Author's response to reviews


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Author's response to reviews: see over
**Author`s response to reviewers:**

**Title:** Epidemiology and recent trends of severe sepsis in Spain: a nationwide population-based analysis (2006-2011).

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Thank you for consideration our manuscript for publication in your journal. We have reviewed the manuscript according to the reviewer`s comments. We have also made some changes (highlighted text), to ensure that our manuscript conforms to the journal style.

**Author`s response to reviewers:**

Reviewer #2:

My main concern is a lack of accuracy of the data. I suspect that patients coded as having a severe sepsis were not in fact “severe”. It is a matter of definition of organ dysfunction qualifying the patient for having SS. The organ supports required by the patients’ condition are important to report in order to sort out severe patients. The studies should focus on “real severe patients”. That is the one that could benefit from optimized treatment.

We completely agree with the reviewer that only the adequate identification of patients with severe sepsis will allow them to benefit from the therapeutic advances and improvements in treatment. Personally, as a physician specialized in intensive care medicine with a long clinical experience, I am in complete agreement with your appreciation and this is the path we have tried to keep to in the work we present, even if not focused in the treatment of an individual patient.

Severe sepsis represents an important and growing issue in the ICU but also constitutes an important challenge for healthcare systems. In this scenery, accurate and consistent estimates of national incidence, mortality and other epidemiological data are critical steps for the
assessment of the full burden of severe sepsis, for distribution of limited healthcare resources,
assignment of research priorities and uniform benchmarking of metrics across hospital systems
and geographic regions.

Just as in the clinical setting, for estimating the national incidence and other epidemiological
characteristics of severe sepsis is essential to have a reliable definition of the cases. Two
decades ago the American College of Chest Physicians and the Society of Critical Care Medicine
(ACCP/SCCM) defined severe sepsis as sepsis associated with organ dysfunction,
hypoperfusion abnormality or hypotension (Bone et al. 1992). This specific consensus
definition standardized criteria for diagnosis and enrollment into research studies. However,
these criteria are challenging to use for national epidemiologic estimates of severe sepsis
because their application require extensive and complex medical record review and
prospective collection of such data at a national level appears elusive (ref 18).

As a practical alternative, to date, the identification of severe sepsis cases has relied on
International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), in large
administrative databases. Recent epidemiologic studies based on these methods have had a
large impact on the scientific debate on the epidemiology of severe sepsis (ref 4-7).
The use of ICD-9 codes has been shown to be highly sensitive for severe sepsis (ref 18), but has
also raised concerns for its lack of specificity, giving rise to some estimates which tend to
underrepresent the cases of severe sepsis. Here, it should be recognized that the process for
assigning ICD-9 codes is not standardized and inconsistencies between various methods
remain (refs 18, 29, 33). In this study, after reviewing the corresponding literature, we have
used a combination of codes of great amplitude and specificity. Thus we have selected and
used the combination of infection and organ dysfunction codes initially described by Martin et
al (ref 5), and later extended by Dombrosky et al (refs 6,7) after the introduction in 2002-2003
of the new ICD-9 criteria-specific codes for sepsis (995.91), severe sepsis (995.92) and septic
shock (785.82). As regard the infection codes, those employed by Martin present a great
specificity (ref 29) with a positive predictive value of 97.7% (ref 42). On the other hand, code
995.92 has a specificity close to 100% (ref 33), but recent publications (ref 18,33 ) point out
that the use of this code is limited and not recommended as a single code for the estimation of
national data, but most always be combined with ICD-9 codes for infection plus organ
dysfunction.

Regarding the organ dysfunction codes, we have also used those previously used by
Dombrosky et al. in 2005 and 2007 (refs 6,7). These authors include dysfunctions of the six
systems commonly used to evaluate organ dysfunction: respiratory, cardiovascular,
coagulation, renal, hepatic and neurological systems, and extends, to a small degree, those defined by Angus in his publication of 2001 (4). In addition, we have included the definition of metabolic dysfunction provided by Martin (ref 5) and Sundarajan (ref 14).

For all of these reasons, we believe the cases included are truly severe sepsis cases and not milder conditions. Given the codes selected and the results achieved, both with respect to the incidence and mortality rates as well as case-fatality, it may be that our estimation, as commented in our manuscript, may have a bias towards greater severity, but never towards lesser severity.

Lastly, we would like to point out that the design of our study does not allow us to extract specific data on treatment in an ICU, except for the use of mechanical ventilation and hemodialysis.

