Sepsis in European intensive care units: Results of the SOAP study*

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Objective: **To better define the incidence of sepsis and the characteristics of critically ill patients in European intensive care units.**

Design: **Cohort, multiple-center, observational study.**

Setting: **One hundred and ninety-eight intensive care units in 24 European countries.**

Patients: **All new adult admissions to a participating intensive care unit between May 1 and 15, 2002.**

Interventions: **None.**

Measurements and Main Results: **Demographic data, comorbid diseases, and clinical and laboratory data were collected prospectively. Patients were followed up until death, until hospital discharge, or for 60 days. Of 3,147 adult patients, with a median age of 64 yrs, 1,177 (37.4%) had sepsis; 777 (24.7%) of these patients had sepsis on admission. In patients with sepsis, the lung was the most common site of infection (68%), followed by the abdomen (22%). Cultures were positive in 60% of the patients with sepsis. The most common organisms were *Staphylococcus aureus* (30%, including 14% methicillin-resistant), *Pseudomonas* species (14%), and *Escherichia coli* (13%). *Pseudomonas* species was the only microorganism independently associated with increased mortality rates. Patients with sepsis had more severe organ dysfunction, longer intensive care unit and hospital lengths of stay, and higher mortality rate than patients without sepsis. In patients with sepsis, age, positive fluid balance, septic shock, cancer, and medical admission were the important prognostic variables for intensive care unit mortality. There was considerable variation between countries, with a strong correlation between the frequency of sepsis and the intensive care unit mortality rates in each of these countries.**

Conclusions: **This large pan-European study documents the high frequency of sepsis in critically ill patients and shows a close relationship between the proportion of patients with sepsis and the intensive care unit mortality in the various countries. In addition to age, a positive fluid balance was among the strongest prognostic factors for death. Patients with intensive care unit acquired sepsis have a worse outcome despite similar severity scores on intensive care unit admission. (Crit Care Med 2006; 34:344–353)**

Recent years have seen several studies providing important national and international epidemiologic data on the frequency, associated factors, and even costs of sepsis (1–7). Angus and coworkers (1) analyzed >6 million hospital discharge records from seven states in the United States and estimated that 751,000 cases of severe sepsis occur annually in the United States, with a mortality rate of 28.6% and leading to average costs per case of $22,100. Using the National Hospital Discharge Survey database, Martin et al. (2) identified 10,319,418 cases of sepsis from an estimated 750 million hospitalizations in the United States over a 22-yr period, with an increase in frequency from 82.7 cases per 100,000 population in 1979 to 240.4 cases per 100,000 population in 2000. Alberti and colleagues (3) examined 14,364 patients in six European countries and Canada with >4,500 documented infectious episodes and reported a hospital mortality rate of 16.9% for noninfected patients and 53.6% for patients who had repeated courses of infection while in the intensive care unit (ICU).

The European Prevalence of Infection in intensive Care (EPIC) study (8), now >10 yrs old, demonstrated how international collaboration can succeed in providing valuable information regarding disease prevalence and demographics of critically ill patients. In that prevalence

*See also p. 552.

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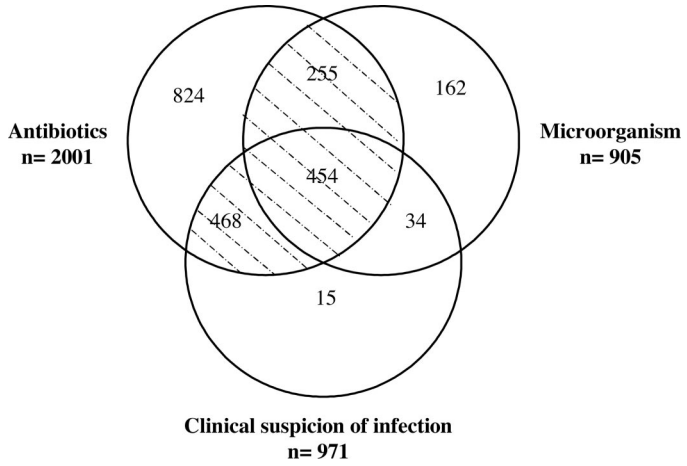

Figure 1. Venn diagram representing the basic criteria used for defining infection. Shaded area represents patients with identified infection.

study, data were collected on all patients present in the participating ICUs on a single day. For the present Sepsis Occurrence in Acutely Ill Patients (SOAP) study, we collected a large amount of data on all patients admitted to the ICU during a 2-wk period, to identify the frequency of sepsis in European ICUs and identify various etiological, diagnostic, therapeutic, and prognostic factors in this population.

METHODS

Study Design. The SOAP study was a prospective, multiple-center, observational study, designed to evaluate the epidemiology of sepsis and other characteristics of ICU patients in European countries, and was endorsed by the European Society of Intensive Care Medicine. Institutional recruitment for participation was by open invitation and was voluntary, with no financial incentive. Since this observational study required no deviation from routine medical practice, institutional review board approval was either waived or expedited in participating institutions and informed consent was not required. All adult patients (>15 yrs) newly admitted to the ICU of a participating center (see the Appendix for a list of participating countries and centers) between May 1 and May 15, 2002, were included. Patients were followed up until death, until hospital discharge, or for 60 days. Those who stayed in the ICU for <24 hrs for routine postoperative observation were excluded. Patients who were readmitted and had been included on their first admission were not included for a second time.

Definitions. Infection was defined as the presence of a pathogenic microorganism in a sterile milieu (such as blood, abscess fluid, cerebrospinal fluid, or ascitic fluid) and/or clinically suspected infection, plus the administration of antibiotics (Fig. 1). Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus conference definitions by infection plus two systemic inflammatory response syndrome criteria (9). Severe sepsis was defined by sepsis plus at least one organ failure, except when that organ failure was already present 48 hrs before the onset of sepsis. Organ failure was defined as a Sequential Organ Failure Assessment (SOFA) score >2 for the organ in question (10). ICU-acquired sepsis was defined as sepsis identified ≥48 hrs after ICU admission. Non-ICU-acquired sepsis was defined as sepsis present on admission or within 48 hrs of ICU admission. Surgical admissions were defined as surgery within 2 wks preceding admission. Emergency surgery was defined as a nonscheduled operation within 24 hrs of the onset of symptoms or injury. Patients were also classified according to their primary cause of admission into cardiovascular, respiratory, renal, central nervous system, gastrointestinal, hematologic, and hepatic diagnoses. Considered comorbidities included the presence of insulin-dependent diabetes mellitus, chronic obstructive pulmonary disease, hematologic malignancy, solid malignancy, cirrhosis, heart failure class III or IV according to the New York Heart association definitions, and the presence of human immunodeficiency virus infection.

Data Collection and Management. Data were collected prospectively using preprinted case report forms. Detailed instructions, explaining the aim of the study, instructions for data collection, and definitions for various items were available for all participants at www.intensive.org before starting data collection and throughout the study period. The steering committee was easily accessible to the investigators and processed all queries during data collection.

Data collection on admission included demographic data and comorbid diseases. Clinical and laboratory data for the Simplified Acute Physiology Score (SAPS) II (11) were reported as the worst value within 24 hrs after admission. Microbiological and clinical infectious data were reported daily as well as the antibiotics administered. Daily fluid balance was calculated as the total fluid balance over the ICU stay divided by the ICU length of stay. Cumulative fluid balance within the first 72 hrs of onset of sepsis was also calculated. A daily evaluation of organ function that was based on a set of laboratory and clinical variables according to the SOFA score (10) was performed, with the most abnormal value for each of the six organ systems (i.e., respiratory, renal, cardiovascular, hepatic, coagulation, and neurologic) being collected on admission and every 24 hrs thereafter. For single missing values, a replacement was calculated using the mean value of the results on either side of the absent result (10). When first or last values were missing, the nearest value was carried backward or forward, respectively. When more than one consecutive result was missing, it was considered to be a missing value in the analysis. Missing data represented <6% of the collected data, of which only 2% were replaced.

