INTRODUCTION

A bladder stone is a rare condition that affects 5% of all urinary calculi. Bladder stones are usually affecting males older than 60 years old. However, in the case of endemic regions, this abnormality could be affecting children due to dietary intake, especially in low resource countries. The stone composition mainly consists of uric acid and calcium oxalate. Although mainly consist of these substances, there great varieties in different regions due to many risk factors, such as genetic inheritance, dietary, socio-economic factors, and climate.

Bladder stones are characterized by painful and irregular voiding haematuria. Other symptoms in bladder stones are urgency, dysuria, haematuria, frequency, strangury, urinary retention, and/or fever. Therefore, in children these severe cases, could manifest as anemic, stunted growth, and osteodystrophy. In making the diagnosis of bladder stone, ultrasound is the primary test, with cystoscopy as the most accurate method to confirm the presence of bladder stone. Traditionally, open cystolithotomy is an accepted treatment modality for bladder stones. Despite of that, minimally invasive treatments are widely used. But, there is lack of study that conducted to investigate or report bladder stone especially in children. Therefore, the aim of this study is to make a review of bladder stones in children based on current literature to be used as a reference for other researchers and clinicians.

METHODS

We conducted extensive research in the database of PubMed. We use the following keywords to conduct a further investigation: “children” or “paediatric” or “childhood” associated with “bladder stone” or “vesicolithiasis”. The publication date of the last 5 years was an inclusion criterion. Eighty-three articles were identified as potentially relevant studies. We include the articles in English language and human studies; thus, we exclude twenty-three studies due to these matters. In the end, sixty studies met the inclusion criteria.

Figure 1. Process of inclusion of studies in the review
criteria. We are aiming to make a literature review of bladder stone in children, specifically based on etiology, risk factors, epidemiology, differential diagnosis, diagnosis method, and treatment based on the studies included in this literature review. Twenty-six articles were excluded due to similarity to other articles, unclear statements, irrelevant correlation with the main topic, or focusing more on other diseases rather than bladder stone.

**Epidemiology**

Pediatric urolithiasis is still common in low-income countries, affecting children with ages less than 1 to 15 years old, with babies accounting for about 17–40% cases worldwide. Meanwhile, the cases of pediatric urolithiasis in high-income countries only constitute 5% of all cases. When bladder calculi form in children without infection, obstruction, or neurogenic disease, they are referred to as endemic calculi. Risk factors such as poverty, malnutrition, diarrheal diseases, and chronic dehydration are linked to these cases. Although the incidence of bladder stone in childhood has been decreased slowly in some regions, bladder as the anatomical location of the stone account for about 46.9% of all cases in these low-income countries such as Middle East Nations, South Asia, and Southeast Asia, including Indonesia. Ammonium acid urate (AAU) was found in 74.37% of all bladder stones cases, while calcium oxalate (CaOx) was found in 39.5% of the cases. Uric acid (UA) was found in 11.46%, followed by calcium phosphate apatite (CaP) that was found in 9.25%, Struvite (magnesium ammonium phosphate) was found in 4.34%, cystine was found in 1.16%, and xanthine was found in 3.85% of all the cases. The chemical compositions are varied due to many factors like genetic inheritance, dietary, socio-economic factors, and climate.

In Indonesia, especially in West Sumatra, bladder stones were common in children, with an annual prevalence of 8.3 per 100,000 population, which peaked at the age of 2–4 years and frequently happened in poor families with a low phosphate and protein diet. Different prevalence of bladder stones in all urolithiasis cases varies in every country. In India, bladder stones are found in 80% of all cases, 18.4% of all cases in Iran, 42% of all cases in Turkey, 70% of all cases in Turkey and Cameroon, 46% of all cases in Ethiopia. The average temperature and annual rainfall are linked to these incidences.

Different new-born feeding practices in these countries also accounted as precipitating events of bladder stone formation. Substitute carbohydrate feedings to new-borns, such as masticated rice in Southeast Asia and pap or panada in England during the eighteenth and nineteenth centuries, were accounted as precipitating events. Even though rice is the major staple food in China, a study by Ye Z et al shows the different characteristics of urinary stone composition from Afro-Asian countries we mentioned above. The most frequent bladder stone constituents in China were: calcium oxalate (CaOx) with 65.9% of all cases, carbapatite with 15.6% of all cases, urate with 12.4% of all cases, struvite with 2.7% of all cases, and brushite with 1.7% of all cases. The majority of CaOx components are thought to be influenced by high carbohydrate intake and a vegetarian diet.

