# Epidemiologic trends of sepsis in western countries

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*Contributions:* (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** Since the American College of Chest Physicians (ACCP) and the Society of Critical care Medicine (SCCM) published the first consensus definition of syndromes related to sepsis in 1992, the knowledge of epidemiology of sepsis has clearly improved, although no prospective studies have been performed to analyse the incidence of sepsis in general population. There are differences in epidemiologic trends in sepsis between western countries and low-income and middle-income countries. In the United States (US), most of epidemiologic studies have been based on large, administrative databases, reporting an increase in the incidence of severe sepsis over years. In general, studies describing epidemiology of sepsis outside the US use clinical definitions and intensive care unit (ICU) observational cohort designs instead of administrative databases and definitions. Incidence of sepsis has increased over years, probably due to progressive aging of population, the existence of more comorbidities and maybe the liberal use of sepsis codification, by including patients with less severity. Notwithstanding, mortality due to sepsis is clearly decreasing over years, probably to improvement in ICU care, although absolute mortality is growing on account of the raise in incidence. Risk factors for sepsis are the two ends of life, male sex, US black race, presence of comorbidities and certain genetic variants. Respiratory tract infections are the most common source of sepsis, and, nowadays, Gram-positive infections are more frequent that Gram-negative sepsis in most prospective studies.

**Keywords:** Sepsis; severe sepsis; septic shock; epidemiology

Submitted Jul 31, 2016. Accepted for publication Aug 23, 2016.
doi: 10.21037/atm.2016.08.59
**View this article at:** http://dx.doi.org/10.21037/atm.2016.08.59

## Introduction

Patients that are admitted to hospital due to sepsis or develop sepsis during hospital stay require very frequently intensive care unit (ICU) admission, especially if organ dysfunction is present.

There are significant differences in epidemiologic trends in sepsis between western countries and low-income and middle-income countries. Indeed, we can find differences between pathogens involved in sepsis from geographic areas in western countries when these are compared to Asia and Latin America.

This work attempts to review the modern epidemiology of sepsis in western countries, including risk factors and clinical characteristics of affected population.

## Incidence of sepsis

The American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) published the first consensus definition of syndromes related to sepsis in 1992, defining the clinical criteria for systemic inflammatory response syndrome (SIRS), sepsis as SIRS in the presence of known or suspected infection, and severe sepsis and septic shock as the progression to organ dysfunction (1). Since then over the last two decades, the knowledge of epidemiology of sepsis has clearly improved. No prospective studies have been performed to analyse incidence of sepsis

in general population. The recent publication of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) should provide greater clarity and consistency for future epidemiologic studies (2).

In the United States (US), most of epidemiologic studies have been based on large, administrative databases. Several studies have defined sepsis cases using combinations of diagnostic codes on hospital discharge records (National Hospital Discharge Survey) and the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (9-CM).

The first report of epidemiology of sepsis in the US was performed by the Center for Disease Control and Prevention in 1990, before the consensus definition, estimating and increase of septicemia codes from 76 to 176 per 100,000 people from 1979 through 1987 (3).

More than a decade later, several studies estimated the incidence and mortality in sepsis (4-7). Angus *et al*. (4) reported and incidence of severe sepsis of 300 per 100,000 population in seven states in 1995. Martin *et al*. (5) observed an increase in the incidence or severe sepsis from 83 to 240 per 100,000 population from 1979 to 2000. Gaieski *et al*. (8), by applying these various definitions to a single national dataset from 2004 to 2009, reported a wide variation according to the employed definition, with similar average annual increase of 13%. One of the reasons that may explain these differences is the choice of ICD-9-CM codes. Angus *et al*. (4) used 1,286 codes indicating the infectious process, while Martin *et al*. (5) employed only six to identify systemic infection.

