□ORIGINAL ARTICLE□

Current Practice of Management of Bacteremic Sepsis: A Study in a Tertiary Care Teaching Hospital in Japan

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Abstract

Objective **To investigate how patients with bacteremic sepsis are managed in a tertiary care teaching hospital.**

Patients and Methods **Prospective observational study on patients with bacteremic sepsis. Clinical and microbiological characteristics of bacteremic sepsis were analyzed in relation to prognosis. Severity of the illness was quantitatively analyzed by the APACHE (Acute Physiology, Age, Chronic Health Evaluation) III scoring system. Also investigated was how closely physicians paid attention to acute physiological alterations in patients.**

Results **The 28-day mortalities in fifty hemodynamically stable patients and in twenty-three septic shock patients were 26% and 52%, respectively (p=0.028). Gram-positive organisms accounted for 54% of all organisms, with the mortality and incidence of septic shock being the same as with Gram-negative infections. The mean APACHE III score was 42.9 in survivors, and 76.5 in non-survivors ($p < 0.001$). Although serum levels of C-reactive protein and acute physiology score (APS) was significantly higher in non-survivors than in survivors, the correlation with APACHE III score was more prominent in APS. The number of vital signs recorded was 1.67 in physicians and 3.6 in nurses ($p < 0.001$).**

Conclusions **The present study proved that the APACHE III score accurately discriminates between survivors and non-survivors of patients with sepsis. By addressing the need for an objective evaluation of severity of illness, it strongly recommends that physicians should be made aware of physiologically defined sepsis and that they should pay closer attention to patients' physiological alterations to identify the development of sepsis in critically ill patients.**
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Key words: APACHE III score, Acute Physiology Score, risk prediction, severity of illness, vital signs

Introduction

Recent increases in the elderly population, advances in sustaining critically ill patients by improved treatment modalities, and chemotherapy for the growing number of patients with malignancies all predispose the public at large to an increase in the number of nosocomial infections. At the extreme end of this hospital-acquired infection lies bloodstream infection not uncommonly complicated by sepsis; it is a life-threatening condition with a reported mortality rate ranging from 25% to 75% (1–3).

Because of the poor prognosis of sepsis with bacteremia, the prognostic scoring systems such as APACHE (4–6), SAPS II (7), and MPM II (8) have been considered useful for development of new treatment modalities. In such an attempt, care should be taken to enroll patients with comparable disease severities, to improve quality assessment of hospital resources, and determine a method of objective evaluation of severity of illness by medical staff involving attending physicians, nurses, and residents (9). The APACHE (Acute Physiology, Age, Chronic Health Evaluation) scoring system, a prototype of a classification system for disease severity, has continued to evolve into newer versions over the last twenty years through validations of discrimination and calibration regarding prognosis (4–6). The APACHE III scoring system as a methodology of risk prediction of hospital mortality (6) is currently used in many studies worldwide (10–13).

As is the case in most of the tertiary care teaching hospitals in Japan, there are no full-time staff members for infection control practice nor subspecialty division of infectious diseases in Saga Medical School Hospital (SMSH). Instead, a part-time infection control board consisting of physician department chairs and nurse administrators is in charge of surveillance of nosocomial infections and its control. A given patient with infectious disease as a primary disorder, or as a complication during hospitalization, is treated entirely by physicians in a subspecialty division for some individual organ system. As mentioned above, they have no resource for infectious disease

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consultation services. It is true that sepsis is not a pathological condition that calls for mandatory and exclusive consultation with an infectious disease subspecialist. However, since patients with a complication of sepsis or bacteremia are taken care of independently by non-subspecialist physicians primarily on the basis of their subjective clinical judgement, fundamental clinical practice such as diagnostic clues or assessment of disease severities for bacteremic sepsis varies considerably from physician to physician.

In the present study, patients with bacteremic sepsis were prospectivelly enrolled, and analyses were made on correlation between quantitative disease severity as measured by the APACHE III score and patients' prognosis, or on clinical microbiological background. Since mortality rates easily obtainable from the hospital database are not generally considered as a sensitive measure for an entire hospital (14), the primary objective of this study was set to find out about the demographic and clinical characteristics of sepsis in reference to patients' death. We also set out to investigate how closely physicians should examine septic patients with bloodstream infection so that they can identify those problems they are likely to encounter in their daily clinical practice of infectious diseases in an institution where expert consultation for infectious disease is not currently available.

For editorial comment, see p 867.

