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# Predictors of urosepsis in struvite stone patients after percutaneous nephrolithotomy

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**Purpose:** This study aims to identify clinical factors that may predispose struvite stone patients to urosepsis following percutaneous nephrolithotomy (PCNL).

**Materials and Methods:** A retrospective review was conducted on patients who received PCNL for struvite stones. The Systemic Inflammatory Response Syndrome (SIRS) criteria and quick-Sepsis Related Organ Failure Assessment (q-SOFA) criteria were used to identify patients who were at an increased risk for urosepsis. Statistical analysis was performed using Fisher's exactness test, Wilcoxon rank test, and logistic regression.

**Results:** Chart review identified 99 struvite stone patients treated with PCNL. Post-operatively, 40 patients were SIRS positive (≥2 criteria) and/or q-SOFA positive (score ≥2). Using SIRS as an approximation for urosepsis, longer operative times (p<0.001), higher pre-operative white blood cell counts (p=0.01), greater total stone surface area (p<0.0001), and pre-operative stenting (OR, 5.75; p=0.01) were identified as independent risk factors for urosepsis. Multivariate analysis demonstrated pre-operative stenting (OR, 1.46; p=0.01) to be a risk factor. With q-SOFA, univariable analysis found that antibiotic use within 3 months prior to a PCNL (OR, 4.44; p=0.04), medical comorbidities (OR, 4.80; p=0.02), longer operative times (p<0.001), lengthier post-operative hospitalization (p<0.01), and greater total stone surface area (p<0.0001) were risk factors for urosepsis. Multivariate analysis revealed that bladder outlet obstruction (OR, 2.74; p<0.003) and pre-operative stenting (OR, 1.27; p=0.01) significantly increased odds of being q-SOFA positive.

**Conclusions:** Several risk factors for urosepsis following PCNL for struvite stones have been identified. These risk factors should be taken into consideration in peri-operative care to mitigate the risks of urosepsis.

**Keywords:** Nephrolithotomy, percutaneous; Quick-sepsis related organ failure assessment; Struvite; Systemic Inflammatory Response Syndrome; Urosepsis



## INTRODUCTION

Struvite stones account for approximately 10%–15% of all urinary calculi [1]. These stones are produced in the presence of urea-splitting bacteria. Due to their association with bacteria, several infection-related complications can arise following stone treatment. One such complication is urosepsis [2]. The rates of urosepsis following the treatment of urinary

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calculi have been reported to range from 0.3% to 4.7% [3]. Although urosepsis is an uncommon sequela following stone treatment, it is a life-threatening complication that struvite patients are at an increased risk of developing [2].

Urosepsis is a dysregulated systemic inflammatory response to a urogenital infection. Generally, it occurs secondary to the dissemination of a previously localized uropathogenic bacterial infection into the blood stream [4]. Patients that experience urosepsis have a mortality rate of 20%–40%, which increases to 50% in patients who experience refractory septic shock [4,5]. Given the high mortality rates, investigation into predictive factors for urosepsis in struvite stone patients receiving treatment is warranted.

Several different criteria have been developed to identify patients at high risk for developing sepsis, including the Systemic Inflammatory Response Syndrome (SIRS) criteria. SIRS is composed of a constellation of symptoms which include: fever ≥38℃, tachycardia (>90 beats per minute), tachypnea (>20 breaths per minute), and elevated white blood cell (WBC) count of >12,000/dL [6]. The most recent classification, known as the Sequential (sepsis-related) Organ Failure Assessment (SOFA), was introduced by the Third International Sepsis Consensus Definition Task Force. With this new classification, a bedside quick SOFA (q-SOFA) scoring system was also adapted to facilitate the diagnosis of sepsis. This q-SOFA scoring system classified patients at high risk of progressing to sepsis if at least two of the following criteria are fulfilled: Glasgow Coma Scale (GSC) <15, systolic blood pressure of ≤100 mmHg and tachypnea of ≥22 breaths per minute [6]. The q-SOFA scoring system was shown to have higher specificity and positive predictive value than the SIRS criteria in identifying sepsis cases in a multi-institutional Endourologic Disease Group for Excellence (EDGE) Research consortium study [7].

Currently, the available literature has documented risk factors for sepsis in patients with urinary stones following percutaneous nephrolithotomy (PCNL). Some of these risk factors include pre-operative bacteriuria, stone size, and operative time [8]. Particular to struvite stones treated with PCNL, their inherent infectious nature and the presence of pre-operative multi-drug resistant (MDR) bacteriuria have been identified as variables that may predict sepsis post-operatively [9]. However, to date, no research has been conducted to differentiate the clinical factors that put some struvite patients at an increased risk of developing urosepsis following stone treatment. Our study aims to identify predictor variables for urosepsis status post-PCNL for struvite stones.

## MATERIALS AND METHODS

This study was approved by the University of British Columbia's Clinical Research Ethics Board (approval number: H19-01362). Written informed consent was waived by the Board. A retrospective analysis of medical records of patients who underwent PCNL for the treatment of struvite stones at University of British Columbia between 2009 and 2015 was conducted. Inclusion criteria for this study were patients above the age of 19 who underwent PCNL and had confirmed struvite stones on post-operative stone-analysis. Exclusion criteria for this study were: patients under the age of 19 and patients who had non-struvite stones. Table 1 shows the demographic data for the study population. Data collected included: age, sex, body mass index (BMI), related medical and urologic history. Target stone characteristics, pre-operative data, intra-operative data, and post-operative data until their discharge from hospital or transfer to another institution were also collected. Patients with pre-operative positive urine culture were treated with antimicrobials. The primary outcome was sepsis, as calculated by both the SIRS and q-SOFA indices post-operatively. The data was separated into two patient populations: patients who experienced urosepsis following struvite stone treatments (satisfying either SIRS or q-SOFA criteria) versus patients who had no infectious complications following struvite stone treatment.

