ปัจจัยทำนายภาวะติดเชื้อในกระแสโลหิตในผู้ป่วยติดเชื้อทางเดินปัสสาวะจากชุมชน : การศึกษาแบบสังเกตการณ์ไปข้างหน้า

Predicting Factors for Bacteremic Urinary Tract Infection in Community Setting : a Prospective Observational Study

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วัตถุประสงค์: เพื่อศึกษาลักษณะทางคลินิกและการตรวจทางห้องปฏิบัติการพื้นฐานในการทำนายภาวะติดเชื้อในกระแสโลหิต

วัสดุและวิธีการศึกษา: เป็นการศึกษาไปข้างหน้าในผู้ป่วย 106 ราย ที่เข้ารับการรักษาในโรงพยาบาลนครปฐม ระหว่างเดือนธันวาคม 2558 ถึงเดือนสิงหาคม 2559 กลุ่มตัวอย่างที่เลือกเข้าทำการศึกษาคือ ผู้ป่วยอายุมากกว่า 18 ปี มีไข้ ร่วมกับอาการของการติดเชื้อทางเดินปัสสาวะอย่างน้อย 1 อาการ และตรวจพบภาวะเม็ดเลือดขาวในปัสสาวะ ทำการวิเคราะห์ข้อมูลด้วยการวิเคราะห์การถดถอยโลจิสติกพหุนามเพื่อหาปัจจัยทางคลินิก และการตรวจทางห้องปฏิบัติการเพื่อหาปัจจัยทำนายภาวะติดเชื้อในกระแสโลหิตในผู้ป่วย

ผลการศึกษา: ผู้ป่วย 16 ราย (ร้อยละ 15) มีภาวะติดเชื้อในกระแสโลหิต ปัจจัยที่สัมพันธ์กับภาวะติดเชื้อในกระแสโลหิต ได้แก่ ระดับ C-reactive protein มากกว่าหรือเท่ากับ 20 มก/ดล. (adjusted OR = 10.8; 95%CI: 1.3, 93.4, p = 0.03) และ BUN/Cr ratio มากกว่าหรือเท่ากับ 16 (adjusted OR = 4.5; 95%CI: 1.1, 18.7, p = 0.04)

สรุป: C-reactive protein และ BUN/Cr ratio เป็นการตรวจที่ง่าย ทราบผลได้เลยตั้งแต่แรก สามารถนำมาใช้ทำนายการเกิดภาวะติดเชื้อในกระแสโลหิตในผู้ป่วยติดเชื้อทางเดินปัสสาวะจากชุมชน

คำสำคัญ : ติดเชื้อทางเดินปัสสาวะ ปัจจัยทำนายภาวะติดเชื้อในกระแสโลหิต
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ABSTRACT

Objective: To evaluate the clinical and simple laboratory parameters to predict risk of bacteremia in patients presented with community-acquired UTI.

Material and methods: This prospective observational study was conducted on 106 patients at Nakhonpathom Hospital during December 2014 and August 2015. Inclusion criteria were age ≥ 18 years, fever, presence of at least 1 symptom of UTI, and pyuria. Clinical factors and laboratory data associated with bacteremia were analyzed by multivariable logistic regression.

Result: Sixteen patients (15%) had bacteremia. The probability of bacteremia increased with C-reactive protein level ≥ 20 mg/dl (adjusted OR 10.8; 95%CI: 1.3, 93.4, p = 0.03) and BUN/Cr ratio ≥ 16 (adjusted OR 4.5; 95%CI: 1.1, 18.7, p = 0.04)

Conclusions: C-reactive protein and BUN/Cr ratio are simple, rapid and can be utilized to predict bacteremia in patients presented with community-acquired UTI.

Keywords : urinary tract infection, predictors of bacteremia
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Introduction

Urinary tract infection (UTI) is among the most common community acquired bacterial infection.[1] Up to half of all women experience UTI sometime during their lifetime.[2] Most patients presented with uncomplicated illness. An outpatient therapy for selected patients is as safe as inpatient therapy and is much less expensive[3] However, bloodstream infection complicating UTI is observed in 15-33% of cases.[4-7] Mortality was higher in bacteremic patients (7.5-30%) when compared to those who were not (0.3%).[2,8]

Predicting risk of bacteremia can help the clinicians determine the appropriate site of care and therapy. Hemoculture is currently the gold standard for detection of bacteremia, nevertheless it is time-consuming and the results are not available immediately.[9-10] Numerous factors influence the likelihood of detecting bacteremia, including the volume and the number of blood cultures performed. False negative result was very common when blood was taken in the presence of ongoing antibiotics treatment.[11] Moreover, there are limited laboratory capacities for microbiologic culture in several resource limited healthcare settings.

Previous studies were performed on factors predicted bacteremia in UTI patients. These predictors included: (1) demographic characteristics e.g., old age, diabetes, neurologic disease, receiving corticosteroid and/or immunosuppressive therapy; (2) clinical manifestations e.g., tachycardia, chill, vomiting; (3) laboratory findings e.g., a high leukocyte count in urine, bandemia, neutrophilia, lymphopenia, high c-reactive protein (CRP), high procalcitonin (PCT) and low albumin level.[5,7,12-19]

The objectives of this study was to identify clinical and laboratory characteristics to predict bacteremia in community-acquired UTI.

