Commentary

Severe sepsis epidemiology: sampling, selection, and society

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Related to *Research* by Silva *et al*., Flaatten and van Gestel *et al*., see page 292

Abstract

Three new articles in *Critical Care* add to an expanding body of information on the epidemiology of severe sepsis. Although there have been a range of approaches to estimate the incidence of severe sepsis, most studies report severe sepsis in about 10 ± 4% of ICU patients with a population incidence of 1 ± 0.5 cases per 1000. Importantly, the availability of ICU services may well determine the number of treated cases of severe sepsis, and it seems clear that these studies are reporting the treated incidence, not the incidence, of severe sepsis. In the future, we must focus on whether all severe sepsis should be treated, and, consequently, what level of ICU services is optimal.

Keywords epidemiology, prevalence, sepsis syndrome, septicemia, severe sepsis

In 1991 a consensus of international experts was reached that defined the syndrome of severe sepsis as the presence of infection, a systemic inflammatory response, and acute organ dysfunction [1]. Severe sepsis quickly became one of the defining 'diseases' of intensive care. An explosion in our understanding of the underlying pathophysiology led to a profusion of large multicenter trials of prospective agents in patients who met severe sepsis criteria. Entire tracks at national and international intensive care meetings were dedicated to sepsis, and, most recently, several intensive care professional societies launched a public and clinician educational effort, entitled the 'Surviving Sepsis' campaign (www.survivingsepsis.org) [2–4].

Despite this huge investment of time, funding, and expertise in severe sepsis, we were slower to understand some basic epidemiologic and health services research questions, such as population incidence, risk factors for the development and progression of disease, long-term outcomes, costs of care, and variation in practice patterns. This is now changing.

Three new articles published in *Critical Care* [5–7] add to an expanding body of information on the epidemiology of severe sepsis. These studies, together with several others reported in the past few years, highlight several issues that are worthy of further comment.

The three papers show the range of approaches to estimating severe sepsis incidence and the difficulties that arise in trying to compare results. The study conducted by van Gestel and coworkers [7] is a carefully crafted analysis of the prevalence of severe sepsis on 1 day (11 December 2001) in Dutch intensive care units (ICUs). Those investigators reported an incidence rate of 0.54 cases/1000 population, and found that 11% of ICU admissions have severe sepsis. The study nicely highlights the care required when generating annual estimates from a short observation period. Silva and colleagues [5] reported the results of a prospective multicenter ICU screening study conducted in Brazil over 9 months in 2001, in which they found an incidence density of 57 per 1000 patient-days and 27.3% of

ARDS = acute respiratory distress syndrome; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modifications; ICD-10 = International Classification of Diseases, 10th Revision; ICU = intensive care unit.

ICU admissions. Flatten [6] reported on a retrospective database study of hospital discharges using International Classification of Diseases, 10th Revision (ICD-10) codes for septicemia, estimating the incidence of sepsis (without acute organ dysfunction) and severe sepsis (with acute organ dysfunction) in a database that does not identify ICU use. The incidence for severe sepsis was 0.30% of hospitalizations and 0.47/1000 population. Summary results for these studies and the other published studies of the incidence of severe sepsis are shown in Table 1.

A number of other studies [8–11], like that reported by van Gestel and coworkers [7], sampled over a short time frame. In addition to the careful analysis needed to estimate population incidence as shown by van Gestel and coworkers, the results of such studies are susceptible to seasonal considerations. Seasonal variation is likely to be particularly problematic for severe sepsis arising from infections, such as community-acquired pneumonia.

Although most studies used prospective screening for the international consensus criteria for severe sepsis, the study by Flatten [6] and two others [12,13] used coded data in administrative databases to mirror the consensus criteria. Because the administrative data were collected and coded for other purposes, it is of paramount importance that validation exercises be used to ascertain the validity of the identification. Angus and coworkers [12] compared results of their selection with hospitals reported in the study by Sands and colleagues [9], and found similar incidence, ICU use, site of infection, resource use, and mortality. Martin and coworkers [13] conducted a validation study at a single hospital and found an excellent positive predictive value (97.7%) but a negative predicted value of only 80.0%. Coupled with the overall detection rate achieved with the criteria used by Martin and coworkers in their study population, this negative predictive value yields a sensitivity of only 18.8%, implying that the search missed four out of five cases of severe sepsis. This is not surprising because Martin and coworkers, like Flatten, looked only at a small subset of codes for infection to define sepsis. ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) codes prior to 2003 and ICD-10 codes, while using the term 'sepsis' in their indices and names, do not have codes that correspond to the consensus definitions of sepsis and severe sepsis. In 2003, codes for sepsis and severe sepsis (995.91 for sepsis and 995.92 for severe sepsis) were introduced in the USA for the first time. However, these codes are not yet in common use. Correcting the findings reported by Martin and colleagues for the poor sensitivity yields an overall incidence of 4/1000 population for hospital severe sepsis – a result close to that reported by Angus and coworkers [12]. Unfortunately, Flatten [6] did not include any validation exercise, making it difficult to place that result in context with other measurements. Finally, neither Flatten nor Martin and colleagues reported findings that apply to ICU severe sepsis, further limiting comparability.