Although in the manuscript we have pointed out, through specific references, the studies on which we have based the selection of codes used, in order to clarify it even further we have changed the material and methods section to include the definitions of the codes used in the section: **Selection of cases and definitions.**

Based on prior studies [4-7,18], severe sepsis cases were identified as the presence, in principal or secondary diagnoses, of ICD-9CM (International Classification of Diseases, 9th revision, Clinical Modification) codes for sepsis and acute organ dysfunction or the presence of ICD-9CM code 995.92 specific of severe sepsis (systemic inflammatory response syndrome due to infectious process with organ dysfunction).

To identify sepsis we employed formerly utilized codes [5-7] that define infection: 038 (0.38.0 (streptococcal septicemia), 038.1 (staphylococcal septicemia), 038.2 (pneumococcal septicemia), 038.3 (septicemia due to anaerobes), 038.4 (septicemia due to other Gram negative organisms), 038.8 (other specified septicemias), 038.9 (unspecified septicemia), 003.1 (salmonella septicemia); 020.2 (septicemic plague); 036.2 (meningococcal septicemia); 036.3 (Waterhouse-Friderichsen syndrome); 054.5 (herpetic septicemia); 098.89 (gonococcemia); 112.5 (systemic candidiasis); 112.81 (candidal endocarditis); 117.9 (other and unspecified mycoses); 771.8 (perinatal infections, septicaemia of newborn) and 790.7 (bacteremia). We also included the ICD-9CM code for sepsis 995.91 (sepsis, systemic inflammatory response syndrome due to infectious process without organ dysfunction), that became effective in our country in January 2004 [19].

For acute organ dysfunction we used the following ICD-9CM codes [5,6,14]: respiratory: 518.81 (acute respiratory failure), 518.82 (other pulmonary insufficiency),
518.84 (acute on chronic respiratory failure), 518.85 (acute respiratory distress syndrome after shock or trauma), 786.09 (respiratory distress, insufficiency), 799.1 (respiratory arrest), 96.7 (invasive mechanical ventilation); cardiovascular: 785.5 with all subcodes (shock without mention of trauma, includes 785.1, 785.52, 785.9), 458 (hypotension, 458.0, 458.8, 458.9), 796.3 (nonspecific low blood pressure reading); renal: 584 with all subcodes (acute renal failure), 580 (acute glomerulonephritis), 39.95 (hemodialysis); hepatic: 570 (acute and subacute necrosis of liver), 572.2 (hepatic coma), 573.3 (hepatitis, unspecified); hematologic: 286.6 (defibrination syndrome), 286.9 (other and unspecified coagulation defects), 287.3-5 (secondary thrombocytopenia, unspecified); neurologic: 293 (acute delirium), 348.1 (anoxic brain damage), 348.3 (encephalopathy, unspecified), 357.82 (critical illness polyneuropathy), 780.01 (coma), 780.09 (drowsiness, unconsciousness, stupor), 89.14 (electroencephalogram) and metabolic: 276.2 (acidosis metabolic or lactic).

In addition, we have made some changes on page 14 including the following explanatory paragraph (highlighted text, page 14):

However, it should be recognized that although the use of ICD-9 codes has been shown to be highly sensitive for severe sepsis [18], the extracting coding strategy is not standardized and inconsistencies between various methods remain [18,29,33]. Different algorithms used to identify severe sepsis cases in administrative data, select cases of varying disease severity sometimes resulting in estimates with low specificity which tend to underrepresent the real cases of severe sepsis [29]. With this data in mind, to carry out this study we have selected and used the combination of infection and organ dysfunction codes initially described by Martin [5], and later extended by Dombrosky et al. [6,7] after the introduction of the new ICD-9 criteria-specific codes for sepsis, severe sepsis and septic shock. The codes employed by Martin et al [5] have shown a high specificity for capturing severe sepsis cases [18,29], with a positive predictive value of 97.7% [42]. In addition, code 995.92 has a specificity close to 100% [33]. However, recent publications [18,33] point out that the use of this code is limited and not recommended as a single code for the estimation of national data, but most always be combined with ICD-9 codes for infection plus organ dysfunction. Given the codes selected and the results achieved, both with respect to the incidence and mortality rates as well as case-fatality, we are confident that the cases included in our study are truly severe sepsis cases and not milder conditions.
References


The following references were already included in the manuscript:


We hope you will find these changes to your liking, and we will look forward to hearing from you.

Yours sincerely,

Carmen Bouza, MD, PhD