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Severe Sepsis: A Science of Uncertainty [version 1; referees: not peer reviewed]

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Abstract

An evaluation of a recent study by Kaukonen KM, Bailey M, Suzuki S *et al*: **Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012**. *JAMA* 2014, 311(13):13081316.

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Critique of:

Citation

Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R: **Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012.** *JAMA* 2014, **311**(13):13081316.

Background

Severe sepsis and septic shock are major causes of mortality in intensive care unit (ICU) patients. This study analyzed changes in incidence of severe sepsis and septic shock over time (2000 to 2012) in ICU's across New Zealand and Australia. The study also analyzed mortality rate and discharge to home for these patients. Analysis was made using international consensus conference definitions for severe sepsis, objective definitions of acute organ failure and sensitivity analysis. Authors further used APACHE III scores, treatment facility type and location, age and source and type of infection to further analyze the data.

Methods

The authors studied all patients (101,064) with severe sepsis during the time period from January 1, 2000 through December 31, 2012 in Australia and New Zealand. All hospital outcomes were analyzed including mortality, discharge to rehabilitation, discharge home and discharge to other hospital at 30 days. Subgroup analysis was performed on said patients to include severe sepsis and septic shock, APACHE II or APACHE III scores, operative admission, medical admission, renal failure, respiratory failure, age groups, sepsis with or without shock source urinary in nature and sepsis with or without shock source non-urinary in nature.

Objective

To describe changes in mortality for severe sepsis with and without shock in adult ICU patients. To assess and trend number of severe sepsis cases per year. Subgroup analyses were planned in younger patient's (<45 yrs), UTI vs. other causes, surgical vs. medical patients and patients by APACHE scores.

Design

Retrospective, observational study.

Setting

Over 90% of adult ICU admissions with severe sepsis in Australia and New Zealand from January 1, 2000 to December 31, 2012.

Subjects

Adult ICU patients, within 24 hours of admission, in Australia and New Zealand obtained via the Australian and New Zealand Intensive Care Society adult ICU patient database. The human research ethics committee of Alfred Hospital provided approval of this study.

Analysis

Logistic regression was used to account for incidence changes of severe sepsis over the studied time period. Further logistic regression was used to associate admission year, APACHE scores and locations with outcomes to ensure that the data was robust over years and locations. Finally, sensitivity analysis was performed to ensure consistency of results by studying a subpopulation of 63 hospitals that had data for the entire time period and showing similarities in outcomes.

Results

Absolute mortality in severe sepsis decreased from 35.0% (95%CI, 33.2%-36.8%; 949/2708) to 18.4% (95% CI, 17.8%-19.0%; 2300/12 512; P <0 .001), representing an overall decrease of 16.7% (95% CI, 14.8%-18.6%), an annual rate of absolute decrease of 1.3%, and a relative risk reduction of 47.5% (95% CI, 44.1%-50.8%). After adjusted analysis, mortality decreased throughout the study period with an odds ratio (OR) of 0.49 (95% CI, 0.46-0.52) in 2012, using the year 2000 as the reference (P < .001). The annual decline in mortality did not differ significantly between patients with severe sepsis and those with all other diagnoses (OR, 0.94 [95% CI, 0.94-0.95] vs 0.94 [95% CI, 0.94-0.94]; P = .37). The annual increase in rates of discharge to home was significantly greater in patients with severe sepsis compared with all other diagnoses (OR, 1.03 [95% CI, 1.02-1.03] vs 1.01 [95% CI, 1.01-1.01]; P <0 .001). Conversely, the annual increase in the rate of patients discharged to rehabilitation facilities was significantly less in severe sepsis compared with all other diagnoses (OR, 1.08 [95% CI, 1.07-1.09] vs 1.09 [95% CI, 1.09-1.10]; P < .001). In the absence of comorbidities and older age, mortality was less than 5%.

Conclusions

In critically ill patients in Australia and New Zealand with severe sepsis with and without shock, there was a decrease in mortality from 2000 to 2012. These findings were accompanied by changes in the patterns of discharge to home, rehabilitation and other hospitals.

