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Defining a clinically significant struvite stone: a non-randomized retrospective study

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Abstract

Objective To study the association between a stone's struvite content and clinical outcomes and to determine a clinically significant cutoff for defining struvite stones.

Materials and methods This was a retrospective study of all patients who underwent ureteroscopy or PCNL at our institution between 2012 and 2017 and had any component of struvite in the stone analysis. Patients were divided into four groups based on percent struvite content: A (1–25%), B (26–50%), C (51–75%), and D (76–100%). Bacterial characteristics were compared between groups. Univariate and multivariate analyses were performed to evaluate the association between struvite content and postoperative SIRS. Log-rank test was used to compare between the four groups' recurrence rates.

Results A total of 123 patients were included in the study. Positive preoperative urine culture was found in 31%, 81%, 87%, and 90% of patients from group A, B, C, and D, respectively. *E. Coli* was the most common pathogen in group A (54%), while Proteus was the most common pathogen in groups C (53%) and D (47%). Enterococci isolation rates remained similar between groups A-D, ranging from 23 to 33%. Postoperative SIRS occurred in 2.4%, 21.3%, 26.7%and 47.4% of the patients from groups A, B, C, and D, respectively, and was associated with struvite content and age on multivariate analysis. Increasing struvite content was associated with higher 2-year recurrence rate.

Conclusions Higher struvite content is associated with a higher frequency of traditional urea splitting bacteria in urine culture, higher risk for postoperative SIRS, and higher recurrence rate. Struvite content greater than 25% can be used to define a clinically significant struvite stone.

Keywords Infection · Nephrolithiasis · Struvite · PCNL · Ureteroscopy

Introduction

Struvite (magnesium ammonium phosphate) stones, commonly referred to as "infection stones," constitute only a small fraction of urinary stones, but their medical and economic burden are disproportionally higher, as they comprise one quarter of staghorn stones and are associated with infectious complications [1–3]. The definition of struvite stone varies widely across the literature. While some authors use composition-based definitions from the mere presence of struvite up to 50% of the stone, many studies do not even provided a definition [4–7] (Table 1).

Ideally, stone composition should be determined with respect to its clinical implication. The 50% cutoff usually used for metabolic stones is logical as it allows clinicians to guide their dietary and medical recommendations. However, this definition may not apply for struvite stones, since any amount of struvite implies that the urine was infected with urease-forming bacteria at some point. The aim of this study was to evaluate the association between the stones' struvite content and three characteristics of struvite stones: bacteriologic profile, pre- and postoperative infectious complications, and recurrence rate, and to establish a clinically significant cutoff for struvite stones definition.

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Table 1 A tabulated review of struvite stone studies

Author (year)	*N*	Definition of struvite stone	Aim	Findings
Rivera et al. (2016) [4]	227	Not defined	To describe pre- and postoperative predictors of infection-related complications in individuals undergoing PCNL	Struvite composition was associated with postoperative infectious complications on univariate analysis
Iqbal et al. (2017) [5]	75	Pure—100% magnesium ammonium phosphate ± carbonate apatite Mixed—any amount of struvite with other stone compositions	To determine the rate of metabolic abnormalities in patients with struvite stones To evaluate the impact of metabolic-directed therapy on stone activity	Metabolic abnormalities are common in pure struvite stone formers Directed medical therapy may reduce stone activity in these patients
Parkhomenko et al. (2017) [6]	1191 (50 struvite stones)	> 50% magnesium ammonium phosphate	To study the bacteriologic profile of struvite stones	Non-urease-producing organisms are being identified with greater frequency on struvite stone culture
Englert et al. (2013) [7]	368	Any amount of struvite	To see if carbonated apatite level in stones an indicator of the presence of infectious organisms in the stone	carbonate in the apatite was weakly predictive of positive stone culture
Paonessa et al. (2016) [12]	776 (125 struvite stones)	Not defined	To determine the ability of preoperative urine cultures to predict the presence of infection in kidney stones	A positive urine culture was predictive of positive stone culture in 72.8%
Eswara et al. (2013) [14]	35 (14 struvite stones)	Not defined	To identify risk factors for sepsis after PCNL in patients with neuromuscular disorders	Struvite composition and primary vs secondary PCNL were associated with higher infection rate

