Positive Predictive Value of True Bacteremia according to the Number of Positive Culture Sets in Adult Patients

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ABSTRACT

Background Performing multiple blood culture sets simultaneously is a standard blood culture methodology, although it is often difficult to distinguish true bacteremia from contamination when only one of several blood culture sets is positive. This study clarified the relationship between the number of positive blood culture sets and clinical significance in patients with positive blood culture.

Methods Patients aged 18 years and over with at least 1 positive blood culture were enrolled. Positive blood culture episodes were categorized from clinical records as true bacteremia, contamination, or unknown clinical significance. The associations among episodes of true bacteremia, isolated bacteria, the number of positive blood culture sets from among the performed sets, and the clinical background of patients were analyzed.

Results Among a total of 407 episodes, 262, 67 and 78 were true bacteremia, contamination and unknown clinical significance, respectively. The positive predictive values (PPVs) of 1 out of 1, 1 out of 2 and 2 out of 2 positive sets in cases of *Staphylococcus aureus,* were 81.3%, 50% and 100% respectively; those in cases of coagulase-negative *Staphylococci* were 20.5%, 10.8% and 63.5%, respectively. Almost all cases of *Escherichia coli, Pseudomonas aeruginosa, Klebsiella* species and *Candida* species were true bacteremia. The probability of true bacteremia was strongly associated with recent surgery in multivariate analysis ($P < 0.05$).

Conclusion The probability of true bacteremia based on the number of positive culture sets from among the performed sets varies by microorganism. Therefore, PPVs calculated using this method may help physicians distinguish true bacteremia from contamination.

Key words bacteremia; blood culture; contamination; positive predictive value

Bacteremia is often fatal and requires early diagnosis and treatment with adequate antimicrobial agents.[1, 2] Blood culture is regarded as the gold standard for the diagnosis of bacteremia.[3] However, accurately judging the clinical significance of culture results is challenging because of possible culture contamination. Therefore, methods to help differentiate true bacteremia from contamination are required.

The identification of isolated bacteria from positive blood cultures is a helpful clue for estimating the probability of true bacteremia. This probability, which is often expressed as the positive predictive value (PPV), is reported to vary by microorganism. For example, when *Streptococcus pneumoniae, Escherichia coli,* other members of Enterobacteriaceae, *Pseudomonas aeruginosa* and *Candida albicans* are isolated from blood culture, more than 90% are reported to be true bacteremia or fungemia.[4–7] On the other hand, when coagulase-negative *Staphylococci* (CNS), *Corynebacterium* species and *Bacillus* species are isolated, the probability of true bacteremia is reported to be low.[4–10] However, most of these studies were performed in the 70s through the 90s. Therefore, updated data in current patient populations and treatment methods are needed, because the ratio and causative bacteria of bloodstream infections might have changed over time as a result of the increasing use of intravascular devices and number of patients receiving immunomodulatory treatment.[11, 12]

Another method for distinguishing true bacteremia from contamination is using the number of blood culture sets (each set of blood culture consists of an aerobic and anaerobic bottle containing different nutrients) that grow bacteria from among the performed culture sets. Opportunities to adopt this methodology are increasing, because the recently approved Clinical and Laboratory Standards Institute (CLSI) guideline recommends more than 2 sets of blood culture should be performed simultaneously (within minutes of one another) in patients suspected blood stream infection.[13] However, it is often difficult to interpret the results when only 1 of the

2 blood culture sets is positive. In such cases, the results should be interpreted cautiously according to the identity of the isolated bacteria. In accordance with this strategy, the PPV of positive blood culture according to the number of positive blood culture sets has been examined for CNS.[7, 14] However, data about other microorganisms are rare.

Therefore, this study aimed to provide information to facilitate the interpretation of positive blood cultures by analyzing the clinical significance of isolated microorganisms, the number of positive blood culture sets from among the performed sets, and clinical background characteristics of patients in current clinical settings..

