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Introduction of ICU blood culture protocols and the effect on rates of contamination: A single-center, non-randomized interventional study

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Introduction: Because of increasing medical costs and antibiotic resistance, a blood-culture contamination rate of less than 3% is recommended. This study involved the conceptualization of a novel ICU blood culture sample-collection protocol and an investigation of the effect of its implementation on ICU blood culture contamination rate. Considering the difficulty of sample collection via venipuncture in ICU patients, blood culture sample collection via single venipuncture was evaluated as an alternative method.
Materials and Methods: Adults who were admitted to the ICU and provided blood culture samples collected between June 1, 2018, and May 31, 2021, were prospectively enrolled in this single-center, interventional study. The primary outcome was the change in the blood-culture contamination rate from before to after the introduction of the seven-item ICU blood culture protocol (Intervention 1); the secondary outcome was the change in the blood-culture contamination rate and true positive rate from before to after the introduction of the single venipuncture method (Intervention 2).
Results: During the study period, there were 524 sets of ICU blood culture sample collections. Intervention 1 significantly decreased the blood-culture contamination rate from 20% to 1.8% (p=0.01). Compared with the double venipuncture method, Intervention 2 did not significantly increase the blood-culture contamination or true positive rate.
Discussion: The implementation of the ICU blood-culture sample-collection protocol and subsequent improvements in the quality of blood-culture sample collection significantly decreased the blood-culture contamination rate. The single venipuncture method did not increase the rate of contamination; however, the clinical usefulness of the single venipuncture method should be ascertained.

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Key words: blood-culture contamination, ICU, blood culture sample-collection protocol, single venipuncture

Introduction

Blood culture is essential for the definitive diagnosis of bloodstream infections. To increase detection sensitivity and facilitate the determination of blood-culture contamination, the collection of two or more blood-culture sample sets from different veins (“double venipuncture”) is recommended, except in cases of suspected intravascular catheter infection[1]. Blood culture contamination constitutes a phenomenon wherein microorganisms that are indigenous to the skin, such as coagulase-negative *Staphylococci* (CoNS), *Corynebacterium* sp., and *Bacillus* sp., which are generally nonpathogenic, are introduced into the blood-culture bottle from sources other than the patient's blood because of inadequate asepsis

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during sample collection[2]. Blood-culture contamination increases the risk of drug-resistant bacteria and higher healthcare costs from additional testing and antimicrobial use and should be avoided in clinical practice[3]. International guidelines recommend a blood-sample contamination rate of less than 3%[4]; however, the international and Japanese rates are 0.6%–12.5%[4] and 0.96%–8.5%[5], respectively, with high inter-institutional variation.

In previous studies, staff education, adherence to recommended blood sample collection methods[6,7], and venipuncture sample collection[8,9] have been reported to be effective in reducing blood culture contamination. We hypothesized that the establishment, introduction, and adherence to institutional protocols would improve aseptic sample collection, ensure the collection of an appropriate amount of blood samples, and decrease the rate of blood-culture contamination. There are, however, problems with the recommended blood-sample collection methods. That is, as ICU patients frequently have generalized edema secondary to malnutrition and fluid accumulation, the recommended double venipuncture from different peripheral veins[10, 11] may be technically difficult to perform; thus, alternatively, two sets of blood culture samples may be collected using a single venipuncture. Although the single venipuncture method can potentially decrease the physical burden on patients, the time commitment of medical personnel, and the use of medical resources while ensuring blood culture quality, few studies have investigated the effectiveness of this method[12]. In this study, we developed and implemented an institutional ICU blood culture protocol that specifies the procedural flow and the medical personnel who can collect blood samples. Then we examined the effect of the novel protocol on the rate of blood culture contamination in the ICU. Furthermore, we examined whether the single venipuncture method could be used as an alternative to the conventional double venipuncture method for blood cultures from ICU patients.

