King's Research Portal

DOI:

[10.1097/CCM.0000000000001876](https://doi.org/10.1097/CCM.0000000000001876)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Shankar-Hari, M., Harrison, D. A., & Rowan, K. M. (2016). Differences in Impact of Definitional Elements on Mortality Precludes International Comparisons of Sepsis Epidemiology-A Cohort Study Illustrating the Need for Standardized Reporting*. *Critical Care Medicine*, 44(12), 2223-2230.
<https://doi.org/10.1097/CCM.0000000000001876>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Differences in impact of definitional elements on mortality precludes international comparisons of sepsis epidemiology - a cohort study illustrating the need for standardized reporting

Manu Shankar–Hari^{1,2,3} MD MSc FFICM, David A Harrison³ PhD, Kathryn M Rowan³
MPhil

¹Guy's and St Thomas' NHS Foundation Trust, ICU support Offices, 1st Floor, East Wing,
St Thomas' Hospital, SE1 7EH;

²Division of Asthma, Allergy and Lung Biology, King's College London;

³Intensive Care National Audit & Research Centre, Napier House, 24 High Holborn,
London WC1V 6AZ

Author affiliations

Division of Asthma, Allergy and Lung Biology, King's College London, London, UK
(Shankar-Hari M); Department of Critical Care Medicine, Guy's and St Thomas' NHS
Foundation Trust, London, UK (Shankar-Hari M); Intensive Care National Audit and
Research Centre, London, UK (Harrison D, Rowan K)

Institution where work was performed

Intensive Care National Audit & Research Centre, Napier House, 24 High Holborn,
London WC1V 6AZ

Address for reprints and corresponding author

Dr Manu Shankar Hari MSc (Epi) MD FRCA FFICM

ICU Support Offices, First floor, East Wing, St Thomas' Hospital, London, SE1 7EH, UK

Email: manu.shankar-hari@kcl.ac.uk

Phone: +44 20 7188 8769

Fax: +44 20 7188 2284

Financial support

The Intensive Care National Audit & Research Centre (ICNARC), Napier House, 24 High Holborn, London WC1V 6AZ supported this research. MSH acknowledges the funding of NIHR Biomedical Research Centre at Kings Health Partners.

Keywords

Sepsis; epidemiology; heterogeneity; healthy policy; international benchmarking

Copyright form disclosures: The authors have disclosed that they do not have any potential conflicts of interest.

Abstract

Objective

Sepsis generates significant global acute illness burden. The international variations in sepsis epidemiology (illness burden) have implications for region specific health policy. We hypothesised that there have been changes over time in the sepsis definitional elements (infection and organ dysfunction) and these may have impacted on hospital mortality.

Design:

Cohort study

Setting and patients

To address the proposed hypothesis, we evaluated a high quality, nationally representative, clinical, intensive care unit (ICU) database of 967,532 consecutive admissions to 181 adult ICUs in England, from January 2000 to December 2012, to identify sepsis cases in a robust and reproducible way. Multinomial logistic regression was used to report unadjusted trends in sepsis definitional elements and in mortality risk categories based on organ dysfunction combinations. We generated logistic regression models and assessed statistical interactions with acute hospital mortality as outcome and cohort characteristics, sepsis definitional elements and mortality risk categories as covariates. Finally, we calculated post-estimation statistics to illustrate the magnitude of clinically meaningful improvements in sepsis outcomes over the study period.

Interventions

None

Measurements and Main Results

Over the study period, there were 248,864 (25.7%) sepsis admissions. Sepsis mortality varied by infection sources (19.1% for genitourinary to 43.0% for respiratory; $p<0.001$), by number of organ dysfunctions (18.5% for one to 69.9% for five; $p<0.001$) and organ

dysfunction combinations (18.5% for risk category 1 to 58.0% for risk category 4). The rate of improvement in adjusted hospital mortality was significant (odds ratio 0.939 [0.934–0.945] per-year; $p<0.001$), but showed different secular trends in improvement between infection sources.

Conclusions

Within a sepsis cohort, we illustrate case-mix heterogeneity using definitional elements (infection source, organ dysfunction). In the context of improving outcomes, we illustrate differential secular trends in impact of these variables on adjusted mortality and propose this as a valid reason for international variations in sepsis epidemiology. Our paper highlights the need to determine standardized reporting elements for optimal comparisons of international sepsis epidemiology.

