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ORIGINAL

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Incidence, treatment, and outcome of severe sepsis in ICU-treated adults in Finland: the Finnsepsis study

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Abstract *Objective:* To determine the incidence and outcome of severe sepsis in the adult Finnish population and to evaluate how treatment guidelines in severe sepsis are applied in clinical practice. *Study design:* A prospective study in 24 closed multidisciplinary ICUs in 21 hospitals (4 university and 17 tertiary hospitals) in Finland. *Patients:* All 4,500 consecutive ICU admission episodes were screened for severe sepsis during a 4-month period (1 November 2004 – 28 February 2005). The referral population was 3,743,225. *Results:* The severe sepsis criteria were fulfilled in 470 patients, who had 472 septic episodes. The incidence of severe sepsis in the ICUs in Finland was 0.38/1000 in the adult population (95% confidence interval 0.34–0.41). The mean ICU length of stay was 8.2 ± 8.1 days. ICU, hospital, and 1-year mortality rates were 15.5%, 28.3%, and 40.9%, respectively. Respiratory failure requiring ventilation support was the most common organ failure (86.2%); septic shock was present in 77% and acute renal failure in 20.6% of cases. Activated protein C was given to only 15 of the 55 patients with indication (27%) and low-dose corticosteroids to 150 of 366 (41%) patients with septic shock. *Conclusions:* This prospective study found the incidence of ICU-treated severe sepsis in Finland to be 0.38 per 1,000 of the population. The ICU and hospital mortalities were also lower than earlier reported in United States or Australia. Evidence-based sepsis therapies were not used as often as recommended.

Keywords Severe sepsis · Septic shock · Incidence · Mortality · Treatment protocols

Introduction

Severe sepsis and septic shock has long been a challenge in intensive care because of its common occurrence, high associated costs of care, and significant mortality, which varies between 30% and 50% in different studies [1, 2]. Recent studies have shown that the prognosis of severe sepsis can be improved. The international Surviving Sepsis Campaign (SSC) published severe sepsis guidelines in 2004 [3]. The objective of SSC is to have the treatment recommendations used globally and to reduce the mortality in severe sepsis by 25% within the next 5 years. In Finland the national guidelines for the treatment of severe sepsis in adults were published in August 2005 [4]. The SSC guidelines for severe sepsis treatments are based on studies which show that relatively simple therapeutic interventions make it possible to save a significant number of lives in sepsis. Ventilation with low tidal volumes [5], tight blood glucose control [6], low-dose hydrocortisone for septic shock [7], and activated protein C (aPC) [8] have been selected as the target treatments in the SSC's Sepsis Management Bundle. However, recent studies concerning lung protective ventilation have shown that the compliance to adopt and implement new guidelines into practice is inadequate also in critical care setting [9, 10].

The incidence of severe sepsis and the rate of compliance with recommended sepsis treatments in real life have not been studied prospectively in the Nordic countries. Based on international estimations of incidence [1, 11] these results would mean 3,500–15,000 severe sepsis patients in Finland per year. We therefore conducted a prospective Finnish study to determine the incidence, compliance with treatment guidelines, and outcome of severe sepsis.

Materials and methods

Data source

All 25 ICUs in tertiary and university hospitals belonging to Finnish Quality Consortium on Intensive Care were invited to participate in the Finnsepsis study, which constituted over 82% of multidisciplinary ICUs in Finland. During the study period these ICUs treated 4,500 adult patients. The diagnostic criteria of severe sepsis were met in 470 patients; two patients had two septic episodes with different sources of infection, and two patients were treated twice in ICU for the same sepsis during the study period. Consent from the respective ethics committees was obtained from each hospital. The study period was 4 months, from 1 November 2004 to 28 February 2005.

Definitions

Severe sepsis at admission or during the ICU treatment was defined according to the ACCP/SCCM [12] criteria consisting of a systemic inflammatory response, suspected or confirmed infection and an acute organ dysfunction. Study entry was the time when all three criteria were met. If the patient had more than one severe sepsis episode from the same source, only the first period was taken for severe sepsis incidence, treatment, and outcome analysis, but organ dysfunctions were assessed for all ICU days. If the patient had more than one severe sepsis episode from different sources, all periods were taken into all analysis except mortality. During the study period adult patients treated in the hospital wards receiving antibiotic treatment for infection were screened for severe sepsis in four predetermined days. The data of severe sepsis patients not receiving intensive care were limited to demographic and infection data only. Disseminated intravascular coagulation (DIC) was defined as recommended by the International Society on Thrombosis and Haemostasis [13]. Compliance with treatment recommendations was studied. The hospital and 1-year mortality rates and causes of death in severe sepsis were assessed.

