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Stone culturing: a more effective approach to diagnosing bacterial infections in kidney stone formers

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KEYWORDS
Kidney stones;
Urinary tract infection;
Stone culture;
Urine culture;
Bacteria.

ABSTRACT
According to the bacteria found in stone niduses, these bacteria may be responsible for lithogenesis. Therefore, we considered culturing stone niduses (SN) as the gold standard for comparing bacterial culture results from stone peripheries (SP), renal pelvic urine (RPU), and midstream urine (MSU), including an evaluation of performance. Data from 36 kidney stone formers were collected, including demographics, imaging diagnostics, urinalysis, and preoperative midstream urine culture. The samples of SN, SP, and RPU were cultured to identify microorganisms. SN were also analyzed for their chemical composition. Diagnostic testing, including sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) with 95% confidence intervals (CI), was performed. The results showed that 16 (44.44%) SN, 17 (47.22%) SP, 12 (33.33%) RPU, and 18 (50.00%) MSU were positive for bacterial culture. For the performance testing that compares SN and the other three specimens, the sensitivity, LR+, PPV, NPV, and AUC of SP culture (sensitivity = 100%, LR+ = 20.00, PPV = 94.10%, NPV = 100%, AUC = 0.975) demonstrated a high level, exceeding that of RPU and MSU cultures. The level of agreement between SN and SP cultures was almost perfect (0.94). *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* were the most commonly isolated bacteria from stone and urine cultures. Moreover, *P. mirabilis* and *E. coli* were the most common bacteria isolated from struvite and calcium oxalate monohydrate (COM) stone compositions, respectively. Our data indicate that culturing SN exhibited higher concordance with SP than the urine culture. *P. mirabilis* and *E. coli* were the most commonly isolated from infection-induced (i.e., struvite) and non infection-induced (i.e., COM) stones, respectively. Integrating stone and urine cultures into the diagnostic workflow for bacterial infections in KSFs is recommended.

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Introduction

Nephrolithiasis and urinary tract infections (UTIs) are often associated, but the etiological relationship remains unclear[1,2]. A dilemma arises: (i) infection-induced stones result from UTIs, commonly caused by urease-producing bacteria such as *Proteus* spp., which are typically composed of struvite (SV), carbonate apatite (CA), or ammonium urate[1-5]. UTIs caused by certain secretory products and/or virulence factors of microorganisms can also induce stone formation; (ii) for stones with subsequent infection,[2] the occurrence of uroliths can lead to subsequent UTIs by urease or non-urease producing bacteria, which have metabolic chemical components such as calcium oxalate (CaOx), and uric acid (UA) [2-3,5-6]. In a 2012 study, 45 bacteria were isolated from the urine and/or stones of 36 patients with nephrolithiasis[7]. Subsequently, a 2017 study revealed that *Escherichia coli* within the stone may adapt to survive in the microenvironment and subsequently cause recurrent UTIs in kidney stone formers (KSFs)[8]. Consequently, bacterial identification within the stone and urine is crucial for completely eradicating these bacteria. Nevertheless, conventional midstream urine cultures, the most routine procedure for evaluating UTIs in KSFs, may often provide insufficiently reliable results[2,9-10]. Previous studies in urosepsis[11-12] have recommended culturing kidney stone and renal pelvic urine samples collected during nephrectomy for bacterial infections. Additionally, the diagnostic performance of these samples for bacterial infections in KSFs remains limited. Based on previous studies conducted in 2012 and 2017, the bacteria present in the stone sample, particularly within the stone nidus, may be the causative agents involved in stone formation and pathogenesis[7-8]. Herein, we selected the culture results from the stone niduses (SN) as the gold standard. Moreover, the stone peripheries (SP) and the renal pelvic urine (RPU) were also collected during the perioperative period. Accordingly, this study was conducted to compare the results of bacterial culture from midstream urine (MSU), RPU, and kidney stone samples in KSFs, aiming to identify the most appropriate sampling culture for accurately detecting the bacterial infection, including determining the concordance between stone and urine culturing results. The types of microorganisms from SN, SP, and RPU were identified. SN were also analyzed for their chemical composition.

