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ARTÍCULO ORIGINAL

Epidemiology of sepsis in Colombian intensive care units

Guillermo Ortíz[1], Carmelo Dueñas[2], Ferney Rodríguez[3], Lena Barrera[4], Gisela de La Rosa[5], Rodolfo Dennis[6], Marcela Granados[7], Darío Londoño[8], Francisco Molina[9], Fabián Jaimes[10]

[1] Departamento de Cuidado Intensivo, Hospital Santa Clara, Bogotá, D.C., Colombia
[2] Departamento de Cuidado Intensivo, Hospital Bocagrande, Cartagena, Colombia
[3] Departamento de Medicina Interna, Universidad de Antioquia, Medellín, Colombia
[4] Departamento de Epidemiología, Universidad del Valle, Cali, Colombia
[5] Departamento de Cuidado Intensivo, Hospital Pablo Tobón Uribe, Medellín, Colombia
[6] Departamento de Medicina Interna, Fundación Cardio-Infantil, Bogotá, D.C., Colombia
[7] Departamento de Cuidado Intensivo, Fundación Valle de Lili, Cali, Colombia
[8] Departamento de Cuidado Intensivo, Pontificia Universidad Javeriana, Bogotá, D.C., Colombia
[9] Departamento de Cuidado Intensivo, Universidad Pontificia Bolivariana, Medellín, Colombia
[10] Departamento de Cuidado Intensivo, Universidad de Antioquia, Medellín, Colombia

Introduction: Currently, there is not enough data available concerning sepsis in developing countries, especially in Latin America.
Objective: We developed a study aimed at determining the frequency, clinical and epidemiological characteristics, and the consequences of sepsis in patients requiring admission to intensive care units in Colombia.
Materials and methods: This was a secondary analysis of a prospective cohort study carried out over a six-month period, from September 1, 2007, to February 28, 2008, in ten medical/surgical intensive care units in four Colombian cities. Patients were considered eligible if they had a probable or confirmed diagnosis of infection according to medical records. We recorded demographic characteristics, first admission diagnosis and co-morbidities, clinical status, and sepsis, severe sepsis or septic shock.
Results: During the study period, 826 patients were admitted to the intensive care units. From these patients, 421 (51%) developed sepsis in the community, 361 (44%) in the ICU, and 44 (5%) during hospitalization in the general ward. Two hundred and fifty three patients (30.6%) had involvement of one organ system: 20% had respiratory involvement, followed by kidney and central nervous system involvement with 3.4% and 2.7%, respectively.
Conclusions: In our cohort of septic patients, the prevalence of sepsis treated in ICU is similar to that reported in other studies, as well as the overall mortality.

Key words: Sepsis/epidemiology; septic shock; intensive care.

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Epidemiología de la sepsis en unidades de cuidado intensivo en Colombia

Introducción. Actualmente no se cuenta con muchos datos disponibles sobre la sepsis en los países en desarrollo y especialmente en América Latina.
Objetivo. Este estudio tuvo como objetivo determinar la frecuencia, las características clínicas y epidemiológicas y las consecuencias de la sepsis en una población de pacientes que requirieron ingreso en algunas unidades colombianas de cuidados intensivos.
Materiales y métodos. Este fue un análisis secundario de un estudio prospectivo realizado en un período de seis meses contados a partir del 1° de septiembre de 2007 hasta el 28 de febrero del 2008 en diez unidades médico-quirúrgicas de cuidados intensivos de cuatro ciudades de Colombia. Los pacientes se consideraron elegibles si tenían un diagnóstico probable o confirmado de infección según los registros médicos. Se registraron las características demográficas, los diagnósticos de primer ingreso y las enfermedades concomitantes, el estado clínico y la sepsis, sepsis grave o choque séptico.
Resultados. Durante el período de estudio, 826 pacientes fueron ingresados en las unidades de cuidados intensivos seleccionadas para el estudio. De estos pacientes, 421 (51 %) desarrollaron sepsis en la comunidad, 361 (44 %) en la unidad de cuidados intensivos y 44 (5 %) durante la hospitalización en la sala general; 253 pacientes (30,6 %) presentaron afectación de un órgano

