Original Article

# A prospective observational study on the efficacy of procalcitonin as a diagnostic test to exclude lower urinary tract infection and to minimize antibiotic overuse

Swastik Acharya[1], Sanjukta Mishra[2], Arpan Ghosh[3], Shubhransu Patro[1]

[1]Department of General Medicine, Kalinga Institute of Medical Sciences, KIIT Deemed to be University, [2]Department of Biochemistry, Kalinga Institute of Medical Sciences, KIIT Deemed to be University, [3]School of Biotechnology, KIIT Deemed to be University, Bhubaneswar, Odisha, India

## Abstract

**Background:** Urinary tract infection (UTI) stands out as the third-most common infection following gastrointestinal and respiratory tract infections. Over the past decade, the biomarker procalcitonin (PCT) has gained prominence to facilitate the detection of bacterial infections and reduce excessive antibiotic exposure.

**Objective:** The objective of this study was to mitigate the overuse of antibiotics, by promoting the noninitiation or early discontinuation of empirical antibiotics, which would significantly help minimize the proliferation of multidrug-resistant bacteria.

**Methodology:** A prospective observational study was carried out at the tertiary care center in the Department of General Medicine of Kalinga Institute of Medical Sciences, Bhubaneswar, involving 200 patients with symptoms of lower UTI such as increased frequency, urgency, burning micturition, retention, and suprapubic tenderness with or without positive urinalysis. Detailed demographic profiles along with symptoms at the time of admission were recorded in a pretested structured format. To determine a positive diagnosis of UTI, signs and symptoms of UTI with or without urinary cultures were tested. The PCT level was estimated using enhanced chemiluminescence technique. Other routine tests such as complete blood count, renal function test, liver function test, urine routine microscopy, culture, chest X-ray, and ultrasonography abdomen pelvis were done and recorded. All patients, who had an initial serum PCT level of $< 0.5$ ng/mL, were kept under observation with only conservative and symptomatic treatments. Patients were further reviewed for improvement in symptoms and repeat urine microscopy. All patients, who had an initial serum PCT level of $> 0.5$ ng/mL, were initiated with antibiotics as per the culture and sensitivity reports. Patients were followed up for improvement in symptoms with reports of repeated urinalysis.

**Results:** Our study reported the fact that 9.5% of the patients with initial serum PCT $\geq 0.5$ ng/mL showed no improvement in symptoms despite starting antibiotics while significantly higher number of symptomatic patients (60%) with initial serum PCT $< 0.5$ ng/ml showed improvement in symptoms with conservative treatment without antibiotics.

**Address for correspondence:** Dr. Shubhransu Patro, Department of General Medicine, Kalinga Institute of Medical Sciences, KIIT Deemed to be University, Bhubaneswar - 751 024, Odisha, India.
E-mail: spatro@kims.ac.in

**Received:** 19.04.2021, **Revised:** 25.12.2023, **Accepted:** 15.01.2024, **Published:** 18.04.2024.

| Access this article online | |
|---|---|
| Quick Response Code: | Website: www.urologyannals.com |
| | DOI: 10.4103/ua.ua_73_21 |



**How to cite this article:** Acharya S, Mishra S, Ghosh A, Patro S. A prospective observational study on the efficacy of procalcitonin as a diagnostic test to exclude lower urinary tract infection and to minimize antibiotic overuse. Urol Ann 2024;16:169-74.

**Conclusion:** A lower PCT level rules out bacterial invasion and thus can be used as a novel marker in antibiotic stewardship.

