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ORIGINAL PAPER

Risk factors for urosepsis following percutaneous nephrolithotomy: role of 1 week of nitrofurantoin in reducing the risk of urosepsis

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Abstract The purpose of this study was to analyze the various risk factors for urosepsis following percutaneous nephrolithotomy (PNL) and to study the role of 1-week nitrofurantoin before PNL in reducing the risk of urosepsis. All patients undergoing PNL from April 2007 to November 2008 were prospectively included and grouped into four cohorts according to the following inclusion criteria: group A: stones $\leq$ 2.5 cm, no hydronephrosis, sterile urine; group B: diabetes mellitus, serum creatinine > 2 mg/dl, positive urine culture, stag horn stones, presence of nephrostomy or simultaneous bilateral PNL; group C: stones $\geq$ 2.5 cm and/or hydronephrosis, sterile urine; group D: similar to group C, but received nitrofurantoin 100 mg bid for 7 days before operation. Preoperative urine culture, intraoperative renal pelvic urine culture and stone cultures were obtained. Fever > 380°C and leukocyte counts > 12,000 were considered as systemic inflammatory response syndrome (SIRS). Endotoxemia was assessed in serum samples. A total of 205 patients were included in the study and grouped into four cohorts as group A ($n = 50$), group B ($n = 54$), group C ($n = 53$) and group D ($n = 48$). Overall 23% patients had positive renal pelvic urine and/or stone culture, 25% had endotoxemia and 34% developed SIRS. Female gender, chronic renal failure, anemia, hydronephrosis, stones larger than 2.5 cm and prolonged surgery were found to be risk factors associated with urosepsis. Nitrofurantoin prophylaxis resulted in decreased culture positivity (30.2 vs. 8.3%, odds ratio 0.36, $p = 0.087$), endotoxemia (41.9 vs. 17.5%, odds ratio 0.22, $p = 0.001$) and SIRS (49 vs. 19%, odds ratio 0.31, $p = 0.01$). In conclusion, female gender, chronic renal failure, anemia, hydronephrosis, stones larger than 2.5 cm and prolonged surgery were risk factors for urosepsis. Nitrofurantoin is beneficial in the prevention of endotoxemia and urosepsis especially in patients with larger stones and hydronephrosis.

Keywords Renal stone · Percutaneous nephrolithotomy · Urosepsis · Endotoxemia · Antibiotic prophylaxis

Introduction

Urosepsis following percutaneous nephrolithotomy (PNL) is a potentially catastrophic complication. The reported incidences of various infectious complications following PNL include bacteremia in 23%, endotoxemia in 34%, fever in 25% and septicemic shock in 0.3–2.5% [1–3]. The presence of infected stone and positive pelvic urine culture is considered important risk factors for postoperative urosepsis, which in turn are more frequent in the presence of larger stones and hydronephrosis [3, 4]. Percutaneous and endoscopic upper tract manipulations result in significant intravasation of bacteria and toxins into the blood stream [4]. Large amount of endotoxin is found in renal calculi, especially in infected stones, and the amount increases with the size of the stones [5, 6]. Stone and pelvic urine cultures rather than midstream urine (MSU) culture are better predictors of upper tract infection [4, 7–11]. Larger the stones

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are the more likely that they are infected (6–10%) [10–13]. We analyzed the various factors associated with urosepsis and studied the role of nitrofurantoin (NFT) in its prevention.

Materials and methods

In this prospective analytical and case control study, all adult patients undergoing PNL from April 2007 to November 2008 were grouped into four cohorts according to the following inclusion criteria:

- group A: stones $\leq$ 2.5 cm, no hydronephrosis, sterile urine;
- group B: diabetics, serum creatinine > 2 mg/dl, positive urine culture, staghorn stones, presence of stent or nephrostomy tube and simultaneous bilateral PNL;
- group C: stones $\geq$ 2.5 cm and/or hydronephrosis, sterile urine;
- group D: similar to group C, selected randomly, received prophylactic NFT 100 mg twice daily for 7 days before PNL.

