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Review

Clinical effectiveness in the diagnosis and acute management of pediatric nephrolithiasis

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HIGHLIGHTS

- The incidence of pediatric nephrolithiasis is rising.
- Children/adolescents represent a unique patient population with higher risks from radiation exposure as compared to adults and high recurrence rate.
- Ultrasound is the first-line modality for diagnosing suspected nephrolithiasis in children.
- First line therapy for stable patients is most cases is observation/analgesics with alpha-blockers as MET.
- Surgical management of pediatric nephrolithiasis is similar to adults with ESWL and URS first-line for smaller stones and PCNL reserved for larger renal stone burden.
- Clinical effectiveness in children/adolescents with nephrolithiasis centers around ED pathways that limit CT imaging, adherence to ALARA principles and use of US during surgical procedures.
- Patient/Family education on the risks of repeat ionizing radiation exposures during follow up is essential.

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ABSTRACT

The incidence of pediatric nephrolithiasis has risen over the past few decades leading to a growing public health burden. Children and adolescents represent a unique patient population secondary to their higher risks from radiation exposure as compared to adults, high risk of recurrence, and longer follow up time given their longer life expectancies. Ultrasound imaging is the first-line modality for diagnosing suspected nephrolithiasis in children. Although data is limited, the best evidence based medicine supports the use of alpha-blockers as first-line MET in children, especially when stones are small and in a more distal ureteral location. Surgical management of pediatric nephrolithiasis is similar to that in adults with ESWL and URS first-line for smaller stones and PCNL reserved for larger renal stone burden. Clinical effectiveness in minimizing risks in children and adolescents with nephrolithiasis centers around ED pathways that limit CT imaging, strict guidance to ALARA principles or use of US during surgical procedures, and education of both patients and families on the risks of repeat ionizing radiation exposures during follow up and acute colic events.

1. Introduction

The increasing burden of nephrolithiasis in the pediatric population has been brought to the foreground recently by several studies showing the rapid rise in the incidence of stone disease in children and adolescents [1–3]. As would be expected from this, the number of hospitalizations, emergency department visits, use of medical therapy and surgical interventions for children with nephrolithiasis have also seen a steady rise [1,3–6]. While the exact etiology for this increasing incidence rate is unclear, the morbidity associated with nephrolithiasis is especially concerning in the pediatric population. Risks from ionizing radiation, especially when repeated, and from surgical interventions may be magnified in children and adolescents both because of physiological differences from adults and because of the longer life expectancy and thus

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longer time period of exposure and follow up [7,8]. In addition to the impact on the pediatric patient, pediatric nephrolithiasis is estimated to cost the United States at least $375 million annually in hospital and emergency department costs [9]. This economic burden is likely even higher when considering outpatient visits, medical therapy and imaging study costs, and missed work/lost wages by caregivers. As a consequence, strategies and protocols to optimize the evaluation and clinical treatment of children and adolescents with nephrolithiasis are necessary. In this review, the clinical effectiveness of diagnostic imaging, medical therapy, and surgical interventions for pediatric nephrolithiasis will be explored, with specific emphasis on minimizing risk in this unique patient population.

2. Epidemiology

As mentioned above, pediatric nephrolithiasis is a growing public health burden with a 6–10% annual rise in incidence over the past 20 years [1,4]. Estimates of contemporary mean annual incidence of pediatric nephrolithiasis range from 36 to 57 per 100,000 children in US population-based observational studies [1,2,4]. In one recent study, the greatest increase in nephrolithiasis was noted among 15–19 year olds where the incidence increased 26% per 5 years from 1997 to 2012 [3]. In addition, this same study observed that annual incidence of stones increased most drastically among adolescent girls and African-Americans. This effect of gender on incidence of pediatric nephrolithiasis has been shown in other studies and interestingly, the risk of stones appears to be higher among boys in the first decade of life and among girls in the second decade of life [3,10]. The incidence of stone disease shifts towards a male predominance around 26 years of age, which is sustained throughout adulthood. The association between body mass index (BMI) and pediatric nephrolithiasis has been a controversial topic with the majority of studies showing no association between the two [2,11,12]. In fact, the prevalence of obesity in children and adolescents has remained constant from 1999 to 2010 while the incidence of kidney stone disease has doubled, suggesting other factors may be related to the rise in pediatric nephrolithiasis [13].