All patients had radiologically confirmed calculi visualized with either CT (computed tomography) imaging or plain film X-rays. Total stone surface area was calculated using Mayo Clinic qSAS Stone Analysis software (Mayo Clinic, Rochester, NY, USA). Staghorn calculi were defined as calculi that occupied the renal pelvis and at least two calyces. The standard PCNL procedure was used for all patients.

SIRS was defined as having two or more of the following:

- Body temperature ≥38℃
- Heart rate >90 beats per minute
- Respiratory rate >20 breaths per minute
- WBC >12,000/dL or <4,000/dL

The q-SOFA score was defined as being positive for sepsis if two or more of the following were true:

- GCS <15
- Systolic blood pressure ≤100 mmHg
- Respiratory rate ≥22 breaths per minute

To determine differential significance when comparing each variable between the arms of the study, the Wilcoxon rank sum test and Fischer exactness tests were used. A multivariable logistic regression analysis was also conducted with the p-value cut-off point being 0.05 from univariate


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Table 1. Patient demographics and history

| Variable | Negative sepsis criteria (SIRS or q-SOFA) | Positive sepsis criteria (SIRS or q-SOFA) | All patients |
|---|---|---|---|
| Number of patients | 59 (59.6) | 40 (40.4) | 99 (100.0) |
| Age (y) | 50.1±19.1 | 56.1±18.5 | 52.6±17.9 |
| Sex, M/F | 24/35 (40.7/59.3) | 14/26 (35.0/65.0) | 38/61 (38.4/61.6) |
| BMI (kg/m$^2$) | 28.2±9.2 | 28.7±6.7 | 28.5±8.3 |
| Patients BMI >30 kg/m$^2$ | 16 (27.1) | 17 (42.5) | 33 (33.3) |
| Diabetes mellitus | 4 (6.8) | 7 (17.5) | 11 (11.1) |
| Hypertension | 18 (30.5) | 15 (37.5) | 33 (33.3) |
| Coronary artery disease | 0 (0.0) | 1 (2.5) | 1 (1.0) |
| Immunocompromised | 1 (1.7) | 2 (5.0) | 3 (3.0) |
| Comorbidities | 23 (39.0) | 15 (37.5) | 38 (38.4) |
| History of urolithiasis | 41 (69.5) | 28 (70.0) | 69 (69.7) |
| History of UTI | 18 (30.5) | 9 (22.5) | 27 (27.3) |
| History of urosepsis | 10 (16.9) | 9 (22.5) | 19 (19.2) |

Values are presented as number (%) or mean±standard deviation.
SIRS, Systemic Inflammatory Response Syndrome; q-SOFA, quick-Sepsis Related Organ Failure Assessment; M/F, male/female; BMI, body mass index; UTI, urinary tract infection.

analysis. All statistical data analysis was conducted using RStudio Software Version 1.2.5001 (R Studio, Boston, MA, USA).

# RESULTS

## 1. Patient characteristics

Retrospective chart review revealed that 99 patients who presented with struvite stones (based on stone analysis) were treated with PCNL during the study time period. Table 1 summarizes the patient characteristics. Overall, the patient population consisted of a total of 38 males (38.4%) and 61 females (61.6%). The mean age of patients was 52.6±17.9 years. The mean BMI was 28.5±8.3 kg/m$^2$. Only 43 patients (43.4%) were found to have no comorbidities and were otherwise healthy. The SIRS criteria and q-SOFA were used to assess for the risk of urosepsis post-PCNL. A total of 40 patients (40.4%) were found to be either SIRS positive (≥2 criteria) and/or had q-SOFA score ≥2 (Table 1). There were 38 SIRS positive (38.4%) patients, 11 patients (11.1%) considered high risk for in hospital mortality as determined by a q-SOFA, and 9 patients (9.1%) who satisfied both SIRS and q-SOFA criteria. For patients that were SIRS positive, 15 (15.2%) patients had a positive urine culture and 1 (1.0%) patient had a positive blood culture. In q-SOFA positive patients, 4 (4.0%) had a positive urine culture, while none had a positive blood culture.

## 2. Predictor variables for urosepsis

Using SIRS criteria to identify predictive variables of urosepsis post-PCNL, it was discovered that sepsis patients had longer operative times (242.24±83.22 vs. 215.43±71.78 minutes, p<0.001), higher mean pre-operative WBC (8.49±2.45×10$^9$/L vs. 7.54±2.55×10$^9$/L, p=0.01), and stones with significantly greater total surface area (1,064.58±1,170.37 mm$^2$ vs. 811.24±783.48 mm$^2$, p<0.0001). Furthermore, patients with pre-operative stents had significantly higher odds of urosepsis (univariable odds ratio [OR], 5.75; 95% confidence interval [CI], 1.42–23.24; p=0.01) (Table 2). Similarly, on multivariate analysis (Supplementary Table 1), patients who had a stent pre-operatively were found to be at increased risk of urosepsis as determined by the SIRS criteria (OR, 1.46; 95% CI, 1.12–2.22; p=0.01) (Table 3).

