Urol Res (2006) 34: 96–101
DOI 10.1007/s00240-005-0018-0

ARTICLE

K. Sarica

Pediatric urolithiasis: etiology, specific pathogenesis and medical treatment

Accepted: 12 October 2005 / Published online: 24 January 2006

Abstract Pediatric urolithiasis is an endemic disease in certain parts of the world, namely Turkey and the Far East. As a recurrent pathology which may reveal functional as well and morphologic changes in the urinary tract, environmental factors together with urogenital abnormalities should be evaluated thoroughly in each patient. The aims of management should be complete clearance of stones, treatment of urinary tract infections, preservation of renal function and prevention of stone recurrence. In addition to certain minimally invasive stone removal procedures, treatment of pediatric urolithiasis requires a detailed metabolic evaluation in all patients on an individual basis. Obstructive pathologies have to be corrected immediately and children with a positive family history should be followed carefully with respect to a high likelihood of stone re-growth and recurrence. Although specific management of each metabolic abnormality seems to be the key factor in the medical management of stone disease, as general advice each child should be forced to adequate fluid intake which will reveal the urine volume increase in accordance with the body mass index. Moreover, medical therapeutic agents which increase urine citrate levels should be encouraged.

Keywords Pediatric urolithiasis · Medical management · Risk factors · Recurrence

Introduction

Urinary stones, the prevalance of which varies widely among geographic regions, are being recognized more frequently in children, and the incidence has decreased significantly in the past 100 years. Although renal stone disease is a frequent consideration in the evaluation of many kidney diseases of childhood, its diagnosis is rarely confirmed. Regarding the incidence of the pathology, the disease is an endemic problem especially in certain developing regions of the world, such as the Far East, to a certain extent of the Middle East and Turkey. Stones are uncommon in African-American children. When compared with the upper tract calculi, bladder stones are commonly encountered and the predominant stone types are ammonium acid urate and uric acid, depending on the dietary factors. On the other hand, regarding the European countries, such as the United Kingdom, majority of the treated calculi are composed of organic matrix and struvite and located in the upper parts of the urinary tract. Again the urinary tract infection along with the congenital abnormalities is commonly associated with the formation of these calculi. In contrast, infectious stones are rare in the United States and Scandinavia.

With respect to the prevalence, the pathology varies widely among geographic regions in the United States and accounts for 1 per 1,000 to 1 per 7,600 pediatric hospital admissions [1]. Children of all ages may suffer from the disease, and although there is no gender preference in children with urolithiasis, boys are slightly more affected than girls. Calcium oxalate or calcium phosphate stones are the most common types, being detected in more than 75% of all children evaluated when compared with adults [2, 3]. Infection stones which represent 15–25% of the total are the second most common form of calculosis [2, 4–6]. Again studies dealing with the underlying metabolic abnormalities have shown that metabolic conditions were found to account for greater than 50% of diagnoses in children [2, 3]. Finally a variety of genitourinary anomalies are found in 30% of children with urolithiasis [2].

K. Sarica
Medical School, Þahinbey Medical Center,
Department of Urology, University of Gaziantep,
Gaziantep, Turkey
E-mail: kemalsarica@superonline.com

Pathophysiology

Formation of crystals in urine is a complex process which is predominantly promoted or inhibited by a number of

physicochemical or anatomic factors. Among the factors responsible for this event, the excretion of certain risk factors, urinary supersaturation, tubular flow rate, urinary pH and developmental anomalies of the urinary tract are the commonly discussed ones. Apart from the risk factors such as hypercalciuria, hyperoxaluria, hyperuricosuria and hypomagnesuria, normal urine contains a number of organic and inorganic inhibitors, i.e. magnesium, glycosaminoglycans, glycoproteins, citrate, pyrophosphate and nephrocalcin [7]. As another critical factor, urinary pH affects the saturation of some potential stone-forming solutes by altering their solubility while acidic urine lowers the solubility of uric acid and cystine. An alkaline pH is usually responsible for the formation of struvite and calcium-containing stones.

