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Positive blood cultures in outpatients: predictors of poor outcome

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Introduction : *Blood culture is a standard diagnostic test for bacteremia. In patients with suspected bacteremia who are treated as outpatients, blood cultures are commonly performed before discharge.*

Objective : *To identify the predictors of poor outcome in patients discharged from the Outpatient Department (OPD) and the Emergency Departments (ED).*

Setting : *King Chulalongkorn Memorial Hospital*

Research design : *A retrospective study based on medical record review.*

Patients : *All patients with positive blood culture who were treated as outpatients from September 2005 to December 2006.*

Methods : *Demographic data, history of present illness, medical history, physical examination, and laboratory investigation of 53 eligible patients were retrospectively reviewed. Univariate and multivariate analyses were used to identify independent prediction factors of poor outcome.*

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Results : *Hemoglobin in patients with poor treatment outcome was significantly lower than those with good outcome. (9.9 vs 11.8 g/dl, $p < 0.05$). No significant difference in the age, WBC count, percentage of neutrophils, antibiotic administration before discharge, and proportion of true pathogen in positive blood culture was demonstrated among patients with good and poor outcome.*

Conclusion : *In this study low hemoglobin was shown to be a predictor of poor outcome in hemoculture-positive outpatients.*

Keywords : *Blood culture, Bacteremia, Outpatients, Predictors.*

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ครองวงศ์ มุสิกถาวร, พงศ์ธร เกียรติดำรงวงศ์, กัญชลี เลิศโภคะสมบัติ, กนิษฐา ภัทรกุล. การศึกษาเพื่อหาตัวทำนายผลการรักษาในผู้ป่วยที่มีการเพาะเชื้อจากเลือดให้ผลบวกโดยได้รับการรักษาแบบผู้ป่วยนอกที่โรงพยาบาลจุฬาลงกรณ์. จุฬาลงกรณ์เวชสาร 2551 พ.ย. – ธ.ค.; 52(6): 431 – 45

บทนำ : *การเพาะเชื้อจากเลือดถือเป็นวิธีการตรวจทางห้องปฏิบัติการที่เป็นมาตรฐานในการใช้วินิจฉัยการติดเชื้อในกระแสเลือด และเป็นการส่งตรวจที่พบบ่อยในผู้ป่วยที่สงสัยมีการติดเชื้อในกระแสเลือดที่ได้รับการรักษาแบบผู้ป่วยนอก*

วัตถุประสงค์ : *เพื่อหาตัวทำนายผลการรักษาในผู้ป่วยที่มีการเพาะเชื้อจากเลือดให้ผลบวกโดยได้รับการรักษาแบบผู้ป่วยนอก*

สถานที่ที่ทำการศึกษา : *โรงพยาบาลจุฬาลงกรณ์*

รูปแบบการวิจัย : *การศึกษาแบบย้อนหลังโดยอาศัยการทบทวนบันทึกทางการแพทย์*

ผู้ป่วยที่ได้ทำการศึกษา : *ผู้ป่วยที่มีผลการเพาะเชื้อจากเลือดให้ผลบวก โดยได้รับการรักษาแบบผู้ป่วยนอกตั้งแต่เดือนกันยายน พ.ศ.2547 ถึงเดือนธันวาคม พ.ศ.2549*

วิธีการศึกษา : *ผู้วิจัยได้ทำการรวบรวมข้อมูลทางระบาดวิทยา ประวัติการเจ็บป่วยปัจจุบันโรคประจำตัว ผลการตรวจร่างกาย และผลการตรวจทางห้องปฏิบัติการณ์ของผู้ป่วยที่มีผลการเพาะเชื้อจากเลือดให้ผลบวกโดยได้รับการรักษาแบบผู้ป่วยนอก จำนวน 53 ราย และนำมาใช้หาตัวทำนายผลการรักษาโดยใช้วิธีทางสถิติแบบ univariate และ multivariate*

ผลการศึกษา : *ระดับฮีโมโกลบินในกลุ่มผู้ป่วยที่มีผลการรักษาไม่ดีมีค่าต่ำกว่ากลุ่มผู้ป่วยที่มีผลการรักษาดี (9.9 และ 11.8 g/dl) แต่ผู้ป่วยทั้ง 2 กลุ่มไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติในด้านอายุ จำนวนเม็ดเลือดขาวและร้อยละของเม็ดเลือดขาวชนิดนิวโตรฟิลในเลือด การให้ยาปฏิชีวนะก่อนอนุญาตให้กลับบ้าน และสัดส่วนการให้ผลการเพาะเชื้อจากเลือดเป็นผลบวกจริง*

