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ORIGINAL

Epidemiology of sepsis in Germany: results from a national prospective multicenter study

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Abstract *Objective:* To determine the prevalence and mortality of ICU patients with severe sepsis in Germany, with consideration of hospital size. *Design:* Prospective, observational, cross-sectional 1-day point-prevalence study. *Setting:* 454 ICUs from a representative nationwide sample of 310 hospitals stratified by size. Data were collected via 1-day on-site audits by trained external study physicians. Visits were randomly distributed over 1 year (2003). *Patients:* Inflammatory response of all ICU patients was assessed using the ACCP/SCCM consensus conference criteria. Patients with severe sepsis were followed up after 3 months for hospital mortality and length of ICU stay. *Measurements and results:* Main outcome measures were prevalence and mortality. A total of 3,877 patients were screened. Prevalence was 12.4% (95% CI, 10.9–13.8%) for sepsis and 11.0% (95% CI, 9.7–12.2%) for severe sepsis including septic shock. The ICU and hospital mortality of patients with severe sepsis was 48.4 and 55.2%, respectively, without significant differences between hospital size. Prevalence and mean length of ICU stay of patients with severe sepsis were significantly higher in larger hospitals and universities ($\leq$ 200 beds: 6% and 11.5 days, universities: 19% and 19.2 days, respectively). *Conclusions:* The expected number of newly diagnosed cases with severe sepsis in Germany amounts to 76–110 per 100,000 adult inhabitants. To allow better comparison between countries, future epidemiological studies should use standardized study methodologies with respect to sepsis definitions, hospital size, and daily and monthly variability.

Keywords Sepsis · Severe sepsis · Epidemiology · Prevalence · Incidence · Mortality

Introduction

Severe sepsis remains a major challenge in medicine. Its mortality rate is high and its incidence is increasing worldwide [1, 2]. Sound and representative data are needed to evaluate frequency and outcome in different countries and health care systems, and to improve patient care and allocation of health care resources. Such information may also help to better understand the external validity of the results from recent and future sepsis trials, and thus contribute to progress in sepsis research.

Several studies have been published on the epidemiology of sepsis, using different methodological approaches such as prospective cohort studies [3, 4, 5, 6, 7, 8, 9, 10], cross-sectional surveys [11, 12, 13], or retrospective analyses of coded hospital discharge diagnoses [1, 2, 14, 15]. Perhaps not surprisingly, incidence and mortality of sepsis obtained from these epidemiological studies show considerable variation. For sepsis incidence, the reported rates vary from 51 cases per 100,000 population per year within the first 24 h in the ICU [15] to 300 cases per 100,000 using hospital discharge data [1]. Mortality rates range from about 38% [4] to 59% [5], although similar definitions for severe sepsis (ACCP/SCCM) were employed.

Most studies to date are limited with regard to their representativeness since they were restricted to hospitals of a certain size, type or geographical region, and disregard seasonal fluctuation [16]. This prompted us to initiate a prospective cross-sectional survey in ICUs from a representative nationwide sample of hospitals. The primary goal of this survey was to determine the prevalence, mortality, and morbidity of ICU patients with severe sepsis as defined by the ACCP/SCCM criteria, with consideration of hospital size.

Materials and methods

Unless otherwise specified, the term "severe sepsis" includes also patients with septic shock.

Study design and conduct

The study was carried out by the German Competence Network Sepsis (SepNet; see Appendix for a list of members). Data were collected prospectively on a cross-sectional (1-day) basis in a representative random sample of German hospitals. The sample was drawn from a hospital list which was generated from the systematic directory of hospitals issued by the German Federal Statistical Office [17], using additional information provided by a pharmaceutical company (Fresenius, Bad Homburg, Germany) and the German Public Health Insurance Fund (pers. commun.). Facilities limited to rehabilitation and pediatric ICUs were excluded. The final list comprised 1380 hospitals (total number of beds: 488,727) with 2075 ICUs (total number of beds: 19,084). Hospitals were separated into five strata as follows: strata 1–4 comprised all non-university hospitals with ≤ 200, 201–400, 401–600, and > 600 beds, respectively, and stratum 5 comprised all university hospitals. Assuming a prevalence of 8%, we calculated that about 3,600 patients (from about 260 hospitals) would have to be screened in order to obtain a prevalence estimate which does not differ by more than 10% from the true unknown prevalence at a 95% confidence level. In order to account for incomplete ICU bed occupancy (assumed to be 78%), a total of 333 hospitals were randomly drawn from the list using a single-stage cluster sampling procedure [18]. The drawing probability was proportional to the total number of beds of all ICUs of the hospital, that is, hospitals with larger ICUs were more likely to be drawn. This method ensured that each ICU bed had the same probability of being chosen. Furthermore, sampling was performed with replacement, that is, multiple drawings of single hospitals were possible. The sample contained 300 different hospitals (269, 29, and 2 hospitals were selected once, twice and thrice, respectively). Within each stratum, the same fraction of hospitals was sampled (proportional allocation).