Materials and methods

Data and specimen collection

This study represents a diagnostic investigation for bacterial infections in KSFs. The Khon Kaen University Ethics Committee approved this study for Human Research based on the Declaration of Helsinki (HE611387 and HE651324). Informed consent was obtained from all patients. A total of 63 KSFs who underwent percutaneous nephrolithotomy or open nephrectomy between 2018 and 2021 were included. Seven of the 63 KSFs without RPU were excluded. Data from 20 KSFs' midstream urine cultures with mixed microorganisms and incomplete data were also excluded. Therefore, 36 KSFs were enrolled in this study. Patient data were collected as follows: (i) demographic, (ii) imaging diagnostics, and (iii) urinalysis and MSU culture data. Samples of SN, SP, and RPU were collected aseptically during PCNL or open nephrectomy, cultured, and identified for the presence of microorganisms. In this study, the stone nidus culture was considered the gold standard for evaluating the characteristics of the remaining sample culture. SN were also analyzed for their chemical composition.

Identification of bacteria isolated from stone and renal-pelvic urine samples

The samples of SN, SP, and RPU were processed and cultured on blood and MacConkey agar at 35-37 °C for 18-24 h[7]. All microorganisms were identified by morphology (e.g., colony shape, size, and color), microscopic examination

of cell morphology and Gram staining, and standard biochemical methods that assess bacterial enzymatic activity and metabolic capabilities, further refining the identification process[13].

Analysis of the chemical composition of kidney stones

After drying, the SN were ground into powder. Subsequently, the chemical compositions were analyzed using an Attenuated Total Reflection Fourier-transform infrared (ATR-FTIR) spectrometer (model Tensor-II; Bruker Optics, Germany) with a resolution of 4 cm^{-1}, co-add scans at 32 cm^{-1}, and a spectral range of 4,000-400 cm^{-1}. The FTIR spectral data of each sample were analyzed using Bruker's spectral libraries to determine the chemical composition of uroliths. The chemical compositions of stone samples were obtained by matching the RENAL, RENAL01, and RENAL02 spectral BLG libraries with the hit quality of the main components[14]. Based on the main chemical compositions of the stone niduses, they were categorized into two groups: infection-induced stones (IIS) and non infection-induced stones (non-IIS)[5]. IIS mainly comprises SV, CA, whitlockite (Wk), amorphous carbonated calcium phosphate, or ammonium urate stones[5,15]. Others were considered to be non-IIS or metabolic stones.

Statistical analysis

Statistical significance was defined as a *p*-value of less than 0.05. Statistical analyses were conducted using STATA version 18.0 (College Station, Texas, USA). Descriptive statistics summarized the data, and results were reported as means with standard deviations (mean ± SD) or medians with interquartile ranges (IQR) for continuous variables. For the categorical data section, frequencies and percentages were reported.The independent t-test was used to compare the continuous data. Pearson's chi-squared or Fisher's exact test was used to compare categorical data outcomes. The diagnostic testing of each sample culture, including sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), positive predictive value (PPV), and negative predictive value (NPV) with 95% confidence intervals (CI), was performed. The areas under the curve (AUC) were also calculated for each sample culture, and the results were compared to identify the most suitable sample for optimal performance.

Results

Demographic data of kidney stone formers

A total of 36 KSFs (Table 1) were divided into two groups: males (n=23) and females (n=13). The average ages of males and females were 56.83 ± 9.14 and 55.77 ± 11.56 years, respectively. Among the underlying diseases, including hypertension (HT), dyslipidemia, chronic kidney disease, and gout, there were no statistically significant differences between the two groups. Only diabetes mellitus (DM) was statistically significantly more frequent in the female group (30.77%) compared to the male group (4.35%) (p-value < 0.05). Furthermore, HT showed a high frequency in KSFs. The average stone size in females (4.52 ± 1.66 cm) was greater than in males (4.15 ± 1.12 cm). Females exhibited a significantly higher frequency in IIS compositions than males (*p*-value < 0.05). In the urinalysis, urinary nitrite positivity and urinary pH showed higher frequencies and values in females compared to males (all *p*-values < 0.05). Furthermore, the culture results from all four specimens in females demonstrated a notably higher positivity rate than in males (all *p*-values < 0.05).

