RESEARCH ARTICLE

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# Detection of PCT and urinary β₂-MG enhances the accuracy for localization diagnosing pediatric urinary tract infection

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**Objective:** The purpose of this article was to investigate whether the combination of urinary beta 2 microglobulin (urinary β₂-MG) and procalcitonin (PCT) diagnosis could enhance the localization diagnostic precision of pediatric urinary tract infection comparing with single diagnosis.

**Methods:** A study was conducted in the Nephrology Department of Wuhan women and children's health care centre. This study incorporated 85 participants, including 35 children who were diagnosed as upper urinary tract infection (UUTI) with the symptom of fever and 50 children who conducted lower urinary tract infection (LUTI). Levels of PCT and urinary β₂-MG in both UUTI and LUTI patients were measured and compared.

**Results:** The level of PCT and β₂-MG were both significantly higher in UUTI group compared with in LUTI group. AUC of urinary β₂-MG ROC (sensitivity of 71.4%, specificity of 90.0%) was significantly smaller than that of PCT ROC (sensitivity of 77.1%, specificity of 96.0%) in the single diagnosis. Although in the combined diagnosis, the sensitivity and specificity increased to 88.6% and 98%, respectively.

**Conclusions:** Both PCT and β₂-MG could be used to localize the UTI. Introducing urinary β₂-MG into PCT diagnosis could increase the sensitivity and specificity of UTI lesion diagnosis in clinical practice.

**KEYWORDS**
children, localization diagnosis, procalcitonin, urinary tract infection, urinary β₂-MG

## 1 | INTRODUCTION

Urinary tract infections (UTIs) commonly occur in young febrile children and they trigger a wide range of bacterial infections.[1] For children under the age of 6 years old, the prevalence of male and female pediatric UTI was nearly 2% and 7%, respectively.[2] Since UTI symptoms are non-typical among febrile newborns and children, distinguishing upper UTI from lower UTI is challenging. Apart from that, UTI may result in renal scarring which is characterized by many different forms including hypertension, poor renal growth, and end-stage renal failure. Many studies have been conducted to assess the appropriateness of diagnostic approaches and treatments for UTI.[3,4] Conventional serum markers for diagnosing UTI include total white blood cell count (WBC), C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), and interleukin (IL)-6.[5] Procalcitonin (PCT) generates a relatively desirable diagnostic accuracy compared with other serum markers.

Procalcitonin (PCT) is a 116-amino acid propertide of calcitonin, which could be an indicator of bacterial infections. PCT has been reported to be a reliable diagnostic biomarker of bacterial infections due to its specificity, short time of induction and long half-life.[6-8] Common biomarkers for UTI includes serum leukocyte or neutrophil counts, C-reactive protein (CRP) and interleukins, compared with which, PCT has been proved to be more specific in terms of

differentiating acute pyelonephritis from LUTIs.[7,9-11] PCT is also specific in terms of differentiation of viral and bacterial infections particularly in children.[12,13] In addition, PCT can be detected in serum 2 hours after the infections and the PCT levels, thereafter, rises and reaches a plateau 12 hours after the infections.[12,14] Serum PCT concentration is lower than 0.5 µg/L under normal circumstances in healthy individuals.[14-16] However, the association between PCT production and bacterial infection still remains not elucidated. It is believed that the *CALC1* gene is overexpressed in liver and peripheral blood mononuclear cells in response to the bacterial infections and thereafter produces calcitonin precursors.[12,17] Recent researches have demonstrated a correlation between high concentrations of serum PCT and renal parenchymal inflammation (RPI) and renal scarring in UTI patients.[16,18] Children with higher PCT levels (>0.5 ng/mL) could have a high risk of renal damage and acute RPI.[14,19]