Introduction

Sepsis is a syndrome defined by life-threatening organ dysfunction due to a dysregulated host response to infection(1). Understanding the true global illness burden generated by sepsis has important implications for both policy and practice (2-4) – as substantial resources are directed towards campaigns to enhance recognition and improve management and outcomes, nationally and internationally. This knowledge might inform region specific health policy.

Considerable international variation in incidence of (6.0% to 27.0%) and mortality from (as high as 80.0%) sepsis has been reported across ICU cohorts(3-6), with recent trended data indicating a decrease in mortality.(7-9) However, interpretation of these data is challenging as it is likely that differences in the timing and trajectories of pre- and within hospital care, enhanced recognition (through campaigns such as the Surviving Sepsis Campaign(10) and the Sepsis Six in the UK(11)) and available ICU resources (the provision and use of ICU beds), will influence the characteristics of the sepsis population admitted to ICU. (3, 12-16) Currently, no international consensus exists for standardised reporting of the characteristics of and outcomes for a sepsis population.

Using a nationally representative, clinical, ICU database to identify sepsis cases in a robust and reproducible way using physiological and diagnostic data within the first 24 hours of admission, we set out to describe sepsis case mix (by source of infection and by number and combination of systemic inflammatory response syndrome [SIRS] criteria and of organ dysfunctions), its impact on mortality, and to illustrate the potential role that differences in sepsis case mix might play in the interpretation of ICU epidemiology – all with a view to initiating a dialogue for more standardised reporting.

Materials and Methods

Data source

The Case Mix Programme is the national clinical audit for adult general ICUs in England.

For consecutive admissions, trained data collectors collect sociodemographic, comorbidity and physiological data to precise rules and definitions, during the first 24 hours following admission to ICU, and outcomes. Diagnostic data are determined clinically and coded using the hierarchical ICNARC Coding Method (additional information provided in S-Methods-1).(17) Collected data undergo extensive local and central validation prior to pooling into the Case Mix Programme Database (CMPD).(18) Support for the collection and use of these data has been obtained under Section 251 of the National Health Service (NHS) Act 2006 (approval number PIAG 2–10(f)/2005).

Case selection and definitions

Using contemporaneous physiological data, definitions for each of the four systemic inflammatory response syndrome (SIRS) criteria and each of five organ dysfunctions were applied and deemed to be met/not met. A sepsis admission was defined as any admission clinically coded as infection and at least one organ dysfunction (additional information provided in S-Methods-1).

Analysis

The annual number and proportion of sepsis admissions, between January 2000 and December 2012, were calculated from the CMPD. The primary outcome was hospital mortality. Population incidence for severe sepsis admissions in England was estimated using extrapolation. Actual numbers for participating ICUs were extrapolated to the total number of ICUs in England for each year. Extrapolated numbers were converted to population incidences by dividing by mid-year population estimates obtained from the Office for National Statistics (ONS).(19)

For each year, *cohort characteristics* were described by age, sex, presence of severe co-morbidities, source of admission/surgical urgency, cardiopulmonary resuscitation (CPR) within 24 hours prior to admission and illness severity (APACHEII and ICNARC physiology scores). For each year, *sepsis specific case mix* was described by source of infection, by the number and combination of SIRS criteria and by number, type and combination of organ dysfunctions. Based on the report by Padkin et al (20) (Supplementary Appendix, S-Table1), we generated four mortality risk categories to illustrate the relationship between number(s) of and type(s) of organ dysfunction combinations and associated unadjusted hospital mortality. After summarizing study cohort characteristics, we reported the change over time in proportion of sepsis admissions, unadjusted hospital mortality and univariate analyses to show the heterogeneity and the associations between definitional elements and unadjusted hospital mortality. Multinomial logistic regression was used to report unadjusted trends for source of infection, number of SIRS criteria, number of organ dysfunctions and risk categories.

