Renal struvite stones—pathogenesis, microbiology, and management strategies

Ryan Flannigan, Wai Ho Choy, Ben Chew and Dirk Lange

Abstract | Infection stones—which account for 10–15% of all urinary calculi—are thought to form in the presence of urease-producing bacteria. These calculi can cause significant morbidity and mortality if left untreated or treated inadequately; optimal treatment involves complete stone eradication in conjunction with antibiotic therapy. The three key principles of treating struvite stones are: removal of all stone fragments, the use of antibiotics to treat the infection, and prevention of recurrence. Several methods to remove stone fragments have been described in the literature, including the use of urease inhibitors, acidification therapy, dissolution therapy, extracorporeal shockwave lithotripsy, ureteroscopy, percutaneous nephrolithotomy (PCNL), and anatrophic nephrolithotomy. PCNL is considered to be the gold-standard approach to treating struvite calculi, but adjuncts might be used when deemed necessary. When selecting antibiotics to treat infection, it is necessary to acquire a stone culture or, at the very least, urine culture from the renal pelvis at time of surgery, as midstream urine cultures do not always reflect the causative organism.

Flannigan, R. *et al. Nat. Rev. Urol.* **11**, 333–341 (2014); published online 13 May 2014; corrected online 27 May 2014; doi:10.1038/nrurol.2014.99

Introduction

Struvite (magnesium ammonium phosphate) stones are a subset of kidney stones that form as a result of UTI with urease-producing pathogens. As such, they are often referred to as infection stones. Overall, they comprise 10–15% of all urinary stones,[1] and are known to occur more frequently in women than in men (at a 2:1 ratio)[2]—a finding that might be attributable to the higher incidence of UTI in women. In an Australian study, the incidence of struvite stones was shown to have decreased from 14% in the 1970s to 12% in the 1980s, and to 7% in 2013.[3] However, this stone type still accounts for 24.4% of staghorn calculi.[4] Infection stones do not always present with typical renal colic, as seen with many other stone types; nearly 70% present with flank or abdominal pain, 26% present with fever, 18% with gross haematuria, 8% are asymptomatic, 1% present with sepsis, and others can present with recurrent UTI.[5,6] Factors that predispose patients to struvite stones include female gender, extremes of ages, congenital urinary tract malformations, stasis from urinary obstruction, urinary diversion, neurogenic bladder, indwelling Foley catheters, distal renal tubular acidosis, medullary sponge kidney, and diabetes mellitus.

Struvite stones can form in either the kidney or bladder; when formation occurs in the kidney, stones are bilateral in nearly 15% of cases.[5] Infection stones are one of the most common aetiologies of staghorn morphology, and have been known to form rapidly (within 4–6 weeks); calcium-based stones, on the other hand, can take more than 13 weeks (range 2–28 weeks) to form, even in high-risk, hot environments.[7,8] Composition is often heterogeneous but stones typically contain a component of magnesium ammonium phosphate, with or without components of monoammonium urate or carbonate apatite.[8] Here, we provide an overview of our current understanding of the microbiology, pathogenesis, treatment, and prevention of struvite stones.

The Stone Centre at Vancouver General Hospital, Jack Bell Research Centre, 2660 Oak Street, Vancouver, BC V6H 3Z6, Canada (**R.F.**, **W.H.C.**, **B.C.**, **D.L.**).

Correspondence to: D.L.
dirk.lange@ubc.ca

Competing interests
B.C. declares consulting associations with Boston Scientific, Cook Medical, Olympus ACMI, PercSys, and Bard Medical. D.L. declares consulting associations with Boston Scientific, Olympus, Cook Medical, PercSys, and Bard Medical. R.F. and W.H.C. declare no competing interests.

Microbiology

Struvite stone formation is exclusively associated with bacteria that produce the enzyme urease, including both gram-positive and gram-negative species from genera such as *Proteus, Staphylococcus, Pseudomonas, Providencia*, and *Klebsiella*. The number of urease-producing strains within a bacterial species can be highly variable, and not every strain produces the urea-splitting enzyme. A study of bacterial isolates from patients with complicated UTIs showed that only 84% of *Klebsiella* spp and 55% of *Staphylococcus* spp produced urease, compared with 100% of *Proteus* spp, *Providencia* spp, and *Morgenalla morganii* spp.[8] In 2005, *Serratia ureilytica* sp was identified as a novel urease-containing species.[9] Despite being a major cause of UTI, only 1.4% of *Escherichia coli* spp are thought to produce urease and are, therefore, not considered a major cause of struvite stone formation. This finding highlights the importance of identifying the urease-producing species based on stone culture rather than urine culture alone, as bacteria cultured from the stone itself do not always match those identified by urine culture.[10–12] That said, some studies have reported a concordance between stone

Key points

- Struvite stones form a subset of kidney stones that are exclusively associated with urease-producing bacteria
- Stone culture at the time of treatment or urine culture from the renal pelvis provides useful clinical information for directing antibiotic therapy
- Percutaneous nephrolithotomy (PCNL) is the gold-standard approach for treatment of staghorn infection calculi but other interventions might have an adjunctive role in therapy
- Residual stone fragments can be removed using urease inhibitors, acidification therapy, dissolution therapy, extracorporeal shockwave lithotripsy, ureteroscopy, PCNL, or anatrophic nephrolithotomy
- Repeat imaging and urine cultures should be performed within 3 months of the procedure to confirm a stone-free status or identify recurrence

and urine cultures of up to 70%.[4] Notably, many of the bacteria cultured from stones and urine in these series were not typical urease-producing bacteria, suggesting that additional urease-producing bacteria were present during the initiation or crystallization of stones, but were not successfully cultured. Although less than perfect, stone culture is probably the best way to identify urease-producing bacteria. In the absence of stone culture, urine should be sampled from the closest site to the infection, meaning directly from the kidney.

The probability of obtaining a positive stone culture is higher for nonstruvite stones than for struvite stones, largely because nonstruvite stones are more common. A study from Thailand revealed that, among 100 stone formers, a total of 45 bacterial isolates were obtained from the stone or urine for 36 patients. Struvite stones were identified in just eight of these 36 patients; the rest were nonstruvite stones, which are traditionally thought of as metabolic stones (including calcium oxalate and calcium phosphate stones). Indeed, calcium oxalate stones were the most common stone type, accounting for 75% and 64% of stones in patients with positive stone or kidney urine cultures and those with negative cultures, respectively. Specifically, the most common type of stone in patients with positive bacterial cultures was composed of calcium oxalate, phosphate, struvite, and uric acid.[13] Similarly, a group from Indianapolis, USA, found that 54% of nonstruvite stones and 73% of struvite stones were identified by positive cultures. This group also reported a positive culture rate of 65% for stones containing carbonate apatite, leading them to conclude that if carbonate apatite is identified in the stone, it is likely that bacteria will also be present, although they note that this approach lacks specificity as other nonstruvite stones also harbour bacteria.[14]

New applications of technology that could be used to identify bacteria in infection stones include scanning electron microscopy and powder neutron diffraction.[15] Using these techniques, the mesoscopic structure of the stone can be assessed and bacterial imprints on the fine crystals of carbonated apatite stones can be seen; unfortunately, these imprints cannot be seen on the larger struvite crystals. The identification of bacterial morphology might be clinically relevant if urine and stone cultures are negative to tailor antibiotic therapy.[16] At present, clinical barriers to these technologies include availability and cost.

