



Original Article

Comparison of the delta neutrophil index with procalcitonin, erythrocyte sedimentation rate, and C-reactive protein as predictors of sepsis in patients with acute prostatitis

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ARTICLE INFO

Article history:

Received 13 December 2017

Received in revised form

20 April 2018

Accepted 25 May 2018

Available online 1 June 2018

Keywords:

Acute bacterial prostatitis

Bacteremia

Biological markers

Escherichia coli

Sepsis

ABSTRACT

Background: We investigated the usefulness of inflammatory markers including the delta neutrophil index (DNI), erythrocyte sedimentation rate, C-reactive protein, and procalcitonin as early predictors of sepsis in patients with acute prostatitis (AP). In addition, we evaluated the efficacy of intermittent catheterization for the initial management of acute urinary retention (AUR) in patients with AP.

Materials and methods: All patients who presented to the emergency department and were admitted to the urology department from January 2011 to December 2013 were retrospectively reviewed. The clinical features, prostate-specific antigen levels, inflammatory marker levels, and urine and blood culture results were obtained from medical records. Patients who underwent urethroscopy or prostate biopsy within 7 days were excluded.

Results: Of 132 patients (mean age, 64.8 years) in this cohort, 17 (12.9%) had sepsis and 22 (16.7%) had positive blood cultures. *Escherichia coli* was the most common isolate in blood and urine cultures. In multivariate analysis, the DNI and prostate-specific antigen were identified as predictors of sepsis. The DNI was a significant prognostic factor for bacteremia. In patients with AP, procalcitonin was not a significant predictor of sepsis. Of 19 patients with AUR, 10 needed Foley catheterization because of refractory AUR. C-reactive protein was a significant predictor of failure of the initial management of AUR.

Conclusions: The DNI is useful as a predictive factor for sepsis and bacteremia in patients with AP. Without mandatory cystostomy, intermittent catheterization could be one of the useful management options of AUR in patients with AP.

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1. Introduction

Acute prostatitis (AP) is a common and clinically important genitourinary infection. AP is characterized by acute inflammation of prostatic tissues and presents symptoms similar to those of lower urinary tract infection. *Escherichia coli* is the predominant pathogen in AP.¹ Ascending urethral infection and intraprostatic reflux are believed to be the main causes of AP.² Acute urinary

retention (AUR) can increase the risk of bacteremia and can progress to a serious infection such as sepsis in patients with AP. Therefore, it is generally recommended that patients with AP with AUR undergo mandatory suprapubic catheterization to avoid bacteremia and pain associated with Foley catheterization.^{3,4} However, in practice, intermittent catheterization seems to be used as an initial management with no clinical evidence of its benefit.²

Patients who are suspected to have inflammatory disease or serious infection may undergo a diagnostic workup that involves multiple laboratory tests. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are among the most widely used diagnostic markers in detecting inflammatory conditions.⁵ The European Association of Urology recommended procalcitonin level as a useful marker for predicting the development of systemic inflammatory response syndrome (SIRS) and differentiating between infectious and noninfectious causes of severe inflammatory status.⁴

Abbreviations: AP, acute prostatitis; AUR, acute urinary retention; BPH, benign prostatic hyperplasia; CRP, C-reactive protein; DNI, delta neutrophil index; ESR, erythrocyte sedimentation rate; IPSS, International Prostate Syndrome Score; PSA, prostate-specific antigen; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

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<https://doi.org/10.1016/j.pnil.2018.05.001>

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Recently, the serum delta neutrophil index (DNI) has been suggested as a new inflammatory marker for the early prediction of sepsis.^{6–8} However, to the best of our knowledge, no study has evaluated the efficacy of biomarkers such as ESR, CRP, DNI, and procalcitonin to guide treatment decisions in patients with AP.

Because AP related to transrectal prostate biopsy is becoming more common, data are lacking on the pathogens and management of patients with AP without prior biopsy.³ The aim of this study was to compare the efficacy of inflammatory markers as early predictors of sepsis in patients with AP without a prior biopsy. Furthermore, we introduce our experience with intermittent catheterization as the initial management in patients with AP with AUR.

