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# High positivity of blood cultures obtained within two hours after shaking chills

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ABSTRACT

*Objective:* To determine whether the time lag between blood culture draw and the start of shaking chills is associated with blood culture positivity.
*Methods:* A prospective observational study was undertaken from January 2013 to March 2015 at a referral center in Okinawa, Japan. All enrolled patients were adults with an episode of shaking chills who were newly admitted to the division of infectious diseases. The study exposure was the time lag between blood culture draw and the most recent episode of shaking chills.
*Results:* Among patients whose blood cultures were obtained within 2 h after shaking chills started, the blood culture positivity was 53.6% (52/97), whereas among patients whose blood cultures were obtained after more than 2 h, the positivity was 37.6% (44/117) ($p = 0.019$). The adjusted odds ratio of blood culture positivity for samples drawn within 2 h after shaking chills was 1.88 (95% confidence interval 1.01–3.51, $p = 0.046$). *Escherichia coli* were the most frequently detected bacteria (58/105).
*Conclusions:* The positivity of blood cultures obtained within 2 h after the start of the most recent shaking chills was higher than that for blood cultures obtained after 2 h.


## Introduction

Although various types of testing modality have been developed for the detection of bacteria, including molecular techniques, blood culture is currently the gold standard method for identifying the etiological pathogens of bacteremia (Aronson and Bor, 1987; Liesenfeld et al., 2014). The timing of blood draw for culture, however, remains controversial (Coburn et al., 2012).

A study reported in the 1950s recommended that blood cultures should be drawn during the hour preceding an expected chill (Bennett and Beeson, 1954). This was because it was believed that there was a time lag of around an hour between the abrupt influx of bacteria and the onset of chills (Bennett and Beeson, 1954). The most severe degree of chills, namely shaking chills or shivering, has been considered a strong predictor of bacteremia (Bates et al., 1990; Tokuda et al., 2005). Shaking chills have been a useful indicator of bacteremia even in elderly patients with dementia, because they are easily recognized (Taniguchi et al., 2013).

To date, no study has demonstrated whether the time to blood culture collection affects blood culture positivity among patients with a history of shaking chills. The objective of this research was to determine whether blood culture positivity is higher in patients whose blood cultures are drawn earlier after shaking chills begin than in patients whose blood cultures are drawn later. The results could be used to improve the treatment of patients with severe bacterial infection and could aid the medical staff who take blood cultures.

## Methods

### *Study design and setting*

This was a hospital-based, prospective, observational study at Okinawa Chubu Hospital, which is located in the central region of Okinawa Island in Japan. Approximately 39 000 patients visit the emergency center and nearly 7000 patients are hospitalized through the emergency center per year. The division of infectious diseases treats adults with all kinds of infectious diseases, except for those with severe lung disease (who are admitted to the division of respiratory medicine), those with febrile neutropenia (hematology and oncology), those with chronic kidney disease who are on hemodialysis (nephrology), and those who need

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endoscopic or surgical management (gastrointestinal medicine or surgery). Over 500 patients per year are hospitalized in the division of infectious diseases. The study period was from January 1, 2013 to March 12, 2015.

*Participants*

All patients over 16 years of age who had a history of shaking chills and were newly admitted to the division of infectious diseases on suspicion of bacterial infection were enrolled. The suspicion of bacterial infection was based on both a clinical decision and laboratory tests including point-of-care Gram stain on admission (Taniguchi et al., 2015). Exclusion criteria were as follows: (1) not diagnosed with a bacterial infection clinically or after laboratory tests including culture results; (2) infectious agents that were not incubated in the usual blood culture bottles: viruses, Bartonella, Chlamydia, *Clostridium difficile*, Legionella, Leptospira, *Mycobacterium tuberculosis*; and (3) the time of onset of shaking chills was not recorded, unclear, or more than 48 h before.

*Exposures*

The exposure was the time lag between the start of shaking chills and the blood culture draw. Shaking chills or shivering was defined as chills plus persistent involuntary muscle tremors. The time that blood cultures were obtained was defined as the moment that a resident physician requested two sets of blood cultures by printing identification data labels. The time of onset of shaking chills was collected from the medical charts of the emergency center. If the time of onset was not recorded, the co-authors directly asked the patient, their family members, or the healthcare workers and confirmed the time. When shaking chills occurred more than once, the time of onset of the last episode of shaking chills was used, following which blood cultures were taken.