Materials and Methods

Study design

This single-center, interventional trial to evaluate the effects of an ICU blood culture protocol, which defined blood sample collection techniques, on the blood culture contamination rates (Intervention 1) and to evaluate single and double venipuncture methods (Intervention 2) qualitatively and comparatively for blood-culture sample collection was conducted at Yokosuka General Uwamachi Hospital, which has 417 beds. The participants were all medical or surgical adult patients (age ≥18 years) who were admitted, between June 1, 2018, and May 31, 2021, to the ICU (8 beds), after surgery or deterioration in the general condition in the general ward or the emergency room, and underwent ICU-based sample collection for blood culture. If blood cultures were repeated from the same patient, each episode was counted as one case. Also, if more than three sets of blood culture samples were collected and all specimens obtained by venipuncture, each episode was counted as one case.

Description of each intervention

Preintervention phase and ICU blood-culture protocol development

Figure 1 comprises a flowchart that depicts the sequence of processes in this study. The results of blood cultures performed from June 1, 2018, to May 31, 2019, were used as the baseline data. During the abovementioned period, an

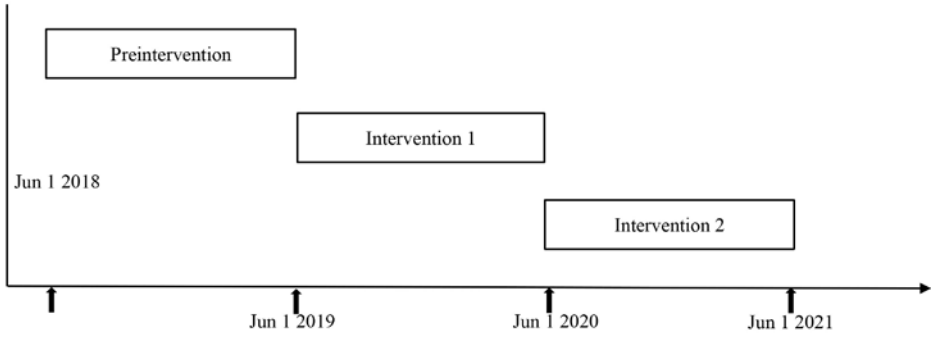

Figure 1. The timeline of the study
Comprises a flowchart that depicts the sequence of processes in this study. After the preintervention period of one year, Intervention 1 was introduced in June 2019 followed by Intervention 2 in June 2020.

ICU blood culture protocol was conceptualized and developed by the hospital's Antimicrobial Stewardship Team (AST) to improve the quality of blood culture sample collection techniques and promote the use of the double venipuncture method for sample collection (preintervention phase). Nurses who collected blood culture samples in the ICU were required to attend at least one face-to-face training lecture on the ICU blood culture protocol during the last month of the preintervention period (May 1–31, 2019), and any questions were answered during the question-and-answer session. ICU nurses were allowed to perform blood culture sample collection immediately after completing the training course.

ICU blood culture protocol

With reference to the results of previous studies, the ICU blood-culture sample collection protocol that was introduced in this study included the following seven items: 1) two sets of blood culture sample collection by venipuncture in all patients except in cases of suspected catheter-related bloodstream infection (CRBSI)[1,2,9,13,14]; 2) blood culture sample collection by only trained ICU nurses who understood the novel protocol[2,15]; 3) use of surgical masks and sterile gloves during sample collection[15-19]; 4) use of 1% chlorhexidine alcohol solution as a skin disinfectant and waiting for at least 30 seconds after disinfection before drawing the sample[20-21]; 5) collection of at least 10-mL sample in each blood culture bottle[22-25]; 6) pre-collection disinfection of the top of the blood culture bottle with isopropyl alcohol and ensuring complete drying before sample collection[5,26,27]; and 7) changing the puncture needle when transferring specimens to the blood culture bottle[28]. This protocol was applied similarly in both Intervention 1 and Intervention 2.

Interventions 1 and 2

The ICU blood culture sample-collection protocol was introduced on June 1, 2019, and was implemented until May 31, 2020 (Intervention 1). From June 1, 2020, for the collection of two blood samples per culture, the blood culture sample-collection method for all patients was changed from the conventional double venipuncture method to the single venipuncture method, which was continued until May 31, 2021 (Intervention 2), while continuing to implement the ICU blood culture sample-collection protocol. In the single venipuncture method, a single peripheral vein was punctured and, using two 20-mL syringes, two sets of samples were collected simultaneously and 10 mL of blood from each 20-mL syringe was dispensed into an aerobic bottle first. Then the remaining 10 mL of blood was dispensed into an anaerobic bottle separately.

