STONE AND PELVIC URINE CULTURE AND SENSITIVITY ARE BETTER THAN BLADDER URINE AS PREDICTORS OF UROSEPSIS FOLLOWING PERCUTANEOUS NEPHROLITHOTOMY: A PROSPECTIVE CLINICAL STUDY

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ABSTRACT

Purpose: Urosepsis due to manipulation during percutaneous nephrolithotomy (PCNL) can be catastrophic despite prophylactic antibiotic coverage, and negative midstream urine culture and sensitivity testing (C&S). It has been postulated that bacteria in the stone may be responsible for systemic infection. In this prospective study we determined the correlation between different sites of urine sampling, including stones, and also ascertained which is more predictive of urosepsis.

Material and Methods: All patients undergoing PCNL who fulfilled our selection criteria were recruited. The samples collected were 1) midstream urine and bladder urine at cystoscopy, 2) renal pelvic urine collected at percutaneous puncture of the pelvicaliceal system and 3) extracted and later fragmented stones. They were sent immediately for C&S. Patients were monitored for systemic inflammatory response syndrome (SIRS).

Results: A total of 54 procedures were suitable for analysis. Midstream urine C&S was positive in 11.1% of cases, stone C&S was positive in 35.2% and pelvic C&S was positive in 20.4% (p = 0.009). Pelvic urine C&S predicted infected stones better than bladder urine C&S. Of the patients 37% had SIRS and 3 experienced septic shock. Patients with infected stones or pelvic urine were found to be at a relative risk for urosepsis that was at least 4 times greater (p = 0.0009). Bladder urine did not predict SIRS. Stone C&S had the highest positive predictive value of 0.7. Preoperative hydronephrosis correlated with infected pelvic urine. No patients with urosepsis had positive blood C&S.

Conclusions: The results of this study suggest that positive stone C&S and pelvic urine C&S are better predictors of potential urosepsis than bladder urine. Therefore, routine collection of these specimens is recommended.

KEY WORDS: kidney; kidney calculi; urine; nephrolithotomy, percutaneous; sepsis syndrome

Percutaneous nephrolithotomy (PCNL) is the most frequently performed intrarenal surgery for stone disease at our institution. Indications are failed extracorporeal shock wave lithotripsy, larger stones (greater than 2.5 cm) and stones in anatomically abnormal kidneys. Septicemia during or following surgery can be catastrophic despite sterile preoperative urine and prophylactic antibiotics.[1, 2] In patients with sterile bladder urine from specimens taken 1 week prior to surgery our practice has been to operate, giving a single dose of gentamicin at anesthesia induction. When midstream urine (MSU) is infected, the procedure is deferred until sterile urine is achieved. Despite this, patients still have life threatening systemic infections. Infected stones, obstructed kidneys, prolonged manipulation, difficult access and comorbidity have been held responsible[3] for this complication, which often results in high dependence or intensive care that escalates the total cost of treatment.

In this study we analyzed various culture specimens, namely bladder urine, renal pelvic urine and crushed stones, and identified that most predictive of urosepsis. We also identified other preoperatively determinable factors that might contribute to systemic infection.

MATERIALS AND METHODS

We performed a prospective clinical study in all our patients undergoing PCNL between June 1, 2003 and March 31, 2004. The Appendix lists study exclusion criteria.

MSU or a clean, straight catheter specimen of urine was sent for culture and sensitivity testing (C&S) 1 day prior to surgery. Patients were given 5 mg/kg body weight gentamicin intravenously at anesthesia induction, according to our standard protocol.

After antiseptic preparation with chlorhexidine a standard cystoscope with a working channel is introduced into the bladder and a urine sample is collected for C&S. The corresponding ureterovesical opening is cannulated with a sterile 0.0035-inch straight guide wire and under image intensification it is passed into the pelvicaliceal system. A sterile 8Fr ureteral catheter is then threaded on the guide wire until the tip is confirmed to lie within the collecting system.

The patient is then turned prone and sterile preparation is performed. Percutaneous access into the ipsilateral pelvicaliceal system is achieved under image intensification using a fine, 14 gauge Kellet needle. Urine from the pelvicaliceal system is first aspirated and sent as pelvic C&S.