In addition to stone culture, stone size is also a predictor of a positive culture result. Marriappan and colleagues[10] reported positive stone culture rates of 21.3% and 43.6% with <20 mm and >20 mm diameter stones. Margel *et al.*[17] compared positive urine and stone culture rates in 75 consecutive patients who received percutaneous nephrolithotomy (PCNL), and found that the urine cultures had a sensitivity of 30%, a specificity of 94%, a positive predictive value of 84%, and a negative predictive value of 58% compared with gold-standard stone cultures.[17]

Bacterial isolates also predict stone composition; stones with >80% struvite or apatite always culture positive for 'strong' urease-producing bacteria such as *Proteus spp* (which produce high levels of urease), whereas those with <20% struvite or apatite largely culture *E. coli*, which does not produce excessive amounts of urease.[18] Despite the fact that urease activity is linked to struvite stone formation, infection with urease-positive bacterial species does not always result in struvite stone formation. Bichler and colleagues[8] showed that at their institution, over a 5-year period from 1992 to 1997, 32–39% of UTIs were caused by urease-producing bacteria, whereas the incidence of struvite stones was around 12–16%. These results suggest that factors other than infection with a urease-positive pathogen contribute to struvite stone formation (for example, the absence of natural struvite inhibitors). Thus, studying the composition of urine from patients infected with urease-positive bacteria but without struvite stones is likely to be of interest, potentially revealing factors other than urinary pH that regulate struvite stone formation.

The formation of bacterial biofilms within the kidney as part of the infection process complicates things further (Figure 1). Aside from increasing the urinary pH to promote the crystallization of magnesium ammonium phosphate, ammonia production also facilitates struvite stone formation by damaging the glycosaminoglycan layer that covers urothelial cells and protects them from bacterial pathogens.[19] Once this barrier has been breached, bacteria are able to attach to, and colonize, the surface of the urothelium, resulting in the formation of a bacterial biofilm. More than 30 years ago, it was suggested that the production of alkaline urine alone is insufficient to result in the rapid crystal growth and aggregation required for the formation of clinically relevant stones, and that a matrix is also required to bind the particulate matter together.[20,21] Close microscopic analysis of the structure of surgically removed struvite stones by Nickel *et al.*[22] revealed that the 3D structure of these stones is formed by large numbers of bacteria that grow within a matrix produced by the bacteria themselves. Further studies by this group revealed that this matrix is composed of protective exopolysaccharides secreted by the bacteria as part of the biofilm formation process. The initial steps of struvite stone formation were shown to begin within the bacterial matrix itself, where urease activity resulted in the local deposition of ammonia, followed by an increase in pH within the biofilm and, eventually, in the urine.[23] This process, in turn, results in the precipitation of struvite and apatite crystals within the growing biofilm. The original nidus for crystallization continues to grow as the

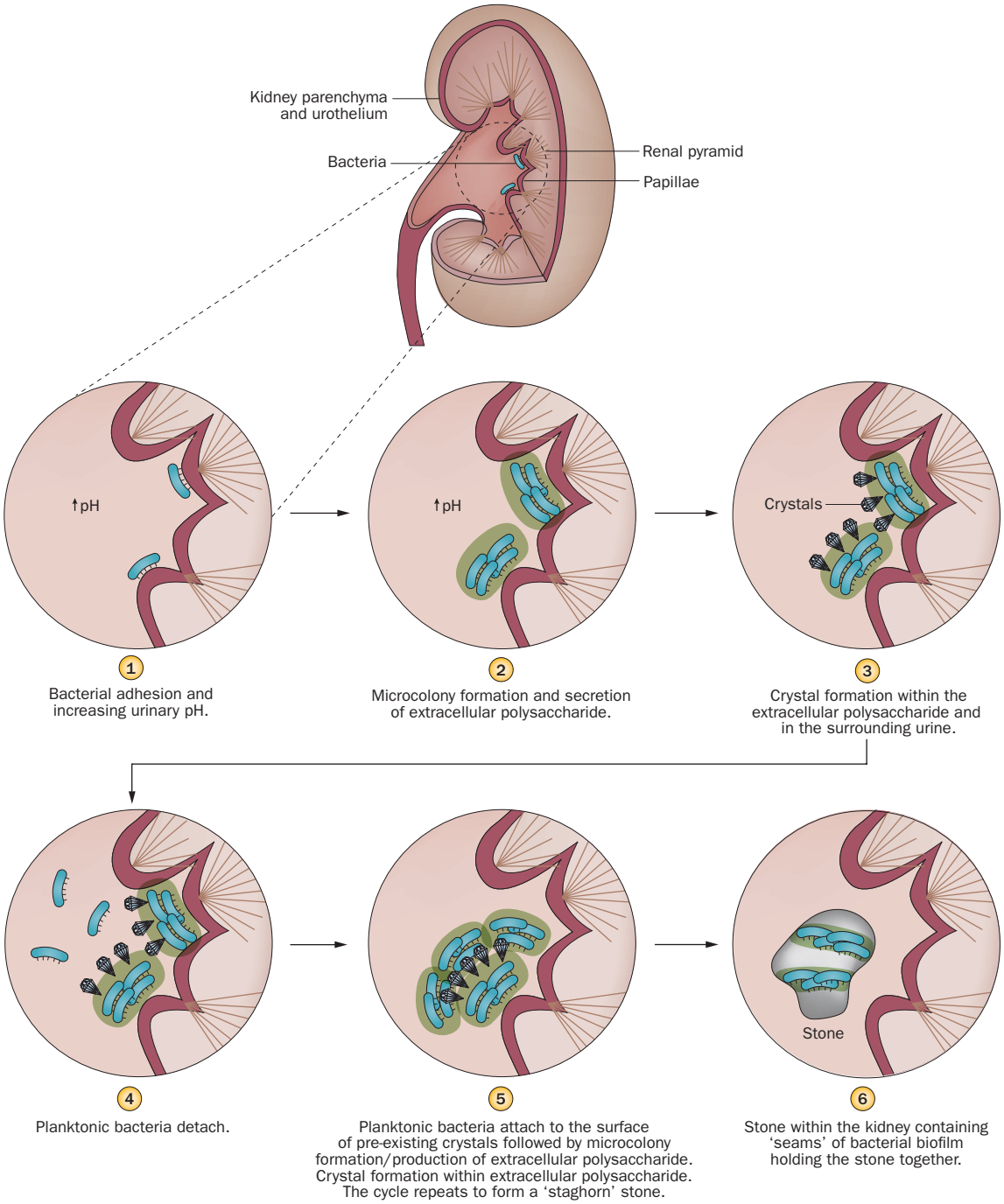

Figure 1 | The process of biofilm formation. The formation of biofilm involves bacterial adhesion and increasing urinary pH (1) followed by the formation of microcolonies and the excretion of extracellular polysaccharides (2), which encase the bacteria leading to crystal formation (3). The bacteria detach from the microcolonies (4) and reattach to crystals (5). The process is repeated until a mature biofilm forms with extracellular polysaccharides encasing the bacteria on stone surfaces, the urothelium, and the urinary tract (6).

