J Infect Chemother xxx (2017) 1–5

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Integration of DPC and clinical microbiological data in Japan reveals importance of confirming a negative follow-up blood culture in patients with MRSA bacteremia

Naoki Miyamoto [a, 1], Koji Yahara [b, *, 1], Rie Horita [a], Tomomi Yano [a], Naotaka Tashiro [a], Daiichi Morii [b], Atsuko Tsutsui [b], Kenichiro Yaita [c, d], Keigo Shibayama [b], Hiroshi Watanabe [c, d]

[a] Department of Laboratory Medicine, Kurume University Hospital, Kurume, Fukuoka 830-0011, Japan
[b] Antimicrobial Resistance Research Center, National Institute of Infectious Diseases, Higashimurayama, Tokyo 189-0002, Japan
[c] Division of Infection Control and Prevention, Kurume University Hospital, Kurume, Fukuoka 830-0011, Japan
[d] Department of Infection Control and Prevention, Kurume University School of Medicine, Kurume, Fukuoka 830-0011, Japan

ARTICLE INFO

Article history:
Received 1 April 2017
Received in revised form
13 June 2017
Accepted 19 July 2017
Available online xxx

Keywords:
MRSA
Bacteremia
DPC
Survival
Infection control
Epidemiology

ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia is one of the commonest and most life-threatening of all infectious diseases. The morbidity and mortality rates associated with MRSA bacteremia are higher than those associated with bacteremia caused by other pathogens. A common guideline in MRSA bacteremia treatment is to confirm bacteremia clearance through additional blood cultures 2–4 days after initial positive cultures and as needed thereafter. However, no study has presented statistical evidence of how and to what extent confirming a negative follow-up blood culture impacts clinical outcome. We present this evidence for the first time, by combining clinical microbiological data of blood cultures and the DPC administrative claims database; both had been systematically accumulated through routine medical care in hospitals. We used electronic medical records to investigate the clinical background and infection source in detail. By analyzing data from a university hospital, we revealed how survival curves change when a negative follow-up blood culture is confirmed. We also demonstrated confirmation of a negative culture is significantly associated with clinical outcomes: there was a more than three-fold increase in mortality risk (after adjusting for clinical background) if a negative blood culture was not confirmed within 14 days of the initial positive blood culture. Although we used data from only one university hospital, our novel approach and results will be a basis for future studies in several hospitals in Japan to provide statistical evidence of the clinical importance of confirming a negative follow-up blood culture in bacteremia patients, including those with MRSA infections.

1. Introduction

Bacteremia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the commonest and life-threatening of all infectious diseases. Although prevalence of MRSA bacteremia has decreased in several developed countries since 2005 due to improvements in infection control procedures [1], it is still associated with a higher morbidity and mortality than bacteremia caused by other pathogens [2–5]. The mortality rate at 30 days has been reported to be approximately 30% [6,7], but it has also been reported to be higher than 50% in a hospital [8]. Treatment failure occurs in up to 50% of cases [9], resulting in a persistent or recurrent bacteremia that is difficult to successfully eliminate [10–13].

According to the clinical practice guidelines for the treatment of MRSA infections by the Infectious Diseases Society of America, “additional blood cultures 2–4 days after initial positive cultures and as needed thereafter are recommended to document clearance of bacteremia” [14]. Confirming a negative blood culture is vital to decide duration of therapy for MRSA bacteremia because the

* Corresponding author. Antimicrobial Resistance Research Center, National Institute of Infectious Diseases, Higashimurayama, Tokyo 189-0002 Japan.
E-mail address: k-yahara@nih.go.jp (K. Yahara).
[1] contributed equally to this article.

http://dx.doi.org/10.1016/j.jiac.2017.07.009
1341-321X/

recommended treatment duration is at least 14 days of intravenous antibiotics from the first negative blood culture [12].

However, no study thus far has presented statistical evidence of how and to what extent confirming a negative follow-up blood culture is related to clinical outcomes. Here, we aim to present evidence of this, for the first time, by combining clinical microbiological data of blood cultures and the Japanese Diagnosis Procedure Combination (DPC) administrative claims database, both of which have been systematically accumulated through routine medical care in hospitals adopting them. Data from the former include the results of both positive and negative blood cultures while data from the latter include treatment history and clinical outcome at discharge of each patient in a particular hospital. We also used electronic medical records to investigate the clinical background and source of infection in detail.

We analyzed data from the Kurume University Hospital (Kurume, Japan), and present a novel classification of survival curves according to the results of follow-up blood cultures and whether they were done or not. We found that confirming a negative follow-up blood culture was significantly associated with a favorable clinical outcome, with overall more than three-fold increase in the risk of death if a negative blood culture was not confirmed within 14 days of the initial blood culture testing positive for MRSA.

