Sepsis incidence and outcome: Contrasting the intensive care unit with the hospital ward*

Andrés Esteban, MD, PhD; Fernando Frutos-Vivar, MD; Niall D. Ferguson, MD, MSc; Oscar Peñuelas, MD; José Ángel Lorente, MD, PhD; Federico Gordo, MD, PhD; Teresa Honrubia, MD, PhD; Alejandro Algora, MD; Alejandra Bustos, MD; Gema García, MD; Inmaculada Rodríguez Diaz-Regañón, MD; Rafael Ruiz de Luna, MD

Objective: **To describe the outcome of patients with sepsis according to location on a ward or in an intensive care unit.**

Design: **Prospective multicentered observational study.**

Setting: **Three academic hospitals in Madrid, Spain.**

Patients: **Consecutive patients with sepsis admitted to participating hospitals from March 1 to June 30, 2003.**

Interventions: **None.**

Measurements and Main Results: **During the study period, 15,852 patients >18 yrs of age were admitted. Sepsis was identified in 702 patients, giving an estimated cumulative incidence rate of 367 cases per 100,000 adult area residents per year and a cumulative incidence rate among patients admitted to the hospital of 4.4%. Most septic patients had a community-acquired infection (71%). Severe sepsis developed in 199 patients (incidence rate, 104 cases per 100,000 adult area residents per year), and 59 patients developed septic shock (incidence rate, 31 cases per 100,000 adult area residents per year). Most of the patients met the criteria for severe sepsis or septic shock on the same day that they would have qualified for the septic status one step down the scale. In the other patients, the median time between sepsis and severe sepsis was 2 days (interquartile range, 2–5) and between severe sepsis and septic shock was 3 days (interquartile range, 1–4). Only 32% of severe sepsis patients received intensive care. The hospital mortality for all septic patients was 12.8%; for severe sepsis, 20.7%; and for septic shock, 45.7%.**

Conclusions: **This study shows the high incidence of sepsis in a general population of patients admitted to hospital. A significant proportion of patients with severe sepsis are not transferred to the intensive care unit. (Crit Care Med 2007; 35:1284–1289)**

KEY WORDS: sepsis; septic shock; intensive care unit; epidemiology; mortality

Sepsis is one of the most prevalent illnesses among hospitalized patients and is one of their main causes of death (1). It has been reported that up to half of patients with sepsis require intensive care. Severe sepsis accounts for one in five admissions to intensive care units (ICUs) and is the leading cause of death in the noncoronary ICU (2, 3).

In recent years, several studies have reported a high incidence of sepsis in the general population that appears to be increasing over time (1, 4–7). These studies, conducted using hospital discharge databases, included a large number of patients but have several limitations. These limitations include the accuracy of discharge diagnosis codes for capturing sepsis syndrome and severe sepsis and the use of various definitions of sepsis, each of which complicates the interpretation of their results. Similarly, there are difficulties in extrapolating from the occurrence rates of sepsis documented in the select population of patients admitted to an ICU to the occurrence rate in the general population. The available large prospective observational studies on severe sepsis are heterogeneous with regard to patients and ICU characteristics. They focus only on patients admitted to the ICU, and few provide a clear picture of the evolution of the condition over time (8–17).

We therefore carried out a prospective multicenter epidemiologic study in an area with a numerically well-defined adult population. Our objectives were a) to describe the demographic, clinical, microbiological, and outcome characteristics of patients with sepsis in three general hospitals; and b) to describe the incidence of sepsis, severe sepsis, and septic shock in the hospital and in the ICU.

METHODS

The ethics committee at each of the participating hospitals approved the study protocol and waived the need for informed consent.

Patients

Patients were recruited from three hospitals in the south of metropolitan Madrid, Spain, over a 4-month period from March 1 to June 30, 2003. This study duration was chosen arbitrarily based upon available resources for data collection. The study hospitals each have tertiary ICUs, residency training programs, and active research programs. According to

*See also p. 1422.