**Keywords:** Antibiotic resistance, bacterial infection, procalcitonin, urinalysis, urinary tract infections

## INTRODUCTION

Urinary tract infections (UTIs) are among the most prevalent bacterial infections acquired in the community and hospitals. In individuals with no structural or physiological anomalies, UTIs are normally self-confined but possessing a propensity to recur.[1] The prognosis and treatment of UTI, however, depends on both the area of infection and other predisposing factors and appears to be quite distressing. In primary care, antibiotics stand out as standard treatment for UTI and incorrect prescription of the same often leads to antibiotic resistance. Furthermore, a meta-analysis of five UTI primary care trials inferred that there was a high risk of antibiotic resistance that lasted for about 1 year and that multiple antibiotic courses were associated with a higher risk to the patients.[2] Burgeoning bacterial resistance to antibiotics calls for more rigorous attempts to minimize the overuse of the said therapeutics.[3] The antibiotic stewardship initiatives aimed at minimizing antibiotic overuse by customizing antibiotic treatment to the particular needs of patients have demonstrated substantial interest in the laid objective.[4] Despite the promising application of diagnostic biomarkers in various fields of medicine, accurate and prompt detection of bacterial infections remains a problem.[5] There was a significant shortage of accurate clinical or microbiological methodologies that can be used to identify bacterial infections and filter out other infections that may not need antibiotic therapy. Diagnostic disruptions, sub-optimal specificity, and poor accuracy due to contamination are some of the noted drawbacks of many modern microbiological methods, whereas some are not conducive to routine diagnosis due to their invasive nature.[6]

In such a context, procalcitonin (PCT) has generated considerable interest as a theoretically more accurate marker for bacterial infection. PCT is generated in response to endotoxins or mediators released in response to bacterial infections such as interleukin (IL)-1 β, tumor necrosis factor-α, and IL-6, and is closely associated with the degree and severity of bacterial infections.[7] Owing to the fact that interferon-γ, a cytokine released in response to viral infections attenuates the upregulation of PCT, it becomes imperative to state that PCT is more specific to bacterial infections and can help to differentiate bacterial infections from viral ones.[8] PCT has been presented as a profound candidate marker for diagnosis and antibiotic stewardship in patients with systemic infections.[9] Pertinently, PCT needs to be used and integrated in clinical algorithms suited to the form of infection and the clinical setting and situation, as with any diagnostic instrument. Hence, serum PCT is a valid and excellent noninvasive procedure that can be helpful in deciding on UTI management for the clinician. In predicting renal parenchymal injury, it is a clinically significant biomarker used in the UTI phase as well. Further, clinical trials have shown that only bacterial inflammation and sepsis, but not any viral, fungal infections, or autoimmune disorders, could induce elevated serum levels of PCT.[10] The high negative predictive value (NPV) of PCT can be beneficial as a complement to the findings of urinalysis to rule out UTI and facilitate nominations or quicker discontinuation of empirical antibiotics.

Therefore, at our tertiary treatment facility, the current research study was performed to determine the efficacy of PCT as a diagnostic test to exclude lower UTI and to minimize antibiotic overuse by encouraging the noninitiation or early discontinuation of prescribed antibiotics.

## METHODOLOGY

A prospective observational study was carried out at the tertiary care center in the Department of General Medicine of Kalinga Institute of Medical Sciences and Pradyumna Bal Memorial Hospital, Bhubaneswar, after due permission from the institutional ethics committee and review board and after obtaining written informed consent from the patients.

After approval from the Institutional Ethics Committee, valid consent was taken from each of the patients. A thorough medical history and physical examination were carried out in the enrolled patients as per proforma. A written informed consent was taken from the patients or patient's attendant.

### Inclusion criteria

- Patients aged more than 18 years
- At least one symptom of lower UTI (dysuria, hematuria, frequency, urgency, urinary retention, and suprapubic tenderness)

- Urine analysis revealing leukocyte esterase (LE) positive and nitrite dipstick positive.

### Exclusion criteria

- Pregnancy
- Transplant patients
- Spinal cord injury with paralysis
- Immunocompromised
- Patients presenting with more than one episode of UTI
- Patients on antibiotics
- Acute Pyelonephritis
- Patients with recurrent UTI
- Burns
- Surgery/Trauma
- Clinical examination revealing any other infections.

All patients visiting the medicine outpatient department and admitted to the medicine ward during the study period with symptoms of lower UTI such as increased frequency, urgency, burning micturition, retention, suprapubic tenderness with or without positive urinalysis, and who qualified the inclusion criteria were included in the study. After admission, detailed demographic profile along with symptoms at the time of admission were recorded in a pretested structured format. To determine a positive diagnosis of UTI, signs and symptoms of UTI with or without urinary cultures were tested. 2 ml of serum was collected within 24 h for measuring initial PCT for all patients positive for lower UTI. The PCT level was estimated using enhanced chemiluminescence technique. Other routine tests such as complete blood count, renal function test, liver function test, urine routine microscopy, culture, chest X-ray, and ultrasonography abdomen pelvis were done and recorded.