Materials and methods

After obtaining approval from the institutional ethics committee, we performed a retrospective study of all patients who underwent ureteroscopy or percutaneous nephrolithotomy (PCNL) for the treatment of kidney stones at our institute between 2012 and 2017 and had any component of struvite in the stone analysis (done in a single laboratory—Quest Diagnostic, Pittsburgh, PA, using Fourier Transform Infra-Red Spectroscopy). Medical records were reviewed for demographic and clinical data, recurrent urinary tract infections (two or more symptomatic UTIs in the year prior to the surgery), and urine cultures results collected during 12 months before the surgery, as well as for operative and postoperative data, including postoperative vital signs and follow-up imaging studies.

Positive urine culture was defined as any positive culture within 12 months prior to the surgery. Every patient with a positive urine culture received a full course of culture-guided antibiotic, followed by a second culture to verify urine sterility before surgery.

Patients were divided into four groups based on the percent of struvite (magnesium ammonium phosphate) content in the stone: group A (10–25%), group B (26–50%), group C (51–75%), and group D (76–100%). Bacteriological findings, postoperative SIRS, length of stay (LOS), and recurrence rates based on follow-up images, when available, were compared between the groups. Recurrence was defined as any new stone or increasing stone size in serial abdominal CT studies done for any indication within 24 months of the surgery. Systemic inflammatory response syndrome (SIRS) was defined in accordance with International Guidelines for Management of Severe Sepsis and Septic Shock: 2012, as urinary tract infection in the presence of temperatures > 38 °C or < 36 °C within 48 h of surgery in addition to one or more of the following: heart rate > 90 beats/min, respiratory rate > 20 breaths/min or arterial carbon dioxide pressure < 32 mmHg, systolic blood pressure < 90 mmHg, mean arterial pressure < 70 mmHg, or a systolic blood pressure decrease > 40 mmHg, and white blood cell count > 12,000/mm^3 or < 4000/mm^3 or > 10% bandforms [8].

Statistical analysis

Due to the variability in reporting complications after endourologic procedures and the difference in SIRS rates after ureteroscopy and PCNL, determining SIRS rates of groups A-D was extremely difficult. Assuming a 2% risk in the very low risk group, we determined that a SIRS rate of 10% in groups B–D would be clinically significant. We calculated that a sample of approximately 137 patients in each group had 95% power to detect a difference.

Continuous variables are described as the median and IQR. Categorical variables are described as the number and percent. Chi-square or Fisher's exact tests, and T test or Mann–Whitney U test, were used to compare nominal and continuous variables, respectively. The association of struvite component and additional preoperative characteristics with postoperative SIRS was evaluated by univariable and multivariable logistic regression analyses. Recurrence probability was calculated by the Kaplan–Meier method with statistical differences evaluated by the log rank test. Univariate and multivariate cox proportional hazard model was used to correlate time to stone recurrence with potential prognostic indicators. All statistical analyses were 2-sided. Data were analyzed with SPSS® Statistics, version 21.0 with $p < 0.05$ considered statistically significant.

Results

Overall, 123 patients met the study inclusion criteria. Median age was 59 years, and 41 (33.3%) patients were male. Sixteen (13%) patients had neurogenic bladder, and 25 (20.3%) patients had an indwelling catheter. Median stone size was 20 mm, and 42 (34.1%) patients underwent PCNL. Positive preoperative urine culture was noted in 81 (65.9%) patients. Thirty-eight (30.9%) patients had recurrent UTIs during the year prior to the surgery, and postoperative SIRS occurred in 24 (19.5%) patients. Patient characteristics stratified by struvite content are presented in Table 2. In comparison with group A, groups B, C, and D had higher proportions of female patients, neurogenic bladder, prior UTIs and indwelling catheters, as well as a higher cumulative stone size, and longer operative time and length of stay. These differences were not found between groups B, C, and D. The rate of diabetes mellitus, as well as the median age, BMI, and Charlson comorbidity index was different only between groups A and D.