From the Intensive Care Unit, Hospital Universitario de Getafe (AE, FFV, NDF, OP, JAL, AB, IRD-R), Fundación Hospital de Alcorcón (FG, AA, RRL), and Hospital de Móstoles (TH, GG), Madrid, Spain; and the Interdepartmental Division of Critical Care Medicine and Department of Medicine (Respirology), University Health Network, University of Toronto, Toronto, ON, Canada (NDF).

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For information regarding this article, E-mail: aesteban@ucigetafe.com

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the organization of the Public Health System in Madrid, each hospital services a well-defined geographic area with a known population. Public hospitals provide services to all inhabitants in their assigned geographic area. The areas of the three hospitals in this study are adjacent and include a total of 573,149 individuals >18 yrs of age, based on 2001 census data (18). According to this census, the general characteristics of our cohort, such as age, gender, and ethnicity, were similar to the overall Spanish population. One of the participating hospitals, the Hospital Universitario de Getafe, also served as the coordinating center.

Consecutively admitted patients to any of the designated risk areas in a participating hospital (medical-surgical ICU, general and specialty medical wards, general surgery ward, orthopedic and trauma surgery ward, neurosurgical ward, and gynecology ward) were followed up to discharge from hospital to detect the presence of sepsis, defined as a systemic inflammatory response secondary to infection. (See subsequent detailed definition.)

We excluded patients who a) were <18 yrs old; b) were discharged from hospital alive within 48 hrs of admission; c) had been transferred from another hospital with a preexisting diagnosis of sepsis; or d) had previously been admitted to the study cohort.

Screening Procedures

In the medical-surgical ICUs and each at-risk ward area, all admitted patients were actively screened for the presence of sepsis. Investigators in charge of the enrollment were physicians from the ICUs with experience in the identification of patients with sepsis criteria. In addition to reviewing admission records and patient charts, investigators conferred with the nurse in charge of each ward and with other nurses and physicians during their daily ward visits to ensure that potentially eligible patients were not missed.

Cohort Follow-Up and Data Collection

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 investigators before starting data collection.

At the time of enrollment we recorded demographic data, reason for admission to hospital, McCabe score (19), medical vs. surgical reason for admission, presence of comorbidities, origin of primary infection (pulmonary, gastrointestinal, urinary-gynecologic, central nervous system, catheter-related, or skin-muscle), date of diagnosis of infection, and cultures performed along with their results. From the inclusion day (day 1), patients were monitored daily for the next 7 days to identify those patients evolving to severe sepsis and septic shock. Follow-up was prolonged for 15 days for patients meeting the criteria for the diagnoses of severe sepsis or septic shock. At days 3, 5, and 7 after enrollment, we recorded as much of the following information that was available: a) severity of illness graded on the Simplified Acute Physiology Score II scale (20); b) number of organ failures and Multiple Organ Dysfunction Score (21); c) hemodynamic data (heart rate, mean arterial pressure, central venous pressure); d) management data (mechanical ventilation, vasoactive drugs, administration of drotrecogin alpha, dialysis); and e) arterial blood gases. All enrolled patients were followed to capture relevant outcome data, including hospital mortality and length of hospital stay, and, if applicable, ICU mortality, the length of stay in the ICU, and the duration of mechanical ventilation. In case of death, we determined whether the patient had any of the following orders: transfer to ICU, do not resuscitate, or treatment withdrawal.

Data Coordination and Validity Checking

During the study, there were monthly meetings among physicians at all centers and the coordinating center to resolve problems with definitions or enrollment. Completed data forms were mailed to the coordinating center and double-entered in a database. Errors or blank fields generated queries that were returned to each center for correction. A data validation study was conducted on a random 10% of records; the coordinating center selected a random sample of surveyed patients at each hospital, and data were reabstracted from the medical records by study personnel from one of the other hospitals. A consistency of 99% per case report form was observed during this process.