Material and methods

Study design and ethical issues

The study was conducted as part of “a prospective, open-label, randominzed multicenter study to compare the efficacy and

safety of oral sitafloxacin with a subsequent regimen of intravenous ceftriaxone followed by oral cefdinir in the treatment of cUTI and APN in asian population"

This prospective study was conducted at Nakhonpathom Hospital, a 670-bed tertiary care hospital that provides both primary and tertiary care in central Thailand during December 2014 and August 2015. The study was approved by the local ethics committees and all included patients gave written informed consent.

Inclusion and exclusion criteria

Patients who admitted to hospital and met the inclusion criteria were enrolled. Inclusion criteria were age ≥ 18 years, fever, presence at least 1 symptom of UTI (dysuria, frequent or urgent urination, flank pain or costovertebral tenderness), and pyuria (defined by a presence of ≥ 5 WBC per high power field in a centrifuged sediment).

Patients were excluded if they: (1) were pregnancy or lactation (2) presented with nosocomial infection (defined as infection that presented 48hr after hospitalization or within 4 weeks after a previous hospital discharge); (3) had taken antibiotics during 72 hour prior to hospitalization; (4) had history of urologic examination by manipulation or with instruments within 1 month; (5) were admitted with an indwelling urinary catheter; (6) had immune-compromising illness (HIV infection, corticosteroid or immunosuppressive treatment); (7) had kidney failure (defined as an estimated or measured glomerular filtration rate < 60 ml/min/1.73 m^2); (8) presented with severe sepsis/septic shock.

Clinical factors associated with bacteremia including demographics, medical history, symptoms and signs were collected. Laboratory data were obtained at the time of admission, before the start of the antibiotic therapy. These included complete blood counts, blood urea nitrogen, creatinine, liver function tests, ESR, CRP and urine culture.

Two aerobic culture bottles were obtained from blood before administering antibiotics and incubated for at least 5 days. All isolates were identified by standard microbiologic procedures. The following isolates were considered to be contaminants: coagulase-negative staphylococci, *Corynebacterium* sp., *Bacillus* sp., *Micrococcus* sp., *Propionibacterium* sp. and *Diphteroid* sp.

Statistical analysis

All statistical analysis was performed using SPSS v. 16.0 (SPSS Inc., Chicago, IL, USA). The chi-square test and Student's t test were used for hypothesis testing as appropriate. Two tailed p-values of 0.05 or less were regarded as significant. For logistic regression analysis, all variables with $p < 0.1$ on univariate analysis were entered into the multivariate model. Odds ratios (OR) and 95% confidence interval (CI) were calculated for risk estimates.

Results

Patient characteristics and microbiologic results

A total of 106 patients were included in the study. The median age was 46 years (range 18-70 year) and 99 (93%) were female. Twenty-

two patients (21%) had diabetes mellitus, while 9 (8%) and 4 (4%) had stone, and structural abnormality of urinary system, respectively. Details of the baseline characteristics are listed in table 1.

Urine cultures revealed the following: *Escherichia coli*, n = *38* (36%); Methicillin sensitive *Staphylococcus aureus*, n = 1; *Proteus mirabilis,* n =1; *Enterobacter aerogenes,* n = 1; *Staphylococcus saprophyticus,* n = 1; *Citrobacter diversus,* n = 1 and negative urine culture, n = 63 (59%). In those of whom no definite uropathogen was isolated, had antibiotic treatment at the hospital before obtainment of the urine culture sample.

Bacteremia was present in 16 (15%) patients: *E.coli*, *n* = 13, (81%); MSSA *n* = 2, (13%); and *P.mirabilis*, *n* = 1 (6%). Six of 13 isolates (46.2%) of *E.coli* were ESBL producer.

There were no deaths due to UTI in this study.

Table 1 Baseline characteristic of patients presented with UTI

Variables	No (%) of patients
Median age, years (min ; max)	46 (18 ; 70)
Female	99 (93)
Underlying diseases	
-DM	22 (21)
-KUB stone	9 (8)
-KUB structural abnormality	4 (4)
Clinical presentations	
-Chill	61 (58)
-Mean temperature, ℃ (±S.D.)	37.9 (1.1)
-Mean arterial pressure, mmHg (±S.D.)	91 (14)
Complete blood count	
-Median WBC, cells x10^3/mm^3 (min ; max)	12.4 (1.5 ; 31.1)
-Median neutrophil, percent (±S.D.)	76.7 (11.4)
-Median lymphocyte, percent (±S.D.)	18.1 (10.6)
-Median NLC ratio (±S.D.)	7.3 (5.3)
-Median CRP, mg/dl (min ; max)	48.1 (0.4 ; 482.1)
-Median ESR, mm/hr (min ; max)	58 (9 ; 105)
-Median BUN/Cr ratio (min ; max)	15 (6 ; 31)

Predictors of bacteremia

Univariate analysis revealed that bacteremic patients were more likely to be older (54 ± 13 vs 42 ± 17 year, p = 0.004). A higher prevalence of diabetes mellitus was found in bacteremic group (40% vs 16%, p = 0.04). Most of the patients (94%) with bacteremia presented with shaking chills, whereas only half of non-bacteremia group had shaking chills at presentation. Higher body temperature at the time of admission were documented among bacteremic patients (38.5 ± 0.9 vs 37.8 ± 1.1 ℃, p = 0.04). Regarding of laboratory findings, CRP level was higher in bacteremic group than those in non-bacteremic group (101.9 vs 29.1 mg/dl, p = 0.05), whereas there was no significant difference in WBC count, neutrophil leucocyte count (NLC) ratio, ESR, and albumin levels between two groups (table 2).