Patients

All patients over 18 years of age in intensive care were screened for severe sepsis at admission or during their ICU stay. Each center had one or more study nurses who were responsible for screening, patient records, and follow-up. If a severe sepsis or septic shock diagnosis was approved by the investigator at each site, the patient was included in the incidence, organ failure, and outcome study. Patients' demographic data are shown in Table 1. Although the less strictly defined ACCP/SCCM organ failure criteria were used, most patients (95.8%) also met one or more severe sepsis organ failure criteria used in PROWESS study [8].

Data

The following patient information was collected into the Quality Consortium's database (Intensium): demographic data, diagnosis by *International Classification of Diseases* 10th edn., Simplified Acute Physiology Score (SAPS) II score [14], Acute Physiology and Chronic Health Evaluation (APACHE) II score [15], Therapeutic Intervention Scoring System (TISS) points [16], and discharge data from intensive care. Data concerning the source of infection and use of antibiotic treatments were recorded. In addition, the course of various organ dysfunctions and supportive treatments, for example, vasoactive and ventilator therapies and renal replacement therapies were recorded, as well as the use of activated protein C and

Table 1 Patient characteristics and outcome (470 patients, 472 Septic episodes) (*LOS* length of stay, *IQR* interquartile range)

Gender: M	315 (67%)
Age, mean (years)	59.6 ± 15.2
Age cohort 0–44	78 (16.6%)
Age cohort 45–54	81 (17.3%)
Age cohort 55–64	126 (26.9%)
Age cohort 65–74	92 (19.6%)
Age cohort 75+	93 (19.8%)
Underlying comorbidity	
Chronic lung disease	64 (13.6%)
Chronic alcohol use	124 (26.3%)
Diabetes	101 (21.5%)
Hypertension	163 (34.9%)
Metastatic cancer	22 (4.6%)
Immunosuppression	38 (8.1%)
Organ transplant	7 (1.5%)
Chronic liver disease	22 (4.8%)
Chronic renal disease with hemodialysis	7 (1.5%)
APACHE II, mean	24.1 ± 9.1
SAPS II, mean	44.8 ± 16.9
TISS per day, mean	36.5 ± 7.8
Postoperative admissions	136 (29%)
Postoperative elective	20 (14.7%)
Postoperative emergency	116 (85.3%)
Emergency admissions	445 (94.7%)
LOS (days)	
ICU	
Mean	8.2 ± 8.1
Median (IQR)	5.8 (3.0–11.5)
Hospital	
Mean	24.9 ± 24.4)
Median (IQR)	18.0 (11.0–33.7)
Died in ICU	73 (15.5%)
Died in hospital	133 (28.3%)

low-dose hydrocortisone. The Sequential Organ Failure Assessment (SOFA) score [17] was calculated daily to assess the severity of organ dysfunction. Maximum SOFA score (SOFAmax) [18] was used to represent the severity of organ dysfunction. The ICU physician evaluated daily the association between existing organ dysfunction and severe sepsis. Severe organ dysfunction or organ failure was defined as SOFA score of 3 or greater. Patients having chronic dialysis treatment at admission were excluded from acute organ dysfunction assessment as well as patients with chronic liver disease. Two infectious disease specialists (E.K. and E.M.R.) assessed the data concerning adequacy of microbiological treatment based on data on positive blood cultures and first antibiotic treatment. Causes of hospital deaths and restrictions of care were independently evaluated from patient data records by two of the investigators (S.K. and E.R.).

Calculation of population incidence

Statistics Finland maintains annual Finnish population records, which are also available for different age groups in hospital district areas. The population used in this study was that announced 31 December 2004 (http://www.tilastokeskus.fi/tup/tilastotietokannat/index.html; accessed 25 August 2005).