Regarding the prediction of new stone formation, urinary supersaturation indexes which evaluate the lithogenic and inhibitory substances in the urine have been shown to be useful in adults to predict the risk of stone recurrence [8]. In children however, although the reference ranges have not yet been well defined, these indexes are more sensitive predictors of recurrent stone risk [9] in this specific population.

Urinary risk factors

Hypercalciuria

Hypercalciuria is the most common cause of urolithiasis in children, accounting for up to 34% of all pediatric stones [2]. Normal calcium excretion during childhood has been defined as less than 4 mg/kg per day measured in a 24-h urine collection with the patient consuming a routine diet [10–12], preferably confirmed with second sample values greater than 0.2 in a 24-h urine sample [13, 14] are considered elevated. Forty-six percent of children with hypercalciuria have a positive family history of urolithiasis, supporting the impression that idiopathic hypercalciuria is a hereditary trait [15]. Although the genetic basis of hypercalciuria is unknown, idiopathic hypercalciuria seems to follow an autosomal dominant pattern of inheritance and can be diagnosed in approximately 4% of an unselected pediatric population [10, 15, 16]. In children and adults, absorptive and renal forms of hypercalciuria most likely represent a continuum of a single disease. Dent disease is an X-linked recessive disorder of urolithiasis secondary to a form of Fanconi syndrome with hypercalciuria, low molecular weight proteinuria, nephrolithiasis and nephrocalcinosis [17].

Two other conditions, X-linked recessive hypercalciuric hypophosphatemic rickets and low molecular weight proteinuria with nephrocalcinosis, have been described with similar phenotypes [18].

Hyperuricosuria

Having been formed as the end product of purine metabolism, nearly 8% of children with metabolic stones have hyperuricosuria [2]. In addition to uric acid precipitation hyperuricosuria may also lead to calcium oxalate lithiasis. Two major factors promote uric acid precipitation: supersaturation of the urine with uric acid and a low urinary pH of < 5.8.

Hyperuricosuria may result from uric acid overproduction or may occur in the presence of normal serum uric acid levels. The presence of urate stones and elevated serum uric acid may be secondary to inborn errors of metabolism, such as Lesch–Nyhan syndrome (hypoxanthine quanine phosphoribosyltransferase deficiency), type I glycogen storage disease, myeloproliferative disorders or other causes of cell breakdown. Primary gout owing to partial hypoxanthine guanine phosphoribosyltransferase deficiency with uric acid calculi occasionally occurs in older children. Uric acid stones may also be seen in 5–10% of children placed on a ketogenic diet for seizure control [19, 20]. These children may have hypercalciuria, acidic urine or low urinary citrate excretion which, in conjunction with low fluid intake, places these children at high risk (5–10% incidence) for uric acid and calcium stone formation [19]. Hyperuricosuria can also occur secondary to excessive dietary purine/protein intake or uricosuric drugs such as sulfinpyrazone, high-dose aspirin (> 2 g/day), ascorbic acid (> 4 g/day), phenylbutazone and probenecid. Uric acid excretion is extremely high in the neonatal period and remains substantially higher than adult values throughout early childhood.

Infection stones

Infection-related stones account for 2–24% of children with nephrolithiasis [2–6] and as many as 75% of European children suffer from these stones. Boys are more commonly affected and are usually detected before the age of 6 years. Genitourinary anomalies are common among these children, affecting more than half of all children with infection-related stones [2]. Persistent pyuria, bacteriuria and struvite crystalluria are characteristic findings.

Cystinuria

Cystinuria accounts for 2–7% of children with metabolic urolithiasis in industrialized countries [2, 4]. The solubility of cystine in urine is about 250 mg/l up to pH 7 but sharply rises with higher pH, up to 500 mg/l or more above 7.5 pH. Urine analysis reveals the characteristic flat hexagonal cystine crystals in 26% of patients. A positive nitroprusside test indicates a level of greater than 75 mg/dl of urinary cystine, and this result needs to be confirmed by a 24-h collection. Because the genetic transport defect exists from birth, stone formation begins in the first decades of life, with 25% of affected patients passing their first stone in childhood. The permanent excretion of excessive amounts of cystine is spontaneously associated with the relentless formation of stones, which can have a staghorn development.

