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# Risk factors for treatment failure in renal suppurative infections

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**Abstract** There are conflicting results of published studies about prognostic value of various factors in purulent renal infections. The purpose of this study was to identify and quantify potential risk factors for early and late treatment failure in such infections. A retrospective review of 75 renal suppurative infections, at three tertiary Serbian Clinics of Urology, was conducted. We considered numerous potential risk factors in a multivariate analysis. This series was comprised of 49 women and 26 men, with mean age of 56.7 years. There were 38 and 37 patients who experienced successful and unfavorable early treatment outcome, respectively. Overall mortality rate was 9.3%. Comorbidity [odds ratio (OR) = 1.6], complex suppurative pathological findings (OR = 3.6), presence of *Pseudomonas* spp. (OR = 6.7), multiple bacterial strains (OR = 2.7), and positive culture itself (OR = 3.6) were the predictors of poor early prognosis. A urological intervention and presence of pyonephrosis significantly increased the chance for good initial outcome (OR = 0.32 and 0.37, respectively). In the late treatment failure analysis presence of comorbidities (OR = 5.8) and treatment complications (OR = 7.5) significantly increased chance for fatal outcome. Patients' baseline health status and complexity of suppuration itself were the most important predictors of clinical outcomes. Surgical drainage dominated over antimicrobial therapy.

**Keywords** Suppurative renal infections · Outcome · Risk factors

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## Introduction

Urinary tract infections are usually classified into the two groups, uncomplicated or complicated, depending on the presence of morphological and functional abnormality of the kidney. This classification system is useful for the practising physician in order to categorize patients according to risk of treatment failure and need for further, as a rule more complex, diagnostic and therapeutic exercises [1]. However, it seems that suppurative renal infections do not fit this classification pattern exactly. They represent an array of pathological processes that are difficult both to diagnose and to treatment, placing them in the class of complicated medical conditions, whether underlying urological abnormality exists or not. Taking into account their low incidence, the great heterogeneity of patients' characteristics and pathological processes, and the large number of possible therapeutic approaches, it is not surprising that our knowledge about prognostic factors in these disorders is far from complete.

To date, several studies have identified a number of underlying conditions and other factors that predispose patients to good or bad outcome [2–5]. In essence, almost all prognostic factors reported to date belong to one of several groups: urological abnormality, general diseases that impair ability to combat infection, treatment choices, properties of microorganisms, symptoms, signs or diagnostic findings, and general clinical circumstances or patient status. Furthermore, there is no general agreement on which particular set of such prognostic factors is the most important for clinical failure or success [6] and, particularly, what is their significance for the appropriate selection of initial treatment mode(s). Little is also known about the relative (quantitative) importance of a particular factor on final patient outcome.

The aim of this study was to identify relevant prognostic factors for outcome in patients with suppurative renal infections, observed early in the disease course.

## Patients and methods

Medical records from three tertiary referral Serbian University Clinics of Urology (Belgrade, Kragujevac, and Nis) dating from the years 1999 to 2006 were reviewed retrospectively. We identified 75 patients who had final diagnosis of suppurative renal infections. Clinical and laboratory data on admission and during hospitalization were obtained including: past medical and surgical history, urological status, blood analysis, urinalysis, renal function tests, nutrition status, radiological investigations, microbiological cultures, antibiotic therapy, treatment complications, and final outcome throughout a 12-month period of follow-up.

For the purpose of the study analysis all purulent infections were categorized into three main classes. Suppurative collections confined to the renal parenchyma and not extending beyond renal capsule or disrupting the collecting system were considered as the simplest ones (class 1). The second class of purulent collections (class 2) was defined by the presence of pyonephrosis or xanthogranulomatous pyelonephritis. The third suppuration (class 3) was defined by extended renal capsule infection into adjacent tissue, gas-forming infections, and bilateral or multiple collections. Complications of urologic treatment were defined by inadequate drainage procedure or approach that directly influenced outcome, the appearance of serious intra- or post-treatment complications, or inadequate supporting therapy. The success of treatment outcome was assessed by three reviewers, two urologists and a clinical pharmacology consultant, specialized in antibiotic therapy prescribing, according to the predefined criteria. Each expert revised a patient's chart independently and categorized the patient into the clinical success or failure group. If a discrepancy in the allocation of the patients between the experts was found, the medical history was reevaluated and discussed, and consensus was achieved.