β-2-microglobulin ($β_2$-MG) is a small protein, approximately 100 amino acids long, which is found on the surface of all nucleated cells.[20] It is identified as the light chain of the major histocompatibility complex I.[20,21] Urinary $β_2$-MG is the indicator of glomerular filtration rate and tubular reabsorption.[21,22] Comparisons of $β_2$-MG to other serum biomarkers such as creatinine and cystatin C levels have been generally used to estimate kidney functions and prognose the outcomes of chronic kidney disease.[20,22] The abnormal urinary and serum $β_2$-MG levels were associated with post inflammation in urinary tract.[23] High $β_2$-MG levels were correlated with a high grade of vesicoureteral reflux.[24] Combined use of $β_2$-MG and enzymuria could increase the diagnosis sensitivity up to 75%, however, the levels of $β_2$-MG and enzymuria were too variable to be a stable diagnostic indicator.[25] In addition, serum and urine $β_2$-MG have been reported to be elevated in the both acute and chronic renal transplant rejection.[26,27]

The following study was designed to explore the potential value of the combination of PCT and urinary $β_2$-MG in localization diagnosing paediatric urinary tract infections. Conclusions based on this study may be generalized to clinical practice.

## 2 | MATERIALS AND METHODS

### 2.1 | Study objects

A total of 85 children aged between 1 and 13 years old were consecutively enrolled into this study. These children were selected from patients who were admitted in Wuhan Women and Children's Health Care Center due to febrile urinary infection from August 2014 to September 2015. They were divided into two groups as UUTI and LUTI on the basis of UTI diagnosis treatment guidelines. The exclusion criteria were specified as: children with severe liver damage or incomplete kidney functions; children with congenital immunodeficiency; children with severe congenital heart disease; children who had received antibiotics in the last week before study commencement; children with recurrent urinary infections. This study was approved by the Ethics Committee of Wuhan Women and Children's Health Care Center and agreed by all participants.

### 2.2 | Sample collection and the detection of PCT and $β_2$-MG

Five milliliter urine and 5 mL venous blood samples were collected and stored in tubes before antibiotics were applied. 2 mL blood was then centrifuged and preserved at temperature ranging from −20 to −70°C. Then enzyme-linked fluorescent analysis was carried out, in which the relevant kits were purchased from Bio Mérieux, Lyons, France. Quantitative measurement was conducted using Mini VIDAS automatic quantitative fluorescence immunoassay analyzer also purchased from Bio Mérieux. The results were considered positive when the PCT concentration was higher than 0.5 ng/mL. Urinary $β_2$-MG levels were detected using DPC1000 automatic chemiluminescence meter (DPC company, Omaha, NE). The relevant kits were purchased from DPC company and the instructions were strictly followed.

### 2.3 | Statistical analysis

Statistical analysis was performed using SPSS 21.0 program (IBM, Armonk, NY). Simple descriptive statistics were used to describe participants' characteristics. Continuous biomarkers in two groups were compared using student *t*-test. Counted data were expressed in the form of frequency and percentage. Differences in counted data were analyzed using the chi-square test. Diagnostic accuracy of makers was evaluated using the ROC curve analysis.

Logistic regression analysis was conducted to determine the correlation between the dependent variable (UUTI) and independent variables (PCT and $β_2$-MG).

## 3 | RESULTS

### 3.1 | Demographic features of participants

Ten boys and 25 girls were enrolled in the UUTI group (age <1 year: n=19, age between 1 and 3 years: n=13, age between 4 and 7 years: n=2, age between 8 and 13 years: n=1). The average age in the UUTI group was 1.55±1.28 years old. The LUTI group consisted of 18 boys and 32 girls (age of <1 year: n=16, age between 1 and 3 years: n=16, age between 4 and 7 years: n=12, age between 8 and 13 years: n=6) with an average age of 3.59±1.81 years old. The age distribution and average age showed significant differences between two groups (P<.01). There were significant differences in clinical symptom of fever between two groups (P=.02), while there were no significant differences in other clinical symptoms (P>.05). The demographic characteristics were shown in Table 1.