บทสรุป : *ในการศึกษานี้พบว่าระดับฮีโมโกลบินต่ำเป็นตัวทำนายผลการรักษาที่ไม่ดีในผู้ป่วยที่มีการเพาะเชื้อจากเลือดให้ผลบวกโดยได้รับการรักษาแบบผู้ป่วยนอก*

คำสำคัญ : *การเพาะเชื้อจากเลือด, การติดเชื้อในกระแสเลือด, ผู้ป่วยนอก, ตัวทำนายผล*

Blood culture is considered to be the gold standard test for diagnosing bacteremia. It is a commonly ordered laboratory investigation at the Outpatient Department (OPD) and Emergency Department (ED). Patients with bacteremia may present with fever as their chief complaint or as one of associated symptoms. Early diagnosis is required for appropriate management. However, the definite diagnosis may not be certain due to the absence of specific symptoms of localized organ involvement. Patients are discharged from the OPD or the ED if their conditions do not meet the criteria for admission, which are usually based on their severity at presentation including the presence of signs and symptoms of sepsis, hemodynamic instability, and requirement for in-hospital care such as administration of parenteral antibiotics. If bacteremia cannot be excluded, blood cultures are performed before discharge. However, the results of blood cultures are not immediately available. To facilitate early diagnosis and proper treatment in our institute, physicians are promptly notified of all cases with positive blood cultures regardless of their admission status. In outpatient cases, ED physicians are responsible for making contact with these patients to obtain their current clinical status and requirement for hospitalization.

Previous studies demonstrated a poor yield for blood cultures taken at ED resulting in its little influence on clinical management.[1-4] Unfortunately, contamination of blood cultures has also been reported to be a common problem that may lead to errors in clinical interpretation and treatment.[5] Hence, identification of the factors that increase the likelihood of obtaining true pathogens from blood cultures is useful and will therefore improve the cost-effectiveness of this procedure. Identification of patients at high risk for poor outpatient treatment outcome at the early stage could help target patients who should be hospitalized instead of being discharged from the OPD and the ED. Therefore, in the current study, we retrospectively reviewed data of blood culture-positive patients who were discharged from OPD and ED to identify the clinical predictors of poor treatment outcome among those patients.

Materials and Methods

Study patients

King Chulalongkorn Memorial (KCM) Hospital is a 1,500-bed, university-affiliated tertiary care hospital in Bangkok, Thailand.

We conducted a retrospective study by screening medical records of all patients who presented at OPD and non-trauma ED of KCM Hospital and had positive blood cultures during a sixteen-month period (September 2005 to December 2006). Included in the study were patients above the age of 15 years who were suspected to have infection and had a positive blood culture result in at least 1 specimen, had no clinical presentations of sepsis or unstable hemodynamic status, and were discharged from the OPD and ED after obtaining blood samples. Cases were excluded if their clinical conditions were required for hospitalization and were admitted either at KCM or transferred to other hospitals.

Study protocol

A retrospective design was utilized. Blood culture of the patient from OPD and ED must be done at least one specimen according to the physician's

consideration. All positive blood cultures during the study period were identified by assigned laboratory personnel and promptly notified to the ED physicians. Patients with positive blood cultures who were discharged as outpatients for home care were included in the study. The patients or their family members were contacted by the ED physicians to determine their current clinical status and whether they subsequently accessed an acute care service at any medical centers within two weeks of blood culture draw. The information was used to determine the outcome of the patients.

All medical records of 53 eligible subjects were reviewed. The basic demographic information, patient history, clinical presentations, laboratory data including hematologic, biochemical, and microbiological results obtained at the same date of blood sample draw were recorded (Table 1). The data were coded in the record forms and subsequently filled in the datasheet of Statistical Package for Social Sciences version 13.0 (SPSS, Chicago, IL, USA) for further data analysis at the end of study period.