After a first sampling round, the ICU directors were asked in writing for study participation. Rejections were followed up by telephone inquiry. Upon further refusal, another ICU of the same type was randomly sampled from another hospital of the same stratum. Consent was obtained from 77% of all ICUs after the first sampling round, and from 21% after one or more replacements. Two percent of rejecting ICUs could not be replaced successfully after four rounds. In order to allow for possible seasonal variations, a randomly selected date (the "study day" at which the prevalence had to be determined) within a 1-year period between 15 January 2003, and 14 January 2004 was assigned to each participating hospital (the same day could be assigned to more than one hospital).

A total of 402 ICUs in 278 hospitals (randomly assigned to 195 different study days) from the primary sample were visited by a previously trained intensivist from the nearest SepNet clinical center. The remaining 22 hospitals were not evaluated since data could not be completely acquired due to withdrawal of consent at short notice, hospital shutdown or because visits could not be conducted. Hospitals which were selected two or three times were visited only once. The data from these hospitals were repeatedly listed in the final data set; thus, the final data set comprised information on 454 ICUs and 310 hospitals.

Patient screening

For all patients occupying an ICU bed between 6:00 a.m. of the study day and 6:00 a.m. of the following day, the presence of infection, SIRS, and organ dysfunction during this specific 24-h time period was assessed and documented [based on modified consensus criteria of the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) as outlined in the Appendix]. Patients were considered to have an infection if this was microbiologically documented according to the standard definitions of the Centers for Disease Control and Prevention (CDC) [19] or at least clinically suspected requiring evidence such as presence of white blood cells in a normally sterile body fluid, perforated viscus, chest X-ray consistent with pneumonia and associated with purulent tracheal production, or a clinical syndrome associated with a high probability of infection (e.g., ascending cholangitis). In patients with severe sepsis, an extended documentation included major diagnoses and comorbidities, severity of illness (APACHE-II, SAPS-II, and SOFA), diagnostic and therapeutic measures, length of ICU stay, and mortality after 3 months (by telephone or written inquiry).

Data quality

The study was approved by the responsible institutional ethics committees and by the German federal data protection commissioner. Data were collected on paper-based case report forms which were entered into a central database (eResearch Network, eResearchTechnology Inc., Philadelphia, Pa.) with a second look for entry errors. During the study period, data quality was checked for systematic errors by an experienced ICU physician.

Statistical analysis

The SPSS 10.0.7 (SPSS, Chicago, IL) was used for all data analyses. Categorical outcome data are reported as absolute or relative frequencies where appropriate. The chi-square test, the Kruskal-Wallis H-test and the Mann-Whitney U-test were applied to compare categorical and continuous variables where appropriate. Multivariate logistic regression analysis was used to identify predictors

for severe sepsis and death. These models included only those factors which were found to be significantly predictive in preceding univariate analyses. Stratum-specific and total population point and variance estimates for prevalences were calculated using the Hansen–Hurwitz estimator [18]. In this estimation procedure, each hospital is weighted by the inverse of its probability of being in the sample in order for the resulting estimator to be unbiased.

The APACHE-II and SAPS-II scores were calculated from documented physiological and chronic disease variables as described elsewhere [20, 21]. If a single parameter was not documented, the corresponding subscore value was set to zero.

Length of stay (LOS) on the ICU was documented in patients with severe sepsis by prospective follow-up. For all other screened patients, only ICU LOS until day of audit ("duration-to-date") was documented. Duration to-date information was used to calculate the mean LOS for all screened patients assuming a geometric frequency distribution of duration-to-date information [22]. The cross-sectional study design leads to so-called length-biased sampling, reflecting the fact that the probability of registering a single patient increases proportionally with the length of his ICU stay (LOS). To adjust for this systematic bias, the calculation of the mean LOS was performed as described elsewhere [22].

Table 1 The ICU characteristics

Characteristic	All ICUs ($n = 454$)
Specialty of ICU, no. (%)	
Surgery	85 (18.7)
Internal medicine	65 (14.3)
Surgery / internal medicine	187 (41.2)
Neurosurgery	11 (2.4)
Cardiothoracic	28 (6.2)
Cardiology	31 (6.8)
Neurology	17 (3.7)
Traumatology	4 (0.9)
Others	15 (3.3)
Unknown	11 (2.4)
Specialty of ICU head, no. (%)	
Anesthesiologist	251 (55.3)
Internist	122 (26.9)
Surgeon	26 (5.7)
Interdisciplinary	33 (7.3)
Other	18 (4.0)
Unknown	4 (0.9)
Number of beds, median (IQR)	10 (7–12)

Results

ICU characteristics

The ICUs were located in all 16 federal states of Germany and belonged to 310 hospitals of the following categories: university hospitals ($n = 10$, 3.2%); university-affiliated hospitals ($n = 106$, 34.2%); general hospitals ($n = 173$, 55.8%); and others ($n = 21$, 6.8%). Table 1 summarizes basic ICU characteristics. Most ICUs were mixed surgical and medical (41.2%).