Characteristics of bacterial culturing results from SN, SP, RPU, and MSU

Bacterial positivity culture results from SN, SP, RPU, MSU were evaluated (Table 2). SN and SP cultures consistently showed better results than the urine sample cultures. Considering the SN culture as the gold standard, the sensitivity, specificity, LR+, LR-, PPV, and NPV with 95% CI of SP, RPU, and MSU cultures were also calculated (Table 3). SP culture demonstrated high

sensitivity and specificity, with values of 95% or higher. In urine culture samples, RPU exhibited high specificity, whereas MSU revealed high sensitivity. Notably, the PPVs of SP (94.10%) and RPU (91.70%) cultures were higher than that of MSU (83.30%).

Table 1 Characteristics and clinical laboratory data of kidney stone formers

Parameters		Kidney stone formers (n=36)	Male (n=23)	Female (n=13)	*p*-value
Demographic data					
Age (years) [a]		56.44 ± 9.93	56.83 ± 9.14	55.77 ± 11.56	0.764
Age group [c]					
≤ 40 yrs		3 (8.33%)	2 (8.70%)	1 (7.69%)	1.000
> 40 yrs		33 (91.67%)	21 (91.30%)	12 (92.31%)	
Underlying diseases					
Hypertension (HT) [b]	Yes	15 (41.67%)	9 (39.13%)	6 (46.15%)	0.681
	No	21 (58.33%)	14 (60.87%)	7 (53.85%)	
Diabetes mellitus (DM) [c]	Yes	5 (13.89%)	1 (4.35%)	4 (30.77%)	**0.047**
	No	31 (86.11%)	22 (95.65%)	9 (69.23%)	
Dyslipidemia [c]	Yes	6 (16.67%)	2 (8.70%)	4 (30.77%)	0.161
	No	30 (83.33%)	21 (91.30%)	9 (69.23%)	
Chronic kidney disease (CKD) [c]	Yes	3 (8.33%)	3 (13.04%)	0	0.288
	No	33 (91.67%)	20 (86.96%)	13 (100%)	
Gout [c]	Yes	2 (5.56%)	2 (8.70%)	0	0.525
	No	34 (94.44%)	21 (91.30%)	13 (100%)	
Imaging diagnostics and chemical compositions of kidney stones					
Location of stone in kidney [b]					
Left		16 (44.44%)	12 (52.17%)	4 (30.77%)	0.721
Right		20 (55.56%)	11 (47.83%)	9 (69.23%)	
Stone sizes					
Stone sizes; longest length* (cm) [a]		4.28 ± 1.33	4.15 ± 1.12	4.52 ± 1.66	0.428
Chemical compositions [c]					
IIS		9 (25.00%)	3 (13.04%)	6 (46.15%)	**0.046**
Non-IIS		27 (75.00%)	20 (86.96%)	7 (53.85%)	
Urinalysis					
Leukocyte esterase [c]	Positive	29 (80.56%)	17 (73.91%)	12 (92.31%)	0.382
	Negative	7 (19.44%)	6 (26.09%)	1 (7.69%)	
Nitrite [c]	Positive	11 (30.56%)	3 (13.04%)	8 (61.54%)	**0.006**
	Negative	25 (69.44%)	20 (86.96%)	5 (38.46%)	
Pyuria [b]	Yes	21 (58.33%)	11 (47.83%)	10 (76.92%)	0.089
(WBCs in urine >10 cells/HPF)	No	15 (41.67%)	12 (52.17%)	3 (23.08%)	
Urinary pH [a]		6.17 ± 0.85	5.96 ± 0.69	6.54 ± 1.00	**0.048**
Urinary pH ≥7: <7 [c]		7: 29	2: 21	5: 8	0.073

Table 1 Characteristics and clinical laboratory data of kidney stone formers (Cont.)

