The epidemiology of sepsis — is Australasia different?

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ABSTRACT

Sepsis is a common reason for intensive care unit admission and a leading cause of mortality. Recent prospective randomised controlled trials have shown improved outcomes for patients with severe sepsis. Implementation of these findings into clinical practice has varied. Reasons appear complex but may include regional differences in the epidemiology of sepsis. To improve clinicians' understanding of sepsis, multiple epidemiological studies have been performed in the past 15 years. Differences in study populations and methodology make comparison difficult. After allowing for these differences, it is likely that the percentage of patients with severe sepsis in ICUs is less in Australasia than in many other developed nations. However, the population incidence, mortality, site and causative agent of infection are probably similar. This suggests that treatments and strategies whose efficacy has been demonstrated in other jurisdictions will also be effective in Australasia.

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In the past decade, three randomised controlled trials — one multicentre[1] and two single centre[2,3] — have demonstrated decreased mortality in patients with severe sepsis admitted to critical care units. Clinicians have also seen the development of guidelines[4] and implementation strategies.[5] These strategies have been adopted and actively promoted in the United States by the Institute for Healthcare Improvement.

Theoretically, if the epidemiology and nature of sepsis varies across borders or continents, then so may the impact of treatments and quality improvement interventions, and guidelines may need to be tailored to particular populations. Accordingly, over the past 15 years, epidemiological evaluations of sepsis have been performed using data sets,[6-11] prospective cohort[12-18] or point prevalence[19,20] designs. These have been facilitated by the publication of agreed definitions of sepsis, severe sepsis and septic shock.[21] These studies were performed with the aim of providing clinicians with a better understanding of the incidence, cost and outcomes of sepsis. This article reviews our current knowledge of the epidemiology of sepsis, and asks: are Australia and New Zealand different?

Australia and New Zealand

The only published data for Australia and New Zealand are now nearly 7 years old and were provided by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG).[12] Twenty-three intensive care units (ICUs) from 21 hospitals participated in an inception cohort study that was designed to calculate the population incidence of severe sepsis in adult patients treated in Australian and New Zealand ICUs. This represented about 12% of all Australasian ICUs. The study was conducted over 3 months from May to July 1999.

In this period, there were 5878 admissions. Of these, 3547 admissions incorporating 3338 patients were screened daily for sepsis. The remaining 2331 admissions were scheduled postoperative admissions where duration of ICU stay was less than 48 hours, and severe sepsis or other complications did not develop. There were 752 episodes of severe sepsis identified in 691 patients, equating to 11.8 patients with severe sepsis per 100 ICU admissions (95% CI, 10.9–12.6). The population incidence of severe sepsis was 0.77 patients per 1000 population (95% CI, 0.76–0.79). This number was derived from the frequency of severe sepsis in the study population, total number of adult ICU admissions in the period 1 July 1999 to 30 June 2000 (data sourced from a central registry) and national census data.

In the cohort of 691 patients with severe sepsis, the timing and source of infection and causative organism were also recorded. Pulmonary infections accounted for just over 50% of all sepsis episodes. The next two most common sites of infection were intra-abdominal (19.3%) and blood (10.1%). No other site accounted for more than 10% of the total sepsis episodes. In 610 of 752 episodes (81%), sepsis was present on ICU admission; fewer than 20% of cases were acquired in the ICU. Infection was confirmed by positive culture in about 58% of episodes. Of the organisms cultured, 48.3% were gram-positive and 38.5% gram-negative; other organisms, including yeasts, fungi, legionellae and mycobacteria accounted for the remaining 13.2%. Patient outcome data were also reported. Patients with severe sepsis had a median ICU length of stay of 6 days and an ICU mortality of 26.5%. The 28-day mortality was 32.4%, and in-hospital mortality was 37.5%.