Screened patients

A total of 3,877 ICU patients were screened during the study period and their inflammatory response was assessed based on modified ACCP/SCCM criteria (see Appendix). Table 2 describes the characteristics of all screened patients. Table 3 gives details for the subgroup of patients with infection. Infection was present in 1348 (34.8%) of all patients. Community acquired infections were observed in 39.1% of all infected patients, whereas 13.8% of patients had hospital- and 32.9% had ICU-acquired infections. Among patients with a microbiologically proven infection (45.4% of infected patients), the number of Gram-positive and Gram-negative isolates was comparable (55.7 and 54.1%, respectively). In 11.9% of all patients at least one infection related organ dysfunction was present. Sepsis was present in 473 (12.2%) and severe sepsis in 415 (10.7%) patients. Interestingly, 58 patients (1.5%) had infection and organ dysfunction with less than two SIRS criteria.

All characteristics of screened patients shown in Table 2 were significantly different between hospitals of different size. Patients in larger hospitals tended to be younger, were more often male, and more often had infection and antibiotic treatment. Moreover, the proportion of patients fulfilling at least two SIRS criteria was higher in larger hospitals. Among the subgroup of patients with infection the proportions of ICU acquired infections, microbiologically proven diagnosis of infection, and organ dysfunction were significantly higher in larger hospitals.

Prevalence of sepsis and severe sepsis

The estimated country-wide prevalence was 12.4% (95% CI, 10.9–13.8%) for sepsis and 11.0% (95% CI, 9.7–12.2%) for severe sepsis (Table 4). The prevalence of severe sepsis increased significantly from smaller hospitals (6.0% in stratum 1) to larger hospitals (19.3% in stratum 5), but was not dependent on age or gender. Among all screened patients with two or more SIRS criteria, the risk of severe sepsis increased significantly with the number of SIRS criteria present (OR per number of SIRS criteria increase: 3.03; 95% CI: 2.58–3.55).

Table 2 Characteristics of all screened ICU patients

Characteristic	Total[a] $n = 3,877$ (100.0%)	Stratum 1 $n = 664$ (17.1%)	Stratum 2 $n = 1219$ (31.4%)	Stratum 3 $n = 621$ (16.0%)	Stratum 4 $n = 829$ (21.4%)	Stratum 5 $n = 544$ (14.0%)	Significance (p)[b]
Age, median years (IQR)	67 (56–76)	69 (58–78)	68 (57–76)	69 (58–78)	66 (54–74)	64 (51–72)	< 0.0001
Gender, no. (%)							0.0006
Male	2235 (57.6)	355 (53.5)	676 (55.5)	349 (56.2)	509 (61.4)	346 (63.6)	
Female	1624 (41.9)	303 (45.6)	536 (44.0)	271 (43.6)	319 (38.5)	195 (35.8)	
Length of ICU stay (days)							
Mean	8.5	7.2	7.0	7.5	9.8	12.4	
Median (IQR)	3 (2–9)	3 (2–6)	3 (2–7)	3 (2–7)	5 (2–12)	6 (2–15)	< 0.0001
SIRS criteria, no. (%)							< 0.0001
Unknown	277 (7.1)	72 (10.8)	101 (8.3)	15 (2.4)	68 (8.2)	21 (3.9)	
< 2	2017 (52.0)	352 (53.0)	668 (54.8)	354 (57.0)	400 (48.3)	243 (44.7)	
≥ 2	1583 (40.8)	240 (36.1)	450 (36.9)	252 (40.6)	361 (43.5)	280 (51.5)	
Infection, no. (%)							0.0028
Unknown	127 (3.3)	24 (3.6)	56 (4.6)	20 (3.2)	26 (3.1)	1 (0.2)	
No	2402 (62.0)	431 (64.9)	781 (64.1)	375 (60.4)	492 (59.3)	323 (59.4)	
Yes	1348 (34.8)	209 (31.5)	382 (31.3)	226 (36.4)	311 (37.5)	220 (40.4)	
Inflammatory response, no. (%)							< 0.0001
Unknown	358 (9.2)	75 (11.3)	130 (10.7)	49 (7.9)	86 (10.4)	18 (3.3)	
None	1638 (42.2)	284 (42.8)	542 (44.5)	278 (44.8)	341 (41.1)	193 (35.5)	
SIRS	675 (17.4)	124 (18.7)	199 (16.3)	93 (15.0)	134 (16.2)	125 (23.0)	
Sepsis	473 (12.2)	76 (11.4)	136 (11.2)	95 (15.3)	106 (12.8)	60 (11.0)	
Severe sepsis or septic shock	415 (10.7)	44 (6.6)	105 (8.6)	53 (8.5)	110 (13.3)	103 (18.9)	
Infection without SIRS	260 (6.7)	54 (8.1)	84 (6.9)	42 (6.8)	41 (4.9)	39 (7.2)	
Severe sepsis or septic shock without SIRS	58 (1.5)	7 (1.1)	23 (1.9)	11 (1.8)	11 (1.3)	6 (1.1)	

[a]The sum of patient numbers within a variable may be lower than the total patient number due to missing data

[b] p-values indicate differences between strata. Strata 1–4 comprise all non-university hospitals with ≤ 200, 201–400, 401–600, and > 600 beds, respectively, and stratum 5 comprises all university hospitals

Characteristics and mortality of patients with severe sepsis

Table 5 summarizes the characteristics of all patients with severe sepsis, stratified by the presence of septic shock (total $n = 415$). The most frequent sites of infection were the respiratory tract (62.9%) and the abdomen (25.3%). Respiratory and renal dysfunction were the most frequent organ dysfunctions (52.0 and 42.2%, respectively). The mean length of ICU stay was 12.3 days (median 6 days). In patients with septic shock, intraabdominal infections and metabolic acidosis were significantly more frequent and severity scores were higher than in patients without shock.

