Evaluating factors that dictate struvite stone composition: A multi-institutional clinical experience from the EDGE Research Consortium

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Abstract

Introduction: Struvite stones account for 15% of urinary calculi and are typically associated with urease-producing urinary tract infections and carry significant morbidity. This study aims to characterize struvite stones based on purity of stone composition, bacterial speciation, risk factors, and clinical features.

Methods: Retrospective data was collected from patients diagnosed with infection stones between 2008 and 2012. Stone analysis, perioperative urine cultures, bacterial speciation, and clinical data were collected and analyzed. The purity of struvite stones was determined. Statistical comparisons were made among homogeneous and heterogeneous struvite stones.

Results: From the four participating centres, 121 struvite stones were identified. Only 13.2% (16/121) were homogenous struvite. Other components included calcium phosphate (42.1%), calcium oxalate (33.9%), calcium carbonate (27.3%), and uric acid (5.8%). Partial or full staghorn calculi occurred in 23.7% of cases. Urease-producing bacteria were only present in 30% of cases. *Proteus, E. coli,* and *Enterococcus* were the most common bacterial isolates from perioperative urine, and percutaneous nephrolithotomy was the most common modality of treatment. Only 40% of patients had a urinalysis that was nitrite-positive, indicating that urinalysis alone is not reliable for diagnosing infection stones. The study's limitation is its retrospective nature; as such, the optimal timing of cultures with respect to stone analysis or treatment was not always possible, urine cultures were often not congruent with stone cultures in the same patient, and our findings of *E. coli* commonly cultured does not suggest causation.

Conclusions: Struvite stones are most often heterogeneous in composition. *Proteus* remains a common bacterial isolate; however, *E. coli* and *Enterococcus* were also frequently identified. This new data provides evidence that patients with struvite stones can have urinary tract pathogens other than urease-producing bacteria, thus challenging previous conventional dogma.

Introduction

Struvite stones are thought to form in the presence of urease-producing bacteria that create an environment favouring the formation of magnesium ammonium phosphate. They comprise 7–15% of all stone types,[1,2] and 24% of staghorn calculi.[3] They occur more frequently in women compared to men, with a ratio of approximately 2:1.[4] Factors that predispose one to acquiring these stones include female sex, extremes of age, congenital urinary tract malformations, stasis from urinary obstruction, urinary diversion, neurogenic bladder, indwelling urethral catheters, distal renal tubular acidosis, medullary sponge kidney, and those with diabetes mellitus.[5] These stones may form in the kidney or bladder, and when in the kidney, they are bilateral in nearly 15% of cases.[6] Presentation includes flank or abdominal pain in 70%, fever in 26%, gross hematuria in 18%, sepsis and recurrent urinary tract infections (UTIs) in 1%, though up to 8% are asymptomatic.[6,7]

Struvite stones are one of the most common causes of staghorn calculi, which are known to potentially form rapidly, in the order of 4–6 weeks.[8] Composition is often heterogenous, but typically has a component of magnesium ammonium phosphate (struvite), monoammonium urate, and/or carbonate apatite.[8] For the sake of classification, "struvite" stones in this manuscript will also refer to carbonate apatite stones, since they are also considered "infection stones." Pathogenesis of struvite stones requires the presence of bacteria that express the enzyme urease, which breaks down urea to ammonia and carbon dioxide (CO_2), creating a highly alkaline urine (pH 7.2–8.0). Alkaline conditions favour crystallization of magnesium ammonium phosphate. Bacteria that always produce urease include *Proteus* species, *Providencia* species, and *Morganella morganii*. However, other bacterial species heterogeneously produce urease. For example, 84% of *Klebsiella*, 55% of *Staphylococcus*, and 1.4% of *E. coli* species produce urease.[8] Collectively, this illustrates the wide array of bacterial species capable of causing struvite stone formation.