Parameters		Kidney stone formers (n=36)	Male (n=23)	Female (n=13)	*p*-value
Culturing results of stone and urine samples					
SN [b]	Positive	16 (44.44%)	5 (21.74%)	11 (84.62%)	**<0.001**
	Negative	20 (55.56%)	18 (78.26%)	2 (15.38%)	
SP [b]	Positive	17 (47.22%)	6 (26.09%)	11 (84.62%)	**0.001**
	Negative	19 (52.78%)	17 (73.91%)	2 (15.38%)	
RPU [c]	Positive	12 (33.33%)	4 (17.39%)	8 (61.54%)	**0.011**
	Negative	24 (66.67%)	19 (82.61%)	5 (38.46%)	
MSU [c]	Positive	18 (50.00%)	7 (30.43%)	11 (84.62%)	**0.002**
	Negative	18 (50.00%)	16 (69.57%)	2 (15.38%)	

Note: Values are mean±SD; n or n (%), Analyzed by [a] Independent t-test; [b] Pearson's chi-squared; [c] Fisher's exact test, [*] stone sizes were evaluated from plain KUB (kidney, ureter, and bladder) films.
Abbreviations: IIS, infection-induced stones; non-IIS, non infection-induced stones; WBCs, white blood cells; SN, stone niduses; SP, stone peripheries; RPU, renal pelvic urine; MSU, midstream urine.

Table 2 Simultaneous bacterial culturing results from SN, SP, RPU, and MSU

Parameters	Test status of culture	Results of SN	
		Positive	Negative
SP	Positive	16 (100%)	1 (5.00%)
	Negative	0	19 (95.00%)
RPU	Positive	11 (68.75%)	1 (5.00%)
	Negative	5 (31.25%)	19 (95.00%)
MSU	Positive	15 (93.75%)	3 (15.00%)
	Negative	1 (6.25%)	17 (85.00%)
Total		16	20

Abbreviations: SN, stone niduses; SP, stone peripheries; RPU, renal pelvic urine; MSU, midstream urine.

Table 3 Diagnostic testing with 95% CI of bacterial infections in KSFs by bacterial culturing results from SP, RPU, and MSU

Parameters	SP	RPU	MSU
Sensitivity	100% [79.40%, 100%]	68.80% [41.30%, 89.00%]	93.80% [69.80%, 99.80%]
Specificity	95.00% [75.10%, 99.90%]	95.00% [75.10%, 99.90%]	85.00% [62.10%, 96.80%]
LR+	20.00 [2.96, 135.00]	13.80 [1.98, 95.60]	6.25 [2.19, 17.90]
LR-	NA	0.33 [0.16, 0.68]	0.07 [0.01, 0.50]
PPV	94.10% [71.30%, 99.90%]	91.70% [61.50%, 99.80%]	83.30% [58.60%, 96.40%]
NPV	100% [82.40%, 100%]	79.20% [57.80%, 92.90%]	94.40% [72.70%, 99.90%]

Abbreviations: SP, stone peripheries; RPU, renal pelvic urine; MSU, midstream urine; LR+, positive likelihood ratio; LR-, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive

value; NA, not applicable.

Comparison of three sample culturing

SP, RPU, and MSU cultures were evaluated using the receiver operating characteristic (ROC)-derived AUC. The AUC for the three-sample culture demonstrated a significant difference (p-value < 0.05) (Figure 1). The AUC of the SP culture was higher than both the RPU and MSU cultures. Notably, SP culture exhibited a significantly higher AUC than RPU culture alone (p-value < 0.05). On the other hand, no significant difference was found between the AUC of SP versus MSU (p-value = 0.080) and RPU versus MSU (p-value = 0.348).

The agreement levels among the stone and urine cultures

Cohen's Kappa levels of agreement in SN, SP, RPU, and MSU cultures were performed (Figure 2). According to McHugh.[16], on the interpretation of Cohen's Kappa, only SN and SP revealed an almost perfect agreement level (0.94), indicating the strongest concordance in bacterial detection between SN and SP. Meanwhile, the remaining pairs (e.g., SP with MSU or SP with RPU) exhibit varying levels of agreement, ranging from weak to strong.

