Regular Article

Daily Review of Antimicrobial Use Facilitates the Early Optimization of Antimicrobial Therapy and Improves Clinical Outcomes of Patients with Bloodstream Infections

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Insufficient information is available to confirm the beneficial effects of implementing an antimicrobial stewardship program in reducing mortality of patients with bloodstream infections. A single institutional cohort study was conducted to evaluate clinical outcomes after implementation of a daily review of antimicrobials used to treat patients with bloodstream infections. Subjects were allocated to groups receiving either intervention or nonintervention. After implementation of an antimicrobial stewardship program, the day from the onset of infection required to administer effective intravenous antimicrobial treatment was significantly shortened ($p=0.022$), and the rate of de-escalation was significantly elevated ($p<0.001$) compared with the nonintervention group. Further, the rate of 30-d death associated with bloodstream infection was siginificantly reduced from 11.4 to 5.4% ($p=0.030$) compared with the nonintervention group. The incidence of adverse events was significantly lower in the intervention group than in the nonintervention group (7.7 *vs.* 28.0%, $p<0.001$). Our present findings suggest that daily review of the use of antimicrobials was highly effective for optimizing early antimicrobial therapy and improved clinical outcomes of patients with bloodstream infections.

Key words daily review; antimicrobial use; adverse event; mortality; bloodstream infection

Bacteremia is a serious clinical condition associated with high mortality. A multicenter retrospective cohort study conducted in the United States found that the median rate of bloodstream infection in hospital is 3.5 bloodstream infections per 1000 patient days, and the in-hospital mortality rate is 18%.[1] The study further indicated that, for patients with bacteremia, timely and appropriate antimicrobial treatment is crucial.[2] However, the inappropriate use of antibiotics in hospitals ranges from 26 to 57%.[3–5] Therefore, implementation of antimicrobial stewardship is required to ensure appropriate use of antimicrobials.

The guidelines of the Infectious Disease Society of America and the Society for Healthcare Epidemiology of America propose the core strategies for implementing antimicrobial stewardship designated "formulary restriction and pre-authorization" and "prospective audit with intervention and feedback."[6] Evidence indicates that the latter strategy is effective when implemented within 72 h of the initiation of antibiotic therapy.[7] In August 2009, we implemented a hospital-wide, multidisciplinary intervention program based on this strategy to optimize antibiotic use within 24 h after onset of therapy, which was unique in targeting all patients received intravenous antimicrobials, and found it highly effective in decreasing inappropriate use of antibiotics, reducing the length of hospitalization, reducing the rate of appearance of methicillin-resistant *Staphylococcus aureus* (MRSA), and reducing medical expenses.[8]

Improved patient outcomes are an important benefit of implementing antimicrobial stewardship; however, limited data are available to encourage its general use.[9] In contrast, a delay in the choice of appropriate antibiotic therapy contributes to unfavorable clinical outcomes of patients with infections caused by antibiotic-resistant bacteria, particularly patients with bloodstream infections.[10,11]

The aims of the present study were to establish the efficacy of our present antimicrobial intervention system, in which we implement within 24 h after initiating therapy, to ensure the appropriate use of antimicrobials and to evaluate its influence on the clinical outcomes of patients with bloodstream infections.

MATERIALS AND METHODS

Study Design A single-center, prospective cohort study was conducted at the 614-bed Gifu University Hospital that provides tertiary care. Patients with bloodstream infections from August 1, 2008, to July 31, 2009 (nonintervention group), and August 1, 2010, to July 31, 2011 (intervention group), were enrolled in the present study. The Pitt bacteremia score[12] and the Charlson comorbidity index[13] were assessed at the time of onset of bloodstream infection to evaluate the severity of illness. Data were extracted from electronic medical records database in our hospital.