SUBJECTS AND METHODS
Patients and blood culture

Patients aged 18 years and over with at least one positive blood culture from April 1, 2007 to March 31, 2010 at Tottori University Hospital—a 700-bed tertiary-care facility—were evaluated. Blood was collected by the doctors, residents, or nurses and inoculated into standard aerobic and anaerobic bottles (BacT/ALERT FA and FN; Biomerieux, Durham, NC). One pair of these culture bottles was defined as 1 blood culture set. The bottles were incubated in the BacT/ALERT 3D System (Organon Teknika, Durham, NC) until flagged as positive or for 7 days at 37 °C. At least 2 sets of blood cultures were recommended to be obtained simultaneously or in rapid succession from separate vein puncture sites. However, 2 sets performed on the same day (at intervals of up to 24 h) were considered contiguous. Susceptibility testing of isolated bacteria was performed according to the CLSI guidelines. The significance of positive blood culture was judged retrospectively on the basis of clinical records. This study was conducted according to the Ethical Guidelines for Clinical Studies of the Ministry of Health, Labour and Welfare, Japan, and patient consent was not required as this was a retrospective case note review that involved anonymized data.

Definitions

An episode of bacteremia or fungemia was defined as the first positive blood culture result or a new positive blood culture result that occurred more than 48 h after the previous positive result unless it was clear to the investigator that the new positive culture blood was part of the same episode.

The clinical significance of a positive blood culture was determined by 1 infectious disease specialist and 2 residents on the basis of clinical records. Clinical significance was categorized as true bacteremia, contamination or unknown significance. Assessments were made on the basis of the following factors as described by Weinstein et al.:[7] clinical history, physical findings, vital signs (i.e., body temperature, blood pressure and heart rate) at the time of blood culture, white blood cell count, repeated isolation of the same bacteria at intervals more than 24 h, time until positive blood culture result, results of cultures from other sites, imaging results, histopathologic findings, clinical course, response to antimicrobial therapy, presence of a plausible source and clinical manifestations. The number of positive blood culture bottles within a blood culture set was not used as a criterion to differentiate true bacteremia from contamination in the present study, because previous studies have reported on its inefficacy.[8, 15]

Clinical background characteristics

The principal investigator reviewed the medical records and recorded the following clinical characteristics that were possibly related to true bacteremia on a standardized form: demographic variables, renal function, immunosuppressed conditions, presence of vascular catheter, location in the intensive care unit at blood culture collected, preceding antibiotic use, recent surgery, recent trauma and nosocomial acquisition. Preceding antibiotics use was defined as the use of any antibiotics at the time of blood culture collection. Recent surgery or trauma was defined as surgery or trauma within 30 days before blood culture collection. Each episode was classified as community or nosocomial acquired according to the guidelines of the Centers for Disease Control and Prevention.[16] An episode in a patient from another hospital or nursing home was always classified as nosocomial acquired.

Statistical analysis

PPV—which is the probability that an isolated organism would be expected to be a true pathogen rather than a contaminant—was calculated as the number of true bacteremic episodes divided by the number of positive blood culture episodes with the organism. Univariate analysis was performed to explore the association between the collected clinical characteristics and presence of true bacteremia. Categorical variables were assessed by the chi^2 test or Fisher's exact test. Continuous variables were analyzed using Student's t-test. Variables significant in univariate analysis were entered into the multivariate analysis, which was performed by logistic regression. All analyses were performed with SPSS version 19.0 (SPSS Inc., Chicago, IL), the level of significance was set at $P < 0.05$.

Table 1. Microorganisms isolated from the blood of patients suspected of bacteremia at Tottori University Hospital from April 2007 through March 2010