Of 415 patients with severe sepsis, 382 (92.0%) had valid follow-up information on ICU and hospital mortality; of these, 185 (48.4%) died in the ICU and another 26 (6.8%) died on the ward, resulting in a total hospital mortality of 55.2%. Table 6 shows the mortality rates for subgroups of patients and predictors of mortality in univariate and multivariate logistic regression analysis. Neither mortality nor disease severity differed significantly among hospital-size strata. By multivariate analysis, the APACHE-II score and the presence of renal dysfunction were significantly predictive for mortality, whereas gender, admission category, origin of infection and the presence of other organ dysfunctions were not.

Therapeutic measures

Table 7 shows the usage of selected therapeutic measures in patients with severe sepsis on the study day. With regard to enteral and parenteral nutrition, university hospitals used a mixed strategy in half of their patients, which is significantly more frequent than in smaller hospitals. There were also significant differences in usage of pulmonary artery catheter across strata. For all other interventions,

Table 3 Characteristics of ICU patients with infection

Characteristic	Total $n = 1{,}348$ (100.0%)	Stratum 1 $n = 209$ (15.5%)	Stratum 2 $n = 382$ (28.3%)	Stratum 3 $n = 226$ (16.8%)	Stratum 4 $n = 311$ (23.1%)	Stratum 5 $n = 220$ (16.3%)	Significance (p)[b]
Origin of infection, no. (%)							< 0.0001
Unknown	192 (14.2)	33 (15.8)	67 (17.5)	31 (13.7)	45 (14.5)	16 (7.3)	
Community acquired	527 (39.1)	98 (46.9)	164 (42.9)	90 (39.8)	103 (33.1)	72 (32.7)	
Hospital acquired	186 (13.8)	29 (13.9)	45 (11.8)	36 (15.9)	46 (14.8)	30 (13.6)	
ICU acquired	443 (32.9)	49 (23.4)	106 (27.7)	69 (30.5)	117 (37.6)	102 (46.4)	
Diagnosis of infection, no. (%)							< 0.0001
Clinically suspected	736 (54.6)	139 (66.5)	226 (59.2)	133 (58.8)	148 (47.6)	90 (40.9)	
Microbiologically proven	612 (45.4)	70 (33.5)	156 (40.8)	93 (41.2)	163 (52.4)	130 (59.1)	
Type of microbiologically proven infection, no. (%)[a]	$n = 612$	$n = 70$	$n = 156$	$n = 93$	$n = 163$	$n = 130$	
Gram-positive	341 (55.7)	45 (64.3)	95 (60.9)	43 (46.2)	83 (50.9)	75 (57.7)	0.0638
Gram-negative	331 (54.1)	36 (51.4)	84 (53.8)	58 (62.4)	86 (52.8)	67 (51.5)	0.5209
Fungal	109 (17.8)	6 (8.6)	24 (15.4)	14 (15.1)	34 (20.9)	31 (23.8)	0.0505
Organ dysfunction, no. (%)							< 0.0001
Unknown	134 (9.9)	20 (9.6)	34 (8.9)	24 (10.6)	42 (13.5)	14 (6.4)	
No	751 (55.7)	139 (66.5)	224 (58.6)	138 (61.1)	151 (48.6)	99 (45.0)	
Yes (at least one)	463 (34.3)	50 (23.9)	124 (32.5)	64 (28.3)	118 (37.9)	107 (48.6)	

[a] Groups are not mutually exclusive

[b] p-values indicate differences between strata. Strata 1–4 comprise all non-university hospitals with ≤ 200, 201–400, 401–600, and > 600 beds, respectively, and stratum 5 comprises all university hospitals

Table 4 Estimated population prevalence of sepsis and severe sepsis in Germany

Characteristic	Sepsis %	95% CI	Severe sepsis %	95% CI
Overall	12.4	10.9–13.8	11.0	9.7–12.2
Stratum				
1 (non-university, ≤ 200 beds)	9.8	7.2–12.5	6.0	3.9–8.1
2 (non-university, 201–400 beds)	11.5	9.1–13.8	9.5	7.3–11.6
3 (non-university, 401–600 beds)	15.5	11.7–19.2	9.0	6.0–12.0
4 (non-university, > 600 beds)	14.5	10.2–18.8	15.3	11.4–19.2
5 (university)	10.5	3.9–17.2	19.3	13.1–25.4
Gender				
Male	11.5	9.5–13.5	11.9	10.1–13.6
Female	13.5	11.5–15.6	9.7	8.3–11.1
Age (years)				
< 50	12.0	9.0–15.0	11.2	8.4–14.0
50–65	12.4	9.7–15.0	12.2	9.6–14.8
> 65	12.6	10.7–14.4	10.4	8.9–11.9

Note: Estimated population prevalences for Germany differ slightly from the percentages of patients with sepsis and severe sepsis shown in Table 2 due to the estimation method (see Materials and methods)

there were no clear significant differences across strata if multiple testing is considered.

