Chapter 12
Struvite Stones, Diet and Medications

Ben H. Chew, Ryan Flannigan, and Dirk Lange

General Principles

Struvite stones are a major cause of staghorn calculi. Struvite stones are composed of magnesium, ammonium phosphate. Infection-related stones may also contain calcium carbonate apatite, a crystalline phase of calcium phosphate. They are associated with urinary tract infections with certain bacteria that produce the enzyme urease. Removal of the entire stone is paramount to prevent further stone formation and infections.

Epidemiology

- Struvite stones comprise about 10–15 % of all kidney stones
- They occur more frequently in women in an approximate 2:1 ratio. This is thought to be due to the higher prevalence of urinary tract infections in women.
- Presenting signs are not always typical renal colic as in other stone types, but is usually recurrent urinary tract infections and may include the following with their frequency of occurrence:

B.H. Chew, MD, MSc, FRCSC (✉) • R. Flannigan, MD • D. Lange, MD
Department of Urological Sciences, University of British Columbia, Level 6 – 2775 Laurel Street, Vancouver, BC, Canada V52 1M9
e-mail: ben.chew@ubc.ca

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- 70 % flank/abdominal pain
- 26 % fever
- 18 % gross hematuria
- 8 % asymptomatic
- 1 % sepsis

Risk Factors [1, 2]

- Female gender (2:1 ratio compared to males)
- Extremes of ages
- Congenital urinary tract malformations
- Urinary stasis from obstruction
- Urinary diversion
- Neurogenic bladder (from neurologic disorders including spinal cord injury, spina bifida, multiple sclerosis etc.)
- Chronic indwelling Foley catheters
- Distal renal tubular acidosis
- Medullary sponge kidney
- Diabetes mellitus.

Etiology

- Production of an infection stone requires urea, water, calcium (Ca), magnesium (Mg), phosphate (PO_4), urine with pH>6.8–7.2, and the urease enzyme.
- Bacteria that contain the enzyme, urease, break down urea which results in increasing ammonia and carbon dioxide. Both gram-positive and gram-negative organisms can produce this enzyme.
- Carbonate apatite begins to crystallize at urine pH greater than 6.8 and magnesium ammonium phosphate (struvite) crystallizes at pH greater than 7.2.
- Struvite stones can be found bilaterally in 15 % of cases.
- When the urinary environment is receptive, struvite stones can form rapidly; even within 4–6 weeks [3].

Diagnostic Testing

- Definitive diagnosis is made by stone analysis of magnesium ammonium phosphate or carbonate apatite.
- Microbiological culture of stones is the best source to identify which urease-producing bacteria is responsible, but this is not always detectable. The second best site to identify bacteria is from urine sampled directly from the kidney since it is closest to the site of the infected stone.
- Voided urine culture is not always congruent with the underlying urease-producing bacteria responsible for stone formation.
- The most common species that possess the urease enzyme are *Proteus, Providencia, Serratia ureilytica, and Morganella morganii*. Only 1.4 % of *Escherichia coli* species produce urease.
- If urease-producing bacteria are identified on culture, their mere presence does not always result in struvite stone formation. Despite the fact that up to 39 % of UTIs are associated with urease-producing bacteria, the incidence of struvite stones is still only 16 % suggesting that the presence of a urease positive pathogen is not the only criterion and that other factors must be present in order for a struvite stone to form [3].
- Urine pH is typically greater than 6.8 (>6.8 produces carbonate apatite stones and once >7.2, struvite stones form).

Treatment and Prevention

- As with renal calculi in general, a low sodium diet and high water diet may aid in preventing calculi, as well as modifying risk factors for urinary tract infections such as: limiting foreign bodies to urinary tracts, treating constipation, minimizing stasis of urine, and minimizing immune compromised states. High protein diets have been shown to acidify the urine in veterinary studies and reduce struvite crystals [4], but this is not a proven strategy for struvite stone prevention in humans.

- Treatment and directed therapy of struvite stones is necessary. Conservative non-surgical management however carries a higher 10-year mortality (28 %) compared to those who are managed surgically with stone extraction (7.2 %) [5]. The rate of renal failure is also higher in those managed non-surgically (36 %) compared to those treated with surgery (15.9 %) [1].
- Patients with staghorn calculi who did not undergo surgery were more likely to have renal failure and death (67 %) compared to those who were treated successfully with surgery (0 % mortality) [6]. The same study showed that if infected stone fragments were not entirely cleared, the mortality rate rose from 0 to 2.9 %. Furthermore, the recurrence rate rises to 85 % if residual stone fragments remain.
- Three principles are paramount in the treatment of infection stones [3]:
  - All infected stone burden must be removed
  - Antibiotics must be used to treat the infection to ensure that the urine will be sterile even in the absence of antibiotics.
  - Prevent recurrence by ensuring that both principles 1 and 2 are followed. Subsequent infections must be prevented and all stone must be removed or the cycle will continue.
- There is no set diet to prevent infection stones, and dietary recommendations should be developed and implemented individually, on a case-by-case basis. Acidification therapy with cranberry juice has been used in veterinary studies with some success, but the dosage required would have to be high enough to reduce urine pH [7–9]. Currently, the use of cranberry juice to prevent infection stones remains theoretical in human populations.
  - Acidifying the urine can be helpful in reducing the rate of infection stones, although there is no standardized recommended method [9].
  - Avoiding supplemental magnesium has been shown to be helpful in animal studies [9].
  - Phytonutrients in green tea, turmeric, and berries may reduce the risk of infection [9].