Microorganism (episode)	True bacteremia (%)	Contamination (%)	Unknown (%)
Aerobic and facultative bacteria			
Gram positive			
Staphylococcus aureus (80)	67 (83.8)	2 (2.5)	11 (13.8)
Cagulase-negative staphylococci (92)	20 (21.7)	50 (54.3)	22 (23.9)
Bacillus species (30)	14 (46.7)	10 (33.3)	6 (20)
Enterococcus species (26)	15 (57.7)	1 (3.8)	10 (38.5)
Corynebacterium species (4)	0	2 (50)	2 (50)
Streptococcus pneumonia (6)	6 (100)	0	0
Viridans streptococci (4)	3 (75)	0	1 (25)
Other *streptococci* (6)	3 (50)	0	3 (50)
Other gram positive bacteria (5)	0	2 (40)	3 (60)
Gram negative			
Escherichia coli (39)	35 (89.7)	0	4 (10.3)
Klebsiella pneumonia (19)	16 (84.2)	0	3 (15.8)
Klebsiella oxytoca (5)	4 (80)	0	1 (20)
Psudomonas aeruginosa (19)	17 (89.5)	0	2 (10.5)
Enterobacter cloacae (8)	7 (87.5)	0	1 (12.5)
Serratia marcessens (7)	5 (71.4)	0	2 (28.6)
Proteus mirabilis (2)	2 (100)	0	0
Stenotrophomonas maltophilia (2)	2 (100)	0	0
Acinetobacter species (5)	4 (80)	0	1 (20)
Citrobacter species (4)	4 (100)	0	0
Other gram negative bacteria (7)	5 (71.4)	0	2 (28.6)
Anaerobic bacteria			
Bacteroides fragilis (10)	10 (100)	0	0
Fusobacterium necrophorum (2)	2 (100)	0	0
Other gram positive bacteria (8)	7 (87.5)	0	1 (12.5)
Other gram negative bacteria (2)	1 (50)	0	1 (50)
Fungi			
Candida albicans (5)	5 (100)	0	0
Other *Candida* species (10)	8 (80)	0	2 (20)
All Microorganisms (407)	262 (64.3)	67 (16.5)	78 (19.2)

RESULTS

Among a total of 407 episodes, 262, 67 and 78 were true bacteremia or fungemia, contamination and unknown clinical significance, respectively. First, we examined the frequency of each microorganism and the relationships between their identity and clinical significance. As shown in Table 1, the most common microorganisms isolated from blood culture were CNS; only 21.7% (20/92) of these episodes were true bacteremia. Nevertheless, CNS was the third most frequent causative pathogen of true bacteremia because of its high prevalence. The second most frequently isolated microorganism from blood culture was *Staphylococcus aureus*; 83.8% (67/80) of episodes were true bacteremia, making it the most common cause of true bacteremia. All 6 *Streptococcus pneumoniae* isolates were pathogens for true bacteremia. The frequency of isolation and true bacteremia of other gram-positive bacteria were relatively low. *Escherichia coli* was the third most common microorganism isolated from blood culture and the most frequently isolated

gram-negative bacteria. Almost all episodes involving gram-negative bacteria including *Escherichia coli* were true bacteremia and none were contamination. Anaerobic bacteria such as *Bacteroides fragilis* or fungi isolated from blood culture represented true bacteremia; no episodes were contamination. Fungi isolated from blood culture were all *Candida* species; *Candida albicans* was frequently isolated more than other *Candida* species.

As mentioned above, the CLSI guidelines recommend multiple blood culture sets be performed simultaneously, but it is often difficult to determine if an isolate is the true pathogen of bacteremia or a contaminant when only 1 culture set is positive. Knowing the probability of true bacteremia in such situations, i.e., the PPV, is critical. Therefore, we subsequently examined the relationship between the number of positive culture sets and the probabilities of their clinical significance regarding major isolated microorganisms (Table 2). In the case of *Staphylococcus aureus*, the PPVs of a positive culture in 1 positive set out of 1 and 2 positive sets out of 2 were

Table 2. Clinical significance of each microorganism according to the number of positive blood culture sets