Perhaps the most important confounder in our understanding of the incidence of severe sepsis is that all our measurements in the ICU relate not to the incidence of severe sepsis but to its *treated* incidence. This is an important distinction that has long been known in the cancer community. There can be large differences between the number of people with a cancer and the number being treated in a given time period. Thus, cancer epidemiologists distinguish between cancer prevalence, which is often difficult to determine, and cancer treated prevalence. Although an unknown incidence of severe sepsis might be the same in all developed countries, the choices we make regarding who to treat in hospital or admit to an ICU for advanced life support would generate very different treated incidence rates. To meet severe sepsis criteria, organ dysfunction must be detected and treated. Because the detection and treatment takes place predominantly in ICUs, countries with fewer ICU beds will probably have lower treated incidence rates. For example, an elderly patient who develops a stroke, complicated by pneumonia, will not be coded as having severe sepsis if she dies at home but will be coded as having severe sepsis if intubated and admitted to the ICU.

Most studies have expressed 'incidence' as the number of cases per 100 ICU admissions. With the exception of two studies, most reported rates of about 10 ± 4 cases/100 ICU admissions. This rate is remarkably stable and consistent across studies using prospective criteria or retrospective selection. However, the studies from the UK [14] and Brazil [5] report much higher rates. It is likely that this reflects a scarcity of ICU beds in these countries, with less access to intensive care for less sick patients, such as routine postoperative patients. Indeed, comparison of overall ICU populations between the UK and the USA, for example, suggests that far more lower risk patients are admitted to ICUs in the USA, with lower use of organ support, such as mechanical ventilation, and lower mortality rates [15–19]. Thus, the ICU occurrence rates for severe sepsis are probably higher in the UK and Brazil because the ICU beds are reserved only for very sick patients, such as those with sepsis and multisystem organ failure. However, at the same time, treated incidence rates at the population level may be lower than elsewhere.

The idea that ICU bed availability affects the incidence of severe sepsis is probably also true for related conditions, such as the acute respiratory distress syndrome (ARDS). A country that aggressively manages elderly patients with pneumonia will probably have a higher incidence of ARDS than a country with scarce ICU beds and a philosophy of providing less aggressive care to very elderly, moribund patients. Using similar methodologies, a Scandinavian study