Interestingly, the presence of urease-producing bacteria alone does not always result in struvite stone formation. A previous study has shown that out of the 39% of patients infected with a urease-positive bacterial species, only 16% formed struvite stones.[9] Given these findings, a significant need exists to identify and better understand contributory factors that result in struvite stone formation, beyond the presence of a urease-producing microorganism. The present study takes the first step and aims to evaluate stone, patient, and microbiological factors involved with infection stones among four urological centres from the EDGE Research Consortium in North America and one affiliate member from Europe.

Methods

The medical records of patients with struvite-containing calculi at the Vancouver General Hospital (VGH) Stone Centre, Mayo Clinic, Cleveland Clinic, and University Hospital Grosshadern between October 2008 and April 2012 were retrospectively reviewed. Institutional research ethics board approval was obtained at each site. Patients were included in the study if they had a struvite calculus (or carbonate apatite) identified on stone analysis. Patients underwent various surgical techniques for stone removal and stones were obtained intraoperatively if possible. Stones were collected at the time of surgery if they underwent percutaneous nephrolithotomy (PCNL) or shockwave lithotripsy (SWL). Patients undergoing SWL strained their urine and collected stones for analysis. Analysis was performed by the respective hospital laboratories using Fourier-transform infrared (FTIR) spectroscopy and compared to a standardized library. Patients had urine collected prior to surgery, as well as when symptoms arose. Patients were considered to have recurrent UTIs if they had two or more distinct infections within a six-month time period.

Patients who underwent metabolic testing postoperatively, including 24-hour urine tests, were tested at least 90 days after being deemed stone-free. Medical therapy to prevent stone disease was not instituted prior to obtaining the 24-hour urine test. Given that this study was multicentre and retrospective in design, not all stone entries had complete data; as such, denominators are declared in all domains of analysis. Statistical comparisons were made using Mann-Whitney, unpaired T-tests, and Fisher's exact test using Graph Pad, and Instat version 3.0 software.

Results

One hundred and twenty-one struvite stones were identified in this study: 65 from the VGH Stone Centre, 5 from Mayo Clinic (Arizona), 19 from University Hospital Grosshadern, and 32 from Cleveland Clinic. Mean age was 53.4 (range 16–88) years. Female patients accounted for 63% and males for 37% of the study population. The mean body mass index (BMI) was 29.0 kg/m^2, with 34% of patients meeting the BMI definition of obesity (>30kg/m^2). Of all struvite stones, 38% (25/65) were recurrent stones. The mean urinary pH was 6.53±0.86. Among 58 urinalyses performed, 54 (93.1%) were positive for leukocytes, 54 (93.1%) for red blood cells (RBCs), 23 (39.7%) for nitrites, 18 (31.0%) for protein, and one (1.7%) for glucose. Only 16/121 (13.2%) stones were homogenous in composition, while the remaining 105 (86.8%) contained one or more additional components. Specifically, 51 (42.1%) contained calcium phosphate, 41 (33.9%) contained calcium oxalate, 33 (27.3%) contained calcium carbonate, and seven (5.8%) contained uric acid (Table 1).

The most common location of stones was the kidney (100/121; 82.6%), followed by the ureter (13/121; 10.7%), and bladder (8/121; 6.6%). Of these, 31/121 (23.7%) were staghorn or partial staghorn stones in presentation. Many stones required a combination of treatment modalities. Most commonly, stones were treated with PCNL (38/117, 32.5%), followed by ureteroscopy (URS) (23/117, 19.7%), combination of PCNL and SWL (12/117, 10.3%), URS and SWL (12/117, 10.3%), URS and PCNL (10/117, 8.5%), PCNL and SWL and URS (10/117, 8.5%), PCNL and cystoscopic lithopaxy (3/117, 2.6%), cystoscopic lithopaxy (3/117, 2.6%), and SWL (3/117, 2.6%). One patient underwent a laparoscopic nephrectomy, one patient underwent a pyeloplasty and pyelolithotomy, and one patient had URS, SWL, PCNL, and cystoscopy with lithopaxy.