Intervention To implement antimicrobial intervention, the antimicrobial stewardship team (AST) performed daily reviews of prescriptions for inpatients receiving intravenous antimicrobials according to the prospective audit with intervention and feedback strategy. Briefly, we assembled a team to implement antimicrobial stewardship comprising a physician and pharmacist both specializing in infectious diseases and

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other members of the AST who were in charge of daily review of prescriptions for all intravenous antimicrobials within 24 h after initiating therapy for every hospitalized patient. Further, the team's physician and pharmacist intervened in real-time if inappropriate antimicrobials were administered to patients.

Since August 2010, inpatients receiving intravenous antibiotics were reviewed at least twice weekly to enhance the appropriate use of antibiotics, which was determined according to published guidelines, mainly those of the *Sanford Guide to Antimicrobial Therapy*. The team intervened in the daily review as follows: (1) recommendation of appropriate antibiotic use according to the source of infection, prior use of an antimicrobial agent, prior isolation of resistant pathogens, and presence of intravascular devices, (2) modification of antimicrobial selection according to the gram-stain of the isolate when an automated blood culture system detected growth, and (3) recommendation of de-escalation according to antimicrobial susceptibility upon identification of the causative microorganism.

Definitions Clinically significant bloodstream infection was defined according to the modified criteria of the United States Centers for Disease Control and Prevention (CDC) as follows: ≥1 positive blood culture for all bacterial pathogens except common skin contaminants that required ≥2 positive blood cultures within the 48 h period.[14] The day that the first positive blood culture was sampled was designated as the date of onset of the bloodstream infection (day 0). Catheter-related bloodstream infection was considered when clinical signs of catheter infection, positive culture results from the catheter tip, or both were present with no evidence of an alternate source of bloodstream infection. Primary bloodstream infection was diagnosed when an infectious focus was not identified. The source of secondary bloodstream infection was determined from clinical, radiological, and microbiological evidence consistent with the CDC criteria.

Outcomes The number of days until administration of effective intravenous antimicrobials was defined as the interval from the day of onset of infection to the day of administration of the potentially effective antimicrobials for treating the pathogen identified in patients' cultures, which included escalation according to known susceptibility.[15] The rates of de-escalation were defined as the rates of change to antibiotics with a narrower spectrum of efficacy in patients available for de-escalation according to culture results. The rate of 30-d mortality associated with bloodstream infection and the rate of re-infection 30 d after completing treatment were measured to evaluate clinical efficacy. The 30-d re-infection rate was defined as infection caused by the same pathogen within 30 d after the completion of antimicrobial therapy.[16]

Adverse Events Adverse events associated with antimicrobial agents were graded according to patients' physical symptoms or laboratory data using the Japan Clinical Oncology Group/Japan Society of Clinical Oncology's version of the Common Terminology Criteria for Adverse Events version 3.0[17] described in the Japanese Society of Chemotherapy's criteria for assessing adverse reactions and abnormal laboratory values associated with antibacterial agents.[18] The incidence of grade 2 and higher adverse events was compared between the periods of nonintervention and intervention.

Statistical Analysis Data were analyzed using SPSS version 21 (SPSS Inc., Chicago, IL, U.S.A.) and GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, U.S.A.). A *t*-test was used to analyze data with a Gaussian distribution and the Mann–Whitney *U* or chi-square tests were used to analyze data with a non-Gaussian distribution. Mortality was analyzed using the Kaplan–Meier method, and the curves were compared using the Mantel–Cox log-rank test to determine hazard ratios (HRs) and 95% confidence intervals (CIs). Cox proportional hazard analyses were performed to assess potential prognostic factors of bloodstream infection. Variables for 30 d mortality with $p<0.10$ obtained from the comparison of survival group with death group were subjected to the univariate as well as multivariate Cox proportional hazard analyses. Statistically significant differences were defined by $p<0.05$.

Ethical Approval This study was conducted in accordance with the guidelines for human studies of the Ethics Committee of Gifu University Graduate School of Medicine and the government of Japan. The Medical Review Board of Gifu University Graduate School of Medicine approved the study (approval No. 26–148). Acquiring patients' informed consent was waived, because the present study represented customary medical practice.