bacteria within the biofilm continue to secrete exopolysaccharides. As a result, mature struvite stones consist of multiple magnesium ammonium phosphate layers held together by bacterial biofilms, which form the seams within the stone (Figure 1).[24] Thus, the removal of all stone fragments is imperative, as encasement in a thick layer of exopolysaccharide and struvite renders the infecting bacteria highly resistant to antibiotic treatment.

Pathogenesis

The pathogenesis of infection stones requires urea, water, calcium, magnesium, phosphate, urine pH of >6.8–7.2, and the urease enzyme. When urease is present, water and urea are hydrolysed to form carbon dioxide (CO_2) and ammonia; these compounds hydrolyse further to form ammonium and bicarbonate. In the presence of naturally occurring cations in urine (such as magnesium,

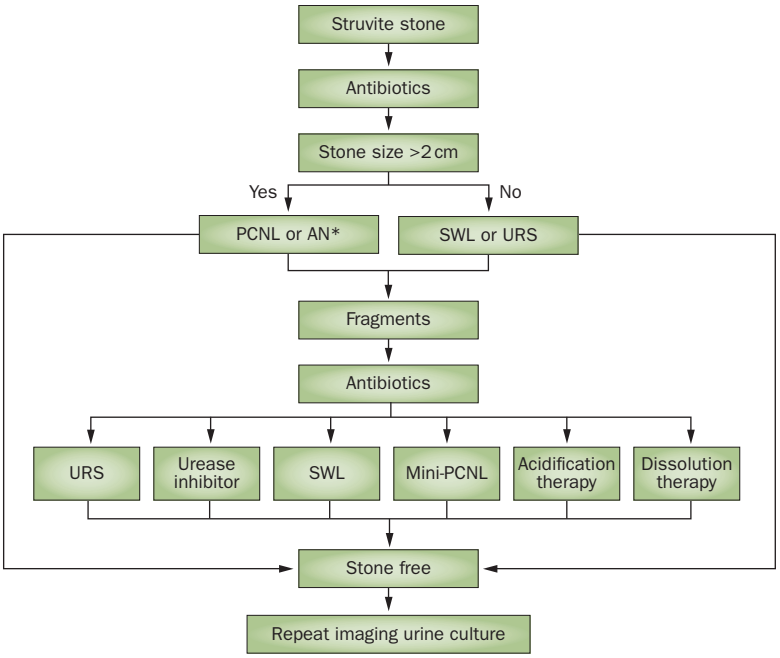

Figure 2 | A proposed algorithm for the management of struvite stones. Antibiotics should be used in the presence of a struvite stone before surgery. If the patient is not a surgical candidate, SWL might be considered (if feasible); otherwise, the gold-standard PCNL should be used. In rare circumstances when PCNL is not possible owing to anatomical abnormalities, AN should be considered. Antibiotics should be considered after the procedure in the presence of fragments. These fragments can be treated with several different modalities; URS, SWL, repeat PCNL, and mini-PCNL are most commonly used to achieve stone clearance. Repeat imaging and urine cultures should be performed postoperatively. *PCNL adjuncts might include mini-PCNL, flexible nephroscopy and retrograde URS. Abbreviations: AN, anatrophic nephrolithotomy; PCNL, percutanous nephrolithotomy; SWL, shockwave lithotripsy; URS, ureteroscopy.

calcium, and anion phosphate), struvite forms if the urine pH is >7.2, whereas carbonate apatite forms if the pH is 6.8–7.2.[8] Struvite is typically created by the crystallization of three components: magnesium, ammonium, and phosphate. The production of ammonia and CO_2 from urea raises the urine pH, often from 7.2 up to around 8.0. Crystallization of struvite and apatite then occurs peribacterially or intrabacterially, and rapid growth ensues. If crystallization occurs intrabacterially, the microlith is formed after bacteriolysis and propagation of stone formation occurs. If crystallization occurs peribacterially, on the other hand, the bacteria are thought to become encased within the stone and, therefore, infection resides in the stone. Natural stone inhibitors, such as citrate, typically protect against stone formation by forming complexes with magnesium and calcium; in infection stones with high concentrations of bacteria, however, the citrate is metabolized and no longer functions as a stone inhibitor.[1]

Kajander and Ciftcioglu[25] described an alternative mechanism of stone formation, involving the excretion of carbonate apatite through the cell membranes of nanobacteria. These bacteria are the smallest bacteria known to retain a cell membrane (10–100-fold smaller than typical bacteria) and exist as a heterogeneous population within the stone matrix. However, it has since been suggested that these nanoparticles are, in fact, not living organisms at all, but tiny components of a mineralo fetuin complex, concluding that fetuin proteins (termed 'nanons') have roles as nucleating factors for hydroxyapatite in renal calculi.[26] Since this discovery, it has become the most accepted theory.

Management

Several methods have been described for the management of infection stones (Figure 2). All patients are eligible for an initial regimen of antibiotics—such as amox-clavulanate, cefixime, or ciprofloxacin—if struvite stone is suspected prior to removal. If the patient is not a suitable candidate for surgery, extracorporeal shockwave lithotripsy (SWL) might be considered when feasible; otherwise, the gold-standard approach of struvite stone removal is PCNL. In rare circumstances when PCNL is not viable owing to anatomical abnormalities—such as a pelvic kidney, retrorenal colon, or spinal deformities that make percutaneous access to the kidney impossible—anatrophic nephrolithotomy might be considered. Today, open stone surgery is rarely performed given the advanced endoscopic techniques that exist. Antibiotics should also be given in the presence of stone fragments, which might later require treatment with several different modalities (ureteroscopy, SWL, or repeat PCNL) to achieve complete stone clearance. Repeat imaging and urine cultures should be performed within 3 months of the procedure to confirm stone-free status, or identify recurrence.

