Original Article

Evaluation of clinical response to empirical antimicrobial therapy on day 7 and mortality in the intensive care unit: sub-analysis of the DIANA study Japanese data

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Aim: It is not clear whether evaluating the clinical response to antibiotic use at day 7 among critically ill patients accurately predicts outcomes. We aimed to evaluate the relationship between clinical response to the initial empiric therapy on day 7 and mortality.

Methods: The determinants of antimicrobial use and de-escalation in critical care (DIANA) study was an international, multicenter, observational study on antibiotic use in the intensive care unit (ICU). ICU patients ages over 18 years in whom an empiric antimicrobial regimen in Japan was initiated were included. We compared patients who were evaluated as cured or improved ("effective") 7 days after starting antibiotic treatment with patients who were evaluated as deteriorated ("failure").

Results: Overall, 217 (83%) patients were in the effective group, and 45 (17%) were in the failure group. Both the infection-related mortality rate in the ICU and the in-hospital infection-related mortality rate in the effective group were lower than those in the failure group (0% versus 24.4%; $P < 0.01$ and 0.5% versus 28.9%; $P < 0.01$, respectively).

Conclusion: Assessment of efficacy of empiric antimicrobial treatment on day 7 may predict a favorable outcome among patients suffering from infection in the ICU.

Key words: Antibiotics, clinical response, infection, intensive care unit, mortality

INTRODUCTION

BROAD-SPECTRUM ANTIBIOTICS AND empirical therapy are widely used to treat critically ill patients in the intensive care unit (ICU).[1–3] Infection and sepsis are among the main diseases in critically ill patients, and antibiotics are the key therapy. However, questions remain about antibiotic use in critically ill patients: what kind of antimicrobial agent is appropriate? How much and how long should the agent be used? When should treatment be de-escalated and when should it be stopped? Several guidelines, including the Surviving Sepsis Campaign Guidelines (SSCG) and the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 (J-SSCG2020), propose answers for many of these questions.[4–6] However, many questions remain unanswered regarding the use of antibiotics in the ICU.

In clinical practice, we may decide to change, continue, or de-escalate antibiotic therapy based on the clinical response observed a few days after starting the antibiotics. The 2021 SSCG recommended the following (a weak recommendation): daily assessment for de-escalation of antibiotics; using antibiotics for a shorter duration; and both procalcitonin and clinical evaluation to decide when to discontinue antimicrobials in cases of sepsis or septic shock, as well as adequate source control.[4,5] However, the guidelines do not mention the need for daily assessment and clinical evaluation.[4] Previous researchers have reported that patients diagnosed with ventilator-associated pneumonia generally showed clinical improvement within the first 6 days after starting antibiotics, and that patients with a good response were treated for a shorter duration.[7,8] These findings suggest that a good

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clinical response several days after the initiation of antimicrobials might be associated with shorter treatment duration and a favorable outcome. Predicting the outcome of antibiotic use by measuring clinical response several days after the initiation of treatment seems reasonable and is easily performed in practice for infected patients in the ICU. However, whether evaluating the clinical response to antibiotic use at day 7 among critically ill patients gives an accurate indication of the outcome has never been properly studied.

The determinants of antimicrobial use and de-escalation in critical care (DIANA) study was a recent international, multicenter observational study on antibiotic use in the ICU.[9] For the current analysis, we aimed to assess the relationship between the clinical response to initial empiric therapy on day 7 and mortality among critically ill patients in Japan.

METHODS

Ethical considerations

THE ETHICS COMMITTEE of the Nippon Medical School Tama Nagayama Hospital approved the present study (reference number 507). Because we analyzed anonymous data, the requirement for written informed consent was waived.

Design of the DIANA study

The DIANA study was an international, multicenter, observational cohort study approved by European Society of Intensive Care Medicine and that included 1,495 patients from 152 ICUs in 28 countries.[9] The aims of the DIANA study were to determine how often antimicrobial de-escalation (ADE) of an empirical treatment is performed in the ICU and to investigate the impact of ADE on clinical cure rate on day 7 of empirical treatment. The head office of the DIANA study gathered all data from participants in various countries, and then distributed subsets of the whole data collected from participants' individual countries to each participant; therefore, we conducted a post hoc analysis of the DIANA study using patient data from 31 participating ICUs from Japan.

