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# Epidemiology of Severe Sepsis and Septic Shock

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## 1. Introduction

Sepsis is defined as the combination of pathologic infection and physiological changes known collectively as the systemic inflammatory response syndrome (Martin, 2003). This response results in physiological alterations that occur at the capillary endothelial level. In the early stages, the clinical manifestations of this process are unspecific and it is often underappreciated in clinical practice. However, early recognition of this syndrome is vital to reducing mortality in sepsis.

From clinical studies sepsis can be seen as a continuum of severity that begins with an infection, followed in some cases by sepsis, severe sepsis – with organ dysfunction – and septic shock. There has been a substantial increase in the incidence of sepsis during the last decades, and it appears to be rising over time, with an increasing number of deaths occurring despite a decline in overall in-hospital mortality (Bone, 1992). Advanced age, underlying comorbidities and number of organ dysfunction are factors which are consistently associated with higher mortality in severe sepsis and septic shock.

In this chapter we are going to review the definitions of sepsis syndromes, the factors that have contributed to the widening of physicians' awareness of sepsis, severe sepsis and septic shock; the incidence of severe sepsis and septic shock; the epidemiological data of patients with severe sepsis and septic shock in the emergency departments and intensive care units; the causative microorganisms, and the changes observed over recent years.

## 2. Definitions

The concept of sepsis syndrome originated during the time of Hippocrates. But it was not until the nineteenth century when Sir William Osler recognized that “except on few occasions, the patient appears to die from the body's response to infection rather than to the infection” (Hodgkin, 2008). During a long period of time great confusion existed as to the description of systemic inflammatory response to infection, and several terms were used

interchangeably: septicemia, sepsis, sepsis syndrome and septic shock. In clinical practice sepsis is the most confusing term used to describe the body's systemic response to infection, and to many clinicians sepsis implies a life-threatening state.

Bacteremia	The presence of viable bacteria in the blood
SIRS	The systemic inflammatory response to a variety of severe clinical insults which is manifested by two or more of the following conditions: <ul style="list-style-type: none"> <li>(1) temperature <math>&gt;38^{\circ}\text{C}</math> or <math>&lt;36^{\circ}\text{C}</math></li> <li>(2) heart rate <math>&gt;90</math> beats per minute</li> <li>(3) respiratory rate <math>&gt;20</math> breaths per minute or <math>\text{PaCO}_2 &lt;32</math> mm Hg</li> <li>(4) white blood cell count <math>&gt;12,000/\text{cu mm}</math>, <math>&lt;4,000/\text{cu mm}</math>, or <math>&gt;10\%</math> immature (band) forms</li> </ul>
Sepsis	The systemic inflammatory response (SIRS) as a result of infection
Severe Sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status
Septic Shock	Sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

Table 1. Definition of bacteremia, SIRS, sepsis, severe sepsis and septic shock.

In 1991, the American College of Chest Physicians and the Society of Critical Care Medicine convened a Consensus Conference and the definitions of sepsis syndromes were published in order to clarify the terminology used to describe the body's systemic responses to infection (Bone, 1992). These definitions are easy to use, based on clinical data of the patients, and describe a clinical continuum response to infection.

In the opinion of the authors of this chapter these definitions have not only been widely used in practice and clinical trials of therapeutic interventions but they have greatly contributed to the recognition of these syndromes. Before analyzing the epidemiology of severe sepsis and septic shock the reader should be familiarized with all these terms. The definitions of bacteremia, systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock are shown in **table 1**, and the relationships between infection, systemic inflammatory response syndrome (SIRS) and septic syndromes are shown in **figure 1**.

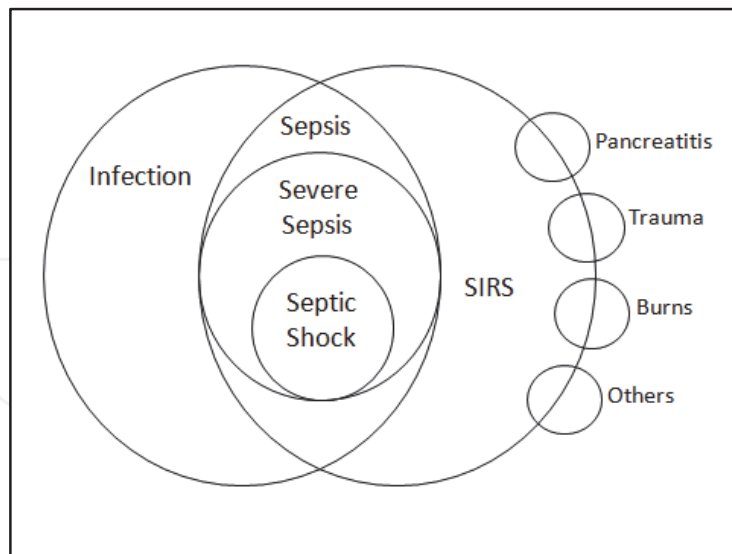


Fig. 1. The relationship between infection, systemic inflammatory response syndrome (SIRS) and sepsis syndromes.

In 2001, an International Sepsis Definitions Conference (Levy, 2003; Dunne, 2003) was sponsored by the Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM), the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS) to revisit the 1992 sepsis guidelines. Based on this conference a consensus document was developed, concluding that there was not enough evidence to support a change to the previous definitions. This document expanded the list of signs and symptoms of sepsis to reflect clinical bedside experience. Besides, the document developed a classification scheme for sepsis, called PIRO (Predisposition, Insult infection, Response, Organ dysfunction), that will stratify patients on the basis of their predisposing conditions, the nature and extent of the insult (in the case of sepsis, infection), the nature and magnitude of the host response, and the degree of concomitant organ dysfunction. This has provided a basis for introducing PIRO as a hypothesis-generating model for future research.

Predisposition (P) was the new element which was added to the IRO model proposed by John Marshall and based on the TNM system used in oncology patients. Factors that predispose patients to outcome in sepsis include genetic factors, environment, cultural factors and pre-existing diseases.

Infections (I) have four categories with a significant impact on outcome: The site, extent, source (hospital vs. community-acquired, etc) and type of organism. Besides, the immune status of a patient is related with opportunistic infections, which are associated with worse prognosis.

Response (R) is affected by several factors, such as: age, type of invading microorganism, genotype and co-morbidities. The use of biomarkers to stratify the degree of response is one of the most promising elements for diagnosis and risk assessment in the future. Given the complexity of the immune response in sepsis a single static measurement of a biomarker (pro-calcitonin or any other biomarker) may not be as important as a dynamic assessment of change over time.

The level of organ dysfunction is similar to the presence of metastatic disease in cancer. The evaluation of organ dysfunction has evolved from describing it in all-or-nothing terms to

use organ failures scores to describe the degree of organ dysfunction developing over the course of critical illness.

The participants in this conference gave priority to the facilitation of bedside diagnosis over standardized sepsis entry criteria for clinical trials. The conclusions of this conference can be summarized as: 1) The current concepts of sepsis, severe sepsis, and septic shock seem to be robust definitions and should remain as described 10 yrs ago. 2) Current definitions do not allow for precise staging of the host response to infection. 3) Signs and symptoms of sepsis are more varied than the initial criteria established in 1991. 4) A list of these signs and symptoms, for the diagnosis of sepsis is presented. 5) The future lies in developing a staging system that will characterize progression of sepsis. A new system, PIRO, is proposed for characterizing and staging the host response to infection.