### 3.2 | The level and distribution of PCT and urinary $β_2$-MG in UUTI and LUTI groups

The mean level of PCT in the UUTI group was 1.37±0.67 ng/mL, whereas that in the LUTI group was 0.53±0.23 ng/mL. The mean levels of urinary $β_2$-MG in the UUTI and LUTI groups were 1.08±0.73 and 0.39±0.21 µg/mL, respectively. The average levels of serum PCT and

**TABLE 1** The basic information of individuals in UUTI group and LUTI group

|  | UUTI | LUTI | P value |
|---|---|---|---|
| Gender |  |  |  |
| Male | 10 | 18 | .47 |
| Female | 25 | 32 |  |
| Age |  |  |  |
| <1 year | 19 | 16 | .03 |
| 1-3 years | 13 | 16 |  |
| 4-7 years | 2 | 12 |  |
| 8-13 years | 1 | 6 |  |
| Mean age (y) | 1.55±1.28 | 3.59±1.81 | <.01 |
| Symptoms |  |  |  |
| Fever | 5 | 19 | .02 |
| Urinary irritation | 12 | 8 | .05 |
| Gross haematuria | 12 | 8 | .05 |
| Turbid urine | 3 | 5 | .82 |
| Back pain or abdominal discomfort | 6 | 5 | .33 |
| Emesis | 1 | 3 | .50 |
| Hypoevolutism | 0 | 1 | .40 |

**TABLE 2** The expression level of PCT and urinary $\beta_2$-MG inside the participators from UUTI group and LUTI group

|  | UUTI | LUTI | P value |
|---|---|---|---|
| PCT (ng/mL) | 1.37±0.67 | 0.53±0.23 | <.01 |
| Urinary $\beta_2$-MG (μg/mL) | 1.08±0.73 | 0.39±0.21 | <.01 |

PCT, procalcitonin; urinary $\beta_2$-MG, urinary $\beta_2$ microglobulin.

urinary $\beta_2$-MG in the UUTI group were significantly higher than those in the LUTI group, respectively ($P<.05$) (Table 2). The distribution of PCT and urinary $\beta_2$-MG were both left-skewed without extreme values (Figure 1).

## 3.3 | ROC curve of urinary $\beta_2$-MG and PCT for diagnosing UTI

ROC curves of PCT and urinary $\beta_2$-MG for diagnosis of UTI were displayed in Figure 2. The AUC of PCT was 0.902 (95% CI=0.818-0.956;

$P<.01$) whereas that of urinary $\beta_2$-MG was 0.830 (95% CI=0.733-0.903; $P<.01$). AUC of PCT was significantly higher than that of urinary $\beta_2$-MG.

## 3.4 | The optimal cut-off values of PCT and urinary $\beta_2$-MG for diagnosis of UTI

As suggested by ROC curves, the optimal cut-off points of PCT and urinary $\beta_2$-MG were 0.91 and 0.64 ng/mL, respectively (Figure 2). The sensitivity of PCT and urinary $\beta_2$-MG associated with the corresponding cut-off points were 77.1% and 71.4%, respectively, whereas the specificity were 96.0% and 90.0%, respectively (Table 3).

## 3.5 | Diagnostic value of incorporating PCT with urinary $\beta_2$-MG

The logistic regression analysis was conducted to predict the relationship between the dependent variable (UUTI) and independent variables (PCT and $\beta_2$-MG), and a strong association was found. Regression coefficients of PCT and urinary $\beta_2$-MG are 16.39314 ($P=.0001$), −12.4977 ($P=.00070$), respectively. The establishment logistic regression model is as follows log (UUTI)=16.39314×PCT−12.4977×$\beta_2$-MG.

The ROC curves of single as well as combined diagnosis was shown in Figure 2. ROC curve of PCT combined with urinary $\beta_2$-MG had an AUC of 0.943, bigger than PCT or urinary $\beta_2$-MG single diagnosis ($P<.05$).