Data were entered centrally by medical personnel using the SPSS version 11.0 for Windows (SPSS, Chicago, IL). A sample of 5% of data were reentered by a different encoder and revised by a third one; a consistency of >99.5% per variable and 98.5% per patient was observed during the whole process of data entry. In cases of inconsistency, data were verified and corrected. Daily frequency tables were revised for all variables, and the investigators were queried when data values were either questionable or missing for required fields.

Statistical Methods. Data were analyzed using SPSS 11.0 for Windows (SPSS, Chicago, IL). Descriptive statistics were computed for all study variables. Difference testing between groups was performed using the two-tailed *t*-test, Mann-Whitney U test, chi-square test, and Fisher's exact test as appropriate. A forward stepwise logistic regression multivariate analysis with the ICU outcome as the dependent factor in patients with sepsis was conducted. Variables considered for the multivariate modeling included the country of origin, demographic data, comorbidities, SAPS II score on admission, site of infection, type of microorganism, organ failure as assessed by the SOFA score on the first day of sepsis, the maximum number of concomitant organ failures, mean SOFA score during the ICU stay, invasive procedures at the onset of sepsis, onset of infection (in days), type of sepsis (ICU-acquired sepsis and sepsis on admission), cumulative fluid balance within the first 72 hrs of the onset of infection, and daily fluid balance. Age, severity scores, and fluid balance were included as continuous variables. Only variables associated with a higher risk of ICU mortality ($p < .2$) on a univariate basis were modeled. The "country" effect was included in the last step of the model as a categorical

Table 1. Number of patients, Simplified Acute Physiology Score (SAPS) II, frequency of sepsis, and intensive care unit (ICU) and hospital mortality rates according to country (listed alphabetically)

Country	No. of Centers	No. of Patients (%)	ICU Mortality, n (%)[a]	Hospital Mortality, n (%)[a]	Characteristics of Sepsis Patients (n = 1177)				
					Frequency, n (%)	SAPS II Score, Mean ± SD	ICU Mortality, n (%)[a]	Hospital Mortality, n (%)[a]	Severe Sepsis, n (%)
Austria	8	68 (2)	14 (21)	16 (24)[b]	26 (38)	42.5 ± 17.2	6 (23)	8 (31)	18 (27)
Belgium	19	703 (22)	86 (12)	120 (17)	188 (27)	38.7 ± 15.0	39 (21)	57 (31)[c]	125 (18)
Eastern Europe[d]	15	174 (6)	41 (24)	53 (31)[b]	83 (48)	40.2 ± 15.0	24 (29)	31 (37)	74 (43)
France	21	332 (11)	63 (19)	70 (21)	136 (41)	43.4 ± 18.0	37 (27)	44 (32)	99 (30)
Germany	21	329 (11)	39 (12)	51 (16)[e]	102 (31)	41.6 ± 15.8	16 (16)	20 (20)	78 (24)
Greece	10	109 (4)	18 (17)	23 (21)	47 (43)	47.1 ± 20.2	14 (30)	16 (34)	41 (38)
Italy	24	237 (8)	61 (26)	73 (31)[e]	89 (38)	43.4 ± 15.3	31 (35)	39 (45)[c]	75 (32)
Netherlands	7	144 (5)	33 (23)	43 (31)	56 (39)	43.8 ± 16.8	18 (32)	25 (47)[c]	49 (34)
Portugal	6	69 (2)	24 (35)	28 (41)	50 (73)	46.2 ± 14.8	16 (32)	19 (38)	44 (64)
Scandinavia[f]	16	209 (7)	29 (14)	51 (24)	74 (35)	41.1 ± 15.7	14 (19)	45 (39)	52 (25)
Spain	13	202 (6)	44 (22)[g]	49 (26)[h]	70 (35)	38.3 ± 17.0	21 (30)	26 (38)[b]	57 (28)
Switzerland	4	114 (4)	9 (8)	16 (14)	20 (18)	38.4 ± 15.4	2 (10)	4 (20)	11 (10)
UK and Ireland	34	457 (15)	122 (27)	154 (34)	236 (52)	42.6 ± 17.6	75 (32)	95 (41)	207 (45)
Total	198	3147	583 (19)[g]	747 (24)	1177 (37)	42.3 ± 16.6	313 (27)	413 (36)[i]	930 (30)

[a]Valid percentages are presented after exclusion of missing values; [b]2 values missing; [c]3 values missing; [d]Czech Republic, Poland, Romania, Slovenia, Slovakia, Hungary, Serbia and Montenegro, and Israel; [e]4 values missing; [f]Denmark, Finland, Sweden, and Norway; [g]1 value missing; [h]12 values missing; [i]13 values missing.

variable with reference to the country with the lowest mortality in sepsis patients (Germany was chosen due to the small sample size in Switzerland.) All variables included in the model were tested for collinearity. A strong collinearity was identified between the initial and the mean SOFA score (R^2 = .76), the initial SAPS II score, and the maximum number of concomitant organ failures (R^2 = .71) and between the cumulative fluid balance within the first 72 hrs of the onset of sepsis and the daily fluid balance (R^2 = .74). These variables were injected separately into the model and were all statistically significant. We used the initial SOFA score, the cumulative fluid balance within the first 72 hrs, and the SAPS II score in the final modeling as we judged them to be more relevant clinically. Interactions involving combinations between comorbid diseases on admission, between sites of infection, and between major classes of microorganisms were tested. Nagelkerke pseudo R^2 classification tables and odds ratios (OR) (95% CI) were computed. The probability of ICU mortality was calculated based on the final model, and the area under the receiver operating characteristic curve was computed. None of the tested interactions were relevant and were, therefore, not considered in the final model. The final model correctly classified 76.9% of cases with adequate performance (Nagelkerke pseudo R^2 = .27; area under the receiver operating characteristic curve, 0.7; 95% confidence interval [CI], 0.67–0.73). Hosmer and Lemeshow test confirmed the goodness of fit (chi-square = 8.8, p = .362) of the model. Linear regression analysis was done to evaluate the correlation between ICU mortality and the frequency of sepsis in all countries. All statistics were two-tailed, and a $p < .05$ was considered to be significant.

RESULTS

A total of 3,147 patients were enrolled; participating countries are shown in Table 1. The median patient age was 64 yrs (mean ± SD, 60.5 ± 17.4), and 62% of patients were male. Medical admissions accounted for 56% of admissions, elective surgery for 25%, and emergency surgery for 19% (Table 2). Cardiovascular diagnoses accounted for 32% of admissions, respiratory for 19%, and neurologic for 16%. The most frequent source of admission was the emergency room and/or ambulance (32%); only 12% of patients were referred from another hospital. The median length of ICU stay was 3 days (interquartile range, 2–7 days; mean ± SD, 6.5 ± 9.2 days).