Early clinical failure was defined as one or more of the following: (a) persistence of symptoms or signs of infection beyond day 4 of hospitalization, regardless of initial treatment mode, (b) use of inadequate antimicrobial treatment, defined as the prescription of initial antimicrobial agents to which microorganisms isolated from the specimens taken just before antibiotic administration were resistant [7], (c) absence or inappropriate drainage procedure in the state of systemic inflammatory response syndrome, when adequate antimicrobial therapy did not improve the clinical course, (d) when applied drainage procedure did not change clinical course in a reasonable time period, (e) when clinical course rapidly deteriorated and required nephrectomy in spite of adequate conservative measures (rescue treatment mode). Unsuccessful final outcome was considered in the case of fatal outcome (during hospitalization or postoperative period of 12 months).

### Statistical analysis

Logistic regression was a primary analytical tool because it allows one to predict a discrete outcome, such as success/failure, from a set of different variables. In addition, it does not assume linearity of relationship between variables, does not require normally distributed data, and in general has less stringent requirements, making it suitable for a highly heterogeneous sample of patients with renal suppurations. Finally, a regression model gives measures of the direction and strength of the relationships between explanatory variables and outcome, such as odds and odds ratios.

Univariate analysis was initially carried out to search for the variables that were statistically significantly associated with possible risk factors for early and late clinical failure. Only variables that showed statistically significant association ($P < 0.05$) were included in the multivariable model. Multiple logistic regression analysis was used (with Backward–Wald stepwise) to adjust for potential confounders and to identify and quantify the independent predictors of treatment failure [8]. The results of regressions were expressed in odds ratios (ORs) with 95% confidential interval (CIs). Hypothesis testing was done in two-sided procedure where the level of statistic significance was established at $P \leq 0.05$.

## Results

Baseline patients' demographic, clinical characteristics, the laboratory findings, predisposing conditions, and treatment outside of urology are detailed in the Table 1.

### Microbiology

In 20 patients (26.7%) no bacteriological sampling was performed at all. From the total of 115 microbiological specimens there were 53 positive findings. From a variety of kidney suppurative collections, all 52 samples were directly obtained (for 47 patients), of which 37 were positive (71.2%). Of 50 urine cultures, at least one organism was isolated in 18 (36%). Swabs of surgical wounds were positive in 11 of 13 samples (84.6%). Finally, blood cultures were all negative (18 sample cultures from 14 patients). In total, microbiological cultures were positive in fewer than one-half of patients (35, 47.5%).

The most frequent species recovered from the total of 53 bacterial cultures was *Escherichia coli*, which was isolated in 17 cases (32%), followed by *Pseudomonas* spp. (12, 22.6%), *Proteus* spp. (10, 18.9%), *Klebsiella* spp. (4, 7.5%), *Staphylococcus aureus* (4, 7.5%), *Enterococcus fecalis* (3, 5.7%), and sporadically *Acinetobacter* sp. (1, 1.9%), *Corynebacterium* sp. (1, 1.9%), and *Providencia rettgeri* (1, 1.9%).

**Table 1** Baseline patients' characteristics (demographic, laboratory, clinical data, predisposing conditions, and treatment outside of urology) ($n$ = 75)

| Variable | Number of patients, mean ± SD (range or %) |
|---|---|
| Age (years) | 56.7 ± 13.6 (21–78) |
| Gender (male/female) | 26 (34.7%)/49 (65.3%) |
| Side (right/left/bilateral) | 38 (50.7%)/36 (48%)/1 (1.3%) |
| Lumbar or abdominal pain | 62 (83%) |
| Fever | 47 (63%) |
| General debility | 46 (61%) |
| Digestive symptoms | 38 (51%) |
| Urine disturbances | 37 (49%) |
| Local redness, warmth or pain | 11 (15%) |
| Erythrocyte sedimentation rate (mm/h) | 101 ± 33 (28–150) |
| Hemoglobin (g/dl) | 10.1 ± 1.8 (6.7–14.1) |
| White blood cell count ($\times 10^9$/l) | 14.4 ± 7.6 (4.5–38) |
| Blood creatinine (μmol/l) | 233 ± 280 (60–1,568) |
| Hyperglycemia (>7 mmol/l) | 35 (47%) |
| Normal urine sediment | 7 (9.5%) |
| Pyuria | 62 (83.8%) |
| Bacteriuria | 38 (51.4%) |
| Hematuria | 24 (32.4%) |
| Diabetes mellitus | 18 (24%) |
| Urolithiasis | 49 (65.3%) |
| Obstructive uropathy | 51 (68%) |
| Tuberculosis | 3 (4%) |
| Congestive heart failure | 4 (5.3%) |
| Malignancy | 7 (9.3%) |
| Chronic renal failure | 13 (17.3%) |
| Nosocomial origin of infection | 10 (13.3%) |
| Predisposing conditions (n) | 2.1 ± 1.1 (1–6) |
| Treatment outside of urology | 25 (33.3%) |