The tract is then dilated using Amplatz or Alken coaxial fascial dilators until a 30Fr Amplatz sheath can be placed. Nephroscopy and ultrasonic lithotripsy are performed under

low pressure irrigation. Stone fragments are collected to be processed for C&S.

We followed the technique of obtaining stones for culture as described by Nemoy and Stamey, which is meant to wash off surface contaminants and culture bacteria within the stone.[4] Essentially fragments were washed in 5 sequential bottles containing sterile saline and then crushed in the fifth bottle, of which the contents were sent as stone C&S. The culture medium used for urine C&S is CPS ID3 (bioMérieux, Marcy l'Etoile, France), a chromogenic medium, whereas crushed stones are cultured on chocolatized blood agar, aerobic blood agar, anaerobic blood agar and broth agar plates.

All patients were left with a nephrostomy tube for 24 hours before it was clamped and removed. Sepsis, fever and pain following nephrostomy clamping necessitate a further period of free drainage until the resolution of these symptoms or antegrade nephrostograms showed free drainage from the collecting system concerned. Patients were monitored closely in the postoperative period to watch for signs of systemic inflammatory response syndrome (SIRS), defined as the development of 2 of 4 criteria, namely fever less than 36C or greater than 38C, heart rate greater than 100 beats per minute, respiratory rate greater than 20 breaths per minute and white cell count greater than $12 \times 10^9/l$ or less than $4 \times 10^9/l$. The development of hypotension below a systolic blood pressure of 90 mm Hg or 40 below baseline for the patient in the presence of SIRS was considered septic shock. Urosepsis in this study was defined as SIRS or shock. Blood culture was performed in patients in whom SIRS developed. Blood was cultured on standard aerobic and anaerobic culture medium. The medium contained TSB broth. The data collected were divided into 3 main groups, that is MSU C&S, pelvic C&S (urine proximal to the obstructing stone) and stone C&S.

We performed statistical analysis of the data obtained using the Fisher exact and Mantel-Haenszel chi-square tests to determine associations among the various groups and subgroups. The t test was used to compare mean stone size among the subgroups analyzed. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and association risks were calculated. Univariate analysis was used to determine the association between SIRS and other parameters. A literature search was done in Index Medicus/MEDLINE to look for comparable information.

RESULTS

A total of 54 patients were recruited based on our selection criteria. Table 1 lists patient and stone demographics. Two patients in this series had ileal conduits, from whom bladder urine was collected by passing a sterile catheter into the stoma of the conduit. Three patients required 2 percutaneous tracks to achieve complete stone clearance. No patient in this series required blood transfusion or had hypovolemia due to blood loss.

The most prevalent culture positive specimen was stone C&S, which was significantly higher than bladder urine C&S

($p = 0.036$, fig. 1). Most infected pelvic urine grew Escherichia coli, whereas bladder urine seemed to have mixed growth most of the time when this specimen was infected (fig. 2).

All 3 specimens were simultaneously culture positive in only 1 patient (1.9%) (table 2). The upper tract was infected (pelvic urine and/or stone) in 23 patients (42.6%) and bladder urine was culture positive in only 3 (5.6%). This gave urine from the bladder a PPV, NPV and RR of 0.5, 0.56 and 1.15 (95% CI 0.48 to 2.73), respectively, of detecting upper tract infection. Pelvic urine C&S and stone C&S grew identical microorganisms in 85.7% of the patients in whom these 2 specimens were simultaneously culture positive (table 3). On the other hand, infected bladder urine did not carry bacteria identical to that found in the upper tract.

Since infected stones were highly prevalent, we used bladder and pelvic urine to predict infection in stones (table 4). Pelvic urine was the more accurate of the 2 specimens with a 2-fold risk of being associated with infection in the stone.

SIRS was seen in 20 patients (37%), of whom 18 had at least 1 culture positive specimen. In 3 patients (5.6%) septic shock developed. There were no deaths. None of these patients had positive blood C&S. Correlation between the various specimens and SIRS revealed that infected stone C&S and pelvic urine C&S carried a 4-fold risk of urosepsis (table 5, fig. 3).