Patients undergoing relook PNL and harboring other foci of infection were excluded from the study. Stone size was estimated as the largest diameter or sum of maximum diameters in case of multiple stones, as visualized on intravenous urogram. Non-contrast computed tomography of KUB region was done in patients with radiolucent stones or difficult anatomy.

Complete hemogram, serum creatinine, metabolic workup for urinary calculi and urine culture (MSU and urine from percutaneous nephrostomy, PCN, if available) were done preoperatively. Intraoperative renal pelvic urine (collected after ureteral catheterization or at first puncture of pelvicalyceal system) and stone cultures were obtained. Vital parameters and leukocytes counts were monitored postoperatively, to look for systemic inflammatory response syndrome (SIRS). Fever > 38°C and leukocytes counts > 12,000 were considered as SIRS [14]. Thrombophlebitis, chest infection and other localized source of sepsis were excluded before attributing the SIRS to urosepsis. Serum samples were separated from blood collected during or immediately after operation and stored in polyurethane tubes at −20°C for endotoxin assay. Nephrostomy tube(s) was kept for 48 h, then clamped and removed.

Prophylactic antibiotics were used as per the European Association of Urology (EAU) guidelines [15]. In patients with sterile urine culture, single dose of intravenous cephalosporin was given at induction. The patients with positive urine culture were treated with appropriate antibiotics to obtain sterile urine culture before surgery. Antibiotics were started at induction according to previous urine culture sensitivity report and continued till 48 h or changed to oral drugs till catheters are removed.

In patients with a PCN tube and positive urine culture, the nephrostomy tube was changed and appropriate intravenous antibiotics were started 48 h prior to surgery. Patients with staghorn stone were given appropriate oral antibiotics 7 days before and intravenous prophylaxis 48 h prior to surgery.

Preoperative urine and intraoperative pelvic urine were cultured on MacConckey and blood agar. Stone fragments were surface-cultured on blood agar, MacConckey agar and brain–heart infusion broth (anaerobic media). All isolates were identified using standard biochemical methods.

Endotoxemia was assessed by Limulus Amoebocyte Lysate (LAL) gelation technique using E-Toxate Kit (Sigma-Aldrich, USA) in the stored serum samples of randomly selected 161 patients (selected by microbiologist who was blind about clinical parameters and culture results). E-Toxate dry concentrate from *Limulus polyphemus* has shown the limit of sensitivity 0.05–0.1 endotoxin units per ml ($\geq$50 pg/ml) [16–18]. A positive test was indicated by formation of a hard gel that does not disrupt even on inversion of the tube. Soft gel, turbidity, increased viscosity or clear liquid were considered negative (Fig. 1a, b).

The study protocol was approved by the institutional ethical committee. Informed consent was obtained from all the patients. Enrollment into group C or D was done using random numbers according to computerized random table.

Statistical analysis was performed on SPSS version 16 software. Quantitative data were described as mean and standard deviation with their range. Chi-square test was used to assess statistical association between categorical variables (frequencies and proportions). Quantitative variables were compared between groups using independent *t* test (for two groups), ANOVA (for more than 2 groups) and Pearson's correlation. Association of positive culture, endotoxemia and SIRS as well as different risk factors was analyzed using univariate and multivariate logistic regression model. p value (two-tailed <0.05 was taken as significant.

Results

A total of 205 patients with a mean age of 40.2 years (range 13–75 years) were included in the study as four cohorts: group A ($n = 50$), group B ($n = 54$), group C ($n = 53$) and group D ($n = 48$).