Urine cultures were collected from patients at the time of stone diagnosis and immediately prior to surgical treatment. *Proteus* species was cultured in 17 (11.3%) and *E. coli* in 23 (15.2%) isolates among all stone patients. Negative cultures were identified in 19 (12.6%) samples. Multiple species were often cultured per sample (Fig. 1). Bacterial isolates were also compared based upon geographic location (Fig. 2). Risk factors for stones and urinary infections are listed in Table 2.

Discussion

The present study was conducted to better understand clinical, bacterial, and urinary factors implicated in the formation of pure or multicompositional struvite stones.

Patients in our study with any component of struvite stone tended to have multiple comorbidities with risk factors for both UTIs and stone disease. Notable comorbidities included neurogenic bladder, recurrent UTIs, and diabetes mellitus, smoking history, dyslipidemia, hypertension, and chronic kidney disease. This emphasizes the importance of effectively treating these individuals in a timely and definitive manner, as conservative treatment of patients suffering from multiple comorbidities has been shown to result in significantly higher morbidity.[10] Patients with homogeneous struvite stones tended to have a greater history of smoking, bowel resection,

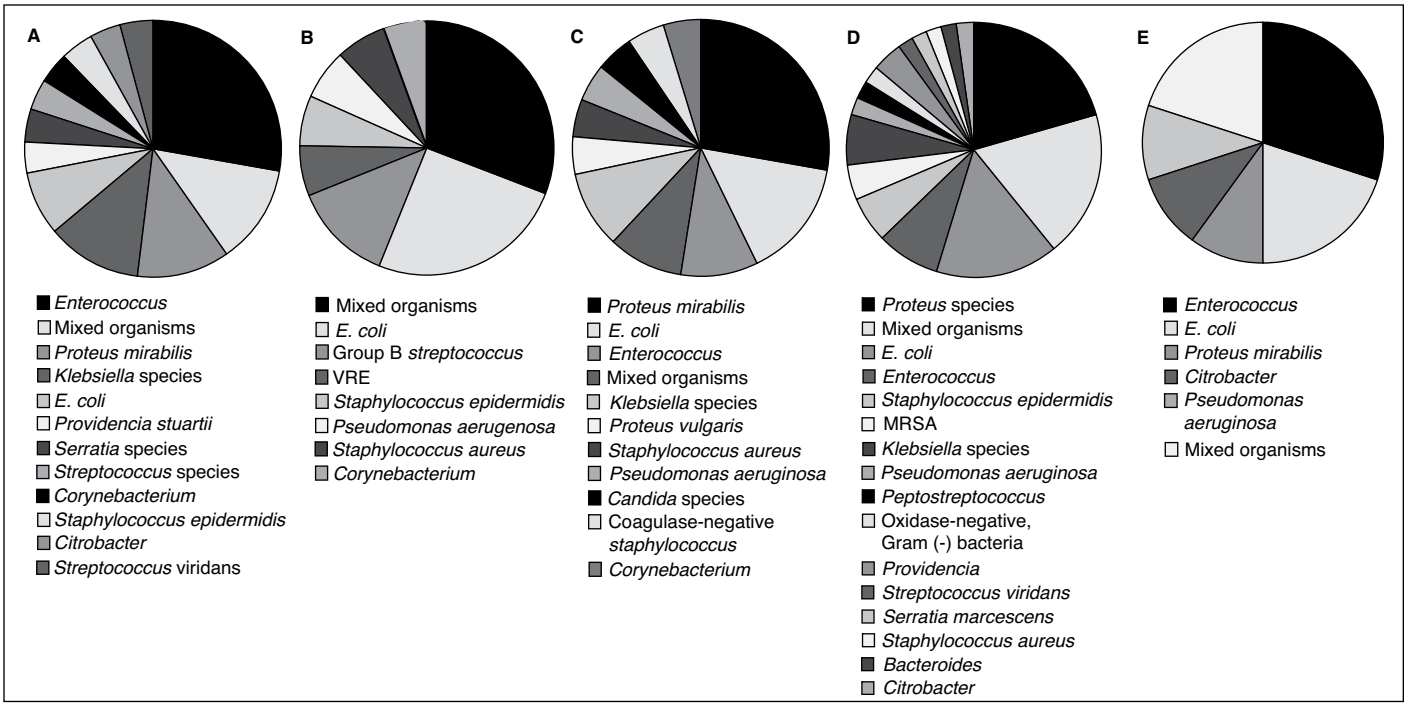

Fig. 1. Graph of bacterial species isolates from patient urine cultures presenting with: ***(A)*** homogeneous struvite stones; ***(B)*** struvite and calcium oxalate; ***(C)*** struvite and calcium phosphate; ***(D)*** calcium carbonate; and ***(E)*** calcium and other stone heterogeneities. MRSA: methicillin-resistant *staphylococcus*; VRE: vancomycin-resistant *enterococcus*.