The study gathered the following data on the participants: age; sex; body mass index (BMI); comorbidities; admission category; diagnosis; Acute Physiology And Chronic Health Evaluated (APACHE) II score and Simplified Acute Physiology Score (SAPS) II on the day of ICU admission; the Sequential Organ Failure Assessment (SOFA) score on the day of ICU admission, and on days 0 and 3; the number and types of antibiotics administered, the duration of antibiotics used, and the timing and types of replaced antibiotics; blood culture results; the presence or emergence of multi-drug-resistant (MDR) bacteria; infection source; clinical response to initial antibiotics on day 7; information about intensive care treatments (ventilator, vasoactive agents, and renal replacement therapy [RRT]) during the 28-day follow-up period; and mortality.

Participants

Inclusion criteria were as follows: ICU patients ages 18 years or older in whom an empirical antimicrobial regimen was initiated. Exclusion criteria were lack of evaluation on day 7 and death within 7 days (Fig. 1).

Definitions and data collection

In the DIANA study, empirical antimicrobial therapy was defined as the treatment of cases in which the causative pathogen and the susceptibility pattern were not identified at the time of initiation of the antibiotics.[9]

The DIANA study also contained a variable to evaluate clinical outcome on day 7 after initiation of empirical therapy.[9] Efficacy was judged by a doctor in charge and classified into four groups: resolution, improvement, failure, or indeterminate. We grouped patients into two groups: the effective group comprised participants who were evaluated as clinically cured or improved on day 7, and the failure group comprised participants who were evaluated as having deteriorated on day 7.

We calculated ventilator-free days as follows: (i) ventilator-free days = 0 if the patient died within 28 days of mechanical ventilation; (ii) ventilator-free days = $28 - x$ if mechanical ventilation was successfully discontinued within 28 days after initiation, where x is the number of days spent receiving mechanical ventilation; or (iii) ventilator-free days = 0 if the patient was mechanically ventilated for >28 days. We calculated vasopressor-free days and RRT-free days using the same method.

Outcome measures

The main outcome measure was infection-related in-hospital mortality. The secondary outcome measures were infection-related mortality in the ICU, duration of antibiotics, ventilator-free days, vasopressor-free days, and RRT-free days.

Statistical analysis

We grouped participants into the effective group and the failure group and compared these groups with regard to the

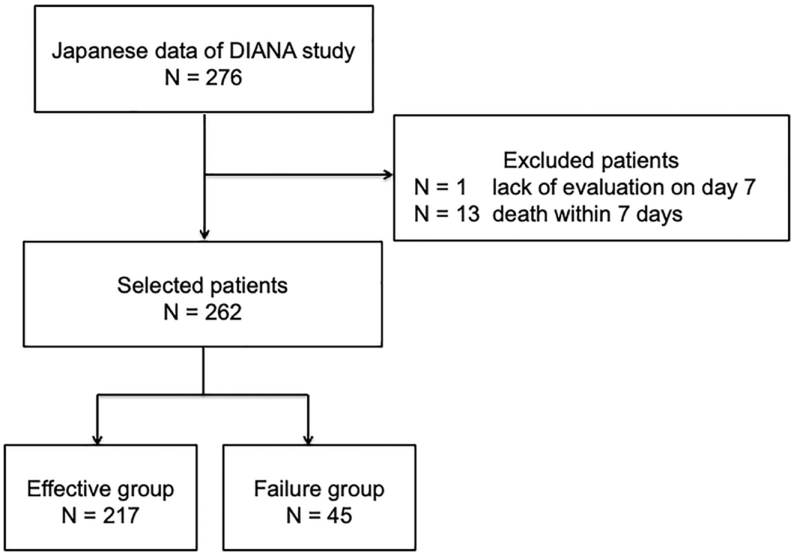

Fig. 1. Patient selection.

following data: patient demographics, final infection foci, causative pathogens, and outcomes. We compared categorical variables using the χ^2 test or Fisher's test, and continuous variables using Student's *t* test or Mann–Whitney *U* test, as appropriate. Numerical values are expressed as median (interquartile range [IQR]) for data not normally distributed. Ventilator-free days, vasopressor-free days, and RRT-free days are presented as mean and standard deviation (SD).[10] The statistical significance threshold was set at $P < 0.05$. All data were analyzed using SPSS software (version 28; IBM Corp., Armonk, NY).