Author contributions:
Fabián Jaimes and Ferney Rodríguez lead the EPI-SEPSIS project in Colombia.
Guillermo Ortiz and Carmelo Dueñas analyzed the data and drafted the section on the subgroup of patients in intensive care units in the final document.
All authors participated in data collection.

del sistema: 20 % tuvo problemas respiratorios, seguido por problemas en los riñones y el sistema nervioso central con 3,4 % y 2,7 %, respectivamente.
Conclusiones. En la muestra de pacientes sépticos, la prevalencia de la sepsis, así como de la mortalidad global, en los pacientes tratados en la unidad de cuidados intensivos fue similar a la reportada en otros estudios.

Palabras clave: sepsis/epidemiología, choque séptico, cuidados intensivos.
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Severe sepsis and septic shock are important causes of morbidity and mortality in patients admitted to intensive care units. These conditions are generally associated with multiple organ failure as final outcome (1-5). Over the past 30 years, the worldwide incidence of sepsis has increased by 13.7% per year (1-5). It is therefore estimated that more than 18 million people suffer from sepsis each year and more than five million of them die (1-5). This increase is arguably due to increasing numbers of people aged over 65 years (60% of septic patients are more than 65 years old), to more frequent diseases and therapies causing immunosuppression, and to widespread use of diagnostic and/or therapeutic invasive procedures.

Despite important advances in the understanding of the pathophysiology of sepsis, its overall mortality is greater than 30% (1-5). These data come from studies carried out in developed countries. Although most of the world's population lives in developing countries, very few studies assessing the frequency and mortality of sepsis in these nations are available. Mortality reports from Pakistan, Thailand, and Turkey range from 80 to 92% for severe sepsis (6-8). These and other publications suggest that mortality due to sepsis is much higher in developing countries than in developed ones (6-9).

Enough evidence substantiates the fact that sepsis is associated with increased consumption of resources. Moreover, it prolongs hospital stays in both the intensive care unit (ICU) and the general ward (9). The estimated cost of treating patients with severe sepsis is about 17 billion dollars per year in the United States (1-5); therefore, the hospital care cost of a patient with severe sepsis is about 10.000 dollars (1-9). In Colombia there are no data allowing calculation of the costs of sepsis for our health system.

Corresponding author:
Guillermo Ortíz, Calle 105 N° 23-30, apartamento 402, Bogotá, D.C., Colombia
Teléfono: (571) 602 8675
ortiz_guillermo@hotmail.com

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Until recently, treatment for septic patients was limited to antibiotic therapy. In recent years, clinical studies have shown improved outcomes due to therapies such as early goal-directed therapy (10), low-dose steroids (11), and drotrecogin alpha (activated) (12). Observational studies have shown that early, adequate instauration of antibiotic therapy can improve the survival rates of these patients (13). Moreover, it has been shown that some interventions can prevent conditions associated with the development of sepsis, such as ventilator-associated pneumonia and intravascular device-associated sepsis (14). It is of critical importance to determine the incidence, the prevalence, and the outcomes of severely ill septic patients in order to calculate the resources required for the management of septic patients in intensive care units, as well as to implement strategies aimed at improving their outcome.

In view of the paucity of information concerning sepsis in developing countries, and especially in Latin America, we have developed a study aimed at determining the frequency, the clinical and epidemiological characteristics, and the consequences of sepsis in a population of patients requiring admission to the intensive care units of ten Colombian reference hospitals.

