

BMJ Open Bacteraemia predictive factors among general medical inpatients: a retrospective cross-sectional survey in a Japanese university hospital

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ABSTRACT

Objectives: The precise criteria for obtaining blood cultures have not been established; they depend on the physician's judgement. We examined clinical parameters to determine predictive factors of bacteraemia and the need for blood cultures among general medical inpatients.

Design: A retrospective cross-sectional survey.

Setting: A Japanese university hospital.

Participants: All general inpatients who had blood cultures taken from 1 January 2011 to 31 December 2012.

Main Measures: Clinical information at or just before blood culture sampling was extracted from medical charts. Factors potentially predictive of bacteraemia were analysed using Fisher's exact test, followed by multivariable logistic regression model analysis.

Main Results: A total of 200 patients (male: female=119:81, 64.3±19.1 years old) comprised this study; 57 (28.5%) had positive blood culture results. Multivariable logistic regression analysis revealed that age >60 years (OR=2.75, 95% CI 1.23 to 6.48, p=0.015), female sex (OR=2.21, 95% CI 1.07 to 4.67, p=0.038), pulse rate >90 bpm (OR=5.18, 95% CI 2.25 to 12.48, p<0.001) and neutrophil percentage >80% (OR=3.61, 95% CI 1.71 to 8.00, p=0.001) were independent risk factors for positive blood culture results. The area under the receiver operating characteristic curve analysis of this model was 0.796.

Conclusions: Our results emphasise the importance of taking blood cultures if the pulse rate is >90 bpm, in elderly patients and in women, and for ordering a differential white cell count.

INTRODUCTION

Bacteraemia is related to the leading causes of inpatient mortality in spite of the introduction of new antimicrobial agents and aggressive therapy.^{1 2} Needless to say, it is very important to take blood cultures both from patients in whom severe infection is suspected and from those patients in whom

Strengths and limitations of this study

- Sensitising physicians to consider bacteraemia remains an ongoing challenge. Obtaining blood cultures should improve management and decrease mortality due to bacteraemia among inpatients with common infectious diseases. There has been no reported analysis of factors predictive of bacteraemia among patients hospitalised in a general internal medicine unit. We aimed to develop precise criteria for obtaining blood cultures for this group of patients.
- Our criteria included age >60 years, female sex, pulse rate >90 bpm and neutrophilia; these are readily available clinical action values.
- The usefulness of our criteria to obtain blood cultures is supported because our model used readily available clinical action values and has sufficient area under the receiver operating characteristic curve analysis (0.796).
- The population enrolled in this study was limited to the inpatient ward of one hospital. Possible biases regarding causes of bacteraemia could make it difficult to generalise the results to different patient groups. In addition, this was a retrospective study without any common criteria for obtaining blood cultures.
- Validation of our model with the establishment of criteria for obtaining blood cultures awaits future studies and computer-based alerts.

severe infections should be suspected. However, the precise criteria for obtaining blood cultures have not been established; the decision depends on the physician's judgement. Moreover, it is often difficult to estimate the probability of bacteraemia based on clinical findings. For example, elderly patients often fail to show the usual clinical features indicative of bloodstream infection.³

A study to evaluate the incidence and clinical impact of bacteraemia on patients' outcomes in the USA revealed that central venous catheter use, other infections,

mechanical ventilation, trauma, haemodialysis and malnutrition were independent risk factors.⁴ Another prospective study showed that mortality due to bacteraemia was related significantly to age, rapidly fatal diseases, septic shock, multiple organ failure, previous use of antimicrobials, infection from *Enterobacteriaceae* species that produced extended-spectrum β -lactamases and inadequate empirical treatment.⁵

There are only a few previous reports of studies designed to identify predictive risk factors through direct comparison of patients with bacteraemia with those with negative blood culture results. One report identified predictive factors among elderly patients as male sex, obesity, low McCabe score on admission, gastrostomy at admission, recent surgery and urinary incontinence.⁶ Another retrospective study, which examined risk factors of bacteraemia among patients in an intensive care unit (ICU) for 5 months, determined that long ICU stays and hospitalisation for trauma were risk factors for bacteraemia.⁷

To the best of our knowledge, there has been no report that contains all hospitalised patients from whom blood cultures were taken in a general internal medicine unit, and analyses predictive factors of bacteraemia. It is necessary to ascertain these predictive factors in order to improve management and decrease mortality due to bacteraemia among inpatients with common infectious diseases. This study was performed in general internal medicine inpatient wards of a Japanese university hospital to identify such predictive factors and to establish which patients should be tested by blood culture.

