[Environmental Health and Preventive Medicine 11, 298–303, November 2006]

Original Article

Incidence and Outcome of Sepsis in Japanese Intensive Care Units: The Japanese Nosocomial Infection Surveillance System

Machi SUKA[1], Katsumi YOSHIDA[1] and Jun TAKEZAWA[2]

[1]*Department of Preventive Medicine, St. Marianna University School of Medicine, Kanagawa, Japan*
[2]*Department of Emergency and Intensive Care Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan*

Abstract

Objectives: To determine the incidence of sepsis in Japanese intensive care units (ICUs) and to evaluate the impact of sepsis on mortality and length of stay (LOS).

Methods: Using the JANIS database for the period between June 2002 and June 2004, 21,895 eligible patients aged ≥16 years, hospitalized in 28 participating ICUs for ≥24 hours, were monitored until ICU discharge. Adjusted hazard ratio (HR) with 95% confidence interval (CI) for the incidence of sepsis was calculated using Cox's proportional hazard model. Standardized mortality ratio (SMR) was calculated on the basis of the crude mortality in patients without nosocomial infection (NI) for respective APACHE II categories. Mean LOS for survivors was assessed by two-way analysis of variance with adjustment for APACHE II.

Results: Sepsis was diagnosed in 450 patients (2.1%), with 228 meeting the definition on ICU admission and 222 during the ICU stay. The overall incidence of sepsis was 1.02/100 admissions or 2.00/1000 patient-days. A significantly higher HR for the incidence of sepsis was found in men (1.54, 95% CI: 1.14–2.07), APACHE II ≥21 (2.92, 95% CI: 1.92–4.44), ventilator use (3.30, 95% CI: 1.98–5.49), and central venous catheter use (3.45, 95% CI: 1.90–6.28). SMR was determined to be 1.18 (95% CI: 0.82–1.21) in NI patients without sepsis and 2.43 (95% CI: 1.88–3.09) in NI patients with sepsis. Mean LOS for survivors was calculated to be 11.8 days (95% CI: 11.3–12.4) in NI patients without sepsis and 15.0 days (95% CI: 13.3–17.0) in NI patients with sepsis compared with 3.8 days (95% CI: 3.8–3.9) in patients without NI.

Conclusions: Sepsis is not very common in Japanese ICUs, but its development leads to further increases in mortality and LOS in patients with NI.

Key words: ICU, sepsis, incidence, mortality, length of stay

Introduction

Sepsis is a clinical syndrome describing infection and subsequent systemic inflammatory response (1, 2). Despite the availability of potent antibiotics, sepsis has been reported to be a major cause of death in hospitalized patients (3, 4). In order to develop effective strategies for the prevention and treatment of sepsis, both clinicians and researchers require reliable information on the epidemiology of sepsis. There have been many studies estimating the incidence and outcome of sepsis in intensive care units (ICUs) (5–13), but reviews of these studies suggested a considerable variation in the reported rates (14–17). It is uncertain whether the estimates in specific populations are applicable to other populations. Little is known about the epidemiology of sepsis in the Japanese population.

The Japanese Ministry of Health, Labour, and Welfare established the Japanese Nosocomial Infection Surveillance (JANIS) system in July 2000, when participating hospitals routinely started to report their nosocomial infection surveillance data for a national database. In the ICU component of the JANIS system, all the patients admitted to the participating ICUs are enrolled in the survey. Data are collected by trained physicians and nurses in each ICU using a specific database-oriented software, and reported to the data management office via the Internet on a monthly basis (18, 19). Because the precise definitions of data items are incorporated into the database-oriented software (20), the JANIS system enables the establish-

Received Jun. 12, 2006/Accepted Aug. 30, 2006
Reprint requests to: Machi SUKA
Department of Preventive Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan
TEL: +81(44)977-8111, FAX: +81(44)977-8356
E-mail: suka@marianna-u.ac.jp

ment of a standardized and formatted database.