Using q-SOFA to assess for urosepsis, patients were found to be at an increased risk for progression to urosepsis if they had used antibiotics within 3 months of their PCNL (univariable OR, 4.44; 95% CI, 1.10–17.94; p=0.04). Furthermore, although patients with diabetes mellitus (DM), hypertension (HTN), coronary artery disease (CAD) and/or an immunocompromising condition individually were not found to be at an increased risk of urosepsis, the presence of pre-existing comorbidities cumulatively, acted as a risk factor for a positive q-SOFA score (univariable OR, 4.80; 95% CI, 1.18–19.46; p=0.02). In addition, q-SOFA positive patients were found to have a significantly greater mean total stone surface area than patients who did not have a q-SOFA score of ≥2 (1,254.26±1,385.62 mm$^2$ vs. 880.95±914.83 mm$^2$, p<0.0001). Significantly longer operative times (253.64±69.75 minutes vs. 223.51±78.60 minutes, p<0.001) and longer hospitalization times (5.40±3.41 days vs. 2.53±2.27 days, p<0.01) were also noted in patients that were q-SOFA positive (Table 4). Longer hospitalization times were likely

Table 2. Univariable analysis of predictor variables for urosepsis as defined by the SIRS criteria

| Variable | SIRS (-) (n=61) | | | SIRS (+) (n=38) | |
|---|---|---|---|---|---|
| | Value | Odds ratio | 95% CI | Value | p-value |
| Age (y) | 49.84±19.03 | - | - | 56.58±15.66 | 0.08 |
| Sex, male | 34.43 | 0.96 | 0.41–2.24 | 36.84 | >0.99 |
| BMI (kg/m$^2$) | 28.46±9.30 | - | - | 28.32±6.47 | 0.49 |
| BMI >30 kg/m$^2$ | 27.87 | 1.74 | 0.73–4.17 | 42.11 | 0.27 |
| Diabetes mellitus | 8.20 | 2.00 | 0.57–7.07 | 15.79 | 0.33 |
| Hypertension | 31.15 | 1.12 | 0.48–2.63 | 36.84 | 0.83 |
| Coronary artery disease | 0.00 | 4.48 | 0.18–112.88 | 2.63 | 0.41 |
| Immunocompromised | 1.64 | 3.03 | 0.26–34.60 | 5.26 | 0.56 |
| Comorbidities | 39.34 | 0.75 | 0.32–1.73 | 36.84 | 0.53 |
| History of urolithiasis | 67.21 | 0.99 | 0.37–2.62 | 73.68 | >0.99 |
| Prior stone procedure | 6.56 | 0.25 | 0.03–2.00 | 10.53 | 0.40 |
| History of UTI | 31.15 | 0.52 | 0.20–1.34 | 21.05 | 0.25 |
| History of urosepsis | 16.39 | 1.37 | 0.49–3.84 | 23.68 | 0.50 |
| Urinary diversion | 0.00 | 0.33 | 0.04–3.07 | 0.00 | >0.99 |
| Neurogenic bladder | 6.56 | 0.33 | 0.04–3.07 | 2.63 | 0.39 |
| Bladder outlet obstruction | 0.00 | 4.27 | 0.17–107.81 | 2.63 | 0.42 |
| Self-intermittent catherization | 4.92 | 0.18 | 0.01–3.64 | 2.63 | 0.26 |
| Long-term indwelling catheter | 0.00 | 4.07 | 0.16–102.76 | 2.63 | 0.43 |
| Renal/UPJ obstruction | 18.03 | 1.00 | 0.36–2.81 | 21.05 | >0.99 |
| Vesicoureteral reflex | 0.00 | 1.35 | 0.03–69.43 | 0.00 | >0.99 |
| Partial or complete staghorn calculi | 49.18 | 0.32 | 0.05–1.90 | 50.00 | 0.45 |
| Overall stone burden (number of stones) | 2.88±2.86 | 3.04 | 0.85–10.86 | 3.44±3.91 | 0.98 |
| Total stone surface area (mm$^2$) | 811.24±783.48 | - | - | 1,064.58±1,170.37 | <0.0001* |
| Stone location | - | - | - | - | 0.33 |
| Hydronephrosis | 14.75 | 0.52 | 0.14–1.86 | 10.53 | 0.37 |
| Urine culture | 29.51 | 0.83 | 0.31–2.24 | 39.47 | 0.69 |
| Antibiotics <3 months before surgery | 37.70 | 1.38 | 0.61–3.12 | 47.37 | 0.53 |
| Pre-operative stent | 4.92 | 5.75 | 1.42–23.24 | 23.68 | 0.01* |
| Pre-operative nephrostomy tube | 8.20 | 1.26 | 0.32–5.00 | 10.52 | 0.74 |
| Serum creatinine (μmoL/L) | 95.43±85.97 | - | - | 87.46±40.89 | 0.54 |
| BUN | 6.64±4.48 | - | - | 5.95±2.79 | 0.68 |
| Pre-operative hematocrit (L/L) | 0.40±0.04 | - | - | 0.39±0.05 | 0.19 |
| Hemoglobin (g/L) | 133.17±16.73 | - | - | 127.08±19.07 | 0.11 |
| Pre-operative WBC (1×10$^9$/L) | 7.54±2.55 | - | - | 8.49±2.45 | 0.01* |
| Subsequent procedures required | 9.83 | 0.67 | 0.09–5.13 | 7.89 | 0.47 |
| Post-operative serum creatinine (μmoL/L) | 101.88±87.20 | - | - | 92.94±44.66 | 0.45 |
| Blood transfusion | 0.00 | 1.47 | 0.03–75.56 | 0.00 | 0.80 |
| Hemoglobin change (g/L) | 102.18±33.69 | - | - | 109.36±13.97 | - |
| Post-operative hematocrit (L/L) | 0.35±0.05 | - | - | 0.34±0.04 | 0.24 |
| Urine culture | 6.55 | 0.60 | 0.12–2.91 | 15.79 | 0.65 |
| Blood culture | 1.64 | 0.47 | 0.03–8.52 | 2.63 | >0.99 |
| Duration of post-operative antibiotics (d) | 45.26±38.43 | - | - | 38.1±38.2 | 0.51 |
| Length of stay at hospital (d) | 2.85±2.62 | - | - | 2.89±2.57 | 0.93 |
| Presence of residual fragments | 39.34 | 1.18 | 0.17–8.02 | 44.73 | 0.84 |
| Number of fragments | 1.59±0.50 | - | - | 0.53±0.61 | 0.76 |
| Largest residual fragment size (mm$^2$) | 2.41±3.79 | - | - | 2.44±3.77 | 0.87 |
| Operative time (min) | 215.43±71.78 | - | - | 242.24±83.22 | <0.001* |