2. Materials and methods

This retrospective observational study was approved by the institutional review board, which allowed collecting data on all patients with AP treated at our institution. Clinical variables relevant to the study included age, initial vital signs, symptoms, findings on abdominal physical examination, prostate-specific antigen (PSA) level, inflammatory markers including white blood cell (WBC) count, ESR, CRP level, DNI, procalcitonin level, and urine and blood culture results, antimicrobial susceptibility results, period of antibiotics use, and voiding patterns after the initial management for AUR.

2.1. Patients

Patients with AP who were admitted to the urology department of a tertiary hospital from January 2011 to December 2013 were initially reviewed. AP was diagnosed according to clinical features (fever, painful voiding, or a painful sensation during digital rectal examination) and the results of laboratory tests. Patients with a hematologic disorder, those discharged against medical advice, those with other causes of urinary tract infection including acute pyelonephritis and sexually transmitted infection, those with procedures including urethrocytoscopy or prostate biopsy within 7 days, and those with a history of prostate cancer at the time of diagnosis were excluded.

2.2. Management protocol for AUR

According to the management protocol at our institution for all patients suspected to have AUR, the initial evaluation consists of residual urine check with a bladder scan (BVI-3000 BladderScan; Verathon Inc., Bothell, WA, USA). AUR was defined as a postvoid residual urine volume of >300 mL or incomplete bladder emptying. The primary treatment for AUR has been intermittent catheterization. Foley catheterization was performed in patients with subsequent AUR after intermittent catheterization for 2 days. Cystostomy was not considered as one of the initial management options.

2.3. Outcomes

Sepsis was defined as activation of the inflammatory process due to infection.^{9,10} SIRS was defined based on two or more of the following conditions: (1) body temperature >38°C or <36°C; (2) heart rate >90 beats/min; (3) respiratory rate >20 breaths/min or PaCO₂ <32 mmHg; and (4) WBC >12,000 cells/mm³ or <4,000 cells/mm³ or >10% immature (band) forms.

2.4. Statistical analysis

Continuous variables are expressed as median (interquartile range). Categorical variables are reported as the number of

occurrences and frequency. Student *t* test and Pearson's Chi-square test were used for statistical comparisons of continuous and categorical variables, respectively. Simple and multiple logistic regression analyses with a forward stepwise procedure were used. The area under the receiver operator characteristic curve was used to determine the optimal cutoffs of DNI for predicting bacteremia and sepsis. All statistical comparisons were conducted using IBM SPSS Statistics, version 23 (IBM Corporation, Armonk, NY, USA). A *P* value <0.05 was considered to indicate a statistically significant difference.

3. Results

Table 1 presents the baseline characteristics of patients with AP. In 132 patients (median age, 64.8 years) with AP, fever was the most common initial symptom (*n* = 108, 81.8%), followed by dysuria and chills. AUR was found in nine of 24 (37.5%) patients with a sense of voiding failure at the initial diagnosis. Positive blood culture results revealed 30 bacterial species in 22 (16.7%) patients. *E. coli* (*n* = 19, 63.3%) was the most common isolate. *Staphylococcus* (*n* = 6, 20.0%) and *Klebsiella* (*n* = 4, 13.3%) species were also reported. Of 106 bacterial species in 95 patients with positive urine culture results, *E. coli* was also the most common isolate (*n* = 53, 50.0%).

The patients were divided into two groups according to the presence or absence of sepsis. A lower PSA level and higher heart and respiratory rates were found in patients with sepsis (*P* = 0.001, *P* = 0.013, *P* < 0.001, respectively). No significant differences were found in the initial symptoms and laboratory values including WBC, ESR, CRP level, DNI, and procalcitonin level.

In simple logistic regression analysis, CRP level, procalcitonin level, PSA level, and DNI were identified as risk factors for sepsis. In multiple logistic regression analysis, DNI [odds ratio (OR) = 1.21 (1.034–1.407), *P* = 0.017] and PSA level [OR = 0.95 (0.906–0.998), *P* = 0.040] were significantly associated with the predictors of sepsis. ESR, CRP level, procalcitonin level, and previous Foley insertion status were not significant predictors of sepsis (Table 2).