Hyperoxaluria

Hyperoxaluria accounts for a small but significant portion of pediatric stone diseases. Oxalate is an end product produced in the liver and excreted primarily by the kidney. Oxalate is also absorbed from the diet and renal excretion reflects the combined endogenous and exogenous oxalate loads. Primary hyperoxaluria usually presents as calcium oxalate stone formation or nephrocalcinosis during childhood. Approximately 50% of children with primary hyperoxaluria have symptoms by 5 years. Primary hyperoxaluria is usually diagnosed by the finding of elevated urinary oxalate in a 24-h urine collection, with hyperoxaluria in children defined as exceeding 1.0–1.5 mmol/1.73 m^2/24 h. Most endogenously produced oxalate is derived from glyoxylate. Any alteration in glyoxylate metabolism that leads to increased hepatocyte glyoxylate levels will lead to increased oxalate production.

Type 1 primary hyperoxaluria (PH1) accounts for most oxalosis and for approximately 1% of chronic renal failure in childhood. In patients with PH1, there is a reduction or absence of alanine glyoxalate aminotransferase (AGT) activity that leads to increased glyoxylate levels with a resultant increased conversion to oxalate. Reduced or absent AGT activity leads to excessive build-up and urinary excretion of oxalate and glycolate with the formation and deposition of insoluble crystals primarily in the urinary tract and renal parenchyma, leading to recurrent urolithiasis, nephrocalcinosis and ultimately, renal failure and systemic oxalosis. Again primary hyperoxaluria type 2 (PH2) is characterized by a less severely affected phenotype and results from a deficiency of hydroxypyruvate reductase activity and glyoxylate reductase. Both forms of the disease are autosomal recessive. Children with PH2 usually do not present symptoms until their second or third decade of life, and the diagnosis is made following documentation of elevated urinary oxalate and L-glycerate levels [21].

Course of the disease

The natural history of pediatric stone disease is not as well defined as it is in adulthood. Regarding the stone recurrence in children after certain types of treatment modalities, the pathology has been found to be associated with considerable morbidity, with recurrence rates ranging from 6.5 to 44% with a mean interval of recurrence of 3–6 years [22–25]. Without follow-up and medical intervention, stone recurrence rates have been reported to be as high as 50% within 5 or 6 years [23, 24]. In children, the rate of recurrence of stones ranges widely from 3.6 to 67% and appears the highest in children with metabolic abnormalities [24, 25]. In our previous study, we were able to evaluate 91 children and a 4.2% recurrence rate and a mean follow-up of 38.2 months [26]. Again in their original study, Rizvi et al. [27] evaluated a large number of children ($N = 1{,}440$) and demonstrated a 2% recurrence rate during a 13-year follow-up period. Identifiable metabolic disorders are established risk factors for recurrent stones than those with no identifiable metabolic disorder by increasing the likelihood of the disease at least fivefold [28].

Again, on the other hand, it is well known that the disease is a destructive pathology that causes progressive decline in renal function together with certain recurrences and etiologies that required careful planning, individualized diagnostic and management protocols. Dramatic changes in the understanding of management of urolithiasis have also influenced the approach to stone disease in children [24, 29, 30]. As most children with stone disease have an underlying metabolic abnormality, it is essential that these children should be carefully evaluated so that the etiology of their disorder can be ascertained. In this way, future stone formation and/or regrowth may be controlled in the pediatric population limiting the morbidity of the disease [31].