Medications

Antibiotics

- There is very good evidence to utilize antibiotics prior to surgical stone removal as well as following surgery; however, the ideal duration of antibiotic use pre- and post-operatively is widely debated.
- Directed antibiotic therapy aimed at the offending organisms is the preferred therapy. Antibiotics should be administered prior to surgery and for some time following surgery. Complete stone removal is mandatory (see surgical management below) to prevent subsequent infections, sepsis, and stone recurrence.
- Pre-operative oral antibiotics followed by intravenous broad-spectrum antibiotics the day prior to procedure reduce the rates of sepsis. Suppressive antibiotics dosed at ½ frequency should be considered and have been reported in the literature to range from 1 week to 1 year. Antibiotic selection should reflect local antibiograms; however, ciprofloxacin, cefixime, and amoxicillin-clavulanate are three typically sensitive antibiotics to common struvite forming bacteria. Patients should be followed with routine urine cultures and imaged post-operatively to ensure that they remain infection and stone-free. Timing varies by institution, however, both stone and urine cultures should be performed at time of operation, and both imaging and cultures should be repeated within the first 12 weeks post-operatively. Imaging should occur more frequently than with other stone types due to the fact that infection stones may grow very rapidly in the order of 4–6 weeks.

Urease Inhibitors

- Urease inhibitors prevent the enzyme urease from producing further ammonia and carbon dioxide and altering the urine pH, to prevent production of making a favorable milieu for struvite stones to form. Their use has been shown to provide only a modest benefit.

- The use of *acetohydroxamic acid* has been shown in a randomized double-blind study in patients with chronic urinary tract infections to reduce struvite stone formation from 46 to 17 % [10].
- Side effects of acetohydroxamic acid were quite prevalent in this study thus not favoring the routine clinical use of this therapy. Side effects included dermatological, hematological, and neurological side effects in 22 % of patients treated.

Dissolution Therapy

- Dissolution therapy is a second line treatment for infection stones. Boric acid and permanganate were the first components used for this purpose but are no longer used clinically today.
- *Solution G* was described by Suby in 1944 and is now also known as *Suby's G Solution* [11]. It is an acidic solution (citric acid) that lowers the pH of the urine to dissolve carbonate apatite or struvite crystals.
- *Renacidin R* also alters the urine pH and consists of citric acid, glucono-delta-lactone, and magnesium carbonate [12].
- Use of dissolution therapy is reserved for those patients who are poor surgical candidates as there is a higher risk of mortality from sepsis.
- Rates of success have been reported between 68 and 80 % of cases for dissolution therapy [13, 14].
- Renacidin is no longer FDA approved due to the high rates of sepsis and death.
- Dissolution therapy should be limited to cases where patients would not tolerate surgery. Patients must be admitted to hospital with a nephrostomy tube, Foley catheter, and a normal nephrostogram to ensure that the nephrostomy tube is properly placed with no chance of extravasation. Mean hospital stays of over 30 days are typically required and can be costly to the health care system [15].

Surgery

- The primary therapy for removal of large stone burdens is percutaneous nephrolithotomy (*PCNL*) as recommended by the American Urology Association guideline for staghorn calculi [16]. Shockwave lithotripsy (*SWL*) should not be first-line therapy for large stone burdens, but can be attempted for smaller stone burdens and only if adequate drainage of the kidney is present *prior* to SWL.
  - PCNL is far superior to SWL in a prospective randomized trial. Stone-free rates were 74 % for PCNL compared to 22 % for SWL in a study involving 50 patients with staghorn calculi [17].
- *Ureteroscopy* (*URS*) is a viable *adjunctive* therapy for treating infection stones in combination with PCNL. URS can be used to treat any small fragments that remain after PCNL. URS can be performed in the same sitting as PCNL in an attempt to minimize the number of percutaneous access tracts and has been shown to reduce the amount of blood loss with good stone-free rates [18, 19].
- *Nephrectomy* should be considered in cases where the kidney has negligible function. Kidneys that are damaged from chronic infection and obstruction with severe parenchymal deterioration may act as a source of further infection and if the contralateral kidney is unaffected, nephrectomy is often the best option in these cases [16].
- Open stone surgery (*anatrophic nephrolithotomy*) is rarely necessary in our age of advanced endoscopic techniques, but should be considered if significant anatomical abnormalities exist and if this technique is thought to reduce the number of procedures in order to render the patient stone-free. Obese patients and those with anatomic abnormalities such as infundibular stenosis are potential candidates for this therapy [20]. A randomized trial of open surgery compared to PCNL showed the stone-free rates to be similar, but with many advantages to PCNL including shorter operative times (127 vs 204 min), lower transfusion rate

(14 vs 33 %), shorter hospital stay (6.4 vs 10 days), and earlier return to work (2.5 vs 4.1 weeks) [21].
- Antibiotic therapy pre- and post-operatively is necessary to reduce morbidity and mortality.

Conclusion

- Infection stones occur when bacteria possess the enzyme urease.
- Surgical management and removal of the entire stone is paramount in treatment making PCNL the surgical treatment of choice.
- Antibiotics are another important aspect both prior to and following surgical stone removal. The ideal duration of therapy is unknown. Ensuring a sterile urine environment after stone removal is key to preventing recurrence stones and sepsis.
- Urease inhibitors and dissolution therapy are not routinely recommended and carry a higher rate of sepsis and mortality as well as increased health care costs.

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