The diagnostic criteria for sepsis in adults are shown in **table 2**. The definition of Systemic Inflammatory Response Syndrome (SIRS) in pediatrics is defined as: "The presence of two or more of the following criteria, one of which must be abnormal temperature or leukocyte count: a) Core temperature of  $> 38.5^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$ . b) Tachycardia, defined as a mean heart

Documented or suspected Infection and some of the following:	
- General variables	Fever (core temperature $>38.3^{\circ}\text{C}$ ) Hypothermia (core temperature $<36^{\circ}\text{C}$ ) Heart rate $>90$ min Tachypnea Altered mental status Significant edema or positive fluid balance ( $>20$ mL/kg over 24 hrs) Hyperglycemia (plasma glucose $>120$ mg/dL or $7.7$ mmol/L) in the absence of diabetes
- Inflammatory variables	Leukocytosis (WBC count $>12,000$ $\mu\text{L}^{-1}$ ) Leukopenia (WBC count $<4000$ $\mu\text{L}^{-1}$ ) Normal WBC count with $>10\%$ immature forms Plasma C-reactive protein $>2$ SD above the normal value Plasma procalcitonin $>2$ SD above the normal value
- Hemodynamic variables	Arterial hypotension (SBP $<90$ mm Hg, MAP $<70$ , or an SBP decrease $>40$ mm Hg) SvO <sub>2</sub> $>70\%$ Cardiac index $>3.5$ L·min <sup>-1</sup> ·M <sup>-2.3</sup>
- Organ dysfunction variables	Arterial hypoxemia (PaO <sub>2</sub> /FIO <sub>2</sub> $<300$ ) Acute oliguria (urine output $<0.5$ mL·kg <sup>-1</sup> ·hr <sup>-1</sup> or $45$ mmol/L for at least 2 hrs) Creatinine increase $>0.5$ mg/dL Coagulation abnormalities (INR $>1.5$ or aPTT $>60$ secs) Ileus (absent bowel sounds) Thrombocytopenia (platelet count $<100,000$ $\mu\text{L}^{-1}$ ) Hyperbilirubinemia (plasma total bilirubin $>4$ mg/dL or $70$ mmol/L)
- Tissue perfusion variables	Hyperlactatemia ( $>1$ mmol/L) Decreased capillary refill or mottling

Table 2. Diagnostic criteria for sepsis in adults

rate  $> 2$  sd above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hour time period *or* for children  $< 1$  year old: Bradycardia, defined as a mean heart rate  $< 10$ th percentile for age in the absence of external vagal stimulus, beta-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hour time period. c) Mean respiratory rate  $> 2$  sd above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia. d) Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or  $> 10\%$  immature neutrophils.

Criteria for sepsis in the pediatric population are different: arterial hypotension is defined as  $< 2$  SD below normal for age; neither  $SvO_2 > 70\%$  nor cardiac index  $> 3.5 \text{ L}\cdot\text{min}^{-1}\cdot\text{M}^{-2.3}$  should be used as signs of sepsis in newborns or children. Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with rectal temperature  $> 38.5$  or  $< 35^\circ\text{C}$ , tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

A bedside diagnosis of sepsis is not frequently based only on these criteria. Instead, experienced clinicians consider some physical and laboratory finding that prompt them to conclude that an infected patient "looks septic". These findings include general variables (altered mental status, significant edema ...), inflammatory variables (plasma C-reactive protein, plasma procalcitonin ...), hemodynamic variables (arterial hypotension,  $SvO_2$  ...), organ dysfunction variables (arterial hypoxemia, acute oliguria, coagulation abnormalities ...), and tissue perfusion variables (decreased capillary refill or mottling, hyperlactatemia).

In summary, the definitions of sepsis, severe sepsis and septic shock established in 1992 are useful to clinicians and researchers. However they are not precise tools to predict the outcomes of these syndromes, so the inclusion of clinical, microbiological and biological factors in clinical practice may aid to better characterize the prognosis of sepsis. Further evidence is needed to support changes in the current definitions of sepsis.

### 3. Incidence of severe sepsis and septic shock

The epidemiology of sepsis, severe sepsis and septic shock is not well known due to the absence of population base prospective cohort studies, and to the fact that most of the studies on the epidemiology of sepsis are based on hospital discharge diagnoses which do not use the consensus definitions. The incidence of severe sepsis and septic shock has notably increased in recent years, and appears to be rising over time (**figure 2**).

A comparison of population incidence and hospital prevalence of severe sepsis reported from several studies is shown in **table 3**.

In 1990, the Centers for Disease Control (CDC), based on data from the National Hospital Discharge Survey, estimated that there were 450,000 cases of sepsis per year in the United States (CDC, 1990). Angus, using ICD-9-CM codes, in a large observational cohort study ( $n=6,621,559$ ) in the United States in 1995, identified 192,980 cases of severe sepsis which represents an estimated incidence of 3.0 cases per 1,000 population, 2.26 cases per 100 hospital discharges, and 11 percent of all admissions to the ICU (Angus, 2001). However, the accuracy of ICD-9-CM coding for the identification of specific medical conditions remains controversial, and Martin (Martin, 2003) suggested that Angus's estimates may overstate the incidence of severe sepsis by as much as a factor of two to four.

Martin et al. (Martin, 2003) identified 10,319,418 cases of sepsis from an estimated 750 million hospitalizations in the United States over a 22-yr period, with an increase in frequency from 82.7 cases per 100,000 population in 1979 to 240.4 cases per 100,000 population in 2000, therefore there was an annualized increase in the incidence of sepsis of 8.7 percent.

Country	Author, yr	Prevalence in hospital per 100 admissions	Prevalence in ICUs per 100 ICU admissions	Estimated incidence per 100,000 population
Australia	Sundarajan, 2005	4.3	NR	76
Australia & N.Zeland	Finfer, 2004	-	11.8	77
Europe	Alberti, 2001	-	15.5	-
Europe	Vincet, 2006	-	30.0	-
Finland	Karlsson, 2007	-	10.5	69
France	Brun-Buisson, 1995	2.9	11.9	-
France	Episepsis, 2004	-	14.6	95
Germany	Engel, 2006	-	11.0	76
Netherlands	Van Gestel, 2004	-	11.0	54
Norway	Flaatten, 2004	3	-	48
United Kingdom	Padkin, 2003	-	27.1	51
Spain	Esteban, 2007	12.4	-	104
USA	Angus, 2001	2.6	11	300
USA	Martin, 2003	4.7	-	81

Table 3. Prevalence of severe sepsis in several studies around the world. (Adapted from Brun-Buisson C. Impact of Sepsis on Public Health. In: Dellinger P, Carlet J, editors. Sepsis handbook. 1<sup>st</sup> ed. Marcy l'Etoile: Editons Biomerieux;2009. p. 8-17).

In a recent prospective, observational study in Iceland, the incidence of severe sepsis and septic shock was 0.48 per 1,000 inhabitants  $\geq 18$  years of age per year [95% confidence intervals (CI) 0.42-0.55] (Vesteinsdottir, 2011).

The Italian SEPSIS study found that in 99 ICUs the prevalence of SIRS, sepsis, severe sepsis and septic shock in patients admitted to ICUs were 58%, 16%, 5% and 6%, respectively (Salvo, 1995). These and other results provide evidence of how the progression from sepsis to septic shock follows a continuum.

In an international multicenter cohort study on sepsis and infection in intensive care unit patients (Artigas 2002), infections had a crude incidence of 21.1%. Among 3,034 infectious episodes 24% were associated with severe sepsis and 30% with septic shock. The frequency of septic shock is increasing with more multiresistant strains. Annane et al analyzed the

epidemiology of septic shock from 100,554 intensive care unit admissions and found that the frequency of septic shock increased from 7.0 per 100 admissions in 1993 to 9.7 per 100 admissions in 2000 (Annane, 2003).