Given the high risk of subsequent calculus formation, it could be argued that all children should undergo some form of evaluation to determine the cause of their kidney stone and to help plan proper management strategies. It is well known that certain groups of children should undergo a full metabolic work-up due to the high risk of recurrence. Through these efforts future stone formation and/or growth may be controlled in pediatric population, limiting the morbidity of this disease [26, 32–34] .

Medical management

Overview of general measures

The objective of stone management in children should be complete stone clearance, prevention of stone recurrence and regrowth, preservation of renal functions, control of UTIs, correction of anatomic abnormalities and correction of the underlying metabolic disorders. Long-term post-operative follow-up is mandatory, especially after using newer technical innovations for urinary calculus management during childhood [35, 36].

To prevent recurrent formation in patients with calcium stones, numerous regimens have been designed and published during recent decades [37]. The patients can be treated conservatively by an increased fluid intake with or without dietary manipulations or by administering pharmacological agents. As a pharmacological agent potassium citrate has been used with acceptable success rates. This agent is obviously effective in reducing the recurrence rate in patients with calcium stone disease by increasing the excretion of citrate mainly by increasing the pH of tubular cells. In this way, it may reduce the supersaturation with calcium oxalate and calcium phosphate and increase the inhibition of growth and aggregation [38, 39].

Being aware of possible stone recurrence during long-term follow-up, although some therapeutic agents, including increased water intake, medical treatment, etc. have been used in adults in an attempt to limit stone regrowth and/or recurrence with varying success rates [28, 38–40], limited information could be derived from the literature on this issue.

During a 3-year follow-up the proportion of the patients remaining stone-free on potasium citrate was 72% while the corresponding value for untreated control patients was 20%. Again, the stone formation reduced from 1.2 to 0.1 [41]. Recently, in a 5-year randomized prospective study, Borghi et al. [42] found a 12% recurrence rate in those who had been encouraged to increase their fluid intake to achieve an output of 2 l/day, and a 27% recurrence rate if they were given no specific advise on urine output.

An increased fluid intake gives an increased urine flow and thereby a reduction in the supersaturation level of all salts important in stone formation. In their original studies, both Borghi et al. [42] and Hoskin et al. [43] were able to show the inverse association between urine volume and recurrent stone formation. There is no doubt that increased urine flow is of great value for patients with stone disease irrespective of stone composition. There are a few studies that support this assumption in adults.

With respect to the preventive measures in children, in their original study, Tekin et al. [44] have treated 64 children with idiopathic hypocitraturia with potassium citrate (1 mEq/kg per day daily dose) while no recurrence could be shown in 44 children with primary stone disease and in the recurrent patient group ($n = 20$); however, although new stone formation rate was noted to be 0.32 per year before treatment, this value has came down to 0.17 per year after the treatment indicating the prophylactic effect of this agent on new stone formation.

Evaluation of data did show that a high fluid intake under close monitoring and the motivation of the parents could be critical in preventing supersaturation of the urine regardless of the cause of urolithiasis and by this way limiting the percentage of children that may show stone regrowth or recurrence after SWL. Children receiving adequate fluid were found to have limited stone recurrence rates when compared with the ones under watchful waiting.

Again it was clear that children suffering from hypocitraturia as primary urinary risk factor will benefit from potassium citrate replacement with reasonably limited regrowth and/or recurrence rates.

Treatment of specific risk factors

Hypercalciuria

Apart from adequate fluid intake (on a body-weight and age-matched basis), dietary sodium restriction along with a high-potassium, low-oxalate diet is recommended for children suffering from hypercalciuric stone disease. On the other hand, however, a low-calcium diet has not found to be effective in reducing the risk of stone recurrence and will pose a substantial risk to the maintenance of bone health. Again, thiazide diuretics are used commonly in conjunction with high urinary flow rates and dietary sodium restriction in children followed-up for a documented stone disease [45, 46].

Like adult patients, potassium citrate could be used successfully in hypercalciuria associated with distal RTA to correct the metabolic acidemia, hypokalemia and to bring the urinary calcium and citrate excretion to normal limits.