RESULTS

Patient Demographics Among 529 patients with bloodstream infection, 396 fulfilled the study criteria. Patients were excluded for the following reasons: 131 patients were considered as bacterial contaminants, and 2 patients were discharged a few days before blood cultures became positive. Of the 396 eligible patients, 175 and 221 comprised the nonintervention and intervention groups, respectively. The demographics of patients are shown in Table 1. No significant differences were noted in patient characteristics between groups, except for height (157.6±14.2 cm, nonintervention *vs.* 160.8±8.9 cm, intervention; mean±standard deviation [S.D.], $p=0.011$). Pitt bacteremia scores were similar for both groups, but the Charlson comorbidity index was higher for the intervention group (6 [4–8] *vs.* 5 [3–7], median [interquartile range], $p=0.021$). The most frequent source of bloodstream infection was primary or unidentified, followed by catheter- or device-associated, surgical site, or skin tissue. No significant differences were noted in the source of bloodstream infection between groups, except for primary or unidentified (32.0% nonintervention *vs.* 22.1% intervention, $p=0.028$) and surgical site or skin tissue (24.0% intervention *vs.* 13.1% nonintervention, $p=0.012$). Isolated organisms were generally similar between groups. The most frequent pathogen was methicillin-resistant coagulase-negative *Staphylococcus*, followed in order by *Staphylococcus aureus* species, *Enterococcus* species, and *Escherichia coli*.

Appropriateness of Antimicrobial Therapy The most frequently used antimicrobial was carbapenems in both groups (Table 2). The prevalence of the use of first generation cephalosporins and glycopeptides was significantly changed in the intervention group (0% intervention *vs.* 5.9% nonintervention for first generation cephalosporins, $p<0.001$; 21.1% intervention *vs.* 9.7% nonintervention for glycopeptides, $p=0.001$). The number of days to effective intravenous antimicrobial treatment from the onset of infection was significantly shorter in the intervention group (median time was 0 d for intervention *vs.* 1 d for nonintervention, $p=0.022$) (Table 2, Fig. 1). Further, on day 2 from the onset of infection, the rate of choice of anti-

Table 1. Comparison of Demographics of Nonintervention and Intervention Groups

	Nonintervention group (n=175)	Intervention group (n=221)	p Value
Gender (male/female), *n*	106/69	144/77	0.347 [a]
Age (years), median (interquartile range)	66 (54–76)	65 (55–75)	0.952 [b]
Height (cm)	157.6±14.2	160.8±8.9	0.011 [c]
Body weight (kg)	57.4±13.9	58.19±14.4	0.603 [c]
Serum albumin (g/dL)	2.9±0.6	2.8±0.6	0.131 [c]
Aspartate aminotransferase (IU/L)	77.4±343.4	48.2±72.4	0.219 [c]
Alanine aminotransferase (IU/L)	68.0±176.9	47.6±79.8	0.157 [c]
Serum creatinine (mg/dL)	0.99±1.0	1.1±1.3	0.430 [c]
Blood urea nitrogen (mg/dL)	23.0±18.3	21.5±16.0	0.387 [c]
White cell count (/mm^3)	10381±7353	10634±13109	0.819 [c]
C-Reactive protein (mg/dL)	9.1±7.8	8.6±7.4	0.470 [c]
Body temperature (°C)	38.6±1.2	38.8±1.0	0.265 [c]
Pitt bacteremia score, median (interquartile range)	2 (1–3)	2 (1–3)	0.686 [b]
Charlson comorbidity index, median (interquartile range)	5 (3–7)	6 (4–8)	0.021 [b]
Infectious source, *n* (%)			
Primary or unidentified	56 (32.0)	49 (22.1)	0.028 [a]
Catheter-associated or device	38 (21.7)	57 (25.8)	0.345 [a]
Surgical site or skin tissue	23 (13.1)	51 (24.0)	0.012 [a]
Intra-abdominal	22 (12.6)	27 (12.2)	0.915 [a]
Urinary	23 (13.1)	23 (10.4)	0.399 [a]
Respiratory	8 (4.6)	12 (5.4)	0.876 [a]
Others	5 (2.9)	2 (0.9)	0.280 [a]
Organisms, *n* (%)[d]			
Methicillin-resistant coagulase-negative *Staphylococcus*	23 (12.8)	39 (17.0)	0.241 [a]
Staphylococcus aureus	19 (10.6)	26 (11.3)	0.810 [a]
Enterococcus species	19 (10.6)	23 (10.0)	0.854 [a]
Escherichia coli	18 (10.0)	18 (7.8)	0.440 [a]
Klebsiella species	13 (7.2)	17 (7.4)	0.948 [a]
Methicillin-resistant *Staphylococcus aureus*	13 (7.2)	15 (6.5)	0.780 [a]
Pseudomonas aeruginosa	10 (5.6)	13 (5.7)	0.996 [a]
Coagulase-negative *Staphylococcus*	13 (7.2)	8 (3.5)	0.139 [a]
Enterobacter species	7 (3.9)	7 (3.0)	0.846 [a]
Streptococcus species	4 (2.2)	10 (4.3)	0.367 [a]
Others	41 (22.8)	54 (23.5)	0.868 [a]