METHODS

Study design and study population

This retrospective, cross-sectional study was performed at the Department of General Medicine in Juntendo University Hospital, a 1020-bed university hospital in Tokyo, Japan. The blood culture results were collected retrospectively from the clinical laboratory database from all general inpatients who had blood cultures taken from 1 January 2011 to 31 December 2012. If blood cultures were taken repeatedly to check treatment effects or to rule out bloodstream infection, only the first culture results for each patient were used for analysis. Positive blood culture results of skin commensals accompanied by no additional antimicrobial treatment were recognised as contaminants and such patients were included in the culture-negative group. This and other clinical information at or just before blood culture sampling was extracted by chart review: age, female sex, admission origin (patient admitted from health facility), artificial devices placed when blood cultures were taken, preceding antimicrobial use within 2 weeks, recent surgical procedures within a month, use of immunosuppressive drugs, history of malignant diseases and HIV infection. We also extracted axillary body temperature, systolic and diastolic blood pressure, pulse rate, white

cell count with percentages of neutrophils and lymphocytes, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), C reactive protein (CRP), body mass index, haemoglobin A1c and albumin levels from the medical charts.

Univariate comparison of each variable between patient groups with and without bacteraemia was performed by Fisher's exact test. Differences with a p value <0.05 were defined as statistically significant. Variables with a p value <0.10 in univariate analysis were entered into univariate and multivariable logistic regression models to determine factors predictive of bacteraemia. We did not enter diagnoses into multivariable analysis because of the small number of patients in each diagnosis. The accuracy of the logistic regression model was assessed by the area under the receiver-operator characteristic curve (ROC-AUC). All statistical analysis was performed using JMP software (V.11.0.0, SAS Institute, North Carolina, USA).

RESULTS

All general medical inpatients having blood cultures obtained during the two-year study interval totalled 200 patients (male: female=119:81, 64±19 years old). Three positive cases were contaminants, so 57 (28.5%) had true positive blood culture results (table 1). A diagnosis of any type of infectious disease was given to 130 (65.0%) patients; 57 (43.8%) had positive blood cultures. The most prevalent diagnosis among patients with bacteraemia was pyelonephritis, followed by infective endocarditis and cholangitis. Analysis of the final infectious disease diagnoses showed that patients with

Table 1 Blood culture (+) patients' diagnoses

| | Males | Females | Total (males +females) |
|-------------------------------|-------|---------|------------------------|
| Pyelonephritis | 3 | 9 | 12 |
| Infective endocarditis | 5 | 1 | 6 |
| Cholangitis | 3 | 2 | 5 |
| Central venous line infection | 1 | 0 | 1 |
| Cellulitis | 2 | 2 | 4 |
| Discitis | 1 | 3 | 4 |
| Suppurative arthritis | 2 | 1 | 3 |
| Cholecystitis | 0 | 3 | 3 |
| Pneumonia | 2 | 1 | 3 |
| Peripheral line infection | 1 | 1 | 2 |
| Central venous port infection | 1 | 0 | 1 |
| Cryptococcal meningitis | 1 | 0 | 1 |
| Prostatitis | 1 | 0 | 1 |
| Others | 6 | 5 | 11 |
| Total | 29 | 28 | 57 |

