnostic and treatment modality were performed applying the following Medical Subject Headings: ("Ultrasound", "kidney-ureter-bladder radiography", "urography", "computed tomography", "magnetic resonance urography", "expulsive therapy", "shock wave lithotripsy", "ureteroscopy", "percutaneous nephrolithotomy", "retrograde intrarenal surgery", "open stone surgery", "laparoscopic stone surgery") and "children". The review was carried out in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses guidelines. Two reviewers (N.G. and T.D.) independently screened titles and abstracts of all citations identified by the search strategy. Full-text copies were also assessed and

disagreements were resolved by a senior panel member. A data extraction form was developed to record the data on characteristics of participants, imaging-interventions and outcomes. Imaging studies using all different imaging methods and reporting stone detection rates (in terms of sensitivity and specificity) and radiation doses as well as treatment studies (conservative and surgical) reporting SFRs and complication rates were included. 2017 records were identified through database searching, 689 abstracts were screened, 404 full texts were assessed for eligibility and 76 studies were finally included (Supplementary Fig. 1). There was extremely high heterogeneity among included studies due to clinical variation in patients' characteristics (such as age) as well as in the application of different imaging modalities and interventions.

Results

Diagnostic imaging

In the imaging evaluation of children, radiation risks need to be considered carefully since children will often need repeat radiological examinations over their lifetimes. The cumulated radiation dose has been associated with an elevated lifetime risk for cancer development [24].

Ultrasound (US)
US is the initial diagnostic examination with the advantages of being easily available and with no radiation exposure for the patient [10]. Although its accuracy is dependent on the physicians experience, sensitivity and specificity for the detection of renal stones are 61—93% and 95—100% respectively [25]. Stones are seen as echogenic foci with posterior acoustic shadow while pelvi-calyceal dilatation is a sign of stone obstruction [26]. The detection rate is much higher for stones in the kidney compared to the ureter [27].

Kidney-ureter-bladder (KUB) radiography
KUB is usually the baseline study in the evaluation of stones with sensitivity and specifity of 69% and 82%, respectively [28,29]. The associated radiation dose is about 0.5 mSv [30].

Calcium oxalate and calcium phosphate have high mineral density and are radiopaque; struvite and cystine are less dense and therefore more difficult to see on KUB, while uric acid stones are radiolucent [31]. It should be noted that possible misleading phleboliths are not common in children [32]. High sensitivity for the detection of ureteral stones can be achieved by combining KUB with US [33].

Intravenous urography (IVU)
Although IVU was the gold standard for the diagnosis of urolithiasis, nowadays only 3% of children are evaluated with IVU for stone detection [34]. Sensitivity and specificity are 92—98% and 59—100% respectively, while radiation dose is approximately 1.4—1.5 mSv [35].

Computed tomography (CT)
Non-contrast helical CT has the highest sensitivity (97—100%) and specificity (96—100%) for the detection of urinary stones [36,37]. Its use as initial examination is

increasing. In a study with 9228 children from 2003 to 2011, 63% underwent a CT examination as the initial diagnostic test for suspected nephrolithiasis vs 24% who were evaluated with US [34]. Nevertheless, the potential danger of developing a hematologic or solid malignancy, especially among those who are frequently exposed to ionizing radiation has led to the adoption of ultra-low dose protocols (0.5 mSv versus 5—8 mSv of standard CT) aiming to reduce the radiation dose without limiting imaging quality [38,39]. CT has been also suggested prior to PNL in children to avoid colon injuries [40].

Magnetic resonance urography (MRU)
Despite the avoidance of radiation exposure, MRU accounts only for 2% of pediatric stone imaging studies [41]. Gadolinium-enhanced excretory MRU has shown 90—100% sensitivity for urolithiasis diagnosis, while it is also effective in identifying the anatomical position (100% sensitivity) and the severity of an obstructing pathology [42]. Limitations such as the longer examination duration, the potential need for general anaesthesia, the motion artifacts and the high cost are definitely an impediment to the widespread use of MRU.