Handling of blood culture specimens

Blood culture samples that were collected in the ICU were immediately transferred to the bacteriology laboratory and cultured for 7 days in an automated blood culture analyzer (Japan BD Bactec™ FX400). Details of the number of blood culture samples collected and the culture results were obtained from electronic medical records.

Definition of blood culture contamination

Regardless of the number of positive sets or culture bottles, blood culture contamination was suspected when CoNS, *Corynebacterium* spp., *Bacillus* spp., *Cutibacterium acnes*, *Micrococcus* spp., or viridans group streptococci were detected[3, 7]. When blood culture reports induced suspicion of blood culture contamination, the AST – which comprised an infectious disease physician, infection control nurse, pharmacist certified in antimicrobial chemotherapy, and clinical laboratory technician – discussed the case at the AST conference to determine whether the patient had blood culture contamination based on the blood culture-positive bottle count and clinical information (fever, chills, hypotension, neutrophilia, antimicrobial administration status, *in situ* catheter, and results of bacterial culture from infectious foci)[7].

Definition of sepsis, septic shock, and CRBSI

Sepsis was diagnosed when a Sequential Organ Failure Assessment (SOFA) score increased by 2 points or more due to a dysregulated host response to infection[29]. Septic shock was also defined if patients with sepsis require a vasopressor to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L.

In this study, a diagnosis of CRBSI was made when the same organism was isolated from at least 1 percutaneous blood culture and a culture of the catheter tip, or when 2 blood samples were drawn (one from a catheter hub and the other from a peripheral vein) that met CRBSI criteria for differential time to positivity (DTP)[30].

Explanation of data analysis methods

Data on the number of ICU admissions were obtained from the ICU admission database. The compliance rate for collecting two sets of blood culture samples from a vein was

determined from the physician's orders for the blood culture test and nurses' electronic medical records. Because of the difficulty of assessing compliance with each item of the ICU blood culture protocol, this study defined blood culture samples taken from more than two sets via the venipuncture method as the compliant cases and the others as the non-compliant cases. Based on this definition, compliance or non-compliance with the protocol during the preintervention period was determined retrospectively.

The rate of blood culture contamination was calculated as:
Intervention 1:

Blood-culture contamination rate (%) = Contaminated cultures among protocol-compliant cases with double venipuncture samples (n) / All protocol-compliant cases with double venipuncture samples (n) × 100
Intervention 2:

Blood-culture contamination rate (%) = Contaminated cultures among protocol-compliant cases with single venipuncture samples (n) / All protocol-compliant cases with single venipuncture samples (n) × 100

Contamination rate among protocol uncompliant cases

Blood-culture contamination rate (%) = Contaminated cultures among protocol uncompliant cases (n) / All protocol uncompliant cases (n) × 100

True positive blood culture rate was calculated as:
Intervention 1:

True positive blood culture rate (%) = Positive blood cultures among protocol-compliant cases with double venipuncture samples (n) - Contaminated cultures among protocol-compliant cases with double venipuncture samples (n)/ All protocol-compliant cases with double venipuncture samples (n) × 100
Intervention 2:

True positive blood culture rate (%) = Positive blood cultures among protocol-compliant cases with single venipuncture samples (n) - Contaminated cultures among protocol-compliant cases with single venipuncture samples (n) / All protocol-compliant cases with single venipuncture samples (n) × 100

The purpose of this study was to evaluate the quality of blood culture from venipuncture samples by analyzing rates of blood culture contamination and positivity, after excluding blood culture samples obtained via arterial puncture.

Statistical analyses were performed using R (R Development Core Team ver. 4.2.2) with the chi-square test for ascertaining the blood culture contamination rate, true blood culture positivity rate, and the percentage of sample sets collected from two or more venipunctures. A *P*-value less than 0.05 in a two-tailed test was considered statistically significant.