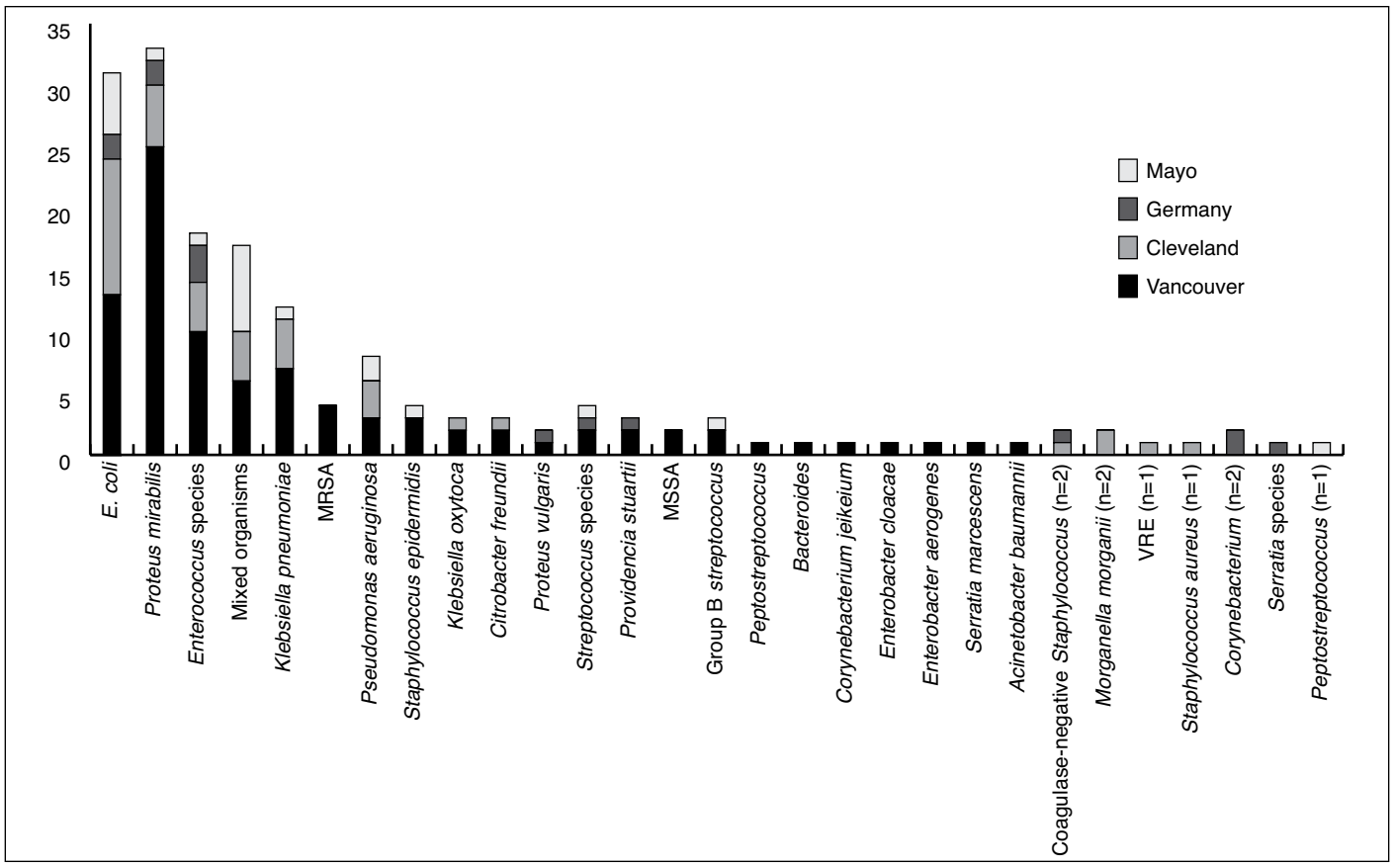

Fig. 2. Graph of the number of urinary bacterial isolates from patients with struvite stones based upon patient geographic location. MRSA: methicillin-resistant *staphylococcus*; MSSA: methicillin-sensitive *staphylococcus*; VRE: vancomycin-resistant *enterococcus*.

Table 1. Comparison of 24-hour urinary values among patients with pure struvite stones and those with heterogeneous (<100%) struvite stones

Urinary parameter	Homogeneous struvite, mean ± SD	Heterogeneous struvite, mean ± SD	p
pH	7.04±1.05 (n=13)	6.55±0.76 (n=69)	0.0871
24-hour Na (mmol/day)	139.33±2.55 (n=15)	139.05±2.49 (n=87)	0.7477
24-hour Ca (mmol/day)	9.40±0.39 (n=5)	9.29±0.62 (n=46)	0.5998
24-hour K (mmol/day)	3.91±0.40 (n=15)	4.02±0.46 (n=96)	0.3713
24-hour Cl (mmol/day)	104.62±4.23 (n=13)	104.89±3.73 (n=74)	0.6637
24-hour HCO_3 (mmol/day)	25.69±2.93 (n=13)	25.28±3.15 (n=81)	0.9519

SD: standard deviation.

and ileal conduit urinary diversions; however, this did not meet statistical significance when accounting for multiple statistical comparisons.

The majority of stones were located in the kidney. Multiple treatment modalities were necessary to achieve a stone-free status, with PCNL most often being used along with perioperative antibiotics in all patients. Aggressive treatment removing all residual fragments is essential in managing struvite stones because they can serve as a nidus for postoperative infection and future stone growth.[11]

Our results show that the diagnosis of infection stones based on urinalysis alone is not very reliable, as only 40% were nitrite-positive and 93% were leukocytes or blood-positive. Furthermore, classically described urease-producing bacteria were isolated in only 30% of cases, indicating that even urinary bacterial culture is not