Definitions. Infection was defined as the presence of a pathogenic microorganism in a sterile milieu and/or clinically suspected infection, plus the administration of antibiotics. Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions as infection plus two systemic inflammatory response syndrome criteria (22). Severe sepsis was defined as sepsis plus at least one organ failure, except when that organ failure already was present 48 hrs before the onset of sepsis. Septic shock was defined as sepsis and at least one of the following criteria: systolic blood pressure <90 mm Hg despite adequate fluid administration, need for inotropes or vasopressors (excluding dopamine <5 μg/kg/min), or systolic blood pressure decrease of ≥40 mm Hg from usual baseline level. Organ failure was defined as a Multiple Organ Dysfunction Score >2 for the organ in question (21).

Statistical Analysis

Results are expressed as mean and SD, medians and interquartile range, or proportions with 95% confidence intervals (CIs) as appropriate. Cumulative incidence rate of sepsis in the hospital was expressed as a percentage. Estimated cumulative incidence rate of sepsis in the health area was expressed as cases per 100,000 adult inhabitants annually, assuming that incidence of sepsis is regular over the course of a year. We used Student's *t*-test or the Mann-Whitney test to compare continuous variables and the chi-square test or Fisher's exact test to compare proportions, as appropriate. Two-tailed *p* values <.05 were used to indicate statistical significance. All analyses were conducted using SPSS version 13.0 (SPSS, Chicago, IL).

RESULTS

Incidence of Sepsis and Origin of Infection

During the 4-month study period, the total number of admitted patients in the three hospitals was 18,512, of whom 15,852 were >18 yrs of age. In this time, 702 patients with sepsis were identified. The cumulative incidence rate of sepsis among patients admitted to the hospital was 4.4% (95% CI, 4.1–4.7). Estimated cumulative incidence in the health area was 367 cases per 100,000 adult residents per year. The characteristics of these patients at hospital admission are shown in Table 1.

Most patients with sepsis had a community-acquired infection (83%; 95% CI, 80–86). The source of the infection is shown in Table 2. In 223 patients with sepsis (32%; 95% CI, 28–35), microbiological samples for the diagnosis of infection were not obtained. Microbiological samples were negative in 278 patients (40%; 95% CI, 36–43) and positive in 201 patients (29%; 95% CI, 25–32): 83 patients were infected by Gram-positive microorganisms, 115 patients by Gram-negative microorganisms, and three patients by other microorganisms (Table 3). Cultures were more likely to be positive in samples obtained in the ICU than outside the ICU (91% vs. 27%). A total of 88 patients (12.5%; 95% CI, 10–15) had positive blood cultures.

Severe Sepsis

Among the 702 patients with sepsis, 199 patients (28%; 95% CI, 25–32) developed severe sepsis (Table 4). Among these

Table 1. Characteristics of patients with sepsis at enrollment

	n = 702
Age, yrs, mean (SD)	69 (19)
Female, n (%)	397 (57)
Diagnosis on admission, n (%)	
Medical	588 (84)
Surgical	92 (13)
Trauma	18 (3)
Acute coronary syndrome	4 (1)
McCabe score, n (%)	
Nonfatal	524 (75)
Ultimately fatal	161 (23)
Fatal	17 (2)
Comorbidities, n (%)	
Arterial hypertension	243 (35)
Diabetes	143 (20)
Chronic pulmonary obstructive disease	129 (18)
Atrial fibrillation	73 (10)
Ischemic heart disease	60 (8.5)
Cerebrovascular pathology	57 (8)
Chronic renal failure[a]	52 (7)
Cancer	47 (7)
Inmunodeficiency[b]	44 (6)
Chronic hepatic disease	42 (6)
Chronic heart failure	42 (6)
Cognitive dysfunction	39 (6)
Alcoholism	37 (5)
Valvular heart disease	26 (4)
Asthma	14 (2)
Hematological malignancy	14 (2)
SAPS II, points, mean (SD)	27 (11)

SAPS, Simplified Acute Physiology Score.