Management of urolithiasis in children

Management of urolithiasis in children depends on the stone size, location and composition, the anatomy of the urinary tract and co-existing metabolic disorders.

Conservative management
There is a lack of evidence on conservative management of paediatric stones with evidence for ureteric calculi coming from the placebo arms of medical expulsive trial while for renal stones from small cohort studies either on primary stones [43,44] or residual fragments remained after extracorporeal shock wave lithotripsy (SWL), retrograde intrarenal surgery (RIRS) or percutaneous nephrolithotomy (PNL) [45]. Expectant management for single, asymptomatic lower pole renal stones could be the initial approach with increased odds of stone passage especially in patients with non-struvite, non-cystine stones smaller than 7 mm, with no anatomic abnormalities [43]. Intervention may be needed for stones located elsewhere independently of their size [43—45]. Dangle et al. showed that ureteral stones had a threefold higher probability for spontaneous passage compared to renal stones, with a size of 3.5 mm as the cut-off limit for spontaneous passage of ureteral stones [46].

Medical expulsive therapy (MET)
There are limited studies on MET as off-label expulsive therapy for children with stones which show conflicting outcomes. A recent meta-analysis of five trials showed that adrenergic alpha-antagonists (tamsulosin 0.2—0.4 mg/day and doxazosin 0.03/mg/kg/day) are effective for MET increasing SFR compared to control (OR = 2.7, p = 0.001) without significantly increasing the treatment-emergent adverse events (OR = 2.01, p = 0.17) [47]. Similarly, an updated systematic review of six placebo-controlled studies showed that alpha-blockers might increase SFR of distal ureteric stones (RR 1.34, 95% CI 1.16 to 1.54; low-

quality evidence) [48]. Due to study limitations and very serious imprecision no conclusion could be drawn regarding the effect of MET on hospital stay, pain episodes or secondary procedures for residual fragments after definitive stone treatment [48].

Extracorporeal shock wave lithotripsy (SWL)
SWL is still the first-line treatment for renal stones <20 mm and for most ureteral stones in children, mainly due to its less invasive character. However, it is less likely to be successful for stones >10 mm in diameter, impacted stones, calcium oxalate monohydrate or cystine stones, or for stones in children with unfavourable anatomy and in whom localisation is difficult [49].

Studies on SWL in children suggest a SFR of 43.8%—82.4% after a single session, reaching an overall SFR of 70—90% after multiple sessions. Retreatment (repeat SWL, URS, PNL) rate ranges between 4 and 50% and need for auxiliary procedures (usually double-J stent) between 4 and 12.5% [50—56] (Table 1). A meta-analysis of 14 studies reporting on 1842 paediatric patients treated with SWL found significantly higher SFR for stones <10 mm than for stones >10 mm and higher retreatment rates as the stone size increased [49]. Although slow-rate of shock-wave delivery (60—80 shockwaves/second compared to 90—120 shockwaves/second) may improve SFR [57,58] a recent meta-analysis on slow shock wave lithotripsy versus rapid shock wave lithotripsy for renal stones revealed very low quality of evidence about the effects of SWL on SFR, serious adverse events or complications of treatment and secondary procedures for residual fragments [48]. SWL is well tolerated by children with complication rates rising up to 15% in modern series; most in the form of ureteral obstruction secondary to steinstrasse formation [59]. Whilst administration of SWL to children often requires a general anaesthesia, improvements in modern (second and third generation) lithotripters, mean that successful treatment using intravenous sedation, patient-controlled analgesia or no medication at all has been increasingly performed in a select population of older, co-operative children [60].

Based on the results of a recent meta-analysis which compared SWL to dissolution therapy for intrarenal stones and SWL to ureteroscopy with holmium laser or pneumatic lithotripsy for renal and distal ureteric stones no certain conclusions can be drawn about the effects of SWL on stone-free rate (SFR), serious adverse events or complications of treatment and secondary procedures for residual fragments [48].