Frequency, Distribution, and Patterns of Sepsis. Overall, 64% of patients received antibiotics at one time or another during the ICU stay. A total of 1,177 (37%) patients had identified infection. Of these, 454 (38.6%) had a suspected clinical infection with identification of pathogens, 468 (39.8%) had clinical infection without identification of pathogens, and 255 (21.7%) had one or more isolated pathogens but without evident clinical infection. There was no difference in ICU mortality between the three groups (29%, 26%, and 25%, respectively). Isolation of microorganisms (n = 196) or clinical suspicion of infection (n = 49), without administration of antibiotics, was not considered as infection (colonization or contamination, Fig. 1).

The lung was the most common site of infection (68%), followed by the abdomen (22%), blood (20%), and urinary tract (14%). Cultures were positive in 60% of the patients with sepsis. Gram-positive organisms were isolated from 40% of patients, Gram-negative from 38%, and fungi from 17%; 18% of infections were mixed. Methicillin-resistant *Staphylococcus aureus* was isolated from 14% of cultures, and *Pseudomonas* species (14%) and *Escherichia coli* (13%) were the most common Gram-negative organisms. *Candida albicans* was thought to be involved in 13% of infections. Patients with ICU-acquired sepsis (n = 279) had a higher incidence of mixed infections (23 vs. 16%, $p < .01$) compared with those with non-ICU-acquired sepsis (n = 898, Table 3). Sepsis in surgical admissions was characterized by a higher frequency of Gram-positive infections (namely *Streptococcus* D group) and *E. coli* compared with medical admissions (Table 3).

There was considerable variation in the rates of sepsis and severe sepsis according to country (Table 1). The rate of sepsis ranged from 18% (Switzerland, n = 114) to 73% (Portugal, n = 69) and that of severe sepsis from 10% (Switzerland, n = 114) to 64% (Portugal, n = 69). The mean SAPS II score in patients with sepsis ranged from 38.3 ± 17.0 (Spain, n = 202) to 47.1 ± 20.2 (Greece, n = 109).

Patients with sepsis (n = 1177) had

Table 2. Demographics of the intensive care unit (ICU) patients and procedures during the ICU stay

	All Patients[a] (n = 3147)	No Sepsis[a] (n = 1970)	Sepsis[a] (n = 1177)
Age, years,[b] median (IQR)	64 (50–74)	64 (49–74)	65 (51–74)
Gender, male/female[c]	62/38	61/39	63/37
Type of admission, n (%)			
Medical	1,759 (56)	1,091 (55)	668 (57)**
Surgical	1,388 (44)	879 (45)	509 (43)
Elective	778 (25)	561 (29)	217 (18)
Emergency	610 (19)	318 (16)	292 (25)
ICU admission source,[e,f] n (%)			
ER/ambulance	913 (32)	652 (37)	261 (25)
Hospital floor	793 (28)	424 (22)	369 (35)
OR/recovery room	784 (28)	508 (29)	276 (26)
Other hospital	345 (12)	190 (11)	155 (15)
SAPS II score, mean ± SD	36.5 ± 17.1	33.1 ± 16.5	42.3 ± 16.6**
SOFA score, mean ± SD			
Initial	5.1 ± 3.8	4.3 ± 3.5	6.5 ± 4.0**
Mean	4.5 ± 3.5	3.9 ± 3.2	5.6 ± 3.7**
Max	6.6 ± 4.4	5.3 ± 3.9	6.5 ± 4.0**
Sepsis, n (%)	1,177 (37)	NA	1,177 (100)
Severe sepsis, n (%)	930 (30)	NA	930 (79)
Septic shock, n (%)	462 (15)	NA	462 (39)
Central venous catheter, n (%)	2,272 (72)	1,246 (63)	1,026 (87)**
Arterial catheter, n (%)	2,240 (71)	1,263 (64)	977 (83)**
Mechanical ventilation, n (%)	2,025 (64)	1,087 (55)	938 (80)**
Pulmonary artery catheter, n (%)	481 (15)	266 (13)	215 (18)**
Hemofiltration, n (%)	211 (7)	61 (3)	150 (13)**
Hemodialysis, n (%)	141 (5)	62 (3)	79 (7)**
Cumulative fluid balance, L[g]			
First 72 hrs[h]	1 ± 4.18	0.51 ± 3.5	1.8 ± 5.0**
Daily fluid balance	0.2 ± 1.3	0.1 ± 1.2	0.2 ± 1.4[d]
Total fluid balance	0.2 ± 11.7	0.1 ± 5.3	0.4 ± 17.8**
Duration of ICU stay, days, median (IQR)	3.0 (1.7–6.9)	2.1 (1.3–4.0)	6.9 (3.1–15.0)**
Duration of hospital stay, days, median (IQR)	15.0 (7.0–32.0)	9.4 (4.2–18.0)	17.8 (8.0–38.2)**
ICU mortality, n (%)[i]	583 (19)	270 (14)	313 (27)**
Hospital mortality, n (%)[j]	747 (24)	334 (17)	413 (36)**

IQR, interquartile range; ER, emergency room; OR, operating room; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

[a]Valid percentages are presented after exclusion of missing values; [b]9 missing (5 with no sepsis and 4 with sepsis); [c]35 missing (27 with no sepsis and 8 with sepsis); [d]$p < .05$ compared with no sepsis; [e]312 missing (196 with no sepsis and 116 with sepsis); [f]$p < .001$ compared with patients with sepsis; [g]47 missing (40 with no sepsis and 7 with sepsis); [h]first 72 hrs after admission in the no sepsis group and after the onset of sepsis in sepsis patients; [i]1 missing; [j]44 missing (32 with no sepsis and 13 with sepsis); **$p < .05$ compared with patients with no sepsis.

greater SAPS II and SOFA scores, underwent more invasive procedures, and had a greater cumulative fluid balance (Table 2) compared with those without sepsis (n = 1970). Sepsis was present on admission in 777 patients (66%), developed on the second day of admission in 121 patients (10.3%), and was acquired during the ICU stay in 279 patients (23.7%). Patients with ICU-acquired sepsis were more likely to be male (67.8 vs. 61%, $p = .002$), and the site of infection was more commonly respiratory (79.6 vs. 63.7%, $p < .001$), catheter-related (13.6 vs. 8.1, $p = .006$), urinary (17.9 vs. 12.1%, $p = .014$), and less commonly abdominal (10.8 vs. 25.9%, $p < .001$) compared with patients who had non-ICU-acquired sepsis (Table 4).

Mortality and Organ Failure. The overall ICU and hospital mortality rates were 18.5 and 24.1%, respectively. The ICU mortality ranged from 8% in Switzerland (n = 114) to 35% in Portugal (n = 69) and the hospital mortality from 14% (Switzerland) to 41% (Portugal). The ICU mortality in patients with sepsis was as low as 10% in Switzerland and up to 35% in Italy (n = 237), and the hospital mortality ranged from 20% in Germany (n = 332) to 47% in the Netherlands (n = 144). There was a correlation between the ICU mortality rate for all patients and the sepsis rate in the various countries (Fig. 2). The ICU mortality rate in patients with sepsis was greater than in those without sepsis (27 vs. 14%, $p < 0.001$). The ICU mortality rate of patients with severe sepsis was 32.2% and 54.1% in those with septic shock. ICU mortality was 27% in patients with sepsis on admission, 20% in patients who developed sepsis on day 2 of admission, and 28% in patients with ICU-acquired sepsis (n = 279, $p = .562$).

Organ failure occurred in 2,244 patients (71%), of whom 1,809 patients (81%) had organ failure on ICU admission. Sepsis was present in 41% (n = 930) of episodes of organ failure. Of 1,970 patients who never had sepsis (no sepsis) during the ICU stay, 1,225 patients (62%) had at least one episode of organ failure (Table 5).