### Pathological findings

Suppurative collections confined to the renal parenchyma were detected in 35 (46.7%) patients and included: minor parenchymal lesions usually invisible to conventional imaging techniques (in 10 cases) and solitary (9) or multiple intrarenal abscesses (26) that were found after pathological examination of renal specimens. The second class of purulent collections appeared in 49 (65.3%) subjects in whom pyonephrosis (49) and xanthogranulomatous pyelonephritis (6) were detected. Class 3 infection was observed in 39 (52%) patients in which the suppuration extended through renal capsule into adjacent tissue or gas formation was appeared. These infections were as following: perinephric (in 39 cases) or psoas (7) abscesses, emphysematous pyelonephritis (7), as well as peritonitis and pleuritis (4). In summary, there were 157 different pathological findings in 75 subjects (mean 2.1 ± 1.3, range 1–6), due to the fact that 27 and 11 subjects, respectively, had two or three classes of pathological processes as classified above concurrently.

## Antibiotics

Antibiotic treatment lasted 9.0 ± 0.3 days per patient (mean ± standard deviation) with a range of 2–19 days and, in total, 21 different antibacterial agents were used. At least one antimicrobial drug was used in all patients and many received multiple agents during the treatment course (range 1–10). The antibiotics used in the observed treatment groups are shown in Table 2 in main drug classes. Only 41.3% of subjects (31 of 75) received at some time antibiotics according to the bacterial sensitivity pattern, but about one third of these (9 of 75) were initially treated with a drug to which the subsequently isolated bacteria were resistant.

## Urological procedures

A total of 111 urological interventions were performed, mainly once (in 44 patients, 58.7%), more infrequently twice (in 27 patients, 36%), and rarely thrice (in 3 patients, 4%) and four times (in 1 patient, 1.3%). Urological procedures during all treatment courses in the observed groups are given in Table 3.

## Complications, patient refusal, and inadequacy

There were eight (10.7%) patients with significant complications of infective process at the beginning of treatment: two (25%) with acute renal insufficiency, one (12.5%) with deep venous thrombosis of upper leg, one (12.5%) with purulent meningitis, one (12.5%) with empyema of pleura, and three (37.5%) with peritonitis. In seven (9.3%) patients there were subsequent urological complications: inadequacy of drainage, multiple organ failures, bleeding from gastric ulcer, and stercoral fistula. Seven (9.3%) patients refused the suggested intervention or were otherwise unsuitable for the planned surgery. Overall, in 22 (29.3%) patients there were 31 complications, mainly one (in 15 patients, 68.2%), more infrequently two (in 5 patients, 22.7%) and rarely three (in 2 patients, 9.1%).

**Table 2** Antibiotic treatments according to main drug classes

| Antibiotic regime and utilization | Early outcome | | Late outcome | |
|---|---|---|---|---|
| | Success | Failure | Success | Failure |
| Adequate antibiotic[a] | 10/28 | 12/25 | 27/41 | 4/3 |
| Any cephalosporin of third generation | 24/14 | 24/13 | 55/13 | 6/1 |
| Any antipseudomonal drug | 6/32 | 10/27 | 26/42 | 5/2 |
| Any aminoglycoside | 9/29 | 10/27 | 30/38 | 4/3 |
| Any fluorohinolone | 15/23 | 13/24 | 46/22 | 4/3 |
| Any other bactericide | 8/30 | 14/23 | 33/35 | 2/5 |
| Any other antibiotic | 3/35 | 7/30 | 16/52 | 4/3 |
| Number of antibiotic drugs per subject[c] | 1.6 ± 0.7 | 2.3 ± 1.3 | 3.4 ± 1.6 | 3.7 ± 2.3 |
| DDD/1,000 HD[b] | n.a.[d] | n.a.[d] | 906 ± 590 | 914 ± 451 |

[a] According to culture sensitivity

[b] Number of defined daily doses (DDD) of all antibiotics per 1,000 hospital days (HD)

[c] Significant difference for early outcome; values represent the number of patients treated with or without the drugs (yes/no) or the mean ± SD