Studies of conservative therapy have identified the necessary role of directed therapy in treating struvite stones. In one series, conservative treatment of staghorn calculi resulted in a 10-year mortality rate of 28% compared with 7.2% for those surgically managed.[27] Chronic renal failure also seems to be higher in patients who are conservatively managed; in one study, 36% of patients who were conservatively managed experienced chronic renal failure over an average follow-up period of 7.8 years, compared with 15.9% of those who received surgical therapy.[5] Additionally, Teichman[28] demonstrated a renal-failure-related mortality rate of 67% for patients with staghorn calculi who declined treatment compared with 0% for those who were stone free following successful treatment and 2.9% for those treated with incomplete stone clearance. Wong and colleagues[29] reported a recurrence rate of 10% for struvite stones following complete irradication of stone and infection, increasing to 85% if residual stone fragments remained. Similarly, a series of 43 patients reported no recurrences among those with complete stone clearance compared with 40% among those with residual fragments, and the strongest predictor of recurrence was residual fragment size.[30] Although no guidelines exist, fragments <4 mm are suitable for observation with serial imaging and urine cultures, whereas fragments of ≥4 mm should be definitively treated.

Diagnosing struvite stones often relies on postoperative stone analysis, typically with CT, which is very accurate in this context. However, it can be difficult to accurately

differentiate between stone types with imaging. One research group evaluated use of the Hounsfield unit (HU) scale, a quantitative scale used to describe radiodensity, for differentiating between stone types. They found large variation among struvite stones (mean of 820 ± 357.9 HU) and significant overlap with other stone types (such as calcium oxalate and uric acid stones), making radiodensity on CT not specific enough to diagnose struvite stones in the body.[31] Others have been successful in differentiating struvite stones from calcium-based stones and uric acid stones *in vitro*, but dual-energy CT (DECT) was required to differentiate struvite from cysteine stones.[32] Clinically, DECT has a 50% accuracy for predicting struvite stones.[33] Newer imaging technologies might facilitate the preoperative identification of struvite stones when used in combination with patient history, urinalysis, and urine or stone culture. Once infection stones are identified, three principles exist for their treatment. Firstly, all stone burden should be removed. Secondly, antibiotics should be used to treat the infection so that subsequent urine is sterile in the absence of antibiotics. Thirdly, recurrence should be prevented, which is a function of the other two principles.[8]

Antibiotics

Antibiotics are clearly important for the safe management of infection stones, but guidelines for the timing and duration of therapy have not yet been established. Streem *et al.*[34] recommend giving 1–2 weeks of enteral antibiotics specific to urine culture, if available, with the addition of parenteral broad-spectrum antibiotics the day before surgery and 1–2 h preoperatively. Using this regimen, fever and sepsis rates were shown to be 33% among patients with struvite stones compared with 12.1% for those with nonstruvite stones. The same group has also given parenteral antibiotics for 24–48 h postoperatively, followed by 1–2 years of low-dose suppression antibiotics. Other groups report using 3–6 months of low-dose suppression antibiotics following procedures,[35] and Bichler *et al.*[8] recommend monthly urine cultures for 3 consecutive months following the cessation of antibiotic therapy, in addition to routine urine cultures at all follow-up visits.

In 2008, Zanetti *et al.*[36] comprehensively reviewed trends in antibiotic use, and associated outcomes, for the treatment of infection stones. Among these studies, use of antibiotics ranged from no prophylaxis to regimens of 1-week duration. Primary end points varied, with reported rates of systemic inflammatory response syndrome and fever of 3–22% and 16–22%, respectively, among patients with infected and noninfected stones treated with PCNL. Predictive factors for infectious complications included positive stone or renal pelvic cultures.[10,17,37–39] Additional risk factors identified to increase risk of infectious complications include: increased stone size,[40,41] hydronephrosis,[41] impaction and obstruction,[42] urinary diversion,[43] diabetes,[44] female sex,[45] and paraplegia.[46] UTIs were noted in 12–14% of patients treated with ureteroscopy and laser lithopaxy, with antibiotic use ranging from no prophylaxis to 21 days of postoperative oral antibiotics.[47–49] Similarly, reported rates of UTI were in the range of 2–17% for patients with stones treated with SWL; although these patients did not receive antibiotic prophylaxis, a negative urine culture was confirmed before treatment.[36,50–52] Based on the best available evidence (level III), the EAU has issued a grade B recommendation that long-term or short-term antibiotic therapy be given to all patients with infection stones.[53] Similarly, the AUA has recommended that all staghorn calculi should be assumed to be struvite and should be treated with prophylactic or suppressive antibiotic therapy.[54] Although the Canadian Urologic Association (CUA) have published guidelines on kidney stones, these do not include guidelines on the management of infection stones.[55] In summary, antibiotics have a pertinent role preoperatively, postoperatively, and potentially in the presence of residual stone fragments; however, high-level evidence for specific antibiotic regimens is presently lacking and current guidelines are not entirely prescriptive with respect to factors such as regimen dose and duration.

Minimally invasive stone removal

Extracorporeal shockwave lithotripsy

SWL is a minimally invasive option for stone management, but has a limited role for staghorn calculi owing to its poor efficacy in the treatment of large stone burdens. Healy and Ogan[56] recommend SWL monotherapy as a viable option in adults with nondilated collecting systems and in children. Orsola and colleagues[57] achieved a 73.3% stone-free rate—determined by complete absence of any fragment on plain radiography or intravenous pyelography at 2 months after treatment—when performing SWL on 14 children with staghorn calculi (mean of two SWL treatments per child). In adult populations, stone-free rates of 18–67% were reported following 2–5.2 SWL sessions, with stone-free definitions ranging from 'no stone fragments' to 'only fragments with <4 mm diameter'.[58–63]

SWL has been associated with several potential complications when used to treat staghorn calculi, including sepsis, obstructive nephropathy from steinstrasse, renal colic, and perinephric haematoma. In one study, 10.8% of patients who underwent SWL developed renal obstruction and high-grade fever, and 18.4% required unplanned secondary procedures.[64] As per the AUA guideline[54] recommendations from 2004, SWL monotherapy should only be considered in adult patients with small-volume (<2 cm) stones and nondilated collecting systems, or in paediatric patients. Additionally, if SWL monotherapy is undertaken, adequate drainage of the treated renal unit—either with an internal ureteral stent or a percutaneous nephrostomy tube—should be established prior to the initiation of treatment.

Ureteroscopy

Ureteroscopy serves as a viable adjunctive method for treating staghorn calculi when combined with a holmium:yttrium-aluminum-garnet (holmium:YAG) laser and stone retrieval baskets. Investigators have used

ureteroscopy followed by PCNL in a single procedure, as well as simultaneously combined ureteroscopy and PCNL. Marguet *et al.*[65] performed supine ureteroscopy followed by prone PCNL to minimize the number of percutaneous access tracts required to remove staghorn calculi. Of the seven patients who underwent this approach, all patients had one percutaneous access site and five (71%) were stone-free at 3 months after the procedure with a mean operative time of 142 min. In another study, Landman *et al.*[66] performed simultaneous ureteroscopy and PCNL on nine patients and found that seven of these patients were stone free according to abdominal radiography on postoperative day 1.