The patients, stone and operative demographics are shown in Table 1. Parameters such as age, sex ratio, mean preoperative hemoglobin and serum creatinine (except patients with chronic renal failure in group B) were

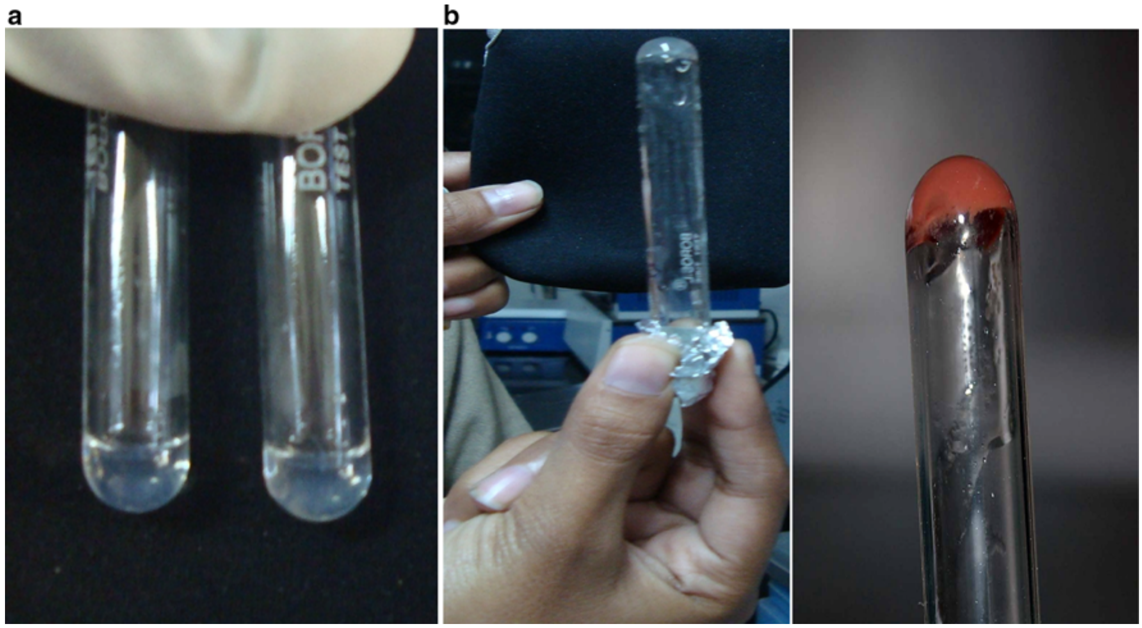

Fig. 1 **a** No gel formation indicating negative endotoxin assay. **b** Positive assays indicated by hard stable gel sticking to glass tube

comparable among all four groups. In group B, 14 patients had chronic renal failure (serum creatinine 2–6.1 mg%, mean 3.38 mg%), 18 patients had PCN, 4 patients had positive urine culture and 7 patients had diabetes mellitus.

Patients in group B, C and D had moderate to severe hydronephrosis. The degree of hydronephrosis was comparable in group C and D. Left PNL was done in 110 patients, right PNL in 86 patients and 9 patients underwent simultaneous bilateral PNL. Median operative time for the 4 groups was 60, 120, 120 and 90 min, respectively, in groups A, B, C and D; the difference was statistically significant ($p < 0.001$). None of the patients had massive blood loss or hypovolemic shock. Table 2 and Figs. 2, 3, 4 show the rate of positive culture, endotoxemia and SIRS. In group D, positive pelvic urine culture rate was five times lower (RR 4.95, $p = 0.026$) and stone culture rate was four times lower compared to group C (RR 3.6, $p = 0.006$).