Data management

All data were collected into the internet based database. Every sixth patient was rechecked for inclusion criteria at study entry and survival status at hospital discharge. In this recheck each patient fulfilled the inclusion criteria. One ICU survivor was registered as nonsurvivor, and this was corrected. One-year mortality data were obtained from Statistics Finland.

Statistical analysis

Data were analyzed by SPSS version 12.1 (SPSS, Chicago, Ill., USA). Data are presented as mean ± SD or with confidence interval or interquartile range (IQR) or as absolute numbers and percentages. Hospital mortality rate between different treatments and age groups were compared by the χ^2 test. Differences with a p value less than 0.05 were considered statistically significant.

Results

Incidence

Inclusion and outcome data are shown in Fig. 1. Severe sepsis was diagnosed in 10.5% of ICU admissions (472/4,500). In the participating 19 hospital districts there were 3,743,265 inhabitants over the age of 18 years, which included 90.6% of the Finnish adult population. The incidence of severe sepsis requiring intensive care was calculated to be 0.38/1000 adults/year (95% confidence interval 0.34–0.41). Eleven hospitals (referral population 2,484,131 inhabitants) screened for severe sepsis, altogether 4,843 adult patients in the wards in four separate predetermined screening days. The incidence of additional severe sepsis patients during the screening days was estimated to be 0.31/1,000 based on those patients who had been admitted to hospital within 24 h before a screening day. Thus the estimated in-hospital incidence of severe sepsis was 0.69/1,000.

Infection data

Infection was community acquired in 58.3% (275/472) of cases and nosocomial in 38.9% (184/472). Blood cultures were taken from 67.6% of patients ($n = 319$) and were positive in 40.1% (128/319). Gram-positive bacteria were found in 58.6% (75/128) and Gram-negative in

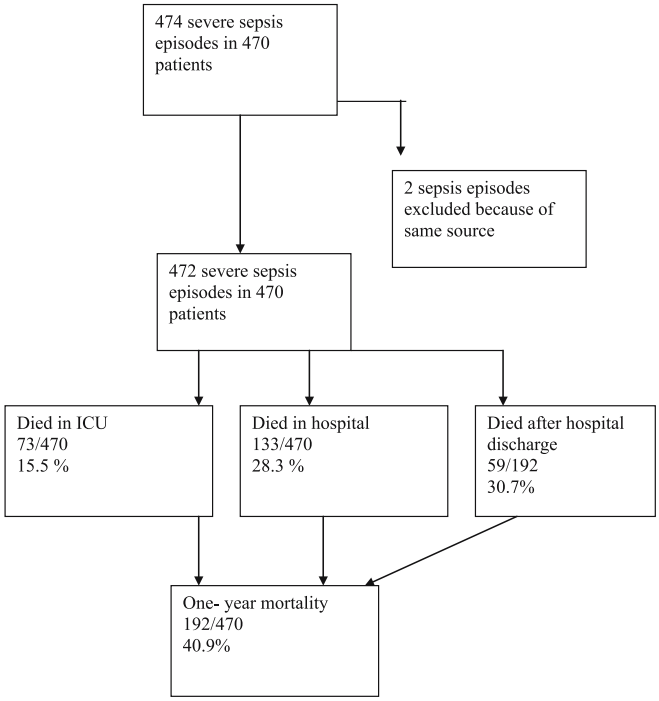

Fig. 1 Severe sepsis patients and their outcomes

32.8% (42/128) of positive blood cultures. Other microorganisms such as yeasts were found in only 3.9% (5/128). Over one-third of patients (121/319, 37.9%) had ongoing antibiotic treatment at the time the samples were taken. The main sources of infection are presented in Table 2. Antibiotic treatment was ongoing at hospital admission in 20% of patients with community acquired infection and in 70.5% of patients with nosocomial infection (before severe sepsis was diagnosed). The antibiotic treatment was considered to be adequate in 90.2% of the blood culture positive patients, ineffective in 7.2%, and uncertain in 2.5% of cases.

Organ dysfunctions

Organ dysfunctions associated with severe sepsis are presented in Table 3. Respiratory failure and septic shock were the most frequent organ dysfunctions. A majority of patients (368/472, 87.3%) needed mechanical ventilation during their stay in ICU, and 12% (44/368) of mechanically ventilated patients needed only noninvasive ventilation (continuous positive airway pressure or bilevel ventilation). Severe oxygenation impairment (SOFAmax score ≥ 3) was found in 71.4% of the patients. In 77% of patients there was septic shock requiring vasoactive treatment.

