

WHAT CLINICIANS MAY LEARN FROM THE EPIDEMIOLOGY OF SEVERE SEPSIS SYNDROME?

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Introduction. Severe sepsis is now recognized as a common syndrome in intensive care units. Its mortality rate is very high and its incidence is increasing world-wide. Sepsis is a complex syndrome with marked heterogeneity of patients affected and wide variations of clinical signs and symptoms with bad outcome. Two decades ago (1991) an ACCP/SCCM consensus conference coined the term systemic inflammatory response syndrome (Bone 1992) and assumed sepsis as a continuum of three clinical stages with different clinical course and outcome : **mild sepsis, severe sepsis and septic shock**. In the past many clinical trials were conducted without clear understanding of natural history of sepsis. Sepsis means systemic inflammatory response syndrome (SIRS) to the infection with high sensitivity (according four SIRS criteria) but low specificity to identify septic patients. Severe sepsis remains a major challenge in medicine. Epidemiology of severe sepsis syndrome with precise and representative data are needed to evaluate frequency and outcome in different countries and health care systems. Epidemiological data may help in better definition of severe sepsis syndrome, in early recognition/diagnosis and improve patient care and allocation of health care resources. We analyzed more than twenty epidemiologic studies for better understanding of the sepsis syndrome. Majority of studies were conducted to define the epidemiology of the four classified syndromes describing the physiolo-

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gic response to infection: SIRS (non-infectious etiology like trauma, shock, ischemia-reperfusion, cardiopulmonary resuscitation), sepsis, severe sepsis (sepsis +MODS), and septic shock.

Methods. We analyzed three categories of epidemiologic studies: prospective cohort studies (Rangel- Frausto 1995, Sands 1997, Brun-Buisson 1995,2004, Alberti 2005, Záhorec 2005, Finfer 2004, Sprung 2006, Karlsson 2007, 2009, Kauss 2010), cross-sectional survey for observation of prevalence of sepsis syndrome (Vincent 1995, Ponce de Leon-Rosales 2000, Engel 2007, van Gestel 2004, Kubler 2007), retrospective analyses of coded hospital discharged diagnoses (Angus 2001, Padkin 2003, Martin 2003, Sundararajan 2005, H-N Shen 2010, Winters 2010). We compared the incidence, mortality and annual number of newly diagnosed cases of severe sepsis syndrome.

Results. The pivotal multicentric epidemiologic study conducted by Rangel-Frausto measured incidence and mortality of different stages of sepsis syndrome: mortality rate of the patients with SIRS was 10%, sepsis (16%) , severe sepsis (20%) and septic shock (46%). Post-hoc analysis of this natural history of sepsis published three years later clearly showed that sepsis is a very dynamic process, before admission and during ICU stay of sepsis patient. The etiopathology of sepsis syndrome is multifactorial: sepsis may start from non-infectious SIRS, or may be induced by community or nosocomial infection together with dysfunction of immune system caused by double /multi-hit supraphysiologic stressors. The individual course of each septic patient is modulated by genetic background, organ, cardiovascular and respiratory reserves. The priority of Rangel-Frausto observation is that each septic patient may go to the severe stages of sepsis and „back“ to the SIRS, eg. after intensive therapy from septic shock may continue to the mild sepsis or to the SIRS/CARS (Rangel-Frausto 1998). This observation was confirmed also by other prospective multinational multicentric cohort study conducted by Corine Alberti (2002, 2004). On the basis of the discharged diagnosis codes for bacteremia and septicemia, the Centres for Disease Control reported a dramatic increase in the incidence of sepsis over the last 15–20 yrs (Angus 2001, Teres 2002, Martin 2003, Shen 2010). Finfer et al. (2004) measured adult-population incidence of severe sepsis in Australian and New Zealand ICUs. This study has brought two original observations : 1.) severe sepsis is a dynamic clinical syndrome , 691 adult patients had 752 episodes of severe sepsis, a small group of patients had two or three cases of severe sepsis or septic shock during one hospital stay. 2.) 3847 ICU patients were classified

into four categories: SIRS patients without MODS (mild SIRS 44%, 1875 pts), SIRS patients with MODS (severe SIRS 26%, 912), patients with severe sepsis (26% , 691 pts). This approach clearly showed that patients with sepsis syndrome should be divided into the group of SIRS patients (non-infectious origin) and group of patients with sepsis (induced by invasive infection). This observation was supported recently by Shen (2010) searching the trends of severe sepsis in Taiwan. The first episodes of severe sepsis increased from 135 per 100,000 in 1997 to 217 per 100,000 in 2006. Among survivors 34% developed at least one subsequent severe sepsis episode. Our group conducted multicenter prospective epidemiologic study in 12 adult ICUs to investigate the number and outcomes of ICU patients who met precise criteria for severe sepsis (Zahorec 2005). We found 7.9% incidence of hospitalized critically ill patients. Mortality rate was 51.2%. Hospital mortality was associated with advanced age (over 60 years), number of failing organs (equal and more than 3 organs) and higher SOFA scores on admission to the ICU (SOFA score higher than 9 points). The SOFA score can be used for a precise diagnosis of severe sepsis syndrome (more than 4 points), and to evaluate the severity and prognosis. The annual incidence of severe sepsis is between 0.8–0.9 per million of inhabitants, 80–90 cases per 100,000 population (Zahorec 2005). Kauss et al. conducted prospective longitudinal study to find out incidence of SIRS and sepsis in ICU . During 2 years study period, 1,694 patients were admitted to the ICU. A total of 1,179 patients were analyzed, SIRS criteria were fulfilled in 1,048 patients (88.9%). Sepsis syndrome were diagnosed 554 patients (47%): mild sepsis 2.5%, severe sepsis had 269 patients (22.8%) and septic shock had 255 patients (21.6 %) with mortality rates 32% for mild sepsis, 49.9% for severe sepsis and 72.7% for septic shock (Kauss 2010). Some discrepancies in ICU incidence, hospital prevalence, mortality rate, and population incidence rates of severe sepsis per year can be explained by differences in inclusion criteria, health-care policy, and organization of health care in hospitals. Retrospective analyses of coded hospital discharged diagnoses may bring some errors and pitfalls (Shen 2010). Administrative databases are known to be subject to possible undercoding and/or overcoding errors. Regarding variability in the time course of organ dysfunction during ICU stay, it is difficult to differentiate whether it is sepsis related , therefore overestimation of the incidence is very likely , see Angus method (Angus 2001). The special item is long-life survival after hospital discharge. Several studies demonstrate that patients with sepsis, severe sepsis and septic shock, continue to die in the months and years after hospital discharge. Patients with sepsis also had additional decrements in quality of life measures over the long term (Winters 2010).