Endotoxin assay could be completed in only 161 samples (selected randomly by the microbiologist who was blinded about culture reports and data on SIRS). Fifty-eight positive assays were obtained (Table 2; Fig. 1b). Positive assays in group A were significantly less compared to group B and C ($p < 0.001$). Positive endotoxin assays in group D were significantly less compared to group C (RR 2.3, $p = 0.016$). Endotoxemia was significantly higher in patients with positive pelvic urine culture [13/18 (72%) vs. 41/138 (33%); $p < 0.001$] and positive stone culture [33/52 (63%) vs. 25/112 (22%); $p < 0.001$] compared to patients

Table 1 Patient demographics, stone characteristics and operative details

	Groups				*p* value
	A	B	C	D	
No. of patients (*n*)	50	54	53	48	
Male:female	32:18	29:25	34:19	32:16	0.53
Mean age (years)	37.5	43.5	40.4	39.2	0.97
Sr creatinine (mg/dl)	0.99	0.92	0.96	0.91	0.001
Preoperative hemoglobin (g/dl)	13	12	12.6	12.7	0.1
Stone burden (mm)	23.3	40	35	35	0.001
Hydronephrosis (*n*, %)	2 (4)	54 (100)	53 (100)	48 (100)	0.001
Duration of operation (min)	60	133	106	90	0.001
Estimated blood loss (ml)	626	750	700	500	0.001

Table 2 Urine culture, stone culture, endotoxin assay and SIRS in various groups

	Groups				Total
	A	B	C	D	
No. of patients (*n*)	50	54	53	48	205
Midstream urine C/S (%)	2 (4%)	28 (52%)	3 (5.7%)	1 (2.1%)	34 (16.6%)
Pelvic urine C/S (%)	0 (0%)	13 (28.3%)	5 (9.8%)	0 (0%)	18 (8.7%)
Stone C/S (%)	0 (0%)	32 (59.3%)	16 (30.2%)	4 (8.3%)	52 (25.3%)
Endotoxin assay (positive/tested) (%)	3/35 (8.6%)	30/45 (65.2%)	18/41 (41.9%)	7/40 (17.5%)	58/161 36%
SIRS (%)	4 (8%)	38 (70%)	26 (49%)	9 (19%)	77 (38%)

C/S culture and sensitivity, *SIRS* systemic inflammatory response syndrome

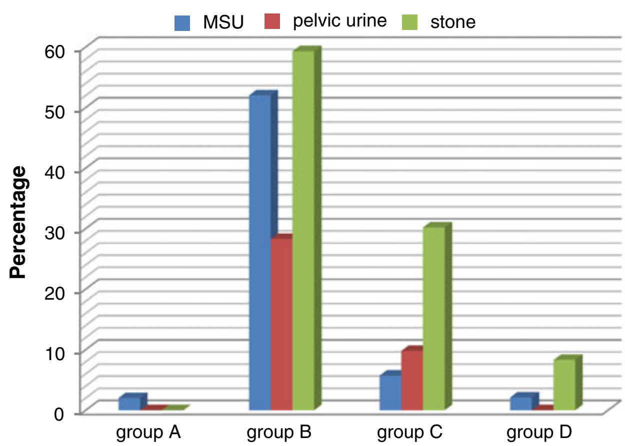

Fig. 2 Rate of culture positivity

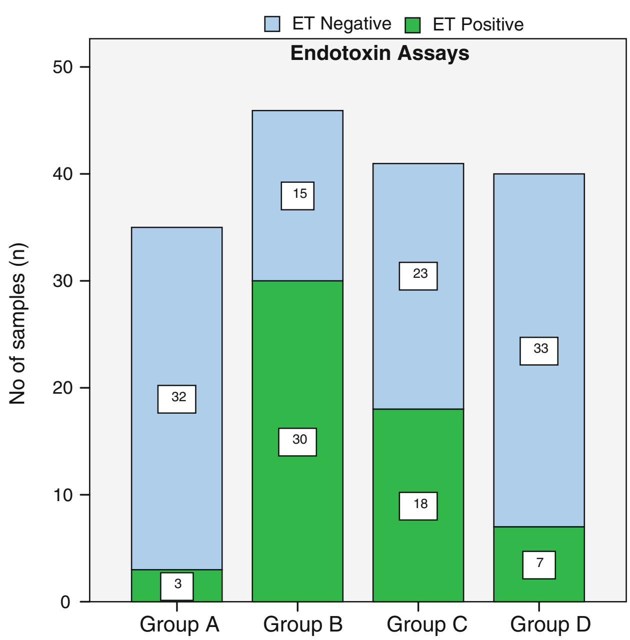

Fig. 3 Results of endotoxin assays

with sterile pelvic urine and stone. Four patients had enterococci in stone culture but negative endotoxin assays, as gram positive organisms do not produce endotoxin.