pneumonia had a significantly low percentage of bacteraemia ($p=0.0058$), whereas those with pyelonephritis ($p=0.0005$), cholangitis/cholecystitis/liver abscess ($p=0.0053$), discitis/ suppurative arthritis ($p=0.0025$) and central line-associated bloodstream infection ($p=0.0077$) had a significantly higher percentage of bacteraemia. The final diagnosis and univariate analysis are shown in [table 2](#). Use of central venous line ($p=0.037$), greater age ($p=0.0030$), greater axillary body temperature ($p<0.0001$), greater pulse rate ($p=0.0022$), greater white cell count ($p=0.0017$), greater neutrophils percentage ($p<0.0001$), greater lymphocytes percentage ($p<0.0001$), greater BUN ($p=0.0004$), creatinine ($p=0.039$) and lower eGFR ($p=0.017$) were associated with bacteraemia.

We conducted univariate logistic regression analysis and, based on the univariate analysis summarised in [table 2](#), multivariable logistic regression analysis. Variables considered for the multivariable regression analysis were female sex, age, pulse rate, axillary body temperature, central venous line, per cent neutrophils, creatinine and eGFR. Since BUN is affected by age, sex and creatinine level, it was not included in the multivariable analysis. Since total white cell count, neutrophils and lymphocytes were highly correlated with each other, a percentage of neutrophils was used in the multivariable analysis as representative of these three variables. Independent risk factors for positive blood culture results were female sex (OR=2.21, 95% CI 1.07 to 4.67, $p=0.038$), age <60 years (OR=2.75, 95% CI 1.23 to 6.48, $p=0.015$), pulse rate >90 bpm (OR=5.18, 95% CI 2.25 to 12.48, $p<0.001$) and neutrophil percentage >80% (OR=3.61, 95% CI 1.71 to 8.00, $p=0.001$) ([table 3](#)). We evaluated the quality of this model using the discrimination of ROC-AUC; the ROC-AUC was 0.796. Thus, the model in this study showed sufficient power to predict bacteraemia in an inpatient ward ([figure 1](#)).

DISCUSSION

This is a report of a direct comparison of patients with positive and negative blood cultures in order to identify factors predictive of bacteraemia among general medical inpatients. Older age, female sex, higher pulse rate and larger neutrophil percentage were identified as independent risk factors for bacteraemia.

Elderly patients often have relatively low temperatures in the setting of severe infectious disease. The febrile response to infection is decreased and baseline temperatures were reportedly generally low in older patients because their immune systems cannot react to infecting microorganisms adequately, resulting in low body temperature and the septic status.^{8 9} A previous study about the relationship between age and fever magnitude among patients with pneumonia revealed an age distribution similar to this study (median age, 64 years; range, 18–97 years) and a significant inverse correlation between age and body temperature.⁸ Our study also

revealed that older age was an independent risk factor for bacteraemia. Therefore, when physicians add an infectious disease to the differential diagnosis of an elderly patient, blood cultures should be obtained, regardless of the body temperature. In addition, older patients may lack symptoms, changes of vital signs and positive physical findings even though elaborate medical examinations are performed.^{10–12} These unique phenomena of the elderly might cause lack of abnormality in Organ Failure Assessment (qSOFA) score (systolic hypotension (≤ 100 mm Hg), tachypnoea (≥ 22 /min) or altered mental status).¹³ In such patients without any signs of sepsis, positive blood culture results could be the only clue to the correct diagnosis, leading to appropriate medical treatment and a good outcome. Tachycardia has been reported as an indicator of sepsis.¹⁴ Our results suggested that bacteraemia could be suspected among patients with tachycardia though the new sepsis definition did not include it.¹³

As shown in [tables 1](#) and [2](#), the most prevalent diagnosis among our patients with bacteraemia was pyelonephritis. Several authors have reported that a positive rate of blood cultures among patients with pneumonia was relatively low compared with other infectious diseases.^{15 16} The percentage of bacteraemia was high in pyelonephritis (21.1%) and low in pneumonia in this study (5.3%), consistent with previous studies. Multivariable logistic regression analysis revealed that female sex was the independent risk factor for the positive blood culture results. Even though we could not enter diagnoses into multivariable analysis because of the small number of patients in each diagnosis, the results might be affected by the pyelonephritis mainly found in female patients.