Patients were clinically evaluated properly to rule out any other source of primary infection. For patients who presented with more than one episode of UTI, only the 1$^{st}$ episode was considered in the study. All patients who had an initial serum PCT level of <0.5 ng/mL were kept under observation with only conservative and symptomatic treatments such as fluids, alkaliser, antispasmodics, nonsteroidal anti-inflammatory drugs, and antipyretics. Patients were further reviewed for improvement in symptoms and repeat urine microscopy.

All patients who had an initial serum PCT level of >0.5 ng/mL were initiated with antibiotics as per the culture and sensitivity reports.

Patients were followed up for improvement in symptoms with reports of repeated urinalysis.

### Statistical analysis

Comparison between the sample groups was performed according to the findings of the normality test with the aid of an unpaired *t*-test. Using a frequency and percentage chart, qualitative data are displayed. With the help of the Fisher test, Student's-*t*-test, and Chi-square test, the relation between the sample groups was tested. The value $P < 0.05$ was taken as significant.

## RESULTS

A hospital-based study was conducted in 200 patients to determine the efficacy of PCT as a diagnostic test to exclude lower UTI and to minimize antibiotic overuse by encouraging the noninitiation or early discontinuation of prescribed antibiotics.

The mean age of the patients enrolled in the study was 43.84 ± 15.09 years and 69.5% of the patients were male while 30.5% of the patients were females. It was observed that 43% of the patients had hypertension while 15.5% suffered from diabetes mellitus. The most common symptom noted was dysuria (97%), followed by increased frequency (94%), urgency (69.5%), suprapubic pain (26.5%), hematuria (19%), and fever (16.5%). Forty percentage of the patients received antibiotics in the study. Analysis of urine samples was done in the patients and the details are presented in Table 1.

Initial serum PCT level was checked in all the patients and the distribution of the patients according to the analyzed level is presented in Figure 1.

The duration of hospital stay in the majority of the patients (65.5%) was 1–3 days, followed by 4–7 days (32.5%) and > 7 days (2%). All the patients were subjected for repeated urine leukocyte count and it was observed that 3% of the patients showed high leukocyte count even after treatment. Out of them, four patients were on conservative management and two patients were on antibiotics.

### Distribution of patients according to improvement in symptoms during follow-up for patients with serum procalcitonin level <0.5 ng/ml

Out of 128 patients who had initial serum PCT level < 0.5 ng/ml and received conservative treatment, 120 patients showed

**Table 1: Distribution of patients according to urine analysis**

| Urine analysis | *n* (%) |
|---|---|
| LE positive | 62 (31) |
| High leukocyte count | 161 (80.5) |
| Growth | 143 (71.5) |
| Nitrite positive | 105 (52.5) |

LE: Leukocyte esterase

improvement in symptoms during subsequent days. Details of the same are presented in Table 2.

### Association of initial serum procalcitonin and repeat urine leukocyte count in patients

Two (1%) patients with initial serum PCT <0.5 ng/ml and 4 (2%) patients with initial serum PCT ≥0.5 ng/mL had high repeat urine leukocyte count. There was no significant association of initial serum PCT and repeat urine leukocyte count as per the Chi-square test ($P > 0.05$) as presented in Figure 2.

### Association of initial serum procalcitonin and improvement in symptoms in patients

Out of 128 patients with initial serum PCT level <0.5 ng/mL, 120 patients (60%) receiving conservative treatment showed improvement in symptoms. Out of 72 patients with initial serum PCT level >0.5 ng/mL who were initiated with antibiotics, 55 (27.5%) improved while 17 patients (8.5%) failed to show any improvement in symptoms. There was a significant association of initial serum PCT and improvement in symptoms as per the Chi-square test ($P < 0.05$) as presented in Table 3.