2. Materials and methods

2.1. Data preparation

We obtained the electronic records of every microbiological test conducted from March 1, 2011 to May 31, 2016, in Kurume University Hospital with 25 diagnostic and treatment departments and 24 wards with 1025 beds. We also obtained data from the DPC during the same period. Specifically, we obtained the File Format 1-file (containing data regarding clinical outcome at the time of discharge of each patient) and EF-file (containing data regarding treatment history). Kurume University Hospital is one of many hospitals that has adopted the DPC system, and submits these files quarterly to the Ministry of Health, Labour and Welfare in Japan. We combined the two datasets by an in-house Perl script using a patient ID as the key. We also manually searched electronic medical records to investigate clinical background and source of infection in detail.

2.2. Criteria for selecting patients with MRSA bacteremia

From the clinical microbiological data, we selected patients whose blood cultures tested positive for MRSA. We limited the selection to patients who had at least two blood cultures positive for MRSA from the first day of taking a blood culture to 4 days afterwards in order to exclude those whose samples were potentially contaminated.

2.3. Survival analyses

We conducted survival analyses for patients with MRSA bacteremia by using time to death or survival at discharge as response variables. First, we generated Kaplan-Meier survival curves for patients with and without a negative follow-up blood culture, and conducted a log-rank test of both samples. We then conducted the same analysis on the data after subclassifying the patients without a negative follow-up blood culture into those “who had no follow-up blood culture” and “others”. In the main text, we showed the survival curves of up to 28 days after the initial positive blood culture in which 71% of the dead cases occurred. Next, we compared the clinical backgrounds of the patients who had a negative follow-up blood culture with others for each variable by the Wilcoxon rank sum test or Fisher's exact test. We then conducted multiple Cox regression analyses adjusting for variables that showed $p < 0.1$ as well as age and sex in order to estimate the hazard ratio of confirmation of a negative blood culture within 7 and 14 days after the initial positive blood culture. We conducted the multiple Cox regression analysis separately in each of the subgroups by using the group who had a negative follow-up blood culture as a reference. The analyses were all conducted by using JMP Pro version 13 (SAS Institute, Cary, NC, USA) and R statistical software version 3.3.1.

2.4. Ethical considerations

The study was approved by the ethics committee of the Kurume University (approval number 16059) and National Institute of Infectious Diseases (approval number 701).

3. Results

A total of 64 patients fit the inclusion criteria for MRSA bacteremia (at least two blood cultures testing positive for MRSA from the first day of taking a blood culture to 4 days after that) and had records of clinical outcome at discharge in the DPC database. Among them, 21 patients died during the entire period, and 15 died within 28 days after an initial positive blood culture. Twenty-five patients were transferred to a different hospital during the entire period. Within 28 days after an initial positive blood culture, 2 patients were transferred to a different hospital and 8 were discharged and returned to their family. In 46 patients, the follow-up blood culture was negative after the initial blood culture tested positive.

Mixed infections were found in 5 patients, 3 of whom died at 19, 26, and 137 days after the initial positive blood cultures. In addition to MRSA, extended spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae*, *Enterococcus faecalis*, and *Streptococcus dysgalactiae* were found in the blood cultures of these 3 patients. The remaining 2 out of the 5 patients had mixed infections with *Streptococcus mitis/oralis* or methicillin-resistant *Staphylococcus capitis*, but were alive at discharge.

Comparison of the clinical backgrounds of the patients who had had a negative follow-up blood culture with others is shown in Table 1. Only the proportion of patients with autoimmune disease showed $p < 0.1$ between the two groups. From the treatment history of each patient derived from the DPC database, we checked the number of patients who were treated by the following four anti-MRSA antibiotics defined in the guideline for the treatment of MRSA infections in Japan and the Clinical and Laboratory Standards Institute (CLSI) (Fig. 1 (a)): 43, vancomycin (VCM); 26, linezolid (LZD); 22, teicoplanin (TEIC); and 18, daptomycin (DAP). The number of patients who were treated by multiple drugs among them was 34 (Fig. 1(a)). We also determined the routes of infection (Fig. 1 (b)). Unknown routes accounted for 44% of the cases, followed by catheter-related bloodstream infection (17%) and wound infection (19%).

Next, we compared the survival curves of patients who had a negative follow-up blood culture with others, and found that the difference was highly significant ($p < 0.0001$, log-rank test). Clearly, patients who had a negative follow-up blood culture (red in Fig. 2(a)) were more likely to survive than others. Furthermore, we considered that the others could be a mixture of patients who had a follow-up blood culture but did not have negative results as well as those who did not have any follow-up blood culture (because it was impossible or was judged as not needed by a doctor). We thus compared survival curves among these two subgroups (blue and

Please cite this article in press as: Miyamoto N, et al., Integration of DPC and clinical microbiological data in Japan reveals importance of confirming a negative follow-up blood culture in patients with MRSA bacteremia, J Infect Chemother (2017), http://dx.doi.org/10.1016/j.jiac.2017.07.009