The mortality rate 1-year after hospital discharge in patients surviving first episode of severe sepsis ranged between + 7% to +33% at 12 months in 18 long-term studies (Winters 2010). Karlsson and Hofthuis have measured the QoL by using measurement tools SF-36 and EuroQoL-5D and found that septic patients had lower QoL scores before disease than did controls. This observation is in agreement with studies which confirm human genetic susceptibility to infection and sepsis (Brouwer 2009).

Tab. 1. Incidence and outcomes of patients with severe sepsis syndrome

Author	Country	Incidence in ICU	Mortality in hospital	Incidence per 100,000 /yrs
Rangel-Frausto 1995	USA	9.4 %	46 %	-
Martin G, 2003	USA	10.5 %	34 %	77
Padkin 2003	UK - G.B	27 %	46 %	51
Brun-Buisson 2004	France	14.6%	35 %	74
Finfer 2004	Australia New Zealand	11.6 %	37.5 %	77
Zahorec 2005	Slovak repub.	7.9 %	51 %	90
Engel 2006	Germany	11 %	55 %	110
Kubler 2007	Poland	16 %	54 %	67
Shen 2010	Taiwan	19%	31 %	135
Kauss 2010	Brasil	44 %	49,9 %	-

Discussion. Sepsis represents a clinical syndrome and not a disease. Three different stages of sepsis with increasing severity and mortality risk are not completely included in the International Code of Diseases, therefore epidemiology of severe sepsis is difficult to measure and can not be done retrospectively from coded hospital discharged diagnosis. Sepsis as a patho-physiologic response to the invasive infection, is a very dynamic syndrome when one patient may survive several attacks of severe sepsis or septic shock and may start or finish in SIRS /CARS during one hospital stay. Several items should be taken into account when we have analyzed some epidemiological studies: 1. sepsis is a clinical syndrome not a disease, the natural history of sepsis can be studied most effectively in prospective longitudinal studies,

2. SIRS (non-infectious) is a different etiopathological entity than sepsis

(infectious origin). 3. Three clinical stages of sepsis do exist: (mild) sepsis, severe sepsis and septic shock, with different morbidity and mortality rates. 4. Two clinical stages of SIRS exist: (mild) SIRS without organ dysfunction and severe SIRS (with MODS). 5. Biomarkers (procalcitonin and CRP) and SOFA score should be used on daily basis for early diagnosis, stratification and monitoring the severity of sepsis affliction, 6. the crude incidence of severe sepsis syndrome varies between 10–27% with high mortality rate (35–55%). 7. Mortality rates depends on the severity of the sepsis syndrome with MODS, as reflected by an increase in mortality from 20–30% in patients with one organ dysfunction to 77% in 3 or more organ dysfunction (Shen 2010). The number of dysfunctioning organs and SOFA score best reflecting the severity of sepsis syndrome. 8. The annual incidence rates of severe sepsis syndrome has varied from 60–240 cases per 100,000 adult population in different countries. 9. Longitudinal prospective studies may provide the information about long-term survival after hospital discharge (Karlsson 2009, Winters 2010). 10. Epidemiologic cohort studies may help health care professionals to evaluate the severity of severe sepsis syndrome and point out an increased resources use in adult patients population (Teres 2002, Martin 2003).

Syndrome of severe sepsis is a critical illness with a high mortality rate. Higher prevalence of sepsis syndrome is in male gender and older population (age over 45–50 years). Martin (2003), Zahorec (2005), Karlsson (2007) have shown that age is an independent risk factor for occurrence of sepsis and sepsis mortality. The mortality rate is tightly associated with the severity of organ dysfunction expressed by the number of failing organs and its severity measured by SOFA score or APACHE II score.

Conclusion. Sepsis syndrome is a frequent cause of intensive care unit admission and very often may develop in patients admitted to the ICU for other reasons with SIRS. The incidence and prevalence of sepsis has increased over the past two decades. The prognosis associated with severe sepsis and septic shock depends on the patient's underlying health status, development of adverse sequelae of the septic insult, genetic factors, the accurate therapy and prevention of complications. The aged population is more susceptible to suffer from this serious clinical syndrome. Increased morbidity and mortality from severe sepsis is associated with advanced aged, higher SOFA scores and number of organ failures. The goal of early causative and supportive therapy should be not only to survive sepsis episode, but to keep and maintain adequate quality of life.

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