Laboratory procedures

All blood samples were cultured at the Bacteriology Laboratory of the Department of Microbiology, Faculty of Medicine, Chulalongkorn University using the VersaTREK automated instrument (TREK Diagnostic Systems, Inc., Ohio, USA). A blood culture set consisted of one to three aerobic culture bottles obtained from a single or multiple blood draw with approximately 15 to 30 minutes time interval. Five to ten milliliters of freshly drawn blood was inoculated into the culture bottle as manufacturer instruction. Inoculated bottles were incubated at 37°C and continuously read for growth in VersaTREK cabinets.

Table 1. Possible risk factors included in the medical record review.

Risk factors	
Demographic data	Age, gender
History of present illness	Duration of fever, presence of organ-specific symptoms, presence of chills or rigor
Medical history	Comorbidity
	Current use of antibiotics
	Smoking and alcohol intake history
	Nosocomial acquisition
	Presence of indwelling catheter or prosthetic device
Physical examination	Vital signs, presence of abnormal physical findings
Laboratory investigation	Hematological (complete blood count (CBC): hemoglobin, hematocrit, leukocyte count, percentage of granulocytes, platelet count)
	Urine analysis
	Stool exam
	Biochemical (blood urea nitrogen, serum creatinine, liver function tests)
	Microbiological (hemoculture, sputum Gram stain, sputum acid-fast stain, sputum modified acid-fast stain)Chest roentgenogram

The bottle with positive signal was subsequently processed according to standard microbiological techniques to identify the organism. All positive blood culture results were reported to the ED physicians regardless of microbiological significance. The significance of the blood culture isolate and/or definite source of infection was reviewed by at least two physicians in the study.

Physicians independently made decisions as to number of blood culture specimens in a set and inquiry of other laboratory data (e.g., hematological, biochemical, microbiological, and radiographic investigation) for individual patient at the time of presentation.

Definitions of terms

Co-morbidity was defined as a disease or therapy that could predispose a patient to infection, alter defense mechanisms, or cause functional impairment, such as diabetes mellitus, liver cirrhosis, renal failure, chronic obstructive pulmonary disease, severe heart disease with symptomatic heart failure, active neoplastic disease, immunosuppressive condition including HIV infection and non-HIV related diseases, administration of immunosuppressive drugs, presence of indwelling catheter.

Current use of antibiotics was defined as a use of any antimicrobial agent for at least 3 days during the week prior to blood culture drawn.

Nosocomial acquisition was defined in patients who had been hospitalized within two weeks prior to presentation or in those who had been transferred from another hospital or nursing home.

The definition of sepsis was based on criteria reported by the American College of Chest Physicians and the Society of Critical Care Medicine's consensus.[6]

We defined patients with clinical deterioration who required medical therapy or hospitalization due to infection-related cause before their follow-up appointments as having a poor treatment outcome. In the contrary, patients with clinical improvement, who neither had further medical therapy nor admission to hospital within two weeks of blood culture draw or before their hospital appointments were designated as having a good treatment outcome.

A significant bacteremia was defined as the growth of the same pathogenic organism from at least two bottles or the growth of clinically relevant pathogenic organism from at least one bottle of blood culture set. The organism was then considered as a true pathogen. Positive blood culture from only one bottle of common contaminants including coagulase-negative staphylococci (CoNS), viridans group streptococci, *Micrococcus*, *Bacillus*, *Corynebacterium*, or *Propionibacterium* species, with no clinical correlation was defined as contamination.

Statistical analysis

Statistical analysis was performed using SPSS version 13.0. Continuous variables were expressed as mean and standard deviation (± SD) or median (range) according to their distribution and homogeneity.

Univariate analysis

Univariate analysis was carried out using crossed tabs chi-square test with 95% confidence interval (95% CI).

Multivariate analysis

Variables that had low p value in the univariate analysis or had potential clinical value were further entered as covariates into binary logistic regression model to identify independent predictive features associated with true pathogen and poor clinical outcome. The results were reported as an adjusted odds ratio with 95% CI and p value.

P value of less than 0.05 was considered significant in all statistical analysis.