Wilhelms *et al*. (9) compared three strategies based on the ICD, Ninth and Tenth Revision (4,5,10), to estimate incidence of severe sepsis in Sweden between 1987 and 2005. Authors found three almost separate cohorts of patients, with an incidence of severe sepsis in 2005 ranging from 130 to 430/100,000 population, concluding that the ICD code abstraction strategies for recording severe sepsis provides an unsatisfactory way of estimating the true incidence of this entity. The incidence increased over the years in the three cohorts.

In general, studies describing epidemiology of sepsis outside the US use clinical definitions and ICU observational cohort designs instead of administrative databases and definitions. Finfer *et al*. (11) found an incidence of severe sepsis of 11.8% in a study performed in 23 ICUs in Australia and New Zealand. Results were similar in a French study that included 206 UCIs, with a reported incidence of 14.6% (12). In the SOAP study (13), that included 198 European ICUs, the average incidence of severe sepsis was 30%, with a wide range between countries. In a retrospective study performed in ICUs from the United Kingdom an incidence of 27.1% was reported during the first 24 h after ICU admission (14). Annane *et al*. (15) reported an increase in the incidence of septic shock from 7 to 9.7 cases per 100 admissions from 1993 to 2000.

Incidence of sepsis has clearly increased, probably due to progressive aging of population, provided that several studies have demonstrated a relationship between age and incidence of sepsis (4,5,16) and a larger number of people with disease comorbidities. Another possible contribution may be an increasing recognition and more frequent and liberal uses of sepsis codes after hospital discharge. In this way, one recent study compared the 2003 to 2012 trends in severe sepsis between administrative definitions and objective clinical markers, including positive blood cultures, vasopressors, and/or lactic acid levels (17), demonstrating a large increase (54–706%) in the rates of sepsis according to administrative definitions without a comparable increase in bacteremia, shock or lactic acidosis according to objective clinical data. Moreover, another study showed an 11% and a 49% increase in infection codes and sepsis codes, respectively, from 2003 and 2009 (18).

## Mortality

Sepsis mortality changes according to organ dysfunction. In patients without organ dysfunction mortality is less than 20% (5,19). In patients with severe sepsis varies between 20% and 50% (5,11,12,20,21) and in patients with septic shock is frequently over 50% (13,15). Variations in the definitions of severe sepsis can explain differences in mortality rates (1,22,23).

Different studies have demonstrated a decrease in mortality related to sepsis over years.

In US, mortality due to severe sepsis had a relative reduction of 51% from 1988 to 2012 (24). This trend has been corroborated in other studies (5,8,25).

Mortality due to severe sepsis in French ICUs decreased from 56% to 35% between 1993 and 2001 (12,26).

Compliance with Surviving Sepsis Campaign bundles may contribute to the decrease in mortality (27). With data from the Surviving Sepsis Campaign crude mortality rates were different between Europe and the US (41.1% *vs*. 28.3%). Nevertheless, when adjusted for disease severity, this difference disappeared (32.3% *vs*. 31.3%) (28), probably due to the effect of ICU bed availability.

 

In a recent retrospective study performed in 171 ICUs from Australia and New Zealand the authors demostrated a decrease in hospital mortality from 35% to 18.4% between 2000 and 2012 (20). This differences remained even after adjustments for disease severity.

Possible reasons for this decrease in mortality are improvements in diagnostic procedures, earlier and broader-spectrum antibiotic treatment, or more aggressive supportive therapy (27,29). In spite of the reduction in mortality, the absolute number of patients that die as a result of sepsis is increasing, on account of the raise in incidence (5). Concurrently to the decrease in mortality, average hospital stay of patients with sepsis has decreased over years. In the US, average stay was reduced in 5 days between 1979 to 2000 (5).

## Factors associated to sepsis

No cohort studies investigating prehospital risk factors have been performed, so risk factors have been based on administrative data and on hospital longitudinal studies.