Treatments

Intravenous fluid therapy data during the first 24 h were available in 59.1% of the patients. The median fluid resuscitation was 5000 ml (IQR 3226–7250 ml) in first 24 h altogether, and median 1000 ml (IQR 500–1600 ml) of these fluids were colloids. During the study period aPC treatment was administered to 15/470 patients (3.2%). However, there were at least more than 40 additional patients with severe sepsis, multiple organ dysfunction, and disseminated intravascular coagulation (DIC) in whom aPC treatment would have been indicated. The hospital mortality rates in patients treated with aPC and patients with DIC without aPC were 40% (6/15) and 52.5% (21/40), respectively. Corticosteroid treatment was given to over one-half of the patients ($n = 256$, 54.2%): low-dose hydrocortisone (200–300 mg/day) for sepsis indication in 36.2% and the rest for acute respiratory distress syndrome (ARDS; 8.1%) to treat the underlying disease or to substitute chronic corticosteroid treatment. The corticotropin stimulation test was performed in 6.6% of patients (17/256) receiving corticosteroids. Septic shock patients ($n = 366$) received hydrocortisone for sepsis indication only in less than one-half of cases (151/366,

Table 2 Sources of infection and hospital mortality

Site of infection	*n*	%	Hospital mortality *n*	Hospital mortality %
Pulmonary	200	43	55	28
Intra-abdominal	150	32	48	32
Skin or soft tissue	49	10	10	20
Urinary	23	5	3	13
Cardiac	11	2	0	–
Central nervous system	7	2	0	–
Foreign body	6	1	0	–
Ear, nose and throat	6	1	0	–
Other	6	1	2	33
Unknown	38	8	14	37
Infection acquired during intensive care	44	9	11	25

Table 3 Organ failures and treatments (*DIC* disseminated intravascular coagulation, *ISTH* International Society of Thrombosis and Haemostasis)

	n	%
Respiratory		
SOFAmax ≥ 3	337	71.4
Mechanical ventilation	412	86.2
Cardiovascular		
Septic shock	363	77.0
Renal		
SOFAmax ≥ 3	109	23.2
Renal replacement therapy	60	12.7
Hematological		
SOFAmax ≥ 3	105	22.2
DIC with ISTH points ≥ 5*	65	36.3*
Hepatic		
SOFAmax ≥ 3	8	1.7

* Data available for calculating ISTH points in 179 patients

41.3%), but there was no difference in hospital mortality between these groups ($p = 0.565$). Implemented tidal volumes were analyzed in the first day of the study. There were 247 ventilated patients (52.3%) with PaO_2/FIO_2 ratio less than 300 mmHg. Tidal volumes per predicted body weight could be calculated in 138 patients (40 women, 98 men): in women 10.2 ± 1.9 ml and in men 8.9 ± 2.1 ml. Only 15% of women were ventilated with tidal volume less than 8 ml/kg and none with less than 6 ml/kg. Men were ventilated with tidal volume less than 8 ml/kg in 42.0% and less than 6 ml/kg in 8.2%. The mean tidal volumes per actual estimated body weight in these patients were 7.9 ± 22 ml/kg. The limit for high blood glucose level target was set in 96% of severe sepsis patients. Blood glucose level was set under 6.5 mmol/l in 41.5% and under 8 mmol/l in 53.6% of patients.

Mortality

ICU and hospital mortality rates were 15.5% and 28.3%, respectively. The number of organ failures affected strongly mortality: with one organ failure (SOFAmax score 3–4) mortality was 11.5% but with three organ failures mortality increased to 34.0%. Table 4 shows the association of mortality with severe organ failure and its combinations. Hospital mortality in patients over 65 years of age was 40.0% and that in patients under 65 years of age 20.4%. The mortality in APACHE age group 55–64 years was 26.2% while it was 40.2% in age group 65–74 ($p < 0.05$). The causes of hospital and 1-year mortality rates and restrictions of care are presented in Table 5. Treatment restriction included the decision to withhold or withdraw the treatment or a do-not-resuscitate order. In 85 patients (18.1% of severe sepsis patients) restrictions of care were set during their ICU stay. In nearly one-half of these cases (45.9%) the restrictions were set when patient was discharged from ICU (indicating no possibility for readmission). Hospital mortality was 89.4% (76/85) in patients whose treatment was in some was limited