Continuous variables are presented by mean±standard deviation. Frequency of patients (%) is presented for binary variables.
SIRS, Systemic Inflammatory Response Syndrome; UTI, urinary tract infection; UPJ, ureteropelvic junction; BMI, body mass index; WBC, white blood cell; BUN, blood urea nitrogen; SD, standard deviation; CI, confidence interval; -, not available.
*Significant variable (p<0.05).

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**Table 3.** Multivariable logistic regression analysis of potential predictors for satisfying SIRS criteria

| Variable | OR (95% CI) | p-value |
|---|---|---|
| Age, per one year older (y) | 1.00 (0.99–1.00) | 0.89 |
| Prior stone procedure, yes | 1.04 (0.97–1.19) | 0.41 |
| Patient stented pre-procedure, yes | 1.46 (1.12–2.22) | 0.01* |
| Pre-operative WBC count (per unit increase) | 0.97 (0.93–1.02) | 0.35 |
| Operative time (min) | 1.00 (1.00–1.00) | 0.25 |
| Total target stone surface area (mm$^2$) | 1.00 (1.00–1.00) | 0.25 |

SIRS, Systemic Inflammatory Response Syndrome; OR, odds ratio; CI, confidence interval; WBC, white blood cell.
*Significant variable (p<0.05).

due to a consequence of infection post-PCNL. On multivariate analysis (Supplementary Table 2), patients with bladder outlet obstruction (BOO) (multivariable OR, 2.74; 95% CI, 1.64–4.56; p<0.003) or had a stent pre-operatively (multivariable OR, 1.27; 95% CI, 1.06–1.53; p=0.01) were at higher odds of developing urosepsis as defined (Table 5).

## DISCUSSION

Patients with struvite stones have been documented to be at an increased risk for experiencing infection-related complications post-operatively [2]. However, within the population of struvite patients, factors that may predispose some to urosepsis have yet to be elucidated. Understanding these factors can play a crucial role in optimizing patient peri-operative care. In this study, we identified 40 (40.4%) patients who were either SIRS positive or had a q-SOFA score of ≥2. SIRS criteria did identify a higher percentage of patients (38.4%) with sepsis compared to using q-SOFA (11.1%). About 9.1% of patients were positive using both SIRS and q-SOFA criteria. Within these two groups of patients several predictor variables for urosepsis were elucidated.

When urosepsis was approximated by SIRS and by q-SOFA, univariable analysis demonstrated that longer operative times and greater total stone surface area were risk factors for urosepsis (Tables 2, 4). While not specific to struvite stones, longer PCNL operative times and a larger stone size have been identified as risk factors for SIRS or post-PCNL sepsis [8,10]. In this study, greater total stone surface areas may have led to longer PCNL procedures due to the increased complexity of treating large stones. Other factors such as difficulty of access, renal bleeding, and patient physiology may have resulted in longer procedures. Given the findings of this and previous studies, consideration should be taken to stage-PCNL procedures for large struvite stones in order to minimize operative time and mitigate the risk of urosepsis.