[d] Not applicable

**Table 3** Percutaneous drainage (PCD), sondage (S), percutaneous nephrostomy (PCN), lumbar drainage (LD), and nephrectomy (NFC) during all treatment courses

| Urological procedure | Success ($n$ = 68) | Failure ($n$ = 7) | $P$-value |
|---|---|---|---|
| PCD | 14 (21%) | 4[a] (57%) | 0.046 |
| S | 10 (15%) | 1 (14%) | n.a.[c] |
| PCN | 13 (19%) | 0 (0%) | n.a.[c] |
| Minor, any | 33 (49%) | 5 (71%) | n.s.[d] |
| LD | 14[a] (21%) | 1[b] (14%) | n.a.[c] |
| NFC | 45 (65%) | 3 (43%) | n.s.[d] |
| Major, any | 54 (66%) | 4 (57%) | n.s.[d] |
| Other conserving procedures | 4 (6%) | 0 (0%) | n.a.[c] |

[a] One repeated procedure

[b] One treated by laparotomy drainage

[c] Not applicable

[d] Not significant; the values represent the number of patients in whom the procedure was fulfilled

### Treatment outcomes

Length of hospital stay was 32.4 ± 16.7 days (range 4–93 days). During that time, 38 and 37 patients experienced successful and unfavorable early treatment outcome, respectively. Patients who survived after hospitalization ($n$ = 71) were observed for 32.9 ± 17.7 months on average (range 2–81 months). Until the end of study follow-up, the majority of patients survived the kidney infection, but seven died, giving an overall mortality rate of 9.3%.

### Predictors of early treatment failure

Among 30 different demographic characteristics, laboratory findings, microbiologic culture results, type of purulent collections, and treatment modes, 9 were significant predictors on univariate analysis (Table 4). However, only three factors, number of predisposing conditions (OR = 1.62, $P = 0.040$), presence of class 3 infections (OR = 3.09, $P = 0.034$), and the institution of any urological procedure (OR = 0.29, $P = 0.021$), were independent predictors of treatment outcome. No particular drug or antibiotic groups influenced the success of initial treatment.

The late treatment failure analysis is detailed in Table 5. Due to rare case events (<10) multivariable logistic regression analysis was considered inappropriate.

## Discussion

According to our results, the patients' baseline health status and complexity of suppuration itself were the most important predictors of clinical outcomes, followed by the particular treatment mode. The isolation of pathogens with high load or virulence, extension of renal infection into surrounding tissues, comorbidities and previous risk factors, anemia, and leukocytes independently or otherwise predicted poor outcome. On the other hand, surgical drainage was a more important treatment mode than antibiotic drug usage. Drug combinations should be strongly discouraged as an additional agent as they almost doubled the risk for early treatment failure and alone preceded all fatal cases.

Previous studies have shown that a variety of host and bacterial factors are crucial for final outcome in renal infections. However, these studies are not common and differ in methodology, particularly in the selection of a particular set of predictors the

**Table 4** Predictors of early treatment failure

| Variable | Success ($n$ = 38) | Failure ($n$ = 37) | OR (95% CI) | $P$-value |
|---|---|---|---|---|
| *Pseudomonas/Acinetobacter* | 2/36 | 10/27 | 6.67 (1.65–32.95) | 0.020 |
| No sterile cultures | 12/26 | 23/14 | 3.56 (1.37–9.24) | 0.015 |
| Class 3 infection | 14/24 | 25/12 | 3.57 (1.37–9.26) | 0.009 |
| Bacteria in isolates ($n$) | 0.4 ± 0.6 | 1.1 ± 1.1 | 2.71 (1.40–5.26) | 0.003 |
| Antibiotics ($n$) | 1.6 ± 0.7 | 2.3 ± 1.3 | 1.85 (1.14–3.01) | 0.013 |
| Predisposing conditions ($n$) | 2.9 ± 1.0 | 3.7 ± 1.4 | 1.60 (1.08–2.37) | 0.022 |
| Hemoglobin (g/dl) | 10.6 ± 1.8 | 9.6 ± 1.6 | 0.96 (0.91–0.99) | 0.015 |
| Class 2 infection | 29/9 | 20/17 | 0.37 (0.14–0.98) | 0.046 |
| Any urological surgery | 24/14 | 13/24 | 0.32 (0.12–0.81) | 0.017 |

Except hemoglobin, values represent either the mean ± standard deviation of the variable per patient ($n$) or the number of patients with or without a particular variable (yes/no)

**Table 5** Possible predictors of late treatment failure

| Variable | Alive ($n$ = 68) | Died ($n$ = 7) | OR (95% CI) | $P$-value |
|---|---|---|---|---|
| Complications | 17/51 | 5/2 | 7.5 (1.33–42.27) | 0.022 |
| Predisposing conditions | 2.5 ± 1.0 | 4.4 ± 1.3 | 5.81 (1.87–18.00) | 0.002 |
| PCD[a] | 14/54 | 4/3 | 5.14 (1.03–25.68) | 0.046 |
| Pathological findings | 2.0 ± 1.0 | 3.1 ± 1.8 | 1.93 (1.09–3.44) | 0.025 |
| WBC[b] ($\times 10^9$/l) | 13.5 ± 6.5 | 22.8 ± 11.7 | 1.13 (1.04–1.25) | 0.007 |