RESULTS

THE NUMBER OF participants in our study was 262; 217 (83%) were in the effective group, and 45 (17%) were in the failure group (Fig. 1). Table 1 shows the patients' characteristics on ICU admission. There were no significant differences in terms of sex, age, BMI, APACHE II score, SAPS II score, or indications for ICU admission. As for comorbidities, the proportion of patients with chronic renal failure was significantly higher in the effective group than in the failure group (14.3% versus 2.2%; $P = 0.03$); however, there were no significant differences in other comorbidities, such as diabetes mellitus, solid tumor, or immunocompromised status. Regarding the admission diagnosis, the proportion of renal and genitourinary disease was significantly higher in the effective group than in the failure group (13.8% versus 2.2%; $P = 0.03$).

As shown in Table 2, there was no significant difference in median total SOFA score on the first day of empirical treatment between the effective group and the failure group (7 [IQR: 5–10] versus 8 [4–12]; $P = 0.33$).

For infection foci, the proportion of genitourinary tract infections was significantly higher in effective group than in the failure group (11.5% versus 0%; $P = 0.02$), and there were no significant differences in other infection foci. With respect to causative pathogens, the blood culture–positive rate and urine sample–positive rate did not differ between the two groups (25.8% versus 15.6%; $P = 0.14$; 10.1% versus 4.4%; $P = 0.23$, respectively); however, the respiratory tract sample–positive rate in the effective group was lower than that in the failure group (10.1% versus 26.1%; $P < 0.01$) (Table 3).

Outcomes are shown in Table 4. Both the infection-related mortality rate in the ICU and the in-hospital mortality rate in the effective group were lower than those in the failure group (0% versus 24.4%, $P < 0.01$; and 0.5% versus 28.9%, $P < 0.01$, respectively). However, there was no difference in duration of antibiotic administration (12 days [7–17] versus 11 days [7–27]; $P = 0.23$). Moreover, the numbers of ventilator-free days, vasopressor-free days, and RRT-free days were significantly higher in the effective group than in the failure group (22 days [9.0] versus 12 days [12.4], $P < 0.01$; 23 days [7.6] versus 15 days [12.8], $P < 0.01$; and 25 days [8.5] versus 16 days [12.9], $P < 0.01$, respectively).

We also assessed outcomes in patients who did not receive antibiotics before study inclusion. Similar trends were shown; the in-hospital mortality rate in the effective group was lower than that in the failure group (0% versus 18.5%; $P < 0.01$), and there was no difference in duration

Table 1. Demographics and clinical characteristics of patients at intensive care unit admission