Patients and Methods

Saga Medical School Hospital (SMSH) is a tertiary care 650-bed teaching hospital, which is an integral part of Saga Medical School. SMSH is for post-graduate clinical training defined by the presence of an accredited residency program and by membership in the Council of Teaching Hospitals. The average length of hospital stay is 31 days in SMSH. The number of beds for the medical and surgical ward is 200 each, with no distinction between acute and long-term care. There is one intensive care unit with six beds which are set aside exclusively for care of post-operative critically ill patients.

During the study period (November 1997 through March 1999), ward patients over 20 years of age who developed bacteremic sepsis during or on hospitalization at SMSH were prospectively enrolled in this observational study. Patients with bacteremic sepsis in the ICU were not included to avoid bias possibly brought about by extremely severe conditions in a very small number of such patients.

Definition and Data

Sepsis was identified based on the definition of ACCP/SCCM Consensus Conference (15). That is; patients were considered as having sepsis if two or more of the following manifestations are present: 1) a body temperature of >38°C or < 36°C; 2) a heart rate of >90 beats/min; 3) tachypnea as manifested by a respiratory rate of >20 breaths/min; 4) an alteration of the WBC count of >12,000 cells/μl, or the presence of >10% bandform neutrophils. Acute physiology score for vital sign (APS) is a total of values of physiological measurements (pulse rate, mean BP, body temperature, and respiratory rate) that partly compose the APACHE III system (6). Bacteremic sepsis that developed while a patient was hospitalized for other underlying medical problems was defined as hospital-acquired sepsis. Patients who showed up at a follow-up clinic or emergency room with clinical features of bacteremic sepsis were considered as having community-acquired sepsis. Sepsis that followed not required, a major surgical operation was defined as surgical sepsis, and sepsis that developed in patients who were medically treated was defined as medical (non-surgical) sepsis. Organisms of bloodstream infection were detected with the use of The VITAL® system (bioMerieux, Lyon, France), which reads the level of fluorescence as the culture bottles are shaken every 15 minute. Prior to the final species identification in a given patient, positive blood cultures were immediately reported to the investigator (Y. A.) from hospital microbiologists (K. K., I. T. and Z. N.) during the study period. Charts of patients with bacteremia were reviewed on the same day of the culture report, then followed a determination whether the individual patient's condition fulfilled the criteria of sepsis, and whether the positive blood culture represented a true bloodstream infection. If the microorganism was of a normal skin flora and the patient's clinical features were not suggestive of infection, that blood culture was considered as probable contaminant. In the case of bacteremia of more than one document, only the first episode was considered in this study. Upon enrollment, the patient's demographic, clinical, and laboratory data as well as informations of his or her co-morbidities required for the APACHE (Acute Physiology, Age, and Chronic Health Evaluation) III scoring were collected. The APACHE III (6) uses a point score based upon values of 16 physio-biochemical measurements (pulse, mean blood pressure, body temperature, respiratory rate, PaO_2 or A-aDO_2, hematocrit, WBC, creatinine, urine output, BUN, sodium, albumin, bilirubin, glucose, acid-base balance, and neurological abnormalities), age, and previous health status (comorbid conditions such as hematological malignancies, metastatic cancer, immunosuppression, cirrhosis, and others) to provide a general measure of severity of disease. A five point increase in APACHE III score (range; 0 to 299) is independently associated with a statistically significant increase in the relative risk of hospital death (6). Laboratory variables that had not been determined within 24 H prior to or after blood cultures were newly ordered by the investigator (Y. A). Although not included in the APACHE III system, serum levels of C-reactive protein that had been determined by physicians ±24H of blood culture were also analyzed. Scores for vital signs that were not measured on the day of blood culture were given a zero point score. Based on the definitions of sepsis (15), the date on which the patient's condition first met the criteria of sepsis was determined by chart review. Patients were attended to by physicians not involved in the study, and followed up for death or survival up to a maximum of 28 days after inclusion into the study. Patients discharged from the hospital within the follow-up period were classified

as survivors.

Statistics

For continuous variables, mean (±SD) values were compared between the groups with non-paired Student's t-tests after correction for equality of variance (F test). Nonparametric data were analyzed with Mann-Whitney U test. Correlation between the two variables was analyzed by Pearson's correlation. Associations of categorical variables with mortality were analyzed by either the χ^2 test or Fischer's exact test (for expected cell frequencies less than five). All tests were two-tailed, and a p value of <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics of Patients