Discussion

The objective of this observational study was to provide representative data on the prevalence and mortality of severe sepsis in German ICUs with particular consideration of hospitals of all sizes. We determined a prevalence of 12.4% for sepsis and 11.0% for severe sepsis (including septic shock) for Germany. In other studies of sepsis epidemiology designed as prospective [3, 4, 5, 6, 7, 8, 9] or retrospective [1, 2, 14, 15] cohort studies, attack rates of severe sepsis vary between 6.3 and 14.6% [4, 5, 6]. A 1-day cross-sectional study on 254 adult ICUs in Mexico showed a prevalence of 16 and 17% for sepsis and severe sepsis, respectively [11].

Thirty-five percent of all screened patients in our study presented with infection. This is higher than the 21% reported by Alberti et al. [3], who determined infection at ICU admission only, and lower than 45% found by Vincent et al., who excluded patients staying less than 24 h on the ICU [12], both studies being European surveys. We

Table 5 Characteristics of ICU patients with severe sepsis

Characteristic	Total ($n = 415$)	Severe sepsis without septic shock ($n = 211$)[a]	Severe sepsis with septic shock ($n = 190$)[a]	Significance (p)
Admission category, no. (%)				0.0226
Medical	158 (38.1)	92 (43.6)	60 (31.6)	
Surgical unscheduled	164 (39.5)	81 (38.4)	79 (41.6)	
Surgical scheduled	93 (22.4)	38 (18.0)	51 (26.8)	
Site of infection, no. (%)[b]				
Respiratory	261 (62.9)	141 (66.8)	111 (58.4)	0.0940
Intraabdominal	105 (25.3)	40 (19.0)	62 (32.6)	0.0021
Bone/soft tissue	36 (8.7)	20 (9.5)	16 (8.4)	0.7002
Gastrointestinal	35 (8.4)	19 (9.0)	15 (7.9)	0.7032
Genitourinary	27 (6.5)	17 (8.1)	8 (4.2)	0.0998
Scores, median (IQR)				
APACHE II	19; 13–24	18; 12–23	21; 14–25	0.0026
SAPS II	47; 35–60	42; 33–55	52; 41–64	< 0.0001
SOFA	8; 5–11	6; 4–9	10; 7–13	< 0.0001
Organ dysfunctions, no. (%)[b]				
Acute encephalopathy	115 (27.7)	74 (35.1)	41 (21.6)	0.4706
Hematologic	92 (22.2)	40 (19.0)	52 (27.4)	0.0385
Respiratory	216 (52.0)	105 (49.8)	109 (57.4)	0.1603
Renal	175 (42.2)	82 (38.9)	92 (48.4)	0.0428
Metabolic acidosis	74 (17.8)	25 (11.8)	49 (25.8)	0.0004
Mean length of ICU stay (days)	12.3	13.7	10.9	

[a] Severe sepsis/septic shock status was unknown in 14 of 415 patients

[b] Groups are not mutually exclusive

found that infection was community-, hospital- and ICU-acquired in 39.1, 13.8, and 32.9% of these patients, respectively. This is in a range similar to the findings of Ponce de Leon-Rosales et al. [11], but in the EPIC study, the rates of hospital- and ICU-acquired infections were higher [12]. These differences may be due to differences in study designs, patient populations, or health care structures. Our figures may be more accurate because we placed major emphasis on representative selection of a country-wide sample.

We found a hospital mortality for severe sepsis of 55%, which is higher than reported in other surveys in which hospital mortality was between 29 and 47% [1, 4, 6, 14, 15]; however, the median age of our study population (68 years) was somewhat higher than in these studies (range 61–65 years) and the mortality rate from severe sepsis has been shown to increase with age [1]. Furthermore, we found that patients were significantly younger in universities and large hospitals; thus, over-representation of large hospitals in other studies may explain this difference of age and mortality. It is noteworthy that our study population also differed from populations of previous interventional sepsis trials. The median age in those populations (ranging from 58 to 61 years) as well as mortality rates (ranging between 31 and 39%) were much lower [23, 24, 25]. These findings may have to be taken into account when discussing the results of these trials and their clinical applicability.

Interestingly, mortality did not depend on hospital size. Furthermore, disease severity as measured by APACHE-II and SAPS scores was not different between hospital-size strata; however, because severity scores were derived from different days within the disease course, they should be interpreted with care. These findings may be influenced by patient characteristics, referral policies, and treatment habits.