Another risk factor for urosepsis in our study was patients who had a stent prior to surgery. Pre-operative stent placement can aid access. Pre-operative stenting was found to greatly increase the odds of a patient meeting ≥2 SIRS criteria post-operatively. Univariate and multivariate analysis revealed a significant association between having a stent pre-operatively and a positive SIRS classification (Tables 2, 3). In further support, when urosepsis was approximated by q-SOFA, pre-operative stenting significantly increased the odds of urosepsis by 27% (Table 5). To our knowledge, there have been no studies that have found pre-PCNL stenting to be a risk factor for urosepsis. However, a prior study by Moses et al. [11] found that patients who were pre-stented were at greater risk of a serious infection-related complication following ureteroscopy, possibly due to bacterial colonization and biofilm formation [12]. When these colonized stents are manipulated intra-operatively, bacterial spread can result, thereby increasing the risk of urosepsis [13]. Ureteral stents may also predispose patients to urosepsis as stents are thought to facilitate retrograde bacterial ascent from the bladder to the kidneys by serving as a conduit [14]. An *in vitro* study conducted by Hobbs et al. [15] demonstrated the ability of *Proteus mirabilis*, a urea-splitting bacteria, to migrate from bladder to kidneys by forming distinct biofilm communities along the length of an ureter analog. Ureteral stents may enhance this process as conditioning films readily form on stent surfaces and provide the necessary substrate for bacterial adhesion [14]. Together, these mechanisms can contribute to the systemic dissemination of bacteria initially localized in the urinary tract.

The severity of urinary tract obstruction is known to directly influence the incidence of urosepsis [16]. Our results are consistent with this finding as patients with BOO were at increased odds for progressing to urosepsis as characterized by q-SOFA (Table 5). Obstructive uropathy likely contributes to urosepsis as it causes more endotoxins (normally released from calculi during stone manipulation in PCNL) to enter the systemic circulation and result in an exacerbated systemic inflammatory response [17]. This inflammatory response can be further worsened by the treatment of struvite stones as infection stones are known to contain higher levels of endotoxins compared to non-infection stones [18].

Higher pre-operative WBC was found to be an independent risk factor for a positive SIRS classification post-PCNL for struvite stones. Patients that were SIRS positive had a significantly greater mean pre-operative WBC count (Table 2). Although the WBC levels in our study do not reflect true leukocytosis, patients with elevated but normal WBC may

Table 4. Univariable analysis of predictor variables for urosepsis as defined by the q-SOFA score

| Variable | q-SOFA (-) (n=88) | | | q-SOFA (+) (n=11) | |
|---|---|---|---|---|---|
| | Value | Odds ratio | 95% CI | Value | p-value |
| Age (y) | 52.54±18.29 | - | - | 52.90±16.01 | 0.97 |
| Sex, male | 61.40 | 1.53 | 0.43–5.43 | 54.50 | 0.52 |
| BMI (kg/m$^2$) | 28.38±8.52 | - | - | 28.62±5.92 | 0.73 |
| BMI >30 kg/m$^2$ | 32.95 | 1.17 | 0.31–4.50 | 36.36 | 1.00 |
| Diabetes mellitus | 9.09 | 3.75 | 0.83–17.03 | 27.27 | 0.10 |
| Hypertension | 32.95 | 1.10 | 0.30–4.08 | 36.36 | 1.00 |
| Coronary artery disease | 0.00 | 24.43 | 0.93–639.04 | 9.09 | 0.11 |
| Immunocompromised | 2.27 | 4.15 | 0.34–49.98 | 9.09 | 0.31 |
| Comorbidities | 34.09 | 4.80 | 1.18–19.46 | 72.27 | 0.02* |
| History of urolithiasis | 69.31 | 1.31 | 0.26–6.69 | 72.27 | 1.00 |
| Prior stone procedure | 1.13 | 0.57 | 0.04–7.74 | 9.09 | 0.40 |
| History of UTI | 7.95 | 0.95 | 0.23–3.90 | 27.27 | 1.00 |
| History of urosepsis | 27.27 | 1.78 | 0.40–7.93 | 27.27 | 0.49 |
| Urinary diversion | 18.18 | 9.24 | 0.17–495.92 | 0.00 | 1.00 |
| Neurogenic bladder | 0.00 | 0.79 | 0.04–15.49 | 0.00 | 1.00 |
| Bladder outlet obstruction | 0.00 | 31.40 | 1.17–840.48 | 9.09 | 0.09 |
| Self-intermittent Catherization | 3.41 | 1.25 | 0.06–26.36 | 0.00 | 1.00 |
| Long-term indwelling catheter | 0.00 | 27.35 | 1.03–725.53 | 9.09 | 0.10 |
| Renal/UPJ obstruction | 18.18 | 2.40 | 0.52–11.11 | 27.27 | 0.36 |
| Vesicoureteral reflex | 0.00 | 9.35 | 0.17–502.20 | 0.00 | 1.00 |
| Partial or complete staghorn calculi | 51.13 | 1.29 | 0.06–26.75 | 36.36 | 0.28 |
| Overall stone burden (number of stones) | 3.22±3.43 | 7.80 | 0.42–146.19 | 2.18±1.99 | 0.23 |
| Total stone surface area (mm$^2$) | 880.95±914.83 | - | - | 1,254.26±1,385.62 | <0.0001* |
| Stone location | - | - | - | - | 0.29 |
| Hydronephrosis | 13.63 | 0.69 | 0.08–6.14 | 9.09 | 1.00 |
| Pre-operative urine culture | 32.95 | 0.55 | 0.14–2.18 | 36.36 | 0.50 |
| Antibiotics <3 months before surgery | 37.50 | 4.44 | 1.10–17.94 | 72.72 | 0.04* |
| Pre-operative stent | 10.22 | 4.33 | 0.88–21.29 | 27.27 | 0.09 |
| Pre-operative nephrostomy tube | 10.22 | 0.36 | 0.02–6.68 | 9.09 | 0.59 |
| Serum creatinine (μmol/L) | 92.76±73.02 | - | - | 87.09±49.43 | 0.99 |
| BUN | 6.56±4.01 | - | - | 4.84±2.07 | 0.07 |
| Pre-operative hematocrit (L/L) | 0.40±0.05 | - | - | 0.38±0.06 | 0.39 |
| Hemoglobin (g/L) | 131.69±17.03 | - | - | 122.45±22.76 | 0.24 |
| Pre-operative WBC (1×10$^9$/L) | 7.92±2.39 | - | - | 8.10±3.59 | 0.87 |
| Subsequent procedures required | 6.82 | 8.08 | 0.35–187.34 | 27.27 | 0.15 |
| Post-operative serum creatinine (μmol/L) | 101.60±74.72 | - | - | 72.27±40.04 | 0.17 |
| Blood transfusion | 0.00 | 8.05 | 1.52–427.30 | 18.18 | <0.001* |
| Hemoglobin change (g/L) | 106.22±26.54 | - | - | 97.18±33.67 | - |
| Post-operative hematocrit (L/L) | 0.34±0.04 | - | - | 0.32±0.05 | 0.12 |
| Urine culture | 7.95 | 1.82 | 0.32–10.34 | 27.27 | 0.65 |
| Blood culture | 2.27 | 0.60 | 0.03–14.19 | 0.00 | 1.00 |
| Duration of post-operative antibiotics (d) | 40.48±38.09 | - | - | 56.00±38.68 | 0.34 |
| Length of stay at hospital (d) | 2.53±2.27 | - | - | 5.40±3.41 | <0.01* |
| Presence of residual fragments | 42.04 | 0.77 | 0.21–2.83 | 36.36 | 0.76 |
| Number of fragments | 0.53±0.67 | - | - | 0.44±0.53 | 0.86 |
| Largest residual fragment size (mm$^2$) | 2.55±3.89 | - | - | 1.25±1.91 | 0.49 |
| Operative time (min) | 223.51±78.60 | - | - | 253.64±69.75 | <0.001* |