Using the large cohort database of the JANIS system, we determined the incidence of sepsis in Japanese ICUs and assessed the impact of sepsis on mortality and length of stay (LOS). In our previous study, we showed the impact of nosocomial infection (NI) on mortality in patients admitted to the ICUs (21). In this study, we revealed that the development of sepsis leads to further increases in mortality and LOS in patients with NI.

Subjects and Methods

The ICU component of the JANIS system is the only source of information on the epidemiology of NI in Japanese ICUs. The details of data collection and quality control in the JANIS system have been described elsewhere (21–24). For all the patients admitted to the participating ICUs, the following data were collected using a specific database-oriented software in standardized forms: sex, age, underlying disease, severity of illness (APACHE II (25)), ICU admission and discharge (date, time, and route), operation (elective and urgent), device use (ventilator, urinary catheter, and central venous catheter), infection (pneumonia, urinary tract infection, catheter-related blood stream infection, sepsis, wound infection, and others), and hospital discharge (date and outcome). APACHE II uses a point score based on the initial values of 12 routine physiological measurements, age, and previous health status to provide a general measure of severity of illness (25). The point score was automatically computed with the database-oriented software when the relevant data were input. Information on infection included diagnosis date and culture results (strain and drug-resistant pattern) for a maximum of three episodes for each infection site. A drug-resistant pattern was recorded for each pathogen in compliance with the database-oriented software.

Infections were diagnosed according to the JANIS definitions (20), which are based on and modified from those of the National Nosocomial Infections Surveillance (NNIS) system in the United States (26). A diagnosis of sepsis was defined as the presence of infection along with at least one of the following clinical manifestations: (1) body temperature ≥38°C or ≤36°C, (2) heart rate ≥90 bpm, (3) respiratory rate ≥20 bpm or $PaCO_2$ ≤32 mmHg, or (4) white blood cell count ≥12000/mm^3 or ≤4000/mm^3. Causative pathogens were classified as drug-susceptible or drug-resistant on the basis of the data on the drug-resistant pattern.

From the JANIS database for the period between July 2002 and July 2004, we identified 28 ICUs where more than 100 patients were available for analysis. The study cohort consisted of 21,895 eligible patients, aged 16 years or older, who stayed in the ICU for 24 to 1000 hours and were not transferred to another ICU. They were surveyed for the diagnosis of sepsis during the ICU stay. The incidence of sepsis was determined in the cohort of 21,667 patients, excluding 228 who had met the definition of sepsis on ICU admission. The incidence of sepsis was calculated as the total number of sepsis episodes divided by (1) the total number of admissions (×100) (i.e., cumulative incidence) or (2) the total number of patient-days (×1000) (i.e., incidence rate) (27). The effects of sepsis on mortality and LOS were assessed in the cohort of 20,909 patients, excluding 986 who had been infected on ICU admission. The 20,909 patients were classified into the following groups: (1) those who developed at least one infection and subsequent sepsis during the ICU stay (n=168; NI patients with sepsis), (2) those who developed at least one infection during the ICU stay but did not develop sepsis (n=760; NI patients without sepsis), and (3) those who did not develop infection during the ICU stay (n=19,981; patients without infection). Crude mortality was calculated as the total number of deaths during the ICU stay divided by (1) the total number of admissions (×100) or (2) the total number of patient-days (×1000). LOS was summed up for patients who were discharged from the ICU alive.

We observed the ethical guidelines for epidemiological studies by the Japanese Ministry of Health, Labour, and Welfare and the Japanese Ministry of Education, Culture, Sports, Science, and Technology. We paid particular attention to the protection of the anonymity of the patients and the confidentiality of the available data.