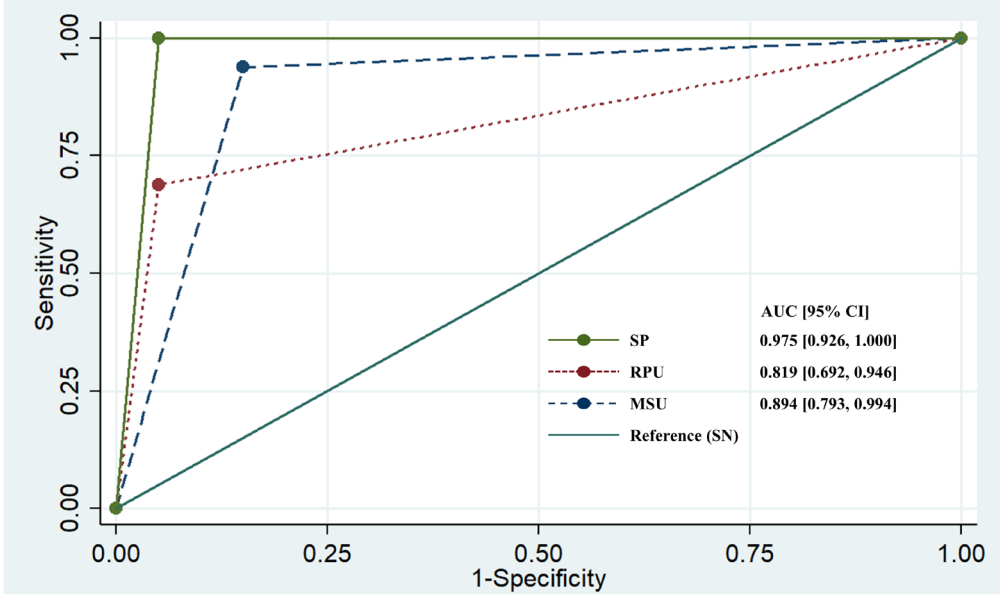

Figure 1 Receiver operating characteristic (ROC) curves for stone peripheries (SP), renal pelvis urine (RPU), and midstream urine (MSU) cultures with the area under the curve (AUC) and its 95% confidence intervals (CI)

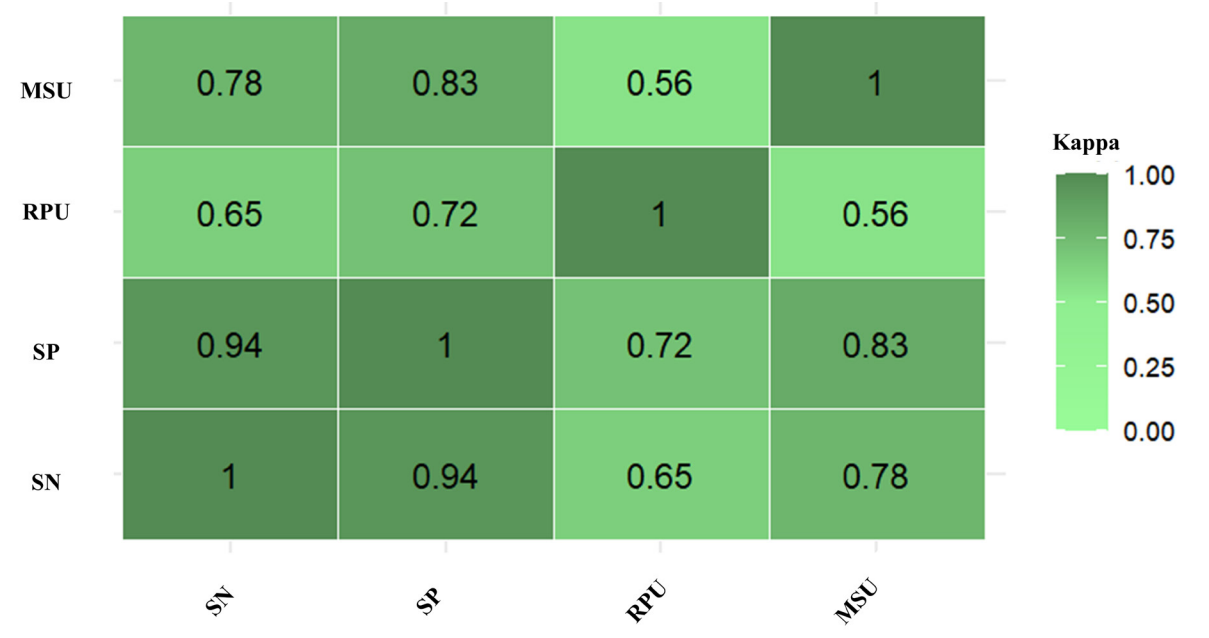

Figure 2 Cohen's Kappa agreement between stone niduses (SN), stone peripheries(SP), renal pelvic urine (RPU), and midstream urine (MSU)
The level of agreement is interpreted based on the Kappa level as > 0.90 (Almost perfect), 0.80-0.90 (Strong), 0.60-0.79 (Moderate), 0.40-0.59 (Weak), 0.21-0.39 (Minimal), < 0.20 (None)[16]