Table 4 Mortality in combination with one or more organ failures: total number of patients in each organ failure group according to maximum SOFA score and hospital mortality (% within the respective group)

	Respiratory		Coagulation		Liver		Cardiovascular		CNS		Renal	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
One organ dysfunction SOFAmax ≥ 3	339	34.5	106	44.3	28	57.1	366	32.5	108	44.4	111	57.7
Respiratory	–	–	28	64.3	24	66.6	283	37.8	96	47.9	88	63.9
Coagulation	–	–	–	–	19	63.2	91	47.3	32	56.3	32	56.3
Liver	–	–	–	–	–	–	25	60.0	11	72.7	14	71.4
Cardiovascular	–	–	–	–	–	–	–	–	94	45.7	99	61.6
CNS	–	–	–	–	–	–	–	–	–	–	35	68.6

Table 5 Causes of ICU and hospital deaths in severe sepsis (*MODS* multiple organ dysfunction syndrome)

	Died in ICU		Died in hospital		Died after hospital	
	n	%	*n*	%	*n*	%
No. of patients	73/470	15.5	60/470	12.8	59/470	12.6
MODS	34/73	46.6	19/60	31.7	–	–
Refractive shock	18/73	24.7	–	–	–	–
Uncontrolled infection	6/73	8.2	7/60	11.7	2/59	3.4
Respiratory failure	7/73	9.6	17/60	28.3	6/59	10.2
Cardiac, brain ischemia	7/73	9.6	14/60	23.3	20/59	33.9
Malignancy	8/59	13.6	–	–	–	–
Gastrointestinal	11/59	18.6	–	–	–	–
Other	1/73	1.4	8/59	13.6	–	–
Unknown	4/60	6.7	–	–	–	–

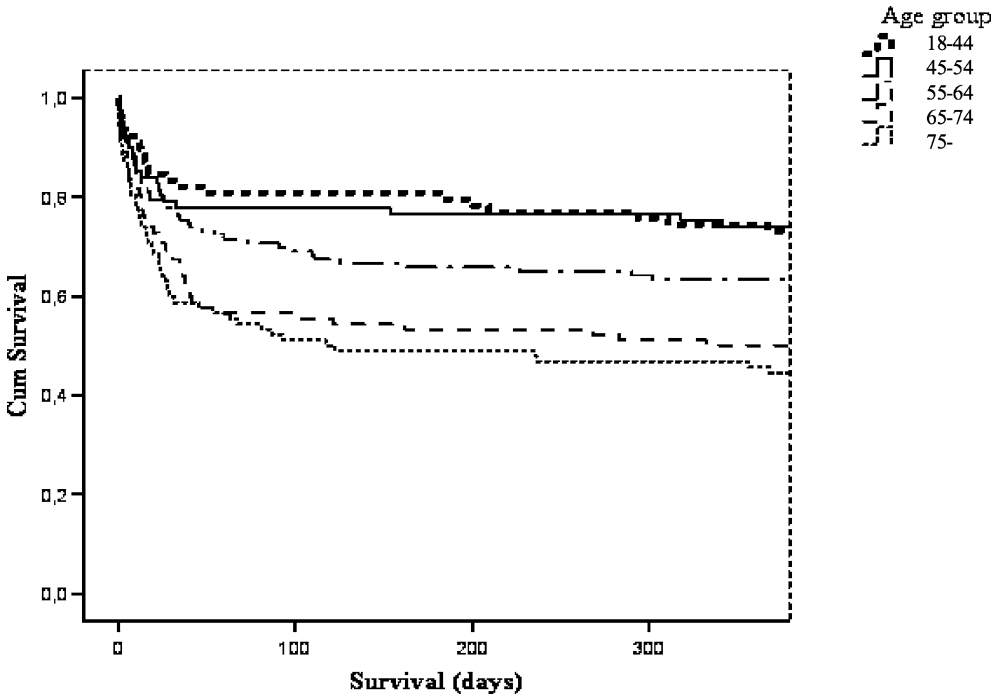

Fig. 2 Kaplan–Meier curve on survival of 470 severe sepsis patients in different age groups

during ICU stay or at discharge. Hospital mortality of patients receiving full-scale care whose treatment was not limited was 14.5%. One-year mortality was 40.9%. The Kaplan-Meier curve on survival is presented in Fig. 2.