White cell counts with differential and CRP levels are frequently used as markers of a systemic inflammatory reaction, but CRP was not associated with bacteraemia in our study. Several studies have shown the usefulness of CRP for estimating the risk of bacteraemia in patients with neutropenia with cancer,¹⁷ or ICU patients,¹⁸ whereas another study concluded that CRP was not a sensitive or specific marker for bacteraemia in patients with signs of sepsis.¹⁹ Our study results suggest that the increased neutrophil percentage was a timely and reliable response to bacteraemia. It is important to consider obtaining blood cultures when patients have a high neutrophil percentage, even when the CRP level is not high.

On the basis of multivariable analysis and the ROC analysis, the model in this study showed sufficient power to predict bacteraemia in an inpatient ward. Our AUC of 0.796 especially indicates that our prediction model has a high likelihood of discriminating patients with positive bacteraemia from patients with negative bacteraemia. Our model could be used for the establishment of minimum criteria for obtaining blood cultures, as well as for instituting an automatic alert system for detection of bacteraemia among inpatients. A recent publication reported that a computerised clinical

Table 2 Extracted patient variables and results of univariate analysis

| Variables | Total n=200 (% BC) Mean±SD | Blood culture+ n=57 (% BC+) | Blood culture– n=143 (% BC–) | p Value |
|---|---|-------------------------------------|--------------------------------------|----------------|
| Demographic data of patients | | | | |
| Age | 64±19.0 n (%=/BC total (200)) | 71.3±14.9 n (%=/BC+ (57)) | 61.5±19.8 n (%=/BC– (143)) | 0.0030* |
| Female sex | 81 (40.5%) | 29 (51.0%) | 52 (36.4%) | 0.079 |
| History of malignant diseases | 26 (13%) | 7 (12.3%) | 19 (13.2%) | 1.00 |
| Recent surgical procedures within a month | 13 (6.5%) | 3 (5.3%) | 10 (7.0%) | 0.65 |
| Use of immunosuppressive drugs | 12 (6.0%) | 5 (8.8%) | 7 (5.0%) | 0.33 |
| HIV infection | 9 (4.5%) | 1 (1.8%) | 8 (5.6%) | 0.24 |
| Patient admitted from health facility | 14 (7.0%) | 4 (7.0%) | 10 (7.0%) | 0.99 |
| Preceding antimicrobial use within 2 weeks | 40 (20%) | 11 (19.3%) | 29 (20.3%) | 0.88 |
| Medical devices | | | | |
| Nasogastric tube | 3 (1.5%) | 2 (3.5%) | 1 (0.7%) | 0.14 |