Materials and methods

This is a secondary analysis of a prospective cohort study carried out over a period of six months, from September 1, 2007 to February 28, 2008, in 10 medical/surgical intensive care units in four Colombian cities among patients admitted to the ICU. These units have an average availability of 274 beds per month. Patients were considered eligible if they were older than 18 years; had a probable or confirmed diagnosis of infection according to medical records, or had changes in temperature (>38 °C or < 36 °C) or hypotension without a specific cause. Furthermore, as definitive inclusion criterion, patients must have had an infection fulfilling standard CDC definitions (15). Patients were excluded if they refused to participate, were screened for eligibility more than 24 hours after suspicion of infection, stayed more than

48 hours in another institution immediately before the current hospitalization, were not available for 28-day follow-up, or were discharged less than 24 hours after hospitalization or their diagnosis changed toward a non-infectious disease during hospitalization. The study protocol was approved by the institutional review board at each center. Oral informed consent was obtained in all hospitals except in two where written informed consent was requested. Data from patients requiring admission to ICU due to infection were taken into account. The need for hospital and ICU admission was decided by the medical team responsible for the patient and it was independent of the research group.

There were one or two trained nurses according to the number of beds in each hospital. They followed a study protocol standardized twice in two-day workshops developed within a three-month pilot study which was conducted immediately before starting the recruitment. In each hospital there was also a co-investigator clinician in charge of checking data accuracy and consistency, as well as the patient´s diagnosis. In addition, the case report forms (CRF) were checked and revised weekly in a double-entry form in the Data Coordinating Center (DCC, Universidad de Antioquia). Any inconsistency, inaccuracy or missing data implied returning the specific CRF to the co-investigator for correction within the next week after the DCC review. There was also on-site evaluation during the first month of the study at each hospital by one of the principal co-investigators.

The severity of illness was assessed using the Acute Physiologic and Chronic Health Evaluation II (APACHE II) score, and the frequency and magnitude of organ dysfunction was measured with the Sequential Organ Failure Assessment (SOFA) score, both determined within the first 24 hours after enrollment of the patient. We recorded also demographic characteristics, first admission diagnosis and comorbidities, clinical status as sepsis, severe sepsis or septic shock, any microbiological report and antibiogram during the first seven days after enrollment, and vital status at hospital discharge. Patients were evaluated daily during their hospital stay. For patients discharged before 28 days, their vital status was confirmed by phone call or outpatient control.

Results are expressed as mean and standard deviation (SD), median and interquartile range (IQR), or proportions according to the type and distribution of the variable. Patients were analyzed in three groups according to where their sepsis developed: patients who developed sepsis in the community, patients who developed sepsis in the general ward, and patients who developed sepsis in the ICU. There was not a formal calculation of sample size given the expected variability in the frequency of sepsis and severe sepsis within and among hospitals. The database was recorded in Access (Microsoft Office, USA, 2007) and all the statistical analyses were performed with STATA (State corp, Release 10, College Station, TX, USA).

Results

Demographic data

During the study period, 6,768 patients were admitted to the ten ICU, of whom 826 (12%) were diagnosed with sepsis. Of these patients, 421 (51 %) developed sepsis in the community, 361 (44%) in the ICU, and 44 (5%) during hospitalization in the general ward. The average age of the population under study was 54.5 ± 20 years, with predominance of the male gender (53%). There were no significant differences with regard to age or gender among the three groups of patients. Mean APACHE II scores were different among the three groups at the moment of diagnosis. The group that developed sepsis in the ICU had the lowest score and SOFA scores behaved likewise. Latin American patients were the most common, with 90.5% of cases. Table 1 summarizes the general characteristics of the patients. The most frequent comorbidities were: previous surgery or trauma (48%), chronic obstructive pulmonary disease, heart failure, and diabetes (13% each) (table 2). Within the total population, the primary diagnosis of infection was intra-abdominal infection in 18.6% of cases, followed by hospital acquired pneumonia, and community-acquired pneumonia, with 17% and 12.4%, respectively. Other types of infection are listed in table 3.