During the study period (November 1997 through March 1999) 79 patients were positive for blood culture at least on one occasion (1.1 case per 100 admissions >20 year of age). Excluding six patients, in whom *Bacillus* species were retrieved from a single set of blood culture and the definition of sepsis was not met, a total of 73 patients were eligible as having bacteremic sepsis. There were 44 male and 29 female patients enrolled. Age ranged from 33 to 90 years (median: 66 years) for male, and from 20 to 82 years (median: 65 years) for female. Demographic and clinical characteristics of the patients are shown in Table 1. Sex and age did not differ between survivors and non-survivors. Twenty-five patients (16 male and 9 female) died during the 28 days of follow-up period, with the overall mortality rate of sepsis being 34.2%. There were 47 medical, and 26 surgical (10 emergency surgical and 16 elective surgical) sepsis patients. The fatality rates of sepsis did not differ between these admission categories: They were 31.9% (15/47) for medical and 38.4% (10/26) for surgical patients [40% (4/10) for emergency surgical, and 37.5% (6/16) for elective surgical], respectively. The APACHE III scores were not different between medical and surgical sepsis patients (data not shown). The number of patients with community-acquired sepsis was 17, and hospital-acquired sepsis 56, with no significant difference in mortality rate between these categories (29.4% vs. 35.7%; $\chi^2=0.23$, p=0.056; chi-square test). There were 28 patients with malignant diseases, 14 with hematological malignancies and the other 14 with solid neoplasms. Although there was a trend for higher mortality related with bacteremic sepsis in patients with malignancy (46%; 13/28) as compared with those with non-malignant diseases (26%; 12/45), the difference in mortality was not statistically significant. Being on long-term immunosuppressive therapy was not associated with higher mortality in the present study. There were six patients on an oral glucocorticoid treatment and one with glucocorticoid plus oral cyclophosphamide; four of them were discharged from the hospital (data not shown). The mortality of patients with septic shock was 52.1%, making a significant difference from that of non-shock patients (26%) ($\chi^2=4.79$, p=0.028; chi-square test). The mean APACHE III score was higher in patients with hospital-acquired sepsis (56.4 ± 24.5) than in community-acquired sepsis (47.88 ± 23.3), even though it did not reach statistical significance (p=0.21; chi-square test).

Clinical relevance of microbiological analyses

A list of microorganisms isolated from blood culture and their relation to clinical outcome of sepsis are shown in Table 2. A total of 79 strains were isolated from the 73 patients. The numbers of Gram-positive organisms and Gram-negative or-

Table 1. Demographic and Clinical Characteristics of Patients with Bacteremic sepsis (n=73)

		Survivors (n=48) male 28/female 20	Non-survivors (n=25) male 16/female 9	p value
Age (yr)§	Male	67 (33–90)	66(53–80)	NS†
	Female	65 (24–82)	65(20–73	NS†
Disease category of sepsis¶				
	Medical	32	15	NS*
	Surgical	16	10	
	Emergency	6	4	NS††
	Elective	10	6	
	Community-acquired	12	5	NS*
	Hospital-acquired	36	20	
	Malignant disease	15	13	NS*
	Non-malignant disease	33	12	
Hemodynamic state¶				
	Shock	11	12	0.028*
	Not shock	37	13	

§ Data represent median values, with ranges shown in parentheses. ¶Data represent the number of patient. †: Mann-Whitney U tast, *: chi-square test, ††: Fischer's exact test.

Table 2. Organisms Isolated from Blood Culture and Clinical Features of Bacteremic Sepsis

Organisms	Number of patients (%)			
	Survived	Death	Mortality	Septic shock
Coagulase-negative staphylococci*	7	2	(22.2)	1 (11.1)
*Staphylococcus aureus**	8	5	(38.5)	3 (23.1)
Enterococcus species*	4	1	(20.0)	2 (40.0)
Streptococcus species*	8	2	(20.0)	3 (30.0)
Subtotal Gram-positive (37)	27	10	(27.0)	9 (24.3)
Pseudomonas aeruginosa	3	3	(50.0)	2 (33.3)
*Escherichia coli**	5	0	(0.0)	1 (20.0)
Enterobacter species*	2	0	(0.0)	1 (50.0)
*Klebsiella pneumoniae**	2	0	(0.0)	0 (0.0)
Acinetobacter calcoaceticus	1	1	(50.0)	1 (50.0)
Others[§]	4	2	(33.3)	2 (33.3)
Subtotal Gram-negative (23)	17	6	(26.1)	7 (30.4)
Anaerobic flora[†]*	2	2	(50.0)	2 (50.0)
Candida species	0	4**	(100.0)	2 (50.0)
Polymicrobial infection[¶]	2	3	(60.0)	3 (60.0)
	48	25	(34.2)	23 (31.5)