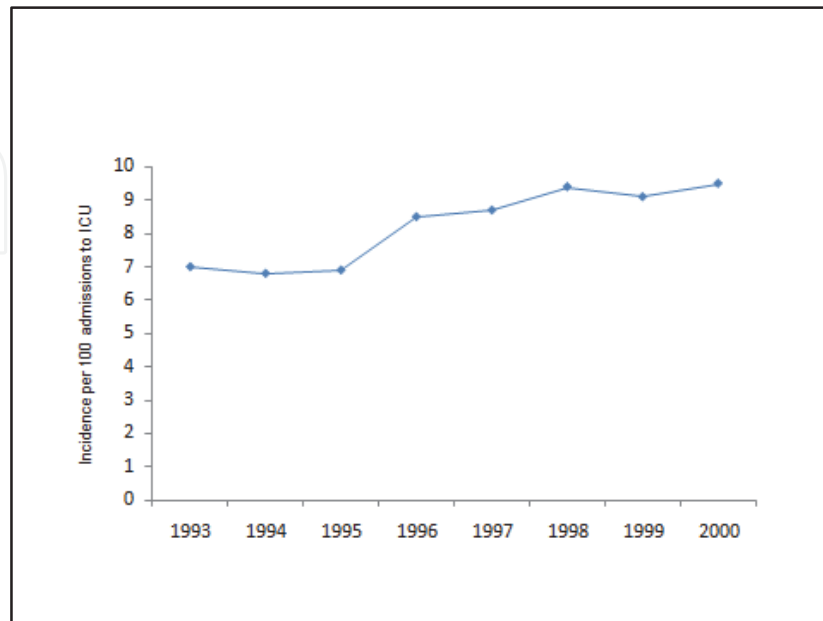


Fig. 2. Incidence of septic shock. Data collected over an 8-year period from 22 hospitals (adapted from Annane et al Am J Respir Crit Care Med 2003; 168:165-72).

Using the Emergency Department data of 2001-2004 from the National Hospital Ambulatory Medical Care Survey, and applying the 2003 international consensus criteria, Wang et al (Wang 2007) estimated the burden of severe sepsis in Emergency Departments as more than 500,000 adult patients per year, with individual patients spending an average of almost 5 hrs in the Emergency Department. Due to limitations of the study, such as not having access to data of respiratory rate, the true number of cases may be even higher.

Most cases of severe sepsis occur in patients who are already hospitalized for other reasons. In a series of 166 patients with bloodstream infections admitted to an intensive care unit we found that 82.5% of patients had nosocomial acquired infections, and the nosocomial origin of the bacteremia was associated with inadequate empirical antimicrobial treatment (Zaragoza, 2003).

Dombrovskiy et al. used the NIS to show that from 1993 to 2003, the age-adjusted rate of hospitalization for severe sepsis increased from 66.8 to 132.0 cases per 100,000 persons (Dombrovskiy, 2007).

Sepsis remains a significant cause of morbidity and mortality in pediatric population. Watson et al (Watson, 2003) using 1995 hospital discharge and population data from seven states analyzed the incidence of severe sepsis in children in the United States (see **figure 3**). The incidence was highest in infants (5.16 cases per 1000) and over 20% were low birth weight neonates. The respiratory tract (37%) and primary bloodstream infections (25%) were the most common sources of infection.

Sepsis is an important source of postoperative morbidity and mortality. Recently, Bateman et al studied the temporal trends in the epidemiology of severe postoperative sepsis after elective surgery in patients aged 18 years or older for any of the 20 most common primary procedure types who had a length of stay more than 3 days from the NIS dataset for the



years 1997–2006, and found that the rate of severe sepsis increased from 0.3% in 1997 to 0.9% in 2006. This trend persisted after adjusting for relevant covariables – the adjusted odds ratio of severe sepsis per year increase in the study period was 1.12 (95% CI, 1.11–1.13;  $P = 0.001$ ) (Bateman, 2010). Abdominal surgery has been described as the most prevalent class of surgical procedure in severe postoperative sepsis. The reasons for the increased rate of severe postoperative sepsis are unknown, but possible causes are an increase in the proportion of infections caused by resistant microorganisms and an increase in the comorbidities that predispose to sepsis.

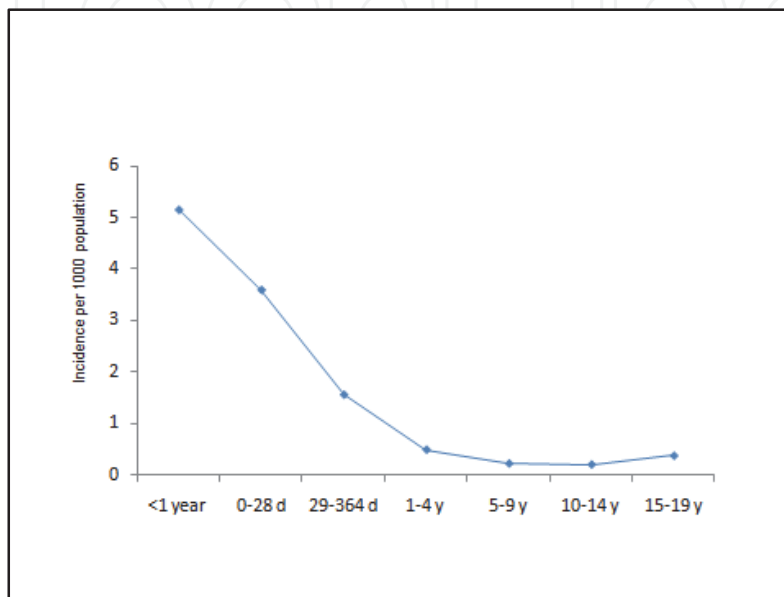


Fig. 3. Annual incidence of severe sepsis by age in the pediatric population of the United States (Modified from Watson RS et al. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med* 2003;167:695-701).

#### 4. Epidemiological data of patients

##### Age

There is a direct relationship between advanced age and the incidence of severe sepsis y septic shock, with a sharp increase in incidence in elderly people (Wang, 2007; Angus, 2001). The incidence of severe sepsis in infants is also elevated, with an annual rate of 5.3 cases per 1,000 population (Angus, 2001).

The median age of patients with severe sepsis in most studies is between 60 to 65 years, and when the patients are stratified at the age of 65, the relative risk for sepsis was 13 times higher for patients aged 65 and above. Martin et al (Martin, 2006) found that the incidence rates of sepsis increased 20.4% faster among older patients 65 years of age or older than among younger patients from 1979 to 2002 (mean increase per year, 11.5% versus 9.5%;  $P < .001$ ). Epidemiological studies analyzing data from the 1990s found an increased incidence of severe sepsis in young people, especially men in their thirties, which could be attributed to patients with human immunodeficiency virus related conditions. However, the better control of the HIV epidemic in developed countries is changing this trend.

Gram-negative microorganisms are more frequent in older patients than in younger patients. *Escherichia coli* has found to be the most common microorganism in patients older

than 65 years, whereas *Staphylococcus aureus* was the most frequent microorganism in younger patients with community acquired bacteremia (Diekema, 2002). Likewise, the source of infection has also been different among older patients with sepsis than among younger patients. Urinary tract infection is more frequently the source of sepsis in older patients than in younger patients.

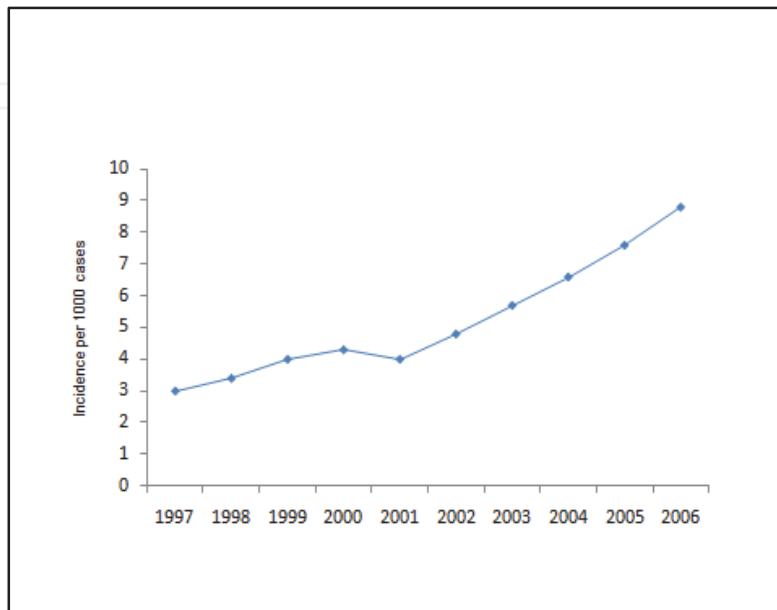


Fig. 4. Rate of severe postoperative sepsis after elective surgery by year (adapted from Bateman, *Anesthesiology* 2010).