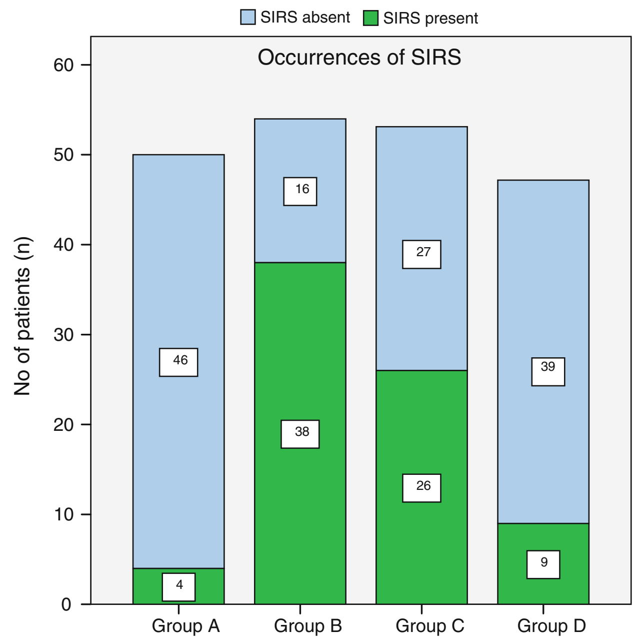

Fig. 4 Groupwise occurrence of SIRS

Factors associated with SIRS

Overall 77 of 205 (38%) patients had SIRS (Table 2; Fig. 4). Group B and C patients had higher grade of fever (mean temperature 38.5°C and 38.06°C) and leukocytosis (mean leukocytes counts 14,900 and 12,200), respectively. Four patients in group B and one in group C had septic shock without mortality (Fig. 5).

Significantly more number of patients with positive pelvic urine culture (94 vs. 38%; $p < 0.001$) and stone culture (91 vs. 25%; $p < 0.001$) had SIRS, compared to patients with sterile pelvic urine and stone. Micro-organisms isolated in urine and stone cultures are shown in Table 3. Thirty-eight of 56 (67%) patients with endotoxemia had SIRS, compared to 20 of 79 (24.8%) patients without endotoxemia; the association was statistically significant (Chi-square 68.7, $p < 0.001$). 61% patients with moderate to severe hydronephrosis had SIRS compared to

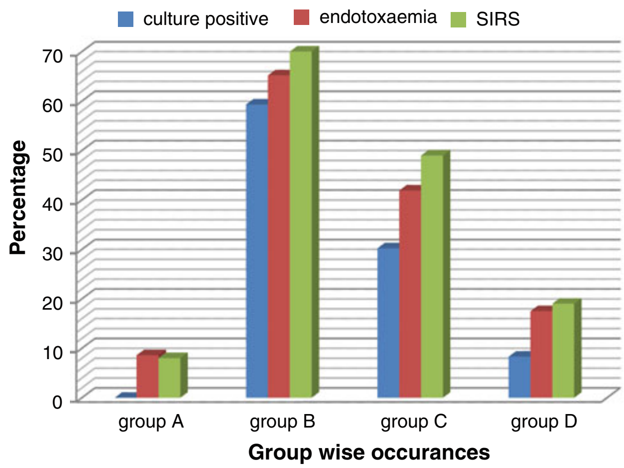

Fig. 5 Correlations of culture, endotoxemia and SIRS

Table 3 Micro-organisms isolated in urine and stone cultures

Organisms isolated	No of samples/patients (*n*)		
	Preop-C/S	Pelvic urine C/S	Stone C/S
E. coli	21	10	27
Klebsiella	04	04	08
Pseudomonas	05	02	08
Enterococcus	03	01	04
Enterobacter	01	01	01
Acinetobacter	00	01	00
Staph aureus	01	01	01
Morganella	00	01	01

6% patients without hydronephrosis (Chi-square 41.15, $p < 0.001$).