Statistical analyses

Statistical analyses were performed with the Statistical Analysis Systems (SAS, version 8.2). The chi-square test was used to compare the distributions of the characteristics of the patients. To examine the difference in the incidence of sepsis, incidence curves from ICU admission were computed using the Kaplan-Meier method and compared using the log rank test. Moreover, adjusted hazard ratio (HR) with 95% confidence interval (CI) for the incidence of sepsis was calculated using Cox's proportional hazard model (28). To examine the difference in mortality, the proportions of deceased patients were compared using the chi-square test. Moreover, standardized mortality ratio (SMR) was calculated by the indirect standardization method on the basis of the crude mortality in the patients without infection for respective APACHE II categories (0–10, 11–20, and 21+). Mean LOS for survivors was assessed by the two-way analysis of variance with adjustment for APACHE II. Because LOS had a skewed distribution, the logarithms of LOS, which would be normally distributed, were analyzed (29, 30). The back-transformed (i.e., antilog) means and 95% CIs are shown in the Results section. All statistics were two-tailed, and a value of $p<0.05$ was considered to be significant.

Results

Incidence of sepsis

Sepsis was diagnosed in 450 patients (2.1%), with 228 meeting the definition of sepsis on ICU admission and 222 during the ICU stay. There were no significant differences in sex, age, and APACHE II distributions between the patients diagnosed on ICU admission and the patients diagnosed during the ICU stay. Drug-resistant pathogens were detected in 22.9% of the sepsis episodes. This rate was significantly higher in the patients diagnosed during the ICU stay (27.0%) than in the patients diagnosed on ICU admission (18.9%).

Table 1 shows the incidences of sepsis in the cohort of 21,667 patients without sepsis on ICU admission. The overall incidence of sepsis was 1.02/100 admissions or 2.00/1000

patient-days. Of the 222 sepsis episodes, 29.3% occurred within the first 3 days of the ICU stay and 59.5% occurred within the first week of the ICU stay. The percentage of drug-resistant pathogens in the sepsis episodes increased with LOS: 22.0% in the cases developed within the first week of the ICU stay vs. 34.4% in the cases developed at least 7 days after ICU admission ($p<0.05$). In the comparison of incidence curves, being male, a high APACHE II, urgent operation, ventilator use, and central venous catheter use were significantly associated with a high incidence of sepsis; no significant difference was found in age and urinary catheter use. Multivariate analysis showed a significantly higher HR for the incidence of sepsis in men (1.54, 95%CI: 1.14–2.07), APACHE II ≥21 (2.92, 95% CI: 1.92–4.44), ventilator use (3.30, 95% CI: 1.98–5.49), and central venous catheter use (3.45, 95% CI: 1.90–6.28).

Outcome of sepsis

Over 103,765 patient-days of the 20,909 patients, there were 928 episodes of NI including 168 episodes of sepsis (18.1%). Table 2 shows the characteristics of the patients without infection, the NI patients without sepsis, and the NI patients with sepsis. The percentages of men, high APACHE II, ventilator use, central venous catheter use, and urgent operation in the patients who developed NI were significantly higher than

Table 1 Incidences of sepsis

		n	Number of sepsis episode	Incidence	
				/100 admissions	/1000 patient-days
All		21667	222	1.02	2.00
Sex	Men	13889	163	1.17	2.29
	Women	7778	59	0.76	1.48
Age	16–54	5337	59	1.11	2.21
	55–74	10771	110	1.02	2.00
	75+	5559	53	0.95	1.80
APACHE II	0–10	10268	34	0.33	0.84
	11–20	7948	72	0.91	1.66
	21+	3451	116	0.36	4.26
Operation	None	9177	101	1.10	1.99
	Elective	8947	50	0.56	1.40
	Urgent	3543	71	2.00	2.88
Ventilator	No	12671	20	0.16	0.46
	Yes	8996	202	2.25	2.97
Urinary catheter	No	3107	16	0.51	1.55
	Yes	18560	206	1.11	2.04
Central venous catheter	No	8630	14	0.16	0.46
	Yes	13037	208	1.60	2.58

Table 2 Characteristics of patients without infection, NI patients without sepsis, and NI patients with sepsis