3. Acute management

3.1. Diagnostic imaging

In contrast to adults where use of computerized tomography (CT) is widely considered the first-line diagnostic study for the evaluation of suspected nephrolithiasis, ultrasound (US) is recommended as the initial imaging modality [14,15]. The reason for this is that while noncontrast CT has a nearly 100% sensitivity and specificity for detecting nephrolithiasis, there are concerns for cumulative and long-term effects of ionizing radiation including increased risk of cancer [16]. Cancer risk may be even greater in the pediatric population because of the longer life expectancy and the greater sensitivity of developing tissues/organs (ie, higher mitotic rates) to radiation effects.

Although US is less specific and sensitive than CT in detecting urinary tract stones, it does allows direct visualization of urinary stones and of signs of urinary tract obstruction such as dilation of the ureter and/or pelvicalyceal system, increased renal echogenicity, or increased renal size. When compared to the gold-standard of CT, one study noted that ultrasound had a 70% sensitivity, 100% specificity, 96% positive predictive value, and 62% negative predictive value for the detection of urinary tract stones in patients younger than 18 years. Furthermore, the stones that were missed on ultrasound were in most cases clinically insignificant (ie, small in size or non-obstructing) [17]. The use of additional criteria such as renal resistive indices, gray-scale acoustic shadowing and the "twinkling artifact" on color Doppler evaluation have been investigated in adults to help improve the diagnostic accuracy of ultrasound for nephrolithiasis [18–20]. However, to date, no studies have evaluated the use of any of these criteria in children with stones and therefore their validity in the pediatric population is unknown. In particular, the role of renal resistive index in children with urinary tract obstruction is complicated by the fact that RI is age dependent – highest at birth and decreases gradually to adult levels at about 4–5 years of life [21]. Future studies are warranted to help shed light on what role these criteria may play in pediatric nephrolithiasis.

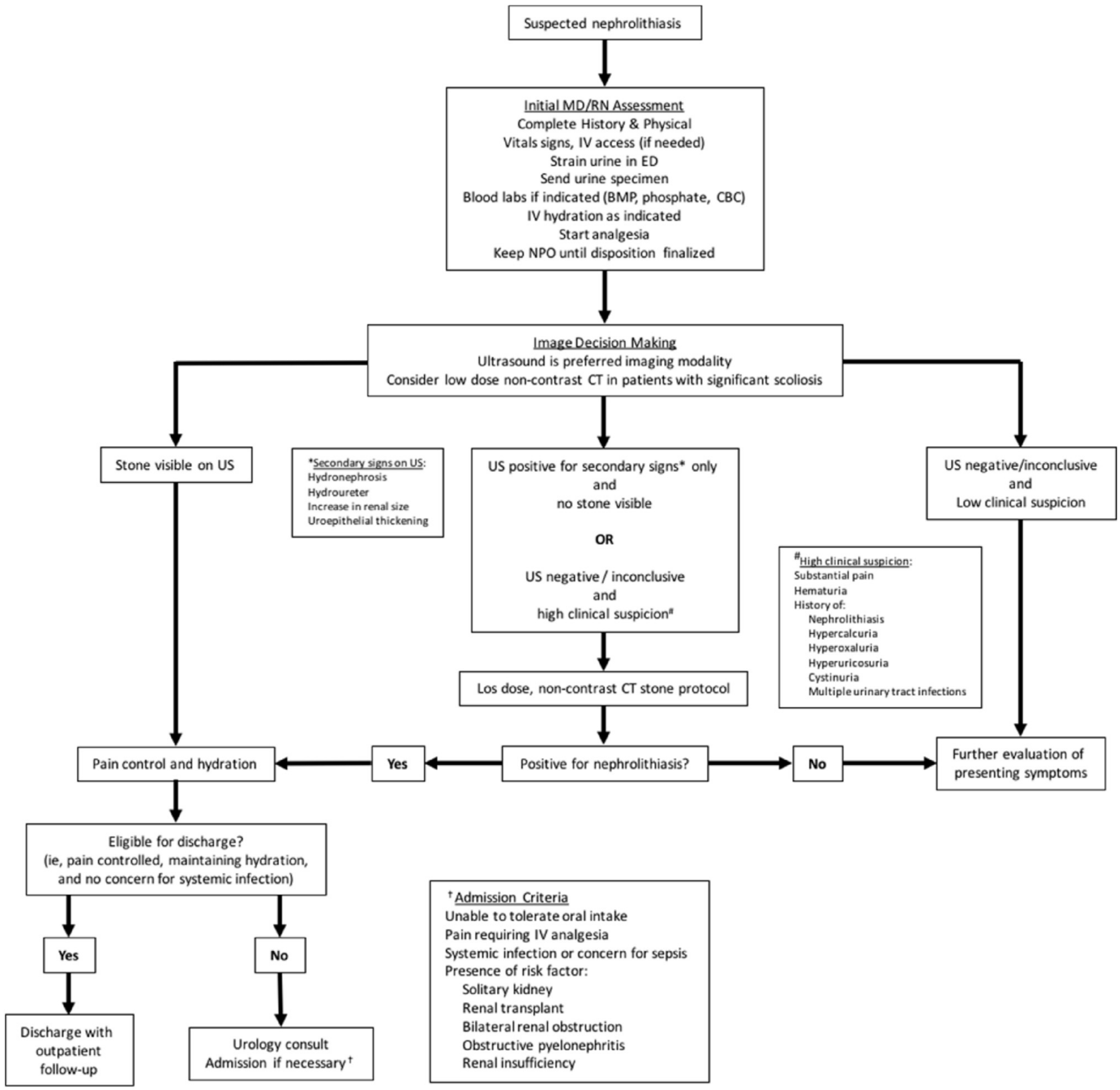
Given the concerns of ionizing radiation exposure with CT and the relatively high sensitivity and specificity of ultrasound in detecting nephrolithiasis of clinical importance, both the American Urological Association (AUA) and the European Society of Pediatric Radiology (ESPR) recommend obtaining a renal and bladder ultrasound as the first-line imaging in children and adolescents, with CT scans reserved for equivocal or non-diagnostic US results in which the clinical suspicion for stones is high [14,15]. Likewise, the European Association of Urology (EAU) guideline for the diagnosis of urolithiasis recommend renal and bladder ultrasound as the primary diagnostic imaging tool in all patients [22]. In addition to these national and international organizations, the Alliance for Radiation Safety in Pediatric Imaging, which includes the Society for Pediatric Radiology and American College of Radiology, started the Image Gently® campaign in 2007 to decrease the use of ionizing radiation in pediatric patients undergoing diagnostic imaging [23].