When SWL was compared to mini-percutaneous nephrolithotripsy for lower pole renal stones 1—2 cm in size SWL resulted in lower SFR (RR 0.88, 95% CI 0.80 to 0.97; moderate quality evidence) and higher rates of secondary procedures (RR 2.50, 95% CI 1.01 to 6.20; low-quality evidence). However, SWL showed less severe adverse events (RR 0.13, 95% CI 0.02 to 0.98; low quality evidence) [61].

Semi-rigid ureteroscopy (URS)
In recent years ureteroscopy is increasingly used in children with ureteral stones especially for those not amenable to SWL [62]. URS proved to be effective with SFR of 81—98% [62—65], retreatment (repeat URS or SWL) rates of 6.3%—

Table 1 Summary of shockwave lithotripsy outcomes.

Study	N	Mean age (years)	Mean stone size (mm)	Success rate (%) after single session	Overall success rate after multiple sessions (%)	Retreatment rate (%)	Auxiliary treatment rate (%)	Complications rate (%)		Lithotripter	Follow-up (months)
								Clavien 1 + 2	Clavien 3 + 4		
Salem 2014 [57]-80 Shock waves/min	30	5.35	15.02	60	90	40	10	6.67	0	Dornier Lithotripter S	NR
Salem 2014 [57]-120 Shock waves/min	30	6.67	13.85	26.6	73.3	73.33	26.7	13.33	0	Dornier Lithotripter S	NR
Dogan 2015 [50]	383	4	9	60	70	40	6.5	0.7	6.5	Siemens LithostarModularis	11
Alsagheer 2017 [51]	100	6	13.1	47	90	50	4	19	4	Dornier Gemini	3
Kaygisiz 2018 [58]-60 Shock waves/min	30	3 (median age)	9.57	46.6	80	43.3	10	13.3	0	Elmed Medical Systems Electrohydraulic	NR
Kaygisiz 2018 [58]-90 Shock waves/min	27	6 (median age)	10.41	37.7	74.1	55.6	14.8	3.7	0	Elmed Medical Systems Electrohydraulic	NR
Zeng 2012 [52]	22	1.96	21.7	50	86.3	50	4.5	27.3	18.2	Dornier Compact Delta-lithotripter	3
Badawy 2012 [53]-Kidney stones	500	8.63	9.8	82.4	89	6.6	2.2	6.8	1.2	Siemens LithostarModularis	NR
Jee 2013 [54]	55	8.5	9.4	NR	90.9	NR	NR	1.8	3.6	Medispec Extracorporeal Shockwave Lithotripter E-3000	3
Dobrowiecka 2018 [59]	170	10	NR	NR	94.3	NR	NR	5.6	11.6	Lithoskop Siemens multi-function lithotripter	NR
Cevik 2018 [60]	251	4.5	7.08	NR	NR	NR	NR	NR	NR	Dornier Compact Sigma	NR
Kumar 2015 [61]	106	10.7	12.9	58.5	83	41.5	14.2	2.8	0.9	Dornier Alpha Compact	3
Habib 2013 [56]	150	6.6	13.5	50.5	89.24	NR	4	12	0	Dornier electromagnetic Do Li S lithotripter	13
ElSheemy 2016 [55]	64	4.06	14.87	43.8	81.2	50	9.4	9.3	3.1	Dornier electromagnetic Lithotripter S EMSE 220F-XXP	33.14

NR, not reported.

Table 2 Summary of semirigid ureteroscopy outcomes.

Study	n	Mean age (years)	Mean stone size (mm)	Success rate (%)	Retreatment rate (%)	Pre-stenting (%)	Complications rate (%)		Follow-up (months)
							Clavien 1 + 2	Clavien 3 + 4	
Tanriverdi 2010 [66]	33	8.67	9.45	100	12.2	6.1	0	0	3
Dogan 2011 [67]	642	7.5	8.9	92.8	NR	NR	3.6	0.9	13
Wang 2012 [62]	189	11.8	NR	NR	NR	NR	NR	NR	NR
Jurkiewicz 2014 [63]	157	7.5	9.6	98	10	NR	0.6	1.2	NR
Elsheemy 2014 [64]	104	4.7	11	81.25	17.1	NR	23,4	0	6
Gokce 2016 [68]	251	8.9	9.2	80.5	NR	18.7	11.5	2	NR

NR, not reported.