## 4 | DISCUSSION

Early identification and diagnosis of UTI is important, yet remains challenging because the symptoms of UTI are usually neither apparent nor disease-specific during infancy and early childhood.[28,29] The baseline characteristics analysis showed that urinary irritation and gross hematuria were not significantly different between UUTI and LUTI groups whereas fever and average age demonstrated significant group difference.[30] However, fever is such a common symptom in many infection diseases, thus loses its value in specificity for diagnosis of UTI. The analysis of baseline characteristics in this study further explained the difficulties to distinguish UUTI from LUTI among children through identification of just symptoms.

The misdiagnosis rate of UTI is still unexpectedly high due to the limitation of current diagnostic methods. At present, the urine bacteria



**FIGURE 1** The levels of serum PCT and urinary $\beta_2$-MG in participants. Case 1: children with upper urinary tract infection (UUTI). Case 2: children with lower urinary tract infection (LUTI).
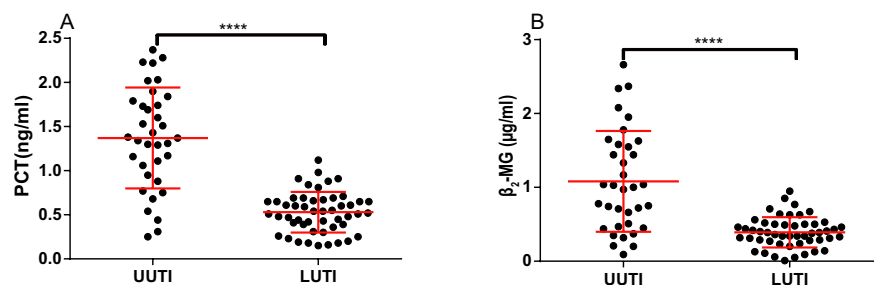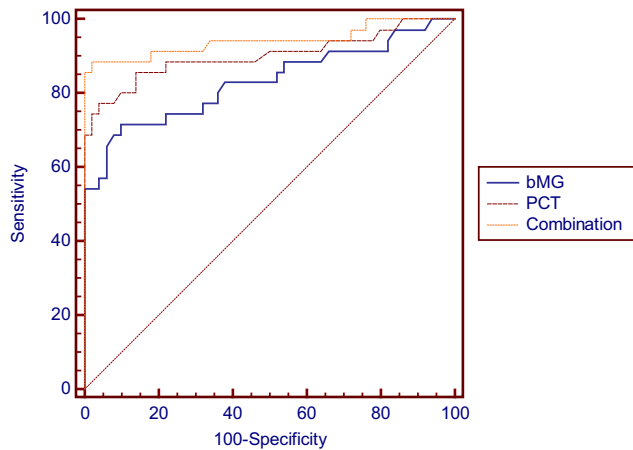
**FIGURE 2** The ROC curves of single diagnosis and combined diagnosis of PCT and urinary $\beta_2$-MG.

**TABLE 3** The value of PCT and urinary $\beta_2$-MG in the localization diagnosis of UTI in children along

| Index | AUC | Cut-off point | Sensitivity % | Specificity % |
|---|---|---|---|---|
| PCT | 0.902 | 0.91 | 77.1 | 96.0 |
| Urinary $\beta_2$-MG | 0.830 | 0.64 | 71.4 | 90.0 |
| Combined | 0.943 | 6.53 | 88.6 | 98.0 |

AUC, area under the curve of ROC.

culture is the most precise method to identify urinary tract infection, but is time-consuming.[13] The $^{99m}$Tc-dimercaptosuccinic acid (DMSA) scintigraphy is a wide-applied sensitive technology for UTI diagnosis, but is too expensive to be popularized nation-widely. In addition, there have been some traditional biomarkers for UTI diagnosis, but few have appropriate specificities.[6,16] Therefore, it is necessary to develop quick, economical, and specific diagnosis approaches for pediatric UTI. Novel molecules such as PCR, CRP, and $\beta_2$-MG, etc. have been identified as biomarkers in diagnosing UTI.[13,30,31]