Data represent the number of patients, not the number of microbial strains. * For total number of strains isolated, add strains from polymicrobial infections. [§] One strain each for *Citrobacter freundii, Klebsiella oxytoca, Stenotrophomonous. maltophilia, Proteus mirabilis, Morganella morganii,* and *S. marcescens.*[†] Three strains of *Bacteroides fragilis,* and one strain of *Fusobacterium necrophorum.* [¶] *E. faecalis* + *S. hemolyticus, S. intermedius* + *B. fragilis, E. aerogenes* + *S. marsescens* + *E. faecalis, Methicillin*-resistant *S. aureus* + *E. faecalis,* and *E. coli* + *K. pneumoniae.* ** p=0.013 (Fischer's exact test); Candidal vs. non-Candidal infection .

ganisms were 43 (37 from subtotal + 6 from polymicrobial), 32 (23 from subtotal + 4 from anaerobes + 5 from polymicrobial), respectively. Candidal species were isolated in four patients. Thus, the incidence of Gram-positive, and Gram-negative microorganisms was 54%, and 41%, respectively. *Staphylococcus aureus* was the leading organism of bacteremia in the present study (13 out of 79 strains; 16.4%). Eleven out of 13 strains (84.6%) of bacteremic *Staphylococcus aureus* were methicillin-resistant ones, and death resulted in 6 of 11 patients (54.5%). A total of nine strains of CNS (coagulase-negative staphylococci) including six strains of *S. epidermidis* accounted for 23.2% of Gram-positive organisms, ranking as the second most frequent cause of bloodstream infection. In all six patients with *S. epidermidis* bacteremia, central lines had been in place on the day of blood culture. Mortality rates between unimicrobial Gram-positive infections (10/37=27%) and Gram-negative infections (6/23=26%) were almost the same. Additionally, there was no difference in the incidence of septic shock between the two groups (24.3% vs. 30.4%, p=0.32; chi-square test). The rate of mortality and of septic shock in patients with polymicrobial bloodstream infections was much higher (60% for both) than in those with unimicrobial infections. Of note is that all four patients in whom bloodstream infections were due to Candidal species (two strains each for *C. albicans* and *C. glabrata*) died, which makes a striking difference from non-candidal infections (p=0.013; Fischer's exact test).

Quantification of severity of illness

The distribution of the APACHE III scores for survivors and non-survivors is shown by box-wisker plot in Fig.1. The median, 75 percentile, and 25 percentile values were 39, 55, and 31 for survivors versus 74, 82, and 64 for non-survivors. Although there was some overlap between the lowest quartile of the APACHE III scores in non-survivors and the two highest quartiles of APACHE III scores in survivors, the difference in the APACHE III scores between the two groups was markedly significant (p<0.001, Student's t-test). When the cut point of APACHE III score was set at 63, the positive likelihood ratio and negative likelihood ratios for mortality were 10.6 and 0.13, respectively, with the odds ratio for death being >80.

Serum levels (mean±SD) of CRP, an acute phase reactant routinely measured in Japan as an index of severity of inflammation, were determined within 24H prior to blood culture in all patients. As shown in Fig. 2, it was 11.7±8.0 mg/dl for survivors (n=48), and 16.5±10.1 mg/dl for non-survivors (n=25) (p=0.031; Student's t-test).

Deterioration of patients' vital conditions on the day of blood culture sampling were quantified by acute physiology scores (APS: a sum of scores for body temperature, heart rate, respiratory rate, and mean arterial pressure), then a comparison was made between survivors (n=27) and non-survivors (n=21) for whom all the four vital signs had been recorded in charts (Fig. 3). The mean APS (±SD) for survivors was 12.9 (±9.2), and it was 18.5 (±9.2) for nonsurvivors. The difference in APS between the two groups was significant (p=0.046; Student's t-