Risk-adjusted trends in hospital mortality were evaluated using a logistic regression model adjusted for *cohort characteristics and sepsis specific case-mix characteristics*. To assess the presence of interactions between source of infection, organ dysfunctions and longitudinal trends, three further logistic regression models were created with interaction terms and adjusted for case-mix characteristics. In the first model, the interaction between sources of infection over time on risk-adjusted mortality was assessed. The second model assessed the interaction between organ dysfunctions (by risk category) over time on risk-adjusted mortality. The third model (Model-3) assessed the interaction between both source of infection and organ dysfunctions (by risk category) over time on risk-adjusted mortality and was also used to generate all the adjusted odds ratios (OR) reported. Finally, we assessed whether, if the case mix characteristics had remained the same as in 2000 but all characteristic-specific improvements in mortality had occurred as

they did, the sepsis mortality by infection source and risk category had truly improved over time. Post-estimation predictive margins were used to estimate the marginal predicted mortality for each year for sources of infection and risk categories using regression Model-3, holding all other covariates at the values observed in 2000. All logistic regression models excluded readmissions of the same patient during the same hospital stay, were fitted with robust standard errors to account for clustering by ICU, and were reported as OR with 95% confidence intervals (CI).

Sensitivity analyses were performed to check the robustness of the findings for the the 62 ICUs contributing data over the complete study period. Reported p values are two sided and $p < 0.05$ was considered to represent a statistically significant result.

Continuous data were summarized as mean and standard deviation (SD), where normally distributed, and median and interquartile range (IQR), where not. Categorical data were presented as frequency and percentage. Admissions with unmeasured physiology were assumed not to have met the sepsis case definition. Data completeness exceeded 98% in all fields used for case selection, thus complete case analyses were used. All analyses were performed using Stata/SE Version 13.0 (StataCorp LP, College Station, TX, USA).

Results

Over the study period, 248,864 of the 967,532 admissions to adult general ICUs in England met the sepsis case definition. The proportion and numbers of sepsis admissions increased from 23.5% in 2000 to 25.2% in 2012 (Table-1; sFigure-1). Age and sex of sepsis admissions remained relatively stable. The proportion of sepsis admissions with severe co-morbidities increased from 16.1% to 19.2% and non-surgical admissions formed the majority (from 68.2% in 2000 to 72.9% in 2012). There was a decrease in APACHE II and ICNARC Physiology Scores (S-Table-2). The unadjusted

hospital mortality for sepsis admissions decreased from 45.5% in 2000 to 32.1% in 2012 (Table-1).

Source of infection and unadjusted mortality

For sepsis admissions, the source of infection changed significantly over time (test for homogeneity, $p < 0.001$). Respiratory tract was the most common source of infection, increasing from 40.1% in 2000 to 45.1% in 2012. Relative to admissions with respiratory infections, there was a significant increase in the proportions of admissions with genitourinary and musculoskeletal/dermatological infections and a significant reduction in the proportions with gastrointestinal, neurological and unknown source infections (all $p < 0.001$ for change over time; Figure 1A; S-Table3). Unadjusted hospital mortality varied by source of infection from 19.1% (95% CI 18.2–20.0%) for genitourinary to 43.0% (95% CI 42.7–43.4%) for respiratory (Figure 1B).

SIRS criteria and unadjusted mortality

The number of SIRS criteria met amongst sepsis admissions changed significantly over time (test for homogeneity, $p < 0.001$). The proportion meeting all 4 SIRS criteria decreased from 45.4% in 2000 to 38.4% in 2012. Relative to admissions meeting all 4 SIRS criteria, there was a significant increase in the proportions of admissions with 0, 1, 2 or 3 SIRS criteria (all $p < 0.001$ for change over time; Figure 1C; S-Table3). Unadjusted hospital mortality varied by number of SIRS criteria, from 24.7% (95% CI 21.7–28.1%) for 0 SIRS to 41.2% (95% CI 40.9–41.6%) for 4 SIRS (Figure 1D).

Number of organ dysfunctions and unadjusted mortality

The number of organ dysfunctions amongst sepsis admissions changed significantly over time (test for homogeneity. $p < 0.0001$). Sepsis admissions with 2 organ dysfunctions increased from 28.2% in 2000 to 31.0% in 2012. Relative to admissions with 2 organ dysfunctions, there was a significant increase in the proportions of admissions with one organ dysfunction and a decrease in admissions with 3, 4 or 5 dysfunctions (all $p < 0.001$

for change over time; Figure 1E; S-Table3). Unadjusted hospital mortality varied by number of organ dysfunctions from 18.5% (95% CI 18.1–18.9%) for 1 organ dysfunction to 69.9% (95% CI 69.1–70.8%) for 5 organ dysfunctions (Figure 1F).

Illustration of organ dysfunction number and combinations trends using risk category and relationship to unadjusted mortality

Overall hospital mortality by different combinations of number(s) and type(s) of SIRS criteria and of organ dysfunctions was variable (Figure 2A and 2B).