The relationship between age and incidence of severe sepsis and septic shock in a series of 455 adult patients with these disorders admitted to an ICU at the Hospital Universitario Dr. Peset, in Valencia (Spain) is shown in **figure 5**.

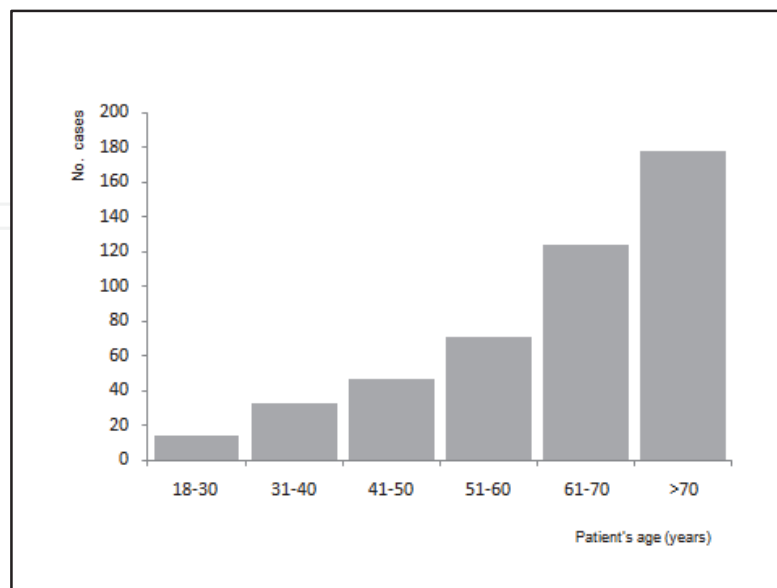


Fig. 5. Relationship between the incidence of severe sepsis and septic shock and patient's age in a series of 455 cases with these disorders admitted to ICU at the Hospital Universitario Dr. Peset, Valencia, Spain.

## Race

Epidemiologic studies have shown a higher incidence of severe sepsis and septic shock in black people, suggesting a possible genetic predisposition. Alternatively, a higher prevalence of renal disease and diabetes in the black population might explain the higher incidence of these syndromes (Mayr 2010; Martin 2003).

Besides, a higher incidence of severe sepsis and septic shock in black people could be related to the higher percentage of black people living in poverty. Otherwise, the mean age of black people has been found to be lower in black people than in white people.

A higher infection rate and a higher risk of acute organ dysfunction in black as compared to white individuals could explain racial differences in severe sepsis (Mayr 2010). Lastly, race specific genetic polymorphisms in the host response to infection may predispose certain racial groups to increased incidence or worse outcomes with sepsis (Berkowitz 2007).

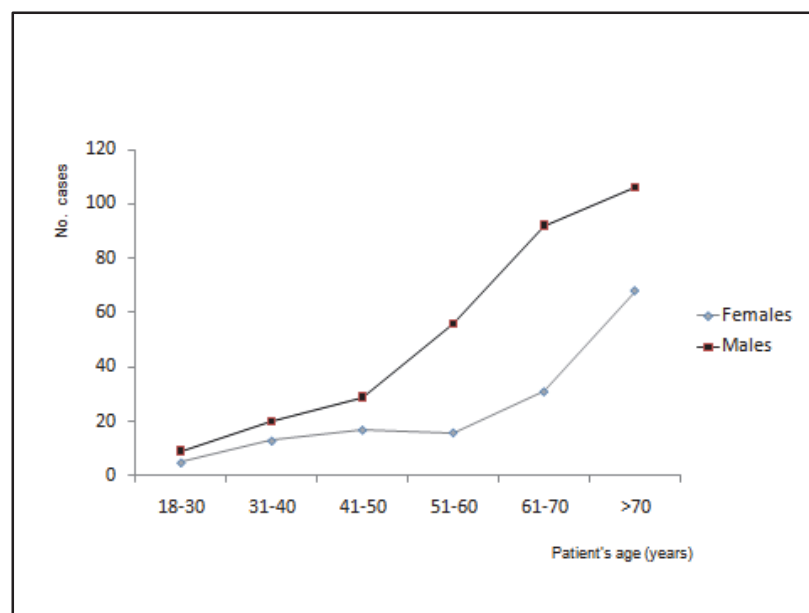


Fig. 6. Relationship between gender and the incidence of severe sepsis and septic shock according to the patient's age in a series of 455 cases with these disorders admitted to ICU (see text).

## Sex

Men are more likely than women to develop sepsis, with a mean annual relative risk of 1.28 (95% CI 1.24-1.32) (Martin, 2003). However, it is not clear whether this difference could be due to a higher prevalence of comorbidities in men, or whether women are protected against the inflammatory changes that occur in severe sepsis and septic shock (Angus, 2001).

2001; Martin, 2003). Female gender has been found to substantially decrease the risk for developing severe sepsis, independent of other patient and surgical risk factors, after elective surgery (Bateman, 2010).

In **figures 5 and 6** are shown the distribution of severe sepsis and septic shock according to gender and age in a series of 455 patients with these disorders admitted to an ICU at the Hospital Universitario Dr. Peset in Valencia (Spain).

The absence of a link between the incidence of severe sepsis and menopause argues against the gender differences being solely mediated through sex hormones. Also, women appear to have a lower rate of age-adjusted severe sepsis as a consequence of fewer episodes of respiratory origin (Angus 2001).

The sources of infections in severe sepsis are different between genders. Women are more likely than men to have genitourinary infections urinary tract infections, whereas men are more likely to have respiratory infections, but other sources of sepsis appears to have a similar distribution.

### Comorbidities

Patients with severe sepsis and septic shock frequently have underlying comorbidities which predispose them to infections and may have an additive contribution to mortality. McCabe classification has been widely used for assessing the severity of underlying diseases in patients with severe sepsis and septic shock.

McCabe Class	Frequency
0 = No underlying disease	27%
1 = Non-fatal disease or expected death within >5 years	33%
2 = Ultimately fatal disease or expected death within 1-5 years	30%
3 = Rapidly fatal disease or expected death within <1 year	10%

Table 4. Frequency of underlying diseases according to McCabe classification among patients with severe sepsis (adapted from Brun-Buisson et al, Care Med 2004).

Angus et al in a large observational study on severe sepsis (n=192,980) found that any underlying comorbidity occurred in 55.5% of cases, and the most prevalent coexisting conditions were chronic obstructive pulmonary disease (12.3%) and nonmetastatic neoplasm (11.6%) (Angus, 2001). Annane et al analyzed 8,251 cases of septic shock from 22 intensive care units and found a high proportion of patients having underlying disease with presumably reduced life expectancy (Annane, 2003). In this series the most common comorbidities were: Immune deficiency (21.9%), chronic pulmonary disease (9.2%) and hematologic malignancy (8.4%). Martin et al over a 22-year period identified 10,319,418 cases of sepsis with a proportion of organ failure in 33.6 percent of patients during the most recent subperiod, resulting in the identification of 184,060 cases of severe sepsis in 1995 and 256,033 in 2000. In this series the most frequent comorbidities were diabetes (12.2-18.7%), hypertension (7.0-18.6%), cancer (14.5-18.0%) and congestive heart failure (8.6-15.2%).