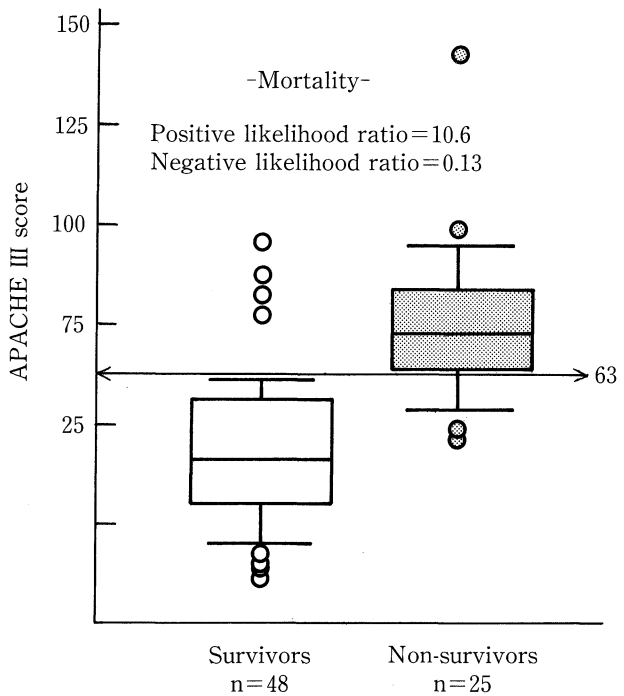

Figure 1. APACHE III scores in survivors (n=48) and non-survivors (n=25). Distribution of APACHE III scores are shown by box and whisker plotting. The box represents interquartile range [Δ (75–25) percentile] divided by a line at the median point. Bars indicate 10 and 90 percentile points. Difference in distribution of APACHE III scores between the two groups was significant (p<0.001; Student's t-test). At APACHE III cut-off point of 63 (arrow bar), positive likelihood ratio for death (sensitivity/1-specificity) was 10.6, and negative likelihood ratio for death (1-sensitivity/specificity) was 0.13. p<0.001; Student's t-test. APACHE: Acute Physiology, Age, Chronic Health Evaluation.

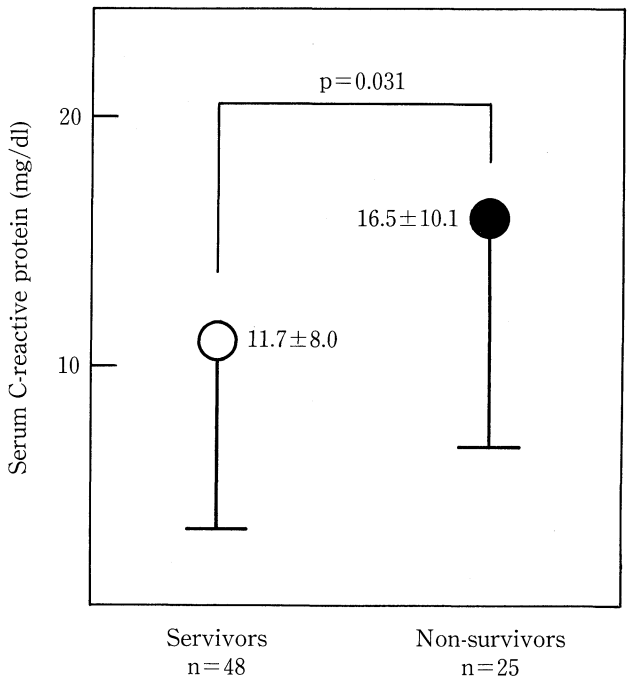

Figure 2. Serum levels of C-reactive protein in survivors (n=48) and non-survivors (n=25). Open and closed circles represent mean values, and bars indicate standard deviations of the mean. Difference between the two groups was statistically significant (p=0.031; un-paired two-tailed Student's t-test).

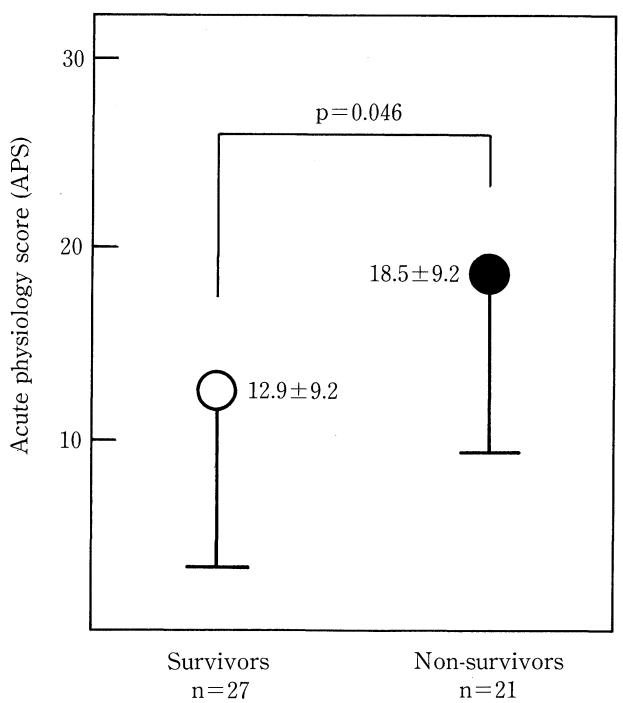

Figure 3. APS in survivors (n=27) and non-survivors (n=21). APS was analyzed in patients in whom all four vital signs were recorded. Open and closed circles represent mean values, and bars indicate standard deviations of the mean. Difference between the two groups was statistically significant (p=0.046; un-paired two-tailed Student's t-test). APS: Acute Physiology Score.