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Commentary

True rates of sepsis and mortality from sepsis have remained elusive. In the past, studies have looked at sepsis incidence, and estimations have been made that there are over 1 million sepsis patients in the US yearly as of 2012[1]. Sepsis rates seem to be increasing based on recent studies[2–4], with sepsis being ranked the most expensive reason for hospitalization in the US in 2011[5]. Unfortunately, prior studies were plagued by coding problems and limitations in study population, as data was only partial representation of populations studied. This led to concerns that there were errors in obtaining results and limitations of the data sets, leading to potential confounders.

The data set used in this study comprises over 90% of the ICU admissions in Australia and New Zealand. Admission diagnosis were screened for severe sepsis and studied over a 12-year period from 2000 to 2012. The primary outcomes studied were rates of severe sepsis and all hospital outcomes including mortality, discharge to home, discharge to rehab and discharge to other hospitals. Subgroup analysis was performed to evaluate whether or not patient

differences during this time frame accounted for outcome differences. Results showed severe sepsis rates appeared to have increased over this time period from 2,700 patients in 2000 to 12,512 in 2012. This rise is surprisingly high and represents a large increase in incidence of disease. To this end, the authors identified causes of infection and used objective criteria to identify organ dysfunction. The data was studied using sensitivity analysis and, in particular, studied ICU's that contributed data over all years, suggesting increased incidence of severe sepsis. Furthermore, mortality appears to have decreased significantly from 35% to 18%. Subgroups were similar and discharge to home was markedly improved with severe sepsis patients and more patients went to rehab over this time period.

Strengths of this study include robustness of data set, comprising almost the entire ICU admissions in Australia and New Zealand. This is the only study to assess changes in mortality in septic patients, adjusted for APACHE score, over such a large time period. Additionally, this study data was prospectively collected, leading to less bias. This data set was robust to sensitivity analysis, implying accuracy of the conclusions of declining mortality with increasing severe sepsis patients.

There are a number of limitations to this study. The study only analyzed patients within the first 24 hours of ICU admission. It is possible that less sick patients (early sepsis diagnosis) are being counted and more ill patients (late sepsis diagnosis) are dying at increased rates. This is not a significant limitation as comparisons were being made across the 12 year study time period using the same definition such that the results reflect a temporal change by that standard. Hospital mortality was the only mortality reported. It is possible that patients are not doing better over a longer time period after discharge; however based on the large proportion of patients discharged to home this is unlikely. This study did not differentiate etiologies of severe sepsis, and this may have accounted for changes in mortality. The accuracy of severe sepsis data collection was also not monitored and the marked increase in severe sepsis rates begs the question whether increasing numbers of less sick patients are being admitted to the ICU. Arguing against this is the APACHE score adjustments which reflect do not reflect a drop in severity. Nonetheless the substantial increase in incidence over such a brief time is surprising and yet to be explained.

The Kaukonen *et al.*[6] study is the largest, most robust study assessing sepsis incidence and outcomes to date. This study seems to strongly suggest that sepsis mortality is decreasing despite increases in sepsis rates. This would suggest that our care of sepsis is improving from both a diagnostic and therapeutic standpoint. Improved septic patients' discharge to home suggests that severe sepsis patients are also having improved quality of life outcomes. Of note, recent prospective clinical trials in sepsis (ARISE[7] and PROCESS[8]) have noted similar mortality rates to this study, corroborating declining sepsis rates.

Recommendation

This is an important epidemiological study that suggests that severe sepsis mortality has decreased significantly over time in the face of increased severe sepsis rates. This study further suggests that all critical care mortality appears to be declining. Patients with severe sepsis do seem to fare better as compared to other critical care illnesses based on increased home discharges. The declining rate of mortality has important implications in the design of future therapeutic trials targeting sepsis.

Competing interests

The authors declare that they have no competing interests.

Grant information

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