Discussion

Our study found that in Finland the incidence of severe sepsis in intensive care is 0.38/1,000 adults, and that the treatment compliance with the Sepsis Management Bundle's guidelines was poor. The incidence of severe sepsis and septic shock has varied in different studies from 0.5 to 3 cases per 1,000 inhabitants, depending on the population studied, time frame and methods [1, 19]. In the Nordic countries the incidence of sepsis has been studied only retrospectively. In Norway the national health database was screened for cases of sepsis and the incidence was determined to be 9.5/1,000 hospital admissions and 1.49/1,000 inhabitants [20]. Of sepsis patients 31.8% were diagnosed to have severe sepsis, which gives a calculated incidence of 0.48/1,000 inhabitants. A prospective study conducted over 3 months in Australia and New Zealand in 2004 [11] found that severe sepsis was present in 11.8 cases per 100 ICU admissions, and the population incidence was calculated to be 0.77/1,000 adults. In the Finnsepsis study the incidence of severe sepsis (0.38/1,000 adults/year) was lower than in other European or Australian prospective studies [11, 21, 22]. The proportion of ICU admissions with severe sepsis (10.5%) is, however, similar to that in other Australian studies [11, 22]. There may be several reason for lower severe sepsis incidence in Finland and other Nordic countries than other regions in the world. First, resistant microbes are causing increasing number of septic infections [23]. Finland has long been a country with a low prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) and over 99% of *S. aureus* bloodstream infections are caused by methicillin-sensitive strains [24]. In the Finnsepsis study there was no multidrug-resistant microbes causing infections such as MRSA or vancomycin-resistant enterococci. Only one of the Finnsepsis patients was HIV positive. Secondly, 60% of community acquired severe sepsis patients had previous physician contact. Finnish health care system with health centers and general hospitals is easily accessible, and it is likely that early treatment of infections affects their severity. In the recent published SOAP [25] study there was a considerable variation in the severe sepsis rates between different countries.

Martin et al. [26] have shown that age is an independent risk factor for sepsis and sepsis mortality. The effect of age on mortality was clearly demonstrated in our study: mortality in patients over 65 years was twofold that in younger patients (40.5% vs. 20.4%). Hospital mortality in sepsis without an organ failure has varied between 15% and 18.4% [21, 27], and in severe sepsis between 28.6% and 70.0% [1, 27]. In the present study ICU mortality was 15.5% and hospital mortality 28.3%. The former is lower than other studies reporting mortalities of over 20% [11, 27], but hospital mortality in the present study is similar to other surveys. A proportion of patients have significant un-

derlying diseases which affect the final outcome. The decision to limit treatment was made during intensive care or at the time of discharge in 18.0% of patients. These patients had a hospital mortality of 89.4%. On the other hand, the hospital mortality was low in those patients (14.5%) whose treatment was not restricted in ICU or at discharge. This is consistent with findings reported by Azoulay et al. [28] whose conclusion was that the most powerful predictor of post-ICU mortality is limitation of care in ICU.

Compliance with recommended treatments for severe sepsis in this study was poor. This is not surprising since many recent studies have reported difficulty in implementing clinical guidelines in practice. Many of these reports concern the use of low tidal volumes [10, 29], but the problem applies to any recommendation or guideline [30]. Recommended low-dose corticosteroid treatment was administered to fewer than one-half of the patients with septic shock. On the other hand, 19.6% of patients without confirmed septic shock received low-dose cortisone administered with sepsis indication. Treatment with aPC was given to only one-third of the patients with indications according to Finnish recommendations published in 2003 [31], which include at least one acute organ dysfunction with DIC. Blood cultures were absent nearly in one-third of patients. Ventilating acute lung injury/acute respiratory distress syndrome patients with low tidal volumes according to ARDSnet recommendations was poor and comparable with other studies [9, 10]. Calculation of tidal volumes per predicted body weight and not per actual, often estimated body weight and height seems to be one confusing factor concerning the implementation of ARDSnet recommendations. Recently published studies show the impact of compliance with severe sepsis treatment guidelines on hospital mortality [32, 33]. In the study by Kortgen et al. [34] 28-day mortality decreased from 53% to 27% when standard operating procedures in treatment of severe sepsis and septic shock were used. The hospital mortality in our study was 28.3% before implementation of national sepsis guidelines.