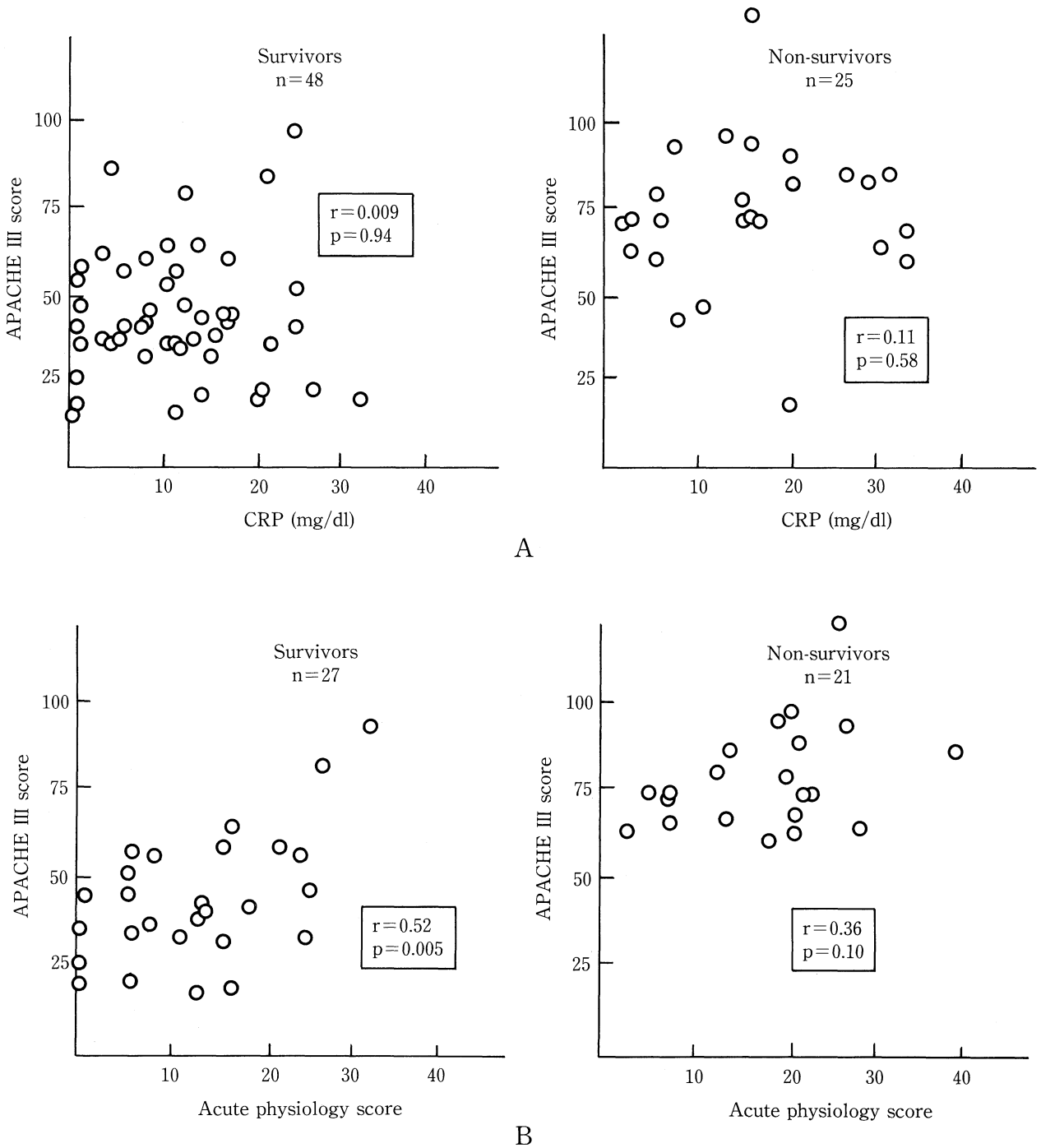

Figure 4. Correlation between APACHE III scores and serum levels of CRP (A), or APS (B). Serum CRP values were not correlated with APACHE III scores in either survivors (left panel) or non-survivors (right panel). APS were in good correlation with APACHE III in survivors (r=0.52, p=0.005; Pearson's correlation). In non-survivors, the correlation between the two scores was less significant (r=0.36, p=0.10; Pearson's correlation). APACHE: Acute Physiology, Age, Chronic Health Evaluation, APS: Acute Physiology Score.

test).