In multivariate analysis for predicting bacteremia, DNI [OR = 1.15 (1.000–1.318), *P* = 0.049] and previous Foley insertion status [OR = 3.46 (1.161–9.289), *P* = 0.001] were considered as predictive factors (Table 3).

Of 19 patients with AUR during admission [initial diagnosis (*n* = 9), delayed onset (*n* = 10)], 10 needed Foley catheterization because of refractory AUR after intermittent catheterization for 2 days. There was no significant difference in the basic characteristics between patients with and without a need for Foley catheterization. A CRP level >257 mg/L [OR = 1.73 (1.045–3.071), *P* = 0.043] was a significant predictor of failure of intermittent catheterization for 2 days.

4. Discussion

This is the first report to identify the efficacy of inflammatory markers including WBC, ESR, CRP level, procalcitonin level, and DNI for predicting the presence of sepsis in patients with AP. We found that the predictive value of DNI was higher than that of other inflammatory markers including ESR, CRP level, and procalcitonin level. In addition, intermittent catheterization was safe and useful for the initial management of AUR in patients with AP, contrary to the long-standing belief that suprapubic catheterization is mandatory.

The most common cause of AP is assumed to be reflux of infected urine from the urethra into the prostate.¹¹ Previous studies reported *E. coli* as the causative pathogen in 50–80% of cases.¹² In this study, *E. coli* was the most common isolate in urine cultures (50.0%) and blood cultures (63.3%). However, the diagnostic and

Table 1
Baseline characteristics of patients with acute prostatitis.

	Total	Sepsis (+)	Sepsis (-)	P
No. patients	132	17 (12.9)	115 (87.1)	
Age (years)	64.8 (53.9–76.3)	75.9 (55.3–78.4)	62.9 (53.0–72.8)	0.271
Body mass index (kg/m ²)	24.2 (22.2–25.5)	24.0 (21.8–26.7)	24.2 (22.3–25.5)	0.951
Prostate volume (cm ³)	39.4 (30.4–54.3)	31.2 (27.6–47.5)	40.7 (30.6–54.9)	0.177
Initial symptom				
Fever	108 (81.8)	15 (88.2)	92 (80.0)	0.458
Dysuria	93 (70.5)	9 (52.9)	84 (73.0)	0.648
Chills	92 (69.7)	15 (88.2)	76 (66.1)	0.987
Myalgia	30 (22.7)	3 (17.6)	26 (22.6)	0.573
Sense of voiding failure	24 (18.2)	3 (17.6)	21 (18.3)	0.939
Initial laboratory values				
WBC ($\times 10^3/\mu\text{L}$)	15.5 (10.5–19.0)	15.6 (11.1–18.9)	15.4 (10.4–19.0)	0.803
ESR (mm/h)	34.5 (15.0–62.5)	40.5 (21.5–76.5)	34.0 (14.0–60.0)	0.363
CRP (mg/L)	117.3 (32.1–162.6)	113.8 (31.1–170.4)	131.1 (113.8–170.4)	0.194
DNI	2.3 (0.4–3.9)	3.5 (0.8–6.1)	2.2 (0.4–3.8)	0.088
Procalcitonin (ng/mL)	4.9 (0.6–34.8)	16.6 (9.2–63.9)	0.9 (0.3–18.5)	0.209
PSA (ng/mL)	14.2 (6.3–31.8)	7.05 (5.01–10.97)	16.8 (6.5–36.3)	0.001
Blood culture (+)	22 (16.7)	17 (100.0)	5 (4.3)	<0.001
Urine culture (+)	95 (72.0)	14 (82.4)	81 (70.4)	0.307
No. meeting sepsis criteria				
Heart rate	56 (42.4)	12 (70.6)	44 (38.3)	0.013
Respiratory rate	9 (6.8)	16 (94.1)	68 (59.1)	<0.001
Body temperature or PaCO ₂	84 (63.6)	3 (17.6)	6 (5.2)	0.221
WBC	89 (67.4)	12 (70.6)	76 (66.1)	0.750
Period of antibiotics use	15.0 (13.0–17.0)	17.0 (16.0–18.0)	15.0 (13.0–17.0)	0.031

Data are *n* (%) or median (interquartile range).