The addition of ureteroscopy to PCNL for patients who received treatment for large renal calculi led to a decreased operative time of 120.5 min compared with 134.1 min for conventional (30 Fr tract size) PCNL and 181.9 min for mini-PCNL (18 Fr tract size).[67] In this series, stone-free rate 4 weeks after the procedure was highest in patients who underwent combined ureteroscopy and mini-PCNL at 81.7%, compared with 45.1% for conventional PCNL and 38.9% for mini-PCNL; febrile events trended lower in the combined and mini-PCNL groups compared with the conventional PCNL group.[67] Ureteroscopy is a reasonable adjunct to PCNL if small stone fragments remain, but has a limited role in treating staghorn infection calculi when combined with flexible nephroscopy.

Surgical stone removal

Anatrophic nephrolithotomy

The AUA guidelines recommend anatrophic nephrolithotomy in patients for whom treatment of a struvite staghorn calculus is not likely to be successful with a "reasonable number of [treatments]" using PCNL or SWL.[54] Assimos[68] suggests consideration of anatrophic nephrolithotomy for poorly compliant or obese patients, and those with anatomical abnormalities, such as infundibular stenosis. For such patients, Assimos[69] reported a stone-free rate of 89–100% with anatrophic nephrolithotomy, compared with 12–25% for PCNL (with or without SWL). However, it should be noted that anatrophic nephrolithotomy is an invasive procedure; Paik *et al.*[70] reported a mean operative time of 216 min and an estimated blood loss of 750 ml when using this approach. Furthermore, the open surgical incision necessitates a longer time for recovery compared with endoscopic procedures.

Percutaneous nephrolithotomy

PCNL is the gold-standard treatment for struvite staghorn calculi. Evidence to support its superiority over other approaches dates back to the late 1980s and early 1990s. The first prospective randomized trial comparing PCNL with SWL was published in 1997.[58] Of 50 patients with staghorn calculi, 27 were treated with SWL and 23 underwent PCNL with or without SWL. Stone-free rates were 74% and 22% for PCNL and SWL, respectively. The patients who received SWL experienced significantly more complications and were more likely to undergo ancillary procedures. In a later prospective study comparing PCNL with open surgery,[71] 43 and 45 patients with staghorn calculi were randomized to receive PCNL and open surgery, respectively. Stone-free rates were not statistically different between these two groups at time of discharge (49% for PCNL and 66% for open surgery) or at 3-month follow-up assessment (74% and 82%, respectively). Additional benefits of PCNL over open surgery included shorter operative time (127 min versus 204 min), a lower intraoperative complication rate (16% versus 38%), a lower transfusion rate (14% versus 33%), shorter hospital stay (6.4 days versus 10 days), and earlier return to work (2.5 weeks versus 4.1 weeks).

Stone-free rates were subsequently improved with the addition of flexible nephroscopy and the holmium:YAG laser; Wong and Leveillee[72] reported a 95% stone-free rate using this technique in a series of 45 staghorn calculi. Multiple percutaneous tracts can be used to improve stone-free rates, although multiple tracts also increase the risk of complications.[73] Reports suggest that a staged procedure is required in 25% of patients to achieve stone-free status.[30] The AUA guideline recommends that PCNL be performed as the last intervention if a multimodal approach is used, in order to attain optimal stone-free rates. Use of mini-PCNL combined with conventional PCNL has shown promising results in the treatment of staghorn calculi. A recent study yielded a stone-free rate of 89.7% in the combined group compared with 78.5% in the conventional PCNL group; no statistical increase in complications was observed between groups.[74] Mini-PCNL, flexible nephroscopy and retrograde ureteroscopy serve as valid adjuncts to PCNL in achieving optimal stone-free rates.

Treatment of residual fragments

Urease inhibitors

To date, urease inhibitors have demonstrated only modest benefit for the treatment of struvite stones. Griffith and colleagues[75] used acetohydroxamic acid (AHA) in a randomized double-blind study of 94 patients with struvite stones and chronic UTI. 17% of the patients in the treatment group had stone growth compared with 46% of the placebo group, and growth was accompanied by dermatological, haematological, and neurological adverse effects in 22% of patients. In another study, time to stone recurrence was delayed in patients receiving AHA compared with placebo (15 months and 9 months, respectively).[76] Adverse effects were noted in 62% of AHA-treated patients versus 29% of controls.[76] A third randomized double-blind trial found that none of 18 AHA-treated patients experienced an increase in the 2D surface area of their stone burden over 16–19 months of therapy, compared with 100% of the 19 patients who received placebo.[77] Despite its effectiveness for stabilizing struvite stone growth, clinical use of AHA is hampered by its unfavourable adverse effect profile including tremulousness and phlebothrombosis.[77]

New agents are currently being tested, including citrus medica juice, herbal extracts of *Commiphora wightii*, *Boerhaavia diffua Linn*, *Rotula aquatica Lour*, curcumin,

and polyphenols, all of which demonstrate inhibition of struvite crystallization *in vitro*.[78–80] One research group identified vanillic acid as a phenolic compound that can successfully inhibit urease activity, inhibit increases in synthetic urinary pH normally produced by urease, and inhibit struvite crystallization at a concentration of 2.5 mg/ml.[81] The future of medical management for struvite stones holds promise, but further research and human clinical trials are required.

Dissolution therapy

Medical dissolution therapy has been described as a second-line treatment for struvite and carbonate apatite calculi of both the bladder and kidney. This approach was first described in 1938 using boric acid and permanganate.[82] Two notable solutions include solution G (first used in 1943) and renacidin R (first used in 1959), which produce similar results *in vitro*.[83] Success rates in the literature suggest stone dissolution occurs in 68–80% of cases,[84,85] although this therapy has been associated with a substantial risk of sepsis and death in the past, resulting in the withdrawal of FDA approval for renacidin in 1962.

Dissolution therapy has been used in the intervening period, but generally only in nonsurgical candidates. Tiselius *et al.*[86] assessed a cohort of 118 patients who underwent SWL and received renacidin R and reported a stone-free rate of 60% and a mean hospital stay of 32 days. Time spent in hospital accrues a substantial cost, with daily rates reaching US$1,200 at our local institution; as such, administration of dissolution therapy can be costly to the health-care system as patients must be admitted to hospital to have solutions instilled through a nephrostomy tube. Currently, its use in kidney stone treatment is limited to patients unable to tolerate any form of surgical therapy.

Urine acidification

Urinary acidification with agents such as ascorbic acid, ammonium chloride, ammonium sulphate, ammonium nitrate, and L-methionine has been used to clear residual fragments and to prevent future stone formation following stone clearance. However, it can be difficult to maintain acidification of the urine with these agents, particularly in the presence of infection. Bichler *et al.*[8] note that ammonium chloride and ammonium sulphate have been used for short-term and long-term therapy, respectively. Collectively, urinary acidification has a very limited role in managing infection stones and is seldom used today.