A total of 24 patients had radiological evidence of a dilated pelvicaliceal system, that is hydronephrosis, caliectasis or a caliceal diverticulum, and the incidence of positive pelvic urine C&S in this subgroup was significantly higher than in those without obvious dilatation ($p = 0.046$, fig. 4). Despite this, hydronephrosis did not correlate with SIRS ($p = 0.529$). Operative time had a positive linear relationship with stone bulk ($r = 0.723$, $p = 0.01$, fig. 5), although neither of these factors correlated with urosepsis ($p = 0.362$ and 0.504, respectively). Infected stones appeared to be larger than noninfected ones. However, the pooled 2-tailed t test revealed no statistical difference in the mean bulk of infected and noninfected stones ($t = 1.463$, $p = 0.151$). It is of interest that 17 stones (43.6%) greater than 20 mm were culture positive compared with 2 (13.3%) that were 20 mm or less ($p = 0.039$), which may have reflected their etiology.

Six patients had turbid urine at the time of puncture of the pelvicaliceal system, of whom 4 (66.7%) had SIRS and 3 had positive pelvic urine and stone C&S. However, the statistical correlation was poor ($p = 0.18$ and 0.12, respectively). There was a similarly poor correlation between SIRS and age ($p = 0.66$), sex ($p = 0.44$), difficult access ($p = 0.903$) and residual stones postoperatively ($p = 0.857$). Previous urinary tract infection, defined as culture positive urine samples during the year prior to surgery requiring antibiotics, also did not increase the risk of SIRS ($p = 0.221$).

Two of the 3 patients with septic shock had an ileal conduit. Bladder urine samples in these conduit cases did not

TABLE 1. *Patient and stone demographics*	
Age:	
Range	24–83
Mean	53
SD	15.9
No. sex (%):	
M	28 (51.9)
F	26 (48.1)
Stone size (mm):	
Range	15–80
Mean	32.8
Operative time (mins):	
Range	30–180
Mean	70.7
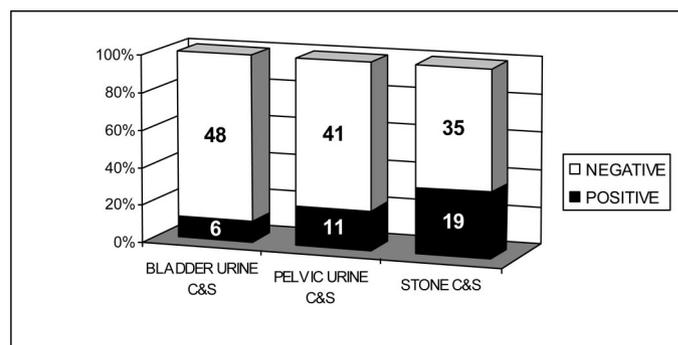
FIG. 1. Culture positive specimens
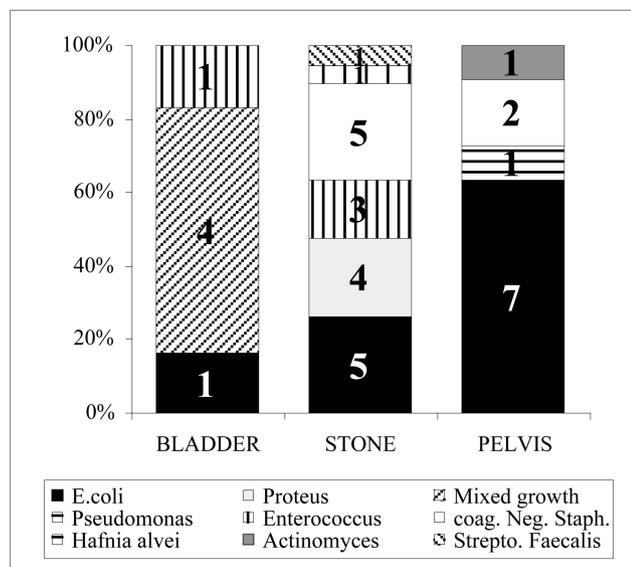
FIG. 2. Types of microorganisms cultured

TABLE 5. *Predicting SIRS using various specimens*

	Bladder Urine C&S	Pelvic Urine C&S	Stone C&S
% Sensitivity	50	72.7	73.7
% Specificity	63	70.7	81.8
PPV	0.15	0.4	0.7
NPV	0.91	0.91	0.84
RR (95% CI)	1.6 (0.36–7.17)	4.27 (1.28–14.22)	4.48 (1.91–10.53)
p Value	0.67	0.009	0.00009