10% [63,66] and complication rates of 1.9−23% [63−65,67] (Table 2). Similar to adults, routine stenting is not necessary before URS. However, pre-stenting may facilitate URS, increase SFR and decrease complication rates [68]. Stenting after ureteroscopy was found to be a strong predictor of retreatment requiring anesthesia, perhaps due to its association with more complex or planned staged procedures [69].

Flexible ureteroscopy (FURS)/retrograde intrarenal surgery (RIRS)

Retrograde intra-renal surgery with flexible ureteroscopes has become an efficacious treatment modality for paediatric renal stones <20 mm. Recent studies report SFR of 76−100%, retreatment (repeat URS, SWL or PNL) rates of 0−19% and complication rates of 0−28% [70−75] (Table 3). Younger age, cystine composition [76], large stone diameter [75] and lack of pre-stenting predispose [68] to FURS failure in children.

Although high level of evidence is lacking to support strong recommendation [48], FURS may be a particularly effective treatment option for lower calyx stones in the presence of unfavourable factors for SWL [65,72,77]. For large and complex kidney stones RIRS has a significantly lower SFR compared to PNL (71% vs 95%), but it is associated with less radiation exposure, lower complication rates and a shorter hospital stay [78].

Similarly, retrospectively derived data indicate that RIRS may achieve lower SFR compared to mini- or micro-percutaneous surgery in favour of shorter operative time, shorter fluoroscopy time and less hospitalization time [79,80]. A recently published meta-analysis confirmed the aforementioned results [81].

Percutaneous nephrolithotomy (PNL)

Indications for PNL in children are similar to those in adults, and include renal stones >2 cm, or smaller stones resistant to SWL and ureteroscopic treatment. Reported SFR with paediatric PNL are 70.1−97.3% after a single session [78−80,82−88] reaching 84.6%−97.5% after second-look PNL [82,85,87], for an overall complication rate of 20% [89] (Table 4). High degree of hydronephrosis, increased number of tracts and operative time [90] and large tract size [91,92] are associated with higher blood loss rates. Older age [93] and higher stone burden [84] predispose to the use of larger instruments during PNL in children. Miniaturisation of equipment increases the opportunity to perform tubeless PNL in appropriately selected children, which can reduce the length of hospital stay and postoperative pain [94,95].

Concerns have been raised regarding possible adverse effects of PNL on the renal parenchyma of the developing child. However, focal damage is only reported in 5% of cases [96]. Using pre- and post-PCNL DMSA scans, Cicekbilek et al. demonstrated that PNL tracts between 12 and 24Ch in size did not cause significant harm to paediatric kidneys [82].

Open and laparoscopic/robot-assisted stone surgery

With the advances in ESWL, PNL and RIRS, very few cases of paediatric urolithiasis require open surgery. Data extracted from the National Inpatient Sample (NIS) databases for 2001−2014 showed that in the USA incisional procedures (mainly nephrolithotomy, pyelolithotomy and ureterotomy) was performed in 2.6% of the hospitalized patients who required surgical intervention for urinary stones [96].

Laparoscopy for the management of paediatric renal and ureteric stones is rare but safe and effective when specific indications are followed. SFRs of up to 100% have been reported for laparoscopic procedures for: a ≥1 cm single stone located in an extrarenal pelvis [97], impacted ureteric stones ≥1.5 cm, ureteric stones refractory to SWL or URS [98]. Although there are extremely limited data available on efficacy and complications of robot-assisted laparoscopic management of paediatric urolithiasis, Swearingen et al. recently concluded that both robotic pyelolithotomy and nephrolithotomy are reasonable options for renal stones removal even among patients who are <18 yrs of age [99].

Discussion

The rarity of diagnostic and therapeutic studies of high-level evidence, lead to uncertainty about the ultimate way to evaluate and treat urinary stones in children. Urinary

Table 3 Summary of flexible ureteroscopy outcomes.