Our study did not allow the accurate determination of incidence rates, which would have required a longitudinal study design; however, prevalence and incidence of a disease are interconvertible if information about the disease duration is available [22]. Under steady-state conditions, the relationship between prevalence (P), incidence (I), and mean disease duration (D) is given by $P/(1–P) = I*D$. Length of stay in the ICU for patients with sepsis and severe sepsis can serve as an upper estimate for disease duration. Given an absolute nationwide number of ICU patients of 14,074 as derived from our study, a prevalence of 12.4% for sepsis and 11.0% for severe sepsis, and corresponding disease durations of 12.6 and 12.3 days, respectively, the annual number of newly diagnosed cases on German ICUs would amount to approximately 58,000 for sepsis and 52,000 for severe sepsis. Extrapolating these figures to a total adult population of about 68,000,000 in Germany, the population based incidence amounts to 85 and 76 cases, respectively, per 100,000. Own data from a longitudinal survey of 371 patients at one SepNet Clinical Center (University of Jena) using the same diagnostic sepsis criteria as in the present study revealed a mean disease duration of 9.2 days for sepsis and 8.5 days for severe sepsis (unpublished data). Using these estimates

Table 6 Hospital mortality of patients with severe sepsis

Characteristic	Hospital mortality[a]		Univariate		Multivariate[b]	
	Percentage	95% CI	OR	*p*-value	OR	95% CI
Overall	55.2	50.2–60.2				
Stratum				0.346		
1 (non-university, ≤ 200 beds)[c]	48.8	34.6–63.3	1.00			
2 (non-university, 201–400 beds)	52.0	42.3–61.7	1.14			
3 (non-university, 401–600 beds)	46.8	33.0–60.8	0.92			
4 (non-university, > 600 beds)	60.6	50.8–69.7	1.61			
5 (university)	60.0	50.0–69.3	1.57			
Gender				0.869		
Male[c]	56.5	49.9–62.8	1.00			
Female	53.8	46.0–61.5	0.97			
Age (years; tertiles)[d]			1.01	0.051	1.01	0.99–1.02
18–59	46.0	37.5–54.7				
60–72	60.8	52.2–68.7				
≥ 73	58.6	49.9–66.8				
Septic shock				0.041		
No[c]	47.3	40.3–54.5	1.00			
Yes	62.4	55.2–69.2	1.46		1.20	0.80–1.80
Admission category				0.678		
Medical[c]	55.8	47.5–63.8	1.00			
Surgical unscheduled	52.9	45.1–60.5	0.89			
Surgical scheduled	58.6	48.1–68.4	1.12			
Origin of infection				0.474		
Community-acquired[c]	51.5	43.0–60.0	1.00			
Hospital-acquired	60.3	49.2–70.4	1.43			
ICU-acquired	54.4	46.4–62.3	1.12			
Organ dysfunctions						
Acute encephalopathy	52.3	43.0–61.4	0.79	0.096		
Hematological	58.3	47.7–68.3	0.98	0.904		
Respiratory	54.0	47.1–60.7	0.86	0.399		
Cardiovascular	62.8	56.0–69.1	1.65	0.008		
Renal	69.1	61.7–75.6	2.16	< 0.001	1.75	1.15–2.66
Metabolic acidosis	71.2	59.4–80.7	1.75	0.018	0.98	0.57–1.69
APACHE II score (tertiles)[d]			1.07	< 0.001	1.06	1.03–1.09
≤ 17	38.0	29.4–47.4				
18–24	54.1	45.7–62.4				
≥ 25	69.5	61.5–76.5				

[a] Of 415 patients with severe sepsis, 382 patients had valid mortality information
[b] Includes only variables which were significant in univariate analysis
[c] Reference category
[d] Odds ratio per unit increase

for incidence calculation, we expect an absolute annual number of newly diagnosed cases of approximately 79,000 for sepsis and 75,000 for severe sepsis, or 116 and 110 per 100,000, respectively.

A similar approach to calculate incidence from prevalence data was used in a cross-sectional study of van Gestel et al. investigating severe sepsis in Dutch intensive care units [13]. Two recent studies from Australia and New Zealand reported severe sepsis incidences of 77 and 76, respectively [4, 14]. Padkin et al., who limited their study to patients meeting severe sepsis criteria within the first 24 h after ICU admission, found an incidence of 51 [15]. The French EPISEPSIS study group reported an incidence of 95 for the year 2001 [6]. Angus et al. [1] determined an incidence of severe sepsis of 300 per 100,000. This estimate is based on hospital discharge data and suspected to be overestimated for methodological reasons [16, 26].

We cannot rule out that we missed some patients with short-term minor organ dysfunctions who were treated on regular wards; however, given the relatively high number of ICU beds in Germany (28.6 beds per 100,000 inhabitants), which is several times higher than in other countries [27], it is unlikely that patients with acute organ dysfunctions would not be referred to an ICU in Germany.