Conclusions

Infection stones—which represent 10–15% of the total stone population—cause substantial morbidity and mortality, particularly in patients who are treated conservatively. However, active therapy is associated with very high success rates for stone clearance, low rates of recurrence, and low rates of associated morbidity and mortality. The primary goal of therapy is the complete eradication of calculi with use of perioperative antibiotic therapy, as well as postoperative antibiotics in the presence of stone fragments. Although we know that antibiotics are important for the prevention and treatment of infection stones, no definitive guidelines exist for the timing and duration of therapy. Future studies should address this gap in our knowledge. Stone culture at the time of treatment or urine culture from the renal pelvis can provide useful clinical knowledge for directing antibiotic therapy. As struvite stones can form around a metabolic stone nucleus and only a fraction of stone fragments are collected and sent for analysis, the original nucleus might not be analyzed; as such, it is necessary to check the patient's history for metabolic risk factors that could precipitate further metabolic stone episodes.

PCNL is currently the gold standard for treatment of staghorn infection calculi but other interventions might have an adjunctive role in therapy. In particular, SWL is useful in the paediatric population as the rate of success is higher than in adults and might potentially avoid a more invasive surgical procedure. Radiological and microbiological follow-up assessment should be performed the day after definitive therapy, with continued follow-up assessment at a local institution.[30] Current evidence suggests that this assessment period should last for about 3 months, but further evidence is required to determine the optimal follow-up interval. In summary, infection stones are a serious cause of morbidity and mortality in urological practice, and treatment involves complete eradication and antibiotic therapy.

Review criteria

This review was conducted by searching the PubMed database for the terms "struvite stones", "infection stones", "struvite calculi", "infection calculi", "management and struvite stones", and "management and struvite calculi", with no restriction on date of publication. The references of recent review articles were searched to identify landmark studies in their respective areas of struvite stone pathology, microbiology, and management.

1. Hesse, A. & Bach, D. Harnsteine, Pathobiochemie and Klinisch-chemische Diagnostik (eds Breuer, H., Buttner, H. & Stamm, D.) (Thieme Verlag, 1982).
2. Resnick, M. I. Evaluation and management of infection stones. *Urol. Clin. North Am.* **8**, 265–276 (1981).
3. Lee, M. C. & Bariol, S. V. Changes in upper urinary tract stone composition in Australia over the past 30 years. *BJU Int.* **112** (Suppl. 2), 65–68 (2013).
4. Shafi, H. *et al.* Bacteriological study and structural composition of staghorn stones removed by the anatrophic nephrolithotomic procedure. *Saudi J. Kidney Dis. Transpl.* **24**, 418–423 (2013).
5. Koga, S., Arakaki, Y., Matsuoka, M. & Ohyama, C. Staghorn calculi–long-term results of management. *Br. J. Urol.* **68**, 122–124 (1991).
6. Schwartz, B. F. & Stoller, M. L. Nonsurgical management of infection-related renal calculi. *Urol. Clin. North Am.* **26**, 765–778 (1999).
7. Evans, K. & Costabile, R. A. Time to development of symptomatic urinary calculi in a high risk environment. *J. Urol.* **173**, 858–861 (2005).
8. Bichler, K. H. *et al.* Urinary infection stones. *Int. J. Antimicrob. Agents* **19**, 488–498 (2002).
9. Bhadra, B., Roy, P. & Chakraborty, R. Serratia ureilytica sp. nov., a novel urea-utilizing species. *Int. J. Syst. Evol. Microbiol.* **55**, 2155–2158 (2005).
10. Mariappan, P., Smith, G., Moussa, S. A. & Tolley, D. A. One week of ciprofloxacin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: a prospective controlled study. *BJU Int.* **98**, 1075–1079 (2006).
11. Gault, M. H. *et al.* Bacteriology of urinary tract stones. *J. Urol.* **153**, 1164–1170 (1995).