		No infection		NI without sepsis		NI with sepsis	
		n	%	n	%	n	%
Sex	Men	12684	63.5	529	69.6	121	72.0¶
	Women	7297	36.5	231	30.4	47	28.0
Age	16–54	4989	25.0	179	23.6	46	27.4
	55–74	9917	49.6	406	53.4	83	49.4
	75+	5075	25.4	175	23.0	39	23.2
APACHE II	0–10	9933	49.7	150	19.7	23	13.7¶‡
	11–20	7253	36.3	328	43.2	56	33.3
	21+	2795	14.0	282	37.1	89	53.0
Operation	None	8294	41.5	303	39.9	70	41.7¶
	Elective	8574	42.9	238	31.3	41	24.4
	Urgent	3113	15.6	219	28.8	57	33.9
Ventilator	No	12350	61.8	105	13.8	12	7.1¶†
	Yes	7631	38.2	655	86.2	156	92.9
Urinary catheter	No	2993	15.0	32	4.2	12	7.1¶
	Yes	16988	85.0	728	95.8	156	92.9
Central venous catheter	No	8398	42.0	55	7.2	10	6.0¶
	Yes	11583	58.0	705	92.8	158	94.0

NI: nosocomial infection (ICU acquired).
¶ $p<0.001$ among 3 groups (with chi-square test).
† $p<0.05$ between NI without sepsis group and NI with sepsis group (with chi-square test).
‡ $p<0.001$ between NI without sepsis group and NI with sepsis group (with chi-square test).

Table 3 Crude mortalities of patients without infection, NI patients without sepsis, and NI patients with sepsis

	APACHE II	Mortality	
		/100 admissions	/1000 patient-days
No infection	All	5.3	11.9
	0–10	0.5	1.5
	11–20	3.0	6.2
	21+	28.4	44.5
NI without sepsis	All	14.2	9.2
	0–10	6.7	4.6
	11–20	10.7	7.3
	21+	22.3	13.2
NI with sepsis	All	39.3	20.5
	0–10	34.8	17.1
	11–20	37.5	19.4
	21+	41.5	22.2

NI: nosocomial infection (ICU acquired).

those in the patients without infection. The percentages of high APACHE II and ventilator use in the NI patients with sepsis were significantly higher than those in the NI patients without sepsis.

Table 3 shows the crude mortalities of the patients without infection, the NI patients without sepsis, and the NI patients with sepsis. The proportion of deceased patients significantly differed between the groups ($p<0.001$). The mortality of the NI patients with sepsis was higher than that of the patients without infection and the NI patients without sepsis. The mortality increased with APACHE II in all the groups, but this increase was more pronounced in the NI patients without sepsis than in those with sepsis. SMR was determined to be 1.18 (95% CI: 0.82–1.21) in the NI patients without sepsis and 2.43 (95% CI: 1.88–3.09) in the NI patients with sepsis.

For the patients who were discharged from the ICU alive, a prolonged ICU stay was more frequently observed in those who developed NI than in those without infection: the percentages of LOS ≥14 days and ≥28 days were 66.7% and 21.6% in the NI patients with sepsis and 50.2% and 10.4% in the NI patients without sepsis compared with 4.1% and 0.4% in the patients without infection ($p<0.001$), respectively. After adjusting for APACHE II, mean LOS for survivors was calculated to be 11.8 days (95% CI: 11.3–12.4) in the NI patients without sepsis and 15.0 days (95% CI: 13.3–17.0) in the NI patients with sepsis compared with 3.8 days (95% CI: 3.8–3.9) in the patients without infection.

Of the NI patients with sepsis, 126 (74.6%) were infected by drug-susceptible pathogens and 43 (25.4%) were infected by drug-resistant pathogens. Mortality was significantly higher in the patients infected by drug-resistant pathogens (53.5/100 admissions, 26.6/1000 patient-days) than in the patients infected by drug-susceptible pathogens (34.4/100 admissions, 18.3/1000 patient-days). After adjusting for APACHE II, mean LOS for survivors was calculated to be 16.4 days (95% CI: 14.1–19.0) in the patients infected by drug-susceptible pathogens and 16.3 days (95% CI: 12.5–21.1) in the patients infected by drug-resistant pathogens.