Despite these various recommendations and guideline statements, one recent review of a commercial insurance claims database found that ultrasound was only obtained as the initial imaging in 24% of children and adolescents with suspected nephrolithiasis [7]. Conversely, 63% of children underwent initial CT imaging with substantial regional variation within the United States [7]. This inappropriate use of initial CT imaging in children has been confirmed by other studies. Johnson and colleagues performed a retrospective cohort study of the Nationwide Emergency Department Sample from 2006 to 2010 and found that 87% of pediatric patients with suspected nephrolithiasis underwent CT alone [24]. Factors associated with use of CT alone included older age of patient, evaluation at a non-teaching hospital, visit on a weekend and visit EDs that serve smaller proportions of pediatric patients [24]. On the other hand, children who presented at EDs that utilized clinical care pathways emphasizing the use of US as the first-line imaging in children were found to have lower odds of undergoing initial CT [25] (see Fig. 1).

At the Children's Hospital of Philadelphia (CHOP), we have utilized an ED clinical pathway for the evaluation and treatment of children with suspected nephrolithiasis since 2009. The clinical pathway is accessible online by all clinicians in the hospital system and was developed in collaboration between the pediatric emergency medicine, pediatric radiology and the pediatric urology departments. The goals of the pathway are to standardize patient evaluation, expedite appropriate radiologic studies with US as first-line, and to reduce the time to disposition. Use of the clinical pathway at CHOP has led to lower rates of CT use in children suspected of nephrolithiasis compared to other regional EDs with no clinical pathway [25].

3.2. Immediate urinary decompression

Similar to the evaluation of the adult with nephrolithiasis, the initial step in the acute management of the child is determining the need for immediate urinary decompression. Emergency decompression of the obstructed urinary system by a ureteral calculus can



BMP = basic metabolic panel
CBC = complete blood count
CT = computerized tomography
ED = emergency department
IV = intravenous
MD/RN = health care provider (ie, physician, registered nurse, or physician assistant)
NPO = nil per os
US = ultrasound

Fig. 1. Flowchart for emergency department pathway for evaluation and treatment of children with suspected nephrolithiasis. (Modified from Zonfrillo M, Lavelle J, Piro J, Kim S, and Darge K; accessed from The Children's Hospital of Philadelphia website for clinical pathway website: http://www.chop.edu/clinical-pathway/nephrolithiasis-suspected-emergent-care-clinical-pathway#).