There was a direct relationship between the number of organs failing and the ICU mortality. Figure 3 shows the frequency of organ failure and the corresponding ICU mortality rates; patients with no organ dysfunction on admission had ICU mortality rates of 6% whereas those with four or more organ failures had mortality rates of 65%.

Table 3. Simplified Acute Physiology Score II (mean ± SD) and distribution of various microorganisms (%) in sepsis patients stratified according to the onset of sepsis and the type of admission

		Onset of Sepsis		Type of Admission	
	No. (%)	Non-ICU-Acquired (n = 898)	ICU-Acquired (n = 279)	Surgical (n = 509)	Medical (n = 668)
Gram-positive	466 (40)	335 (37)	131 (47)[b]	219 (43)	247 (37)[a]
Any *Staphylococcus*	353 (30)	241 (27)	112 (40)[c]	163 (32)	190 (28)
MRSA	164 (14)	115 (13)	49 (17)[a]	79 (16)	85 (13)
Staphylococcus, others	223 (19)	150 (17)	73 (26)[c]	101 (20)	122 (18)
Any *Streptococcus*	211 (18)	158 (18)	53 (19)	104 (20)	107 (16)
Streptococcus D group	123 (11)	90 (10)	33 (12)	77 (15)	46 (7)[c]
Streptococcus pneumoniae	46 (4)	35 (4)	11 (4)	7 (1)	39 (6)[c]
Streptococcus, others	54 (5)	41 (5)	13 (5)	25 (5)	29 (4)
Cocci Gram-positive, others	23 (2)	17 (2)	6 (2)	11 (2)	12 (2)
Bacillus Gram-positive	29 (3)	23 (3)	6 (2)	15 (3)	14 (2)
Gram-negative	451 (38)	303 (34)	148 (53)[c]	209 (41)	242 (36)
Escherichia coli	158 (13)	110 (12)	48 (17)[a]	81 (16)	77 (12)[a]
Klebsiella	71 (6)	47 (5)	24 (9)[a]	35 (7)	36 (5)
Enterobacter	67 (6)	44 (5)	23 (8)[a]	35 (7)	32 (5)
Proteus	49 (4)	27 (3)	22 (8)[c]	24 (5)	25 (4)
Pseudomonas species	163 (14)	105 (12)	58 (21)[c]	82 (16)	81 (12)
Haemophilus	37 (3)	20 (2)	17 (6)[b]	14 (3)	23 (3)
Acinetobacter	42 (4)	26 (3)	16 (6)[a]	20 (4)	22 (3)
Gram-negative, others	82 (7)	63 (7)	19 (7)	35 (7)	47 (7)
Anaerobes	41 (4)	33 (4)	8 (3)	23 (5)	18 (3)
Atypical microorganisms	7 (1)	7 (1)	—	3 (1)	4 (1)
Fungi	195 (17)	140 (16)	55 (20)	96 (19)	99 (15)
Candida albicans	156 (13)	111 (12)	45 (16)	76 (15)	80 (12)
Candida non-*albicans*	49 (4)	37 (4)	12 (4)	21 (4)	28 (4)
Fungi, others	17 (1)	14 (2)	3 (1)	11 (2)	6 (1)
Viruses and parasites	13 (1)	12 (1)	1 (0)	2 (0)	11 (2)
Only clinical	468 (40)	398 (44)	70 (25)[c]	188 (37)	280 (42)[a]
Mixed infection	207 (18)	144 (16)	63 (23)[a]	109 (21)	98 (15)[b]

ICU, intensive care unit; MRSA, methicillin-resistant *S. aureus*; *Staphylococcus*, others: methicillin-sensitive *S. aureus* and *Staphylococcus* coagulase negative methicillin sensitive; *Streptococcus*, others: *Streptococcus* A, B, C, G group and others; *Bacillus* Gram-positive: *Moraxella* and others; Gram-negative, others: *Salmonella*, *Serratia*, *Citrobacter*, *Stenotrophomonas maltophilai*, *Campylobacter*, other enterobacteroids, other Gram-negative bacilli, Gram-negative cocci; Anaerobes: *Clostridium*, *Bacteroides*, anaerobic cocci, and others; atypical microorganisms: *Mycobacteria*, *Chlamydia*, *Rickettsia*, *Legionella pneumoniae*, *Aspergillus*, and others; any: the microorganism was considered once per patient even if present in more than one site.

[a] $p < .05$; [b] $p < .01$; [c] $p < .001$ compared with the corresponding group (non-ICU-acquired or surgical admission).

Predictors of Mortality in Sepsis Patients. By univariate analysis, *Staphylococcus* (especially methicillin-resistant *S. aureus*), *Pseudomonas* species, and *C. albicans* were associated with a higher mortality and *Streptococcus pneumoniae* with a lower ICU mortality rate (Table 6). Other factors included female gender (OR, 1.4; 95% CI, 1.1–1.8; $p = .013$); older age (OR, 1.0 per year; 95% CI, 1.0–1.0, $p < .001$); comorbid diseases on admission; hematologic cancer (OR, 2.8; 95% CI, 1.6–5.0; $p < .001$), cirrhosis (OR, 2.1; 95% CI, 1.2–3.7; $p = .01$), medical admissions (OR, 1.4; 95% CI, 1.1–1.9; $p = .007$); admission SAPS II score (OR, 1.1 per point increase; 95% CI, 1.1–1.1; $p < .001$); SOFA score at the onset of sepsis (OR, 1.2 per point increase; 95% CI, 1.2–1.2; $p < .001$); the occurrence of septic shock (OR, 5.5; 95% CI, 4.5–7.9; $p < .001$); invasive procedures at the onset of sepsis: the use of pulmonary artery catheter (OR, 2.6; 95% CI, 1.9–3.5; $p < .001$), invasive mechanical ventilation (OR, 7.0; 95% CI, 4.1–12.0; $p < .001$), or hemodialysis (OR, 1.9; 95% CI, 1.2–3.0; $p = .009$); cumulative fluid balance within the first 72 hrs of onset of sepsis (OR, 1.1 per liter increase; 95% CI, 1.1–1.1; $p < .001$) and daily fluid balance (OR, 1.8 per liter increase; 95% CI, 1.6–2.0; $p < .001$); the maximum number of concomitant organ failures (OR, 2.9 per one organ failure increase; 95% CI, 2.5–3.3; $p < .001$); the mean SOFA score (OR, 1.6 per point increase; 95% CI, 1.5–1.6; $p < .001$), abdominal infections (OR, 1.4; 95% CI, 1.1–1.9; $p < .001$); and primary bloodstream infections (OR, 2.0; 95% CI, 1.4–2.6; $p < .001$). Other factors associated with a trend toward higher mortality included heart failure ($p = .187$) and diabetes mellitus ($p = .117$) on admission, sepsis on admission ($p = .092$) and ICU-acquired sepsis ($p = .091$) with reference to sepsis on the first day of admission, and respiratory tract infection ($p = .093$).

All the preceding variables from the univariate analysis were modeled in the multivariate analysis, and variables retained in the final multivariate model, and hence associated with increased mortality in sepsis patients, included SAPS II score on admission, the cumulative fluid balance within the first 72 hrs of the onset of sepsis, age, SOFA score at the onset of sepsis, bloodstream infection, cirrhosis, *Pseudomonas* species infection, and medical admissions (Table 7). Country effect was not retained in the final model as it was not statistically significant.