Discussion

Using the large cohort database of the JANIS system, we determined the incidence of sepsis in Japanese ICUs and assessed the impact of sepsis on mortality and LOS. To our knowledge, this is the first report on the epidemiology of sepsis in the Japanese population. The JANIS system takes various measures to establish a standardized and formatted database: a specific database-oriented software and a written operating manual with uniform definitions and surveillance protocols are prepared in advance; workshops for data collectors are conducted on demand; and reliability checks are routinely performed at the data management office. Accordingly, this study can provide reliable information on the incidence and outcome of sepsis in Japanese ICUs.

In the 28 ICUs that participated in the JANIS system, the overall incidence of sepsis was 1.02/100 admissions or 2.00/1000 patient-days. This rate was considerably lower than that observed in previous multicenter cohort studies: 20% in 8 ICUs in the United States between 1993 and 1994 (6), 61.4/1000 patient-days in 5 ICUs in Brazil between 2001 and 2002 (10), and 37% in 198 ICUs in 24 European countries in 2002 (13). In this study, the patients who met the definition of sepsis on ICU admission were excluded from the calculation of the incidence of sepsis, whereas in the previous studies, these patients were included. When we recalculated the incidence of sepsis in the total cohort of 21,895 patients, the overall incidence of sepsis was 2.06/100 admissions or 3.98/1000 patient-days. This study differed from the previous studies in definitions, surveillance protocols, and settings. Although it is difficult to compare the reported rates accurately, the incidence of sepsis in Japanese ICUs seems to be lower than that in ICUs in other countries.

As in other studies, being male, a high APACHE II, ventilator use, and central venous catheter use were significantly associated with an increased incidence of sepsis. These factors have also been reported to be risk factors of NI (22). The increased incidence of sepsis in this study might be due in part to increasing NI in relation to these factors. Information on the risk factors of sepsis may be useful for identifying high-risk subgroups who need particular attention to prevent sepsis from developing during the ICU stay. Several studies have reported that organ dysfunction along with severity of illness and device use were significantly associated with an increased incidence of sepsis (5, 7, 12). Moreover, patients admitted from medical and emergency surgical wards showed a higher incidence of sepsis than those admitted from surgical wards (5, 7, 12); however no significant association with operation was observed in this study. Further studies may be required to investigate the risk factors of sepsis in detail.

APACHE II is an indicator of severity of illness, which is commonly used for estimating the probability of death (25). Mortality increased with APACHE II in the patients with NI, but this increase was more pronounced in the patients without sepsis than in those with sepsis. It seems that sepsis had greater and more direct effects on mortality than APACHE II. The patients with sepsis showed a significantly higher SMR and a significantly longer mean LOS than those without sepsis, suggesting that the development of sepsis imposes a substantial

burden on patients with NI independent of severity of illness. Preventive measures against sepsis should be emphasized to improve survival and avoid prolonged hospitalization in patients admitted to the ICU. As a matter of course, basic infection control practices are indispensable for reducing the risk of NI.

The patients with sepsis caused by drug-resistant pathogens showed a significantly higher mortality than those with sepsis caused by drug-susceptible pathogens. Many studies have compared the outcomes of sepsis caused by drug-resistant and drug-susceptible pathogens, which have varied from no difference in mortality to a significant increase in mortality (31). Overall, drug-resistant pathogens contribute to increasing the mortality in patients with sepsis. Drug-resistant pathogens were frequently detected in the patients who developed sepsis during the ICU stay, and the percentage of drug-resistant pathogens in the sepsis episodes increased with LOS. Antibiotic use is one of the major determinants of the shift toward resistant strains (32–34). Exposure to antibiotics may increase the probability of sepsis caused by drug-resistant pathogens with increasing LOS. An adequate antibiotic treatment along with preventive measures against sepsis should be emphasized to reduce the burden of sepsis in ICU patients (31, 35, 36).