The risk category distribution amongst sepsis admissions changed significantly over time ($p<0.0001$). Risk categories 2 and 3 each constituted one quarter of the cohort, every year over the study period and were stable. Between 2000 and 2012, the proportion of sepsis admissions categorized as risk category 1 increased from 18.4% to 21.9% while those categorized as risk category 4 decreased from 31.0% to 27.3%. Relative to admissions in risk category 2, the changes in risk categories 1 and 4 were statistically significant (both $p<0.001$ for change over time), whilst for risk category 3 it was not ($p=0.47$). As anticipated, unadjusted hospital mortality increased across risk categories from 18.5% (95% CI 18.1–18.9%) to 58.0% (95% CI 57.7–58.4%) (Figure 2C and 2D; S-Table3).

Adjusted trends in hospital mortality by infection and organ dysfunction

The adjusted trend for improvement in hospital mortality for sepsis admissions was significant (OR 0.939 [95% CI 0.934–0.945] per year; $p<0.001$). Adjusted hospital mortality decreased significantly within each category of infection source and the rate of change over time varied significantly by infection source (respiratory, OR for risk category 1, 0.947 [95% CI 0.938–0.956] per year; cardiovascular, 0.937 [0.918–0.957] per year; gastrointestinal, 0.941 [0.933–0.950] per year; genitourinary, 0.938 [0.918–0.959] per year; musculoskeletal/dermatological, 0.943 [0.925–0.962] per year;

neurological, 0.939 [0.919–0.960] per year; unknown, 0.919 [0.907–0.932]; all individual trends and test of homogeneity $p < 0.001$).

Adjusted hospital mortality also decreased significantly within each risk category but the rate of change was consistent across the risk categories (risk category 1, OR for respiratory source 0.947 [95% CI 0.938–0.956] per year; risk category 2, 0.947 [0.939–0.955] per year; risk category 3, 0.943 [0.935–0.950] per year; risk category 4, 0.947 [0.940–0.955] per year; all individual trends $p < 0.001$, test of homogeneity $p = 0.48$).

Finally, the improving trends in hospital mortality appeared truly representative of sepsis mortality improvements when the case mix (in terms of all other variables in the model) was held constant at the values observed in 2000 (Figure 3 and S-Table 4).

Sensitivity analyses

Results from the sensitivity analyses (by restricting analyses to the same 62 ICUs contributing data over the complete study period), were consistent with the primary analyses (S-Table5 and S-Figure-2).

Discussion

Main findings

We report an increase in incidence and significant improvements in adjusted hospital mortality amongst adult critical care admissions with sepsis in England between 2000 and 2012. Sepsis admissions represented a heterogeneous population, and a population that was changing over time as highlighted by differential trends in definitional elements (infection source, SIRS, number and type of organ dysfunctions). The independent impact of these definitional elements on mortality was also different. Post-estimation predictive margins used to estimate the marginal predicted mortality show clinically

relevant improvement in sepsis outcomes between risk categories (such as 12.1% for risk category-1; 15.8% for risk category 4) and between infection sources (such as 13.2% for respiratory infection; 12.3% for urinary infections), despite differences in baseline mortality (year 2000) in these sepsis definitional elements.

Relevance

Our study introduces the concept that differences in the contribution of each sepsis definitional element such as source of infection and type and number of organ dysfunctions potentially contributes to the international variation observed across ICU cohorts. This concept was implicitly seen when different administrative database algorithms were applied(7, 9) but has not been formally tested before. Consistent with the published literature, we report an association between sepsis mortality with source of infection(21) and with type and number of organ dysfunctions.(22) We also show that, within a number of organ dysfunction group, mortality varies by organ dysfunction combinations (Figure 2B).

Illustrative direct comparison

To further illustrate this issue, we compared the sepsis mortality over from 2000 to 2012 and the 2012 case-mix characteristics reported by Kaukonen et al for sepsis and septic shock admissions from Australia/New Zealand (ANZ).(8) The rationale for this comparison includes use of a national ICU database similar to ours over the same time period (between 2000 and 2012), the similarities in per capita healthcare spending (~US\$3,000) and life expectancy at birth (~80 years), albeit there are uncertainties around critical care bed provision per 100,000 population (3.5 to 7.4 in United Kingdom versus 8.0 to 8.9 in ANZ).(23) Both studies also show similar improvements in adjusted hospital mortality for sepsis admissions over time (OR 0.94 per year).