Table 1

Comparison of epidemiologic studies of severe sepsis

			Methods				Results for severe sepsis in the ICU						
Reference	Year	Region	Design	Case identification	Time frame	Sampling frame	No. of patients screened	No. of cases identified	Age (years; mean)	Sex (% male)	% of ICU ads	Pop. incid.	Hospital mortality (%)
[22]	1995	Italy	Prospective	Consensus criteria	April 1993–March 1994	First 3 cases each month in 99 ICUs in northern Italy	1101	128	NA	NA	11.6	NA	52.2[a]
[8]	1995	France	Prospective	Consensus criteria	January–February 1993	All cases in 170 medical ICUs	11,828	742	61.4	63	6.3	NA	59
[23]	1995	USA	Prospective	Consensus criteria	August 1992–April 1993	All cases in 3 ICUs and 3 floors in one hospital	3708[b]	467	55.1[b]	60[b]	12.6[b]	NA	20[b]
[9]	1997	USA	Prospective	Consensus criteria	January 1993–April 1994	All ICU patients and all floor patients with blood cultures at 8 hospitals	9763	990	59[b] (median)	56[a]	10.1	NA	34[b] (28-day)
[12]	2001	USA	Retrospective	ICD-9-CM codes representing Consensus criteria	1995	All cases at all hospitals ($n = 936$) in 7 US states	880,473	98,613	63.8[b]	49.6[b]	11.2	1.53/1000	34.1
[14]	2003	UK	Retrospective	Consensus criteria	December 1995–February 2000	All cases on day 1 in 91 ICUs in national registry	56,673	15,362	65 (median)	54.3	27.1	0.51/1000	47.3
[24]	2003	USA	Retrospective	Consensus criteria	1998–1999	All cases on day 1 in 50 ICUs in Project IMPACT	21,480	2434	63.6	NA	11.3	NA	36.3
[25]	2003	Europe, Canada, Israel	Prospective	Consensus criteria	May 1997–May 1998	All cases in 28 ICUs	14,364	2124	NA	NA	14.8	NA	19.6–49.3 in subgroups
[13]	2003	USA	Retrospective	ICD-9-CM code for septicemia only	1979–2000	NHDS, a 1% subset of all US hospital admissions	750 M[b]	10.3 M[b]	57.4–60.8[b] (1979–2000)	49.6–46.8[b] (1979–2000)	NA	NA	27.8–17.9[b]
[10]	2004	France	Prospective	Consensus criteria	2 weeks in November–December 2001	All cases in 206 ICUs	3738	546	65 (median)	66.9	14.6	NA	41.9 at 2 2 months
[11]	2004	Australia/NZ	Prospective	Consensus criteria	May–August 1999	All cases in 23 ICUs	5878	691	60.7	56.9	11.8	0.77/1000	37.5
[7]	2004	Netherlands	Prospective	Consensus criteria	24 hours in December 2001	All cases in 47 ICUs	455	134	64	63	11	0.54/1000	NA
[6]	2004	Norway	Retrospective	ICD-10-CM codes representing Consensus criteria	1999	All cases in all Norwegian hospitals	NA		57.9	NA	NA	0.47/1000	27
[5]	2004	Brazil	Prospective	Consensus criteria	8 months in May 2001–January 2002	5 ICUs	1383	241	66.2 median, all septic patients	NA	17.4	NA	46.9

[a]Mortality rate was reported only for patients admitted with severe sepsis to the intensive care unit (ICU) but not for those who developed severe sepsis later. [b]Results are for all patients (both ICU and non-ICU) with severe sepsis in the study. ads, admissions; Pop. incid., population incodence; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; Project IMPACT, A proprietary dataset of Cerner Corporation, which contains organisational, patient-care and outcome data for over 100 ICUs in US and Latin America; NHDS, US National Hospital Discharge Survey.

reported a population ARDS incidence of 13.5 cases/100,000 [20], while a US study reported a much higher incidence of 53 cases/100,000 [21]. In the US severe sepsis study conducted by Angus and coworkers [12], the incidence of severe sepsis was predominantly in the very old, such that the average age of their cohort was 63.8 years despite the fact that they included children and neonates. This suggests that the USA may have many elderly ICU patients with severe sepsis who would never be admitted to the ICU, and consequently never develop established severe sepsis, if they were treated in other countries.

There are five studies that generated population incidence rates, quoting a range from 0.5 to 1.5 cases/1000 persons. This magnitude of variation is narrower than that reported in ICU occurrence rates if all studies are included, but remarkably similar to the variation from 6–14 cases/100 ICU admissions if one excludes the two very high ICU rates from the UK and Brazil. It is also very similar to the variation in ARDS incidence between countries. Given that approaches for measuring these conditions have become increasingly standardized, it seems likely that the variation is not methodologic but rather reflects differences in treated incidence, driven by differences in the provision of ICU services.

In summary, in a relatively short time span, we now have a large array of national epidemiologic studies of severe sepsis. Although studies from developing nations are still lacking, and although there are some differences in approaches across studies, the most dominant feature is the consistency of methods and findings. In most countries, about one in 10 ICU patients have severe sepsis. However, there is a threefold variation, and some countries with much higher rates, probably representing fewer ICU resources. The availability of ICU resources drives the treated incidence of severe sepsis, and variation in availability probably explains the variation in population incidence. We would favor adopting from oncology the terminology of treated incidence, because this better describes the rates reported in these studies. The next step is to address the consequences of different treated incidence rates between countries. A higher rate reflects more care but not necessarily better care. As we strive to raise awareness of sepsis in the public conscience, we must also expect debate from all sides about 'whither to treat'. Indeed, when thinking about the patients who might have manifested severe sepsis if admitted to the ICU, the words of the prominent sepsis researcher, John Marshall, come to mind: 'What was the old name for severe sepsis? Natural causes.'

Competing interests

None declared.

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