Hyperoxaluria

Primary hyperoxaluria could be best managed initially by reducing oxalate excretion along with increasing the solubility of calcium oxalate in urine. To accomplish this task, high water intake should be the essential part of the therapy. Additionally, like in adults, children should avoid oxalate-rich foods although most excreted oxalate is endogenously produced. Among the medical agents used, pyridoxine has been found to reduce urinary oxalate in primary hyperoxaluria successfully when compared with the other agents (magnesium oxide). In recent years, however, potassium citrate has also been commonly applied in such cases as a direct inhibitor of calcium oxalate crystallisation. This medication has been found to decrease urinary calcium oxalate supersaturation rates and eventually to limit the stone recurrence [45, 47].

The ultimate and definitive therapy for PH1 will be hepato-renal transplantation in the majority of the cases suffering from kidney failure, only liver transplantation could be performed in the earlier phase of the disease although the timing of transplant and the selection of appropriate subjects remain controversial [47].

Treatment of diet-dependent hyperoxaluria consists of restriction of high-oxalate foods and maintenance of a normal calcium intake to limit intestinal oxalate absorption and possibly, avoidance of excessive protein consumption. Dietary calcium restriction has been shown to increase the stone formation rate in patients with idiopathic hypercalciuria owing to increased urinary oxalate excretion

Uric acid stones

With respect to the medical management of uric acid calculi, enforced fluid intake together with alkalinization of the urine to a pH value of 6.5–7.0 with an appropriate agent (potassium citrate or sodium bicarbonate) are the main preventive measures in children suffering from uric acid stones. In case of failure with these measures, reduction of dietary protein and use of the xanthine oxidase inhibitor allopurinol may be indicated to pre-

vent stone recurrence. In the majority of the cases adequate fluid intake and urinary alkalinization can lead to dissolution of uric acid stones with minimal need for more invasive procedures unnecessary [45, 46].

Infection stones

Infection stones are successfully managed by the complete elimination of urinary stones and fragments (if possible) together with the correction of anatomic or functional obstruction, and sterilisation of the urine. Long-term suppressive, culture-specific antibiotic therapy (particularly if there are residual stone fragments) is often necessary [45].

Cystine calculi

In case of a cystine stone, treatment aims to increase the urinary flow rates, to restrict the dietary protein and sodium, and urinary alkalinization with potassium citrate to maintain a urinary pH above 7.5. The daily intake of fluid and alkali should be sufficient to maintain urinary cystine concentration below 300 mg/l. The fluid intake should be distributed throughout the day and night.

Regarding the use of medical agents, apart from some established effects of chelating agents, such as D-penicillamine and α-mercaptopropionyl glycine as adjunctive therapies, Captopril has been used in recent years with less encouraging success rates [45, 46, 48].

Again, it is well known that cystine stones are often resistant to ESWL; therefore, percutaneous surgery or ureteroscopy is often the preferred method of stone extraction.

Conclusions

It is clear that in addition to stone removal, treatment of pediatric urolithiasis requires a thorough metabolic and environmental evaluation of all patients on an individual basis. Obstructive pathologies should be corrected immediately and apparent metabolic abnormalities should also be treated with appropriate medical agents. Children with a positive family history should be followed carefully with respect to stone recurrence. Apart from the management of specific risk factors, urine volume increases in parallel with the body mass index, and medical therapeutic agents which increase urine citrate levels should be encouraged.