Data are the mean±S.D. unless otherwise specified. *a*) Chi-square test. *b*) Mann–Whitney *U*-test. *c*) *t*-test. *d*) Duplicate was included.

microbials appropriate to the pathogens increased significantly in the intervention group, from 64.5 to 79.2% (p=0.001) (Table 2). The rate of de-escalation in patients available for de-escalation according to culture results was significantly elevated after intervention (55.5% nonintervention *vs.* 81.7% intervention, p<0.001).

Clinical Outcomes The rate of 30-d mortality associated with bloodstream infection was significantly lower in the intervention group (5.4% intervention *vs.* 11.4% nonintervention, p=0.030) (Table 2). Kaplan–Meier plots for cumulative survival indicated a significant increase in survival among subjects in the intervention group (HR: 0.48; 95% CI: 0.26–0.90; p=0.037) (Fig. 2). Further, the rate of re-infection within 30 d was lower in the intervention group (2.8% intervention *vs.* 8.2% nonintervention, p=0.063). However, the median period of treatment and the length of hospitalization after onset of infection were not significantly different between groups.

Prognostic Factors of Mortality in Patients with Bloodstream Infections The demographics of survival and death groups were shown in Table 3. Following variables for 30 d mortality with p<0.10; age (p=0.068), serum albumin (p=0.002), serum creatinine (p=0.033), Pitt bacteremia score (p=0.013), implementation of antimicrobial stewardship (p=0.030), intra-abdominal infection (p=0.047), MRSA infection (p=0.091), were considered for entrance into Cox proportional hazard analysis. The blood urea nitrogen was not tested in the Cox proportional hazard analysis since the value was highly correlated with the serum creatinine. Univariate Cox proportional hazard analysis showed that renal impairment (serum creatinine >1 mg/dL), implementation of antimicrobial stewardship, hypoalbuminemia (≤2.5 g/dL), MRSA infection, intra-abdominal infection, and high Pitt bacteremia score (>4) were found to be significant prognostic factors for 30-d mortality (Table 4). Multivariate Cox proportional hazard analysis indicated that the implementation of antimicrobial intervention was the only factor reducing mortality associated with bloodstream infection (HR: 0.41; 95% CI: 0.19–0.86, p=0.018). In contrast, hypoalbuminemia (≤2.5 g/dL) (HR: 2.80; 95% CI: 1.37–5.72; p=0.005), MRSA infection (HR: 2.83; 95% CI: 1.04–7.69; p=0.042), intra-abdominal infection (HR: 2.92; 95% CI: 1.26–6.75; p=0.012), and high Pitt bacteremia score (>4) (HR: 4.08; 95% CI: 1.67–9.99; p=0.002) were significant