Table 4. Demographic characteristics, Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) score, and site of infection in sepsis patients according to the onset of sepsis[a]

	Non-ICU-Acquired[b] (n = 898)	ICU-Acquired (n = 279)	*p* Value
Age,[c] mean ± SD	61.7 ± 16.7	60.0 ± 17.4	.164
Male,[d] n (%)	545 (61)	187 (68)	.002
Medical admission, n (%)	532 (59)	136 (49)	.054
SAPS II, mean ± SD	42.9 ± 17.1	40.4 ± 14.7	.066
Admission SOFA, mean ± SD	6.6 ± 4.2	6.1 ± 3.4	.177
Max SOFA, mean ± SD	8.6 ± 4.6	9.1 ± 4.0	.029
Mean SOFA, mean ± SD	5.7 ± 3.8	5.4 ± 3.0	.991
Site of infection, n (%)			
Respiratory	572 (64)	222 (80)	<.001
Abdominal	233 (26)	30 (11)	<.001
Skin	122 (14)	36 (13)	.841
Others	113 (13)	37 (13)	.758
Unknown	48 (5)	12 (4)	.489
Bloodstream	175 (20)	63 (23)	.261
Urinary	109 (12)	50 (18)	.014
Catheter	73 (8)	38 (14)	.006
Cerebrospinal fluid	14 (2)	1 (0)	.216

ICU, intensive care unit.

[a]Valid percentages are presented after exclusion of missing values; [b]of 898 patients, 777 had sepsis on admission, 121 on the second day after admission; [c]13 missing (4 with non-ICU-acquired and 9 with ICU-acquired sepsis); [d]8 missing (5 with non-ICU-acquired and 3 with ICU-acquired sepsis).

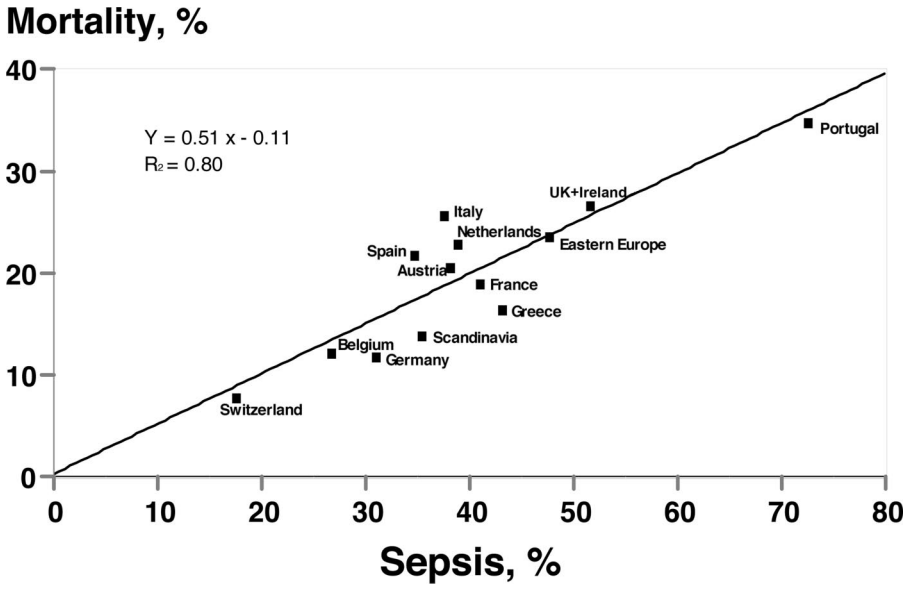

Figure 2. Relationship between intensive care unit mortality rates for all patients and frequency of sepsis in the various European countries.

DISCUSSION

This observational study documents the high frequency of sepsis in European ICUs, with >35% of patients having sepsis at some point during their ICU stay, and the high mortality rates, with 27% of patients with sepsis dying in the ICU, rising to >50% in patients with septic shock. Interestingly, all patients with infection fulfilled the criteria for systemic inflammatory response syndrome, reflecting the lack of specificity of these criteria. We report higher rates of severe sepsis than in some other recent studies; for example, the Episepsis study in France reported that 15% of patients had severe sepsis (6), and a UK study reported a rate of 27% (4). However, unlike the present SOAP study, these studies included patients admitted for routine postoperative surveillance who are likely to have lower rates of complications. Alberti et al. (3) reported the incidence of severe sepsis in a population of 14,364 patients; excluding those patients admitted for routine postoperative monitoring, the authors reported a frequency of severe sepsis of 34% (3,608 of 10,620), similar to the 30% reported in the current study. We defined severe sepsis as the presence of sepsis associated with organ failure, which could limit interpretation of these data as we did not specifically determine that the organ failure was due to sepsis, but other large epidemiologic sepsis studies have used similar definitions (1, 2, 5).

The large number of patients receiving antibiotics (64%) is striking, especially when one considers that patients admitted for routine surveillance after surgical operations (who may have received prophylaxis) were not included. Data on antibiotic use in the general ICU population are rare, but in the EPIC study 10 yrs ago, of 10,038 patients screened for ICU-acquired infection, 6,250 (62.3%) received antibiotics during the ICU stay (8). These numbers are remarkably similar, confirming that antibiotics remain widely used in the ICU.

As in other studies, microbial isolates were obtained in only 60% of patients with sepsis, a figure comparable to the 60–70% reported in other studies (12). The cultures showed an equal frequency of Gram-positive and Gram-negative organisms, largely due to the high rate of staphylococcal infections. Eighteen percent of infections were polymicrobial, at the lower end of the 16–55% range quoted in other recent studies (3, 8, 13–15). The lung was the most common site of infection, as in other recent reports (1, 6–8, 13, 14). Alberti et al. (14) reported that the lung contributed to 62% of infections, with intra-abdominal infections contributing to 15% of infections. Likewise, Angus et al. (1) reported that the lung was the site of infection for 44% of patients with severe sepsis with abdominal infections involved in only 9%. Some earlier studies reported a higher incidence of abdominal infection, with Brun-Buisson et al. (16) noting abdominal infection in 32% of 1,052 patients with microbiologically documented infection; however, the lung still contributed to 40% of infections.

Several factors were associated with an increased mortality in the patients with sepsis by multivariate analysis. That the degree of organ dysfunction, patient age, and cirrhosis are associated with a worse outcome is perhaps not surprising, but mean fluid balance is a noteworthy and new finding. Indeed, the fluid balance

Table 5. Incidence and intensive care unit (ICU) mortality rates in patients with organ failure stratified according to the concomitant presence of sepsis[a]

	No Sepsis (n = 1970)		Severe Sepsis (n = 930)	
	Incidence, No. (%)	ICU Mortality, No. (%)	Incidence, No. (%)	ICU Mortality, No. (%)
No organ failure	745 (37.8)	12 (1.6)	—	—
Any organ failure	1225 (62.2)	258 (21.1)	930 (100.0)[d]	299 (32.2)[c]
Number of failed organs				
1	698 (56.9)	51 (7.3)	235 (25.3)[d]	17 (7.2)
2	340 (27.8)	97 (28.5)	356 (38.3)[d]	95 (26.7)
3	144 (11.8)	76 (52.8)	219 (23.5)[d]	100 (45.7)
≥4	43 (3.5)	34 (79.1)	120 (12.9)[d]	87 (72.5)
Type of organ failure (alone or in combination)				
Renal	608 (49.6)	137 (22.5)	476 (51.2)[d]	196 (41.2)[d]
Respiratory	544 (44.4)	143 (26.3)	463 (49.8)[d]	244 (34.5)[c]
Cardiovascular	443 (36.2)	152 (34.3)	582 (62.6)[d]	246 (42.3)[b]
CNS	433 (35.3)	176 (40.6)	384 (41.3)[d]	169 (43.9)
Coagulation	113 (9.2)	40 (35.4)	187 (20.1)[d]	99 (52.9)
Hepatic	51 (4.2)	14 (27.5)	113 (12.2)[d]	51 (45.1)[c]
Isolated organ failure				
Renal	330 (26.9)	15 (4.5)	84 (9.0)[d]	8 (9.5)
Respiratory	181 (14.8)	3 (1.7)	108 (11.6)[b]	6 (5.6)
Cardiovascular	98 (8.0)	8 (8.2)	51 (5.5)	7 (13.7)
Central nervous system	131 (10.7)	27 (20.6)	20 (2.2)[c]	1 (5.0)
Coagulation	30 (2.4)	1 (3.3)	11 (1.2)	1 (9.1)
Hepatic	15 (1.2)	0 (0.0)	10 (1.1)	0 (0.0)