Severity of infection

Out of the 826 patients admitted to the ICUs, 12% (n=97) had no organ involvement. Two hundred and fifty three patients (30.6%) had involvement of one organ system: 20% had respiratory involvement, followed by kidney and central nervous system involvement with 3.4% and 2.7%, respectively. Two hundred and forty five patients (29.6%) had involvement of two organs, 16% (n=132) had involvement of three organs, 8.5% (n=70) had involvement of four organs, and 3% (n=25) had involvement of five organs

Table 1. Demographic characteristics of patients with sepsis who required management in the intensive care units

	Community n=422 (51%)	Intensive care units n=360 (44%)	Hospital wards n=44 (5%)
Age, mean ± SD	56.2 ± 20	52.1 ± 20	58.3 ± 18.8
Male gender (%)	51.7	53.1	56.8
Latin American origin (%)	94.1	85.6	97.7
SOFA, mean ± SD	6.47 ± 3.7	5.60 ± 3.1	6.3 ± 3.4
Apache II, mean ± SD	16.2 ± 6.8	13.7 ± 6.4	15.3 ± 6.5
Median hospital stay (days)	12	24	10.6

SD: Standard deviation

Table 2. Comorbidities of patients managed in the intensive care units*

Comorbidities	Community n=422 (%)	Intensive care units n=360 (%)	Hospital wards n=44 (%)
Trauma or surgery	128 (30.3)	230 (63.9)	20 (45.4)
None	119 (28.2)	57 (15.8)	6 (13.6)
Chronic obstructive pulmonary disease	57 (13.5)	44 (12.2)	8 (18.2)
Congestive heart failure	63 (14.9)	40 (11.1)	6 (13.6)
Diabetes mellitus	65 (15.4)	38 (10.5)	6 (13.6)
Chronic renal failure	51 (12.1)	45 (12.5)	9 (20.4)
History of cancer during the last year	40 (9.5)	22 (6.1)	2 (4.5)
Use of steroids	33 (7.8)	14 (3.9)	4 (9.1)
Drug addiction/alcoholism	23 (5.4)	15 (4.2)	2 (4.5)
Organ transplantation	16 (3.8)	7 (1.9)	0
HIV/AIDS	10 (2.4)	1 (0.3)	2 (4.5)
Cirrhosis	6 (1.4)	6 (1.7)	0

*Some patients may have more than one.

Table 3. Diagnosis of infection in patients with sepsis managed in the intensive care units

Main infection	Community n=422 (%)	Intensive care units n=360 (%)	Hospital wards n=44 (%)
Intraabdominal infection	84 (19.9)	63 (17.5)	3 (6.8)
Hospital-acquired pneumonia	1 (0.2)	119 (33.1)	21 (47.7)
Community-acquired pneumonia	103 (24.4)	0	0
Symptomatic urinary tract infection	55 (13.0)	40 (11.1)	1 (2.3)
Clinical sepsis	35 (8.3)	40 (11.1)	2 (4.5)
Soft-tissue infections	47 (11.1)	11 (3.1)	2 (4.5)
Bloodstream infection	17 (4.0)	33 (9.2)	1 (2.3)
Catheter-associated urinary tract infection	4 (0.9)	16 (4.4)	4 (9.1)
Bacteremia associated with arterial or central venous catheter	4 (0.9)	13 (3.6)	0
Meningitis or ventriculitis	13 (3.1)	4 (1.1)	0
Intracranial infection	14 (3.3)	1 (0.3)	0
Endocarditis	13 (3.1)	1 (0.3)	0
Mediastinitis	8 (1.9)	0	1 (2.3)
Other infections of the urinary tract	5 (1.2)	4 (1.1)	0
Other	19 (4.5)	15 (4.2)	9 (20.5)

on admission. Table 4 shows the classification of patients according to the severity of infection. For the population under study, the frequency of severe sepsis without shock on the first day of the follow-up was 53.2%.