The coexisting conditions represented in observational studies (Zaragoza 2003 and Artero 2010) are probably more representative of those in all patients with severe sepsis and septic shock than are the conditions documented in participants in clinical trials, from which patients with certain medical conditions (e.g., HIV infection, or cancer) may be excluded. In our series of 455 patients with severe sepsis and septic shock admitted to ICU diabetes mellitus was the most prevalent comorbidity, followed by chronic heart failure and CPOD (See **table 5**).

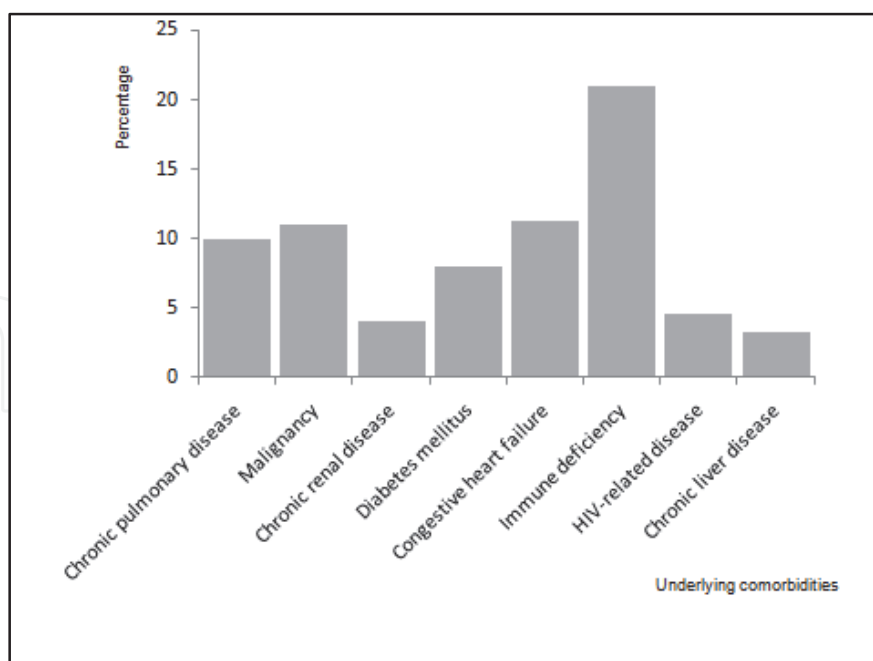


Fig. 7. Coexistent conditions in patients with severe sepsis and septic shock (adapted from several large observational studies).

## 5. Sources of severe sepsis and septic shock

The lung is the primary source of infection both in severe sepsis and in septic shock, followed by the abdomen, the urinary tract, soft tissues and primary blood stream infection (Annane 2003, Blanco 2008, Kumar 2010). The sites of infection in a series of 4,662 patients with septic shock is shown in **figure 8**, and the sites of infection in a cohort study of 192,980 cases of severe sepsis is shown in **figure 9**.

Comorbidities	Number	Percentage
Diabetes mellitus	102	22.4
COPD	81	17.8
Heart failure	99	21.7
Alcoholism	49	10.7
Malignancy	51	11.2
Liver cirrhosis	26	5.6
Chronic renal insufficiency	39	8.5
HIV	17	3.7

Table 5. Underlying comorbidities in 455 adult patients with severe sepsis and septic shock in an ICU.

Intra-abdominal and respiratory sources of sepsis have been considered as risk foci of infection, because these foci were associated with a higher mortality than other sources of sepsis. These foci have also been related to inadequate empirical antimicrobial treatment (Zaragoza, 2003).

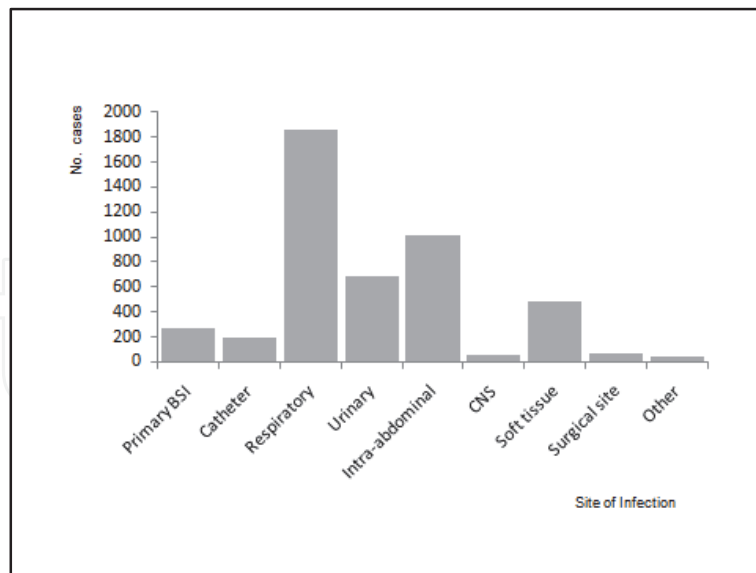


Fig. 8. Sources of septic shock (adapted from Kumar et al, Crit Care Med 2010; 38:1773–85).

## 6. Microorganisms that cause severe sepsis and septic shock

The proportion of severe sepsis and septic shock with unidentified pathogen is about one third. In some studies the infection was not documented in 40% of cases, possibly due to the increase in empiric antibiotic treatment (Guidet 2005). The percentage of positive blood culture increases with the severity of the sepsis syndrome.

Traditionally, Gram-negative bacilli - mostly represented by *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia* - were more prevalent than Gram-positive cocci - *Staphylococcus aureus*, *Streptococcus pneumonia*, *Enterococcus spp.* - . However, Gram-positive microorganisms have become the most common microorganisms isolated in the more recent

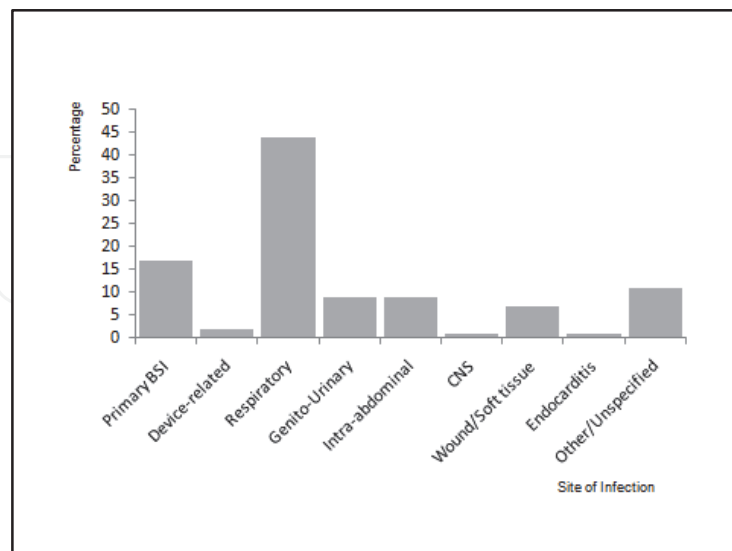


Fig. 9. Sources of severe sepsis (adapted from Angus et al, Crit Care Med 2001; 29:1303–10).

studies (Guidet, 2005). The percentage of polymicrobial infection as well as the proportion of multiresistant bacteria like *Pseudomonas* and methicillin-resistant *Staphylococci*, has

significantly increased over time (Annane 2003). The incidence of fungi has also been reported to be increasing in recent years.