[a]89 patients had organ failure not related to the sepsis episode (onset >48 hrs before the onset of sepsis (n = 71) or 48 hrs after disappearance of evidence of the septic process (n = 18)), mostly single organ failure (n = 61), range: 1–3 organs with overall ICU mortality of 10.1%; [b]$p < .05$, [c]$p < .01$, [d]$p < .001$ compared with patients with no sepsis.

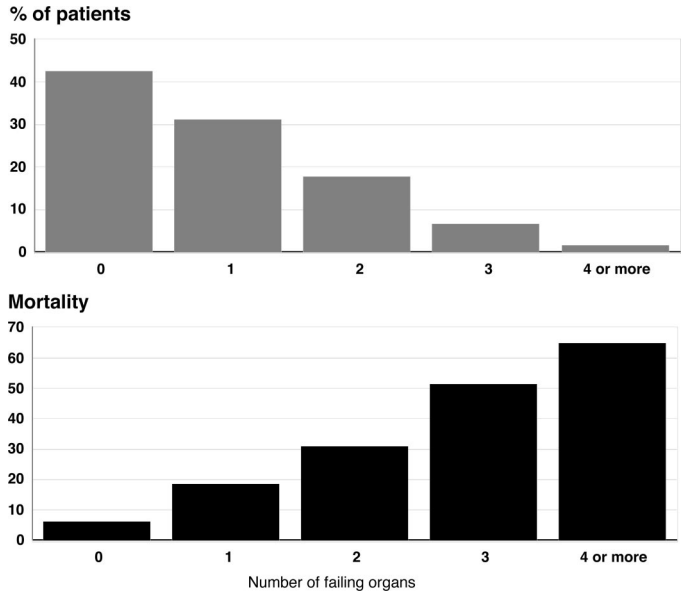

Figure 3. Frequency of organ failure on admission and corresponding intensive care unit mortality.

is often not reported in sepsis studies. Of course, positive fluid balance may be just a marker of the severity of sepsis, but here a multivariate analysis suggested that it is more than just an indicator of severity and is an independent predictor of outcome. Previous studies noted that a positive fluid balance was an independent predictor of mortality in ICU patients with pulmonary edema (17), but in patients with sepsis, only one pilot, retrospective study of 36 patients with septic shock has reported any effect of fluid balance: Alsous et al. (18) noted that ≥1 day of negative fluid balance (≤ −500 mL) achieved by the third day of treatment was a good predictor of survival in patients with septic shock. The finding from our study raises the hypothesis that reducing fluid balance may result in better outcomes from sepsis, and this needs further investigation. The importance of *Pseudomonas* infection as a predictor of outcome is also interesting. Although it has been identified as an important prognostic indicator in other studies (13), here it was the only microorganism associated with a greater mortality rate by multivariate analysis.

There was a clear association between the frequency of sepsis and overall mortality rate in the various countries. Such associations do not necessarily mean a cause-and-effect relationship but underline the higher mortality rates in patients with sepsis and again can be important in the design of and data analysis from clinical trials. In the EPIC study (8), we found a similar relationship for ICU-acquired infections. However, the slope of the relationship was quite different, suggesting that ICU-acquired infections are associated with higher mortality rates than non-ICU-acquired infections.

Our study has limitations. Participation was on a voluntary basis, and it is impossible to evaluate whether the relative contributions of academic and nonacademic centers reflect reality or are truly representative of European ICUs as a whole. In addition, there was no data

Table 6. Outcome according to microorganisms in patients with sepsis (n = 1177)

	No.	% ICU Mortality	% Hospital Mortality	OR (95% CI)[a]	*p* Value
Gram-positive	466	140 (30.0)	175 (37.6)	1.3 (1.0–1.7)	.031
Any *Staphylococcus*	353	111 (31.4)	139 (39.4)	1.4 (1.1–1.9)	.014
MRSA	164	54 (32.9)	70 (42.7)	1.4 (1.0–2.0)	.049
Staphylococcus, others	223	68 (30.5)	84 (37.7)	1.3 (0.9–1.8)	.146
Any *Streptococcus*	211	56 (26.5)	72 (34.1)	1.0 (0.7–1.4)	.987
Streptococcus D group	123	37 (30.1)	49 (39.8)	1.2 (0.8–1.8)	.395
Streptococcus pneumoniae	46	6 (13.0)	9 (19.6)	0.4 (0.2–1.0)	.034
Streptococcus, others	54	15 (27.8)	18 (33.3)	1.1 (0.6–2.0)	.843
Other Gram-positive cocci	23	5 (21.7)	6 (26.1)	0.8 (0.3–2.0)	.594
Bacillus Gram-positive	29	10 (34.5)	16 (55.2)	1.6 (0.7–3.2)	.334
Gram-negative	451	119 (26.4)	159 (35.3)	1.0 (0.8–1.3)	.917
Escherichia coli	158	36 (22.8)	55 (34.8)	0.8 (0.5–1.2)	.242
Klebsiella	71	17 (23.9)	22 (31.0)	0.9 (0.5–1.5)	.600
Enterobacter	67	22 (32.8)	25 (37.3)	1.4 (0.8–2.3)	.237
Proteus	49	12 (24.5)	17 (34.7)	0.9 (0.5–1.7)	.731
Pseudomonas species	163	56 (36.2)	70 (42.9)	1.7 (1.2–2.4)	.002
Haemophilus	37	6 (16.2)	8 (21.6)	0.5 (0.2–1.3)	.146
Acinetobacter	42	11 (26.2)	11 (26.2)	1.0 (0.5–2.0)	.949
Gram negative, others	82	27 (32.9)	32 (39.0)	1.4 (0.9–2.2)	.180
Anaerobes	41	8 (19.5)	9 (22.0)	0.7 (0.3–1.4)	.298
Atypical microorganisms	7	4 (57.1)	6 (85.7)	3.7 (0.8–16.7)	.067
Fungi	195	62 (31.8)	76 (39.0)	1.4 (1.0–1.9)	.073
Candida albicans	156	53 (34.0)	63 (40.4)	1.5 (1.1–2.2)	.026
Candida non-*albicans*	49	14 (28.6)	21 (42.9)	1.1 (0.6–2.1)	.752
Fungi, others	17	3 (17.6)	4 (23.5)	0.6 (0.2–2.1)	.402
Viruses and parasites	13	8 (61.5)	7 (61.5)	4.5 (1.5–13.9)	.004
Only clinical	468	118 (25.2)	160 (34.3)	1.0 (0.7–1.4)	.844
Mixed infection	207	59 (28.5)	72 (34.8)	1.1 (0.8–1.6)	.499

ICU, intensive care unit; OR, odds ratio; CI, confidence interval; MRSA, methicillin-resistant *S. aureus*; *Staphylococcus*, others: methicillin-sensitive *S. aureus* and *Staphylococcus* coagulase negative methicillin sensitive; *Streptococcus*, others: *Streptococcus* A, B, C, G group and others; *Bacillus* Gram-positive: *Moraxella* and others; Gram-negative, others: *Salmonella*, *Serratia*, *Citrobacter*, *Stenotrophomonas maltophilai*, *Campylobacter*, other enterobacteroids, other Gram-negative bacilli, Gram-negative cocci; Anaerobes: *Clostridium*, *Bacteroides*, anaerobic cocci and others; atypical microorganisms: *Mycobacteria*, *Chlamydia*, *Rickettsia*, *Legionella pneumoniae*, *Aspergillus*, and others; any: the microorganism was considered once per patient even if present in more than one site.