Microbiology

In total, 1,133 samples were taken for bacterial cultures: blood (n = 449, 40%), urine (n= 290, 26%), sputum (n= 162, 14%), peritoneal fluid (n = 105, 9.3%) and other (n=127, 11.2%). Gram-negative bacilli were the most frequently isolated microorganisms (n=360 isolations). Table 5 shows the predominant isolations according to type of sample.

Outcomes

Day-28 mortality of patients admitted to the ICU with sepsis but with no organ dysfunction was 19.4%. It was higher in patients diagnosed with septic shock (45.1%) than in patients with sepsis

Table 4. Number of patients with sepsis, severe sepsis, and septic shock from day 1 to day 7 of their stay at the intensive care unit

Patient classification	Day of follow-up						
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)
Infection without sepsis	5 (0.6)	18 (2.2)	16 (2.1)	21 (2.9)	27 (3.9)	39 (5.9)	46 (7.4)
Sepsis without organ dysfunction	62 (7.5)	118 (14.7)	142 (18.3)	158 (21.7)	153 (22.3)	147 (22.4)	146 (23.5)
Severe sepsis without shock	440 (53.3)	384 (47.9)	405 (52.2)	394 (54.0)	388 (56.6)	374 (56.9)	354 (57.0)
Septic shock	319 (38.6)	281 (35.1)	212 (27.3)	156 (21.4)	117 (17.1)	97 (14.8)	75 (12.1)
Total number of patients	826	801	775	729	685	657	621

Table 5. Number of isolations and samples gathered from patients with sepsis admitted to intensive care units

	Community n=548	Intensive care units n=536	Hospital n=49
Microorganisms isolated by cultures:			
Total (%)	223 (41.0)	300 (56)	27 (55)
Gram-negative	145 (65.0)	203 (68)	20 (74)
Gram-positive	68 (30.5)	89 (30)	7 (26)
Fungi	10 (4.5)	8 (2)	0
Samples with positive isolations: Requested, positive (%)			
Blood cultures	235.85 (36)	192.89 (46)	22.9 (41)
Urine cultures	150.63 (42)	127.68 (53)	13.8 (61)
Sputum	54.24 (44)	104.74 (71)	4.3 (75)
Peritoneal fluid	48.26 (54)	55.41 (74)	2.2 (100)
Cerebrospinal fluid	16.2 (12.5)	17.2 (12)	2 (0)
Skin and soft tissues	16.9 (56)	13.10 (77)	2.2 (100)
Other	29.14 (48)	28.16 (57)	

but without shock (27.5%). The overall mortality rate at the time of discharge was 33.6%.

Discussion

Sepsis is an important cause of morbidity and mortality in our intensive care units. In recent years, clinical studies assessing interventions aimed at the management of sepsis have reported benefits concerning the mortality of critically ill patients (10-13). In Colombia, however, there are no general data that allow us to calculate the true impact of sepsis in critically ill patients.

The results of our study are important for the following reasons: The prevalence of septic patients treated in the ICU was similar to that reported in other studies (16-19), as well as the overall mortality. However, it was greater than that observed in some treatment arms of clinical studies (12). This can be analyzed as an opportunity to intervene such pathological condition.

These data are highly important in order to calculate the impact of sepsis on the health system, to assess the risk stratification of patients admitted to hospitals with a diagnosis of sepsis, and for future clinical studies. Recent studies from Europe, the United Kingdom, Australia, and New Zealand have shown the incidence rates of sepsis and its mortality in the ICU (16-20). North American studies are limited to data obtained in four Canadian intensive care units that participated in a multinational study (Alberti), or taken from administrative databases (1). These data revealed an incidence of sepsis in the ICU ranging from 11.8 to 37.4%, with mortality between 35 and 53.6% (both in the hospital and after 30 days). A prospective study carried out in eight academic medical centers in the United States revealed an incidence of sepsis in 2% of all hospital admissions and 59% of ICU admissions (21).