Study outcomes

The primary outcome was the difference in the rates of true blood culture positivity and blood culture contamination between the preintervention and intervention periods in cases of two or more blood culture sample collections by venipuncture. The secondary outcome was the difference in the rates of true blood culture positivity and blood culture contamination during interventions 1 and 2.

Ethics statement

This study was approved by the institutional review board of Yokosuka General Uwamachi Hospital (approval no. 2019021). Consent to participate in the study was obtained in the form of an opt-out via the institutional website (https://www.jadecomhp-uwamachi.jp/ndc/), and patients who declined to participate were excluded from the study. Moreover, this study was registered (Identification No. 000048856, Receipt No. R000055671) in the University Hospital Medical Information Network (UMIN) registry.

Results

Total ICU admissions and blood culture sets

During the study period, there were 1738 ICU admissions and 524 sets of ICU blood culture sample collections (Table 1). No patient withdrew from participation in the study. In all cases, except two sets of blood cultures, blood culture sample collection by venipuncture complied with the ICU blood culture protocol.

The detail of CRBSIs diagnosed during the study period is shown in Table 1, and all isolated organisms are consistent with the causative organisms for CRBSI. At the end of the study period, the total number of ICU admissions had decreased owing to the coronavirus pandemic-associated restrictions on ICU admission since March 2020.

Preintervention phase

To understand the results and causes of blood contamination at our institution, we previously validated 170 sets of blood cultures collected in our ICU for 1 year from June 1, 2018, to May 31, 2019. As a result, two sets of specimens were

Table 1. Characteristics of the patients admitted to the ICU

Period	Preintervention (2018/6/1–2019/5/31)	Intervention 1 (2019/6/1–2020/5/31)	Intervention 2 (2020/6/1–2021/5/31)	Total
Total number of ICU admission	626	604	508	1738
ICU admission type				
Elective surgery	406	401	330	1137
Emergency surgery	113	82	61	256
Medical	107	121	117	345
Age in years	73.2 (16-103)	73.3 (17-97)	74.2 (24-99)	73.5 (16-103)
Male sex - no (%)	368 (58.8%)	344 (57.0%)	304 (59.8%)	1016 (58.5%)
APACHEII score (mean)	15.9	16.2	16.4	16.1
SAPSII score (mean)	32.0	31.9	33.3	32.4
Underlying diseases				
Cardiovascular	234	191	189	614
Musculoskeletal	88	100	94	282
Gastrointestinal	95	106	68	269
Neurological	108	80	49	237
Respiratory	46	41	37	124
other	55	84	71	210
Sepsis or Septic shock				
Yes	73	79	65	217
No	553	525	443	1521
Total number of cases with blood cultures obtaine	170	182	172	524
Total number of CRBSI	6	6	4	16
Causative organisms	MSSA (1) *C. albicans*(1) *C. glabrata*(1) *C. parapsilosis*(1) *E. coli* (1) *E. cloacae* (1)	*S. maltophilia* (3) *S. hominis* (2) *S. epidermidis* (1)	*C. parapsilosis* (1) *P. aeruginosa* (1) *S. epidermidis* (1) *S. mitis* (1)	

collected by double venipuncture from only 15 patients (8.8%) whereas at least one of the two sample sets was collected from an arterial or intravascular catheter for the remaining 155 patients (91.2%). In many cases, femoral artery puncture was used for arterial sampling, which has a risk of contamination similar to that of sampling from intravascular catheters. Among the 15 cases of double-venipuncture-based peripheral blood sampling, four (26.7%) were culture-positive and, of these, three (20%) were contaminated.