Continuous variables are presented by mean±standard deviation. Frequency of patients (%) is presented for binary variables.
q-SOFA, quick-Sepsis Related Organ Failure Assessment; UTI, urinary tract infection; UPJ, ureteropelvic junction; BMI, body mass index; WBC, white blood cell; BUN, blood urea nitrogen; SD, standard deviation; CI, confidence interval; -, not available.
*Significant variable (p<0.05).

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Table 5. Multivariable logistic regression analysis of potential predictors for satisfying q-SOFA criteria

| Variable | Odds ratio (95% confidence interval) | p-value |
|---|---|---|
| Antibiotics <3 months before procedure, yes | 1.11 (1.00–1.32) | 0.05 |
| Bladder outlet obstruction, yes | 2.74 (1.64–4.56) | <0.003* |
| Comorbidities, yes | 1.14 (1.00–1.32) | 0.06 |
| Patient stented pre-procedure, yes | 1.27 (1.06–1.53) | 0.01* |
| Blood transfusion, yes | 0.88 (0.70–1.11) | 0.28 |
| Operative time (min) | 1.00 (1.00–1.00) | 0.38 |
| Total target stone surface area ($mm^2$) | 1.00 (1.00–1.00) | 0.36 |

q-SOFA, quick-Sepsis Related Organ Failure Assessment.
*Significant variable (p<0.05).

be at higher risk for progressing to urosepsis post-operatively as this has been reported to indicate a state of increased systemic inflammation and/or subclinical disease [19]. During PCNL, surgical trauma can induce further inflammation and may enhance bacterial dissemination into the circulation, thereby predisposing these individuals to fulfilling SIRS criteria and in turn, urosepsis.

With regards to comorbidities, our current study did not find any specific association between the following existing medical conditions and a positive SIRS or q-SOFA: DM, HTN, CAD, or immunosuppression (Tables 2, 4). However, we did demonstrate that the presence of any other comorbidities (excluding: CAD, HTN, DM, or immunosuppression) cumulatively acted as an independent risk factor for obtaining a q-SOFA score of ≥2 (Table 4). Our findings are supported by previous reports that an increase in the number of comorbidities in bacteremia patients (secondary to urinary tract infections) has been associated with higher mortality rates [20,21]. However, where our results differ is with regards to patients with DM. DM has been described by others to be a general risk factor for urosepsis post-PCNL [10] and has been documented to increase the odds of urosepsis by 80% [22] but not in our study. The lack of an association with DM maybe due to the study being underpowered to see a difference. A detailed analysis will be needed to delineate which specific comorbidities may increase the risk of progression to urosepsis in struvite patients.

Duration of hospitalization was also identified as an independent risk factor for a positive q-SOFA score (Table 3). Longer hospitalizations are known to be associated with a risk of infection especially in those with co-morbidities and those who have had invasive procedures [23]. Although we have shown longer hospitalizations increase the odds for a positive q-SOFA, we were not able to discriminate for certain whether urosepsis was the cause of longer hospitalization or vice-versa. It is likely that the prolonged stay in these cases was a consequence of the infection necessitating a longer hospitalization.