References

1. Stapleton FB (1989) Nephrolithiasis in children. Pediatr Rev 11:21–30
2. Milliner DS, Murphy ME (1993) Urolithiasis in pediatric patients. Mayo Clin Proc 68:241–248
3. Stapleton FB, McKay CP, Noe HN (1987) Urolithiasis in children: the role of hypercalciuria. Pediatr Ann 16:980–992
4. Choi H, Snyder III HM, Duckett JW (1987) Urolithiasis in childhood: current management. J Pediatr Surg 72:158–164
5. Gearhart JR, Herzberg GZ, Jeffs RD (1991) Childhood urolithiasis: experiences and advances. Pediatrics 87:445–450
6. Polinsky MS, Kaiser BA, Baluarte HJ (1987) Urolithiasis in childhood. Pediatr Clin North Am;84:683–710
7. Ryall RL (1996) Glycosaminoglycans, proteins, and stone formation: adult themes and child's play. Pediatr Nephrol 10:656–666
8. Parks JH, Coward M, Coe FL (1997) Correspondence between stone composition and urine saturation in nephrolithiasis. Kidney Int 51:894–900
9. Battino BS, DeFoor W, Coe F, Tackett L, Erhard M, Wacksman J et al (2002) Metabolic evaluation of children with urolithiasis: are adult references for supersaturation appropriate? J Urol 168:2568–2571
10. Kruse K, Kracht U, Kruse U (1984) Reference values for urinary calcium excretion and screening for hypercalciuria in children and adolescents. Eur J Pediatr 143:23–31
11. DeSanto NG, DiIorio B, Capasso G, Paduano C, Stamler R, Langman CB et al (1992) Population based data on urinary excretion of calcium, magnesium, oxalate, phosphate and uric acid in children from Cimitile (southern Italy). Pediatr Nephrol 6:149–157
12. Ghazali S, Barratt TM (1974) Urinary excretion of calcium and magnesium in children. Arch Dis Child 45:97–101
13. Stapleton FB, Noe HN, Roy S III, Jerkins GR (1982) Hypercalciuria in children with urolithiasis. Am J Dis Child 136:675–678
14. Stapleton FB, Noe HN, Jerkins GR, Roy S III (1982) Urinary excretion of calcium following an oral calcium-loading test in healthy children. Pediatrics 69:594–597
15. Coe FL, Parks JH, Moore ES (1979) Familial idiopathic hypercalciuria. N Engl J Med 300:337–340
16. Stapleton FB (1990) Idiopathic hypercalciuria: association with isolated hematuria and risk for urolithiasis in children. Kidney Int 37:807–811
17. Dent CE, Friedman M (1964) Hypercalciuric rickets associated with renal tubular damage. Arch Dis Child 39:240–249
18. Igarashi T, Hayakawa H, Shiraga H, Kawato H, Yan K, Kawaguchi H et al (1995) Hypercalciuria and nephrocalcinosis in patients with idiopathic low molecular weight proteinuria in Japan. Nephron 69:242–247
19. Furth SL, Casey JC, Pyzik PL, New AM, Docimo SG, Vining EPG et al (2000) Risk factors for urolithiasis in children on the ketogenic diet. Pediatr Nephrol 15:125–8
20. Herzberg GZ, Fivush BA, Kinsman SL, Gearhart JP (1990) Urolithiasis associated with the ketogenic diet. J Pediatr 117:743–745
21. Asplin JR (2002) Hyperoxaluric calcium nephrolithiasis. Endocrinol Metab Clin N Am 31:927–949
22. Pietrow PK, Pope JC, Adams MC, Shyr Y, Brock III JW (2002) Clinical outcome of pediatric stone disease. J Urol 167:670–673
23. Kroovand RL (1997) Pediatric urolithiasis. Urol Clin North Am 24(1):173–185
24. Cohen TD, Ehreth J, King LR, Preminger GM (1996) Pediatric urolithiasis: medical and surgical management. Urology 47(3):292–305
25. Milliner DS, Murphy ME (1993) Urolithiasis in pediatric patients. Mayo Clin Proc 68:241–244
26. Erbağcı A, Erbağcı BA, Yılmaz M, Yağcı F, Tarakçıoğlu M, Yurtseven C, Köylüoğlu O, Sarıca K (2003) Pediatric urolithiasis. Scand J Urol Nephrol 37:127–133
27. Rizvi SAH, Naqvi SAA, Hussain Z, Hashmi A, Hussain M, Zafar MN, Sultan S, Mehdi H (2002) Pediatric urolithiasis: developing nation perspectives. J Urol 168:1522–1525
28. Tefekli A, Esen T, Ziylan O, Erol B, Armağan A, Ander H, Akıncı M (1993) Metabolic risk factors in pediatric and adult calcium oxalate urinary stone formers: Is there any difference? Urol Int 70:273–277