Study	n	Mean age (years)	Mean stone size (mm)	Success rate (%)	Retreatment rate (%)	Pre-stenting (%)	Complications rate (%)		Follow-up (months)
							Clavien 1 + 2	Clavien 3 + 4	
Unsal 2011 [70]	16	4.2	11.5	88	NR	NR	0	6.25	10.3
Cannon 2007 [71]	21	15	12	76	38	38	0	0	11
Erkurt 2014 [72]	65	4.3	14.66	92.3	16.9	26.2	24.6	3	3
Kim 2008 [73]	167	5.2	6.12	97—100	3	56.9	0	0	19.7
Suliman 2018 [74]	36	10.6	8	89	19.64	59	3.6	0	17.1
Xiao 2019 [75]	100	3.51	14.9	89	12	100	69	0	NR
Mokhless 2014 [77] Both semirigid and flexible	30	2.4	NR	86.6	NR	3.3	NR	0	3
Saad 2015 [78]	21	6.44	NR	71	9.5	NR	9.5	0	1
Pelit 2017 [79]	32	3.65	19.3	75	15.6	NR	9.3	3.1	3
Bas 2016 [80]	36	8.39	12.8	86.2	NR	16.7	13.9	2.7	1

NR, not reported.

stone disease is increasingly affecting the pediatric population [5,6]. Symptoms are age-dependent, necessitating a high index of suspicion [18—22]. The onset of urolithiasis in childhood remains one of the main risk factors for stone recurrence [100]. Taking also into consideration that stone disease may affect renal function, leading to chronic kidney disease as well as end-stage renal disease [101], decisive diagnostic, therapeutic and follow-up approaches are mandatory for children with urinary stones. However, as a consequence of the aforementioned necessity, radiation exposure to children with urolithiasis may be increased.

Children are at higher risk to adults for long-term radiation effects such as malignancies [24,102]. A recently published study assessed and evaluated radiation safety in pediatric urology. Study patients had undergone an average of 1.9 fluoroscopy-guided urologic procedures and had averaged 2.7 radiation-based imaging studies over 3.25 years. Of 33 patients with urolithiasis, 22 had diagnostic radiation-based imaging during the study period (66.6%) at an average of 3 studies per child [103].

Ultrasound is the first and safest imaging modality showing high sensitivity and specificity for detecting renal stones [25—27]. To avoid unnecessary radiation exposure the treating physician should decide upon the need for further imaging. Although KUB is related to low-dose exposure the additional diagnostically useful information it provides, must be assessed on a case-by-case basis. It should be used for those children with relative symptoms, hydronephrosis and no detection of stone in the kidney on ultrasound as well as for follow up of radio-opaque stones [104].

Further imaging should be carefully questioned. NCCT scan shows the highest accuracy in stone detection and is increasingly used as the first-line imaging modality in children with stones [36,37]. Low dose protocols should be preferred to standard dose protocols [105]. However, children may still receive unnecessarily high doses of radiation and the physician should carefully consider what additional information he will take from the study. Indeed, in a recently published study, CT examinations of the abdomen and pelvis may lead to absorbed doses of 20 mSv or higher in 25% of children [106]. To avoid radiation exposure and to adhere to ALARA principles routine use of CT for diagnosis and follow-up of urolithiasis in children should be done cautiously.

Differential diagnosis of renal colic from various clinical situations could be an indication for CT scan, especially in the emergency department. CT is often used to diagnose nephrolithiasis in children even though Johnson et al. demonstrated that approximately 90% of children do not require a CT scan for diagnosis [104].

Extracting information for planning surgical approaches, for example, the precise stone burden, the best calyx to puncture or the relation of the colon to the targeted kidney during PNL, could be another indication for a CT scan. We strongly believe that such planning can be done with the intraoperative use of ultrasound and retrograde urography. An RCT comparing SFR, complication rate and radiation exposure, between the use of preoperative NCCT and the combination of intraoperative US and retrograde urography during PCNL in children should be performed. As CT has been increasingly used nowadays for the detection of stones in children we believe that such a study is ethical to design and accomplish.