| Indwelling urinary catheter | 5 (2.5%) | 3 (5.3%) | 2 (1.4%) | 0.11 |
| Central venous line | 15 (7.5%) | 8 (14.0%) | 7 (4.9%) | 0.037* |
| Peripheral venous line | 24 (12%) | 9 (15.8%) | 15 (10.5%) | 0.34 |
| Other artificial devices | 17 (8.5%) | 5 (8.8%) | 12 (8.4%) | 0.93 |
| Final diagnoses | | | | |
| Infectious diseases | 130 | 57 | 73 | |
| Pneumonia | 33 (16.5%) | 3 (5.3%) | 30 (21.0%) | 0.0058* |
| Pyelonephritis | 18 (9%) | 12 (21.1%) | 6 (4.2%) | 0.0005* |
| Cellulitis | 13 (6.5%) | 4 (7.0%) | 9 (6.3%) | 1.00 |
| Cholangitis/cholecystitis/liver abscess | 12 (6.0%) | 8 (14.0%) | 4 (2.8%) | 0.0053* |
| Discitis/suppurative arthritis | 9 (4.5%) | 7 (12.3%) | 2 (1.4%) | 0.0025* |
| Central line-associated bloodstream infection | 6 (3%) | 1 (1.7%) | 5 (3.4%) | 0.0077* |
| Infective endocarditis | 6 (3%) | 6 (10.5%) | 0 (0.0%) | NA |
| Empyema/lung abscess | 5 (2.5%) | 0 (0.0%) | 5 (3.4%) | NA |
| Intra-abdominal infection | 5 (2.5%) | 0 (0.0%) | 5 (3.4%) | NA |
| Bacteraemia of unknown origin | 8 (4.0%) | 8 (14.0%) | 0 (0.0%) | NA |
| Other infectious diseases | 15 (7.5%) | 4 (7.0%) | 11 (7.6%) | NA |
| Non-infectious diseases | 45 (22.5%) | 0 (0.0%) | 45 (31.4%) | NA |
| Fever of unknown origin | 25 (12.5%) | 0 (0.0%) | 25 (17.4%) | NA |
| Clinical and laboratory findings | Mean±SD | | | |
| Axillary body temperature (°C) | 37.6±1.0 | 38.3±1.1 | 37.4±0.9 | <0.0001* |
| Systolic blood pressure (mm Hg) | 120.1±18.7 | 123.3±23.2 | 118.9±16.5 | 0.34 |
| Diastolic blood pressure (mm Hg) | 65.0±10.9 | 67.4±14.0 | 64.1±9.4 | 0.16 |
| Pulse rate (/min) | 85.6±16.7 | 92.5±20.3 | 82.9±14.2 | 0.0022* |
| White cell counts (×10 ⁴ /μL) | 10.5±5.8 | 11.9±5.0 | 10.1±6.0 | 0.0017* |
| Neutrophils (%) | 78.0±13.2 | 84.8±9.3 | 75.3±13.6 | <0.0001* |
| Lymphocytes (%) | 13.9±8.9 | 10.1±7.3 | 15.4±9.1 | <0.0001* |
| Blood urea nitrogen (mg/gL) | 19.6±14.2 | 25.2±18.4 | 17.4±11.6 | 0.0004* |
| Creatinine (mg/dL) | 0.90±0.80 | 1.09±1.23 | 0.82±0.53 | 0.039* |
| Estimated glomerular filtration rate (mL/min) | 81.7±40.2 | 70.3±34.4 | 86.3±41.7 | 0.017* |
| C reactive protein (mg/dL) | 8.0±7.1 | 9.0±7.9 | 7.7±6.9 | 0.49 |
| Body mass index (Kg/m ²) | 21.6±3.9 | 21.9±4.0 | 21.6±3.9 | 0.56 |
| Haemoglobin A1c (%) | 5.8±0.9 | 5.9±0.9 | 5.9±0.9 | 0.77 |
| Albumin (g/dL) | 2.9±0.7 | 3.0±0.7 | 2.9±0.7 | 0.82 |

