Author's response to reviews

Title: How many general and inflammatory variables need to be fulfilled when defining sepsis due to the 2003 SCCM/ESICM/ACCP/ATS/SIS definitions in critically ill surgical patients: a retrospective observational study

Authors:

Manfred Weiss (manfred.weiss.ulm@online.de)
Markus Huber-Lang (markus.huber-lang@uniklinik-ulm.de)
Michael Taenzer (michael.taenzer@uniklinik-ulm.de)
Martina Kron (martina.kron@uni-ulm.de)
Birgit Hay (birgit.hay@uni-ulm.de)
Maximilian Nass (maximilian.nass@uni-ulm.de)
Moritz Huber (huber.moritz@googlemail.com)
Marion Schneider (marion.schneider@uni-ulm.de)

Version: 3 Date: 22 March 2010

Author's response to reviews: see over
Dear Dr. Edmunds,

please find enclosed our revised manuscript (ID 1379477723323185) responding item by item to the reviewers’ concerns and describing all changes.

The reviewers queries greatly strengthened the focus and the clarity of the presentation. Briefly, as suggested by the reviewers, we now classified our patients only in the 3 diagnostic categories sepsis, severe sepsis, and septic shock. Moreover, we now focus on the idea of how many general and inflammatory variables of the diagnostic criteria for sepsis of the 2003 definitions are needed to identify the most number of patients with “septic shock” in order to avoid missing patients who may benefit for optimal treatments.

We hope that the revised manuscript adequately addresses the reviewers’ concerns, following below.

Yours sincerely,

Manfred Weiss, MD
For the authors

Author’s Response to reviewer 1

Reviewer’s report
Title: How many general and inflammatory criteria need to be fulfilled when defining sepsis due to the 2003 SCCM/ESICM/ACCP/ATS/SIS definitions in critically ill surgical patients: a retrospective observational study
Version: 2 Date: 18 December 2009
Reviewer: Frank Bloos

Reviewer’s report:
Major Compulsory Revisions

* The study population needs to be better described. Did you collect patients with sepsis only or with SIRS or sepsis? How was this defined and what did you really wanted to diagnose by application of the new sepsis criteria?

All patients admitted to the ICU were scored. For evaluation, now, only patients with infections, sepsis, severe sepsis and septic shock are presented. If 1/8 up to 8/8 of the general and inflammatory diagnostic variables were present together with a documented infection, patients were assigned as sepsis patients. Since it has never been specified how many of the extended general and inflammatory criteria of the 2003 SCCM/ESICM/ACCP/ATS/SIS consensus sepsis definitions are mandatory to define sepsis, we defined sepsis with 1/8 up to 8/8 of these general and inflammatory variables. Instead of the objective “To find out the prevalence of sepsis stages and ICU mortality rates and the case mix within the same collective of patients applying different cut-offs, i. e. 1/8 up to 8/8 of these criteria” we now clarified that we wanted
"To find out how many of these variables are needed to identify almost all patients with septic shock."

* Your study goal was to describe the prevalence (better frequency) of the sepsis stages. However staging, which would be the PIRO concept, were not part of your study. You may want to compare your study to Rubulotta et al. Crit Care Med 2009; 37: 1329 –1335. How do you know that the new criteria correctly diagnose sepsis in your patient population?

For evaluation, now, only patients with documented infections were included. If 1/8 up to 8/8 of the general and inflammatory diagnostic criteria in Table 1 were present together with a documented infection, patients were assigned as sepsis patients (Table 1).

The patients with infections were classified into the 3 groups sepsis, severe sepsis and septic shock, underlying 1/8 up to 8/8 of the general and inflammatory variables of the diagnostic criteria for sepsis.

Severe sepsis was defined as sepsis plus organ dysfunction [3]. Organ dysfunctions were defined according to the limitations for organ dysfunction variables and tissue perfusion variables (hyperlactatemia) as given in the original publication [3] and presented in Table 1.

The study by Rubulotta is now compared with our results in the discussion section. "Recently, a PIRO staging model for risk stratification was generated and validated in a large global sepsis database [10]. Herein, severe sepsis was defined as evidence of infection with at least one sepsis-induced organ dysfunction [10]. In this context, the systemic inflammatory response criteria were not important risk factors...". Moreover, the study by Moreno et al. [11] regarding sepsis mortality prediction with the „SAPS 3 PIRO model“ is discussed now.

* In the manuscript, you write about SIRS/septic shock and SIRS/sepsis when talking about the cut-offs of the new parameters. This is misleading. SIRS is a concept of the SCCM-ACCP-consensus criteria but not of the new diagnostic criteria which only refer to the diagnosis of sepsis. It seems to me that you have applied the new parameters to clearly non-septic patients as well.