CRP, C-reactive protein; DNI, delta neutrophil index; ESR, erythrocyte sedimentation rate; PSA, prostate-specific antigen; WBC, white blood cells.

prognostic values of urine and blood cultures remain unclear.^{13–16} The positive urine culture rate in patients with AP was 30–66%. Lee et al investigated a series of 144 patients with AP and found a positive urine culture in only 51 patients (35.4%).¹⁵ Nagy and Kubej found a positive rate of 66.2% in 347 patients.¹² These results are similar to our finding of a 72.0% positive urine culture result in patients with AP. Etienne et al performed a retrospective analysis of 347 patients with AP and found that 21% had positive blood cultures.¹⁶ A body temperature of >38.4°C at admission and the fever duration were predictive of a positive blood culture. In this study, 16.7% of patients showed positive blood culture results. The DNI and previous Foley insertion status were the predictive factors of bacteremia.

The DNI reflects the number of immature granulocytes in peripheral blood.¹⁷ Polymorphonuclear neutrophil granulocytes function as the host defense against bacteria. After maturation, they migrate into peripheral blood.¹⁸ The presence of immature granulocytes represents increased myeloid cell production, generally accompanied by infection or severe inflammatory disease.¹⁹ The level of immature granulocytes is one of the criteria for the definition of SIRS.¹⁰ However, immature granulocytes can be counted using a manual method with blood film morphology, which has not been widely used.¹⁹ An automatic analyzer measures differential leukocyte counts by using cytochemical myeloperoxidase reaction or light beam reflection from nuclear lobularities in WBCs. The DNI is defined as the difference in counts between the two methods.²⁰ Several recent studies have evaluated the DNI as a diagnostic and prognostic marker of sepsis.^{20–22} Compared with other promising inflammatory markers such as ESR, CRP level, and procalcitonin level, the DNI is a useful marker of early sepsis and a positive blood culture in patients with AP. The present data supported the findings that DNI increase becomes higher as the infection becomes more severe. In an additional analysis to determine the optimal cutoffs for predicting bacteremia, a DNI cutoff of 5.4 was determined, similar to that of previously published studies.^{23–25}

Generally, ESR and CRP are the most widely used markers for the early detection of sepsis. However, ESR has a limited role in early

sepsis detection as it is associated with the late reaction in acute inflammatory disease. CRP reflects the severity of inflammation before 1–3 days.²⁶ In this study, CRP measured at the time of visit to our institution was not identified as a predicting factor. Interestingly, CRP at 2–3 days after treatment was a significant factor for predicting sepsis in the univariate analysis (OR = 1.01, *P* = 0.032). However, this result was not suitable for identifying the early predictors of sepsis. Moreover, our study found that procalcitonin, known as an early predictive marker for bacteremia and sepsis, has no effect on the early prediction of sepsis and bacteremia in patients with AP. Compared with other markers, the DNI can be easily calculated using complete blood count, which is performed as a basic test in patients with suspected infection or sepsis without further examination.

PSA, although generally used in practice as the novel serum marker that revolutionized the early detection and management of prostate cancer, can be elevated owing to several reasons including infection, recent instrumentation, ejaculation, trauma, or voiding difficulty.^{27,28} In previous studies, PSA was usually found to be elevated in AP but is not indicated in the workup.^{3,11} However, at our institution, we have routinely measured PSA level in patients who developed AP. In comparing patients with AP according to the occurrence of sepsis, we found that a lower PSA level was frequently present in sepsis. We assumed that considering that PSA elevation is related to damage of the prostatic structure, lower PSA levels were more frequently observed in cases with hematogenous dissemination of bacterial infection after the damage of periprostatic structures.

The diagnosis of AP is determined based on the clinical symptoms. The common symptoms of AP include pain in the lower abdomen, rectum, and perineum. Acute symptoms of urinary tract infection, including dysuria and frequency, are accompanied by systemic symptoms of fever, chills, and malaise.¹³ AUR occurs in approximately one in 10 patients with AP.²⁸ Cystostomy has been considered important in clearing the infection and providing pain relief. Furthermore, cystostomy may prevent chronic infection.^{29,30} Therefore, several studies reported that 7–48% of patients with AUR

Table 2
Univariate and multivariate analyses for the prediction of sepsis.