TABLE 2. *Culture results in individuals*

	No. Bladder Urine	
	Pos	Neg
Stone pos:		
Pelvic urine pos	1	6
Pelvic urine neg	1	11
Stone neg:		
Pelvic urine pos	1	3
Pelvic urine neg	3	26

TABLE 3. *Specimens simultaneously infected with identical and different organisms*

	No. Identical	No. Different
Bladder urine:		
Stone	0	2
Pelvic urine	0	2
Pelvic urine:		
Stone	6	1
Stone + bladder urine	0	1

TABLE 4. *Predicting infected stones with pelvic and bladder urine*

	Bladder Urine C&S	Pelvic Urine C&S
% Sensitivity	10.5	36.8
% Specificity	82.9	87.9
PPV	0.33	0.64
NPV	0.63	0.71
RR (95% CI)	0.9 (0.27–2.97)	2.17 (1.13–4.18)
p Value	0.619	0.042

show significant growth (greater than 10^5 cfu/ml), even of a mixed nature and, therefore, surgery had been planned. The pelvic urine of 1 patient yielded Pseudomonas in pelvic urine, while the other had Proteus in the stone. The other patient with normal lower tracts and septic shock had Hafnia alvei in the stone. None of them had positive bladder/conduit urine samples preoperatively and blood C&S was also negative. Another patient with severe SIRS (no hypotension) had Actinomyces in the pelvic urine with negative stone and bladder urine samples.

DISCUSSION

It has been standard practice at this unit to test urine for infection at least a week prior to PCNL by MSU C&S. Patients with infection were treated with appropriate antibiotics for 7 days and then urine C&S was repeated. Antibiotics prophylaxis has been done in accordance with European Association of Urology (modified from Infectious Diseases Society of America, and European Society of Clinical Microbiology and Infectious Diseases) guidelines.[5] Despite this careful preoperative preparation patients still have systemic and sometimes catastrophic infection. Urosepsis and shock have been found to occur in direct proportion to the duration of the procedure, urine bacterial load, severity of obstruction by stone and infection in the stone.[3] O'Keefe et al retrospectively reviewed a series of 700 patients undergoing upper tract manipulation.[1] Severe septicemia developed in 9 patients and 66% died. At the same center Rao et al observed minor forms of septicemia in 37% of 27 patients undergoing PCNL.[2] A stark comparison to this is the series of Charton et al of 216 patients who underwent PCNL with no prophylactic antibiotics and no major septic complications, although 35% had infected urine preoperatively.[6]

In our study retrograde contamination of renal pelvic urine was excluded since bladder urine specimens were negative in all except 2 patients with infected pelvic urine and there was a clear discrepancy between the types of microorganisms cultured. The sterile technique practiced and the rigorous washing of stones ensured no cross-contamination and interpretation of bacteria in the stone core.

Those using the Nemoy and Stamey method for culturing stones[4] have described the incidence of infected stones as 5.6% to 77.3%.[7–11] Gault et al attributed the 5.6% rate of infected stones to a longer period of preoperative antibiotics with fluoroquinolones and the lower prevalence of noninfective stones in Canada.[7] Fowler, who reported a stone positive rate of 77.3%, found that urine C&S was simultaneously positive in only 12.5% of patients with infected stones[8] (our rate was 10.5%). Similarly McCartney[9] and Bratell[10] et al confirmed a poor correlation between infection in the stone and in bladder urine specimens.

With regard to infected pelvic urine Pode et al catheterized 135 upper tracts with stones and isolated infected pelvic urine in 75.6%.[12] The higher incidence could be explained by the fact that they included patients with obstructing upper tract stones. Stones were not cultured in this series. In 1984 Lewi et al analyzed stones, pelvic urine and bladder urine from 63 patients, and found that urine C&S was positive in 29%, stones were infected in 38% and pelvic urine was infected in 30%.[13] The trend is similar to that in our study. Mariappan and Loong also corroborated this finding in their series of ureteroscopies in Malaysia, where pelvic urine was infected in 58.6% of cases.[14] They also confirmed the correlation between stone C&S and pelvic urine C&S with the 2 specimens having identical microorganisms two-thirds of the time.