Bacteriological findings

Positive preoperative urine culture was noted in 31%, 81%, 87%, and 90% of patients from group A, B, C, and D, respectively. Among patients with positive urine cultures, the most common Pathogens in group A were *E. coli* (54%), followed by *Enterococcus* (23%), *and Proteus, Klebsiella, and Pseudomonas* (8% each). *E. coli* remained the most frequent Pathogen (31.6) in group B, followed by *Enterococci, Klebsiella, and Proteus* (21% each). *Proteus* was the most common pathogen in groups C and D, accounting for 53 and 47% of positive cultures, respectively. Enterococcal isolation rates remained similar between groups A-D, ranging from 23

Table 2 Patient characteristics stratified by struvite content

Group (number of patients)	All (123)	A (42)	B (47)	C (15)	D (19)
Median age (IQR)	59 (54, 66)	59 (44,70)	58 (54, 65) $p=0.6$	58 (25, 61) $p=0.14$	68 (59, 78) $p=0.01$
Male gender (%)	41 (33.3)	22 (52.4)	14 (29.8) $p=0.03$	2 (13.3) $p=0.01$	3 (15.8) $p=0.01$
Median BMI (IQR)	30.5 (27.7, 36.7)	29 (24.9, 34.3)	30.3 (28.7, 38.6) $p=0.7$	33 (29.1, 41.6) $p=0.15$	32 (24.8, 35.5) $p=0.03$
Diabetes Mellitus (%)	26 (21.1)	7 (16.7)	10 (21.3) $p=0.6$	2 (13.3) $p=1$	7 (36.8) $p=0.1$
Neurogenic bladder (%)	16 (13)	0 (0)	8 (17) $p=0.01$	5 (33) $p=0.01$	4 (21) $p=0.01$
Indwelling catheters	25 (20.3)	0 (0)	14 (29.8%) $p=0.01$	7 (46.7) $p=0.01$	4 (21) $p=0.01$
Median Charlson comorbidity index (range)	1 (0, 7)	1 (0, 4)	2 (1, 4) $p=0.6$	1 (0, 3) $p=0.9$	5 (2, 7) $p=0.03$
Median cumulative stone size in mm (IQR)	20 (12,31)	15 (8.5, 25)	20 (16, 34.5) (0.006)	25 (19,29) (0.056)	23 (20, 44) (0.001)
PCNL (%)	42 (34.1)	8 (19.1)	17 (36.2) $p=0.1$	7 (46.7) $p=0.05$	10 (52.6) $p=0.01$
Median operative time in minutes (IQR)	76 (63, 123)	45 (30, 64)	119 (54, 139) $p=0.01$	116 (54,149) $p=0.01$	90 (64,132) $p=0.01$
Positive preoperative urine culture (%)	81 (65.9)	13 (31%)	38 (80.9) $p=0.01$	13 (86.7) $p=0.01$	17 (89.5) $p=0.01$
Prior UTIs (%)	38 (30.9)	2 (4.8)	16 (34) $p=0.01$	9 (60) $p=0.01$	11 (57.9) $p=0.01$
Postoperative SIRS (%)	24 (19.5)	1 (2.4)	10 (21.3) $p=0.01$	4 (26.7) $p=0.01$	9 (47.4) $p=0.01$
After PCNL (%)	16 (38.1)	1 (12.5%)	7 (41.1) $p=0.2$	2 (28.6) $p=0.57$	5 (50) $p=0.15$
After ureteroscopy (%)	8 (9.9)	0 (0)	3 (10) $p=0.09$	2 (25) $p=0.03$	4 (44.4) $p<0.01$
Median LOS (IQR)	1 (0, 3)	0 (0, 1)	2 (0, 3) $p=0.04$	4 (1, 7) $p=0.01$	2 (1, 4) $p=0.01$