As the authors noted, this study was limited to patients with sepsis in the ICU, and it is possible that other patients

Table 1. Percentage of patients with sepsis and severe sepsis in intensive care units and mortality for all patients with sepsis

	% of ICU patients with		Mortality (%)	
Country or region	Sepsis	Severe sepsis	ICU	Hospital
Australia and NZ[12]	NR	19	26.5*	37.5*
Brazil[15]	30	17	NR	47
Europe[14]				
Austria	38	27	23	31
Belgium	27	18	21	31
Eastern Europe	48	43	24	31
France	41	30	27	32
Germany	31	24	16	20
Greece	43	38	30	34
Italy	38	32	35	45
The Netherlands	39	34	32	47
Portugal	73	64	32	38
Scandinavia	35	25	19	39
Spain	35	28	30	38
UK and Ireland	52	45	27*	36*
Average	**40.8**	**32.6**	**26.3**	**36.2**

* Mortality limited to patients with severe sepsis.
NR = not reported. NZ = New Zealand. UK = United Kingdom. ◆

with severe sepsis were treated outside the ICU. Also, the calculations assumed admissions to the 23 participating ICUs were representative of all adult patients admitted to Australasian ICUs. Despite these limitations, the study's methodology was strong, and it provides the best available data on the epidemiology of sepsis in Australia and New Zealand.

Europe

More has been published in the past 15 years on the epidemiology of sepsis in Europe than any other region. A literature search revealed 12 studies: nine were national[7,9-11,17,18,20,22,23] and three international.[13,14,19] The largest observational cohort study is the Sepsis Occurrence in Acutely Ill Patients (SOAP) study.[14] This study was performed over a 2-week period in May 2002 in 198 ICUs in 24 European countries, and enrolled 3147 patients. Cardiovascular, respiratory and neurological diagnoses accounted for 32%, 19% and 16% of admissions, respectively. Thirty per cent of patients (930) had a diagnosis of severe sepsis. These patients had an ICU mortality of 32.2%; hospital mortality was not reported for this group. The rate of ICU-acquired sepsis was 23.7%. In about 60% of sepsis episodes, an organism was identified: 40% gram-positive organisms, 40% gram-negative, and the remainder polymicrobial, fungal and other infectious agents. The incidence of sepsis varied markedly between European countries; the ICU mortality rate correlated with incidence of sepsis.

In a French study published in 2004 (the EPISEPSIS study[23]), the rate of severe sepsis was only 15%. However, this study included elective postoperative patients, contributing to the apparent dramatic decrease in the prevalence compared with the SOAP study. The population incidence of severe sepsis was not calculated in this study.

An article describing the epidemiology of severe sepsis in England, Wales and Northern Ireland was published recently.[10] Rather than an observational cohort study, this was an interrogation of the Intensive Care National Audit and Research Centre Case Mix Programme Database, analysing the period December 1996 to January 2005. During this period, there were over 343 000 admissions to the 172 participating ICUs. The incidence of severe sepsis in the first 24 hours after ICU admission was 27%. Interestingly, when considered annually, the incidence of severe sepsis during the first 24 hours rose, from 23.5% (1996) to 28.7% (2004), while hospital mortality fell, from 48.3% (1996) to 44.7% (2004). The increase in incidence meant that, despite a reduction in mortality, the estimated total number of patients dying with sepsis increased by about 5000. The treated incidence of severe sepsis per 100 000 population rose from 46 in 1996 to 66 in 2003. These longitudinal data support the argument that the incidence of severe sepsis being treated in ICUs is increasing. Causative organisms were not described in this study.

North America

In contrast to the mixture of observational cohort and database studies performed in European ICUs, North American investigators have focused on analysis of administrative datasets of hospitalised patients.[6,8] The only recent observational study performed in ICU patients was conducted 12 years ago in eight centres.[16] The largest administrative dataset analysis of patients with severe sepsis was published by Martin et al in 2003.[8] This retrospective study reviewed discharge data of about 750 million hospitalisations in the US over 22 years and identified over 10 million cases of sepsis. It reported an annualised increase in the incidence of sepsis of 8.7%, from about 164 000 cases in 1979 (82.7 per 100 000 population) to nearly 600 000 in 2000 (240.4 per 100 000). Similar to the United Kingdom data,[10] the in-hospital mortality from sepsis fell over the study period: from 27.8% during the period 1979–1984 to 17.9% during 1995–2000. This study also reported an increase in

Table 2. Reported population incidence of severe sepsis

Country or region	Year	Incidence (per 1000 population)
Australia and New Zealand[12]	1999	0.77
United States[6]	1995	3
United States[8]	2000	2.4
Norway[22]	1999	1.49
France[23]	2001	0.95
The Netherlands[20]	2001	0.54
England, Wales, Northern Ireland[10]	2003	0.66

the number of gram-positive infections, with over 50% of infections in 1995–2000 related to gram-positive organisms, contrasting with over 50% caused by gram-negative organisms in the period 1979–1984.