However, sepsis mortality in our study was 1.5 times higher and mortality curves of the two studies are parallel over the entire study period. The mortality comparisons when

done using the simple risk categories, the ANZ study mortality is similar to group two unadjusted mortality. With case-mix comparisons, as shown by our study, the mortality in the ANZ study varies by infection source and other case-mix characteristics, which also change with time. In all the case-mix comparisons using 2012 data, the hospital mortality in our study was higher than the ANZ study (Figure 4A, Figure 4B, S-Table6). The SIRS negative population was much lower in our dataset (3.0% compared to 12.1% reported by the ANZ study(24); Figure 4C). These simple illustrative comparisons neither explain the reasons for the observed differences in outcomes nor imply that the sepsis outcomes are worse in England, but support our study hypothesis of heterogeneity in sepsis case mix and the need for standardization of reporting elements to aid direct international comparisons. However, this needs to be confirmed using simultaneous direct comparison of similar databases using the same criteria to identify sepsis cases.

Strengths

The strengths of our study are in the use of a high quality clinical database to identify sepsis admissions using accurate, raw physiological data (for SIRS criteria and for organ dysfunction variables) and synchronous, clinically coded diagnostic data to identify infection for consecutive ICU admissions. Our approach addresses many of the key limitations often highlighted in studies of sepsis epidemiology(7, 9, 25-30) namely, reliance on administrative/insurance claims data and use of either subjective sepsis codes (highly likely influenced by awareness campaigns, influential studies and reimbursement formulae) or separate but asynchronous codes for infection and organ dysfunction, often coded at discharge.

Limitations

There are limitations to our study. First, our database was not primarily designed for ICU sepsis epidemiology and therefore the overall incidence of sepsis may be underestimated (i.e. some admissions may develop sepsis after the first 24 hours in ICU). However, given the relatively low provision of ICU beds in England (higher

threshold for admission)(23, 31) and with 80% of the study cohort having two or more organ dysfunctions in the first 24 hours, the impact would likely be minimal. Second, the ICUs contributing to the dataset varied over time, which we addressed in our sensitivity analyses. Third, the organ dysfunction assessment was cross sectional. Fourth, the dataset contains planned and unplanned ICU admissions, where the physiology-modified secondary to interventions such as fluid management that would not be similarly captured by the organ dysfunction assessment (32) that is a common limitation of large database based epidemiology reports.(33) Finally, changes to the health care system and increasing awareness of sepsis could have influenced some of the observed improvements in outcome(34); however assessment of effects of these changes was not the research question addressed by this study.

Future research

Definitions are descriptions of illness and criteria provide the variables to identify a case(6). To-date, there are neither universally agreed standardized criteria nor reporting elements for sepsis epidemiology, which when interpreted with lack of gold-standard diagnostic tests for sepsis potentially introduces heterogeneity in epidemiology (6, 35). By contrasting our results to similar national database publications (8, 24) over the same study period and in the context of a global need for more accurate measurement of sepsis(4), our study makes a case for research into directed international sepsis epidemiology comparisons using national databases. Global ecological studies will help provide incidence density and identify higher risk areas, which would help design regional health policies to tackle sepsis.

Conclusions

The characteristics of our sepsis ICU population changed over time and so did the impact of definitional elements on hospital mortality, which we propose preclude direct

international comparisons of incidence and mortality. We illustrate a case for developing
an international consensus on standardized reporting of sepsis epidemiology. This has
important implications, both for health policy and benchmarking.

Acknowledgements

The authors wish to thank both staff and patients in the ICUs participating in the Case Mix Programme.

Prior publication or related manuscripts:

This manuscript or related manuscript is not being submitted for consideration for publication elsewhere.

References

1. Singer M, Deutschman CS, Seymour C, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):801-810.
2. Adhikari NK, Fowler RA, Bhagwanjee S, et al. Critical care and the global burden of critical illness in adults. Lancet 2010;376(9749):1339-1346.
3. Vincent JL, Marshall JC, Namendys-Silva SA, et al. Assessment of the worldwide burden of critical illness: the Intensive Care Over Nations (ICON) audit. Lancet Respir Med 2014;2(5):380-386.
4. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis - Current Estimates and Limitations. Am J Respir Crit Care Med 2015.
5. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence 2014;5(1):4-11.
6. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock: For the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):775-787.
7. Gaieski DF, Edwards JM, Kallan MJ, et al. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med 2013;41(5):1167-1174.
8. 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):1308-1316.
9. Stevenson EK, Rubenstein AR, Radin GT, et al. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis*. Crit Care Med 2014;42(3):625-631.
10. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41(2):580-637.