This study had the following potential limitations. First, organ dysfunction may be associated with the incidence and outcome of sepsis. Several studies have reported that organ dysfunction was significantly associated with an increased incidence of sepsis (5, 7, 12). Patients with organ dysfunction in addition to sepsis are considered to have severe sepsis or septic shock (1, 2), and therefore a higher probability of death (14–17). Although organ dysfunction was not directly analyzed in this study, APACHE II was incorporated into the model as a composite index. SMR and mean LOS were calculated with adjustment for APACHE II. Second, antibiotic treatment may be an important determinant of mortality. Several studies have reported that patients who received adequate antibiotic treatment showed a significant lower mortality than those who received inadequate antibiotic treatment (31, 37–39). Unfortunately, the JANIS system does not collect information on antibiotic use. The impact of sepsis on mortality and LOS in this study may be underestimated or overestimated. Third, the JANIS system recruits multidisciplinary hospitals with more than 200 beds. Most of the participating ICUs are in national university hospitals, where the levels of hospital infection control are likely to be high in Japan. The findings of this study may not represent the average for Japanese hospitals. Further studies may be required to confirm our findings in other hospitals.

In conclusion, sepsis is not very common in Japanese ICUs, but its development leads to further increases in mortality and LOS in patients with NI. Because of the possible effect of drug-resistant pathogens on mortality, an adequate antibiotic treatment along with preventive measures against sepsis should be emphasized to reduce the burden of sepsis in ICU patients. Clinicians are supposed to select antibiotics with an appropriate spectrum covering the likely causative pathogens even before they know the culture results. Knowledge of causative pathogens with their drug-resistant patterns may be useful for avoiding inadequate antibiotic treatment. The SOAP study showed that the distribution of causative pathogens was differed between ICU-acquired and non-ICU-acquired sepsis episodes and also between medical and surgical admissions (13). The distribution of causative pathogens in Japanese ICUs should be explored in detail to provide useful information for clinicians.

Acknowledgment

This study was supported by the 2003–2005 Health and Labour Sciences Research Grant (Research on Emergent and Re-emerging Infectious Diseases) from the Japanese Ministry of Health Labour and Welfare and the 2006 Grant-in-Aid for Scientific Research (Grant-in-Aid for Young Scientists 18790406) from the Japanese Ministry of Education, Culture, Sports, Science, and Technology and the Japanese Society for the Promotion of Science.

References

(1) Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest. 1992;101:1644–1655.

(2) Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003; 31:1250–1256.

(3) Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303–1310.

(4) Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348:1546–1554.

(5) Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults: a multicenter prospective study in intensive care units. JAMA. 1995;274: 968–974.

(6) Sands KE, Bates DW, Lanken PN, Graman PS, Hibberd PL, Kahn KL, et al. Epidemiology of sepsis syndrome in 8 academic medical centers. JAMA. 1997;278:234–240.

(7) Padkin A, Goldfrad C, Brady AR, Young D, Black N, Rowan K. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. Crit Care Med. 2003;31:2332–2338.

(8) van Gestel A, Bakker J, Veraart CP, van Hout BA. Prevalence and incidence of severe sepsis in Dutch intensive care units. Crit Care. 2004;8:R153–R162.

(9) Finfer S, Bellomo R, Lipman J, French C, Dobb G, Myburgh J. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. Intensive Care Med. 2004;30:589–596.