Rao et al described preoperative and postoperative changes in endotoxin and tumor necrosis factor (TNF) in their series.[2] However, only 27 of the 117 patients in their study underwent PCNL. Of these patients 74% had fever, 41% had in-
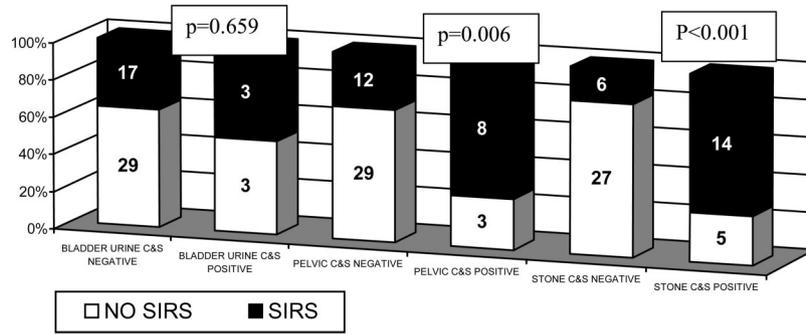
FIG. 3. Correlation between SIRS and various specimens collected
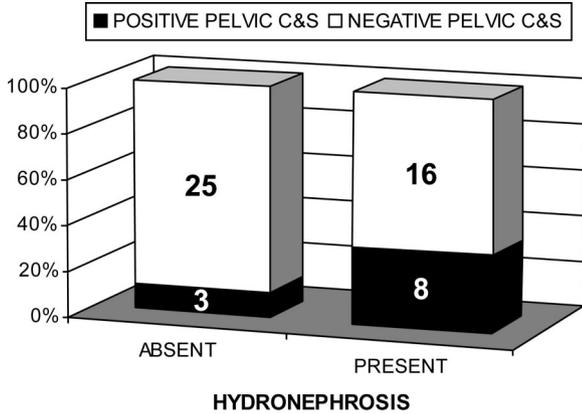

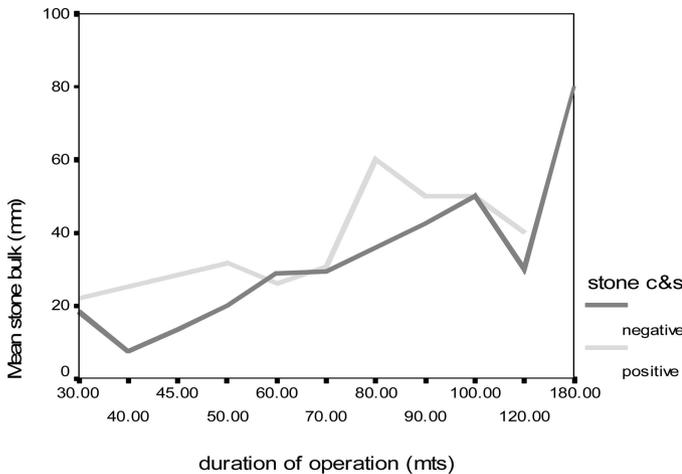FIG. 4. Dilated pelvicaliceal system and positive pelvic urine C&S.

FIG. 5. Relationship among stone size and operative time and infected stones.

creased TNF, 41% had endotoxemia and 37% had bacteremia. Endotoxins were shown to be present in serum even before operative manipulation. Although stones were infected in 47.8% of cases, which was most closely related to bacteremia, the incidence of preoperative bacteriuria in patients undergoing PCNL was not mentioned. Bacteriuria had a PPV of 0.53 for detecting endotoxemia when patients with nephrostomies, ureteropyeloscopy, stenting and prior shock wave lithotripsy were all included. A sensitivity and specificity of 54% and 78%, respectively, appeared to follow a trend similar to our findings. Nevertheless, the correlation between stone C&S and pelvic urine C&S with TNF and endotoxin levels would have been an interesting observation. Blood C&S in our series did not prove to be an accurate test even in

the face of septic shock. Martin et al observed that only 50% of patients with overt sepsis had bacteremia.[15]