[a]Baseline creatinine >3 mg/dL or receiving dialysis; [b]any of hematological malignancy, immunosuppressive therapy, or HIV infection with CD4+ count ≤250/mL.

Table 2. Origin of the primary infection

	Community-Acquired Infection (n = 585)	Hospital-Acquired Infection (n = 106)	Intensive Care Unit-Acquired Infection (n = 11)
Pulmonary, n (%)	331 (56)	28 (26)	6 (54.5)
Gastrointestinal, n (%)	79 (13.5)	27 (27)	—
Urinary-gynecologic, n (%)	15 (20)	26 (24)	2 (18)
Skin and muscle, n (%)	30 (5)	17 (16)	—
Central nervous system, n (%)	4 (0.7)	—	1 (9)
Catheter-related infection, n (%)	2 (0.3)	3 (3)	2 (18)
Other origin, n (%)	24 (4)	5 (5)	—

—, no patients.

cases, 76% of the patients (152 of 199) met the criteria for severe sepsis on the same day that the criteria for sepsis were met. In the other 47 patients, the median time between the diagnosis of sepsis and severe sepsis was 2 days (interquartile range, 2–5). On the day of severe sepsis onset, affected patients had a median Multiple Organ Dysfunction Score of 4 points (interquartile range, 3–6). Patients admitted to the ICU had a higher Multiple Organ Dysfunction Score than patients remaining on a hospital ward: median score 7 points (interquartile range, 4–10) vs. 3 points (interquartile range, 2–5; $p < .001$).

Severe sepsis was more likely to occur in patients with chronic renal disease (46% vs. 27%, $p = .004$), in patients with chronic liver disease (43% vs. 27%, $p = .03$), in patients with ICU-acquired infection (45.5% vs. 28.5% and 25.5% in cases with community- or hospital-acquired infection outside the ICU, respectively, $p = .03$), and in patients with positive blood cultures (38% vs. 27%, $p = .04$).

Septic Shock

Fifty-nine patients (8%; 95% CI, 6.5–11) developed septic shock (Table 4). Twenty-nine (49%) of these patients developed septic shock on the same day that they met the criteria for severe sepsis. In the remaining 30 patients, the median time between severe sepsis and septic shock was 3 days (interquartile range, 1–4). Septic shock was more likely to occur in surgical patients (17% vs. 7% in medical patients, $p < .001$) and in patients with nosocomial infection (18% in ICU-acquired infection, 12% in hospital-acquired infection, and 7.5% in community-acquired infection, $p = .05$). On the day of septic shock onset, the median Multiple Organ Dysfunction Score was 7 points (interquartile range, 4–10) in these patients.

ICU Utilization

Eighty-four patients (12%; 95% CI, 10–14.5) were admitted to the ICU, 47 (56%) from the emergency room and 37 from the ward (Table 4). Patients admitted to the ICU had a greater severity on the day of inclusion compared with those not admitted to the ICU: mean Simplified Acute Physiology Score II 33 ± 16 vs. 26 ± 11 ($p < .001$). Of sepsis patients in the ICU, 61% required mechanical ventilation, with a median duration of 14 days (interquartile range, 6–30). We did not find differences ($p = .64$) in the duration of mechanical ventilation between patients who were admitted because of severe sepsis (median 16 days; interquartile range, 5–36) and patients who developed severe sepsis during their stay in the ICU (median 14 days; interquartile range, 10–22). The median length of stay in the ICU was 9 days (interquartile range, 4–25). The mortality of patients who required mechanical ventilation was 41.2% compared with 12.1% for patients who did not require mechanical ventilation ($p = .004$).