In both groups, correlation between the APACHE III scores and serum CRP levels or APS were analyzed. The serum levels of CRP was not statistically correlated with the APACHE III scores either in survivors (r=0.009; p=0 .94) or in non-survivors (r=0.011; p=0.58) (Fig. 4A). On the other hand, APS in survivors was in good correlation with the APACHE III scores (r=0.52; p=0.005; 95%CI 0.17, 0.75) (Fig. 4B). In non-survi-

Table 3. Clinical Features and Practice of Bacteremic Sepsis

	Survivors	Non-survivors	p value
Interval (Days)[§]			
Admission to sepsis	51 ± 36.9	46.1 ± 29.6	NS*
Sepsis to blood culture	2.36 ± 2.0	2.6 ± 1.9	NS*
No. of blood culture [¶]			
Nurse	3.64±0.48		
	3.54 ± 0.97	3.84 ± 1.03	NS[†]
			p < 0.00001[†]
Physician	1.67±1.11		
	1.41 ± 1.06	2.16±1.06	p = 0.006[†]
No. of blood culture [§]	1.56 ± 1.29	1.55 ± 0.94	NS*

[§] Data were analyzed for patients with hospital-acquired sepsis (n=36 for survivors, and 20 for non-survivors). [¶] Data were analyzed for 17 community-acquired sepsis patients plus 56 hospital-acquired sepsis patients (n=48 for survivors, and 25 for non-survivors). Data represent mean±SD. * Mann Whitney U test. [†] Student's t-test.

vors, the APS was more significantly correlated with the APACHE III (r=0.36; p=0.10) than was serum CRP level.

Practice of sepsis management

As shown in Table 3, the mean (±SD) interval (days) from admission to hospital to the onset of sepsis was similar between survivors (51±36.9) and non-survivors (46.1±29.6) in patients with hospital-acquired bacteremic sepsis. Likewise, the intervals between the onset of sepsis and blood culture sampling were similar between the two groups. In both groups, it was two to three days after a clinically defined sepsis developed when physicians first obtained blood culture (2.36±2.0 vs. 2.6±1.9). The mean number of vital signs recorded in charts (range: 0 to 4), a prerequisite for defining sepsis, was 3.64 by nurses, and 1.67 by physicians (p<0.001; Student's t-test). As far as what the physician was concerned, the mean was 1.41 in survivors, and 2.16 in non-survivors (p=0.006; non-paired Student's t-test). The mean number of blood culture was 1.56 in survivors and 1.55 in non-survivors. The number of patients from whom blood culture was obtained for multiple sets was 14 in 48 survivors (29%), and 7 in 25 non-survivors (28%) (data not shown).

Discussion

The present study included sepsis patients with laboratory-confirmed bacteremia so that detailed analyses could be focused on a patient cohort with greater risks of death. Schwenzer et al (16) reported that death was nearly three times more likely in patients with bacteremic sepsis than in matched controls without bacteremia yet having a similar severity of illness as judged by the APACHE system (16).

The overall mortality in patients with bacteremic sepsis was 34.2% in the present study. Beck and colleagues have reported in a study with a larger number of patients that non-surgical sepsis patients have a slightly higher mortality rate (p=0.0489) than surgical sepsis patients (12). In the present study, the majority (73%) of surgical sepsis was from cardiothoracic surgery (10 patients) and abdominal surgery (9 patients). This is in line with a general observation that the site of infection of sepsis patients of all categories is most predominantly the chest followed by abdomen and urogenital organs (13). The death rate of septic shock patients (52.7%) was significantly higher than that of non-shock patients (26%), a finding consistent with the report from a French ICU group (3). Although some investigators consider that male gender goes with a higher severity of illness (17), the present study did not confirm this finding.