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age	1.02 (0.984–1.059)	0.271		
Body mass index	0.99 (0.823–1.200)	0.950		
Prostate volume	0.96 (0.911–1.017)	0.179		
WBC	1.00 (1.000–1.000)	0.801		
ESR	1.01 (0.990–1.029)	0.361		
CRP	1.00 (0.998–1.009)	0.198		
DNI	1.20 (1.048–1.379)	0.009	1.21 (1.034–1.407)	0.017
Procalcitonin	1.03 (0.984–1.074)	0.220		
PSA	0.95 (0.911–0.999)	0.009	0.95 (0.906–0.998)	0.040
Previous Foley insertion status	4.29 (1.426–12.893)	0.010	2.79 (0.816–9.515)	0.102

CI, confidence interval; CRP, C-reactive protein; DNI, delta neutrophil index; ESR, erythrocyte sedimentation rate; PSA, prostate-specific antigen; WBC, white blood cells.

Table 3
Univariate and multivariate analyses for the prediction of bacteremia.

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age	1.02 (0.986–1.052)	0.271		
Body mass index	0.94 (0.801–1.109)	0.476		
Prostate volume	1.00 (0.971–1.026)	0.904		
WBC	1.00 (1.000–1.000)	0.643		
ESR	1.01 (0.993–1.030)	0.232		
CRP	1.00 (0.998–1.008)	0.258		
DNI	1.13 (1.000–1.286)	0.049	1.15 (1.000–1.318)	0.049
Procalcitonin	1.09 (0.982–1.211)	0.106		
PSA	0.98 (0.961–1.008)	0.199		
Previous Foley insertion status	3.27 (1.194–8.932)	0.001	3.46 (1.161–9.289)	0.001

CI, confidence interval; CRP, C-reactive protein; DNI, delta neutrophil index; ESR, erythrocyte sedimentation rate; PSA, prostate-specific antigen; WBC, white blood cells.

underwent cystostomy.^{12,30} However, in practice, urethral catheterization is an easier option for relieving obstruction.³ In this study, 14.3% of patients with AP experienced AUR, and 52.6% of those were treated with Foley catheterization because of refractory AUR after intermittent catheterization for 2 days. Although we did not compare the efficacy of intermittent catheterization with that of cystostomy as the initial management in patients with AP with AUR, we found no severe complication events in this cohort; therefore, we conclude that intermittent catheterization could be one of the useful management options for AUR in patients with AP.

The present study had several limitations including its retrospective design and the small number of patients owing to the low incidence of AP. First, this study confirms that the DNI is a significant predictor of bacteremia and sepsis in patients with AP. However, the definition of sepsis has recently changed.³¹ Therefore, additional studies evaluating the efficacy of the DNI as an early predictor in the new criteria for sepsis are needed. Second, although we found that intermittent catheterization in patients with AP with AUR is a safe initial management option, the long-term effects of intermittent catheterization remain unclear. Because, until now, intermittent catheterization was not an initial management option in patients with AP, little data have been accumulated. According to the results of this study, if intermittent catheterization is considered an option in the management of AP, more data will be accumulated for elucidating the long-term efficacy of intermittent catheterization.

Finally, we were unable to assess the influence of usual urination symptoms by using uroflowmetry and symptom scoring, such as the International Prostate Syndrome Score, before AP. Although most patients were assessed for recalled International Prostate Syndrome Score, this information was not used in the analysis for accuracy of data. Moreover, some patients were treated with

benign prostatic hyperplasia (BPH) medications before AP. As patients treated with BPH medications and those without BPH may have different predictors for sepsis, we plan to conduct additional studies in the future.

5. Conclusions

In patients with AP, the DNI was a significantly useful marker for predicting early sepsis. Intermittent catheterization could be one of the useful management options for AUR in patients with AP instead of cystostomy.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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