29. Noe HN (2000) Hypercalciuria and pediatric stone recurrences with and without structural abnormalities. J Urol part 2 164:1094–1096
30. Diamond DA, Menon M, Lee PH et al (1989) Etiological factors in pediatric stone recurrence. J Urol part 2 142:606–608
31. Hoppe B, Jahnen A, Bach D, Hesse A (1997) Urinary calcium oxalate saturation in healthy infants and children. J Urol 158:557–559
32. Drach GW (1995) Metabolic evaluation of pediatric patients with stones. Urol Clin North Am 22:95–102
33. Stapleton B (1996) Clinical approach to children with urolithiasis. Semin Urol 16(5):389–397
34. Tekin A, Tekgül S, Atsu N, Şahin A, Özen H, Bakkaloğlu M (2000) A study of the etiology of idiopathic calcium urolithiasis in children. Hypocitraturia is the most important risk factor. J Urol 164:162–165
35. Perrone HC, dos Santos DR, Santos MV (1992) Urolithiasis in childhood: metabolic evaluation. Pediatr Nephrol 6:54–59
36. Pietrow PK, Pope JC, Adams MC, Shyr Y, Brock JW (2002) Clinical outcome of pediatric stone disease. J Urol 160:670–73
37. Özokutan BH, Küçükaydın M, Gündüz Z et al (2000) Urolithiasis in childhood. Pediatr Surg Int 16:60–63
38. Soygur T, Akbay A, Kupeli S (2002) Effect of potassium citrate therapy on stone recurrence and residual fragments after shockwave lithotripsy in lower caliceal calcium oxalate urolithiasis: a randomized controlled trial. J Endourol 16(3):149–152
39. Whalley NA, Meyers AM, Martins M, Margolius LP (1996) Long-term effects of potassium citrate therapy on the formation of new stones in groups of recurrent stone formers with hypocitraturia. Br J Urol 78(1):10–14
40. Pak CYC, Fuller C, Sakhaee K et al (1985) Long-term treatment of calcium nephrolithiasis with potassium citrate. J Urol 134:11–14
41. Barcelo B, Wahl O, Semitge E, Rousaud A, Pak CYC (1993) Randomized double-blind study on potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. J Urol 150:1761–1764
42. Borghi L, Meschi T, Amato F, Briganti A, Navarini A, Giannini A (1996) Urine volume, water and recurrences in idiopathic calcium nephrolithiasis. A 5-year randomized prospective study. J Urol 155:839–843
43. Hoskin DH, Erickson SD, van der Berg CJ, Wilson DM, Smith LH (1983) The stone clinic effect in patients with idiopathic calcium nephrolithiasis. J Urol 13:1115–1118
44. Tekin A, Tekgul S, Atsu N, Bakkaloglu M, Kendi S (2002) Oral potassium citrate treatment for idiopathic hypocitruria in children with calcium urolithiasis. J Urol 168(6):2572–2574
45. Stapleton FB, Kroovand RL (1996) Stones in childhood. In: Coe FL, Favres MJ, Pak CYC, Parks JH, Preminger GM (eds) Kidney stones: medical and surgical management. Lippencott-Raven, Philadelphia, pp 1065–1080
46. Cohen TD, Ehreth J, King LR, Preminger GM (1996) Pediatric urolithiasis: medical and surgical management. Urology 47(3):292–305
47. Asplin JR (2002) Hyperoxaluric calcium nephrolithiasis. Endocrinol Metab Clin N Am 31:927–949
48. Coulthard MG, Richardson J, Fleetwood A (1995) The treatment of cystinuria with captopril. Am J Kidney Dis 25:661–662