The prevalence of Gram-positive bacteremia was 54% in this study. Friedman et al (18) recently reviewed that Gram-positive infections increased worldwide from 10% between 1958 and 1979 to 31% between 1980 and 1997, with Gram-negative infections becoming proportionately less common. *Staphylococcus aureus* bacteremia, the most common Gram-positive infectious agent in another study (19) as well as ours, was associated with the highest crude mortality among unimicrobial infections in this study. The fact that three-fourths of bacteremic *S. aureus* strains were methicillin-resistant indicates a strong need for surveying cultures of patients at risk for developing sepsis or with high APACHE III scores, as has been reported (20, 21). An urgent need also is the implementation of centralized infection control strategies for the containment of antibiotic-resistant organisms. The present study did not preclude patients with CNS bacteremia for two reasons. One reason is that in all the CNS-positive patients, central lines were in place

and clinically defined sepsis was present, and the other reason being that the prevalence of bloodstream infection due to CNS, i.e. *Staphylococcus epidermidis*, has been increasingly associated with clinically relevant episodes of bloodstream infections (19, 22–24). Pittet et al (22) and others have reported that candidal fungemia and polymicrobial infection are microbiological predictors of mortality in patients with hospital-acquired bloodstream infection (2, 19, 25). Consistent with these findings, the mortality rate of candidal fungemia was 100% in this study. Polymicrobial infections (five patients) in our study resulted in higher rates of mortality and complication of hemodynamic disturbance than in unimicrobial infections. But this finding was not of statistical significance, probably due to inadequate statistical power commonly accompanying studies with relatively small numbers of patients.

In terms of clinical practice, the present study brings up the following issues: 1) how, in practice, do physicians evaluate the severity of a given patient's conditions and 2) how do physicians identify patients with sepsis ?

First, our study clearly demonstrates the objective accuracy of the APACHE scoring system for predicting the outcome of the patients' illnesses or making a quantitative evaluation of disease severity. With a cut-off point of 63, the APACHE III scores best discriminated between survivors and non-survivors, with positive/negative likelihood ratio for mortality, and odds ratio, being 10.6/0.13, and 81.5, respectively. It should always be kept in mind, however, that APACHE was initially aimed at classifying groups, not individuals (4), and it should not serve as the basis for limiting or stopping treatment of an individual patient due merely to a high score. Although the number of patients in our study is smaller than that of Beck and colleagues (12), the mean APACHE III scores are very close: they reported 45 in their survivors vs. 42 in ours, and 79 in their non-survivors vs. 76 in ours. This indicates that the APACHE III is reproducible and easily applicable to comparable groups regardless of place and personnel. These findings may suggest that patients' conditions should be objectively evaluated not only for the sake of accuracy or objectiveness of the evaluation methods used, but also for avoidance of subjective, variable, and/or non-reproducible assessment of the conditions of critically ill patients by an attending physician in a teaching hospital, especially if the teaching style stressed in the hospital is primarily dependent on his/her clinical expertise.

Further, this study showed that in all instances, the physicians paid attention, in a routine manner, to laboratory data such as WBC or CRP rather than to acute physiological changes in patients. This can be clearly seen from the average number of vital signs recorded by nurses vs. physicians. In fact, most of the APS were made available in this study by virtue of routine records made by ward nurses. As a matter of course, the more ill a given patient became, the more closely the attending physician tended to pay attention to the patient's physiological disturbances. And as predictable from the report by Presterl and colleagues (10), serum levels of CRP were significantly higher in non-survivors than in survivors. In this respect, one should also note that the acute physiology scores for vital sign is more closely related to the severity of the patient's condition as measured by the APACHE III than are measurements of serum CRP levels. These findings suggest that physicians should always bear in mind that sepsis is primarily defined by deterioration of physiological parameters. First and foremost, the physician attending a sepsis patient should never stop paying close attention to his or her physiological parameters.

In the present series, almost one-third of the patients already had hemodynamics collapsed when first identified by positive results of blood cultures. Moreover, two to three days had elapsed from the onset of sepsis before the first blood cultures were ordered, and blood culture was drawn for a single set in most of the patients. Generally, two to three blood cultures drawn at intervals of at least 20 minutes are recommended in an identification procedure of pathogens and to minimize chances of contamination by normal skin flora (26, 27). While bacteremia is not a prerequisite for the diagnosis of sepsis, an aggressive search by blood culture for an as-yet-undetermined source of infection should be implemented as a crucial element of therapy. Given that the mortality rate of bacteremic sepsis is considerably high, an early and opportune detection of organisms causative for bloodstream infection would have a great diagnostic and therapeutic importance (27).

In conclusion, the APACHE III is a very useful indicator of disease severity in critically ill patients and will help physicians stratify patients that are severely ill in an era of managed care. Since there is a general agreement that a scoring system with which to objectively and reproducibly evaluate disease severity is needed for comparison of the efficacy of intensive care provided in different hospitals or over time (5, 18), this system should be introduced more widely into clinical practice at tertiary care hospitals in Japan. Finally, it is of prime importance that physicians pay attention to patients' vital signs at bedside as a simple, indispensable first line practice with which to start evaluation of their conditions. Reliance upon laboratory parameters should follow, not precede, that first step of vital sign check.

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