For localizing acute UTI, proximal tubular dysfunction testing was thought to be more clinically valuable.[25] In addition, $\beta_2$-MG has been reported to be increased significantly in UUTI patients but normal in patients with cystitis, which indicated that $\beta_2$-MG could be used to distinguish UUTI from LUTI. Schardijn et al. long ago pointed out the possibility of applying the urinary $\beta_2$-MG to localization diagnosis of UTI, unless patients simultaneously suffer from pre-existing tubular damage.[30] Similarly, our study revealed that $\beta_2$-MG showed higher concentrations in UUTI urine samples than in LUTI urine samples, indicating that $\beta_2$-MG could be used to distinguish UUTI from LUTI. The ROC analysis also demonstrated that urinary $\beta_2$-MG had good diagnostic accuracy with an AUC value of 0.830, though a little inferior to that of PCT.

Various studies have been done to investigate the diagnostic value of PCT as a biomarker for infection. For instance, Mahajan et al. suggested PCT a more accurate biomarker compared with other indexes such as white blood cell (WBC) count, absolute neutrophil count (ANC), absolute band count.[32] Leroy et al. conducted a meta-analysis,

in which they asserted that PCT concentration was an independent predictor of UTI and vesicoureteral reflux (VUR).[12,33] Garcia de Guadiana-Romualdo et al. suggested the usefulness of PCT as a diagnostic marker for infection in patients with febrile neutropenia.[34] Pecile et al. identified serum PCT as a sensitive indicator for early diagnosis of febrile UTIs in children.[6] Simon et al. performed a meta-analysis and reported that the diagnostic accuracy of bacterial infection in urinary tract with PCT as the marker was higher than that with CPR marker.[13] Likewise, Kotoula et al. also indicated that PCT was a more reliable marker for UTI recognition.[16] PCT test was reported to show a higher likelihood ratio than CRP test in UUTI diagnosis.[10] In addition, the serum PCT level has been recommended to differentiate and predict acute pyelonephritis (assessed by DMSA) from LUTI.[35] Consistently, Smolkin et al. found that the serum PCT level showed excellent diagnosis accuracy and specificity compared with CRP in terms of acute pyelonephritis diagnosis.[15] Likewise, Xu et al. has reported that PCT demonstrated better specificity than CRP in terms of distinguishing acute pyelonephritis from LUTI.[36] Moreover, Sheu et al. discovered that PCT could be an independent risk factor for renal involvement in urinary tract infection.[37]

Our data showed that both serum PCT and urinary $\beta_2$-MG in patients with UUTI were significantly higher than those in patients with LUTI, indicating that both of them could be used in localization diagnosis of UTI. Despite of the good performance of clinical indexes such as WBC count and the demonstrated good prognosis outcomes of single diagnosis of PCT or $\beta_2$-MG, we have not been completely satisfied. Giorgetti et al. have showed that the combined use of urinary $\beta_2$-MG and N-acetyl-beta-D-glucosaminidase (NAG) could raise the sensitivity of diagnosing the acute UTI in contrast with the single application of $\beta_2$-MG or NAG. We thus investigated the diagnosis accuracy, sensitivity, and specificity of innovative combination diagnosis method i.e., the combination of PCT and $\beta_2$-MG. The ROC analysis suggested that the combination of serum PCT and urinary $\beta_2$-MG diagnosis outperformed the two single diagnoses in terms of accuracy, sensitivity, and specificity.

## 5 | CONCLUSION

In summary, the combination of urinary $\beta_2$-MG and serum PCT could increase the localization diagnosis accuracy, specificity, and sensitivity of paediatric UTI. Nonetheless, we consider a further study conducted within a larger paediatric population is required.