**Table 2: Distribution of patients according to improvement in symptoms during follow-up for patients with conservative management**

| Improvement in symptoms | *n* (%) |
|---|---|
| No | 8 (6.25) |
| Yes | 120 (93.75) |
| Total | 128 (100) |

**Table 3: Association of initial serum procalcitonin and improvement in symptoms in patients**

| Initial serum procalcitonin (ng/mL) | Improvement in symptoms | | | *P* |
|---|---|---|---|---|
| | No, *n* (%) | Yes, *n* (%) | Total, *n* (%) | |
| <0.5 | 8 (4) | 120 (60) | 128 (64) | <0.05 |
| ≥0.5 | 17 (8.5) | 55 (27.5) | 72 (36) | |
| Total | 25 (12.5) | 175 (87.5) | 200 (100) | |

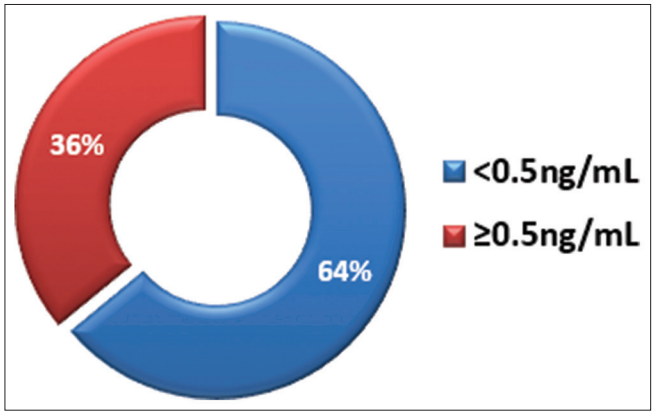


**Figure 1:** Distribution of patients according to initial serum procalcitonin level

### Association of prescription of antibiotics and repeat urine leukocyte count in patients

Four (1%) patients who were prescribed antibiotics had high repeat urine leukocyte counts. There was no significant association of the prescription of antibiotics and repeat urine leukocyte count.

## DISCUSSION

A hospital-based study was conducted with 200 patients to prove that an initial PCT level of < 0.5 ng/ml excludes lower UTI and significantly lowers the use of antibiotics in such cases, thereby reducing antibiotic burdens.

PCT is released into the circulation when there is systemic inflammation, particularly in bacterial infections, under the effect of inflammatory cytokines and bacterial endotoxin, where its level can rise up to 1000 folds. The first quantifiable values are also found 2–4 h after infection, with a maximum of 6–24 h after tissue invasion by bacteria.[11] In clinical practice, if patients have decreased UTI symptoms and have inaccurate urinalysis results or only fulfilled a single criterion for a positive urinalysis, PCT values < 0.5 ng/mL would validate the decision to retain or stop antibiotics.[12]

Current Infectious Diseases Society of America for hospital-acquired pneumonia recommendations advocates the use of PCT in combination with clinical facilities to guide the noninitiation or discontinuation of antibiotics.[13] Similarly, the latest Surviving Sepsis Initiative Recommendations implicate that PCT can be implemented to decrease the length of antibiotics or to stop empiric antibiotics in patients who were initially septic but subsequently had no clinical evidence of tissue invasion or infection.[14,15] The initial serum PCT level of < 0.5 ng/ml is adequate to deter bacterial invasion of tissues.

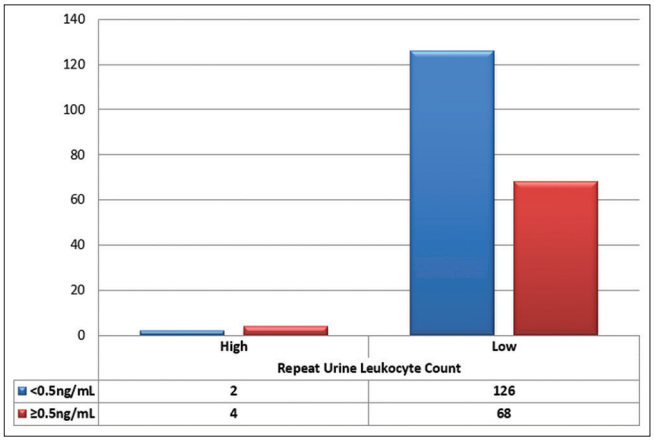


**Figure 2:** Association of initial serum procalcitonin and repeat urine leukocyte count in patients

There was male preponderance and a male-to-female ratio of 2.28:1. The most common symptom in our study was dysuria (97%), followed by increased frequency (94%), urgency (69.5%), suprapubic pain (26.5%), hematuria (19%), and fever (16.5%). The urinalysis of 62 (31%) patients showed LE positive while 161 (80.5%) patients had high leukocyte count. The urine samples of 143 (71.5%) and 105 (52.5%) patients showed growth and positive nitrite, respectively. This is concordant to the study of Levine *et al*.[16]