[a] Percutaneous drainage

[b] White blood cell counts; chi-square with Yates' corrections used for categorical variables (frequencies) and univariate logistic regression for continuous numerical variables

assignment of their relative importance. In one study involving 52 patients with renal and perinephric abscesses, size of abscess, method of treatment, and any interaction between the two putative risks did not significantly affect outcome [6]. Age, gender, diabetes mellitus, presence of bacteremia, identity of infecting organisms, blood glucose level, leukocyte count, urinary white blood count, presence or absence of urinary tract obstruction or urolithiasis, modes of treatment, and "type 2" infection did not influence mortality in 38 patients with emphysematous pyelonephritis. Instead, only low platelet count, high serum creatinine, urinary red blood counts, and pathological "type 1" were more frequent in the nonsurvivors [9]. On the other hand, in another sample of 48 subjects with the same infections, antibiotic treatment alone and more than two risk factors in patients with extensive infection were found to be predictors for mortality, in contrast to the combination of PCD and antibiotics (for mild to moderate infections) as well as nephrectomy (particularly for severe infection), which were more frequent in patients who persisted with treatment [10].

In some cases less rigorous statistical analyses weakened the strength of final conclusions. It has been shown, for example, that shock, bedridden status, age over 65 years, and previous antibiotic treatment were factors which put subjects with acute pyelonephritis in the group of high risk for fatal outcome [11]. However, the prediction was not based on single-factor analysis; instead they were combined in a categorical scoring scale and, therefore, little is known about the influence of particular risks when they are present separately from others. The soundest data come from a large-scale, retrospective analysis in which six underlying conditions (congestive heart failure, advanced diabetes, angioplasty, quadriplegia, hypoalbuminemia, and hydronephrosis) and two surgical parameters (the length of surgery and transfusions) were found to be predictors of 1-month postoperative morbidity after common urological major surgery [12]. Conflicting results were obtained for elderly [9, 11], and acute or chronic disturbances in glucose metabolism, favoring advanced stages of diabetes mellitus as an important predictor of poor outcome [9, 10].

It seems that weaknesses in statistical analyses of many previous clinical researches limit the usefulness of their final reports. Most recommendations in the field are based on local experience or results from observational, case–control studies of small to medium sample size. They usually include too many variables in the prediction model, and are "too enthusiastic" in their conclusions. In one such study, supposed risks were combined in a categorical scoring scale, then analyzed, but finally present separately from each other [11]. Furthermore, in the absence of more reliable data, some studies used a remarkable clinical feature as a presumed proxy for treatment failure. In such a way, the presence of infected renal tumors [13], foreign body or obstruction [14], biomaterial in urinary tract and recurrent urinary tract infections [15], obesity and high fever [16], poor patient's performance status, very old age, and female gender [17] were identified as possible risk factors for septicemia or related conditions in renal infections. However, the validity of such findings could be questioned because tested factors, although they represent an important treatment hurdle, are not directly related to final outcome. Other investigators have also reasonably suggested that additional, as yet unidentified, factors influence treatment outcome in urinary tract infections [18].

The most surprising finding in our study concerned the antibiotic treatment as results suggested that no drug or regime favored good outcome. However, at least three arguments could explain this (apparent) inconsistency with available knowledge. In the first place, the percentage of positive bacterial cultures was lower than in previous studies [19], increasing chances for inadequate choice of antibiotic treatment. Secondly, with ciprofloxacin and ceftriaxone, the most commonly used drugs, highly prevalent bacterial resistance has been widely reported, directing clinicians to use more effective empiric regimes such as de-escalation antibiotic strategy [20]. Finally, incorrect combinations [21] and inaccuracy in drug dosing and timing might be contributing factors [22].

Our results, which indicated patients' baseline health status to be the primary determinant of both early and final treatment outcome, should be extrapolated to routine clinical practice with caution due to the retrospective data sources used, the great heterogeneity of the subjects, the diversity of treatment options, the relatively small sample size, and the limited number of case events for late outcome (mortality). In order to eliminate or mitigate such shortcomings we used elaborate statistical analysis. However, only sufficiently powered prospective, controlled clinical trials with carefully selected host, pathogen, and treatment variables could give reliable conclusions.

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