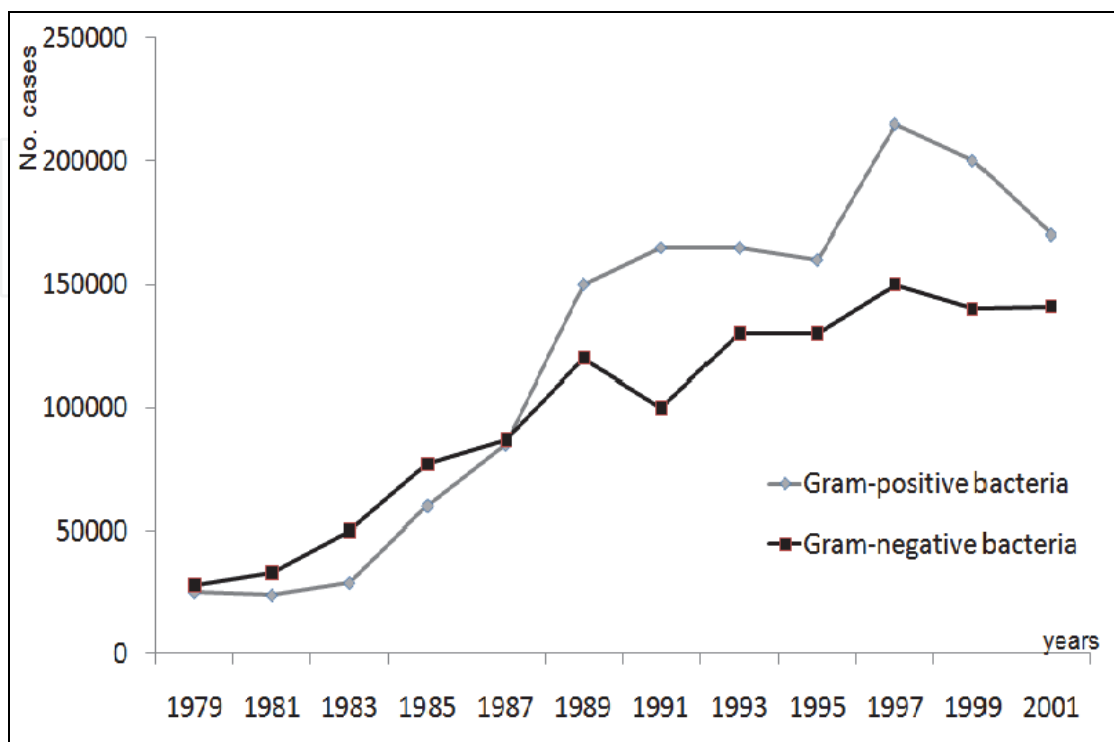


Fig. 10. Cases of severe sepsis according to the causative origin (adapted from Martin et al New Engl J Med 2003;348:1546-1554).

Age influence the etiology of severe sepsis and septic shock in the pediatric population. During the neonatal period the most frequent microorganisms isolated are group B streptococci and enteric bacilli, such as *Escherichia coli*. *Listeria monocytogenes*, enterococci, *Haemophilus influenzae*, and *Streptococcus pneumoniae* are less common pathogens isolated. The incidence of coagulase-negative staphylococci, *Staphylococcus aureus*, gram-negative bacilli, and fungi are increasing in the pediatric population as a consequence of the advances in neonatology. *S. pneumoniae*, *Neisseria meningitidis*, and *H. influenzae* type B are common pathogens beyond the neonatal period.

Immunodeficiency predispose children to some specific microorganisms, such as gram-negative bacteria, alpha-hemolytic streptococci, Viridans group streptococci and cytomegalovirus in neutropenic patients; *Streptococcus pneumoniae*, *P. aeruginosa*, *Staphylococcus aureus*, and *Haemophilus influenzae* type B in patients with acquired immunodeficiency virus; and *Streptococcus pneumoniae*, *Salmonella* spp., *Haemophilus influenzae* type B, and *N. meningitidis* in patients with asplenia.

## 7. Morbidity

Half of severe sepsis survivors are readmitted to hospital within a year, and their quality of life is comparable with survivors of polytrauma. Jagodič et al studied the long-term survival and quality of life of patients treated in a surgical ICU because of sepsis or trauma, and found that the quality of life (assessed after 2 years following ICU admission using the EuroQol 5D questionnaire) was reduced to the same level in both groups (see figure 12), and

82% of patients reported a problem (moderate or extreme) in at least one dimension of EuroQol 5D (Jagodič, 2006).

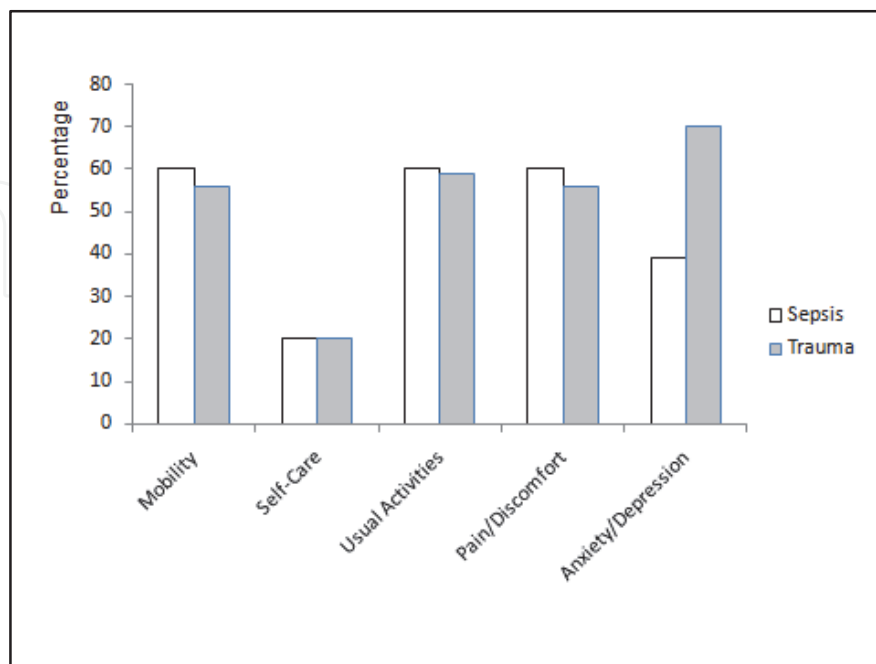


Fig. 11. Quality of life of 164 patients with sepsis or trauma after 2 years following ICU admission using the EuroQol 5D questionnaire (Jagodič et al, Crit Care 2006).

Acute respiratory distress syndrome, myocardial dysfunction, acute renal failure and chronic dysfunction, disseminated intravascular coagulation (DIC), and liver failure are all significant sequels of severe sepsis and septic shock. Furthermore, recent evidence shows that septic shock in elderly persons leads to significant long-term cognitive and functional disability as a consequence of prolonged tissue hypoperfusion (Iwashyna 2010).

## 8. Mortality

The Centers for Disease Control and Prevention has estimated that sepsis is the tenth leading cause of death overall in the United States (Hoyert 2001). Severe sepsis is considered to be the most common cause of death in noncoronary critical care units. The deaths related to severe sepsis exceed the numbers of persons with other diseases that attract higher public awareness, such as breast cancer and AIDS (Moss 2005). The mortality rates of severe sepsis and septic shock are 25 to 30% and 40 to 70%, respectively.

The mortality rate according to sepsis diagnostic criteria is shown in **figure 12**.

In this picture the global in-hospital mortality rate in 624 patients with sepsis syndromes admitted to the ICU in our hospital was 37.7%, 55.9% and 66.2% in sepsis, severe sepsis and septic shock, respectively. However the related mortality to infection was quite a few lower (7.7%, 16.7% and 30.1% in sepsis, severe sepsis and septic shock, respectively).

The crude mortality rate of septic shock is decreasing, but patients with septic shock still have a high excess risk of death than critically ill patients who are nonseptic. Annane et al in an epidemiological study analyzed 100,554 intensive care unit admissions on the Collège des Utilisateurs de Bases de données en Réanimation (CUB-Re'a) database, collected from



22 hospitals over a 8-year period, 1993 to 2000, and found an overall frequency of septic shock of 8.2 per 100 admissions, and a crude mortality of 60.1% and declined from 62.1% (in 1993) to 55.9 (in 2000) ( $p < 0.001$ ). As compared with matched intensive care unit admissions without sepsis, the excess risk of death due to septic shock was 25.7 (95% confidence interval, 24.0–27.3) and the matched odds ratio of death was 3.9 (95% confidence interval, 3.5–4.3) (Annane, 2003).