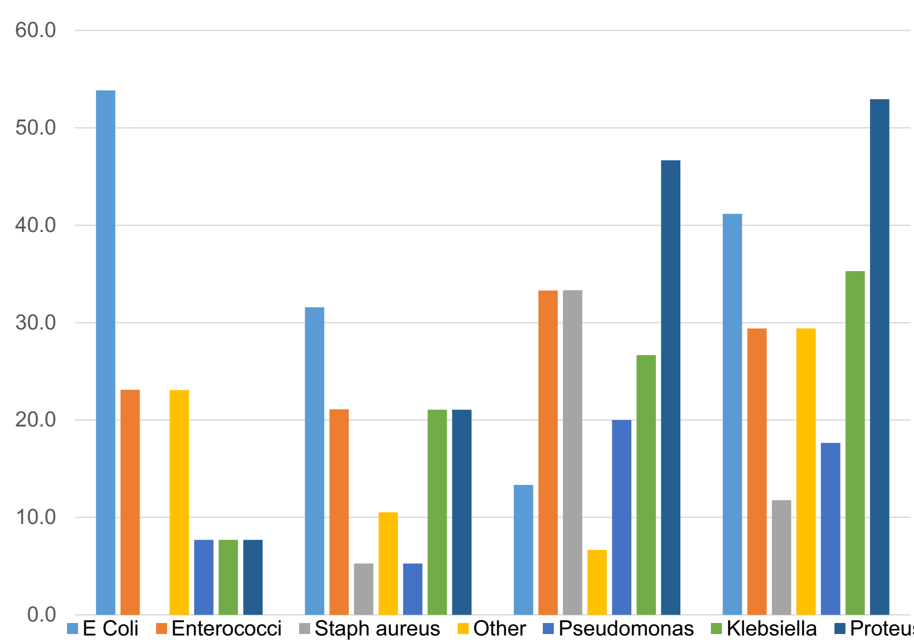
p values in comparison with group A

to 33%. Figure 1 shows the distribution of specific pathogens between the groups.

Infectious complications

UTI in the year prior to the surgery was more frequent among patients in groups B (34%, $p<0.01$), C (60%, $p<0.01$), and D (57.9%, $p<0.01$), than in group A (4.8%). Only one (2.4%) patient in group A met postoperative SIRS criteria, while SIRS rates in groups B, C, and D, were 21.3% ($p<0.01$), 26.7% ($p<0.01$), and 47.4% ($p<0.001$), respectively. Differences in SIRS rates between groups B, C, and D were not statistically significant. Procedure-specific sepsis rates were also studied. Post-ureteroscopy SIRS occurred in

Fig. 1 Distribution of urinary pathogens between groups A–D



0%, 10% ($p = 0.09$), 25% ($p = 0.034$), and 44.4% ($p < 0.01$), and post-PCNL SIRS occurred in 12.5%, 41.1% (0.2), 28.6% (0.57), and 50% (0.15) in groups A, B, C, and D, respectively. On univariate logistic regression analysis, the type of procedure (OR 5.46, 95% CI 2.09–14.3, $p = 0.001$), struvite component (OR 2.41, 95% CI 1.53–3.77, $p = 0.001$), positive urine culture (OR 7.72, 95% CI 1.72–34.7, $p = 0.01$), stone size (OR 1.04, 95% CI 1.01–1.08, $p = 0.01$), male gender (OR 0.14, 95% CI 0.03–0.62, $p = 0.01$), age (OR 1.04, 95% CI 1.01–1.06, $p = 0.02$), the presence of neurogenic bladder (OR 3.58, 95% CI 1.2–10.73, $p = 0.02$), and operative time (OR 1.01, 95% CI 1.005–1.02, $p = 0.02$) were associated with postoperative SIRS. Struvite component (OR 1.08, 95% CI 1.03–1.13, $p = 0.001$) and age (OR 1.1, 95% CI 1.03–1.19, $p = 0.004$) remained associated with SIRS on multivariate logistic regression. Table 3 presents the univariate and multivariate analysis results.

Recurrence rates

Follow-up images were available for 66 (53.6%) patients. During a median follow-up of 11 months (IQR 8–24), 24 (36.3%) patients developed stone recurrence. There was a statistically significant association between struvite content and stone recurrence ($p = 0.006$). Estimated mean time to recurrence was 20.6, 18.5, 8.4, and 10.4 months, for groups A, B, C and D, respectively. Figure 2 shows the Kaplan–Meier curves for stone recurrence by groups A–D. On univariate Cox regression analysis, recurrent UTI,

Table 3 Univariate and multivariate analysis of risk factors for postoperative SIRS