11. Daniels R, Nutbeam T, McNamara G, et al. The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. *Emerg Med J* 2011;28(6):507-512.
12. Wunsch H, Angus DC, Harrison DA, et al. Variation in critical care services across North America and Western Europe. *Crit Care Med* 2008;36(10):2787-2793, e2781-2789.
13. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006;34(2):344-353.
14. Seymour CW, Rea TD, Kahn JM, et al. Severe sepsis in pre-hospital emergency care: analysis of incidence, care, and outcome. *Am J Respir Crit Care Med* 2012;186(12):1264-1271.
15. Iwashyna TJ, Angus DC. Declining case fatality rates for severe sepsis: good data bring good news with ambiguous implications. *JAMA* 2014;311(13):1295-1297.
16. Levy MM, Rhodes A, Phillips GS, et al. Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med* 2015;43(1):3-12.
17. Young JD, Goldfrad C, Rowan K. Development and testing of a hierarchical method to code the reason for admission to intensive care units: the ICNARC Coding Method. Intensive Care National Audit & Research Centre. *Br J Anaesth* 2001;87(4):543-548.
18. Harrison DA, Brady AR, Rowan K. Case mix, outcome and length of stay for admissions to adult, general critical care units in England, Wales and Northern Ireland: the Intensive Care National Audit & Research Centre Case Mix Programme Database. *Crit Care* 2004;8(2):R99-111.
19. National Statistics Online. <http://www.statistics.gov.uk/hub/population/population-change/population-estimates/index.html>

20. Padkin A, Goldfrad C, Brady AR, et al. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. *Crit Care Med* 2003;31(9):2332-2338.
21. Leligdowicz A, Dodek PM, Norena M, et al. Association between source of infection and hospital mortality in patients who have septic shock. *Am J Respir Crit Care Med* 2014;189(10):1204-1213.
22. Vincent JL, Nelson DR, Williams MD. Is worsening multiple organ failure the cause of death in patients with severe sepsis? *Crit Care Med* 2011;39(5):1050-1055.
23. Prin M, Wunsch H. International comparisons of intensive care: informing outcomes and improving standards. *Curr Opin Crit Care* 2012;18(6):700-706.
24. Kaukonen KM, Bailey M, Pilcher D, et al. Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med* 2015;372(17):1629-1638.
25. Rhee C, Gohil S, Klompas M. Regulatory mandates for sepsis care--reasons for caution. *N Engl J Med* 2014;370(18):1673-1676.
26. Iwashyna TJ, Odden A, Rohde J, et al. Identifying patients with severe sepsis using administrative claims: patient-level validation of the angus implementation of the international consensus conference definition of severe sepsis. *Med Care* 2014;52(6):e39-43.
27. Whittaker SA, Mikkelsen ME, Gaieski DF, et al. Severe sepsis cohorts derived from claims-based strategies appear to be biased toward a more severely ill patient population. *Crit Care Med* 2013;41(4):945-953.
28. Klein Klouwenberg PM, Ong DS, Bonten MJ, et al. Classification of sepsis, severe sepsis and septic shock: the impact of minor variations in data capture and definition of SIRS criteria. *Intensive Care Med* 2012;38(5):811-819.
29. Linde-Zwirble WT, Angus DC. Severe sepsis epidemiology: sampling, selection, and society. *Crit Care* 2004;8(4):222-226.
30. Angus DC, Wax RS. Epidemiology of sepsis: an update. *Crit Care Med* 2001;29(7 Suppl):S109-116.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
31. Rhodes A, Ferdinande P, Flaatten H, et al. The variability of critical care bed numbers in Europe. *Intensive Care Med* 2012;38(10):1647-1653.
32. Rosenberg AL, Hofer TP, Strachan C, et al. Accepting critically ill transfer patients: adverse effect on a referral center's outcome and benchmark measures. *Ann Intern Med* 2003;138(11):882-890.
33. Thygesen LC, Ersboll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. *Eur J Epidemiol* 2014;29(8):551-558.
34. Hutchings A, Durand MA, Grieve R, et al. Evaluation of modernisation of adult critical care services in England: time series and cost effectiveness analysis. *BMJ* 2009;339:b4353.
35. Angus DC, Seymour CW, Coopersmith CM, et al. A Framework for the Development and Interpretation of Different Sepsis Definitions and Clinical Criteria. *Crit Care Med* 2016;44(3):e113-e121.