Antibiotic exposure within three months prior to the scheduled PCNL was observed to be significant on univariate analysis, but not on multivariate analysis as a risk factor for a positive q-SOFA score (Tables 4, 5). The role of antibiotics prior to stone treatment remains a controversial topic. Antibiotic prophylaxis prior to PCNL has been previously demonstrated to reduce the incidence of post-operative sepsis in patients with negative preoperative urine culture [24]. However, a recent study by the EGDE consortium demonstrated that pre-operative antibiotics do not necessarily reduce infections after PCNL [25]. This finding is further supported by Potretzke et al. [26] who found extended pre-operative antibiotic prophylaxis to not reduce the risk of SIRS after PCNL. In fact, antibiotic exposure has been hypothesized to place selective pressure on the urinary microbiome for MDR bacteria and the presence of MDR uropathogens in itself, serves as a risk factor for infectious complications following PCNL [27,28]. In our study, it is likely that these were more complicated cases that required antibiotics preoperatively due to recurrent infections. Interestingly, a study by Tasian et al. [28] showed that exposure to oral antibiotics (especially within 3–6 months of diagnosis) may actually contribute to stone disease by altering the urinary environment to facilitate stone growth. Thus, preoperative antibiotic administration may work both to increase stone burden and, in some cases, may worsen infection.

There are several limitations to this study. Firstly, this study is limited by biases inherent to retrospective analyses. Furthermore, not all known risk factors for infectious complications following PCNL were evaluated as some data were unavailable or inconsistently documented in patient charts. Some of these factors include intraoperative pelvic pressure and number of access tracts [8,10]. This study also approximated urosepsis with the q-SOFA score and SIRS criteria and thus, patients fulfilling these criteria may not be actually be clinically septic. These classification systems were selected for this study as both the SIRS criteria and q-SOFA score have been commonly used to facilitate the identification of septic patients. According to a meta-analysis, a SIRS score of ≥2 is more sensitive for sepsis (81%) than a q-SOFA score of ≥2 (42%) [29]. However, the reverse is true with specificity, where a positive q-SOFA score is more specific (88%) than a positive SIRS criteria (41%) [29]. Due to the difference in specificity and sensitivity between both scoring systems, different patient populations would be selected.

This may potentially account for the identification of different predictive variables for urosepsis under the SIRS criteria as compared to the q-SOFA score. Although, SIRS and q-SOFA differ in their specificity and sensitivity, both have been criticized for their lack of sensitivity which may have resulted in higher false negative urosepsis rates in our study [30].

## CONCLUSIONS

Several risk factors for urosepsis as defined by both SIRS and q-SOFA have been identified in this study. Patients with longer operative times, higher pre-operative WBC, greater total stone surface area, and pre-operative stenting were found to increase the risk for fulfilling SIRS criteria. Patients that had a longer-operative time, greater total stone surface area, longer duration of hospitalization, recent use of antibiotics, pre-operative stenting, and obstructive uropathy were at increased risk of being q-SOFA positive. Understanding these risk factors will enable urologists to optimize peri-operative conditions for their struvite patients and in turn, reduce the likelihood of urosepsis.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

## AUTHORS' CONTRIBUTIONS

Research conception and design: Justin Y.H. Chan, Victor K.F. Wong, Dirk Lange, Kymora B. Scotland, and Ben H. Chew. Data acquisition: Justin Y.H. Chan, Victor K.F. Wong, Julie Wong, Ryan F. Paterson, Dirk Lange, and Ben H. Chew. Statistical analysis: Justin Y.H. Chan and Victor K.F. Wong. Data analysis and interpretation: Justin Y.H. Chan, Victor K.F. Wong, Ryan F. Paterson, Kymora B. Scotland, and Ben H. Chew. Drafting of the manuscript: Justin Y.H. Chan, Victor K.F. Wong, Julie Wong, Kymora B. Scotland, and Ben H. Chew. Critical revision of the manuscript: Justin Y.H. Chan, Victor K.F. Wong, Julie Wong, Ryan F. Paterson, Dirk Lange, Kymora B. Scotland, and Ben H. Chew. Administrative, technical, or material support: Victor K.F. Wong. Supervision: Dirk Lange, Kymora B. Scotland, and Ben H. Chew. Approval of the final manuscript: Justin Y.H. Chan, Victor K.F. Wong, Julie Wong, Ryan F. Paterson, Dirk Lange, Kymora B. Scotland, and Ben H. Chew.

## SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20200319.

## REFERENCES

1. Flannigan R, Choy WH, Chew B, Lange D. Renal struvite stones--pathogenesis, microbiology, and management strategies. Nat Rev Urol 2014;11:333-41.
2. Rivera M, Viers B, Cockerill P, Agarwal D, Mehta R, Krambeck A. Pre- and postoperative predictors of infection-related complications in patients undergoing percutaneous nephrolithotomy. J Endourol 2016;30:982-6.
3. Michel MS, Trojan L, Rassweiler JJ. Complications in percutaneous nephrolithotomy. Eur Urol 2007;51:899-906; discussion 906.
4. Scotland KB, Lange D. Prevention and management of urosepsis triggered by ureteroscopy. Res Rep Urol 2018;10:43-9.
5. Dreger NM, Degener S, Ahmad-Nejad P, Wöbker G, Roth S. Urosepsis--etiology, diagnosis, and treatment. Dtsch Arztebl Int 2015;112:837-47; quiz 848.
6. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
7. Yaghoubian A, Batter T, Mozafarpour S, Sacco D, Chew BH, Monga M, et al. Use of the quick sequential organ failure assessment score for prediction of intensive care unit admission due to septic shock after percutaneous nephrolithotomy: a multicenter study. J Urol 2019;202:314-8.
8. Kreydin EI, Eisner BH. Risk factors for sepsis after percutaneous renal stone surgery. Nat Rev Urol 2013;10:598-605.
9. Gao X, Lu C, Xie F, Li L, Liu M, Fang Z, et al. Risk factors for sepsis in patients with struvite stones following percutaneous nephrolithotomy. World J Urol 2020;38:219-29.
10. Rashid AO, Fakhulddin SS. Risk factors for fever and sepsis after percutaneous nephrolithotomy. Asian J Urol 2016;3:82-7.
11. Moses RA, Ghali FM, Pais VM Jr, Hyams ES. Unplanned hospital return for infection following ureteroscopy-can we identify modifiable risk factors? J Urol 2016;195(4 Pt 1):931-6.
12. Zumstein V, Betschart P, Albrich WC, Buhmann MT, Ren Q, Schmid HP, et al. Biofilm formation on ureteral stents - incidence, clinical impact, and prevention. Swiss Med Wkly 2017;147:w14408.
13. Lifshitz DA, Winkler HZ, Gross M, Sulkes J, Baniel J, Livne PM. Predictive value of urinary cultures in assessment of microbial colonization of ureteral stents. J Endourol 1999;13:735-8.

14. Scotland KB, Lo J, Grgic T, Lange D. Ureteral stent-associated infection and sepsis: pathogenesis and prevention: a review. Biofouling 2019;35:117-27.
15. Hobbs T, Schultz LN, Lauchnor EG, Gerlach R, Lange D. Evaluation of biofilm induced urinary infection stone formation in a novel laboratory model system. J Urol 2018;199:178-85.
16. Sharma K, Sankhwar SN, Goel A, Singh V, Sharma P, Garg Y. Factors predicting infectious complications following percutaneous nephrolithotomy. Urol Ann 2016;8:434-8.
17. Mariappan P, Tolley DA. Endoscopic stone surgery: minimizing the risk of post-operative sepsis. Curr Opin Urol 2005;15:101-5.
18. McAleer IM, Kaplan GW, Bradley JS, Carroll SF, Griffith DP. Endotoxin content in renal calculi. J Urol 2003;169:1813-4.
19. Chmielewski PP, Strzelec B. Elevated leukocyte count as a harbinger of systemic inflammation, disease progression, and poor prognosis: a review. Folia Morphol (Warsz) 2018;77:171-8.
20. Chin BS, Kim MS, Han SH, Shin SY, Choi HK, Chae YT, et al. Risk factors of all-cause in-hospital mortality among Korean elderly bacteremic urinary tract infection (UTI) patients. Arch Gerontol Geriatr 2011;52:e50-5.
21. Tal S, Guller V, Levi S, Bardenstein R, Berger D, Gurevich I, et al. Profile and prognosis of febrile elderly patients with bacteremic urinary tract infection. J Infect 2005;50:296-305.
22. van Nieuwkoop C, Bonten TN, van't Wout JW, Kuijper EJ, Groeneveld GH, Becker MJ, et al. Procalcitonin reflects bacteremia and bacterial load in urosepsis syndrome: a prospective observational study. Crit Care 2010;14:R206.
23. Jeon CY, Neidell M, Jia H, Sinisi M, Larson E. On the role of length of stay in healthcare-associated bloodstream infection. Infect Control Hosp Epidemiol 2012;33:1213-8.
24. Gravas S, Montanari E, Geavlete P, Onal B, Skolarikos A, Pearle M, et al. Postoperative infection rates in low risk patients undergoing percutaneous nephrolithotomy with and without antibiotic prophylaxis: a matched case control study. J Urol 2012;188:843-7.
25. Chew BH, Miller NL, Abbott JE, Lange D, Humphreys MR, Pais VM Jr, et al. A randomized controlled trial of preoperative prophylactic antibiotics prior to percutaneous nephrolithotomy in a low infectious risk population: a report from the EDGE consortium. J Urol 2018;200:801-8.
26. Potretzke AM, Park AM, Bauman TM, Larson JA, Vetter JM, Benway BM, et al. Is extended preoperative antibiotic prophylaxis for high-risk patients necessary before percutaneous nephrolithotomy? Investig Clin Urol 2016;57:417-23.
27. Patel N, Shi W, Liss M, Raheem O, Wenzler D, Schallhorn C, et al. Multidrug resistant bacteriuria before percutaneous nephrolithotomy predicts for postoperative infectious complications. J Endourol 2015;29:531-6.
28. Tasian GE, Jemielita T, Goldfarb DS, Copelovitch L, Gerber JS, Wu Q, et al. Oral antibiotic exposure and kidney stone disease. J Am Soc Nephrol 2018;29:1731-40.
29. Jiang J, Yang J, Mei J, Jin Y, Lu Y. Head-to-head comparison of qSOFA and SIRS criteria in predicting the mortality of infected patients in the emergency department: a meta-analysis. Scand J Trauma Resusc Emerg Med 2018;26:56.
30. Beesley SJ, Lanspa MJ. Why we need a new definition of sepsis. Ann Transl Med 2015;3:296.