The management of urolithiasis in children does not differ from the management in adults. Although a size threshold of 3.5 mm was associated with a higher likelihood for spontaneous ureteral stone passage [46] others advocate expectant management for ureteral stones of up to 7 mm [43].

Table 4 Summary of percutaneous nephrolithotomy outcomes.

Study	n	Tract (scope) size (Ch)	Mean age (years)	Mean stone size (mm)	Stone burden (mm)	Success rate after one session of PNL (%)	SFR after second-look PNL	Hospital Stay (days)	Complications rate (%) Clavien 1 + 2	Clavien 3 + 4	Follow-up (months)
Guven 2013 [93]	107	22.9 (NR)	7.1	NR	272	70.1	NR	NR	Transfusion = 9.3% Fever = 14%	NR	NR
Saad 2015 [78]	22	22 (17)	6.93	NR	NR	95.5	NR	2.59	Bleeding = 13.6% Fever = 18.2%	9.09	1
Pelit 2017 [79]	45	20-22 (17)	3.71	21.06	NR	91.1	NR	3.46	15.5	0	NR
Bas 2016 [80]	45	NR	5.62	13.97	NR	80	NR	2.29	11.1	2.2	NR
Cicekbilek 2015 [82]	40	12-24 (11—22)	9.5	34	34.1	95	97.5	3	25	0	7
Daggulli 2016 [83]	40	4.5 (14)	6.3	16.5	16.5	80 (85)	NR	3.8	25	5	1.5
Aghamir 2016 [94] Single-access	70	30 (NR)	NR 46.33 yrs for both groups	27.9	NR	85.7	NR	3.1	7.1	0	1week
Aghamir 2016 [94] Double-access	37	30 (NR)	NR 46.33 yrs for both groups	29.6	NR	97.3	NR	3.2	10.8	0	1week
Celik 2017 [84] Ultra-mini PNL	50	12 (9.5)	6.67	12.61	126.1	78 (96)	NR	5.2	6	0	NR
Celik 2017 [84] Mini PNL	91	20 (18)	9.52	16.67	166.7	75.8 (90.1)	NR	5.2	5.5	0	NR
Celik 2017 [84] Adut-sze PNL	84	26 (24)	10.8	20.89	208.9	71.4 (91.7)	NR	5.7	10.7	0	NR
Dombrovskiy 2018 [89]	3206	NR	NR	NR	NR	NR	NR	3	NR Total complication rate was 20.7%	NR	NR
Senocak 2018 [90]	105	18—24 (15.9—22)	5	NR	218.4	80.95	NR	4	NR 5.71% required transfusion	NR	NR
Iqbal 2018 [95] Tubed PNL	17	23 (20)	9	16	NR	NR	NR	2.8	5.5% transfusion 5.5% fever	0	3 weeks
Iqbal 2018 [95] Tubeless PNL	18	23 (20)	7.5	19	NR	NR	NR	3.1	11,7% tansfusion	0	3 weeks
Daw 2015 [85]	26	26—28 (24)	3.64	19.61	NR	76.9	84.6	3.8	19.2	7.7	25.31
Yan 2012 [86]	20	14—16 (NR)	3.55	18.5	NR	85.2	NR	8.2	NR	NR	38
Zeng 2012 [87]	24	14—18 (8/9.8)	1.92	21.4	NR	84	96	14.13	16	0	21
Bilen 2010 [88]	12	14 (9.5)	3	NR	192 mm^2	91.6	NR	3.1	0	0	NR

Bilen 2010 [88] (nephrostomy) (Tubeless)	14	14 (9.5)	3.3	NR	416 mm²	78.5	NR	4.9	5	1	NR

NR, not reported; PNL, Percutaneous nephrolithotomy.