**Etiology and Risk Factors**

Bladder stones can be classified into primary and secondary. The term “primary” refers to the process of stone formation with no anatomic, functional, or infectious factors that aid in stone formation. Aside from that, the word “secondary” emphasizes that an etiologic cause can be identified. Primary bladder stones are not rare in pediatric patients, yet their exact etiology is not well understood. There seems to be a lot of factors contributing to stone formation, while the classic association between urinary stasis and bladder calculi is not clear.

The study conducted by Lau et al. reported adenine phosphoribosyl transferase (APRT) deficiency as one of the aetiologies of urinary bladder stone. Excessive synthesis of 2,8-dihydroxyadenine is a hallmark of APRT activity deficiency (DHA) which is a water-insoluble compound that is cleared in the kidney. These substances can precipitate and form crystals that leading to be urolithiasis. A similar result showed by Chong SL et al. where APRT deficiency caused multiple radiolucent renal calculi.

Another rare inborn error metabolism such as Lesch-Nyhan syndrome may also be the cause of urinary calculi due to a high level of uric acid which may lead to kidney and bladder stones.

A rare etiology of bladder stone may be caused by foreign material in the bladder. It could be introduced by migration from the adjacent organ, accidentally or iatrogenically, by self-insertion, or by penetrating injury. Palunrunji et al. reported a case of giant bladder stone in childhood that formed by self-insertion of sewing-needle which later acts as a nidus.

Despite the unclear etiology of bladder stone, recent studies show many risk factors which may lead to this pathological condition. Overweight children have an elevated uric acid level and low urinary volume compared to non-overweight children. Unexpectedly, although there is a correlation between BMI and stone formation in adults, there is no conclusive findings in the pediatric literature have been established.

One’s general condition and dietary intake seem to have more influence in stone formation. Pozzi M et al. study the relationship between urinary stones formation and enteral nutrition facts in children that undergoing rehabilitation of severe brain injury. This study showed that urinary tract infections (UTIs) and higher sodium nutrition content were risk factors OR=11.4 (95% CI. 1.6-83.4) and OR=7.5 (95% CI. 1.6-34.3) respectively, while higher GCS and higher calcium nutrition content were considered as protective factors OR=0.66 (95% CI. 0.43-0.99) and OR=0.14 (95% CI. 0.03-0.73) respectively.

Besides all risk factors mentioned above, familial risks could affect the incidence of stone diseases. A study by Hemminki K et al. investigated familial risks in and between stone diseases, which are urolithiasis (UL), cholelithiasis (CL), and sialolithiasis (SL). This study found standardized incidence ratios (SIRs) for concordant familial risks were 1.94, 1.82, and 2.06, respectively. Related environmental or genetic factors.
can explain comorbidity between two diseases.\textsuperscript{13}

Urology procedure such as double-J ureteral stent (DJ stents) implantation is associated with stone diseases, especially the encrusted ones.\textsuperscript{16} Study by Arkusz K et al. investigated this matter and found that the distal (urinary bladder) and proximal (renal pelvis) of the DJ stents implanted are the most susceptible part for urea salt deposition and post-ureterorenoscopic-lithotripsy procedure (URS-L) fragments.\textsuperscript{17} This could happen due to deposition of foreign body in the bladder that induced recurrent episodes of urinary tract infection especially dysuria and ultimately end up in the formation of calculi around it.\textsuperscript{18}

Furthermore, there were many reports of bladder stones originating from non-absorbable meshes that are used for extrstrophy repair, caesarian section, migration used in stress incontinence for exstrophy repair, posterior urethral valves, spina bifida, traumatic spinal cord injury, sacral agenesis, bilateral ectopic ureter, and non-neurogenic neurogenic bladder.\textsuperscript{19} Even though overcoming problems such as bladder extrstrophy, posterior urethral valves, spina bifida, traumatic spinal cord injury, sacral agenesis, bilateral ectopic ureter, and non-neurogenic neurogenic bladder.\textsuperscript{20} Even though overcoming problems such as bladder extrstrophy could avoid the risk of having bladder stone, a post-operative complication of bladder stone augmentation may occur, including bladder rupture, renal deterioration, malignancy, metabolic abnormalities, and also bladder stones.\textsuperscript{20,21}