Covariate	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Struvite component	2.41 (1.53–3.77)	0.001	1.08 (1.03–1.13)	0.001
Procedure (PCNL)	5.46 (2.09–14.3)	0.001	1.14 (0.15–8.5)	0.9
Positive urine culture	7.72 (1.72–34.7)	0.01	0.79 (0.01–1.06)	0.83
Stone size	1.04 (1.01–1.08)	0.01	1.01 (0.95–1.06)	0.96
Gender (male)	0.14 (0.03–0.62)	0.01	0.35 (0.05–2.43)	0.29
Age	1.04 (1.01–1.06)	0.02	1.1 (1.03–1.19)	0.004
Neurogenic bladder	3.58 (1.2–10.73)	0.02	0.73 (0.14–3.88)	0.71
Operative time	1.01 (1.005–1.02)	0.02	1.01 (0.99–1.03)	0.35
Indwelling catheter	1.642 (0.585–4.5)	0.35		
Charlson index	1.08 (0.89–1.3)	0.47		
Hydronephrosis	1.19 (0.44–3.22)	0.73		
BMI	1.01 (0.96–1.06)	0.84		

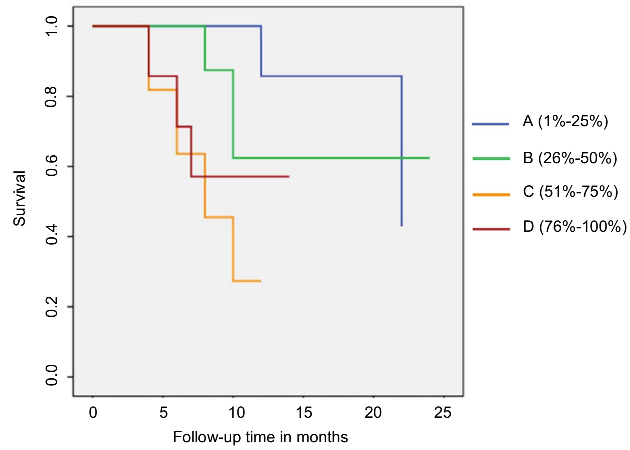


Fig. 2 Kaplan–Meier curves for stone recurrence by groups A–D

struvite content, female gender, and indwelling catheters were associated with earlier recurrence, while age, stone size, and type of surgery were not. On multivariate Cox regression analysis, only recurrent UTI remained associated with earlier stone recurrence (Fig. 2).

Discussion

Struvite stones, commonly referred to as infection stones, exclusively form in the presence of infection with urease producing bacteria. This enzyme hydrolyzes urea and water to ammonium and bicarbonate, resulting in alkaline environment which promotes crystallization struvite crystals [9]. From this unique pathogenesis, it is clear that any component of struvite within a stone indicates prior or current infection, and therefore may have clinical implications. In the current study, we evaluated the association between the struvite content of a stone and the bacterial profile, risk for pre- and postoperative UTI, and recurrence rate. We found that higher struvite content is associated with typical urea splitting bacteria, prior UTI and postoperative SIRS, and to a certain degree, with a higher stone recurrence rate. Struvite content less than 25% had minimal clinical importance.

Urease production is highly variable within different species. While all strains of *Proteus, Providencia*, and *Morganella morganii* spp., and a majority of *Klebsiella* spp. strains produce this enzyme, only 55% of *Staphylococcus* spp. and 1.4% of *Escherichia coli* spp. produce it [10, 11]. In our current study, one-third of the urine cultures obtained from group A were positive, in contrast to nearly 90% in groups C and D. Most species isolated from group A were traditional non-urease producing organisms. Fifty-four and 23 percent of positive urine cultures grew *E. coli* and *Enterococci*, respectively. These two pathogens remained a substantial proportion of urinary pathogens in groups B–D. The rate of traditional urease producing bacteria increased from group A to group D, with *Proteus, Klebsiella, and Pseudomonas* comprising 8% each in group A, and 52%, 35%, and 17% in group D, respectively. Historically, bacterial isolates could be used to predict stone composition as stones with greater than 80% struvite content always contained urea-splitting bacteria, whereas mostly non-traditional urease producing bacteria were isolated from stones with struvite content less than 20% [9]. However, recent studies assessing the bacterial profile of struvite stones have shown an increasing prevalence of non-urease forming bacteria. Paonessa et al. studied the relationship between urine and stone cultures in a large cohort of patients who underwent PCNL. They identified non-urease forming bacteria organisms in urine culture from 23% of patients with struvite stones [12]. Parkhomenko et al. also examined the bacterial profile of struvite stones using a stringent definition (> 50% Struvite composition). Traditional urease producing species were found in only half of positive stone cultures, while *E. coli* and *Enterococci* were isolated in 18% and 12%, respectively [6]. In a study of the EDGE Research Consortium, aiming to identify predictor for struvite stone composition, 12% of the culture were negative, and the most common pathogens were *E. coli*, followed by Proteus. It has been hypothesized that some struvite stones develop in the presence of bacteriuria but no longer contain viable organisms, either because of antibiotic treatment, or due to intra-bacterial formation of struvite crystals [12]. This can explain the finding of a sterile urine culture in a patient with struvite stones. The increasing incidence of *E. coli* in patients with struvite stones be attributed to multi-species infections, in which, this pathogen is more commonly isolated because of its short replication time. Lastly, plasmid-mediated urease gene transfer has been reported as a possible mechanism [9]. The current study introduces another explanation for the variation in results from different studies, that is, that the different cutoffs used to define struvite stones yield different clinical outcomes.