12. Akagashi, K. *et al.* Characteristics of patients with staghorn calculi in our experience. *Int. J. Urol.* **11**, 276–281 (2004).
13. Tavichakorntrakool, R. *et al.* Extensive characterizations of bacteria isolated from catheterized urine and stone matrices in patients with nephrolithiasis. *Nephrol. Dial. Transplant.* **27**, 4125–4130 (2012).
14. Englert, K. M., McAteer, J. A., Lingeman, J. E. & Williams, J. C. Jr. High carbonate level of apatite in kidney stones implies infection, but is it predictive? *Urolithiasis* **41**, 389–394 (2013).
15. Bazin, D., Daudon, M., Combes, C. & Rey, C. Characterization and some physicochemical aspects of pathological microcalcifications. *Chem. Rev.* **112**, 5092–5120 (2012).
16. Bazin, D. *et al.* Absence of bacterial imprints on struvite-containing kidney stones: a structural investigation at the mesoscopic and atomic scale. *Urology* **79**, 786–790 (2012).
17. Margel, D. *et al.* Clinical implication of routine stone culture in percutaneous nephrolithotomy —a prospective study. *Urology* **67**, 26–29 (2006).
18. Balk, N., Strohmaier, W., Schmid, M. & Bichler, K. in *2nd European Symposium on Stone Disease* (Urological Research, 1990).
19. Rahman, N. U., Meng, M. V. & Stoller, M. L. Infections and urinary stone disease. *Curr. Pharm. Des.* **9**, 975–981 (2003).
20. Griffith, D. & Klein, A. in *Stones: Clinical management of urolithiasis* (eds Roth, R. & Finlayson, B.) 210–227 (Williams & Wilkins, 1983).
21. Rose, G. in *Urinary Stones: Clinical and Laboratory Aspects* 257–266 (University Park Press, 1982).
22. Nickel, J. C., Emtage, J. & Costerton, J. W. Ultrastructural microbial ecology of infection-induced urinary stones. *J. Urol.* **133**, 622–627 (1985).
23. Nickel, J. C., Olson, M., McLean, R. J., Grant, S. K. & Costerton, J. W. An ecological study of infected urinary stone genesis in an animal model. *Br. J. Urol.* **59**, 21–30 (1987).
24. Nickel, J. C., Costerton, J. W., McLean, R. J. & Olson, M. Bacterial biofilms: influence on the pathogenesis, diagnosis and treatment of urinary tract infections. *J. Antimicrob. Chemother.* **33** (Suppl. A), 31–41 (1994).
25. Kajander, E. O. & Ciftcioglu, N. Nanobacteria: an alternative mechanism for pathogenic intra- and extracellular calcification and stone formation. *Proc. Natl Acad. Sci. USA* **95**, 8274–8279 (1998).
26. Raoult, D. *et al.* Nanobacteria are mineralo fetuin complexes. *PLoS Pathog.* **4**, e41 (2008).
27. Blandy, J. P. & Singh, M. The case for a more aggressive approach to staghorn stones. *J. Urol.* **115**, 505–506 (1976).
28. Teichman, J. M., Long, R. D. & Hulbert, J. C. Long-term renal fate and prognosis after staghorn calculus management. *J. Urol.* **153**, 1403–1407 (1995).
29. Wong, H., Riedl, C. & Griffith, D. in *Kidney Stones: Medical and Surgical Management* (eds Co, F., Favus, M., Pak, C., Parks, J. & Preminger, G.) 941–950 (Raven Press, 1996).
30. Iqbal, M. W. *et al.* Contemporary management of struvite stones using combined endourologic and medical treatment: predictors of unfavorable clinical outcome. *J. Endourol.* http://dx.doi.org/10.1089/end.2013-0257.ECC13.
31. Marchini, G. S. *et al.* Absolute Hounsfield unit measurement on noncontrast computed tomography cannot accurately predict struvite stone composition. *J. Endourol.* **27**, 162–167 (2013).
32. Mostafavi, M. R., Ernst, R. D. & Saltzman, B. Accurate determination of chemical composition of urinary calculi by spiral computerized tomography. *J. Urol.* **159**, 673–675 (1998).
33. Wisenbaugh, E. S., Paden, R. G., Silva, A. C. & Humphreys, M. R. Dual-energy vs conventional computed tomography in determining stone composition. *Urology* http://dx.doi.org/10.1016/j.urology.2013.12.023.
34. Streem, S. B., Yost, A. & Dolmatch, B. Combination "sandwich" therapy for extensive renal calculi in 100 consecutive patients: immediate, long-term and stratified results from a 10-year experience. *J. Urol.* **158**, 342–345 (1997).
35. Tiselius, H. *et al.* Guidelines on urolithiasis. *EUA Guidelines* [online], http://www.uroweb.org/fileadmin/user_upload/Guidelines/Urolithiasis.pdf (2013).
36. Zanetti, G. *et al.* Infections and urolithiasis: current clinical evidence in prophylaxis and antibiotic therapy. *Arch. Ital. Urol. Androl.* **80**, 5–12 (2008).
37. Charton, M., Vallancien, G., Veillon, B. & Brisset, J. M. Urinary tract infection in percutaneous surgery for renal calculi. *J. Urol.* **135**, 15–17 (1986).
38. Cadeddu, J. A. *et al.* Clinical significance of fever after percutaneous nephrolithotomy. *Urology* **52**, 48–50 (1998).
39. Dogan, H. S. *et al.* Antibiotic prophylaxis in percutaneous nephrolithotomy: prospective study in 81 patients. *J. Endourol.* **16**, 649–653 (2002).
40. Gonen, M., Turan, H., Ozturk, B. & Ozkardes, H. Factors affecting fever following percutaneous nephrolithotomy: a prospective clinical study. *J. Endourol.* **22**, 2135–2138 (2008).
41. Chen, L. *et al.* Systemic inflammatory response syndrome after percutaneous nephrolithotomy: an assessment of risk factors. *Int. J. Urol.* **15**, 1025–1028 (2008).
42. Cheung, M. C., Lee, F., Yip, S. K. & Tam, P. C. Outpatient holmium laser lithotripsy using semirigid ureteroscope. Is the treatment outcome affected by stone load? *Eur. Urol.* **39**, 702–708 (2001).
43. Fernandez, A., Foell, K., Nott, L., Denstedt, J. D. & Razvi, H. Percutaneous nephrolithotripsy in patients with urinary diversions: a case-control comparison of perioperative outcomes. *J. Endourol.* **25**, 1615–1618 (2011).
44. Gutierrez, J. *et al.* Urinary tract infections and post-operative fever in percutaneous nephrolithotomy. *World J. Urol.* **31**, 1135–1140 (2013).
45. Sharifi Aghdas, F., Akhavizadegan, H., Aryanpoor, A., Inanloo, H. & Karbakhsh, M. Fever after percutaneous nephrolithotomy: contributing factors. *Surg. Infect. (Larchmt)* **7**, 367–371 (2006).
46. Draga, R. O., Kok, E. T., Sorel, M. R., Bosch, R. J. & Lock, T. M. Percutaneous nephrolithotomy: factors associated with fever after the first postoperative day and systemic inflammatory response syndrome. *J. Endourol.* **23**, 921–927 (2009).
47. Knopf, H. J., Graff, H. J. & Schulze, H. Perioperative antibiotic prophylaxis in ureteroscopic stone removal. *Eur. Urol.* **44**, 115–118 (2003).
48. Tenke, P., Kovacs, B., Benko, R., Ashaber, D. & Nagy, E. Continuous versus intermittent levofloxacin treatment in complicated urinary tract infections caused by urinary obstruction temporarily relieved by foreign body insertion. *Int. J. Antimicrob. Agents* **28** (Suppl. 1), 82–85 (2006).
49. Costantino, G. *et al*. The antibacterial chemoprophylaxis in ureteroscopy: the employment of the levofloxacin used as switch-therapy versus oral treatment with a single 500 mg once a day. *Gazz. Med. Ital. Arch. Sci. Med.* **164**, 43–46 (2005).
50. Dincel, C., Ozdiler, E., Ozenci, H., Tazici, N. & Kosar, A. Incidence of urinary tract infections in patients without bacteriuria undergoing SWL: comparison of stone types. *J. Endourol.* **12**, 1–3 (1998).
51. Pettersson, B. & Tiselius, H. G. Are prophylactic antibiotics necessary during extracorporeal shockwave lithotripsy?. *Br. J. Urol.* **63**, 449–452 (1989).
52. Bierkens, A. *et al*. The value of antibiotic prophylaxis during extracorporeal shockwave lithotripsy in the prevention of urinary tract infections in patients with urine proven sterile prior to treatment. *Eur. Urol.* **31**, 30–35 (1997).
53. Turk, C. *et al.* Guidelines on urolithiasis. *EUA Guidelines* [online], http://www.uroweb.org/gls/pdf/22%20Urolithiasis_LR.pdf (2013).
54. Preminger, G. M. *et al.* Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. *J. Urol.* **173**, 1991–2000 (2005).
55. Paterson, R., Fernandez, A., Razvi, H. & Sutton, R. Evaluation and medical management of the kidney stone patient. CUA Guidelines. http://www.cua.org/userfiles/files/guidelines/ksm_2011_en.pdf (2013).
56. Healy, K. A. & Ogan, K. Pathophysiology and management of infectious staghorn calculi. *Urol. Clin. North Am.* **34**, 363–374 (2007).
57. Orsola, A. *et al.* Staghorn calculi in children: treatment with monotherapy extracorporeal shock wave lithotripsy. *J. Urol.* **162**, 1229–1233 (1999).
58. Meretyk, S. *et al.* Complete staghorn calculi: random prospective comparison between extracorporeal shock wave lithotripsy monotherapy and combined with percutaneous nephrostolithotomy. *J. Urol.* **157**, 780–786 (1997).
59. Delaney, C. P., Creagh, T. A., Smith, J. M. & Fitzpatrick, J. M. Do not treat staghorn calculi by extracorporeal shockwave lithotripsy alone! *Eur. Urol.* **24**, 355–357 (1993).
60. Gleeson, M. J. & Griffith, D. P. Extracorporeal shockwave lithotripsy monotherapy for large renal calculi. *Br. J. Urol.* **64**, 329–332 (1989).
61. Lam, H. S. *et al.* Staghorn calculi: analysis of treatment results between initial percutaneous nephrostolithotomy and extracorporeal shock wave lithotripsy monotherapy with reference to surface area. *J. Urol.* **147**, 1219–1225 (1992).
62. Esen, A. A., Kirkali, Z. & Guler, C. Open stone surgery: is it still a preferable procedure in the management of staghorn calculi? *Int. Urol. Nephrol.* **26**, 247–253 (1994).
63. Koko, A. K., Onuora, V. C., Al Turki, M. A., Mesbed, A. H. & Al Jawini, N. A. Extracorporeal shockwave lithotripsy monotherapy is not adequate for management of staghorn renal calculi. *Saudi J. Kidney Dis. Transpl.* **14**, 487–491 (2003).
64. El-Assmy, A. *et al.* Extracorporeal shock-wave lithotripsy monotherapy of partial staghorn calculi. Prognostic factors and long-term results. *Scand. J. Urol. Nephrol.* **40**, 320–325 (2006).
65. Marguet, C. G. *et al.* Simultaneous combined use of flexible ureteroscopy and percutaneous nephrolithotomy to reduce the number of access tracts in the management of complex renal calculi. *BJU Int.* **96**, 1097–1100 (2005).