## REFERENCES

1. Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. *Pediatr Infect Dis J.* 2008;27:302–308.
2. Mingin GC, Hinds A, Nguyen HT, Baskin LS. Children with a febrile urinary tract infection and a negative radiologic workup: factors predictive of recurrence. *Urology* 2004;63:562–565; discussion 565.
3. Coulthard MG. Is reflux nephropathy preventable, and will the NICE childhood UTI guidelines help? *Arch Dis Child.* 2008;93:196–199.

4. Mori R, Lakhanpaul M, Verrier-Jones K. Diagnosis and management of urinary tract infection in children: summary of NICE guidance. *BMJ*. 2007;335:395–397.

5. Tsalkidou EA, Roilides E, Gardikis S, et al. Lipopolysaccharide-binding protein: a potential marker of febrile urinary tract infection in childhood. *Pediatr Nephrol*. 2013;28:1091–1097.

6. Pecile P, Miorin E, Romanello C, et al. Procalcitonin: a marker of severity of acute pyelonephritis among children. *Pediatrics*. 2004;114:e249–e254.

7. Zhang H, Yang J, Lin L, Huo B, Dai H, He Y. Diagnostic value of serum procalcitonin for acute pyelonephritis in infants and children with urinary tract infections: an updated meta-analysis. *World J Urol*. 2016;34:431–441.

8. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet*. 1993;341:515–518.

9. Mohkam M, Maham S, Rahmani A, et al. Technetium Tc 99m dimercaptosuccinic acid renal scintigraphy in children with acute pyelonephritis: correlation with other imaging tests. *Iran J Kidney Dis*. 2010;4:297–301.

10. Gervaix A, Galetto-Lacour A, Gueron T, et al. Usefulness of procalcitonin and C-reactive protein rapid tests for the management of children with urinary tract infection. *Pediatr Infect Dis J*. 2001;20:507–511.

11. Kassir K, Vargas-Shiraishi O, Zaldivar F, Berman M, Singh J, Arrieta A. Cytokine profiles of pediatric patients treated with antibiotics for pyelonephritis: potential therapeutic impact. *Clin Diagn Lab Immunol*. 2001;8:1060–1063.

12. Leroy S, Gervaix A. Procalcitonin: a key marker in children with urinary tract infection. *Adv Urol*. 2011;2011:397618.

13. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis*. 2004;39:206–217.

14. Zaffanello M, Brugnara M, Franchini M, Fanos V. Is serum procalcitonin able to predict long-term kidney morbidity from urinary tract infections in children? *Clin Chem Lab Med*. 2008;46:1358–1363.

15. Smolkin V, Koren A, Raz R, Colodner R, Sakran W, Halevy R. Procalcitonin as a marker of acute pyelonephritis in infants and children. *Pediatr Nephrol*. 2002;17:409–412.

16. Kotoula A, Gardikis S, Tsalkidis A, et al. Comparative efficacies of procalcitonin and conventional inflammatory markers for prediction of renal parenchymal inflammation in pediatric first urinary tract infection. *Urology*. 2009;73:782–786.

17. Muller B, White JC, Nylen ES, Snider RH, Becker KL, Habener JF. Ubiquitous expression of the calcitonin-i gene in multiple tissues in response to sepsis. *J Clin Endocrinol Metab*. 2001;86:396–404.

18. Prat C, Dominguez J, Rodrigo C, et al. Elevated serum procalcitonin values correlate with renal scarring in children with urinary tract infection. *Pediatr Infect Dis J*. 2003;22:438–442.

19. Mantadakis E, Plessa E, Vouloumanou EK, Karageorgopoulos DE, Chatzimichael A, Falagas ME. Serum procalcitonin for prediction of renal parenchymal involvement in children with urinary tract infections: a meta-analysis of prospective clinical studies. *J Pediatr*. 2009;155:875–881 e871.

20. Inker LA, Tighiouart H, Coresh J, et al. GFR Estimation Using beta-Trace Protein and beta2-Microglobulin in CKD. *Am J Kidney Dis*. 2016;67:40–48.