Concordance between bacteria isolated from the stone and urine samples

According to the strongest levels of agreement in SN and SP cultures, the similarity between bacterial isolates from SN and SP, as well as the chemical compositions of SN, was demonstrated (Table 4). Of the 36 KSFs recruited, 16 (44.44%) and 17 (47.22%) patients had bacteria isolated from their SN and SP, respectively. The most commonly isolated bacteria from SN and SP specimens were *E. coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. Of the 16 cases out of 17 KSFs with bacterial isolates from both SN and SP, one remaining case had *Pseudomonas* spp. isolated from SP, RPU, and MSU. In a comprehensive analysis of the bacterial types and SN chemical compositions, *P. mirabilis* and *E. coli* were the most commonly isolated bacteria from SV and COM stones, respectively.

Table 4 Comparative analysis of bacteria isolated from SN and SP samples

Bacteria	Bacteria isolated from SN (cases)	Bacteria isolated from SP (cases)	Chemical compositions of SN
Pure microorganism			
Gram-negative bacteria			
Escherichia coli	5	5	COM
Klebsiella pneumoniae	3	3	COM or UA or CA or Wk
Proteus mirabilis	3	3	SV or CA
Escherichia fergusonii	1	1	SU
Pseudomonas spp.	0	1	COM
Gram-positive bacteria			
Enterococcus faecalis	1	1	COM
Staphylococcus saprophyticus	1	1	SU
Mixed microorganisms			
E. coli & P. mirabilis	1	1	SV
E. coli & K. pneumoniae	1	1	COM
Total	16	17	

Abbreviations: SN, stone niduses; SP, stone peripheries; COM, calcium oxalate monohydrate; UA, uric acid; CA, carbonate apatite; Wk, whitlockite; SV, struvite; SU, sodium urate

Discussion

High prevalence rates of nephrolithiasis have been reported globally and in northeastern Thailand[17-19]. According to sex and underlying diseases in KSFs, previous studies have shown high frequencies of males[20] and HT[21], which align with our findings. Notably, DM was found more frequently in females than in males, consistent with a previous study[22]. In part of the chemical compositions, non-IIS and IIS were observed in most males and females, respectively, consistent with a previous study[23]. Interestingly, our urinalysis results (leukocyte esterase, nitrite, pyuria, and urinary pH) and the culturing of stone and urine samples were consistent in the cases of IIS. A risk of UTIs in females is attributed to the anatomy of their urinary system, such as the shorter urethra compared to males, which may contribute to ascending infections and IIS formation[4,15,23]. Considering that SN culture is the gold standard, the sensitivity, LR+, PPV, NPV, and AUC of SP were high, exceeding those of RPU and MSU. These findings support and reinforce a previous study from 2012, which emphasized the importance of culturing stones rather than relying solely on urine-based diagnostics[7]. MSU culture may not represent the infection status of the upper tract, especially in the presence of obstruction[24]. According to PPV results, intraoperative stones and RPU provided better diagnostic accuracy for bacterial infections in KSFs than MSU, particularly when culture results were positive, consistent with previous studies[9-12,24]. Additionally, SP, RPU, and MSU cultures were evaluated using the receiver operating characteristic (ROC)-derived AUC. SP culture showed the best performance in discriminating against bacterial infections in KSFs. The comprehensive evaluation of the cultures of four specimens (i.e., SN, SP, RPU, and MSU) in KSFs regarding the association between