In our study, it was observed that the initial serum PCT level was <0.5 ng/mL in 128 (64%) patients while it was ≥0.5 ng/mL in 72 (36%) patients. Out of 128 patients who had a serum PCT level <0.5 ng/mL, 8 (6%) patients did not show improvement in symptoms with conservative management and were later initiated with appropriate antibiotics. Eighty (40%) patients received antibiotics in our study which included patients with serum PCT > 0.5 ng/mL and patients who did not improve with conservative management even when serum PCT was < 0.5 ng/mL. Six (3%) patients showed high leukocyte count after treatment. The duration of hospital stay in the majority of the patients (65.5%) was 1–3 days, followed by 4–7 days (32.5%) and > 7 days (2%). The observed results were found to be consistent with the studies reported at Levine *et al*. and Christ-Crain *et al*.[8] The retrospective analysis of Levine *et al*. found that patients with a negative diagnosis of UTI were more likely to be younger, had substantially lower PCT values, white blood cell count, and likeliness of initiating antibiotics was also less. The report published by Christ-Crain *et al*. examined 302 community accquired pneumonia (CAP) patients, in which 151 subjects in the control group were treated with antibiotics in accordance with normal clinical practice, while patients in the PCT group were treated with PCT values (PCT < 0.1 ng/ml and < 0.25 ng/ml-"no antibiotics;" PCT more than 0.5 ng/ml-"mandatory antibiotics"). A substantial reduction in antibiotic exposure was observed in the PCT community, mainly at the cost of individual reduction of the period of antibiotic therapy, on average, from 12 to 5 days. The result of treatment in both groups was similar according to laboratory and clinical parameters.

Our study reported the fact that 9.5% of the patients with initial serum PCT ≥ 0.5 ng/mL showed no improvement in symptoms despite starting antibiotics while a significantly higher number of symptomatic patients (60%) with initial serum PCT < 0.5 ng/ml showed improvement in symptoms with conservative treatment without antibiotics. There was a significant association of initial serum PCT and improvement in symptoms as per the Chi-square test ($P < 0.05$). The above results corroborated with the ones reported by Levine *et al*. and Drozdov *et al*. [16,17] Utility of initial PCT to predict UTI, found that initial PCT values, also at higher thresholds, poorly predict the existence of UTI, and thus PCT more than 0.25 ng/ml could not be used to direct the initiation of antibiotics in these patients. Retrospective analysis carried out by Levine *et al*. on urinalysis tests suggested PCT threshold of < 0.25 ng/ml was a strong predictor to rule out UTI in patients. The strong NPV of PCT can be useful to rule out UTI and to encourage noninitiation or earlier discontinuation of clinical antibiotics as an addition to the findings of urinalysis.

In a randomized controlled trial, Drozdov *et al*. stated that the efficacy of PCT demonstrated a 30% decline in antibiotic usage when compared to conventional treatment. The elaborate algorithm merged analyses of serum PCT concentration and quantitative pyuria.[17] The patients were categorized as outpatients versus inpatients with uncomplicated or complicated UTI, resulting in different antibiotic applications, different periods of treatment, or a controlled approach to PCT assessment and degree of pyuria. There were no adverse effects and the PCT/pyuria-based strategy is healthy in terms of results and has the ability to decrease the use of antibiotics.

In the current report, it was reported that 6 (2%) patients who were prescribed antibiotics had a high urinary leukocyte repeat count. As per the Chi-square examination, there was no substantial correlation between the prescription of antibiotics and repeat urinary leukocyte count ($P > 0.05$). Considering the fact that they associate with bacterial load and infection incidence, the PCT values have prognostic consequences.[18] A low PCT level rules out bacterial invasion and thus can be used as a novel marker in antibiotic stewardship.