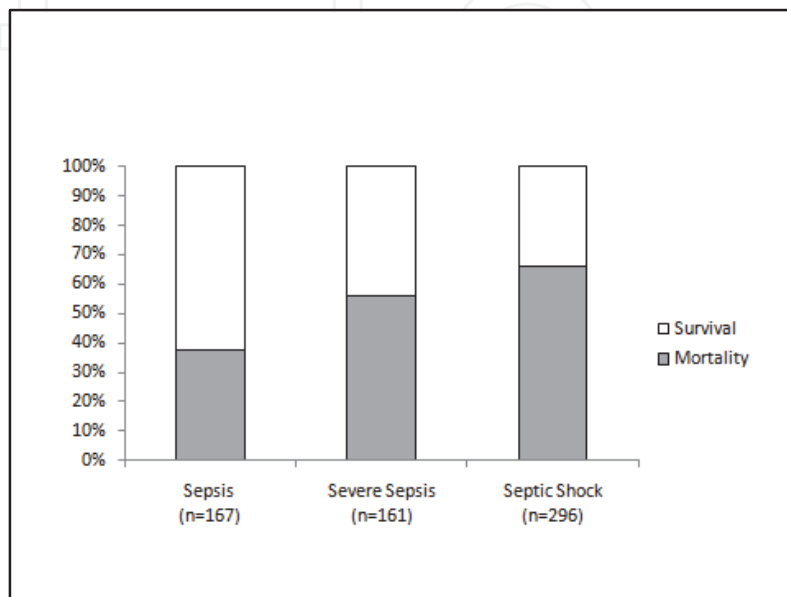


Fig. 12. Mortality rate according to sepsis diagnostic criteria.

The severity of severe sepsis and septic shock do not markedly depend on the source of infection or on its causative microorganism. On the contrary, mortality is directly related to the occurrence of organ failure in sepsis, and this relationship has remained consistent among patients of different races and sexes. However, organ failure scores may have difficulty quantifying the contribution that preexisting organ dysfunction adds to risk.

The patient's underlying comorbidities are directly related to mortality in several studies. The index of McCabe and Jackson is one of the most useful scores used in epidemiological and clinical studies to quantify underlying conditions. APACHE II, Simplified Acute Physiology Score (SAPS II) and the sequential organ failure assessments (SOFA) are prognostic scores based on bedside evaluation which are widely used to predict the prognosis of severe sepsis and septic shock.

The hospital mortality of severe sepsis is about 30% according to several studies, but this rate has been found much lower in children and previously healthy adults. Mirzanejad et al found that mortality from pneumococcal bacteremia varied from 3.2% in children to 43% in the elderly (Mirzanejad, 1996). This fact suggest attributable mortality of sepsis may be much less than the commonly observed 30% and that the mechanism by which sepsis causes death is highly dependent on individual patient factors, many of which may not be reversible by single antisepsis agents (Angus, 2001).

Patients with sepsis who had any organ failure have higher mortality. Besides, organ failure has a cumulative effect on outcomes: mortality in patients without organ failure is approximately 15 percent, whereas it reaches 70 percent in patients with three or more

failing organs (classified as having severe sepsis and septic shock). The organs that failed most frequently in patients with sepsis are shown in **figure 13**.

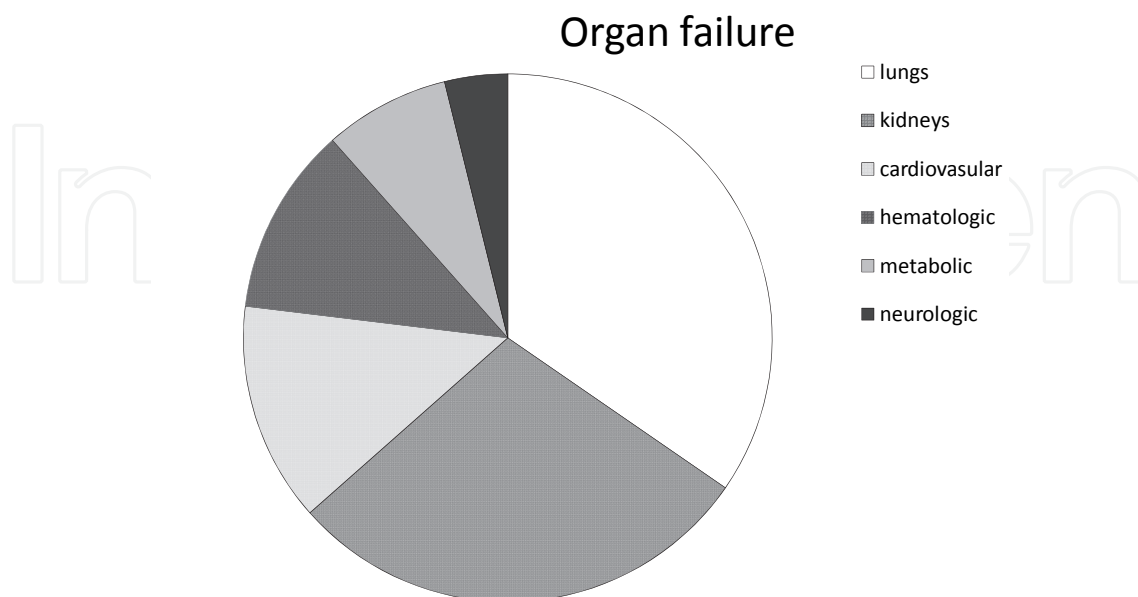


Fig. 13. Organs that fail most frequently in patients with sepsis.

Predictors of mortality in severe sepsis and septic shock in community acquired blood stream infections are shown in **table 3**. In this study (Artero 2010) the global mortality rate was 41.9%, 44.5% in community acquired septic shock and 34.4% in severe sepsis, and by univariate analysis, age, Acute Physiology and Chronic Health Evaluation II score, at least 3 organ dysfunctions, and albumin differed significantly between survivors and nonsurvivors. Acute Physiology and Chronic Health Evaluation II (odds ratio, 1.13; 95% confidence interval, 1.06-1.21) and albumin (odds ratio, 0.34; 95% confidence interval, 0.15-0.76) were independent predictors of global mortality in logistic regression analysis.

	Total (n=112)	Hospital Survivors (n=65)	Hospital Nonsurvivors (n=47)	OR (95%CI)	P
Mean age, y	63.5	61.0	67.1	1.02 (1.00-1.05)	.047
COPD	19	7	12	2.84 (1.02-7.89)	.045
Mean APACHE II	22.0	18.7	26.5	1.16 (1.08-1.23)	<.001
≥3 organ dysfunctions	56	19	37	3.70 (2.04-6.68)	<.001
Unknown source	15	5	10	3.24(1.02-10.23)	.045
Albumin <20g/L	27	10	17	2.85 (1.11-7.33)	.026

Table 6. Predictors of mortality in severe sepsis and septic shock in community acquired blood stream infections (Adapted from Artero et al, J Crit Care 2010).

Recent antibiotic exposure has been associated with increased hospital mortality in Gram-negative bacteremia complicated by severe sepsis or septic shock (Johnson, 2011). A likely explanation for the association between hospital mortality and prior antibiotic exposure is the greater degree of antimicrobial resistance in the causative pathogen(s) of patients receiving prior antibiotics. Clinicians caring for patients with severe sepsis or septic shock

should consider recent antibiotic exposure when formulating empiric antimicrobial regimens for suspected Gram-negative bacterial infection.