In the former version of the paper, the new parameters have also been applied to SIRS patients. Since the new diagnostic criteria only refer to the diagnosis of sepsis [3], we now focus on patients with sepsis. Thus, patients, only revealing SIRS during their stay on the ICU, have been excluded from analysis.

* It would be interesting how the new criteria perform in comparison to the old SCCM-ACCP-consensus criteria. Do the new criteria diagnose sepsis similar than the old criteria? Where are differences in sepsis classification?

We previously compared the 1992 with the 2003 SCCM/ESICM/ACCP/ATS/SIS sepsis definitions. This study has already been mentioned in the discussion section. We now included that „Frequencies of severe sepsis and septic shock were higher and mortality rates lower within the same patient collective, when the 2003 definitions (≥ 2/8 general and/or inflammatory variables) instead of the 1992 definitions (≥ 2/4 variables) were applied in the same collective of postoperative/posttraumatic patients [8]“.

* The authors have altered the published criteria which need to be discussed. Especially the lack of procalcitonin is a limitation since many – including the International Sepsis Forum – are considering this parameter as the most interesting biomarker in this field. Thus, a statistical model, which would have included PCT, might have come to a very different result.

Unfortunately, plasma procalcitonin was not measured routinely in our patients. Thus, case numbers are too low to draw meaningful conclusions. Limitations of the present
study are clearly stated now in the discussions section: “Out of the general and inflammatory variables, altered mental status and plasma procalcitonin were not applied in the present study. Mental status is difficult to apply in analgesedated or intubated patients. Plasma procalcitonin values could not be taken in the statistical evaluation due to low numbers, since procalcitonin is not routinely measured in our ICU. Thus, especially the lack of procalcitonin is limiting our conclusions, since this parameter is considered as one of the most interesting biomarkers in this field. Thus, a statistical model, including procalcitonin, might have come to a different result. The impact of procalcitonin has to be clarified in the future.”

* The Methods are vaguely described in some aspects. It is described that physicians received results and checked and corrected classifications. What does this mean? Please, be more specific. You stated also that cases where selected for before entering them into the database. Were there additional selection criteria than stated before?

Some parts could have been misunderstood and have been changed. In the training phase, cases have been selected for teaching. During the study period, all patients admitted to the ICU entered the database. The process of data acquisition is now described more clearly: “...Directly after complete data entry of the parameters for the different organ systems and infection, the scores were calculated and displayed. Thereby, the physicians directly received the results of the actual scores and the sepsis classification. A longitudinal overview of the scores, in addition to the actual daily scores, regarding the whole ICU course was presented daily to the residents and staff physicians. They checked, corrected, ascertained and re-ascertained the data. Thus, the severity of disease and organ dysfunction scores, and the diagnostic categories of sepsis classifications (sepsis, severe sepsis, septic shock) were verified. Staff physicians corrected the charts before demission of the patients from the ICU and before final saving in the database. ... Only cases ≥ 18 years were selected for the present evaluation because SAPS II score [6] and the 2003 SCCM/ESICM/ACCP/ATS/SIS sepsis definitions have been developed for patients ≥ 18 years, and the SOFA score [7] for patients ≥ 12 years. Neurosurgical patients were excluded from analysis because noradrenaline is often used to achieve an adequate cerebral perfusion pressure and not due to shock associated with accompanying infections and sepsis. Since the new diagnostic criteria only refer to the diagnosis of sepsis [3], we focused on patients with sepsis. Thus, patients only revealing SIRS during their stay on the ICU were excluded from analysis.”

* Discussion (page 9): The discussion of impact of the chosen cut-off on sepsis-research is important but too long since impact on research was not the subject of the study. Please, shorten considerably

This discussion section has been shortened markedly.

Minor Essential Revisions

* I assume that this was a retrospective study (as stated in the title) by chart analysis. Please state this in the Methods

This has been stated in the methods section now.

* Table 1: Did you perform a differential WBC regularly? You should set ‘>10% immature’ to ‘n.a.’ if you did not.

Differential WBC have not been performed regularly. Thus, we set ‘>10% immature’ to ‘n.a.’

* Give frequencies for the causes of infection.

This has not been prospectively monitored and is not in our data base.

* Which parameters of the criteria were fulfilled most frequently?
We did not evaluate this aspect.
* The data shown in table 3 and table 4 are unclear for me. What is the purpose of this analysis?

Table 3 showed the agreement between classifications yielded with 1/8 vs. 2/8 variables and so on. Table 3 has been omitted since we now focus on septic shock. The degree of agreement between the classifications using 1/8 up to 8/8 general and inflammatory variables to classify sepsis was estimated using the Kappa coefficient, showing a value of 1 when there is complete agreement and 0 when the observed agreement is equal to chance agreement. Due to the increasing sum of shock cases with no agreement of 85, 103 and 106 (all) cases in septic shock with 6/8, 7/8 and 8/8 variables as cut-off (now Table 3), respectively, the Kappa coefficient decreases.