Table 2 Clinical factors associated with bacteremia

Variables	No. (%) of patients		P-value
	Bacteremia (n =16)	No bacteremia (n = 90)	
Mean age, years (±S.D.)	54 (13)	42 (17)	0.004
Female	12 (80)	87 (96)	0.06
Underlying diseases			
-DM	6 (40)	15 (16)	0.04
-KUB stone	2 (13)	7 (8)	0.61
-KUB structural abnormality	0	2 (2)	1.0
Clinical presentations			
-Chill	15 (94)	46 (51)	0.01
-Mean temperature, ℃ (±S.D.)	38.5 (0.9)	37.8 (1.1)	0.04
-Mean arterial pressure, mmHg (±S.D.)	90 (15)	91 (14)	0.81
-Mean heart rate (±S.D.)	100 (14)	96 (19)	0.43
Complete blood count			
-Median WBC, cells x10^3/mm^3 (min ; max)	13.2 (8.1 ; 24.4)	12.2 (1.5 ; 31.1)	0.72
-Median neutrophil, percent (±S.D.)	78.5 (6.3)	76.4 (12.0)	0.36
-Median lymphocyte, percent (±S.D.)	15.4 (7.1)	18.5 (11.0)	0.57
-Median NLC ratio (±S.D.)	6 (4.5)	7 (5.4)	0.70

Table 2 Clinical factors associated with bacteremia (con.)

Variables	No. (%) of patients		P-value
	Bacteremia (n =16)	No bacteremia (n = 90)	
-Median ESR, mm/hr (min ; max)	69 (19 ; 96)	54 (9 ; 105)	0.25
-Median BUN/Cr ratio (min ; max)	17.6 (9.0 ; 29.0)	14.9 (6.0 ; 31.0)	0.14
-BUN/Cr ratio ≥ 16	10 (67)	35 (41)	0.07

Clinical variables that were found to have an association with the presence of bacteremia with a *p*-value < 0.1 were entered as covariates into a multivariable logistic regression model. CRP level ≥ 20 mg/dl (adjusted OR = 10.8; 95%CI: 1.3, 93.4, p = 0.03) and BUN/Cr ratio ≥ 16 (adjusted OR = 4.5; 95%CI: 1.1, 18.7, p = 0.04) were associated with increased risk of bacteremia in patients presented with UTI (table 3).

Table 3 Multivariable logistic regression of factors predicting bacteremia in UTI patients

Factors	Odds ratio	95%CI	*p*-value
Age ≥ 60 year	2.5	0.8-8.4	-
Male sex	0.2	0.04-0.9	-
Temperature ≥ 38 °C	2.6	0.7-9.0	-
CRP ≥ 20 mg/dl	10.8	1.3, 93.4	0.03
BUN/Cr ratio ≥ 16	4.5	1.1, 18.7	0.04

Discussion

We demonstrated several clinical and laboratory parameters for predicting bacteremia in adult patients with UTI. Older age and diabetes were the host-related risk factors for bloodstream infection, similar to that observed in previous reports.[5,12,15,17] We also found a statistically significant relationship between bacteremia and clinical presentations such as high temperature and shaking chills.[5,13,16,17]

CRP level was significantly higher among bacteremic group. CRP level ≥ 20 mg/dl showed statistical significance in predicting bacteremia in our study. It is one of the acute phase proteins with a short half-life, rapidly increase during inflammation or infection. There have been three studies evaluated role of CRP for predicting risk of bacteremia in UTI patients but the results were inconclusive. Two retrospective study reported the association of

increased CRP[7,16] whereas one did not.[17] Further studies should be conducted prior to reaching the conclusions.

Patients with bacteremia had significantly higher BUN/Cr ratio than did those without. At a cut-off of 16, BUN/Cr ratio identified patients suffering from bacteremia. One study demonstrated the correlation of BUN/Cr ratio above 16 and risk of bacteremia among patients suspected of community acquired infection.[18] This finding may be explained by patients with bacteremia had more severe infection and high degree of dehydration compared to the other group, which in effect raises the BUN/Cr ratio.

The limitations of this study are the small sample size, single-centered-hospital-based study, only included patients in community setting and excluded patients with abnormal renal function. These may limit the generalization of findings. Therefore a large scale study can be suggested.

Conclusion

This study suggests that CRP and BUN/Cr ratio can be used to predict risk of bacteremia and may have important practical use in triage and hospitalization decisions for UTI patients in community setting.

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