Microorganism (episode)	Number of culture sets Positive	Number of culture sets Performed	True bacteremia		Contamination		Unknown	
Staphylococcus aureus (80)	1	1	39	(67.2%)	2	(3.4%)	7	(12.1%)
	1	2	4	(50%)	0	(0%)	4	(50%)
	2	2	24	(100%)	0	(0%)	0	(0%)
Cagulase-negative staphylococci (92)	1	1	9	(20.5%)	24	(54.5%)	11	(25%)
	1	2	4	(10.8%)	24	(64.9%)	9	(24.3%)
	2	2	7	(63.6%)	2	(18.2%)	2	(18.2%)
Bacillus species (30)	1	1	4	(40%)	4	(40%)	2	(20%)
	1	2	3	(27.3%)	6	(54.5%)	2	(18.2%)
	2	2	7	(77.8%)	0	(0%)	2	(22.2%)
Enterococcus species (26)	1	1	9	(60%)	1	(6.7%)	5	(33.3%)
	1	2	2	(50%)	0	(0%)	2	(50%)
	2	2	4	(57.1%)	0	(0%)	3	(42.9%)
Escherichia coli (39)	1	1	14	(87.5%)	0	(0%)	2	(12.5%)
	1	2	9	(81.8%)	0	(0%)	2	(18.2%)
	2	2	12	(100%)	0	(0%)	0	(0%)
Klebsiella species (24)	1	1	8	(72.7%)	0	(0%)	3	(27.3%)
	1	2	2	(66.7%)	0	(0%)	1	(33.3%)
	2	2	10	(100%)	0	(0%)	0	(0%)
Psudomonas aeruginosa (19)	1	1	9	(90%)	0	(0%)	1	(10%)
	1	2	4	(100%)	0	(0%)	0	(0%)
	2	2	3	(75%)	0	(0%)	1	(25%)
Candida species (15)	1	1	8	(88.9%)	0	(0%)	1	(11.1%)
	1	2	0	(0%)	0	(0%)	0	(0%)
	2	2	5	(83.3%)	0	(0%)	1	(16.7%)

Table 3. Relationship between clinical background and significance in patients with positive blood cultures

	True bacteremia ($n = 262$)		Contamination ($n = 67$)		P
Sex					0.40†
Male	167	(63.7%)	39	(58.2%)	
Female	95	(36.3%)	28	(41.8%)	
Age, years					
Mean ± SD	68.1 ± 14.7		70.0 ± 14.3		0.36§
Range	17–94		22–89		
eGFR, mL/min/1.73m^2					0.85†
< 10.0	11	(5.3%)	2	(4.2%)	
10.0–49.9	54	(26.1%)	11	(22.9%)	
50.0 ≤	143	(68.6%)	35	(72.9%)	
No date	54		19		
Immunosuppressed					
DM	79	(30.2%)	12	(17.9%)	0.046†
Malignant tumor	132	(50.4%)	31	(46.3%)	0.55†
Corticosteroid use	36	(13.7%)	10	(14.9%)	0.80†
Immunosuppressor (except corticosteroid) use	4	(1.5%)	4	(6.0%)	0.057‡
Any vascular catheter present (except arterial catheter)	183	(69.8%)	42	(62.7%)	0.26†
Peripheral IV catheter present	126	(48.1%)	22	(32.8%)	0.025†
CV catheter present	80	(30.5%)	22	(32.8%)	0.72†
CV port system present	19	(7.3%)	2	(3.0%)	0.16‡
Location in ICU	48	(18.3%)	12	(17.9%)	0.94†
Preceding antibiotics use	97	(37.0%)	33	(49.3%)	0.068†
Recent surgery	54	(20.6%)	4	(6.0%)	0.010†
Recent trauma	9	(3.4%)	2	(3.0%)	0.61‡
Nosocominal acquisition	204	(77.9%)	50	(74.6%)	0.57†

CV, Central venous; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ICU, Intensive care unit; IV, intravenous.
† Chi^2 test.
‡ Fisher's exact test.
§ *t*-test.

Table 4. Logistic regression analysis of factors associated with true bacteremia and contamination

Factors	Odds raio	P
DM	1.91	0.065
Peripheral IV catheter present	1.65	0.090
Recent surgery	3.74	0.015

DM, diabetes mellitus; IV, intravenous.

81.3% and 100%, respectively. Meanwhile, the PPV in 1 positive set out of 2 was only 50%. In the case of CNS, a representative bacteria of the normal flora of the skin, the PPVs of 1 positive set out of 1 and 2 positive sets out of 2 were 20.5% and 63.6% respectively. However, when 1 out of 2 sets was positive, the PPV was only 10.8% and almost all cases were contamination. In the case of *Bacillus* species, which are also part of the normal flora of the skin, the PPVs of 1 positive set out of 1, 2 positive sets out of 2 and 1 positive set out of 2 were 40%, 77.8% and 27.3%, respectively. In the case of *Enterococcus* species, the respective PPVs were 60%, 50% and 57.1%. Regarding gram-negative bacteria such as *Escherichia coli*, *Klebsiella* species and *Pseudomonas aeruginosa* as well as fungi, no cases were considered contamination irrespective of the number of positive culture sets, and almost all cases represented true bacteremia.