[a]According to univariate logistic regression analysis with ICU outcome as the dependent factor in patients with sepsis (n = 1177).

Table 7. Multivariate, forward stepwise logistic regression analysis in sepsis patients (n = 1177), with intensive care unit mortality as the dependent factor

	OR (95% CI)	*p* Value
SAPS II score[a] (per point increase)	1.0 (1.0–1.1)	<.001
Cumulative fluid balance[b] (per liter increase)	1.1 (1.0–1.1)	.001
Age (per year increase)	1.0 (1.0–1.0)	.001
Initial SOFA score (per point increase)	1.1 (1.0–1.1)	.002
Blood stream infection	1.7 (1.2–2.4)	.004
Cirrhosis	2.4 (1.3–4.5)	.008
Pseudomonas infection	1.6 (1.1–2.4)	.017
Medical admission	1.4 (1.0–1.8)	.049
Female gender	1.4 (1.0–1.8)	.044

OR, odds ratio; CI, confidence interval; SAPA, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

[a]At admission; [b]within the first 72 hrs of onset of sepsis.

This large pan-European study documents the high frequency of sepsis in critically ill patients and shows a close relationship between the proportion of patients with sepsis and the intensive care unit mortality in the various countries.

monitoring. The study was also conducted over a single period (May 1–15), and the incidence of sepsis may vary with the calendar seasons; the importance of this is difficult to assess, as there are few data on seasonal differences in the incidence of sepsis.

Nevertheless, observational studies such as this have important applications in evaluating etiological, diagnostic, therapeutic, and prognostic issues in selected and specific patient populations. Other epidemiologic studies have used various study designs. Angus et al. (1), Weycker et al. (5), and Martin et al. (2) extracted data retrospectively from cases identified as having had sepsis using the International Classification of Diseases, Ninth Revision, Clinical Modification codes. Such data extraction is relatively imprecise. Other studies had much less data (3, 6). Here we report the results from a vast European study reflecting the situation at

a much broader international level. In the EPIC study (8), we used a 1-day point prevalence design. Here, we prospectively followed all patients admitted in a 2-wk period, achieving a much larger database. The results from this study provide valuable information about the European ICU patient and stress the continuing importance of sepsis in the ICU.

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APPENDIX

Participants by Country (Listed Alphabetically). Austria: University Hospital of Vienna (G. Delle Karth); LKH Steyr (V. Draxler); LKH-Deutschlandsberg (G. Filzwieser); Otto Wagner Spital of Vienna (W. Heindl); Krems of Donau (G. Kellner, T. Bauer); Barmherzige Bruede of Linz (K. Lenz); KH Floridsdorf of Vienna (E. Rossmann); University Hospital of Innsbruck (C. Wiedermann). *Belgium:* CHU of Charleroi (P. Biston); Hôpitaux Iris Sud of Brussels (D. Chochrad); Clinique Europe Site St Michel of Brussels (V. Collin); C.H.U. of Liège (P. Damas); University Hospital Ghent (J. Decruyenaere, E. Hoste); CHU Brugmann of Brussels (J. Devriendt); Centre Hospitalier Jolimont-Lobbes of Haine St Paul (B. Espeel); CHR Citadelle of Liege (V. Fraipont); UCL Mont-Godinne of Yvoir (E. Installe); ACZA Campus Stuivenberg (M. Malbrain); OLV Ziekenhuis Aalst (G. Nollet); RHMS Ath-Baudour-Tournai (J.C. Preiser); AZ St Augustinus of Wilrijk (J. Raemaekers); CHU Saint-Pierre of Brussels (A. Roman); Cliniques du Sud-Luxembourg of Arlon (M. Simon); Academic Hospital Vrije Universiteit Brussels (H. Spapen); AZ Sint-Blasius of Dendermonde (W. Swinnen); Clinique Notre-Dame of Tournai (F. Vallot); Erasme University Hospital of Brussels (J.L. Vincent). *Czech Republic:* University Hospital of Plzen (I. Chytra); U SV. Anny of Brno (L. Dadak); Klaudians of Mlada Boleslav (I. Herold); General Faculty Hospital of Prague (F. Polak); City Hospital of Ostrava (M. Sterba). *Denmark:* Gentofte Hospital, University of Copenhagen (M. Bestle); Rigshospitalet of Copenhagen (K. Espersen); Amager Hospital of Copenhagen (H. Guldager); Rigshospitalet, University of Copenhagen (K-L. Welling); *Finland:* Aland Central Hospital of Mariehamn (D. Nyman); Kuopio University Hospital (E. Ruokonen); Seinajoki Central Hospital (K. Saarinen). *France:* Raymond Poincare of Garches (D. Annane); Institut Gustave Roussy of Villejuif (P. Catogni); Jacques Monod of Le Havre (G. Colas); CH Victor Jousselin of Dreux (F. Coulomb); Hôpital St Joseph & St Luc of Lyon (R. Dorne); Saint Joseph of Paris (M. Garrouste); Hôpital Pasteur of Nice (C. Isetta); CHU Brabois of Vandoeuvre Les Nancy (J. Larché); Saint Louis of Paris (J-R. LeGall); CHU de Grenoble (H. Lessire); CHU Pontchaillou of Rennes (Y. Malledant); Hôpital des Hauts Clos of Troyes (P. Mateu); CHU of Amiens (M. Ossart); Hôpital Lariboisière of Paris (D. Payen); CHD Félix Gyuon of Saint Denis La Reunion (P. Schlossmacher); Hôpital Bichat of Paris (J-F. Timsit); Hôpital Saint Andre of Bordeaux (S. Winnock); Hôpital Victor Dupouy of Argentueil (J-P. Sollet); CH Auch (L. Mallet); CHU Nancy-Brabois of Vandoeuvre (P. Maurer); CH William Morey of Chalon (J-M. Sab); Victor Dupouy of Argenteuil (J-P. Sollet). *Germany:* University Hospital Heidelberg (G. Aykut); Friedrich Schiller University Jena (F. Brunkhorst); University Clinic Hamburg-Eppendorf (A. Nierhaus); University Hospital Mainz (M. Lauterbach); University Hospital Carl Gustav Carus of Dresden (M. Ragaller); Hans Sushemihl Krankenhaus of Emden (R. Gatz); Vivantes-Klinikum Neukoelln of Berlin (H. Gerlach); University Hospital RWTH Aachen (D. Henzler); Kreisklinik Langen-Seligenstadt (H-B Hopf); GKH Bonn (H. Hueneburg); Zentralklinik Bad Berka (W. Karzai); Neuwerk of Moenchengladbach (A. Keller); Philipps University of Marburg (U. Kuhlmann); University Hospital Regensburg (J. Langgartner); ZKH Links der Weser of Bremen (C. Manhold); University Hospital of Dresden (M. Ragaller); Universtiy of Wuerzburg (B. Reith); Hannover Medical School (T. Schuerholz); Universitätsklinikum Charité Campus Mitte of Berlin (C. Spies); Bethanien Hospital of Moers (R. Stögbauer); KhgmbH Schongau (J. Unterburger). *Greece:* Thriassio Hospital of Athens (P-M. Clouva-Molyvdas); Sismanoglion General Hospital of Athens (G. Giokas); KAT General Hospital of Athens (E. Ioannidou); G. Papanikolaou General Hospital of Thessaloniki (A. Lahana); Agios Demetrios of Thessal-