## CONCLUSION

PCT is a responsive indicator that relates to the earlier diagnosis and evaluation of aggressive bacterial infection seriousness and prognosis. Sequenced PCT assessment approaches offer empirical evidence that along with clinical assessment provides the basis on which the PCT recommendations for antibiotic therapy are premised upon. A large number of randomized clinical trials have demonstrated that the treatment of LUTI and sepsis reduces antibiotic tolerance without impacting patient safety and the outcome of therapy. The use of PCT in diagnostic and therapeutic procedures for bacterial infection lowers

the cost of treatment and bacterial multi-resistant strain development. Since UTIs are among the most prevalent causes of antibiotic therapy, the influence of a reduction in treatment time may be profound. This analysis offers irrefutable proof that the original amount of PCT would negate the diagnosis of LUTI when done in patients with symptoms of dysuria, high frequency, and urgency of urination. Such kind of research endeavor also provides ample evidence that the initial PCT level of < 0.5 ng/mL indicates the fact that the symptom-causing organism might be locally present or merely a contaminant without direct invasion of the tissue. Hence, it is pertinent to state that in patients with symptoms of LUTIs, the use of PCT for antibiotic stewardship and the introduction of antibiotics according to original serum PCT levels can significantly minimize excessive antibiotic resistance and the proliferation of multidrug-resistant strains of bacteria.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERNCES

1. Bagga A. Revised guidelines for management of steroid-sensitive nephrotic syndrome. Indian J Nephrol 2008;18:31-9.
2. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: Systematic review and meta-analysis. BMJ 2010;340:c2096.
3. Whitney CG, Farley MM, Hadler J, Harrison LH, Lexau C, Reingold A, *et al*. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. N Engl J Med 2000;343:1917-24.
4. Ohl CA, Luther VP. Antimicrobial stewardship for inpatient facilities. J Hosp Med 2011;6 Suppl 1:S4-15.
5. Lee TH, Goldman L. Evaluation of the patient with acute chest pain. N Engl J Med 2000;342:1187-95.
6. Müller B, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, *et al*. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis 2007;7:10.
7. Gogos CA, Drosou E, Bassaris HP, Skoutelis A. Pro- versus anti-inflammatory cytokine profile in patients with severe sepsis: A marker for prognosis and future therapeutic options. J Infect Dis 2000;181:176-80.
8. Schuetz P, Christ-Crain M, Müller B. Procalcitonin and other biomarkers to improve assessment and antibiotic stewardship in infections – Hope for hype? Swiss Med Wkly 2009;139:318-26.
9. Trautner BW, Gupta K. Urinary tract infections, pyelonephritis, and prostatitis. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill Professional. 2012. p. 2387-96.
10. Bressan S, Andreola B, Zucchetta P, Montini G, Burei M, Perilongo G, *et al*. Procalcitonin as a predictor of renal scarring in infants and young children. Pediatr Nephrol 2009;24:1199-204.
11. Suberviola B, Castellanos-Ortega A, González-Castro A, García-Astudillo LA, Fernández-Miret B. Prognostic value of procalcitonin, C-reactive protein and leukocytes in septic shock. Med Intensiva 2012;36:177-84.
12. Kosanke R, Beier W, Lipecky R, Meisner M. Clinical benefits of procalcitonin.Tanaffos 2008;7:14-8.
13. Grönberg-Hernández J, Sundén F, Connolly J, Svanborg C, Wullt B. Genetic control of the variable innate immune response to asymptomatic bacteriuria. PLoS One 2011;6:e28289.
14. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, *et al*. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017;45:486-552.
15. Agency for Healthcare Research and Quality. Effective Health Care Program. EPC Project. Project Title: Procalcitonin for diagnosis and Management of Sepsis. Research protocol 2011. Available at:http://www.effectivehealthcare.ahrq.gov.
16. Levine AR, Tran M, Shepherd J, Naut E. Utility of initial procalcitonin values to predict urinary tract infection. Am J Emerg Med 2018;36:1993-7.
17. Drozdov D, Schwarz S, Kutz A, Grolimund E, Rast AC, Steiner D, *et al*. Procalcitonin and pyuria-based algorithm reduces antibiotic use in urinary tract infections: A randomized controlled trial. BMC Med 2015;13:104.
18. Schuetz P, Haubitz S, Mueller B. Do sepsis biomarkers in the emergency room allow transition from bundled sepsis care to personalized patient care? Curr Opin Crit Care 2012;18:341-9.