The most frequent complications following PCNL are infectious in nature, yet the literature assessing risk factors for these complications are difficult to interpret, primarily because of a large variability in the definition of infection and in data collection [13]. The association between stone composition and postoperative sepsis remains murky and has been assessed by only handful of studies. In a retrospective study of 227 patients who underwent PCNL, struvite stone composition was associated with infection related complications on univariate, but not on multivariate analysis. Additionally, the authors did not provide their definition for struvite stones [4]. Similarly, sepsis/bacteremia after PCNL were associated with struvite stones in a study evaluating the effect of delayed surgery in 35 patients with neuromuscular disorders [14]. In the current study, patients with struvite content greater than 25% had significantly higher SIRS rate than patients with struvite content less than 25%. The same finding applied for post-ureteroscopy SIRS, but not for post-PCNL SIRS, likely due to the smaller size of this group. Since other predictors were associated with SIRS, we performed a multivariable logistic regression adjusting for stone size and type of procedure. Our results show that a higher percentage of struvite within a stone is an independent predictor for SIRS, and that the SIRS rate is very small for patient with struvite content less than 25%, and similar to the rates reported in large cohorts [5, 12]. By including only patients with struvite stones, we were able to elucidate the impact of struvite content on postoperative SIRS. Had pure metabolic stones also been included in this study, the significance of struvite percentile content may have been diminished. Nevertheless, to our knowledge, this is the only study specifically defining struvite stones based on struvite component. As such, the 25% cutoff can be used with reasonable clinical judgment.

Previous studies assessing stone recurrence have focused on calcium stones, while struvite stones, which are notorious for their rapid formation, have hardly been studied [15–19]. Early studies from the 1990s assessed the recurrence of infection stones following pyelolithotomy or nephrolithotomy. They reported widely variable rates, ranging from 0 to 80% during a median follow-up time of 6.3 years [20]. In the current study, increasing struvite content was associated with higher recurrence rate within the first 2 years of follow-up, likely, as a result of recurrent infections, as demonstrated by the multivariate Cox regression analysis, showing that only recurrent UTI was associated with recurrent stones. These results align with a more recent study of 68 patients undergoing PCNL for struvite stones, in which, recurrent UTIs and anatomical abnormalities were associated with greater stone recurrence [21]. Another study assesses the resolution of UTI after ureteroscopy. While 71% of the patients remained stone and infection free after 12 months, 80% of the patients with stone recurrence also had recurrent UTIs postoperatively [22]. These results should be seen in light of the studies' limitations, including partial follow-up, inconsistent imaging studies, lack of data regarding medical preventive therapy, the composition of recurrent stones, and auxiliary treatment rate.

Data regarding bacteriologic findings are also lacking, as it is well established that there is a discrepancy between urine and stone culture results [23]. Therefore, it is possible that higher rates of traditional urease-forming bacteria would have been identified had stone cultures been obtained. Other limitations of the study are inherent to its retrospective design, as it is underpowered, and, the groups are not comparable with respect to their baseline characteristics. Nevertheless, this is the first study to clinically differentiate struvite stones based on struvite content. As such, it is important both from medical and scientific perspectives, as it may direct clinical decision making and promote a uniform reporting system, respectively.

Conclusion

In this study, a struvite content > 25% was associated with higher rate of traditional urea-splitting bacteria, and with higher risk for postoperative SIRS and stone recurrence. This cutoff can be used to define a clinically significant struvite stone.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

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