Previous antimicrobial use within 48 h prior to arrival was also considered an important exposure.

*Outcome measure*

The outcome measure was blood culture positivity. At least two sets of blood cultures that included aerobic and anaerobic bottles with Bactec Plus resin medium (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) were routinely drawn. These were taken mainly by resident physicians from the upper or lower limbs, not from the femoral vessels to decrease the risk of contamination, before antibiotics were started. The medical staff were encouraged to obtain at least 10 ml in each set. All culture bottles were incubated for at least 5 days in an automated blood culture system, the Bactec 9240 system (Kiyoyama et al., 2009).

Coagulase-negative staphylococci, *Bacillus* species, *Propionibacterium* species, *Micrococcus* species, *Clostridium* species, and also α-streptococci were considered potential skin contaminants (Kiyoyama et al., 2009). With the exception of α-streptococci, if any of these was cultured from only one set of blood cultures, it was regarded as a contaminant. Otherwise, clinical information was used to judge whether contamination had occurred or not.

*Statistical analysis*

In a preliminary study under different settings, which was reported at a conference of the Japanese Association for Infectious Diseases in Kyoto, Japan in 2010, the blood culture positivity values for blood drawn within 2 h after shaking chills and for blood drawn after more than 2 h were 60% (12/20) and 31% (13/42), respectively. Another study demonstrated that the blood culture positivity with a history of shaking chills was approximately 40% in this setting (Taniguchi et al., 2013). It was hypothesized that blood culture positivity might be lower than that in the preliminary study because the study conditions included in-hospital patients who had catheter-related blood stream infections. It was also hypothesized that a more than 15% difference in blood culture positivity between the blood culture obtained early group and the blood culture obtained later group would be clinically meaningful. Therefore, assuming a blood culture positivity in the obtained early group of 50% and in the obtained later group of 30%, an early and later group ratio of 1:1, 80% power, and two-sided alpha level of 0.05, it was calculated that 103 patients per group would be needed. Thus, it was aimed to continue this study until at least 206 patients were included.

After the data collection, if a cut-off of 2 h was chosen, the early and later group ratio was closer to 1:1 than it was with a cut-off of 3 h. Therefore, patients were divided into two groups: (1) those for whom blood cultures were drawn at $\leq$2 h after shaking chills occurred, and (2) those for whom blood cultures were drawn at >2 h after shaking chills occurred.

Patient characteristics were analyzed using the Chi-square test or Fisher's exact test for categorical variables. The Mann–Whitney *U*-test was performed for numerical variables after an analysis of the data distribution.

A multiple logistic regression model was used to investigate the association between the risk of blood culture positivity and the time lag between the start of the most recent shaking chills and time at which blood cultures were obtained. Age and previous antimicrobial exposure were sequentially assigned to the model, because these factors were shown to be correlated with blood culture positivity in previous research (Taniguchi et al., 2013). Next, shaking chills that occurred more than once were added into the model to include the possibility of another correlating variable. In addition, systolic blood pressure, respiratory rate, and body temperature were entered into the model to adjust for severity. This was because the first two vital signs are included as important factors with sepsis in the quick Sequential Organ Failure Assessment (qSOFA) score (Seymour et al., 2016), and body temperature also differed between the two groups. The level of consciousness included in qSOFA was not used because most of the patients were too old to determine a precise Glasgow Coma Scale score. Intra-abdominal infection was finally added into the model to adjust for possible confounding, because it differed among infection sources in the two groups.

The results were calculated using Stata software version 12.1 (StataCorp, College Station, TX, USA).

*Ethics*

This research was an observational study and, therefore, no written informed consent documents were required. The study proposal was approved by the Institutional Review Board of Okinawa Chubu Hospital.

## Results

Two hundred and seventy-three patients were screened, of whom 59 were excluded: 13 had a non-infectious etiology (histiocytic necrotizing lymphadenitis (called Kikuchi's disease in Japan), malignant lymphoma, drug hepatitis, pseudogout, and others), 11 had infectious agents that were not incubated in the usual blood culture bottles (Bartonella, Chlamydia, *Clostridium difficile*, influenza, Legionella, Leptospira, *Mycobacterium tuberculosis*, and mumps virus), and for 35 patients, the time of onset of shaking chills was not recorded, unclear, or more than 48 h before.

Finally, 214 patients were enrolled. Table 1 shows a comparison between the two groups. Performance status was based on the