Table 2. Comparison of Antimicrobial Use, Clinical Outcomes, and Adverse Events between Nonintervention and Intervention Groups

	Nonintervention group (n=175)	Intervention group (n=221)	p Value
Antimicrobial use, n (%)[a]			
Penicillins	8 (4.3)	16 (6.5)	0.437 [b]
Penicillin-β-lactamase inhibitor combinations	31 (16.7)	30 (12.2)	0.186 [b]
First generation cephalosporins	11 (5.9)	0 (0)	<0.001 [b]
Second generation cephalosporins	1 (0.5)	4 (1.6)	0.553 [b]
Third generation cephalosporins	20 (10.8)	30 (12.2)	0.643 [b]
Fourth generation cephalosporins	18 (9.7)	22 (8.9)	0.794 [b]
Carbapenems	44 (23.7)	59 (24.0)	0.937 [b]
Glycopeptides	18 (9.7)	52 (21.1)	0.001 [b]
Quinolones	4 (2.2)	6 (2.4)	0.900 [b]
Others	31 (16.7)	27 (11.0)	0.089 [b]
Day to effective intravenous antimicrobial treatment from the onset of infection (median, interquartile range)	1 (0–4)	0 (0–2)	0.022 [c]
Rate of choice of antimicrobials appropriate to the pathogens on Day 2	113 (64.5)	175 (79.2)	0.001 [b]
De-escalation, n (%)	66/119 (55.5)	94/115 (81.7)	<0.001 [b]
Rate of 30-d death associated with bloodstream infection, n (%)	20 (11.4)	12 (5.4)	0.030 [c]
Rate of 30-d re-infection, n (%)	11/134 (8.2)	5/176 (2.8)	0.063 [c]
Median period of treatment (days, interquartile range)	13 (8–23)	12 (7–17)	0.106 [c]
Median length of hospital stay after onset of infection (days, interquartile range)	32 (16–66)	35 (17–76)	0.350 [c]
Adverse events, n (%)	49 (28.0)	17 (7.7)	<0.001 [b]
Hepatotoxicity, n (%)	27 (15.4)	5 (2.3)	<0.001 [b]
Nephrotoxicity, n (%)	17 (9.7)	10 (4.5)	0.042 [b]
Thrombocytopenia, n (%)	3 (1.7)	0 (0)	0.171 [b]
Allergy, n (%)	2 (1.1)	2 (0.9)	0.786 [b]

a) Duplicate was included. *b*) Chi-square test. *c*) Mann–Whitney *U*-test.

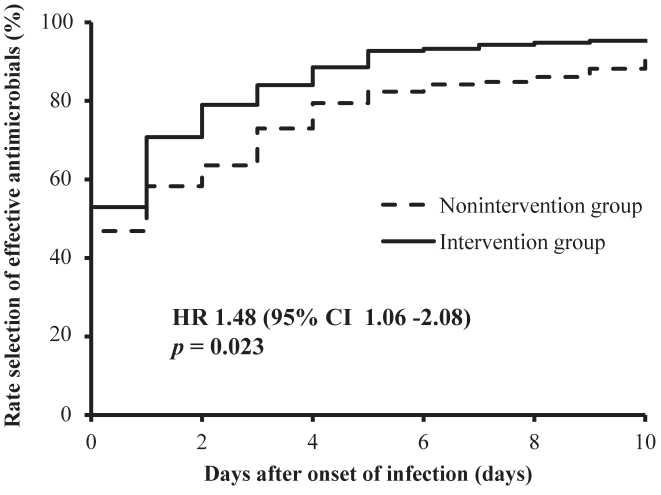

Fig. 1. Kaplan–Meier Plots Comparing the Cumulative Rates of Administration of Effective Antimicrobials against Isolated Pathogens between Nonintervention and Intervention Groups