Variables	Effective group (n = 217)	Failure group (n = 45)	P-value
Age, years	72 (59–80)	71 (59–81)	0.43
Male sex	122/217 (56.2)	28/45 (62.2)	0.46
Body mass index	21.6 (19.5–24.6)	22.9 (19.4–25.8)	0.30
APACHE II	20.0 (15.0–25.8)	22.5 (15.3–30.6)	0.12
SAPS II	44.0 (31.0–57.0)	50.5 (30.8–61.0)	0.77
Allergy to antibiotics	5/214 (2.3)	1/44 (2.3)	0.98
Antibiotics use prior ICU admission	75/215 (34.9)	17/44 (38.6)	0.64
Baseline MDR pathogens colonization	8/172 (4.7)	3/36 (8.3)	0.37
Comorbidity			
Cardiovascular disease	51/217 (23.5)	11/45 (24.4)	0.89
Diabetes mellitus	49/217 (22.6)	8/45 (17.8)	0.48
Solid tumor	36/217 (16.6)	4/45 (8.9)	0.19
Cerebrovascular	31/217 (14.3)	2/45 (4.4)	0.07
Chronic renal failure	31/217 (14.3)	1/45 (2.2)	0.03
Chronic pulmonary disease	18/217 (8.3)	8/45 (17.8)	0.05
Chronic hepatic disease	12/217 (5.5)	1/45 (2.2)	0.35
Hematologic malignancy	6/217 (2.8)	3/45 (6.7)	0.19
No chronic illness	67/217 (30.9)	11/45 (24.4)	0.39
Immunocompromised host	26/213 (12.2)	9/43 (20.9)	0.13
ICU admission category			
Medical	148/217 (68.2)	39/46 (64.4)	0.55
Surgical	65/217 (30.0)	14/45 (31.1)	
Burns	4/217 (1.8)	2/45 (4.4)	
Surgical admission category			
Elective surgery	55/65 (84.6)	9/14 (64.3)	0.08
Emergent surgery	10/65 (15.4)	5/14 (35.7)	
Admission diagnosis			
Respiratory	66/217 (30.4)	18/45 (40.0)	0.21
Digestive	62/217 (28.6)	7/45 (15.6)	0.07
Cardiovascular/vascular	51/217 (23.5)	14/45 (31.1)	0.28
Neurologic	32/217 (14.7)	5/45 (11.1)	0.52
Renal/genitourinary	30/217 (13.8)	1/45 (2.2)	0.03
Skin	21/217 (9.7)	2/45 (4.4)	0.26
Metabolic	9/217 (4.1)	1/45 (2.2)	0.54
Hematologic	6/217 (2.8)	2/45 (4.4)	0.55
Pregnancy related	1/217 (0.5)	0/45 (0)	0.65
Other	8/217 (3.7)	1/45 (2.2)	0.62

APACHE II, Acute Physiology and Chronic Health Evaluated II; ICU, intensive care unit; MDR, multi-drug-resistant; SAPS II, Simplified Acute Physiology Score II.
Data are shown as the number of positive observations/total number of observations (%) or as median (interquartile range). For each variable, the number of missing observations can be obtained as the difference between the total number of patients in each group and the total number of observations.

of antibiotic administration (12 days [7–16] versus 11 days [6–16]; P = 0.36).

DISCUSSION

THE RESULTS OF our analysis indicated that improvement measured on day 7 of empirical antimicrobial therapy was positively correlated with low mortality and lesser need for intensive care (e.g., ventilation therapy, vasopressor use, and RRT) among critically ill patients with bacterial infection in Japan. Among participants in the effective group, in-hospital mortality was 6.9% and infection-related in-hospital mortality was 0.5%. In other words, if an improvement is seen after 7 days of empiric antibiotic

Table 2. SOFA scores on the first day of empirical antibiotic therapy

Variables	Effective group (n = 217)	Failure group (n = 45)	P-value
Respiratory SOFA	2 (1–2)	2 (1–3)	0.07
Coagulation SOFA	0 (0–1)	1 (0–2)	0.10
Liver SOFA	0 (0–1)	0 (0–1)	0.16
Cardiovascular SOFA	3 (0–4)	2 (0–4)	0.97
Central nervous system SOFA	1 (0–3)	1 (1–3)	0.18
Renal SOFA	0 (0–2)	0 (0–1)	0.03
Total SOFA	7 (5–10)	8 (4–12)	0.33

SOFA, Sequential Organ Failure Assessment.
Data are shown as median (interquartile range).