Effects of Intervention 1

Table 2 presents the results from the preintervention phase and during Intervention 1. During the preintervention phase, 170 sets of blood culture samples were collected, of which 15 (8.8%) were collected by two venipunctures, 147 (86.5%) by one or more sets by arterial puncture, and 8 (4.7%) by one set of blood cultures. During Intervention 1, 182 blood cultures were collected, among which 113 (62.1%) were collected by double venipuncture, which indicated a significant increase from the preintervention level in the double-venipuncture-based sample collection ($p<0.01$). After the introduction of the ICU blood culture protocol, the contamination rate in the double venipuncture group was significantly lower from before to after Intervention 1 (20% vs. 1.8%, $p = 0.01$). The true blood culture positivity rates among protocol-compliant cases before and after Intervention 1 were 6.7% and 9.7%, respectively, and showed an increasing trend; however, there was no significant intergroup difference ($p=1.00$). The rate of contamination or true positive blood culture among protocol

Table 2. The effect of Intervention 1 and Intervention 2

Period	Preintervention (2018/6/1–2019/5/31)	Intervention 1 (2019/6/1–2020/5/31)	Intervention 2 (2020/6/1–2021/5/31)	*P*-value	
				Control vs Intervention 1	Intervention 1 vs Intervention 2
Total cases collecting blood cultures in ICU	170	182	172		
Rate for ICU blood culture protocol (*1)					
Compliant	15 (8.8%)	113 (62.1%)	99 (57.6%)	<0.01	0.58
Uncompliant	155 (91.2%)	69 (37.9%)	73(42.4%)		
Contamination rate among protocol-compliant cases	3/15 (20%)	2/113 (1.8%)	3/99 (3.0%)	0.01	0.66
Contamination rate among protocol-uncompliant cases	8/155 (5.2%)	4/69 (5.8%)	3 /73 (4.1%)	1.00	0.72
True positive blood culture rate among protocol-compliant cases	1/15 (6.7%)	11/113 (9.7%)	8/99 (8.1%)	1.00	1.00
True positive blood culture rate among protocol-uncompliant cases	11/155 (7.1%)	8 /69 (11.6%)	4 /73 (5.5%)	0.31	0.37

(*1) Compliance rate with recommended venipuncture method in each period (double venipuncture in the Preintervention and Intervention 1 groups, and single venipuncture in the Intervention 2 group)

uncompliant cases was comparable from before to after Intervention 1. The analysis of contaminants in both groups showed that the three cases identified before Intervention 1 were all positive for *S. epidermidis*, whereas one of the two cases identified after the initiation of Intervention 1 was positive for *S. epidermidis* and *B. subtilis*. In all these cases, one or two bottles of two sets (four blood culture bottles) were positive.

Effects of Intervention 2

Table 2 shows the effects of Intervention 2, during which 172 sets of blood culture samples were collected, and 99 (57.6%) participants had two or more sets of blood culture samples collected from a single venipuncture. Comparisons of the cases with adherence to the ICU blood culture sample-collection protocol with the double venipuncture method in Intervention 1 and the single venipuncture method in Intervention 2 revealed rates of blood culture contamination of 2 (1.8%) and 3 (3.0%) and true blood culture positivity of 11 (9.7%) and 8 (8.1%) that did not significantly differ (p = 0.66 and p =1.00), respectively. The rate of contamination or true positive blood culture among protocol uncompliant cases was comparable from before to after Intervention 2. The bacteria identified as contaminants in Intervention 2 were *S. haemolyticus, S. hominis*, and *S. epidermidis* in one case each, and only one bottle of two sets (four blood culture bottles) was positive.

Discussion

This study investigated the effects of the newly introduced ICU blood culture sample-collection protocol, which significantly decreased the rate of blood culture contamination. Moreover, the rate of contamination did not increase when the conventional double venipuncture technique was compared with the single venipuncture method for sample collection. We considered the main reasons for the significant reduction in the rate of blood contamination with Intervention 1 as follows: First, blood sample collection via intravascular catheter was replaced by venipuncture-based sample collection. Regarding the method of sample collection for blood culture, contamination is significantly less with venipuncture than with sample collection from an intravascular catheter, and the results of this study indicate a similar finding[2,9]. Second, a 1% chlorhexidine alcohol solution was introduced as a skin disinfectant, with a specific protocol for its use. We suspected that the 10% povidone-iodine solution had been used until now, and the waiting time to achieve sufficient sterilization may not have been adequately thorough. Chlorhexidine alcohol significantly decreased the rates of blood culture contamination compared to the use of povidone-iodine for skin disinfection before sample collection for blood culture[20]. The main reason for this change is the volatility of alcohol in the chlorhexidine–alcohol formulation that achieves maximal bactericidal effect within only 30 s whereas the povidone-iodine solution requires 1.5–2 min for maximal bactericidal