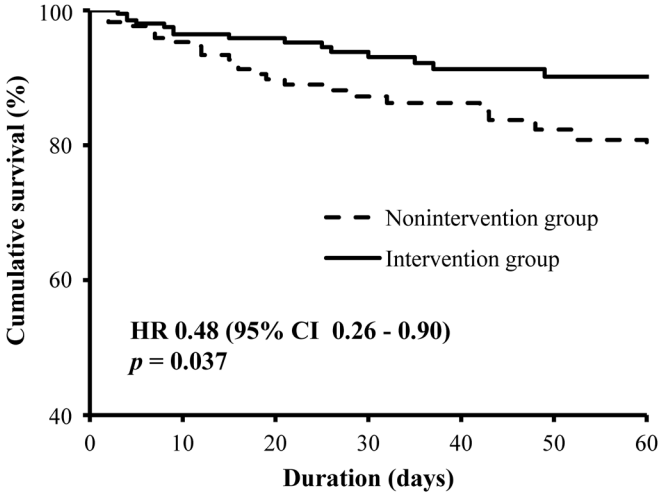

Fig. 2. Kaplan–Meier Plots Comparing the Cumulative Survival between Nonintervention and Intervention Groups

risk factors for 30-d mortality.

Incidence of Adverse Events Associated with Antimicrobials The most frequent adverse event (grades ≥2) in the nonintervention group was hepatotoxicity caused predominantly by carbapenems or penicillin-β-lactamase inhibitor combinations, followed by nephrotoxicity caused mainly by carbapenems or glycopeptides (Table 2). The incidence rates of hepatotoxicity and nephrotoxicity were significantly lower in the intervention group (2.3% intervention *vs.* 15.4% nonintervention for hepatotoxicity, p<0.001; 4.5% intervention *vs.* 9.7% nonintervention for nephrotoxicity, p=0.042). In addition, the incidence rates of hepatotoxicity and nephrotoxicity in patients administered with carbapenems were lower in the intervention group (3.4% intervention *vs.* 25% nonintervention for hepatotoxicity, p=0.003; 5.1% intervention *vs.* 13.6% nonintervention for nephrotoxicity, p=0.128). The overall incidence of adverse events was significantly lower in the intervention group than in the nonintervention group (7.7 *vs.*

Table 3. Comparison of Demographics of Survival and Death Groups

	Survival group (n=364)	Death group (n=32)	p Value
Gender (male/female), n	233/131	17/15	0.221 [a]
Age (years), median (interquartile range)	65 (54–75)	73 (59–78)	0.068 [b]
Height (cm)	159.5±12.0	156.9±7.2	0.111 [c]
Body weight (kg)	57.8±14.0	58.0±16.5	0.957 [c]
Serum albumin (g/dL)	2.9±0.7	2.4±0.7	0.002 [c]
Aspartate aminotransferase (IU/L)	61.4±243.8	58.1±75.3	0.859 [c]
Alanine aminotransferase (IU/L)	56.4±132.4	60.7±130.7	0.859 [c]
Serum creatinine (mg/dL)	1.0±1.1	1.4±1.2	0.033 [c]
Blood urea nitrogen (mg/dL)	21.6±16.9	29.3±18.0	0.025 [c]
White cell count (/mm^3)	10521±11237	10534±6673	0.995 [c]
C-Reactive protein (mg/dL)	8.7±7.5	10.5±7.9	0.234 [c]
Body temperature (°C)	38.7±1.0	38.5±1.3	0.265 [c]
Pitt bacteremia score, median (interquartile range)	2 (1–3)	3 (1–4)	0.013 [b]
Charlson comorbidity index, median (interquartile range)	6 (4–8)	7 (5–8)	0.229 [b]
Implementation of antimicrobial stewardship, n (%)	209 (57.4)	12 (37.5)	0.030 [a]
Infectious source, n (%)			
Primary or unidentified	96 (26.4)	9 (28.1)	0.995 [a]
Catheter-associated or device	89 (24.5)	6 (18.8)	0.611 [a]
Surgical site or skin tissue	68 (18.7)	6 (18.8)	0.820 [a]
Intra-abdominal	41 (11.3)	8 (25.0)	0.047 [a]
Urinary	45 (12.4)	1 (3.2)	0.200 [a]
Respiratory	19 (5.3)	1 (3.2)	0.922 [a]
Others	6 (1.6)	1 (3.2)	0.717 [a]
Organisms, n (%)[d]			
Methicillin-resistant coagulase-negative *Staphylococcus*	60 (15.9)	2 (6.3)	0.229 [a]
Staphylococcus aureus	41 (10.8)	4 (12.5)	0.994 [a]
Enterococcus species	36 (9.5)	6 (18.8)	0.177 [a]
Escherichia coli	34 (9.0)	2 (6.3)	0.840 [a]
Klebsiella species	27 (7.1)	3 (9.4)	0.911 [a]
Methicillin-resistant *Staphylococcus aureus*	23 (6.1)	5 (15.5)	0.091 [a]
Pseudomonas aeruginosa	23 (6.1)	0 (0)	0.992 [a]
Coagulase-negative *Staphylococcus*	20 (5.3)	1 (3.1)	0.908 [a]
Enterobacter species	14 (3.7)	0 (0)	0.548 [a]
Streptococcus species	14 (3.7)	0 (0)	0.548 [a]
Others	86 (22.8)	9 (28.1)	0.636 [a]