Mortality

Ninety of 702 patients died in the hospital (12.8%; 95% CI, 10–15) (Table 4). Mortality rates for sepsis, severe sepsis, and septic shock are shown in Figure 1. Patients with severe sepsis (not shock) who were not admitted to the ICU had a mortality rate of 26% (35 of 136). Among the 19 ICU patients with severe sepsis but without septic shock, there were two deaths (11%). Patients with severe sepsis who were not admitted to the ICU were older than those admitted to the ICU (75 ± 16 yrs vs. 61 ± 18 yrs; $p < .001$) and had a worse McCabe score (39% had a fatal or ultimately fatal score vs. 24% in the admitted group; $p = .03$).

Patients with septic shock who were not admitted to the ICU had a higher mortality rate (8 of 15; 53.3%; 95% CI, 29–77) than those admitted to the ICU with the diagnosis of septic shock (8 of 24; 33%; 95% CI, 17–54) but had a similar rate compared with patients who developed septic shock after ICU admission (11 of 20; 55%; 95% CI, 33–75).

Among the 90 patients who died, we found a higher percentage of do-not-resuscitate orders in the patients who were not admitted to the ICU (30 of 65 or 46% vs. 2 of 25 or 8%; $p < .001$). However, orders for withdrawal or withholding of treatment were seen with similar frequency on the ward and in the ICU (33 of 65 or 51% vs. 11 of 25 or 44%; $p = .56$).

DISCUSSION

The main findings of our study are a) the estimated cumulative incidence rate

Table 3. Microorganisms causing infection in patients with microbiological sample

Gram positive	n = 85[a]
Staphylococcus coagulase negative	22
Streptococcus pneumoniae	18
Methicillin-sensitive *Staphylococcus aureus*	15
Other *Streptococcus* species	12
Enterococcus species	13
Methicillin-resistant *S. aureus*	4
Listeria monocytogenes	1
Gram negative	n = 116[a]
Escherichia coli	73
Klebsiella species	11
Pseudomonas species	10
Proteus species	7
Enterobacter species	5
Salmonella species	5
Haemophilus influenzae	2
Morganella morganii	1
Stenotrophomonas maltophilia	1
Providencia stuartii	1
Other	n = 3
Mycobacterium tuberculosis	3

[a]Three infections were polymicrobial.

Table 4. Clinical syndrome rates and outcomes

	Sepsis Syndrome	Severe Sepsis	Septic Shock
No. (%) of all sepsis patients	702 (100)	199 (28)	59 (8)
Incidence, cases per 100,000 adult population per year	367	104	31
Overall mortality, n (%)	90 (13)	56 (28)	27 (46)
ICU admissions, n (%)	84 (12)	63 (32)	44 (75)
ICU incidence, ICU cases per 100,000 adult population per year	44	33	23
ICU mortality, n (%)	25 (30)	21 (33)	19 (43)

ICU, intensive care unit.