a reliable predictor for the presence of infection stones during preoperative evaluation. Similar to previous reports in the literature, we found significant heterogeneity among the bacterial isolates,[12-14] with the two most common being *E. coli* and *Proteus*. While this may suggest an increase in the number of urease-positive *E. coli* strains, it is more likely that patients are suffering from multispecies UTIs, and *E. coli* is the most commonly isolated species due to the fact that its short replication rate results in it outcompeting and outgrowing other bacterial species. This is especially true in the high pH environment associated with the presence of urease-positive bacteria, which tends to be inhibitory for bacterial growth, including *P. mirabilis*. Given that conventional urine culture techniques rely on the viability and growth of different bacterial species, only those that actually survive high urine pH conditions accompanying infection stones will be identified. This is verified by studies that have demonstrated that only approximately 25% of midstream urine cultures correlated to urease-positive isolates from stone cultures, raising the importance of both stone cultures and stone composition to verify the culprit and also the stone as struvite composition.[15] The reason that urease-positive bacterial species can still be isolated from stone cultures despite the unfavourably high pH of the urine is that they are protected from a potentially unfavourable urinary environment by the surrounding stone, allowing them to survive. Further research, both clinical and laboratory-based, are required to further evaluate coexistence and relationship among common urinary pathogens identified in this study and urease-producing organisms in the setting of infection stones.