The inclusion of clinical information facilitates the interpretation of positive blood culture results. Therefore, we subsequently evaluated the associations between clinical background characteristics and the existence of true bacteremia (Table 3). There were no significant differences in sex, age or estimated glomerular filtration rate between cases of true bacteremia and contamination. Regarding immunosuppressive conditions, the prevalence of diabetes was significantly higher in true bacteremia than contamination (30.2% versus 17.9%, respectively, $P < 0.05$). The presence of malignancy and corticosteroid and immunosuppressor use were not significantly different between groups. An intravenous catheter was introduced in 69.8% and 62.7% of cases of true bacteremia and contamination, respectively, and the indwelling peripheral intravenous catheters were more frequently observed in cases of true bacteremia than in cases of contamination (48.1% versus 32.8%, respectively, $P < 0.05$). However, such significant differences were not observed with central venous catheters and central venous port systems. With regard to other clinical factors, the patients with true bacteremia were more likely to have recent surgery, compared with those with contamination (20.6% versus 6.0%, respectively, $P < 0.05$). There was no significant difference between the 2 groups with respect to location in the intensive care unit, previous antibiotic use, recent trauma or nosocomial acquisition. Finally, the significant clinical factors in the univariate analysis were entered into the multivariate model (Table 4). However, the presence of recent surgery was the only independent risk factor for true bacteremia (odds ratio: 3.74, $P < 0.05$).

DISCUSSION

This study investigated the clinical significance of isolated microorganisms, the number of positive blood culture sets from among the performed culture sets, and presence of predisposing factors in order to facilitate the interpretation of positive blood culture results. In particular, this study is the first to report the probabilities of true bacteremia and contamination based on the number of positive culture sets with microorganisms besides CNS. Our data suggest that taking into account the number of positive blood culture sets in combination with the identity of isolated bacteria and clinical background characteristics is helpful for distinguishing between true bacteremia and contamination.

In this study, we revealed that causative pathogens of true bacteremia in order of frequency were *Staphylococcus aureus* (25.6%), *Escherichia coli* (13.4%), CNS (7.6%), *Pseudomonas aeruginosa* (6.5%) and *Klebsiella pneumoniae* (6.1%). These frequencies have been changed over time. In the middle of 1970's, the causative pathogen of true bacteria were reported that *Escherichia coli* (16.3%), *Staphylococcus aureus* (10%), *Streptococcus pneumoniae* (6.3%), *Klebsiella pneumoniae* (6.3%) and *Pseudomonas aeruginosa* (5.3%).[6] The same authors analyzed the data in 1990's and reported the frequencies as *Staphylococcus aureus* (18.9%), *Escherichia coli* (15%), CNS (9.2%), *Klebsiella pneumoniae* (6.9%) and *Enterococcus* species (6.9%).[7] In the beginning of 2000's, Pien et al. reported the frequencies as *Staphylococcus aureus* (23.1%), *Escherichia coli* (12.5%), *Enterococcus* species (9.4%), *Klebsiella pneumoniae* (8.2%) and CNS (7.7%).[4] Comparing these historical data with ours, the emerging increase of *Staphylococcus aureus* and CNS as causative pathogen of true bacteremia is obvious. The increasing use of intravascular catheters and devises, in the modern medical settings may contribute to this drastic change. Therefore, we need to carefully interpret the clinical significance of these bacteria, when they isolated from blood cultures.