The rate of bladder stones incidences in this particular procedure is between 11% and 52%.\textsuperscript{20} Szymanski KM et al. conducted a study showing that 30.8% of bladder stones among patients with bladder augmentation were infectious, containing carbonate apatite, ammonium acid urate, or struvite.\textsuperscript{22} Furthermore, there are several metabolic derangements noted among this patient, including elevated urine pHi (100%), hypocitraturia (100%), low urine volume (70%), and hyperoxaluria (35%).\textsuperscript{23} An interesting case report by Nang R et al. presented giant vesical lithiasis of 8 cm in length and 935 gram in weight from a patient caused by a complication of enterocystoplasty.\textsuperscript{24}

Several methods have been investigated to achieve the goal of reducing bladder stone formation caused by bladder augmentation. Odeh RI et al. investigate the possibility of reducing these cases by replacing ileocystoplasty as the standard technique used for bladder augmentation with seromuscular bladder augmentation (SMBA).\textsuperscript{25} This study showed a difference in the rate of bladder calculi formation between SMBA (0/0%) and the standard procedure (8/27%) (p = 0.06).\textsuperscript{25} In the future, tissue engineering (TE) based on stem cell is considered one of the most promising strategies to replace the current bladder augmentation procedure.\textsuperscript{26}

Diagnosis and Treatment
Vesicolithotomy as the first bladder stone removal procedure is most likely originated in India until it was perfected by Chelseldon, an eighteenth-century English surgeon.\textsuperscript{27} Since then, the techniques in overcoming this issue have evolved with retrograde approaches like cystolithotripsy that become the standard approach is only used when it is needed. By diagnosing the etiology properly, we could avoid unnecessary treatments and support a conservative approach.\textsuperscript{30}

Another method like shock wave lithotripsy (SWL) that less invasive has its own benefit, such as shorter length of stay but the stone-free rate (SF) compared with the more invasive approaches such as trans-urethral open cystolithotomy (TUCL) and cystolithotripsy (CL) (p <0.00001 and p<0.000001).\textsuperscript{5}

Another procedure such as percutaneous cystolithotomy (PCCL), has its own benefit compared to CL with the shorter procedure, length of hospital stay, and catherization, even though there is no significant difference in SFR (100% in all), major postoperative complication (4.6% vs. 0%), or unplanned procedure (6.2% vs. 1.4%), was higher with this procedure.\textsuperscript{5} Mishra DK et al. conducted a study comparing Transurethral Cystolithotripsy and Mini-Percutaneous Cystolithotripsy (mPCCL). This study found that both are appropriate for smaller bladder stones, while PCCL could be used as preferred management for larger bladder stones.\textsuperscript{31} Interesting recent studies by Ganpule AP et al. used the MicroPercTM micro percutaneous nephrolithotomy armamentarium for unusual indications such as bladder, urethral, or ureteric stones, and for treating non-calculus diseases like VUR and PUVs.\textsuperscript{32}

In a special condition such as a patient with bladder augmentation, minimally invasive techniques have been used.\textsuperscript{33} Thomas JS et al. conducted a study for pediatric cystolitholapaxy by approaching the Mitrofanoff/Monti channel.\textsuperscript{33} This study found that Mitrofanoff cystolitholapaxy was safe and did not result in difficulty catherizing or leakage with appropriate care.\textsuperscript{33} The author suggests further investigation, considering that there are still few studies on this procedure.

A small quasi-RCT by Gangkak G et al. compared TUCL with Holmium: yttrium–aluminum–garnet (Ho:YAG) laser and pneumatic lithotripsy.\textsuperscript{34} This study showed that the operative time of patients who were treated with Ho:YAG was significantly lower for stones in size <1,5 cm, while operating time for patients with stone size between 1,5 and 3 cm were similar.\textsuperscript{34} Thus, this study suggests using TUCL with Ho:YAG for treating bladder stones less than 1.5 cm.\textsuperscript{34}

CONCLUSION
Bladder stones in children are still a major problem, especially in developing countries. Risk factors and thorough
examination should be considered in diagnosing patients with bladder stone signs and symptoms. Appropriate surgical approaches should be done rather than using cystolithotripsy as the standard protocol only.

**CONFLICT OF INTEREST**

None of the authors have any conflicts of interest to disclose.

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**AUTHOR CONTRIBUTION**

Dahril is responsible in conceiving, designing, defining intellectual content, literature searching, manuscript preparation, manuscript editing, and review. Jufriady Ismy responsible in designing, defining intellectual content, literature searching, data analysis, manuscript editing, and manuscript review. Iman Akbar Hasibuan is responsible for defining intellectual content, literature searching, manuscript preparation, and manuscript editing. Meanwhile, Andreas is responsible for designing, literature searching, manuscript preparation and manuscript review.

**ETHICAL STATEMENT**

Not Applicable

**REFERENCES**