Results

Demographics

During the sixteen-month period of data collection, 569 blood culture specimens were collected at OPD or ED. 53 patients had any of their blood culture specimens grown for an organism. Of the 53 patients, 54 blood culture specimens out of 83 were positive for any organism. Demographic data of all eligible cases is shown in Table 2. The patient ages ranged from 20 to 83 years old with the mean ± SD of 43.1 ± 18.4 years old. Forty-three (81.1 %) patients were 60 years old or younger. Thirty-one (58.5%) patients were female. Forty-four patients (83 %) had fever as a chief complaint or associated symptom. However, twenty (37.7%) patients had no fever (body temperature below 37.8°C) at the time of presentation. Duration of fever varied between 2 hours and 90 days (median of 5 days). Onset of fever was within 72 hours and 7 days in 20 patients (37.7%) and 35 patients (66%), respectively. The most common organ-specific symptoms were related to urinary tract infection (12 of 53 cases). Twelve patients (22.6%) had history of chills. Preexisting medical illnesses were reported in twenty-two (41.5%) patients. Fourteen cases (26.4%) had been diagnosed with HIV infection, which was the most common co-morbidity in the study. Data of CD_4 cell count within the 6-month period was available in only 7 HIV-positive patients and six of them had CD_4 cell count of less than 200/mm.^{3} Four patients (7.5%) currently took antibiotics prior to their hospital visit. In addition to blood culture, the most common laboratory procedures that had been investigated simultaneously were complete blood count (CBC) in 49 cases (92.5%), followed by serum creatinine in 33 cases (62.3%), blood urea nitrogen (BUN) and urine analysis in 32 cases (60.4%), and chest roentgenogram in 22 cases (41.5%) of total 53 cases (Table 3). Abnormal findings were demonstrated in 79.6% (39 of 49 cases), 18.2% (6 of 33 cases), 40.6% (13 of 32 cases), and 50% (11 of 22 cases), respectively (Table 3).

Etiology of positive blood cultures

The rate of blood culture to yield true pathogenic organism in our outpatients was 2.11% (12/569). The most frequently isolated pathogen was *E. coli,* followed by *Salmonella* spp. and *S. aureus* (Table 4). The growth of 42 potential contaminants was found in 41/53 patients (77.4%). The most common contaminants were coagulase-negative staphylococci (CoNS; 30 of overall 42 contaminant isolates) (Table 4). One blood sample grew two different contaminants, which were *Micrococcus* spp. and *Moraxella* spp. *Alcaligenes* spp. was considered to be a contaminant in one sample. It is noteworthy to mention that anaerobic blood culture is not part of routine blood culture set at our hospital. After medical record review, no anaerobic blood culture was found to be performed in any patients included in the present study.

Table 2. Characteristics of 53 blood culture positive patients included in the study.

Characteristic	Occurrence n = 53 (%)
Demographic data	
Age	
≤ 60 years old	43 (81.1)
> 60 years old	10 (18.9)
Gender	
male	22 (41.5)
female	31 (58.5)
History of present illness	
Fever	44 (83.0)
onset of fever	
≤ 3 days	20 (37.7)
4-7 days	15 (28.3)
> 7 days	9 (17.0)
Organ-specific symptoms	
urinary tract infection	
gastrointestinal or hepatobiliary tract infection	12 (22.6)
respiratory tract infection	4 (7.5)
soft tissue infection	8 (15.1)
Chills	2 (3.8)
Medical history	12 (22.6)
Comorbidity	
diabetes mellitus	22 (41.5)
renal insufficiency	3 (5.7)
chronic liver disease	0 (0)
chronic obstructive pulmonary disease	0 (0)
hemoglobinopathy	0 (0)
malignancy	2 (3.8)
Immunosuppressive condition	1 (1.9)
HIV infection	16 (30.2)
known CD_4 cell count (within 6 mo)	14 (26.4)
< 200 /mm^3	7/14 (50.0)*
≥ 200 /mm^3	6/7 (85.7)*
non-HIV infection	1/7 (14.3)*
Current use of antibiotics	2 (3.8)
Smoking history	4 (7.5)
Alcohol intake history	0 (0)
Nosocomial acquisition	2 (3.8)
Presence of indwelling catheter	0 (0)
Physical examination	0 (0)
Body temperature ≥ 37.8 °C	
Abnormal physical findings	33 (62.3)
	23 (43.3)

* percentage in the parenthesis was calculated based on total number of patients with available data

Table 3. Other laboratory investigation performed among 53 eligible patients and percentage of abnormal findings.