Boussekey et al in a five-year observational study in an ICU identified six independent mortality risk factors in septic shock: mechanical ventilation (OR = 4.97), Simplify Acute Physiology Score (SAPS) II > 60 (OR = 4.28), chronic alcoholism (OR = 3.38), age >65 years (OR = 2.65), prothrombin ratio <40% (OR = 2.37), and PaO<sub>2</sub>/FiO<sub>2</sub> ratio <150 (OR = 1.91). The identification of these risk factors recovered in the multivariate analysis can easily be available on admission and allow screening immediately a group of patients with a high mortality risk in septic shock (Boussekey, 2010).

Mortality of sepsis appears to be higher in ICU-acquired sepsis than in community-acquired sepsis. Vincet et al described a direct relationship between intensive care unit mortality rates for all patients and frequency of sepsis in various European countries (Vincent, 2006).

Winters et al performed a systematic review of studies reporting long-term mortality and quality-of-life data (>3 months) in patients with severe sepsis and septic shock using defined search criteria and found that patients with sepsis showed ongoing mortality up to 2 yrs and beyond after the standard 28-day in-hospital mortality end point. Patients with sepsis also had decrements in quality-of-life measures after hospital discharge (Winters, 2010).

## 9. Cost of care

The information on the cost of care of patients with severe sepsis and septic shock is quite scarce. The cost of care for patients with sepsis has been related to their length of stay in the intensive care unit and hospital. However, several studies have found that many patients with sepsis did not receive intensive care unit care. The length of stay for patients with severe sepsis has been reported to be twice higher than in sepsis (Brun-Buisson, 2004). The average total cost per intensive care unit day is estimated at approximately 1200 Euro for countries with a highly developed healthcare system (based on various studies conducted between 1989 and 2001 and converted at 2003 currency rates). US cost-of-illness studies focusing on direct costs per sepsis patient have yielded estimates of 34,000 Euro, whereas European studies have given lower cost estimates, ranging from 23,000 Euro to 29,000 Euro (Burchardi, 2004).

The introduction of new biotechnology products to treat patients with severe sepsis and septic shock should also be considered in cost analysis. In order to achieve the greatest benefits from these drugs they should be used in selected patients.

Indirect costs associated with severe sepsis account for 70-80% of costs and arise mainly from productivity losses due to mortality. Sepsis is an acute disease and so most studies of sepsis have been done in the hospital environment. However, other important factor related to the cost of care is the long-term sequels of sepsis, which unfortunately is not usually taken into account.

The cost of care of patients with sepsis presents notable variation among hospitals, and there is not good correlation between cost and mortality. Recently, Lagu et al in a large multicenter study analyzed data from 166,931 patients with sepsis found that hospital spending and adjusted mortality rates for patients with sepsis vary substantially, and higher hospital expenditures are not associated with better survival (Lagu, 2011).

## 10. Conclusion

Severe sepsis and septic shock have a significant and increasing impact on public health, and are one of the leading causes of mortality. Studies done in the last decades have shown

that the incidence of these syndromes has increased over the last thirty years, with an increasing number of deaths occurring despite a decline in overall in-hospital mortality.

The definitions of sepsis syndromes established in 1992 and 2001 have contributed to improve not only epidemiological research, but also bedside diagnosis. Severe sepsis is defined as the presence of sepsis (systemic inflammatory response + probable or confirmed infection); severe sepsis defined as sepsis + acute organ dysfunction, hypoperfusion abnormality, or transient hypotension, independent of other cause than sepsis; and septic shock is defined as sepsis + hypotension persisting for more than 1 hour despite adequate fluid resuscitation. The syndromes of sepsis can be seen as a continuum of severity that starts with an infection and can progress to septic shock. However, these definitions are not good enough tools to predict outcomes.

The epidemiology of severe sepsis and septic shock is not well known mainly due to the absence of population base prospective cohort studies. Reported rates of severe sepsis from different studies ranged from 50 to 104 per 100.000 population, with an incidence of 300/100.000 in a single study from the United States (Angus, 2001). However, the incidence of severe sepsis in this last study could have been overstated due to the authors used ICD-9-CM coding for the identification of the syndromes. The prevalence of severe sepsis and septic shock in patients admitted to intensive care units is 11-30% and 6-10%, respectively. Studies using data from admissions to emergency departments and intensive care units have also found increasing rates of severe sepsis and septic shock in the last decades.

The increasing aging of the population and the increased prevalence of underlying comorbidities in developed countries are the main variables influencing the incidence of severe sepsis and septic shock. The relative risk for sepsis is thirteen times higher for patients aged 65 and above than in younger patients. *Escherichia coli* has been found to be the most frequent microorganism in patients older than 65 years, and urinary tract infection the most frequent source of infection in older population. Patients with severe sepsis and septic shock frequently have coexisting conditions, such as chronic pulmonary diseases, immune deficiency, malignancy or diabetes mellitus. McCabe classification has been widely used in epidemiological studies to assess comorbidities which predispose patients to infections and may have an additive contribution to mortality.

Black people have a higher incidence of severe sepsis and septic shock than white people, and the age of black population with these disorders is lower than the age of white people. There is no consensus about whether the worse outcomes of black people with severe sepsis and septic shock is due to genetic factors or a higher prevalence of subjacent comorbidities in black population.

Men have a higher prevalence of severe sepsis and septic shock than women. The fact that this lower rate of sepsis syndromes observed in women is present over all range of age argues against the gender differences being solely mediated through sex hormones.

Respiratory infections are the major source of severe sepsis and septic shock, which is more prevalent in men than in women, followed by intra-abdominal infections, urinary tract infections and primary bloodstream infections. Respiratory infections and abdominal infections appear to have a worse prognosis than other foci.

Gram-positive cocci have become the most common microorganisms over the past decades, taking precedence over Gram-negative bacilli. The proportion of fungi and multiresistant bacteria (multiresistant *Pseudomonas* spp, methicillin-resistant *Staphylococci* ...) has significantly increased over the last few years, which has contributed to increase the rates of inappropriate empirical antimicrobial treatment.

The mortality rates of severe sepsis and septic shock are 25 to 30% and 40 to 70%, respectively. Sepsis is the tenth leading cause of overall death in the United States and severe sepsis is the most common cause of death in noncoronary critical care units. There are several independent risk factors of mortality of severe sepsis and septic shock. Among these, the number of organ failures (commonly assessed by SOFA), the underlying comorbidities and the severity of acute illness (APACHE II) are the most constantly identified in epidemiological studies. The quality of life of survival patients of sepsis assessed after 2 years from admission to intensive care unit is markedly reduced, with more than 80% of patients reporting a problem.

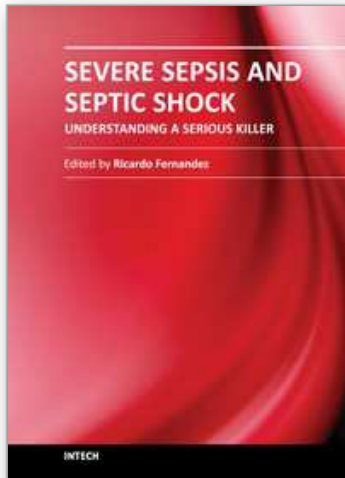
The direct cost of care for patients with severe sepsis is about 30,000 Euro, with notable variations among hospitals and without good relationship between cost and mortality. The length of stay in intensive care unit and hospital are the major determinants of cost. However, 75% of the global cost is dependent of indirect cost, which is mainly caused by productivity losses due to mortality. Besides, the cost of long-term sequels is not usually included in cost-effectiveness analysis of severe sepsis and septic shock.

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## **Severe Sepsis and Septic Shock - Understanding a Serious Killer**

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Despite recent advances in the management of severe sepsis and septic shock, this condition continues to be the leading cause of death worldwide. Some experts usually consider sepsis as one of the most challenging syndromes because of its multiple presentations and the variety of its complications. Various investigators from all over the world got their chance in this book to provide important information regarding this deadly disease. We hope that the efforts of these investigators will result in a useful way to continue with intense work and interest for the care of our patients.

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