The incidence figures derived from our study are considerably higher than the 39,216 newly diagnosed cases reported by the German Federal Statistical Office for the year 2002 using coded national hospital discharge diagnoses. This discrepancy is largely explained by the fact that the ICD-10 definition of sepsis does not adequately describe

Table 7 Therapeutic measures in patients with severe sepsis

Variable	Total[a] ($n=415$; 100%)	Stratum 1 ($n=44$; 10.6%)	Stratum 2 ($n=105$; 25.3%)	Stratum 3 ($n=53$; 12.8%)	Stratum 4 ($n=110$; 26.5%)	Stratum 5 ($n=103$; 24.8%)	Significance (p)[b]
Mechanical ventilation, no. (%)	331 (79.8)	31 (70.5)	80 (76.2)	43 (81.1)	88 (80.0)	89 (86.4)	0.0717
Vasopressors, no. (%)	271 (65.3)	27 (61.4)	61 (58.1)	32 (60.4)	72 (65.5)	79 (76.7)	0.0145
Hemodynamic monitoring							
Pulmonary artery catheter, no. (%)	14 (3.4)	5 (11.4)	0 (0.0)	0 (0.0)	5 (4.5)	4 (3.9)	0.0053
$ScvO_2$, no. (%)	70 (16.9)	9 (20.5)	20 (19.0)	1 (1.9)	18 (16.4)	22 (21.4)	0.0296
Transpulmonary indicator dilution, no. (%)	33 (8.0)	0 (0.0)	6 (5.7)	7 (13.2)	9 (8.2)	11 (10.7)	0.0601
Renal replacement therapy, no. (%)	84 (20.2)	9 (20.5)	14 (13.3)	9 (17.0)	19 (17.3)	33 (32.0)	0.0116
Nutrition, no. (%)							0.0003
Enteral only	80 (19.3)	10 (22.7)	22 (21.0)	6 (11.3)	30 (27.3)	12 (11.7)	
Parenteral only	140 (33.7)	12 (27.3)	43 (41.0)	14 (26.4)	42 (38.2)	29 (28.2)	
Enteral and parenteral	138 (33.3)	15 (34.1)	26 (24.8)	21 (39.6)	24 (21.8)	52 (50.5)	
No nutrition	41 (9.9)	6 (13.6)	10 (9.5)	10 (18.9)	8 (7.3)	7 (6.8)	
Thrombosis prophylaxis							
Unfractionated heparin, no. (%)	177 (42.7)	15 (34.1)	48 (45.7)	20 (37.7)	46 (41.8)	48 (46.6)	0.5444
Low molecular weight heparin, no. (%)	165 (39.8)	22 (50.0)	45 (42.9)	18 (34.0)	48 (43.6)	32 (31.1)	0.1933

[a] The sum of patient numbers within a variable may be lower than the total patient number due to missing data

[b] p-values indicate differences between strata. Strata 1–4 comprise all non-university hospitals with ≤ 200, 201–400, 401–600, and > 600 beds, respectively, and stratum 5 comprises all university hospitals

the degree of the systemic inflammatory response caused by infection. Furthermore, many physicians may not recognize sepsis clinically and may fail to note correct discharge diagnoses. This may also contribute to an underestimation of mortality rates.

Therapeutic measures in patients with severe sepsis were not largely different between hospital-size strata; however, there were differences in the frequencies of enteral and parenteral nutrition across strata. A detailed analysis of this aspect will be provided elsewhere.

Conclusion

In conclusion, our study shows that the incidence and mortality of severe sepsis in Germany is considerably higher than reported thus far. Both ICU and hospital mortality, as well as age, were higher than in other studies which may result from the inclusion of smaller hospitals in our representative nationwide survey but may also be attributable to differences in the quality of care, distribution of comorbidities or genetic polymorphisms among study populations, as well as to national ICU bed availability and admission policies. The results of this study underline the immense medical and health economic burden of severe sepsis. To further improve our understanding of the global epidemiology of sepsis and allow better comparison between nations and the quality of the respective health care systems and ICU care, authors of future epidemiological studies of sepsis should harmonize study methodologies and sepsis definitions as much as possible.

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Appendix

Definitions of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock based on the ACCP/SCCM consensus conference definition [28]:

1. Systemic inflammatory response syndrome (SIRS). At least two of the following criteria need to be fulfilled: (a) temperature ≤ 36 or ≥ 38 °C; (b) tachycardia with heart rate ≥ 90 beats/min; (c) tachypnea with ≥ 20 breaths/min and/or paCO2 ≤ 32 mmHg or mechanical ventilation; (d) white blood cell count ≤ 4 or ≥ 12 g/l and/or left shift $\geq 10\%$
2. Sepsis: SIRS due to infection (clinically or microbiologically documented)
3. Severe sepsis: sepsis associated with at least one organ dysfunction
4. Septic shock: sepsis or severe sepsis with persistent hypotension despite adequate fluid resuscitation or the necessity of vasopressor administration to maintain a mean arterial blood pressure of 70 mmHg

If an infection and at least one organ dysfunction without SIRS was present within the 24-h period, the presence of SIRS within the preceding 48 h was assessed. If SIRS was present within this period, the patient was considered to have severe sepsis or septic shock.