Data are the mean±S.D. unless otherwise specified. *a*) Chi-square test. *b*) Mann–Whitney *U*-test. *c*) *t*-test. *d*) Duplicate was included.

Table 4. Univariate and Multivariate Cox Proportional Hazard Analysis for the Prognostic Factors of 30-d Mortality in Patients with Bloodstream Infection

Factors	Univariate analysis 95% CI				Multivariate analysis 95% CI			
	HR	Lower	Upper	p Value	HR	Lower	Upper	p Value
Age ≥65 years	1.44	0.71	2.91	0.312				
Serum creatinine >1 mg/dL	1.83	0.9	3.7	0.093	1.55	0.75	3.2	0.236
Implementation of antimicrobial stewardship	0.47	0.23	0.96	0.038	0.41	0.19	0.86	0.018
Serum albumin ≤2.5 g/dL	2.43	1.21	4.87	0.012	2.8	1.37	5.72	0.005
MRSA infection	2.47	0.95	6.41	0.063	2.83	1.04	7.69	0.042
Intra-abdominal infection	2.34	1.05	5.2	0.038	2.92	1.26	6.75	0.012
Pitt bacteremia score >4	2.88	1.24	6.66	0.013	4.08	1.67	9.99	0.002

28.0%, respectively, RR: 0.26; 95% CI: 0.16–0.46; p<0.001).

DISCUSSION

Antimicrobial stewardship is an essential strategy for improving the appropriate prescription of antibiotics. However, little evidence is available suggesting that this strategy reduces mortality. Further, procedures used to implement antimicrobial stewardship intervention may differ radically depending on healthcare and cultural settings.[6,19] Unfortunately, antimicrobial stewardship is not implemented in numerous medical institutions in Japan, indicating a gap between suggestions in

guidelines and actual clinical practice. We reported previously that extensive implementation of an antimicrobial stewardship program for all inpatients receiving parenteral antimicrobials reduces the length of hospitalization as well as the costs of procuring antimicrobials and providing healthcare[7]; however, the effect of our extensive intervention on mortality is unclear. Therefore, in the present study, we evaluated the effect of our early optimization strategy of antimicrobial use on clinical outcomes of patients with bloodstream infections, which is one of the most crucial infections. Here, we showed that implementation of antimicrobial stewardship facilitated the use of appropriate antimicrobials at an early stage of infection and increased the rate of de-escalation with a concomitant remarkable reduction in mortality and adverse events in patients with bloodstream infections.