be accomplished via cystoscopy and retrograde ureteral stent placement or percutaneous nephrostomy (PCN) tube placement. As in adults, indications for decompression in children and adolescents include obstructed urinary tract infection or evidence of pyelonephritis, solitary kidney, or intractable pain, nausea, or emesis. Clinical evidence to support one intervention over the other in the acute setting in lacking in children with only one prospective study available. ElSheemy and colleagues randomized 90 children ≤12 years with anuria or acute renal failure secondary to bilateral ureteral stones to bilateral ureteral stent placement or bilateral PCN tube placement [26]. While there was significantly more complications in the PCN tube cohort, the authors noted higher rates of failure and mucosal complications in the ureteral stent cohort when the stone size was >2 cm [26]. Therefore larger stones may benefit from PCN tube decompression although additional well designed studies are needed to draw definitive conclusions.

3.3. Medical expulsion therapy

Management options in the child or adolescent diagnosed with an obstructed stone include observation with pain control, medical expulsive therapy (MET), and surgery. Spontaneous stone passage rates without MET favor passage in older rather than younger children, with smaller stone size (especially <5 mm) and for stones located in the distal ureter versus upper ureter or kidney [27,28]. While the majority of studies on the use of MET have been performed in adult patients, the success of alpha-blockers and calcium-channel blockers in facilitating stone passage, reducing analgesic use, and increased cost-effectiveness compared to analgesics alone, has led to the use of both in the pediatric population [29]. The rationale for MET in increasing stone passage is that both alpha-receptors type 1a and 1d, and calcium-channel receptors are found in high concentrations in the smooth muscle of the distal 1/3 of the ureter and at the ureterovesical junction. These receptors when activated cause smooth muscle contraction and thus blockage of these receptors with alpha and/or calcium-channel blockers leads to dilation of the ureter and easier passage of urinary stones.

To date there are only 4 small randomized controlled trials of alpha-blocker use in MET for children with distal ureteral stones and no studies have been reported evaluating the use of calcium-channel blockers as MET in children [30–33]. In addition, Tasian and associates performed a multi-institutional retrospective cohort study investigating the efficacy of tamsulosin as MET for ureteral stones <10 mm. The authors noted a statistically significant higher stone expulsion rate in children treated with tamsulosin (56%) compared to those treated with analgesics alone (44%) with an adjusted odds ratio of 3.31 for stone passage in favor of the tamsulosin cohort [34].

Aydogdu and colleagues from Turkey reported the first RCT evaluating doxazosin, a first-generation selective alpha-1 antagonist, and found no difference in stone expulsion rate for distal ureteral stones up to 10 mm in size between the treatment group compared with children receiving analgesic alone [30]. However, this study may have been underpowered to detect a real difference between the treatment and control arms. Ertuhan and associates also performed a small RCT in Turkey of 45 children comparing doxazosin against analgesics alone [31]. The authors noted a significantly higher stone expulsion rate in the doxazosin cohort (71%) versus the control cohort (29%) and they reported a significant reduction in pain attacks and shorter stone expulsion period in the doxazosin arm [31].

The other two RCTs studied the use of tamsulosin, a selective alpha-1 blocker with preferential selectivity for the alpha-1a receptor, for MET [32,33]. Mokhless and colleagues from Egypt reported their results in 61 children with distal ureteral stones <12 mm randomized to tamsulosin and analgesic or placebo and analgesic [32]. The authors found a statistically significant difference in both stone-free rate (88% vs. 64%) and mean stone expulsion time (8.2 vs. 14.5 days) in favor of the tamsulosin group compared with the placebo control group [32]. The validity of these results are uncertain, however, due to unclear randomization methods since the authors note that almost half of the children in the tamsulosin arm had retained stones after prior surgical treatment while all of the patients in the control arm had untreated stones [32]. Similar to this study, in the most recent RCT, Aldaqadossi and associates noted an 87% stone-free rate in 33 children treated with tamsulosin (0.4 mg) compared to a rate of 63% in 34 children treated with analgesics alone ($p = 0.025$) [33]. This study also reported a reduced mean time to stone expulsion in the tamsulosin group compared with the analgesic cohort (7.7 vs. 18.0 days; $p < 0.001$) [33]. Overall, tamsulosin appeared effective and safe in children despite its off-label use, with only 3 patients reporting mild nasal congestion and no patient stopping treatment secondary to side effects [32,33].