Laboratory investigation	**abnormal finding/total laboratory performed (%)**
Hematological (complete blood count; CBC)	39/49 (79.6)
Biochemical	
blood urea nitrogen	2/32 (6.3)
serum creatinine	6/33 (18.2)
liver function test	7/22 (31.8)
Urine analysis	13/32 (40.6)
Stool exam	1/11 (9.1)
Microbiological	
sputum gram stain	2/6 (33.3)
sputum acid-fast stain	2/4 (50.0)
sputum modified acid-fast stain	1/3 (33.3)
chest roentgenogram	11/22 (50.0)

Table 4. True pathogens and contaminants among 53 patients with blood culture positive

Organism	**Occurrence n=53* (%)**
True pathogens	12 (22.6)
Escherichia coli	4 (7.5)
Non-typhoidal *Salmonella* spp.	3 (5.7)
Staphylococcus aureus	2 (3.8)
Rhodococcus equine	1 (1.9)
Cryptococcus neoformans	1 (1.9)
Moraxella spp.	1 (1.9)
Contaminant organisms	42 in 41 patients (77.4)
coagulase-negative staphylococci	30 (56.6)
Bacillus spp.	4 (7.5)
Micrococcus spp.	4 (7.5)
Corynebacterium spp.	2 (3.8)
Moraxella spp.	1 (1.9)
Alcaligenes spp.	1 (1.9)

* n (%) was calculated based on total number of cases (53); total number of organisms was 54 due to 2 organisms reported in 1 case

Predictors associated with poor outcome in patients with positive blood culture

To identify factors associated with poor outcome, six factors were further analyzed by binary logistic regression model (Table 5). Of 53 patients, 49 patients had sufficient data of all six variables in the medical records. Patients with poor outcome had significantly lower hemoglobin than those with good outcome (11.8 *vs* 9.9 g/dl; $p < 0.05$). However, there was no difference in the age, WBC count, percentage of neutrophils, antibiotic administration before discharge, and proportion of true pathogen in positive blood culture. Twenty-five patients (47.1%) received antibiotics before discharge. Ceftriaxone at a dose of either 1 or 2 grams was the most commonly prescribed empirical antibiotics (17 of 25 patients). Twelve of them received a single dose of Ceftriaxone and 5 cases had additional oral antibiotics such as fluoroquinolone or macrolide as home medication.

Discussion

Due to the considerable healthcare reform in recent years, treatment of patients as community-based outpatients has been enhanced to reduce the cost of hospitalization. The performance of blood culture before discharge is a common practice on outpatients with suspected bacteremia. However, clinicians must determine whether positive blood culture represents clinically significant bloodstream infection associated with great risk of morbidity and mortality. This study aimed to identify predictors of poor clinical outcome in blood culture-positive outpatients at the OPD and ED. The information obtained from the study may guide clinicians to a better decision to admit patients with increased risk of poor clinical outcome when being treated as outpatients.

Table 5. Predictors of poor treatment outcome in blood culture-positive patients.

Variable	Treatment outcome		Odds ratio (95% CI)	p value
	Good (n=34)	Poor (n=15)		
Age (years; mean ± SD)	46.1 ± 18.6	37.2 ± 18.1	0.96 (0.92-1.00)	0.067
Hemoglobin (g/dl; mean ± SD)	11.8 ± 3.0	9.9 ± 3.0	0.77 (0.59-0.99)	0.046*
WBC count (/mm^3; mean ± SD)	10.7 ± 7.1	11.5 ± 5.4	1.00 (1.00-1.00)	0.609
%Neutrophil (mean ± SD)	72.8 ± 15.0	75.3 ± 14.5	1.04 (0.98-1.10)	0.128
Antibiotic administration before discharge (%)	15/34 (44.1)	10/15 (66.7)	1.50 (0.33-6.85)	0.601
Positive blood culture result of true pathogen (%)	7/34 (20.6)	3/15 (20.0)	0.34 (0.05-2.32)	0.273