Figure Legends

Figure 1: Sepsis specific case-mix

Trends in sepsis admissions to adult general intensive care units in England by source of infection (panel A) and hospital mortality by source of infection (panel B), by number of SIRS criteria (panel C) and hospital mortality by number of SIRS criteria (panel D), number of organ dysfunctions (panel E) and hospital mortality by number of organ dysfunctions (panel F). The panels A, C and E show the changes over the study period. The panels B, D and F show the overall hospital mortality over study period by each sepsis definitional element. Abbreviation: No. = Number

Figure 2: Simple illustration of heterogeneity using number and combinations of organ dysfunction (risk categories) and SIRS combinations

Trends in sepsis admissions to adult general intensive care units in England by SIRS combinations (panel A); heterogeneity within number and combinations of organ dysfunctions (panel B); risk category (panel C) and hospital mortality by risk category (panel D). For description of risk-categories please refer to methods and S-table-1 for further details.

Abbreviations:

Figure 2A: SIRS = systemic inflammatory response syndrome; T= temperature; H = heart rate; R = respiratory rate; W = white cell count

Figure 2B: R = respiratory; C = cardiovascular; K = renal; H = hematologic; M = metabolic

Figure 3: Post-estimation predictive margins to estimate the marginal predicted mortality

Yearly trends in mortality by infection source (panel A) and by risk category (panel B) amongst the sepsis admissions with year 2000 as the referent year are shown. Year 2000 and 2012 characteristics are shown in S-Table-4.

Figure 4: Comparisons of current study with Kaukonen et al(8)

Unadjusted sepsis outcomes to adult general intensive care units in England and in Australia and New Zealand (panel A); by number and type of organ dysfunction (risk category) (panel B) and adjusted sepsis mortality by SIRS positive and negative status (panel C). Abbreviations: CMP = Case Mix Programme; SIRS = systemic inflammatory response syndrome.

Table Legend

Table 1: Numbers of participating adult general intensive care units in England, admissions (total and sepsis) and unadjusted mortality

Figure-1

Figure-2

Figure-3

Figure-4

Table 1: Numbers of participating adult general intensive care units in England, admissions (total and sepsis) and unadjusted mortality

Parameters	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Adult general ICUs contributing data (n)	101	116	132	143	141	141	141	149	158	162	174	179	181
Total ICU admissions (n)	35,548	42,261	53,434	62,123	66,294	67,316	67,281	72,820	80,507	85,389	99,688	113,519	121,352
ICU admissions meeting sepsis case definition (n (%))	8,366 (23.5)	9,938 (23.5)	12,557 (23.5)	15,108 (24.3)	16,642 (25.1)	17,761 (26.4)	18,086 (26.9)	19,587 (26.9)	21,625 (26.9)	23,066 (27.0)	26,799 (26.9)	28,703 (25.3)	30,626 (25.2)
Extrapolated ICU admissions with sepsis	18,400	20,100	21,100	23,100	25,000	26,900	27,700	29,700	30,700	31,700	33,400	34,100	36,100
ICU mortality for severe sepsis admissions (n (%))	2876 (34.4)	3337 (33.6)	4154 (33.1)	5005 (33.1)	5374 (32.3)	5445 (30.7)	5478 (30.3)	5601 (28.6)	5968 (27.6)	6254 (27.1)	7031 (26.2)	7093 (24.7)	7316 (23.9)
Hospital mortality for sepsis admissions (n (%))	3469 (45.5)	3968 (44.6)	5053 (44.1)	6019 (44.0)	6527 (43.2)	6780 (41.6)	6750 (40.9)	7020 (39.1)	7446 (37.3)	7807 (36.7)	8772 (35.3)	8797 (33.2)	9115 (32.1)

ICU – Intensive Care Unit

[Click here to access/download](#)

Supplemental Data File (.doc, .tif, pdf, etc.)
CCMED-D-15-02080.Suppl.Clean.R1.doc