To further understand the results of these studies, Velazquez and colleagues performed a systemic review and meta-analysis of first three RCT (the fourth was published after the review) and two additional retrospective studies [35]. The pooled results demonstrated that MET with an alpha-blocker significantly increased the odds of stone passage compared to placebo or analgesic alone (OR 2.21, 95% CI 1.40–3.49) [35]. Furthermore and consistent with the adult literature, alpha-blocker use was safe in children with only 1 of 175 patients (0.6%) withdrawing from treatment due to adverse effects (somnolence) [35]. The authors conclude that the available evidence supports the use of MET in treatment algorithms for pediatric nephrolithiasis.

In October 2016, the AUA and Endourological Society released a guideline for the surgical management of patients with kidney and/or ureteral stones [36,37]. According to the guideline, pediatric patients with uncomplicated ureteral stones ≤10 mm should be offered "observation with or without MET using alpha-blockers" [36]. This recommendation is categorized as moderate with a grade B level of evidence based on the RCTs described above. The guideline states that parents should be informed that the use of alpha-blockers is off-label and that the maximum time duration of MET is unknown but should be capped at 6 weeks [36].

3.4. Surgical interventions

Surgical intervention is estimated to be necessary in 22–60% of children with nephrolithiasis [28,38]. As in adults, surgical options in pediatric patients include extracorporeal shockwave lithotripsy (ESWL), retrograde intrarenal surgery (RIRS) including ureteroscopy (URS) with stone basketing and laser lithotripsy, and percutaneous nephrolithotomy (PCNL). Open and laparoscopic pyelolithotomy are rarely performed in the modern era. In fact, over the past couple of decades, both URS and PCNL have seen rises due to technological advances in optic system quality and development of smaller ureteroscopes (<8Fr) and instruments for use in the smaller caliber pediatric ureter and kidney [38]. The choice of specific intervention depends on multiple factors including location and size of the stone, availability of equipment and instruments, geographic location and surgeon preference. [39].

Stone-free rates for each surgical modality appear similar in observational studies although the indications for interventions, patient populations, and follow-up were varied amongst the studies. One recent review of the literature noted stone-free rates of 80–83% for ESWL, 85–88% for URS, and 70–97% for PCNL [40]. Unfortunately only a few studies have compared surgical interventions head-to-head in children with nephrolithiasis, but the results of these studies and extrapolating the more robust, higher quality data available in adults has led to the AUA and Endourological Society to recommend URS or ESWL as first line therapy for the pediatric patient with ureteral stones who have failed observation or MET [36]. Furthermore, the guideline recommends either ESWL or URS as first-line therapy in children with total renal stone burden ≤20 mm [36]. Our preference for stones <15 mm is URS given the concern for an increased risk of hypertension from ESWL to the kidney [41].

3.4.1. Ureteroscopy

Since the first pediatric URS was described by Ritchey and associated in 1988, URS in the pediatric population has been shown to be safe and effective from infants to adolescents [42–44].

One recent systemic review of URS identified 14 studies with over 1700 procedures in children aged 0.25–18 years old [45]. Mean stone-free rate was 87.5% and complications (Clavien I-III) were noted in 10.5% of patients including 3 patients with ureteral strictures and 18 patients with ureteral perforation (1.0%) [45]. A higher failure rate and higher complication rate (24.0 vs. 7.1%) were noted in children <6 years old compared to those older than 6 years [45]. Given the smaller caliber ureter in children, especially in infants and toddlers, some authors have recommended pre-stenting 2–8 weeks prior to URS to passively dilate the ureter and ureterovesical junction [46]. Others, however, have shown that primary ureteroscopic access can be achieved in 50–60% of children, including those that are prepubertal, with low complication rates [47,48]. To decrease number of procedures and anesthetic events, these authors favor an initial attempt at URS with stent placement for passive dilation only if upper tract access is unsuccessful. Likewise, the AUA/Endourological Society recommends against the use of routine pre-stenting prior to URS although they note that this recommendation is based on expert opinion and stenting may be necessary in some accesses were access is difficult [36].

3.4.2. Extracorporeal shockwave lithotripsy

ESWL has been used in children and its rise in popularity stems from increased access to lithotripsy machines, its non-invasive approach, and reported high rates of success [49]. The short-term effects of ESWL have been well characterized, including hematuria (in up 44%) and subcapsular or perirenal hematoma, and these complications for the most part are self-limiting without the need for intervention [49]. In addition, children treated with ESWL still need to pass stone fragments and are at risk for intermittent renal colic, ED visits for pain control, and steinstrasse just like their adult counterparts. Difficulty with ESWL focusing can lead to injury to adjacent structures including the colon, vasculature, lung, spleen, and pancreas [50].