When assessing stone composition, nearly 87% of the stones identified as struvite were actually of mixed composition. Interestingly, no trends were identified among bacterial species and stone composition. This suggests that the formation of infection stones is not solely determined by the presence of urease-positive bacterial species, but also requires additional urinary features. To explore this possibility, we compared 24-hour urine compositions between patients with pure struvite and mixed struvite stones. We did not find any significant differences in the most commonly tested parameters despite previous reports identifying hypercalciuria as a risk factor.[16] Our lack of findings could be due to variation in 24-hour urinary values, a limited denominator in this data set, and the fact that the majority of our patients did not have urease-producing bacterial species. Studying the role of specific urinary components in promoting struvite stone formation warrants further investigation, as the exact physico-chemical parameters that influence struvite crystallization kinetics in urine have not been established. Kinetic studies in response to struvite formation in wastewater treatment has shown that supersaturation and pH are the most influential parameters determining struvite formation, indicating that the concentration of individual parameters are important determinants for this process.[17] In this setting, higher NaCl salt concentrations were also shown to result in higher struvite growth kinetics.

Homogeneous struvite stones tended to have a higher urinary pH of 7.04 compared to heterogeneous struvite stones (urinary pH of 6.55), but failed to reach statistical significance (p=0.087). This may be due to these urine tests being performed in the absence of active infection and thus do not represent the urine during present infection with urease-producing bacteria. Alternatively, it may suggest that homogeneous struvite stones tend to form when the normal urinary pH is closer to the K_{sp} for struvite formation, while a more acidic starting pH means struvite formation may occur with a lower threshold in the presence of heterogenous nucleation with commonly identified calcium-based stones. Here, calcium-based stones may create a nidus, making subsequent struvite nucleation more likely in the setting

Table 2. Known risk factors for nephrolithiasis and urinary tract infections (UTIs) based upon struvite stone composition.

Risk factors	All struvite stones (%)	Heterogeneous struvite (%)	Homogenous struvite (%)	p
Recurrent UTIs	42 (34.7)	36 (34.2)	6 (37.5%)	0.785
Hypertension	29 (22.3)	27 (25.7)	2 (12.5)	0.353
Smoking	26 (21.5)	18 (17.1)	8 (50.0)	0.006*
Diabetes mellitus	25 (20.7)	22 (21.0)	3 (18.8)	1.000
Wheelchair-dependent	15 (12.4)	10 (9.5)	5 (31.3)	0.028*
Neurogenic bladder	14 (11.6%)	11 (10.5%)	3 (18.8)	0.396
Obesity	13 (10.7)	11 (10.5)	2 (12.5)	0.682
Dyslipidemia	12 (9.9)	11 (10.5)	1 (6.3)	1.000
Pyelonephritis	11 (9.1)	10 (9.5)	1 (6.3)	1.000
Hyperparathyroid	9 (7.4)	9 (8.6)	0 (0.0)	0.605
Prior bowel resection	9 (7.4)	5 (4.8)	4 (25%)	0.018*
Chronic kidney disease	8 (6.6)	6 (5.7)	2 (12.5)	0.285
Retained ureteral stent	8 (6.6)	6 (5.7)	2 (12.5)	0.285
Indwelling catheter	8 (6.6)	7 (6.7)	1 (6.3)	1.000
UPJO/pyeloplasty	7 (5.8)	6 (5.7)	1 (6.3)	1.000
Calyceal diverticulum	6 (5.0)	6 (5.7)	0 (0.0)	1.000
Nephrocalcinosis	5 (4.1)	5 (4.8)	0 (0.0)	1.000
Ureteral obstruction	4 (3.3)	4 (3.8)	0 (0.0)	1.000
Medullary sponge kidney	4 (3.3)	4 (3.8)	0 (0.0)	1.000
Bladder augment/Mitrofanoff	4 (3.3)	3 (2.9)	1 (6.3)	0.437
Ileal conduit	3 (2.5)	1 (1.0)	2 (12.5)	0.046*
Self-catheter	3 (2.5)	2 (1.9)	1 (6.3)	0.349
Atrophic non-functioning kidney	2 (1.7)	2 (1.9)	0 (0.0)	1.000
Stented	1 (0.8)	1 (1.0)	0 (0.0)	1.000
HIV	1 (0.8)	0 (0.0)	1 (6.3)	0.125
Extrophy	1 (0.8)	1 (1.0)	0 (0.0)	1.000