Organ dysfunctions were defined as follows:

1. Acute encephalopathy: reduced vigilance; unrest; disorientation or delirium not influenced by psychotropic drugs
2. Hematological dysfunction: platelet count ≤ 100 g/l or decrease of $> 30\%$ over 24 h not caused by hemorrhage
3. Respiratory dysfunction: $PaO_2/FiO_2 \leq 250$ mmHg if not caused by manifest pulmonary or cardiac disease or $PaO_2/FiO_2 \leq 200$ mmHg in case of pneumonia as the only focus
4. Cardiovascular dysfunction: systolic blood pressure of ≤ 90 mmHg over 1 h in a patient being normotonous beforehand, or sustained decrease of ≥ 40 mmHg compared with the blood pressure at absence of other causes of shock
5. Renal dysfunction: urine output ≤ 0.5 ml/kg h^{-1} for at least 1 h despite adequate fluid resuscitation and/or increase of serum creatinine to ≥ 2 times the upper limit of the normal reference range of the reporting laboratory (at presence of pre-existing impairment of renal function only one criterion need to be met)
6. Metabolic acidosis: pH ≤ 7.30 or base deficit ≥ 5.0 mmol/l or plasma lactate concentration ≥ 1.5 times the upper normal limit of the report-breaking laboratory

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29:1303–1310
2. Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348:1546–1554
3. Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, Sicignano A, Palazzo M, Moreno R, Boulme R, Lepage E, Le Gall R (2002) Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med 28:108–121
4. Finfer S, Bellomo R, Lipman J, French C, Dobb G, Myburgh J (2004) Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. Intensive Care Med 30:589–596
5. Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, Mercier JC, Offenstadt G, Regnier B (1995) Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. J Am Med Assoc 274:968–974
6. Brun-Buisson C, Meshaka P, Pinton P, Vallet B (2004) EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med 30:580–588
7. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP (1995) The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. J Am Med Assoc 273:117–123
8. Zahorec R, Firment J, Strakova J, Mikula J, Malik P, Novak I, Zeman J, Chlebo P (2005) Epidemiology of severe sepsis in intensive care units in the Slovak Republic. Infection 33:122–128
9. Sands KE, Bates DW, Lanken PN, Graman PS, Hibberd PL, Kahn KL, Parsonnet J, Panzer R, Orav EJ, Snydman DR, Black E, Schwartz JS, Moore R, Johnson BL Jr, Platt R (1997) Epidemiology of sepsis syndrome in 8 academic medical centers. J Am Med Assoc 278:234–240

10. Sprung CL, Sakr Y, Vincent JL, Le Gall JR, Reinhart K, Ranieri VM, Gerlach H, Fielden J, Groba CB, Payen D (2006) An evaluation of systemic inflammatory response syndrome signs in the Sepsis Occurrence in Acutely Ill Patients (SOAP) study. Intensive Care Med 32:421–427
11. Ponce de Leon-Rosales SP, Molinar-Ramos F, Dominguez-Cherit G, Rangel-Frausto MS, Vazquez-Ramos VG (2000) Prevalence of infections in intensive care units in Mexico: a multicenter study. Crit Care Med 28:1316–1321
12. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M (1995) The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. J Am Med Assoc 274:639–644
13. van Gestel A, Bakker J, Veraart CP, van Hout BA (2004) Prevalence and incidence of severe sepsis in Dutch intensive care units. Crit Care 8:R153–R162
14. Sundararajan V, Macisaac CM, Presneill JJ, Cade JF, Visvanathan K (2005) Epidemiology of sepsis in Victoria, Australia. Crit Care Med 33:71–80
15. Padkin A, Goldfrad C, Brady AR, Young D, Black N, Rowan K (2003) Epidemiology of severe sepsis occurring in the first 24 h in intensive care units in England, Wales, and Northern Ireland. Crit Care Med 31:2332–2338
16. Moss M, Martin GS (2004) A global perspective on the epidemiology of sepsis. Intensive Care Med 30:527–529
17. Anonymous (1997) Systematisches Verzeichnis der Krankenhaeuser und Vorsorge- oder Rehabilitationseinrichtungen in Deutschland – Stand 31.12.1995
18. Hansen HP, Hurwitz WN (1943) On the theory of sampling from finite populations. Ann Math Stat 14:333–362
19. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM (1988) CDC definitions for nosocomial infections, 1988. Am J Infect Control 16:128–140
20. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. J Am Med Assoc 270:2957–2963
21. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
22. Freeman J, Hutchison GB (1980) Prevalence, incidence and duration. Am J Epidemiol 112:707–723
23. Warren HS, Suffredini AF, Eichacker PQ, Munford RS (2002) Risks and benefits of activated protein C treatment for severe sepsis. N Engl J Med 347:1027–1030
24. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709
25. Panacek EA, Marshall JC, Albertson TE, Johnson DH, Johnson S, MacArthur RD, Miller M, Barchuk WT, Fischkoff S, Kaul M, Teoh L, Van Meter L, Daum L, Lemeshow S, Hicklin G, Doig C (2004) Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. Crit Care Med 32:2173–2182
26. Wenzel RP, Edmond MB (2001) Severe sepsis-national estimates. Crit Care Med 29:1472–1474
27. Wild C, Narath M (2003) Evidenzbasierte Intensivbettenplanung: Eine Übersicht zu rezenten internationalen Planungen und Planungsansätzen. Intensivmedizin und Notfallmedizin 40:412–419
28. Anonymous (1992) American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20:864–874