Ten of 14 patients with chronic renal failure had PCN (bilateral in 5 patients) before PNL. Incidences of positive PCN urine culture (71%), stone culture (78%), endotoxin assays (71%) and SIRS (78%) were much higher than all the other groups (Table 4). Seven patients had diabetes mellitus. These patients had significantly higher incidence of positive urine culture (27%), positive stone culture (57%), positive endotoxin assay (71%) and SIRS (57%) when compared to the usual stone patients in all groups.

Seventeen patients had PCN (bilateral in 7) and one patient was on double J stent (solitary kidney, pelviureteric junction stone). Ten patients had chronic renal failure requiring PCN for renal salvage or treatment of infected hydronephrosis. Preoperative urine culture was positive in all 17 patients with PCN. The urine culture grew multiple organisms in two patients. Stone culture was positive in 14 (82%) patients. The organisms isolated were same as the preoperative urine culture. Endotoxin assay was positive in 13 (76.4%) patients and 15 (88.2%) patients developed SIRS, including septicemic shock in 2 patients. The patient on double J stent had positive endotoxin assay but did not develop SIRS.

Predictors of SIRS: univariate analysis (Table 4)

Seventeen risk factors were assessed for association with SIRS in univariate analysis. Group B and C compared to C and D, positive culture (pelvic urine/stone), hydronephrosis, higher stone burden, duration of operation, estimated blood loss, anemia and high serum creatinine were found to have significantly higher association with SIRS (Table 4).

Multivariate (logistic regression) analysis: (Table 5)

Predictors of positive urine culture

Seven variables were evaluated in the multivariate logistic regression model to find out independent predictors for positive cultures (pelvic urine/stone). Final model retained only four variables. Female gender was found to be a strong predictor of culture positivity (OR 2.43, 95% CI 1.09–5.42, $p < 0.03$); i.e. females have 2.5 times higher risk of developing urosepsis compared to males (after adjusting for other confounding variables).

Preoperative serum creatinine levels were also very strongly predictive of positive culture (OR 3.71, 95% CI 1.36–10.07, $p < 0.01$). This means odds of having positive

Table 4 Odds ratio of various risk factors for the development of systemic inflammatory response syndrome

S. no.	Risk factors	Odds ratio	95% CI	*p* value
1	Intervention groups			
1 (a)	Gr B vs. Gr A	27.3	8.4–88.6	0.0001
1 (b)	Gr C vs. Gr A	11.5	3.6–36.5	0.0001
1 (c)	Gr D vs. Gr A	20.7	4.6–92.4	0.0001
1 (d)	Gr D vs. Gr C	1.8	0.53–6.1	0.35
2	Age (years)	1.02	0.99–1.04	0.23
3	Sex (female vs. male)	1.95	1.05–3.63	0.03
4	Stone burden	1.12	1.07–1.17	0.0001
5	Hydronephrosis	23.1	6.8–78.6	0.0001
6	Preoperative serum creatinine	2.47	1.2–4.94	0.01
7	Preoperative hemoglobin	0.6	0.45–0.8	0.0001
8	Operative time (min)	1.03	1.02–1.04	0.0001
9	EBL (ml)	1.002	1.001–1.004	0.0001
10 (a)	Preoperative urine culture	6.63	2.69–16.34	0.0001
10 (b)	Pelvic urine culture	28.2	3.65–218.5	0.0001
10 (c)	Stone culture	34.8	11.5–104.8	0.0001