*p-value < 0.05

Our finding that *E. coli*, the most common true pathogen, was related to urinary tract infection was consistent with previously published reports in outpatient setting.[7 - 9] However, non-typhoidal *Salmonella* spp., *Rhodococcus equine*, and *Cryptococcus neoformans* were also found to be causative agents of infection in the present study, an observation that may be explained by high HIV infection rate in patients included in the study. Like other studies, coagulase-negative staphylococci were the leading contaminants of positive blood culture. [5,10,11] In addition, all coagulase-negative staphycocci were considered contaminants since at the time that the blood samples were obtained patients in our study had no risk of CoNS bacteremia including indwelling intravascular catheters and prosthetic devices. Occult *Moraxella* bacteremia has been reported in outpatients with respiratory tract infections.[12 - 14] *Moraxella* was considered as a true pathogen in one of blood samples because the patient presented with symptoms of respiratory tract infection comparable to previous reports. However, another positive blood sample of *Moraxella* spp. was categorized as a contaminated specimen since the patient had inflammatory diarrhea which has never been reported to be a clinical manifestation of *Moraxella* infection and bacteremia. *Alcaligenes* spp. was cultured in one specimen and classified as contamination since the patient had no risk factors of *Alcaligenes* pathogenic bacteremia, which were neutropenia, previous hospitalization, or indwelling catheter.[15, 16]

Our results indicated that low hemoglobin was the most significant predictor associated with poor outcome in patients with positive blood culture. There was no difference in age, WBC and neutrophil count, which had been previously shown to be predictors of outcome in patients with sepsis. [17 - 20] In addition, we found that patients without sepsis may be treated as outpatients without antibiotic administration prior to discharge because no association between antibiotic administration and poor outcome was demonstrated. However, the decision to discharge patients from the outpatient service should be carefully considered, especially in those who had low hemoglobin concentration.

This study has limitations due to small number of eligible patients during the period of data collection. Although we extended our period of study to obtain more samples, only 53 patients met the inclusion criteria. Since it was a retrospective analysis based upon review of medical records, certain data were not available for all patients and only limited clinical data including laboratory investigation were obtained. Therefore, it is possible that a bias may have been introduced. To overcome this limitation, prospective study of larger sample size including both blood culture positive and negative patients should be further investigated. In addition, the prospective study will enable us to evaluate other variables that have been previously reported to be potential predictors of true bacteremia and clinical outcome such as time to blood culture positivity, level of serum albumin, C-reactive protein, lactate, procalcitonin, and cytokines.[21-28] However, as previously discussed, some observations in this report were consistent with those previously reported in the literatures.

The information presented herein is meant to assist clinicians in deciding how to evaluate and treat septic patients since early recognition and early intervention of sepsis are the most important factors

affecting clinical outcome.[29] Blood culture is the gold standard test for diagnosis of bacteremia. However, the cost effectiveness of blood culture is controversial since low yield was reported in various clinical settings.[1-3, 8, 30-34] The rate of true pathogenic blood culture was only 2.11% in our study, which is comparable to findings in previous reports. [1-3, 8] The cost effectiveness of blood culture needs to be verified. It was suggested in previous literatures that at least two blood culture sets are necessary to interpret contamination.[5, 11] In addition, sterile blood culture techniques should be emphasized to prevent contamination. [35, 36] A laboratory screening strategy should be performed to determine which patients can be treated as outpatients. In view of the low risk of poor outcome in patients with normal hemoglobin concentration, we recommend that well-appearing, non-anemic patients may be safely treated as outpatients with or without antibiotics. However, the treatment of anemic patients as outpatients should be done only when the patients are compliant to the treatment and close follow-up is assured.

Several controversies exist regarding the impact of blood cultures on patient management at the ED and the ambulatory setting. Previous studies revealed that blood culture taken at the ED had little or no effect on medical management, particularly in patients whose initial diagnosis was urinary tract infection, non-facial cellulitis, or community-acquired pneumonia.[1-4, 31, 37-40] On the contrary, other studies reported that blood cultures in patients discharged from ED were useful to achieve the correct diagnosis and to modify the ineffective empirical antimicrobial therapy in a subsequent management, especially in patients with unexplained fever, adult patients as age increases, or patients at risk for multi-drug resistant pathogens.[7, 34, 41-43] Further study is needed to identify specific criteria for selecting patients for whom their blood cultures are cost-effective in outpatient setting.

In conclusion, the present study was aimed to identify predictors of poor treatment outcome in outpatient setting. We support the continuing attempts to improve the management of patients in ambulatory setting based on the best available evidence. Guidelines for obtaining blood culture are warranted to increase the rate of their meaningful clinical consequences. Larger prospective study on specific epidemiologic and clinical criteria will be considered. However, in spite of guideline, physicians may choose to individualize therapies on the basis of unique clinical circumstances of the patient. Close observation and follow-up is necessary when being treated as outpatients.

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