oniki (A. Liolios); Onassis Cardiac Surgery Center of Athens (K. Marathias); University Hospital of Ioannina (G. Nakos); Tzanio Hospital of Athens (A. Tasiou); Athens Gen. Hosp. Gennimatas (H. Tsangaris); *Hungary:* Peterfy Hospital of Budapest (P. Tamasi). *Ireland:* Mater Hospital of Dublin (B. Marsh); Beaumont Hospital of Dublin (M. Power); *Israel:* Hadassah Hebrew University Medical Center (C. Sprung). *Italy:* Azienda Ospedaliera Senese o Siena (B. Biagioli); S. Martino of Genova (F. Bobbio Pallavicini); Azienda Ospedaliera S. Gerardo dei Tintori of Monza (A. Pesenti); Osp Regionale of Saronno (C. Capra); Ospedale Maggiore–University A. Avogadro of Novara (F. Della Corte); Osp. Molinette of Torino (P. P. Donadio); A.O. Umberto I Ancona, Rianimazione Clinica (A. Donati); Azienda Ospedaliera Universitaria Policlinico of Palermo (A. Giarratano); San Giovanni Di Dio of Florence (T. Giorgio); H San Raffaele IRCCS of Milano (D. Giudici); Ospedale Di Busto Arsizio (S. Greco); Civile Di Massa (A. Guadagnucci); San Paolo of Milano (G. Lapichino); S. Giovanni Bosco Torino (S. Livigni); Osp. San Giovanni of Sesto (G. Moise); S Camillo of Roma (G. Nardi); Vittorio Emanuele of Catania (E. Panascia); Hospital of Piacenza (M. Pizzamiglio); Universita di Torino-Ospedale S. Giovanni Battista (V. M. Ranieri); Policlinico Le Scotte of Siena (R. Rosi); Ospedale Maggiore Policlinico IRCCS of Milano (A. Sicignano); A. Uboldo of Cernusco Sul Naviglio (M. Solca); P.O. Civile Carrara of Massa (G. Vignali); San Giovanni of Roma (I. Volpe Rinonapoli). *Netherlands:* Boven IJ Ziekenhuis of Amsterdam (M. Barnas); UMC St Radboud of Nijmegen (E.E. De Bel); Academic Medical Center of Amsterdam (A-C. De Pont); VUMC of Amsterdam (J. Groeneveld); Groningen University Hospital (M Nijsten); Waterlandziekenhuis of Purmerend (L Sie); OLVG of Amsterdam (D. F. Zandstra); *Norway:* Sentralsjukehuset i Rogaland of Stavanger (S. Harboe); Sykehuset Østfold of Fredrikstad (S. Lindén); Aker University Hospital of Oslo (R. Z. Lovstad); Ulleval University Hospitalof Oslo (H. Moen); Akershus University Hospital of Nordbyhagen (N. Smith-Erichsen). *Poland:* Paediatric University Hospital of Lodz (A. Piotrowski); Central Clinic Hospital SLAM of Katowice (E. Karpel). *Portugal:* Garcia de Orta of Almada (E. Almeida); Hospital de St. António dos Capuchos of Lisboa (R. Moreno); Hospital de Santa Maria of Lisboa (A. Pais-De-Lacerda); Hospital S. Joao of Porto (J. A. Paiva); Fernado Fonseca of Masama (I. Serra); São Teotonio Viseu (A. Pimentel). *Romania:* Inst of Cardiovascular Diseases of Bucharest (D. Filipescu). *Serbia and Montenegro:* Military Medical Academy of Belgrade (K. Jovanovic). *Slovakia:* SUSCH of Bratislava (P. Malik). *Slovenia:* General Hospital of Novo Mesto (K. Lucka); General Hospital of Celje (G. Voga). *Spain:* Hospital Universitario Rio Hortega of Valladolid (C. Aldecoa Alvarez-Santullano); Sabadell Hospital (A. Artigas); Hospital Clinic of Barcelona (E. Zavala, A. Escorsell, J. Nicolas); Virgen del Camino of Pamplona (J.J. Izura Cea); Virgen de la Salud of Toledo (L. Marina); 12 de Octubre of Madrid (J. Montejo); Gregorio Maranon of Madrid (E. Palencia); General Universitario de Elche (F. Santos); Puerta del Mar of Cadiz (R. Sierra-Camerino); Fundación Jiménez Díaz of Madrid (F. Sipmann); Hospital Clinic of Barcelona (E. Zavala). *Sweden:* Central Hospital of Kristianstad (K. Brodersen); Stockholm Soder Hospital (J. Haggqvist); Sunderby Hospital of Luleå (D. Hermansson); Huddinge University Hospital of Stockholm (H. Hjelmqvist); *Switzerland:* Kantonsspital Luzern (K. Heer); Hirslanden Klinik Beau-Site of Bern (G. Loderer); University Hospital of Zurich (M. Maggiorini); Hôpital de la ville of La Chaux-de-Fonds (H. Zender). *United Kingdom:* Western General Hospital of Edinburgh (P. Andrews); Peterborough Hospitals NHS Trust of Peterborough (B. Appadu); University Hospital Lewisham, London (C. Barrera Groba); Bristol Royal Infirmary (J. Bewley); Queen Elizabeth Hospital Kings Lynn (K. Burchett); Milton Keynes General (P. Chambers); Homerton University Hospital of London (J. Coakley); Charing Cross Hospital of London (D. Doberenz); North Staffordshire Hospital of Stoke On Trent (N. Eastwood); Antrim Area Hospital (A. Ferguson); Royal Berkshire Hospital of Reading (J. Fielden); The James Cook University Hospital of Middlesbrough (J. Gedney); Addenbrookes of Cambridge (K. Gunning); Rotherham DGH (D. Harling); St. Helier of Carshalton (S. Jankowski); Southport & Formby (D. Jayson); Freeman of Newcastle Upon Tyne (A. Kilner); University Hospital of North Tees at Stockton on Tees (V. Krishna-Kumar); St. Thomas Hospital of London (K. Lei); Royal Infirmary of Edinburgh (S. Mackenzie); Derriford of Plymouth (P. Macnaughton); Royal Liverpool University Hospital (G. Marx); Stirling Royal Infirmary (C. McCulloch); University Hospital of Wales, Cardiff (P. Morgan); St George's Hospital of London (A. Rhodes); Gloucestershire Royal Hospital (C. Roberts); St Peters of Chertsey (M. Russell); James Paget Hospital of Great Yarmouth (D. Tupper-Carey, M. Wright); Kettering General Hospital (L. Twohey); Burnley DGH (J. Watts); Northampton General Hospital (R. Webster); Dumfries Royal Infirmary (D. Williams).