Sepsis, severe sepsis, and septic shock are more frequent in the ICU than in other sections of a healthcare institution (22-25). Several reports have confirmed that severe sepsis is found in 2% of patients admitted to the general ward, while it is found in up to 75% of ICU patients (18, 20, 26, 27). It is logical to consider that severely ill, infected patients should be admitted to the ICU, and this can partly explain the high frequency of sepsis in the

ICU. However, Esteban (28) recently showed that most of these patients are treated outside the ICU (323 cases/100.000 residents *vs*. 44 cases/100.000 residents). Mortality outside the ICU was regrettably much higher, up to 53% (28). This has been confirmed by other reports (29-35), and it strongly suggests that all patients with severe sepsis and septic shock should be admitted to the ICU.

On the other hand, the high rates of acquisition of infection and development of severe sepsis found within hospitals and intensive care units reinforce the pressing need for aggressive measures aimed at preventing the development of hospital-acquired diseases. This means that, besides complying with the therapeutic options recommended by the sepsis survival campaign (23 y 24), pains must be taken to develop strategies aimed at reducing catheter-associated infection, ventilator-associated pneumonia, and infection of operatory site (23).

Based on administrative data from 1995, Angus estimated that the incidence, the mortality, and the consumption of resources for sepsis would increase by 1.5% per year (1). More recent studies have estimated annual increases of up to 10% (36, 37). Gender, diabetes, immunosuppression, and cancer are among the factors associated with these increases. It is therefore arguable that the frequency of sepsis and its impact on clinical outcomes will continue to increase (38-45). On the other hand, statistics can vary according to the criteria by which diseases are defined from an epidemiological standpoint (46, 47). These data become even more important when related to our results, since most of our patients were admitted to the ICU directly from the community (51%), while an important percentage developed sepsis during their stay in the ICU (44%), and only a small number were admitted from the general wards (5%).

The overall mortality rate at discharge in our study was 33.6%. This fits within the ranges reported by recent clinical studies that included patients diagnosed with severe sepsis. The mortality reported for the control groups of the early goal-oriented therapy study was 47% (10), whereas that found in the PROWESS study was 57% (12), and that found in the steroid studies was 31% (11), while the mortality rates of the intervention groups were 31, 47, and 25%, respectively. The differences found among the studies could be explained by their design characteristics and inclusion and exclusion criteria, as well as by the fact that mortality was measured at different moments (in the ICU, on the 28th day, or at hospital discharge). The differences between our findings and the control groups of the clinical studies could represent a good opportunity for intervening on these patients. This is especially true if we take into account recent studies assessing successful therapeutic interventions in patients with severe sepsis and septic shock (48-52).

We think that this study has some strong aspects. Among these, we would like to highlight the fact that the determination of infection, sepsis, severe sepsis, and septic shock was done prospectively, according to the CDC and Survival Sepsis Campaign definitions. Moreover, several healthcare centers from four Colombian cities participated, which allowed inclusion of both medical and surgical patients, as well as details concerning demographic characteristics, comorbidities, severity scores, and site of infection of each patient with a central coordination at every participating healthcare center. Among the limitations of our study, we have to mention the fact that the inclusion of the healthcare centers was voluntary, which limits our ability to generalize its results.

In conclusion**,** we have shown a prospective record of patients with sepsis, severe sepsis, and septic shock who were admitted to 10 medical/surgical intensive care units in four Colombian cities. We determined a prevalence of sepsis of 10.8% and an overall mortality of 33.6%. We pointed out the importance of the place where the infection was acquired for the detection of this group of patients, as well as the development of adequate and timely therapeutic strategies. These observations are useful for improving the quality of septic patients care, as well as for the development of future clinical studies.

Conflict of interest

All authors declare that there is no conflict of interest.

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