nephrolithiasis and UTIs is still limited. Previous studies have emphasized the correlation among MSU, RPU, and stone cultures in KSFs with post-operative sepsis or recurrence complications, in which stone culture is consistently regarded as the most accurate diagnostic method[11-12, 24]. As part of the agreement analysis of four specimens, SN and SP revealed an almost perfect level of agreement, indicating the strongest concordance in bacterial detection between SN and SP. These findings suggest that collecting stone fragments, including SN and SP, could be used to assess the bacterial infection. Meanwhile, the remaining pairs (e.g., SP with MSU or SP with RPU cultures) exhibit varying levels of agreement, ranging from weak to strong. Therefore, SP may prioritize diagnostic bacterial infections in KSFs. The implications for perioperative antimicrobial management and infection control strategies in patients undergoing procedures for kidney stone removal may affect urine samples, potentially influencing the agreement between stone and urine cultures, which can range from weak to strong. To our knowledge, we hypothesized that a bidirectional relationship between nephrolithiasis and UTIs could be elucidated using the culture results from SN specimens, which are regarded as the gold standard in our study. The bacterial isolates from SN and SP were related to the chemical composition of SN. Stone culture may be associated with bacterial infections related to lithogenesis, while urine culture may be involved in distributing stones that lead to subsequent infections. Therefore, incorporating stone and urine cultures into KSFs may be beneficial for elucidating the temporal sequence of challenges between nephrolithiasis and UTIs. Herein, the bacteria isolated from the SN and SP samples were observed. *E. coli*, *K. pneumoniae*, and *P. mirabilis* were the most common bacterial isolates from the stone samples, consistent with a previous study[7]. In a comprehensive analysis of the bacterial types and SN's chemical compositions, almost all bacterial isolates from SN and SP samples were related to the SN compositions. *P. mirabilis* and *E. coli* were the most common bacterial isolates from SV and COM compositions, respectively. These findings were consistent with previous studies[1-3,7,25]. Urea-splitting bacteria, such as *P. mirabilis* and *K. pneumoniae*, use the urease enzyme to break down urea into ammonia and carbon dioxide. As a result, this breakdown produces ammonium and bicarbonate ions, increasing urine alkalinity. When ammonium ions and bicarbonate attach to available ions, they promote the formation of SV or CA. Additionally, some SV crystals may accumulate, damage the urothelium, and potentially lead to the development of massive staghorn SV stones[3-4,26-27]. In contrast to the association between *E. coli* and COM stones, a 2013 study revealed that *E. coli* promoted the growth and aggregation of CaOx crystals in *in vitro* experiments[28]. Following a 2015 *in vivo* murine investigation, a study indicated that *E. coli* could increase CaOx deposition in the kidney[29]. Moreover, previous *in vitro* studies have revealed that certain components of *E. coli* (e.g., elongation factor Tu (EF-Tu), outer membrane vesicles (OMVs), and flagellum) could play significant roles in promoting CaOx crystal growth and aggregation[30-31]. The stone culture diagnostic is highly effective, enabling the identification of bacterial infections in KSFs. At both the PPV and agreement levels, we also identified SP culture positivity as a potential diagnostic marker of bacterial infections in KSFs. Our findings facilitate the development of a diagnostic protocal for bacterial infections in KSFs.

Conclusion

Comparing SN with the other three culture specimens, the sensitivity, LR+, PPV, NPV, and AUC of SP culture were higher, exceeding those of RPU and MSU. The agreement level between SN and SP cultures was almost perfect. *E. coli*, *K. pneumoniae*, and *P. mirabilis* were the most frequently isolated bacteria from stone

samples. A thorough analysis of the types of bacterial isolates and SN chemical compositions revealed that *P. mirabilis* and *E. coli* were the most isolated bacteria from IIS (i.e., SV) and non-IIS (i.e., COM). Stone culture may be associated with bacterial infections related to lithogenesis, while urine culture may be involved in distributing stones that lead to subsequent infections. Herein, integrating stone and urine cultures into the diagnostic workflow for bacterial infections in KSFs is recommended.

Take home messages

Stone cultures demonstrate superior efficacy in detecting bacteria in kidney stones compared to urine cultures. Bacteria, including *E. coli* and *P. mirabilis*, are frequently associated with specific types of stones. Integrating stone cultures with urine cultures significantly enhances the diagnosis for bacterial infections in KSFs.

Conflict of interest statement

The authors declare no conflict of interest.

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Data availability

Data available on request due to privacy/ethical restrictions

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