21. Tubbs KA, Nedelkov D, Nelson RW. Detection and quantification of beta-2-microglobulin using mass spectrometric immunoassay. *Anal Biochem*. 2001;289:26–35.

22. Foster MC, Coresh J, Hsu CY, et al. Serum beta-trace protein and beta2-microglobulin as predictors of ESRD, mortality, and cardiovascular disease in adults with CKD in the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis*. 2016;68:68–76.

23. Kaminska A, Jung A, Olszewski S, Muszynska J, Dadas E. [Beta-2 microglobulinuria in children with vesico-ureteral reflux and recurrent urinary tract infections]. *Pol Merkur Lekarski*. 2000;8:240–241.

24. Chiou YY, Chiu NT, Chen MJ, Cheng HL. Role of beta 2-microglobulinuria and microalbuminuria in pediatric febrile urinary tract infection. *Acta Paediatr Taiwan*. 2001;42:84–89.

25. Sandberg T, Bergmark J, Hultberg B, Jagenburg R, Trollfors B. Diagnostic potential of urinary enzymes and beta 2-microglobulin in acute urinary tract infection. *Acta Med Scand*. 1986;219:489–495.

26. Roberts JL, Lewis EJ. Serum and urine beta-2-microglobulin and lysozyme concentrations in transplant rejection. *Proc Clin Dial Transplant Forum*. 1979;9:145–149.

27. Light JA, Biggers JA, Alijani MR, Smith M, Oddendino K. Serum beta-2-microglobulin: an adjunctive monitoring test in renal transplantation. *Proc Clin Dial Transplant Forum*. 1980;10:67–73.

28. Lutter SA, Currie ML, Mitz LB, Greenbaum LA. Antibiotic resistance patterns in children hospitalized for urinary tract infections. *Arch Pediatr Adolesc Med*. 2005;159:924–928.

29. Hanna-Wakim RH, Ghanem ST, El Helou MW, et al. Epidemiology and characteristics of urinary tract infections in children and adolescents. *Front Cell Infect Microbiol*. 2015;5:45.

30. Schardijn G, Statius van Eps LW, Swaak AJ, Kager JC, Persijn JP. Urinary beta 2 microglobulin in upper and lower urinary-tract infections. *Lancet* 1979;1:805–807.

31. Jantausch BA, Rifai N, Getson P, Akram S, Majd M, Wiedermann BL. Urinary N-acetyl-beta-glucosaminidase and beta-2-microglobulin in the diagnosis of urinary tract infection in febrile infants. *Pediatr Infect Dis J*. 1994;13:294–299.

32. Mahajan P, Grzybowski M, Chen X, et al. Procalcitonin as a marker of serious bacterial infections in febrile children younger than 3 years old. *Acad Emerg Med*. 2014;21:171–179.

33. Leroy S, Romanello C, Galetto-Lacour A, et al. Procalcitonin is a predictor for high-grade vesicoureteral reflux in children: meta-analysis of individual patient data. *J Pediatr*. 2011;159:644–651 e644.

34. Garcia de Guadiana-Romualdo L, Espanol-Morales I, Cerezuela-Fuentes P, et al. Value of lipopolysaccharide binding protein as diagnostic marker of infection in adult cancer patients with febrile neutropenia: comparison with C-reactive protein, procalcitonin, and interleukin 6. *Support Care Cancer*. 2015;23:2175–2182.

35. Benador N, Siegrist CA, Gendrel D, et al. Procalcitonin is a marker of severity of renal lesions in pyelonephritis. *Pediatrics*. 1998;102:1422–1425.

36. Xu RY, Liu HW, Liu JL, Dong JH. Procalcitonin and C-reactive protein in urinary tract infection diagnosis. *BMC Urol*. 2014;14:45.

37. Sheu JN, Chang HM, Chen SM, Hung TW, Lue KH. The role of procalcitonin for acute pyelonephritis and subsequent renal scarring in infants and young children. *J Urol*. 2011;186:2002–2008.