Table 3. Final infection foci and causative pathogens

Variables	Effective group (n = 217)	Failure group (n = 45)	P-value
Final infection foci			
Lower and upper respiratory tract infections	76/217 (35.0)	17/45 (37.8)	0.73
Gastrointestinal tract and intra-abdominal infections	52/217 (24.0)	8/45 (17.8)	0.37
Genitourinary tract infections	25/217 (11.5)	0/45 (0)	0.02
Skin and soft tissue	22/217 (10.1)	2/45 (4.3)	0.23
Catheter-related infections	7/217 (3.2)	2/45 (4.4)	0.68
Cardiovascular and intravascular infections	5/217 (2.3)	0/45 (0)	0.30
Central nervous system infections	4/217 (1.8)	1/45 (2.2)	0.87
Bone and joint infections	2/217 (0.9)	0/45 (0)	0.52
Neutropenic fever	1/217 (0.5)	0/45 (0)	0.65
Other focus of infection	3/217 (1.4)	0/45 (0)	0.43
Causative pathogen positive	110/217 (50.7)	22/45 (48.9)	0.83
Blood culture	56/217 (25.8)	7/45 (15.6)	0.14
Lower respiratory tract sample	22/217 (10.1)	11/45 (26.1)	<0.01
Urine sample	22/217 (10.1)	2/45 (4.4)	0.23
Pre-operative sample	20/217 (9.2)	4/45 (8.9)	0.95
Wound culture	14/217 (6.5)	2/45 (4.4)	0.61
Upper respiratory tract sample	6/217 (2.8)	0/45 (0.0)	0.26
Cerebrospinal fluid	2/217 (0.9)	1/45 (2.2)	0.46
Feces sample	1/217 (0.5)	1/45 (2.2)	0.22
Other sample	7/217 (3.2)	1/45 (2.2)	0.72

Data are shown as the number of positive observations/total number of observations (%). For each variable, the number of missing observations can be obtained as the difference between the total number of patients in each group and the total number of observations.

therapy in a critically ill patient, the patient has a >90% chance of survival.

The current study indicates that assessment on day 7 of antibiotic treatment may accurately predict mortality among infected patients admitted to the ICU. Acute infective disease has a wide spectrum of presentations, from local infection to septic shock, and many factors, such as the causative pathogen, the infection focus, the time from onset to admission, the patient's previous illness and background, the type of antibiotic(s), the need for drainage, and the timing of treatment initiation, affect the prognosis.[4] Because infection and sepsis are serious and widespread diseases, several studies have previously reported on predictive factors in patients with acute infective disease, each focusing on different predictive factors. Some authors reported on the impact of delayed treatment for enterococcal bloodstream infections,[11,12] others assessed the use of procalcitonin usage in the emergency department,[13] and some proposed predictive scores for infection mortality.[14,15] In the present study, we held a different perspective—that of the physician in charge of judging the patient's condition and the efficacy of antimicrobial therapy. This method is subjective and difficult to quantify, but it is very easy to perform and closely reflective of the true clinical situation. In addition, our results suggest that assessing the efficacy of antimicrobial therapy on day 7 of treatment may accurately predict infection-related mortality of patients with bacterial infection in the ICU. This method may be useful for severely infected patients who need intensive care and it may help to decrease mortality in the ICU.

Regarding the timing to assess the efficacy of antibiotic treatment, the DIANA study focused on day 7 following treatment initiation.[9] Magrini *et al.*[13] chose day 5 to evaluate the efficacy of antibiotic treatment, because concentrations of many types of antimicrobial drugs reach a steady state after 2 days and the minimum inhibitory concentration of a

Table 4. Outcomes

Variables	Effective group (n = 217)	Failure group (n = 45)	P-value
No. of infection-related deaths in the ICU	0/217 (0)	11/45 (24.4)	<0.01
No. of deaths in the ICU	5/217 (2.3)	14/45 (31.1)	<0.01
No. of in-hospital infection-related deaths	1/217 (0.5)	13/45 (28.9)	<0.01
No. of in-hospital deaths	15/217 (6.9)	17/45 (37.8)	<0.01
Duration of antibiotics administration, median days	12 (7–17)	11 (7–27)	0.23
1–7	61/217 (28.1)	12/45 (26.7)	0.41
7–14	81/217 (37.3)	13/45 (28.9)	
15 and more	75/217 (34.6)	20/45 (44.4)	
Ventilator-free days, mean days (SD)	22 (9.0)	12 (12.4)	<0.01
Vasoactive agent-free days, mean days (SD)	23 (7.6)	15 (12.8)	<0.01
Renal replacement therapy-free days, mean days (SD)	25 (8.5)	16 (12.9)	<0.01
Septic shock	128/217 (59.0)	28/45 (62.2)	0.69
Infection relapse	12/216 (5.6)	7/45 (15.6)	0.02
Change of antibiotics	94/217 (43.3)	25/45 (55.6)	0.14
Change of antibiotics for de-escalation	53/217 (24.4)	7/45 (15.6)	0.20
Days from initiation of empirical therapy to de-escalation, median days	5 (3–7)	5 (2–7)	0.76