Our previous study showed that AST members, through their daily review of antimicrobial therapy during 1 year, performed 200 interventions against inappropriate antimicrobial administration, and 93% of their recommendations were accepted.[8]

The international guidelines for the management of severe sepsis and septic shock recommend starting the administration of effective antimicrobial agents within 1 h of recognition of severe sepsis.[20] However, before intervention, antibiotics with a narrow spectrum were administered until results of bacterial culture were obtained. Implementation of daily review of antimicrobial prescriptions within 24 h after antibiotic therapy facilitated the choice of the appropriate drugs. Indeed, the rate of choosing appropriate antimicrobials for the pathogens on day 2 after the onset of infection increased significantly after intervention. Further, the rate of de-escalation was markedly elevated after intervention as well. These results indicate that the antimicrobial intervention promoted the appropriate use of antimicrobials.

Intervention led to a significant increase in the survival of patients with bloodstream infection. Rates of 30-d re-infection were reduced, but the difference was not statistically significant after intervention. Tsukamoto *et al.* reported that daily intervention according to positive blood cultures is associated with a decline in 30-d mortality from 22.9% before intervention to 14.3% after intervention ($p=0.02$) in patients with hospital-acquired bloodstream infection.[21] Other investigators have reported the efficacy of matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, which identifies pathogens more quickly, combined with AST intervention on patients' outcomes.[15,22] However, subjects of their intervention were limited to patients with positive blood cultures, indicating a delay in antimicrobial treatment after the onset of infection.

In contrast, the target of our intervention was all patients who received antimicrobial injections, indicating that antimicrobials were administered immediately after the onset of infection, at least 1–2 d early intervention was enabled than those in previous studies. Therefore, while our method of intervention was traditional, it allowed us to intervene rapidly without relying on specialized or expensive equipment such as a MALDI-TOF system.

Few previous studies on the effect of antimicrobial stewardship intervention on mortality demonstrated any remarkable reduction in rate of adverse events.[15,21,22] In our study, the rates of adverse events such as hepatotoxicity and nephrotoxicity were markedly reduced by antimicrobial intervention. Hepatotoxicity and nephrotoxicity in the nonintervention group was mainly caused by carbapenems, suggesting that the facilitation of de-escalation and dose adjustment effectively reduces the onset of such adverse events.

In the previous study, AST reduced median 1 d of hospital stay with large sample size with approximately 6500 in each group.[8] However, sample size was small in the present study. Futhermore, Charlson comorbidity index was higher in the intervention group. Therefore, the length of hospitalization was not significantly different between groups.

In contrast, the frequencies of primary or unidentified infection and surgical site/skin tissue infection were significantly different between the nonintervention and the intervention groups. Therefore, to minimize confounding factors, we conducted multivariate Cox proportional hazard analysis and found that implementation of antimicrobial stewardship was an independent factor that prolonged survival. Conversely, high Pitt bacteremia score, MRSA infection, hypoalbuminemia, intra-abdominal infection were risk factors for mortality. High Pitt bacteremia score and MRSA infection are typical for poor clinical outcome.[12,23] Hypoalbuminemia is common in the acute disease states, including sepsis and infection.[24,25] Charlson comorbidity index, which was higher in the intervention group, was not a risk factor for mortality. This result is consistent with previous report.[21]

Several limitations to the present study warrant mention. First, we conducted a nonrandomized cohort study using a small sample size at a single center. Therefore, multicenter studies of more patients are required. Second, this study was analyzed retrospectively, which might not exclude all information bias. Third, there were several significant differences in the demographics of patients between groups. In particular, a lower incidence of primary or unidentified infection and a higher incidence of surgical site or skin tissue infection were observed in the intervention group, which creates a high risk of mortality. Finally, we were unable to exclude the possibility of unmeasured confounding factors.

In conclusion, we demonstrated that implementation of antimicrobial stewardship facilitated the use of appropriate antimicrobials at an early stage of infection and increased the rate of de-escalation with a concomitant remarkable reduction in mortality and adverse events in patients with bloodstream infections.

Conflict of Interest The authors declare no conflict of interest.

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