*p<0.05.

NA, not analysed.

decision support intervention for reducing the duration of urinary tract catheterisations was successfully integrated within a hospital's healthcare system.²⁰ Similarly, it would be possible to develop an automatic alert system for bacteraemia using patients' fundamental clinical information.

Several studies have shown that the presence of chills is a powerful single predictor of bacteraemia.^{21–25} In Japanese emergency rooms, it was reported that the severity of chill was correlated with the risk of bacteraemia.^{26–27} Since we did not evaluate patients' subjective and objective symptoms in this study, a future study

Table 3 Univariate and Multivariable logistic regression model

| Variables | Univariate OR | Univariate 95% CI ^a | Univariate p value | Multivariable OR | Multivariable 95% CI ^a | Multivariable p value |
|-----------------------------------|---------------|--------------------------------|--------------------|------------------|-----------------------------------|-----------------------|
| Female sex | 1.81 | 0.97 to 3.37 | 0.071 | 2.21 | 1.07 to 4.67 | 0.038* |
| Age >60 years | 2.87 | 1.40 to 5.88 | 0.002* | 2.75 | 1.23 to 6.48 | 0.015* |
| Pulse rate >90 bpm | 2.88 | 1.51 to 5.51 | 0.001* | 5.18 | 2.25 to 12.48 | <0.001* |
| Axillary body temperature >38.0°C | 1.39 | 0.65 to 2.96 | 0.426 | 2.41 | 0.94 to 6.18 | 0.063 |
| Central venous line | 3.17 | 1.09 to 9.20 | 0.037* | 1.07 | 0.51 to 6.56 | 0.336 |
| Neutrophils >80% | 4.29 | 2.13 to 8.66 | <0.001* | 3.61 | 1.71 to 8.00 | 0.001* |
| Creatinine >1.0 mg/dL | 1.53 | 0.74 to 3.16 | 0.253 | 0.92 | 0.36 to 2.35 | 0.877 |
| eGFR <80 mL/min | 0.98 | 0.98 to 0.99 | 0.013* | 0.51 | 0.21 to 1.18 | 0.120 |

*p<0.05.

eGFR, estimated glomerular filtration rate.

should analyse physical findings and symptoms, including chill, in addition to the items we used in this study.

The population enrolled in this study was limited to the inpatient ward of general internal medicine of one hospital. The possible biases regarding causes of bacteraemia could make it difficult to generalise the results to different patient groups. This study is a retrospective study without common criteria for obtaining blood cultures with a small number of patients. In addition, the low percentage of bacteraemia cases with central lines, use of immunosuppressive drugs and HIV infection makes subgroup analysis of each underlying condition difficult in this study. As the next step, a multicentre prospective study of a sufficient number of patients should be conducted after establishment of criteria for obtaining blood cultures based on the results of this study.

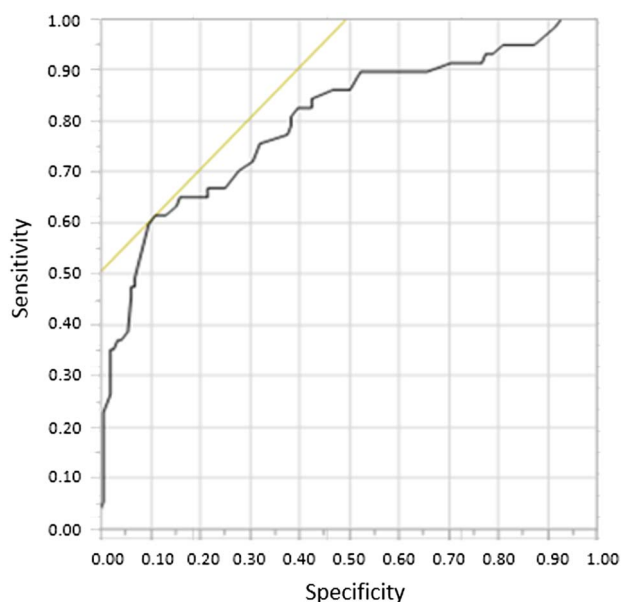


Figure 1 Multivariate analysis was conducted on the basis of results of univariate analysis. As shown in table 3, age >60 years, female sex, pulse rate >90/min and neutrophil percentage >80% were independent risk factors for positive blood culture results. The area under the receiver operating characteristics curve of this model was 0.796.

CONCLUSIONS

In conclusion, the presence of bacteraemia can be highly predicted by fundamental clinical information such as age, female sex, pulse rate and neutrophil percentage. In particular, age >60 years, female sex, neutrophils >80% and pulse rate >90 bpm were found to be associated with greater risk for bacteraemia. Our results emphasise the importance of taking blood cultures if the pulse rate is >90 bpm, from elderly patients, from women and for ordering a differential white cell count in addition to the total count to predict bacteraemia. To confirm our results, a future multicentre prospective study with a sufficient number of patients should be carried out using standardised criteria for obtaining blood cultures based on the results of this study.

Contributors SF and YU contributed to study concept and design. SF, YU and TN were involved in acquisition of participants and data. SF, YU, KF, OT, TN and TH were involved in analysis and interpretation of data. SF and YU were involved in preparation of the manuscript.

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Competing interests None declared.

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