ICU, intensive care unit; SD, standard deviation.
Data are shown as the number of positive observations/total number of observations (%) or as median (interquartile range). Ventilator-free days, vasopressor-free days, and renal replacement-free days are shown as mean and SD. For each variable, the number of missing observations can be obtained as the difference between the total number of patients in each group and the total number of observations.

drug should be guaranteed for 3 consecutive days. Other studies demonstrated that patients with ventilator-associated pneumonia who received appropriate antimicrobial therapy showed a good clinical response within the first 3 to 6 days.[7,8] Therefore, we suggest that day 6 or 7 is an appropriate time to evaluate the clinical response to empirical therapy for bacterial infection in patients in the ICU.

In the current study, patient characteristics such as age, sex, comorbidities, BMI, APACHE II, antibiotic use before ICU admission, baseline MDR pathogens, ICU admission category, and final infection foci were similar. Furthermore, the rate of change of antibiotic agents and de-escalation, and median days from infection of empirical therapy to de-escalation did not differ between two groups. However, in the effective group, the ratio of genitourinary tract infection was statistically higher and infection-related mortality was lower; that is, the infection focus, especially genitourinary infection, might be related to mortality. However, we did not adjust for these factors and we could not judge the relation among the evaluation of clinical response on day 7, infection foci, and outcomes. Further studies with larger numbers of patients are needed to investigate this aspect further.

LIMITATIONS

THERE ARE SOME limitations in the current study. First, we could not perform multivariable analysis on mortality because of insufficient power. The types and changes of antibiotics might affect the outcomes, but we did not adjust for these factors. Second, the time from onset of infection to start of antibiotic therapy might affect severity and mortality, because any delay in the administration of appropriate antibiotics can cause deterioration in the patient's condition and lead to increased mortality.[4,11] However, the DIANA study did not include information about the onset of infection; therefore, we could not adjust for the time from onset to the start of treatment. Instead, we used the APACHE II and SOFA scores to estimate the severity of the general condition. Third, blood culture results, the type and concentration of antimicrobials, and the presence of MDR bacteria might affect the response to empirical therapy.[4] We did not consider these factors in the current study because they are subject to numerous variations and cannot be accurately assessed in a study with a relatively small number of participants. Fourth, clinical response was assessed by the doctors in charge; therefore, this was a subjective variable.

CONCLUSION

OUR FINDINGS SUGGESTED that assessing the response to empirical antimicrobial therapy on day 7 of treatment may be useful for predicting a favorable outcome in patients being treated for severe infection in the

ICU. Additional large-scale prospective studies are required to confirm our results.

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ETHICS STATEMENT

APPROVAL OF THE research protocol: The ethics committee of the Nippon Medical School Tama Nagayama Hospital approved the present study.

Informed Consent: Because we analyzed anonymous data, the requirement for written informed consent was waived.

Registry and registration No. of the study/trial: Committee's reference number is 507.

Animal Studies: Not applicable.

CONFLICT OF INTEREST

THE AUTHORS DECLARE no conflicts of interest.

DATA AVAILABILITY

THE DATA THAT support the findings of this study are available from DIANA study group, but restrictions apply to the availability of these data, which were used under license for the present study, and are not publicly available. However, data are available from the authors on reasonable request and subject to permission from DIANA study group principal investigators.

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