66. Landman, J. *et al.* Combined percutaneous and retrograde approach to staghorn calculi with application of the ureteral access sheath to facilitate percutaneous nephrolithotomy. *J. Urol.* **169**, 64–67 (2003).
67. Hamamoto, S. *et al.* Endoscopic combined intrarenal surgery for large calculi: simultaneous use of flexible ureteroscopy and mini-percutaneous nephrolithotomy overcomes the disadvantageous of percutaneous nephrolithotomy monotherapy. *J. Endourol*. **28**, 28–33 (2014).
68. Assimos, D. G. Anatrophic nephrolithotomy. *Urology* **57**, 161–165 (2001).
69. Assimos, D. G. *et al*. A comparison of anatrophic nephrolithotomy and percutaneous nephrolithotomy with and without extracorporeal shock wave lithotripsy for management of patients with staghorn calculi. *J. Urol.* **145**, 710–714 (1991).
70. Paik, M. L., Wainstein, M. A., Spirnak, J. P., Hampel, N. & Resnick, M. I. Current indications for open stone surgery in the treatment of renal and ureteral calculi. *J. Urol.* **159**, 374–378 (1998).
71. Al-Kohlany, K. M. *et al.* Treatment of complete staghorn stones: a prospective randomized comparison of open surgery versus percutaneous nephrolithotomy. *J. Urol.* **173**, 469–473 (2005).
72. Wong, C. & Leveillee, R. J. Single upper-pole percutaneous access for treatment of > or=5-cm complex branched staghorn calculi: is shockwave lithotripsy necessary? *J. Endourol.* **16**, 477–481 (2002).
73. Aron, M. *et al.* Multi-tract percutaneous nephrolithotomy for large complete staghorn calculi. *Urol. Int.* **75**, 327–332 (2005).
74. Wang, Y. *et al.* Standard-tract combined with mini-tract in percutaneous nephrolithotomy for renal staghorn calculi. *Urol. Int.* http://dx.doi.org/ 10.1159/000354427 (2014).
75. Griffith, D. P. *et al.* Randomized, double-blind trial of Lithostat (acetohydroxamic acid) in the palliative treatment of infection-induced urinary calculi. *Eur. Urol.* **20**, 243–247 (1991).
76. Griffith, D. P., Khonsari, F., Skurnick, J. H. & James, K. E. A randomized trial of acetohydroxamic acid for the treatment and prevention of infection-induced urinary stones in spinal cord injury patients. *J. Urol.* **140**, 318–324 (1988).
77. Williams, J. J., Rodman, J. S. & Peterson, C. M. A randomized double-blind study of acetohydroxamic acid in struvite nephrolithiasis. *N. Engl. J. Med.* **311**, 760–764 (1984).
78. Chauhan, C. K. & Mihir, J. J. *In vitro* crystallization, characterization and growth-inhibition study of urinary type struvite crystals. *J. Cryst. Growth* **362**, 330–337 (2013).
79. Prywer, J. & Torzewska, A. Effect of curcumin against proteus mirabilis during crystallization of struvite from artificial urine. *Evid. Based Complement. Alternat. Med.* **2012**, 862794 (2012).
80. Daglia, M. Polyphenols as antimicrobial agents. *Curr. Opin. Biotechnol.* **23**, 174–181 (2012).
81. Torzewska, A. & Rozalski, A. Inhibition of crystallization caused by Proteus mirabilis during the development of infectious urolithiasis by various phenolic substances. *Microbiol. Res.* http://dx.doi.org/10.1016/j.micres.2013.09.020.
82. Hellstrom, J. The significance of staphylococci in the development and treatment of renal and ureteral stones. *Br. J. Urol.* **10**, 348–372 (1938).
83. Shortliffe, L. M. & Spigelman, S. S. Infection stones. Evaluation and management. *Urol. Clin. North Am.* **13**, 717–726 (1986).
84. Dretler, S. P. & Pfister, R. C. Primary dissolution therapy of struvite calculi. *J. Urol.* **131**, 861–863 (1984).
85. Fam, B., Rossier, A. B., Yalla, S. & Berg, S. The role of hemiacidrin in the management of renal stones in spinal cord injury patients. *J. Urol.* **116**, 696–698 (1976).
86. Tiselius, H. G., Hellgren, E., Andersson, A., Borrud-Ohlsson, A. & Eriksson, I. Minimally invasive treatment of infection staghorn stones with shock wave lithotripsy and chemolysis. *Scand. J. Urol. Nephrol.* **33**, 286–290 (1999).

Author contributions

R.F. and D.L. researched, wrote, edited, reviewed, and discussed the Review with colleagues. W.H.C. helped to research and edit the article. B.C. contributed towards writing and editing.

CORRECTION

Renal struvite stones—pathogenesis, microbiology, and management strategies

Ryan Flannigan, Wai Ho Choy, Ben Chew and Dirk Lange

Nat. Rev. Urol. **11**, 333–341 (2014); published online 13 May 2014; doi:10.1038/nrurol.2014.99

In the version of this article initially published online Wai Ho Choy's name was spelled incorrectly. The error has been corrected for the print, HTML and PDF versions of the article.