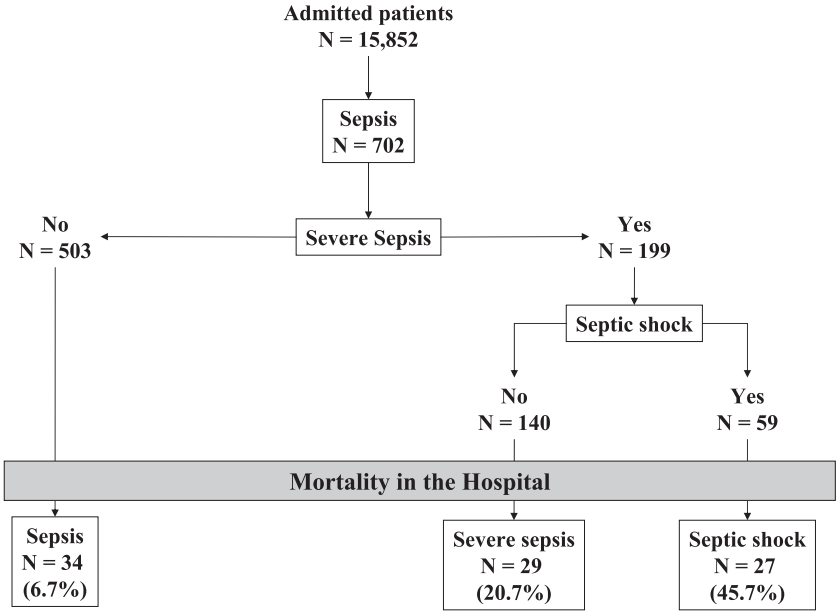

Figure 1. Flow chart of outcome of patients grouped by mutually exclusive categories of septic shock, severe sepsis (excluding shock), and sepsis (excluding severe cases).

of sepsis was 367 cases per 100,000 adult area residents per year, whereas the estimated cumulative incidence rate of sepsis receiving ICU care was 44 cases per 100,000 inhabitants per year; b) most of the patients met the criteria for severe sepsis on the same day that they met the criteria for sepsis or met the criteria for septic shock on the same day as for severe sepsis (in the rest of the patients, the progression from sepsis to severe sepsis to septic shock occurred over an average of 1 day for each step); and c) the mortality rate of patients with severe sepsis who were not admitted to the ICU was high.

Several studies have estimated the incidence of sepsis in different groups of patients, but it is difficult to compare among the different studies. In 1990, the Centers for Disease Control (4) studied 1% of all discharge registers from U.S. hospitals and found an incidence rate of sepsis of 175.9 cases per 100,000 area residents per year. Other studies have estimated the incidence of sepsis in the general population by extrapolating from data extracted from different codes of the International Statistical Classification of Diseases and Related Health Problems (1, 5–7). Martin et al. (5) identified 10,319,418 cases of sepsis from a review of 750 million discharge reports in the United States over a period of 22 yrs. From 1979 to 2000 there was an increasing annual incidence of sepsis from 82.7 cases per 100,000 inhabitants per year to 240.4 cases per 100,000 inhabitants per year, a figure close to the incidence found in our study. Previously, Angus et al. (1) had used *International Classification of Diseases, Ninth Revision* codes and hospital discharge databases to estimate that between 2.1% and 4.3% of hospital admissions and 11% of ICU admissions had severe sepsis. One limitation of these studies based on the International Classification of Diseases system is that there is no specific code for sepsis; the presence of this syndrome must be inferred from codes such as septicemia (038) (5) or by searching a multitude of codes for individual infection (1). Martin et al. (5), however, evaluated the accuracy of the 038 code using a chart review. They found that this code had a positive predictive value of 88.9% (95% CI, 81.6–96.2) and a negative predictive value of 88.9% (95% CI, 67.8–93.2) for identification of real cases of sepsis. Flaatten (6) analyzed patients admitted to all Norwegian hospitals during 1999 (n = 700,107) by searching the database of the Norwegian Patient Registry for markers of sepsis, using *International Classification of Diseases, Tenth Revision* codes for sepsis and severe infections. Their incidence of sepsis was 9.5 per 1,000 hospital admissions and 149 per 100,000 inhabitants per year. More recently, Sundararajan et al. (7) analyzed a population-based hospital morbidity database generated from hospital discharge coding (*International Classification of Diseases, Tenth Revision*) in Australia over 4 yrs. They reported that the prevalence of sepsis was 1.1% of admissions and the incidence rate increased from 166 cases per 100,000 inhabitants per year in 1999 to 194 cases per 100,000 inhabitants per year in 2002. Other studies (2, 8, 10, 12, 14) have estimated the incidence of sepsis using the

Consensus Conference criteria (22, 23), as we did in our study. In these studies, the prevalence of sepsis was between 4% and 17% in patients who were admitted to the ICU, and the incidence was 240–300 cases per 100,000 inhabitants per year, close to our incidence figure. Thus, our prospective study including patients from a well-defined area and using a rigorous methodology supports the findings reported by other studies using discharge diagnostic codes.