Medical expulsive therapy seems to be helpful, especially for the distal ureteral stones, but it should be underlined that its use is off-label [47,48]. Expectant management should follow the same rules as we do for adults, meaning that the patient should stay asymptomatic (no pain or fever), with no increasing pelvicalyceal dilation or deterioration of kidney function within the waiting period. The duration until the spontaneous passage is unknown but it is sensible to be around 4–6 weeks, as in adults [107].

Approximately 22% of children diagnosed with nephrolithiasis ultimately undergo surgical intervention [43]. The indications to treat stones do not differ among adults and children. Management depends on stone size, location, and composition. High-quality comparative studies of various treatment modalities are missing both in adults and in children, with the lack being more obvious in children [108].

Radiation exposure should be one of the endpoint results of studies comparing different treatment options of urolithiasis in children. A recently published study showed that radiation exposure to children with urologic diagnostic procedures (median dose 0.6 mGy) and interventions (median dose 0.8 mGy) is not negligible [103]. Overall, the radiation dosage was <1 mGy per case in 67% of cases and exceeded 5 mGy in 5.7% of cases. When excluding PCNL the average dose was 1.32 mGy per case (median 0.56 mGy). Standardization of fluoroscopic settings and written guidelines for radiation-based imaging are urgently needed to minimize radiation exposure to children [103].

As an example of the lack of unanimous glossary within the guidelines of different radiation and pediatric medical societies, a recent study depicted that the readability of the information provided at their websites was difficult to comprehend, especially for the average adult [109].

Although SWL is one of the first treatment options, the effectiveness of SWL for large (>10 mm) stones is low. Stone size and location are the two most important predictors for success for pediatric SWL. Stones <1.1–1.3 cm, located in the renal pelvis have the best outcome when treated with SWL [56]. SWL in children may require anesthesia depending on age and compliance of the child, making it an invasive procedure. The long-term effects of SWL to renal growth remain unclear. Kidneys treated with SWL showed a decrease of 1.26 ± 0.49 SD units below their expected length (p = 0.02), during a 9-year follow-up. The authors were unable to clarify whether this unsettling effect was due to the first-line lithotripter used or to an underlying pathology intrinsic to pediatric kidneys with urolithiasis [110].

The existing studies comparing SWL to ureteroscopy are of low quality and strict conclusions cannot be extracted. As a consequence, well-designed RCTs comparing these two treatment modalities in children are required. Compared to mini PNL, SWL showed lower SFR and higher retreatment rates even for medium-sized (1–2 cm) stones, although complication rates were lower [61]. However, RCTs comparing the efficacy of these two treatment modalities as well as the exposure of children to radiation should be performed.

Semi-rigid and flexible ureteroscopy are increasingly used in children in recent years. We believe that the

experience gained with these operations in adults alongside with the miniaturization of the instruments is responsible for this increase. The aforementioned parameters led to a significant decrease in operative time, the only independent prognostic factor predictive of complications during pediatric semirigid ureteroscopy [67]. The success of fURS in children depends mainly on the stone location and burden [65], while younger children and children with neurogenic bladders or spinal abnormalities are associated with higher rates of complications [65,111].

Our systematic review indicates that the outcome, including the SFR, retreatment rate and complication rate, of ureteroscopy in children, is similar to the outcomes seen in adults. One difference is the repeated exposure to anaesthesia, which can reach 4 sessions; one session for possible presenting, second for URS, third for stent removal (unless a stent with extraction string is used) and even fourth if retreatment is needed. There is limited literature regarding the use of ureteral access sheaths in the paediatric population. In a retrospective study with 40 patients Wang et al. [112] showed that when a sheath was used a higher intraoperative complication rate (15 vs 2%) was observed. However, there was no increase in long term adverse events such as postoperative strictures and hydronephrosis. Radiation exposure during ureteroscopy is not insignificant. Dudnley et al. showed that the skin entrance dose for procedures including unilateral ureteroscopy (median 0.82 mGy, mean 1.21 mGy, range 0.04–4.45) was significantly higher than the dose for bilateral retrograde pyelograms (median 0.50 mGy, mean 0.29 mGy, range 0.07–0.51; $p = 0.04$) [103]. These doses can be significantly reduced by 87% with introduction of a simple checklist to optimize fluoroscopy settings during ureteroscopy [113]. Randomized trials comparing ureteroscopy to SWL and various sized PCNLs, stratified by stone size and location and taking into consideration the radiation exposure to the child, are needed to determine the indications to apply a specific operation.