We used a clinical definition of SIRS to describe sepsis, as recommended by the Sepsis definition Consensus Committee in 1992, which was reviewed and accepted at the 2001 consensus meeting.[16] To our knowledge our description of SIRS in relation to PCNL is a novel approach. Macdonald[17] and Cadeddu et al[18] also confirmed no correlation between operative time and postoperative fever. Cadeddu et al from The Johns Hopkins retrospectively reviewed 66 records of patients with PCNL who had sterile urine preoperatively. Of the 28.8% of patients in whom fever greater than 38C developed none had positive blood or postoperative urine C&S. Caddedu et al found no correlation between fever and stone composition, although stone culture was not performed. Fever alone cannot be used as an indicator of systemic infection, as noted in the study of Rao et al, in which 74% of patients with PCNL had fever postoperatively but only 41% had endotoxemia.[2]

Although the definitions used vary, septic shock rates have been reported to be 1% to 2%.[19] While the incidence of septic shock in our series is higher, this probably reflects our tertiary referral practice, which deals with complex stones. Septic shock in this series was associated with an ileal conduit in 2 patients. Such patients are generally prone to sepsis/bacteremia and, despite having no frank evidence of infection from stomal bacteriology, they remain at risk for urosepsis. When judging sepsis rates, it would seem advisable to specify the proportion of patients with an abnormal drainage system. To our knowledge the incidence of SIRS has not been described following PCNL but only following ureteroscopic stone surgery.[14] Although this makes critical comparison with other PCNL series difficult, we emphasize that this should be the standard terminology also used in other studies.

Larger stones are more likely to be triple phosphate stones and they have been found to harbor infection. Shigeta et al found infected stones in 10% of their 57 patients with renal stones and they noted that bacteriuria was more prevalent in stones greater than 30 mm in diameter.[20] Although in our series stone bulk did not directly correlate with urosepsis, more of the larger stones (greater than 20 mm) were infected. We also noted that the turbidity of urine at pelvicaliceal system puncture did not correlate with SIRS and positive pelvic urine because only 50% of the patients with cloudy urine had infected stones or pelvic urine. To our knowledge there are no published articles providing similar information with regard to a correlation between urine turbidity and urosepsis. Similarly there is no literature available that attempts to correlate hydronephrosis, age, sex, residual stones and urosepsis in the Index Medicus/MEDLINE.

Because many patients with renal stones, especially struvite, have been treated for recurrent urinary tract infections, the potential for antibiotic resistance becomes high. Empirical antibiotic therapy will salvage the situation in most in-

stances. However, we believe that samples collected from the upper tract will be the best guide to therapeutic antibiotic use when systemic infection arises, as indicated in this series by the patient with Actinomyces in the pelvic urine sample, in whom sepsis developed and who would not have received appropriate antibiotics in the absence of this sample.

The preoperative prediction of urosepsis is the ideal and some groups at high risk can be identified, such as patients with staghorn calculi, abnormal anatomy and diabetes, and immunocompromised patients. In this series we also identified large stones and dilated pelvicaliceal systems as possible predictors of urosepsis. This has enabled us to produce a department protocol to administer antibiotics to these patients for 1 week prior to surgery. It may also be judicious to aspirate percutaneously the pelvic urine in patients who are more prone to sepsis, eg those with an ileal conduit or dilated pelvicaliceal system and immunocompromise, and treat according to this culture. A second puncture for better stone clearance per se did not increase the incidence of sepsis or blood loss in this series.

CONCLUSIONS

The results of this study suggest that in patients undergoing PCNL stone C&S and pelvic urine C&S are better predictors of urosepsis than bladder urine C&S. Also, a dilated pelvicaliceal system and stones larger than 20 mm predicted patients with infected pelvic urine and infected stones, respectively. We recommend that consideration should be given to the pretreatment of patients with dilated pelvicaliceal systems and stones 20 mm or greater with a broad-spectrum antibiotic for 1 week, and the collection of stones and pelvic urine for culture and sensitivity. A prospective study of the outcome of this policy is in progress.

APPENDIX: EXCLUSION CRITERIA

1) Patients with a stent, nephrostomy tube or indwelling catheter
2) Diabetes mellitus
3) Renal failure
4) Fever prior to surgery
5) Previous manipulation/procedure
6) Concomitant bladder stone or tumour
7) On therapeutic antibiotics
8) Contralateral renal/ureteral stone

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