Less understood are the long-term effects of ESWL on the developing pediatric kidney. Despite some studies showing no "long-term" effects of ESWL on a child's risk of developing hypertension, stunting of renal growth, renal scarring, or deterioration of renal function, data in adults is conflicting with one recent study noting that ESWL was associated with a significant increased risk of incident hypertension [41,49–52]. One possibility for the lack of an association in children is that these studies often describe "long term" effects after mean follow ups of 6 months to 5 years which may not be long enough to see effects [51–53]. Therefore, any significant long term consequences of ESWL on the kidney and systemically may not have had time to manifest. At minimum decision of these potential risks and findings in adults must be undertaken with all patients and families prior to ESWL until more long-term studies through puberty and into adulthood are reported.

Unfortunately there are only a limited number of studies directly comparing URS with ESWL in children to help guide evidence based practice. Mokhless and colleagues in Egypt performed a prospective, randomized trial in preschool children between the two modalities and noted similar stone-free rates, operative time, and no major complication in either group [54]. The AUA/Endourological Society guideline also reports results of an unpublished meta-analysis that found similar stone-free rates between SWL and URS in pediatric patients [36]. These limited results are the basis for the recommendation of either SWL or URS as first-line therapy in children with ureteral stones who have failed observation/MET or renal stone burden of ≤20 mm.

3.4.3. Percutaneous nephrolithotomy

For renal stone burden >20 mm, the AUA/Endourological Society guideline recommends on the basis of expert opinion either PCNL or ESWL (with placement of a ureteral stent or PCN tube) as acceptable options [36]. Our preference for stones >20 mm is PCNL given concern with the efficacy of ESWL for large stone burdens in the adults especially when stones are in the lower pole of the kidney [55]. The major risks from PCNL include damage to nearby structure and organs, and hemorrhage requiring blood transfusion, which is reported in as high as 10–16% patients during or after PCNL [40,56]. Several studies have evaluated PCNL versus other surgical modalities in children. When compared with SWL for children with renal stone burden of 1–2.5 cm, mini-PCNL was found to be more efficacious with a higher stone-free rate although with one randomized trial noting longer operative time, higher radiation exposure, and more complications [57,58]. Similarly, Saad and associates noted a higher stone-free rate (96% vs. 71%) at the expense of higher complication rate in children with renal stone burden >2 cm randomized to undergo PCNL compared with URS [59]. The authors noted a 14% blood transfusion rate with PCNL compared to 0% with URS [59]. The advent of smaller equipment and instruments for newer techniques such as mini-PCNL, ultra-mini-PCNL, and micro-PCNL raise the possibility of fewer complications from traditional PCNL and lower risk of hemorrhage [60].

3.4.4. Risk of radiation exposure

Both PCNL and URS traditionally exposure patients to ionizing radiation from intraoperative fluoroscopy. These exposures can become significant with longer operative times, when repeat surgeries are necessary to achieve complete stone removal, by imaging studies (ie, CT or plain film x-rays) during colic episodes or as part of follow up, or due to additional exposures during future stone recurrence events. Given these concerns, techniques to minimize radiation during surgery and to follow the principle of ALARA ("As Low As Reasonably Achievable") are especially important in pediatric stone disease. Recent techniques that utilize ultrasound guidance instead of fluoroscopy during PCNL and URS have been reported in children and show that the techniques can safely and effectively be performed without ionizing radiation [61–63]. Future larger, prospective randomized trials are needed to validate the results of these smaller studies.

4. Conclusions

The incidence of pediatric nephrolithiasis has risen over the past few decades leading to a growing public health burden. Children and adolescents represent a unique patient population secondary to their higher risks from radiation exposure as compared to adults, high risk of recurrence, and longer follow up time given their longer life expectancies. Ultrasound imaging is the first-line modality for diagnosing suspected nephrolithiasis in children. Although data is limited, the best evidence based medicine supports the use of alpha-blockers as first-line MET in children, especially when stones are small and in a more distal ureteral location. Surgical management of pediatric nephrolithiasis is similar to that in adults with ESWL and URS first-line for smaller stones and PCNL reserved for larger renal stone burden. Clinical effectiveness in minimizing risks in children and adolescents with nephrolithiasis centers around ED pathways that limit CT imaging, strict guidance to ALARA principles or use of US during surgical procedures, and education of both patients and families on the risks of repeat ionizing radiation exposures during follow up and acute colic events.

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Author contribution

Jason Van Batavia.
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Both authors have equal contribution in literature search, manuscript planning and writing, and proof reading.

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