Table 5 Multivariate logistic regression analysis to find out independent predictors for the occurrence of SIRS

	B	SE	Wald	*p* value	Odds ratio	95% CI for odds ratio	
						Lower	Upper
Step 4[a]							
Female gender	1.22	0.38	9.99	0.002	3.37	1.59	7.17
Duration (min)	0.02	0.01	9.66	0.002	1.02	1.01	1.03
Preop creatinine (mg/dl)	0.83	0.42	3.84	0.050	2.29	1.00	5.26
Hydronephrosis	1.92	0.72	7.08	0.008	6.81	1.66	28.01
Nitrofurantoin	−1.18	0.46	6.56	0.010	0.31	0.12	0.76

[a] Variable(s) entered on step 1: age, gender, duration of surgery (min), preoperative Hbgm, preop creatinine mg/dl, stone burden, hydronephrosis, nitrofurantoin vs. non-nitrofurantoin

pelvic urine/stone culture were increased by 3.7 times with every 1 mg/dl increase in serum creatinine.

The use of NFT was a weak protective factor against positive culture (OR 0.36, 95% CI 0.12–1.16, $p = 0.087$).

Predictors of endotoxemia

As shown in Tables 4 and 5, hydronephrosis was the strongest risk factor for endotoxemia (OR 17.23, 95% CI 3.91–76.00, $p < 0.0001$), i.e. 17 times increased risk. Preoperative hemoglobin level (OR 0.61, 95% CI 0.43–0.86, $p = 0.005$) and NFT (OR 0.22, 95% CI 0.09–0.55) were protective. Every 1 g/dl increase in preoperative hemoglobin decreased the odds of developing endotoxemia by 39%. Similarly, NFT decreased endotoxemia by 88% (Table 3).

Predictors of SIRS

As shown in Tables 4 and 5, the occurrence of SIRS was significantly increased in females (OR 3.37, 95% CI 1.59–7.17, $p = 0.002$), with hydronephrosis (OR 6.81, 95% CI 1.66–28.01, $p = 0.008$), with increasing duration of surgery (OR 1.02, 95% CI 1.01–1.03, $p = 0.002$) and CRF. With every 1 mg/dl increase in preoperative serum creatinine, odds of developing SIRS increased by 2.3 times (OR 2.29, 95% CI 1.01–5.26, $p = 0.05$). NFT was a significant protective factor against occurrence of SIRS (OR 0.31, 95% CI 0.12–0.76, $p = 0.01$), i.e. decreased SIRS by 69%.

Discussion

Despite careful preparation before PNL, patients still develop systemic and sometimes catastrophic infection. Sepsis (SIRS from infection) is caused by entry of bacteria and/or endotoxins into blood stream [4, 14, 19]. Percutaneous and endoscopic upper tract manipulations are significantly associated with bacteremia, endotoxemia and sepsis [4, 5]. Urosepsis and shock occur in direct proportion to the severity of obstruction by the stone, bacterial load in the pelvic urine, presence of infected stones and duration of operation [4].

MSU samples have been shown not to represent the infection present in the upper tracts [4, 6, 10–12]. Conversely, stone and pelvic urine cultures were better predictors of urosepsis after surgery and large stones appeared more likely to be infected [4]. Shigeta et al. [8] found infected stones in 10% of their 57 patients with renal stones, and bacteriuria was more prevalent in stones > 30 mm in diameter. In our study, overall 25.3% patients had infected stones; 59.3% in the high risk group (group B) and 30.2% patients with stones > 25 mm (group C).

SIRS as a clinical marker of sepsis is reliable, objective and convenient. Septic shock would have been a more conclusive measure, but its rarity precludes meaningful results in a moderate sample. Variables such as pulse, blood pressure and respiration which characterize SIRS may be affected by many confounding factors. Hence, the presence of fever and leukocytosis was considered as SIRS in our study. Endotoxemia can be established within a few hours, and is useful clinical adjunct for diagnosis or exclusion of gram negative septicemia [16].