### *Age*

Risk of sepsis is increased in infants, is reduced in the rest of childhood and is increased again beyond 50–60 years of age (bimodal distribution) (4,30-32). In the study performed by Martin *et al*. (5) the mean age of patients with sepsis increased from 57.4 years in the period 1979–1984 to 60.8 years in the 1995–2000 period. The same author reported that patients 65 years and older constituted 12% of the population but nearly 65% of sepsis cases. A multivariate analysis that was adjusted for comorbid conditions found that patients with sepsis that were aged 65 years or more had a mortality 2.3 times higher (32). The aging of the population probably explains the increasing incidence of sepsis in industrialized countries.

### *Sex*

Most of studies show a greater incidence of sepsis in male sex, ranging from 54% to 66% (10,11,13,14,21,25,26,30-32), what remains unexplained but may imply the effect of sexual hormones on immunity and on the cardiovascular response (33).

### *Race*

Probability of sepsis is 2-fold greater in the US black race (5,34,35) when compared with whites. Besides, sepsis has worse outcomes in this population (5,34). Possible reasons include different access to healthcare, immunizations, poverty, certain comorbid conditions and substance use disorders (35-37). However, these differences trend to persist after controlling many of these factors, suggesting the existence of genetic variables (36,38).

### *Comorbidities*

More than 50% of patients with severe sepsis present at least one comorbid illness (4,12,26). Likewise, comorbid illnesses independently increase mortality in this population (20). Diabetes mellitus, congestive heart failure, chronic pulmonary disease, immunosuppression, liver disease, cancer and chronic renal failure have been associated with sepsis (26,32,34,39,40). Alcohol consumption increases the risk of sepsis too (41).

### *Season*

The season is important in respiratory infections. Respiratory sepsis, but not other causes of sepsis, are more frequent in winter (42).

### *Genetic variants*

A study that included more than 1,000 people who had been adopted from de 1920s to the 1940s in Denmark showed and increased risk of death due to infection before the age of 50 if a biological parent died of an infectious cause (RR, 5.8; 95% CI: 2.4–13.7) (43).

Polymorphisms in toll-like receptor 4 (TLR4) and TLR1 seem to be associated with increased susceptibility to Gram-negative infections, bacteremia, candidemia and invasive aspergillosis (44-49). Recently, variants in *SVEP1* (which encodes a cell adhesion molecule) and in *FER* gene (a cytosolic protein thought to be involved in leukocyte recruitment) have been implicated in increased 28-day mortality in sepsis and in increased survival in patients with pneumonia, respectively (50,51).

## Infection characteristics

### *Source of infection*

Respiratory tract infections are the most common source of sepsis. In most studies performed in ICU patients the

 

rate of respiratory infection is over 50% (4,11,13,21,52). Respiratory infections are more frequent both in ICU patients and in patients outside the ICU (13,21). Abdominal infections are relatively more often in acquired infection outside the ICU.

Respiratory infection rates (as a cause for severe sepsis) seem to be increasing, whereas urinary source is decreasing in frequency (14).

### *Microbiology*

In the Extended Prevalence of Infection in Intensive Care (EPIC II) study 70% of infected patients had positive microbiology (52).

From 1979 to 2000 in the US, Gram-positive bacterial infections rates increased an average of 26% per year, being the predominant class of organisms associated to severe sepsis since 1987 (5). In 2000, Gram-positive bacteria were implicated in 52% of cases, whereas Gram-negative and fungal organisms constituted 38% and 5% of cases, respectively. Fungal infections increased 207% during this period.

At this time, Gram-positive infections are more frequent that Gram-negative sepsis in most prospective studies (11-13).

## Conclusions

Incidence of sepsis in western countries seems to be increasing over years, whereas mortality associated is clearly decreasing. However absolute mortality is growing on account of the raise in incidence. The progressive aging of population and improvements in ICU care may partially explain these results, although liberal use of sepsis codification may play a role too, by recording more number of patients with sepsis and with less severity.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Suarez De La Rica A, Gilsanz F, Maseda E. Epidemiologic trends of sepsis in western countries. Ann Transl Med 2016;4(17):325. doi: 10.21037/atm.2016.08.59

 