The incidence of sepsis in the general population has also been studied using data extrapolated from sepsis cases diagnosed in the ICU (8–17). These incidence rates range from 76 to 149 cases per 100,000 inhabitants per year. This wide range could be due to differences in the populations studied. In our study, we found very different figures when we considered patients admitted to the hospital (104 cases per 100,000 inhabitants per year) or only ICU patients (40 cases per 100,000 inhabitants per year). Our results indicate that a very important group of patients with severe sepsis are admitted to the hospital (71 cases per 100,000 inhabitants per year) but are not transferred to the ICU. This result is in keeping with the findings of Sundararajan et al. (7), who found that 50% of patients with severe sepsis were not transferred to ICU.

It has previously been reported that 70% of patients with sepsis develop severe sepsis and 17% evolve to septic shock (24). These figures are much higher than those found in our study, likely because the previous study included only ICU patients, whereas we included all patients admitted to the hospital with sepsis. More recent studies (7, 25) have reported results similar to ours. Alberti et al. (25), in a study analyzing only ICU patients, reported that 11% of patients with sepsis developed severe sepsis and 13% developed septic shock. In an Australian study (7), 39% of sepsis patients in the ward evolved to severe sepsis. Rangel-Frausto et al. (26) used a Markov model to analyze the progression of sepsis and found that half of patients had spent $\geq$1 day at the previous stage before developing severe sepsis or septic shock. This is congruent with our results.

The mortality of severe sepsis observed in our study (20.7%) was lower than the mortality reported in the Australian study (31.1%) (7). In both studies, the observed mortality of patients with severe sepsis not admitted to the ICU was high: 26% in our study and 29.5% in the study by Sundararajan et al (7). Although comorbidities may make aggressive care inappropriate in some of these patients, this finding nevertheless suggests that there is a population of sepsis patients who are not admitted to the ICU who could potentially benefit from more aggressive resuscitation and innovative therapies for the treatment of sepsis.

This study has several limitations. First, the study was carried out in a small area of Spain, and questions arise regarding whether the results can be generalized over a wider population. In this sense, it is reassuring to note that the characteristics of our study population, along with their types and etiologies of infection, are similar to a recently reported epidemiologic study performed across Europe (17). Second, it is possible that our estimates of incidence rates were influenced by migration of individuals into or out of the study area; we did not check the residency status of all patients admitted to the hospital. However, the organization of the public health system in Madrid may limit this effect; all residents are registered with a particular hospital determined by geography relative to their place of residence. If they require hospital admission, they are promptly transferred to their registered hospital, even if they initially are admitted at another center. Third, because of our relatively short 4-month study period, it is possible that our results are influenced by seasonal variation. The importance of this potential effect is difficult to assess, as there are few data on seasonal differences in the incidence of sepsis (27). Fourth, documentation of progression to severe sepsis may be subject to surveillance or sampling bias as a lab result may be required to document organ dysfunction. To some degree, we may therefore have underestimated the rapidity of disease progression. Fifth, local end-life-practice patterns could have some influence in the outcomes observed in our study. Indeed, regional variability in ICU resource availability and utilization speaks to the importance of our study addressing the entire hospital patient population, not just those admitted to the ICU. Although it has been reported that, in some Spanish ICUs, the attitude of physicians toward limiting life support therapy is conservative relative to other countries (28), in our study we found percentages of both do-not-resuscitate and withdrawal-withholding orders similar to those published in other countries (29, 30).

CONCLUSIONS

We report an estimated cumulative incidence rate of adult sepsis in patients admitted to the hospital of 367 cases per 100,000 population annually, making this a common condition. One important finding of our study is that a significant percentage of patients with sepsis with a high mortality rate are not treated in the ICU. Further study is required to determine the optimal strategies to reduce this mortality rate.

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