Previous studies have reported that the probability of true bacteremia or contamination depends on the identity of the isolated bacteria, and the data of the present study are consistent with those of other studies. Moreover, previous studies analyzed the data from the middle of 1970's to 1990's indicate that 90–100%

of cases isolated of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* or *Candida* species are true bacteremia.[4, 6, 7] In the present study, no episode was judged to be due to contamination. Therefore the probabilities of true bacteremia of these bacteria have not changed over time. On the other hand, the previous studies indicate that 6–12.4% of cases of CNS were bacteremia,[4, 6, 7] in the present study, the probabilities were obviously increased to 21.7%. Thus, the results indicate that the probability of true bacteremia based on the identity of the isolated bacteria can be changeable with the times and should be estimated on the bases of updated data in current patient populations.

Although it is recommended that at least 2 sets of blood cultures taken from separate vein puncture sites be obtained,[13, 18] there is little available information to aid the interpretation of the clinical significance of positive blood cultures, especially in cases in which only 1 of several blood culture sets is positive. To our knowledge, CNS is the only microorganism whose PPV has been determined on the basis of the number of positive blood culture sets from among the performed sets. Weinstein et al. report that the PPVs of 1 and 2 positive sets out of 2 are 2.2% and 60.0%, respectively;[7] in their study, 2 blood culture sets were performed within 48 h but the interval between each blood culture was not documented. Meanwhile, Beekmann et al. report that the PPVs of 1 and 2 positive sets out of 2 were 13% and 69%, respectively;[14] their data were drawn from blood culture sets that were performed within 5 days of the index positive blood culture. In the present study, the PPVs of 1 and 2 positive sets out of 2 were 10.8% and 63.3%, respectively, in cases involving CNS in 2 blood culture sets performed simultaneously. As the recent guideline recommends blood cultures be obtained simultaneously or in rapid succession (< 24 h),[13] the present findings provides consistent evidence of the PPV for CNS bacteremia.

The present study revealed that when gram-negative bacteria such as *Escherichia coli*, *Klebsiella* species and *Pseudomonas aeruginosa* or *Candida* species are isolated, there is no difference in the PPV regardless of the number of positive culture sets from among the performed sets. Therefore, these bacteria should be considered true pathogens if isolated from at least 1 blood culture set. In the case of *Staphylococcus aureus*, the present results highlight the importance of considering the number of positive culture sets when interpreting the clinical significance of the findings, because the PPV of blood culture varied greatly depending on number of positive culture sets. Therefore, when *Staphylococcus aureus* is isolated from blood culture, especially if 1 out of 2 sets is positive, the clinical significance must be judged very cautiously. Regarding other gram-positive bacteria such as *Bacillus* species and *Enterococcus* species, the PPV of 1 positive set out of 2 was comparatively low; even 2 positive sets out of 2 does not always indicate true bacteremia for these bacteria. The present study shows that the PPV of blood culture based on the number of positive culture sets varies with respect to the isolated microorganism. Therefore, the approach utilizing the number of positive culture sets from among the performed sets must be combined with the identity of the isolated bacteria; thus, the probability of true bacteremia should be interpreted cautiously according to the isolated bacteria.

The present study shows that recent surgery is an independent risk factor for true bacteremia. This result is similar to that of Marschall et al., who report that a history of urogenital surgery is associated with urinary-source bacteremia in patients with *Escherichia coli* bacteriuria.[19] In addition to the invasion of bacteria from the wound site, we speculate that immunosuppression due to the stress of surgery is related to bacteremia. Previous experimental and clinical studies provide evidence indicating surgery decreases both cell-mediated and humoral immunity, affecting the host immune system. Major surgical invasion is reported to depress the functions of monocytes and[20, 21] macrophages[22, 23] as well as decrease T-lymphocyte proliferation and cytokine secretion.[24] Furthermore, the decreased interleukin-2 production by T lymphocytes as a result of surgical invasion is suggested to decrease B-cell antibody production.[25] Eventually, considering clinical background characteristics such as the presence of recent surgery may help distinguish between true bacteremia and contamination, especially in cases in which the probability of true bacteremia is ambiguous after considering the number of positive blood culture sets from among the performed sets.

In conclusion, when utilizing the number of positive blood culture sets to distinguish true bacteremia from contamination, the variation in the probability of true bacteremia by the microorganism must be considered. This study demonstrates that PPV calculated on the basis of the number of positive culture sets from among the preformed sets according to the identity of the isolated bacteria is helpful for interpreting the clinical significance of positive blood cultures.

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