A global comparison?

The comparison of epidemiological studies is complicated by the differing methodologies, populations and definitions used. These include differences in the diagnostic criteria for sepsis used for prospective cohorts versus hospital discharge data, differences in critical-care bed availability nationally and in individual hospitals, and differences in patient populations (all hospitalisations, all critical-care admissions, or only cases of severe sepsis within the first 24 hours of ICU admission).[24]

Nevertheless, some consistent themes emerge:

- the incidence of sepsis is increasing;
- the mortality of sepsis is decreasing; and
- gram-positive organisms account for most infections requiring hospital treatment.

Does the incidence of severe sepsis vary between countries, regions, and continents? Table 1 presents information from recent observational cohort studies in three continents — Australasia,[12] Europe[14] and South America[15] — on the percentage of ICU patients with severe sepsis (length of stay over 24 hours), ICU mortality and hospital mortality. The percentage of patients with severe sepsis in Australasian ICUs (19%) is less than the international average (32.6%), while the mortality of patients with sepsis is close to the international averages. Methodological differences and the lack of adjustment for severity of illness preclude formal comparison between studies. Despite this limitation, these data suggest that the incidence of severe sepsis in Australasian ICUs may be less than in other regions, but that its effect on mortality is similar.

The population incidence of severe sepsis is compared between Europe,[10,20,22,23] Australasia[12] and the US[6,8] in Table 2. Angus et al[6] calculated the national incidence of sepsis in the US at 3 per 1000 population. Martin et al, using similar but refined methodology (ICD-9 discharge codes of all hospital admissions), subsequently reported an incidence in the US of 2.4 per 1000 population.[8] In Norway, Flaatten[22] used similar methodology and demonstrated population incidence of 1.49 per 1000 population. These estimates are substantially greater than those reported in ICU cohort studies suggesting that analyses using discharge criteria overestimate the true population incidence of sepsis. The Australasian,[12] UK[10] and Dutch[20] studies showed the lowest population incidence of severe sepsis. In contrast to the studies of Martin et al,[8] Angus et al,[6] and Flaatten,[22] these studies included only patients with severe sepsis in ICUs. It is therefore possible that ICU cohort studies underestimate the true incidence of severe sepsis. After consideration of the strengths and weaknesses of all studies, it appears that the population incidence of severe sepsis in Australia and New Zealand is similar to that in the US, UK and other parts of Europe. The data suggest this is around 1 per 1000 population.

The reported incidence of severe sepsis per 100 ICU admissions[9,10,18,25,26] is shown in Table 3. The incidence in Australasia is similar to that in other countries, with the exception of that found in the two recent UK studies.[9,10] These were retrospective database analyses, while the other studies were all observational cohort studies. This may partly explain the dramatic difference in incidence between the UK and the other regions.

What about the site and nature of infection? Again, Australasia does not appear unique, with pulmonary and abdominal infections accounting for most observed cases of severe sepsis. As in the recent SOAP study,[14] infection is confirmed microbiologically in about 60% of patients with severe sepsis in Australasia. Also, similarly to other studies, gram-positive organisms are now implicated in over 50% of serious infections occurring in the ICU.

Table 3. Reported incidence of severe sepsis per 100 intensive care unit admissions

Country or region	Year	Severe sepsis (per 100 ICU admissions)
Australia and New Zealand[12]	1999	11.8
Italy[18]	1995	11.6
United States[25]	1995	11.8
France[26]	1995	15.3
United Kingdom[9]	2003	27.1
United Kingdom[10]	2004	28.7

Conclusion

In contrast to other regions, Australasia has had only one high-quality epidemiological study of sepsis. Despite differences in study methodology, comparison between continents, regions and countries is possible, with some consistent themes emerging:

- severe sepsis represents a substantial health-care burden in all developed nations;
- the overall incidence is increasing;
- the overall mortality rate is declining; and
- the nature of infections is changing, with infections caused by gram-positive organisms increasing in frequency.

The available data suggest that the population incidence, mortality, sites and causative agents of severe sepsis do not differ significantly between Australasia and the rest of the world. Accordingly, strategies and therapies for the management of severe sepsis which have been demonstrated to be effective in other regions should be utilised in Australasia.

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