Similarly to adults, PNL in children is indicated for stones larger than 2 cm. Recent studies have shown that PNL has no adverse effect in the renal function of the developing child [82,96]. Miniaturized equipment is increasingly used but increasing age of the child and stone burden predispose to the use of larger instruments [84,92]. Currently there no RCTs comparing different-sized instruments in a pediatric population. In preschool aged children min PNL with 14–16 Ch access sheath is effective with primary SFRs of 77–85.7% [85,86,88] and 92% after adjunctive SWL [85,86] though SFR is lower for > 2 stones and for stones >30 mm [85]. Tubeless-mini PNL has been also shown to be effective when compared to nephrostomy-mini PNL showing SFRs of 91.6% vs 78.5% with lower complication rates [88]. Fluoroscopy is mostly used during access with modern studies revealing fluoroscopy times <20 s [103], indicating a 95% reduction when compared with older series [114,115], the urologist should be familiar with methods that reduce radiation exposure. Ultrasound-guided puncture, "single-shot" dilation techniques, use of automatic spectral filters, pulsed fluoroscopy, dose display and last-image-hold can all reduce radiation exposure [103].

For initial urinary drainage in children with obstructive anuria and acute renal failure due to bilateral ureteral calculi a nephrostomy tube or a double J stent can be placed. ElSheemy et al. [116] in a prospective randomized trial showed that there was no difference between the two methods regarding operation duration and imaging time as well as in the duration for return to normal creatinine levels (both <72 h). Nephrostomy tube had more complications while stone size >2 cm and grade 2 hydronephrosis were associated with failure in insertion of double J stent and nephrostomy tube, respectively. Regarding subsequent definitive treatment, patients with nephrostomy tube needed more re-interventions to achieve stone clearance while double J stent resulted in lower intervention rates. Double J stent can facilitate bilateral SWL, bilateral URS and chemolytic dissolution of stones and it should be the initial option for drainage in patients who will be treated in one of the above options [116]. However, it should be avoided in stones >2 cm due to the increased iatrogenic risk of mucosal injury to the delicate child ureter.

Conclusions

Compared with the adult literature, paediatric stone diagnosis and treatment publications provide low levels of evidence with small heterogenous studies or case series. In the initial assessment of paediatric urolithiasis, US is recommended as first imaging modality, while non-contrast CT is the second option. SWL is recommended as first line treatment for renal stones <20 mm and for ureteral stones <10 mm, as it is noninvasive and has high SFRs and low complication rates. Ureteroscopy is a feasible alternative for ureteral stones not amenable to SWL while flexible ureteroscopy can be an alternative for renal stones <20 mm. For renal stones >20 mm PNL is recommended, showing favorable efficacy and safety, especially with the continuing miniaturization of instruments.

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Ethical approval

Not required.

Conflict of interest

Aleš Petřík has received speaker honoraria from Olympus Czech Group, S.R.O., Cook Medical Europe Ltd., fellowship and travel grants from Astellas and consultant fees from Olympus and Cook Medical; Christian Seitz has received consultant fees from Astellas and speaker honoraria from Rowa Wagner; Andreas Neisius has received fellowships/travel grants from Storz, Wolf, Astellas, Astellas, Boston Scientific, Novartis, Janssen, Eichard Wolf, Karl Storz, consultant fees from Novartis, MSD, Roche, speaker honorarium from Siemens Healthcare, Pfizer, Astellas, Ferring, Boston Scientific Europe, Pfizer, MSD, Boston Scientific and

has participated in trials for Bayer, Kendle, Merck, Astellas, MSD, Kendle; Kay Thomas has participated in trials for TISU.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpurol.2020.07.003.