Female gender was an independent predictor of positive pelvic urine and stone culture and SIRS in our study. Bacteriuria, UTI and urosepsis in females are twice more common than the males [20]. Poor perineal hygiene, menopause (estrogen deficiency), atrophic vaginitis, cystocele and use of vaginal pessary are predisposing factors [20, 21]. Underling bacteriuria and contamination of operative field with vaginal and fecal flora during ureteral catheterization may be the cause of increased culture positivity and SIRS.

Hydronephrosis is usually associated with large stones, stag horn stones or stones blocking the UPJ or ureter. In these cases, sterile MSU does not reflect the obstructed and infected upper urinary tract. Pressure in the obstructed system leads to intravasation of bacteria and endotoxin into the blood stream, which may increase further during PNL [2, 3, 5, 11, 19]. Using stone bulk and hydronephrosis as suitable surrogate markers for upper tract infection, ciprofloxacin for 7 days before PNL was shown to reduce the risk of postoperative urosepsis in a study by Mariappan et al. [13].

Higher preoperative serum creatinine level results from obstructing and staghorn stones and is usually associated with malnutrition, anemia, immuno-compromised state and increased sepsis [20, 21]. Most of them require PCN/stenting before PNL, with resultant increased risk of infection. Longer indwelling PCN/stents are more likely to be colonized with bacteria, which are killed by preoperative antibiotics releasing endotoxins. This may be the reason of higher rate of endotoxemia and SIRS in patients with PCN. In our study, positive culture, endotoxemia and SIRS were higher in patients with chronic renal failure and those with PCN. Operating time increases with larger stone burden and difficult anatomy. Larger the stone burden higher is the positive culture rate and the amount of irrigation fluid intravasated [5, 7, 9, 13]. Bacteria and large amount of endotoxins are released on fragmentation of such stones and enters into circulation. Thus, endotoxemia and SIRS are proportionately higher in patients with larger stones.

Anemia due to infection is multifactorial and can be of two types (1) anemia associated with critically ill patients and (2) anemia of chronic disease [21–23]. In our study, preoperative low hemoglobin was a significant predictor of endotoxemia and a weak predictor of SIRS in multivariate analysis. But the causal relationship of anemia with sepsis is not well proven. Patients with staghorn stones and obstructive nephropathy have underlying subclinical infection, fever, malaise, poor appetite and malnutrition leading to anemia and decreased overall immunity, which probably increases susceptibility to chronic infection, endotoxemia and sepsis.

In our study, 1 week of preoperative NFT decreased culture positivity by 64%, endotoxemia by 88% and SIRS by 69%. Our rationale for using nitrofurantoin was based on the local sensitivity pattern. Even most of the multidrug resistant pathogens in our set up were sensitive to NFT. Nitrofurantoin, a synthetic nitrofuran compound, acts by DNA strand breakage directly or indirectly and halts bacterial proliferation. Although it is bacteriostatic, bacterial resistance to NFT is rare. It is absorbed rapidly and completely from the GI tract, 40% is excreted into urine unchanged and yields a concentration in urine of approximately 200 pg/ml [24]. It is a good urinary sterilizer; but penetration into the tissues or stones is poor.

In our study, there was a trend of decreased pelvic urine culture and significant decrease in endotoxemia and SIRS in patients who received NFT. The effect might be due to decreased bacterial load in the pelvic urine at the time of PNL leading to decreased bacteraemia and endotoxemia, with resultant decrease in SIRS.

Conclusion

Female gender, raised serum creatinine, anemia, hydronephrosis, stones larger 2.5 cm and prolonged surgery were independent risk factors for postoperative urosepsis following PNL. There was a trend toward decreased positive pelvic urine culture and significant decrease in the incidence of endotoxemia and SIRS in patients who received nitrofurantoin.

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