(10) Silva E, Pedro Mde A, Sogayar AC, Mohovic T, Silva CL, Janiszewski M, et al. Brazilian sepsis epidemiological study (BASES study). Crit Care. 2004;8:R251–R260.
(11) Zahorec R, Firment J, Strakova J, Mikula J, Malik P, Novak I, et al. Epidemiology of severe sepsis in intensive care units in the Slovak Republic. Infection. 2005;33:122–128.
(12) Adrie C, Alberti C, Chaix-Couturier C, Azoulay E, De Lassence A, Cohen Y, et al. Epidemiology and economic evaluation of severe sepsis in France: age, severity, infection site, and place of acquisition (community, hospital, or intensive care unit) as determinants of workload and cost. J Crit Care. 2005;20:46–58.
(13) Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006;34:344–353.
(14) Rangel-Frausto MS. The epidemiology of bacterial sepsis. Infect Dis Clin North Am. 1999;13:299–312.
(15) Brun-Buisson C. The epidemiology of the systemic inflammatory response. Intensive Care Med. 2000;26 suppl 1:S64–74.
(16) Balk RA. Severe sepsis and septic shock: definitions, epidemiology, and clinical manifestations. Crit Care Clin. 2000; 16:179–192.
(17) Angus DC, Wax RS. Epidemiology of sepsis: an update. Crit Care Med. 2001;29 suppl 7:S109–116.
(18) The 2005 Report of Health and Labour Sciences Research Grant (Research on Emergent or Revival Infections), “Research on network of drug-resistant infection surveillance”, 2006. (in Japanese)
(19) The 2005 Report of Health and Labour Sciences Research Grant (Research on assessment of medical technology), “Research on prevention of nosocomial infection in intensive care units”, 2006. (in Japanese)
(20) The 2000 Report of Health and Labour Sciences Research Grant (Research on Emergent or Revival Infections), “Research on development of drug-resistant infection surveillance system”, 2000. (in Japanese)
(21) Suka M, Yoshida K, Takezawa J. Impact of intensive care unit-acquired infection on hospital mortality in Japan: a multicenter cohort study. Environ Health Prev Med. 2004; 9:53–57.
(22) Suka M, Yoshida K, Takezawa J. Association between APACHE II score and nosocomial infections in intensive care unit patients: a multicenter cohort study. Environ Health Prev Med. 2004;9:262–265.
(23) Suka M, Yoshida K, Takezawa J. A practical tool to assess the incidence of nosocomial infection in Japanese intensive care units: the Japanese Nosocomial Infection Surveillance System. J Hosp Infect. 2006;63:179–184.
(24) Suka M, Yoshida K, Uno H, Takezawa J. Incidence and outcomes of ventilator-associated pneumonia in Japanese intensive care units: the Japanese Nosocomial Infection Surveillance System. Infect Cont Hosp Epidemiol. 2006 (in press).
(25) Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13:818–829.
(26) Garner JS, Javis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections 1988. Am J Infect Control. 1988;16:128–140.
(27) Jarvis WR, Edwards JR, Culver DH, Hughes JM, Horan T, Emori TG, et al. Nosocomial infection rates in adult and pediatric intensive care units in the United States: National Nosocomial Infections Surveillance System. Am J Med. 1991;91(3B):185S–191S.
(28) Cox DR. Regression models and life-tables. J Royal Stat Soc Series B. 1972;34:187–220.
(29) Bland JM, Altman DG. Transformations, means, and confidence intervals. BMJ. 1996;312:1079.
(30) Bland JM, Altman DG. The use of transformation when comparing two means. BMJ. 1996;312:1153.
(31) Turnidge J. Impact of antibiotic resistance on the treatment of sepsis. Scand J Infect Dis. 2003;35:677–682.
(32) Shlaes DM, Gerding DN, John JF, Jr, Craig WA, Bornstein DL, Duncan RA, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Clin Infect Dis. 1997;25:584–599.
(33) Albrich WC, Angstwurm M, Bader L, Gartner R. Drug resistance in intensive care units. Infection. 1999;27 suppl: S19–23.
(34) Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. Ann Intern Med. 2001;134:298–314.
(35) Yu DT, Black E, Sands KE, Schwartz JS, Hibberd PL, Graman PS, et al. Severe sepsis: variation in resource and therapeutic modality use among academic centers. Crit Care. 2003;7:R24–34.
(36) Bodmann KF. Current guidelines for the treatment of severe pneumonia and sepsis. Chemotherapy. 2005;51:227–233.
(37) Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest. 2000;118:146–155.
(38) Weinstein MP, Towns ML, Quartey SM, Mirrett S, Reimer LG, Parmigiani G, et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin Infect Dis. 1997;24:584–602.
(39) Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med. 1998;244:379–386.