*p<0.05; however, accounting for multiple comparisons, this does not reach statistical significance. UPJO: ureteropelvic junction obstruction.

of urease-producing bacteria. However, further research is required to test this hypothesis.

Limitations of the present study exist. Firstly, urine cultures are not always transparently reflective of stone cultures[9] and, thus, cultures demonstrating common urinary tract organisms may be over-represented in the present series. However, management decisions are guided by the urine culture as the stone culture is not available preoperatively. Having multiple centres increased the power of this data and generalizability; however, local practice patterns, bacterial profiles, and laboratory techniques for culture, stone analysis, and urinary profiles may differ. Thirdly, the exact stone sizes were not recorded; therefore, we were unable to discern differences in infected stones according to size. Lastly, the study was retrospective, and optimal timing of cultures in relation to time of stone diagnosis or treatment was not possible. Stone analysis was not available in all patients and may be routinely performed in future analyses to provide more complete information. Further prospective studies are required to most accurately characterize struvite stones, associated bacterial species, and outcomes of definitive therapy. In addition, evidence to support duration of antibiotic use beyond definitive therapy or followup regimens beyond definitive therapy is presently lacking and is important to define, as nearly 40% of struvite stones in the present series represented a recurrent stone.

Conclusion

Patients with struvite stones often have multiple comorbidities. Many have risk factors for both stone formation andUTIs. The majority of struvite stones are heterogeneous in both composition and bacterial isolates. Few differences exist with respect to 24-hour urinary studies when comparing homogeneous struvite stones to those of mixed composition. *Proteus mirabilis* remains a common player in the pathogenesis of struvite stone formation, however, this study identified *Enterococcus* and *E. coli* as common bacterial isolates present in struvite stones and associated infections. This reinforces the importance of obtaining urine and stone cultures when managing struvite stones; bacteria beyond urease-producing species may coexist and contribute to UTI among these patients and the former may not be detectable in urine samples over-populated by non-urease producers. Thus, surgeons should remain suspicious of struvite stones preoperatively among patients fraught with recurrent UTIs,

risk factors for UTIs, or staghorn stones despite absence of a positive urine culture for a urease-producing organism.

Competing interests: Dr. Humphreys has been on advisory boards for Boston Scientific, Mallenkrodt, Olympus, and pocket pal; and has participated in clinical trials supported by Allena. Dr. Chew has been an advisor for ADVA-Tec, Auris, Bard, Boston Scientific, Cook, and Olympus; a speaker for Bard, Boston Scientific, Cook, and Olympus; has received payment/grants/honoraria from ADVA-Tec, Bard, Boston Scientific, Cook, and Olympus; and has participated in clinical trials supported by ADVA-Tec, Boston Scientific, and Cook. Dr. Lange has served as a consultant for and received investigator-initiated research grants from AdvaTec, Bard, BSC, Cook, and UroTech; and has participated in clinical trials supported by AdvaTec and Cook. The remaining authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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