Discretionary Revisions

* Results (3rd paragraph): The risk of death for the different cut-offs may be better visualized by a forest-plot like graph instead of table 2.

The results are given in the text and Table 2 more clearly now. The results are presented in a table rather in a figure to be able to show even slight changes.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests

Author's Response to reviewer 2

Reviewer's report

Title: How many general and inflammatory criteria need to be fulfilled when defining sepsis due to the 2003 SCCM/ESICM/ACCP/ATS/SIS definitions in critically ill surgical patients: a retrospective observational study

Version: 2 Date: 21 December 2009

Reviewer: H. Bryant Bryant Nguyen

Reviewer's report:

In this paper, the authors examined how many of the 2003 Sepsis Definitions “general” and “inflammatory” variables are needed to identify patients with shock. The paper is very interesting and would help us better clarify which variables are needed to identify those patients requiring aggressive therapies.

While the idea is good, I find the writing, data analysis and discussion quite confusing.

MAJOR REVISIONS:

1) The authors note that this was retrospective, but the Methods section suggests a prospective approach, “Charts were checked and corrected by the staff physicians before demission of the patients from the ICU and before final evaluation.” Please clarify.

The methods section has been rewritten for clarity: “A retrospective observational single-centre study in postoperative/posttraumatic patients admitted to an University adult ICU has been performed... Staff physicians corrected the charts before demission of the patients from the ICU and before final saving in the database....”

2) The authors should only use “sepsis”, “severe sepsis”, and “septic shock” to classify patients. Patients should be classified into these 3 groups only. The use
of terminologies “SIRS/sepsis”, “SIRS/septic shock” is confusing and unnecessary.

We now classified our patients only in the 3 diagnostic categories sepsis, severe sepsis, and septic shock.

Table 3 makes it even worse, using the sepsis classifications, “infection, SIRS, sepsis, severe SIRS/sepsis, SIRS/septic shock”. These can simply be stated, “sepsis, severe sepsis, septic shock”.

I assume that this study only includes patients with at least infection and SIRS, or sepsis. To note SIRS only means that patients may not have infection? Again, the authors need to be concise about what types of patients are being included?

All patients admitted to the ICU were scored. For evaluation, now, only patients with documented infections were included. These patients were classified into the 3 groups sepsis, severe sepsis and septic shock, underlying 1/8 up to 8/8 of the general and inflammatory variables of the diagnostic criteria for sepsis.

3) Table 2 – I would expect the OR for death to increase with increasing mortality when applying increasing number of criteria; e.g. why would a mortality of 18% have OR 5.5 for death when using 1/8 cutoff, but a 6/8 cutoff having mortality of 28% only have OR 3.7 for death? Please clarify

This is due to the fact that the odds ratio is measuring the ratio of the odds between exposed and non-exposed subjects. That means that the OR does not only depend on the mortality among septic shock cases but also on the mortality among non-shock subjects.

4) Table 3 – To make this paper more clear, I would delete Table 3. Knowing the agreement for all sepsis classifications is not helpful. The authors should only focus on the idea of how many variables are needed to identify the most number of patients with “septic shock” in order to avoid missing patients who may benefit for optimal treatments.

Table 3 has been deleted. As proposed, we now focus on the idea of how many variables are needed to identify almost all patients with “septic shock”.

5) Table 4 - Why did Kappa decrease when the %no agreement decreased for cutoffs 6/8 vs 7/8 and 7/8 vs 8/8? Please clarify.

The degree of agreement exceeding by chance agreement between the classifications using 1/8 up to 8/8 general and inflammatory variables to classify sepsis was estimated using the Kappa coefficient, showing a value of 1 when there is complete agreement and 0 when the observed agreement is equal to chance agreement. Due to the increasing sum of shock cases with no agreement of 85, 103 and 106 (all) cases in septic shock with 6/8, 7/8 and 8/8 variables as cut-off (now Table 3), respectively, the Kappa coefficient decreases.

6) Figure 1 - Authors should present percentage mortality in the graph (or mortality rate as noted in legend), instead of no. cases of non-survivors. This can be achieved by having two y-axes. The left Y-axis can be no. cases with shock. The right Y-axis can be %mortality. Currently, it is not obvious that there is increasing mortality with higher number of general/inflammatory criteria.

Figure 1 has been changed and it now becomes clear that relative mortality rates increase.

MINOR ESSENTIAL REVISIONS:

The authors should consult a medical writer to improve the clarity of the overall text in the manuscript.

A medical writer has been consulted.

Level of interest: An article of limited interest
Quality of written English: Not suitable for publication unless extensively edited
The English has now been edited by a native speaker.

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
The paper has been conducted under the auspice of two statisticians as co-authors, Martina Kron and Birgit Hay, of the Institute of Biometrics, University of Ulm.

Declaration of competing interests:
I declare that I have no competing interests. HBN