effect. Thus, it is possible that the change in the disinfectant contributed to the decreased rate of contamination in this study. Worldwide, 2% chlorhexidine–alcohol is used as a standard skin disinfectant[10,11]. As 2% chlorhexidine–alcohol is unavailable in Japan, a 1% chlorhexidine–alcohol solution was used in this study. The short disinfection time was advantageous in effectively decreasing the rate of blood culture contamination. Third, ICU nurses with a good understanding of ICU blood culture sample-collection protocols collected blood samples, and this resulted in a higher rate of compliance with the institutional protocol. Contamination is significantly reduced when samples for blood culture are collected by a trained medical team[2,31], and this could have been a contributing factor to this present study as well. Multidisciplinary efforts are effective in decreasing blood culture contamination[18,32,33], and it is possible that departmental efforts, including the introduction of ICU blood culture sample-collection protocols, to minimize blood culture contamination were effective. This consideration is supported by the significant reduction of blood culture contamination rate in protocol-compliant cases compared to protocol-uncompliant cases. Also, the contamination rate among protocol uncompliant cases remained high throughout the study suggesting that compliance with the protocol may reduce the contamination rate. However, since the compliance rate for each item was not evaluated except for item 1, caution should be taken in interpreting the results.

For Intervention 2, the blood culture sample-collection method was changed from the conventional double venipuncture method to a single venipuncture method, which did not significantly increase the rate of blood culture contamination and did not significantly increase the rate of blood culture positivity. The effectiveness of the single venipuncture method in the emergency department has been reported previously[12], and this method could potentially constitute an alternative sample-collection technique for ICU patients, who are often admitted with poor nutritional status and securing peripheral vascular access is difficult which makes it technically challenging to obtain a blood culture sample. However, the single-site sample-collection method may generate difficulties for detecting contamination, and further studies are needed to determine the clinical usefulness of this method. According to our study, it is important to conduct a quality assessment of blood culture collection at each medical facility to identify its current status and problems. Based on the status and problems, it is important to consider and implement solutions to the problems and make qualitative improvements.

This study had several limitations. First, of the seven items listed in the ICU blood culture sample-collection protocol, no individual-item efficacy determination was undertaken, except for the collection of two sets of blood cultures by venipuncture. Therefore, the effect of 1% chlorhexidine-alcohol, which was newly introduced in this study, on the rates of blood contamination could not be confirmed. The magnitude of the effect of each item in decreasing the rate of blood culture contamination rate can be evaluated by determining the effectiveness of each item. However, because data collection is labor intensive, it may be a more realistic and effective strategy to increase the rate of compliance of medical personnel who collect blood samples along with refining of the protocol itself, as was done in this study. Second, the usefulness of arterial puncture was not evaluated. When venipuncture proves difficult in the setting of ICU blood culture, a single or double arterial puncture is often performed to avoid obtaining a specimen from an intravascular catheter. In this study, even after the introduction of the ICU blood culture sample-collection protocol, the percentage of the two sets collected by venipuncture alone was low during Intervention 1 (62.1%) and Intervention 2 (57.6%).

A possible reason is that ICU nurses ask physicians to switch the procedure in case of difficulty collecting blood cultures via venipuncture. In that case, physicians often select arterial puncture instead of venipuncture which may have contributed to a lower compliance rate. Therefore, it is unclear whether arterial puncture was associated with a higher rate of blood culture contamination than venipuncture or varied with the site of arterial puncture.

In conclusion, the introduction of the ICU blood culture sample-collection protocol and the associated improvements in the quality of blood culture sample collection significantly decreased the rate of blood-culture contamination in the ICU. Although blood culture using a single puncture did not increase the rate of contamination in this study, the clinical usefulness of the single venipuncture method needs further investigation.

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