Our study has some limitations. Not all Finnish ICUs participated in our study, but because 90% of Finland's university and central hospitals did participate, we consider it highly representative. In all adult patients under intensive care the criteria for sepsis were monitored prospectively daily during the course of the study. However, during a limited 4-month study period it is possible that seasonal changes in the occurrence of diseases influence the outcome. In a recent retrospective study on 31,040 ICU patients in Finland the proportion of admissions due to respiratory failure was slightly higher in winter (13.6%) than during other seasons (11.6%) [35]. Otherwise, there were no differences between the seasons in the distribution of patients to different diagnostic categories. In that study the data were collected during 1998–2001, and infection-related diagnosis was found in 10.7% of ICU admissions, which is in accordance with our prospective study (10.5%). In addition, a small minority of patients with severe sepsis may have been treated in small regional hospitals. The estimated in-hospital incidence of severe sepsis was 0.69/1,000, but because it was based on a 4-day survey in only two hospitals, it should be considered as an approximation. Also, it must be noted that the availability of beds in ICU wards may affect both the severity of disease during inclusion and the quality of care. However, in our study there were only fewer than 1% severe sepsis patients who were treated outside ICU because of shortage of ICU beds.

In conclusion, in this prospective study the incidence of severe sepsis in Finnish ICUs was 0.38/1,000 adults. The ICU and hospital mortality rates were lower than in most retrospective or prospective studies in United States or Australia, but compliance with evidence based sepsis therapies and Surviving Sepsis Guidelines was poor. A follow-up study will be carried out after education and implementation of Finnish National Adult Severe Sepsis Guidelines and Surviving Sepsis Guidelines.

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Appendix

Participating hospitals, investigators (Inv.), and Study Nurses (SN) in the FINNSEPSIS-study Satakunta Central Hospital Hospital, Dr. Vesa Lund (Inv.), Marika Vettenranta, Päivi Tuominen (SN); East Savo Central Hospital, Dr. Markku Suvela (Inv.), Sari Hirvonen, Anne-Marja (SN); Central Finland Central Hospital, Dr. Raili Laru-Sompa (Inv.), Tiina Kirkhope (SN); South Savo Central Hospital, Dr. Heikki Laine (Inv.), Aki Savinen, Pekka Kettunen (SN); North Carelia Central Hospital, Dr. Sari Karlsson (Inv.), Jaana Kallinen, Vesa Parviainen (SN); Seinäjoki Central Hospital, Dr. Kari Saarinen (Inv.), Johanna Kristola, Niina Tuominen (SN); South Carelia Central Hospital, Dr. Seppo Hovilehto (Inv.), Sari Melto, Marjut Repo (SN); Päijät-Häme Central Hospital, Dr. Pekka Loisa (Inv.), Merja Esselström, Riitta Hallikainen (SN); Kainuu Central Hospital, Dr. Tuula Korhonen (Inv.), Ulla Koponen, Kirsti Pomell (SN); Vaasa Central Hospital, Dr. Pentti Kairi (Inv.), Marianne Ström (SN); Kanta-Häme Central Hospital, Dr. Ari Alaspää (Inv.), Elina Helminen (SN); Lappi Central Hospital, Dr. Outi Kiviniemi (Inv.), Tarja Laurila (SN); Keski-Pohjanmaa Central Hospital, Dr. Tadeusz Kaminski (Inv.), Tea Verronen (SN); Kymenlaakso Central Hospital, Dr. Jussi Pentti, Dr. Seija Alila (Inv.); Helsinki University Hospital, Dr. Ville Pettilä, Dr. Marjut Varpula, Dr. Marja Hynninen (Inv.), Marja Pere, Maiju Salovaara (SN); Helsinki University Hospital (Jorvi), Dr. Tero Varpula (Inv.), Mirja Vauramo (SN); Helsinki University Hospital (Peijas), Dr. Rita Linko (Inv.), Kimmo Kuusisto (SN); Tampere University Hospital,

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