Author's response to reviews

Title: Enhancement of CURB65 score with proadrenomedullin (CURB65-A) for outcome prediction in lower respiratory tract infections: Derivation of a clinical algorithm

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Author's response to reviews: see over
Reviewer's report

Title: Enhancement of CURB65 score with proadrenomedullin (CURB65-A) for outcome prediction in lower respiratory tract infections: Derivation of a clinical algorithm

Version: 1 Date: 14 November 2010
Reviewer: James D Chalmers

Reviewer's report:

The authors have demonstrated that pro-adrenomedullin enhances prediction of adverse outcome in LRTI by the CURB65 score. In general the study is well performed, the cohort is appropriate and the results interesting.

We thank you for your comments and are happy to clarify the manuscript, which has been revised accordingly.

Major compulsory revisions

It is suggested that the authors used standardised ICU admission criteria, but the ICU admission criteria in the methods do not make sense, or correspond to the results- It is suggested that patients with a score >2 CURB65 points would be admitted to ICU, but then only 7.6% of the cohort were admitted to ICU when 20% of the cohort had scores >2- either these standardised criteria were not implemented or were not followed- can the authors explain?

This is important as ICU admission is part of the outcome that CURB65 is supposed to predict. Using CURB65 as part of a standardised ICU admission criteria will artificially increase its predictive value.

Within the ProHOSP trial, we summarized guidelines on the management of all LRTI based on the most recent guidelines by the European Respiratory Society (ERS) and the American Thoracic Society (ATS). These guidelines have been adapted by a panel of local internists, emergency physicians, pneumologists, infectious disease experts and clinical epidemiologists and have been successfully used in the clinical setting. To optimize the implementation of these guidelines for all patients the treating physician was enforced to follow a web-based guideline algorithms. These guidelines also displayed severity criteria for ICU admission. However, ICU admission was still a clinical decision, made by the attending physician in charge. It was suggested to consider ICU admission based on ATS criteria (ref. Ewig, AJRCCM 1998) or based on a CURB65 score >2 (ref – Lim, Thorax 2003). This recommendation, however, was not mandatory. We now more precisely state this in the manuscript as follows: “In brief, ICU admission was a clinical decision made by the attending physician in charge and had to incorporate occasional ICU bed shortages. It was suggested to consider ICU admission for patients with severe CAP (ref- Ewig, 1998), defined as…”

“For COPD patients, ICU admission was suggested based on modified ERS guidelines (ref- Siafakas, 1995), including…”

We agree with the reviewer that the prognostic performance of the CURB65 score for ICU admission may be slightly biased. However, as pointed out above, admission of patients to the ICU was a clinical decision made by the attending and not strictly enforced based on the CURB65 score. We have added a paragraph in the discussion section:

“…because a high CURB65 score was one of the severity criteria which prompted physicians to consider admitting patients to the ICU, its prognostic performance may be artificially improved. As a consequence, this would imply a rather conservative bias in regard of the prognostic performance of ProADM.”
Minor essential revisions
Empyema is not defined in the methods but is included as an end-point
Thank you for pointing this out. All disease-specific complications are now stated in the manuscript: …"ie, persistence or development of pneumonia, lung abscess, empyema, and acute respiratory distress syndrome"

Discretionary revisions
Introduction- i would disagree with the statement that CURB65 has inferior prognostic accuracy to other scores- a recent meta-analysis showed no difference in overall test performance and it really depends on how you define “prognostic accuracy”.
We have deleted the statement that CURB65 has inferior prognostic accuracy.

The word yet is not necessary on lines 11 and 12 of the introduction
The word “yet” was deleted from line 11. The next sentence has been changed to include the 2 references evaluating the CURB65 score outside CAP, which you mentioned.

It is not strictly true to say it has not been tested in non-CAP LRTI- see Chang et al Respirology 2010 sep 30 Epub ahead of print (uses CURB65 in COPD) and Howell MD et al Acad Emerg Med 2007; 14(8);709-14- validation in infection.
Thank you for pointing out these important papers. In addition, a respective paragraph was deleted from the discussion section and another paragraph modified: “This study provides evidence that CURB65 performed similarly for outcome prediction in CAP and non-CAP-LRTI patients, as recently reported (ref-Chang et al, 2010), importantly extending their clinical utility.”

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: AcceptableStatistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare i have no competing interests
Reviewer's report
Title: Enhancement of CURB65 score with proadrenomedullin (CURB65-A) for outcome prediction in lower respiratory tract infections: Derivation of a clinical algorithm
Version: 1 Date: 28 December 2010
Reviewer: ALBERTO CAPELASTEGUI
Reviewer's report:
General comments:
This is an interesting analysis aimed at assessing whether the prognostic information provided by ProADM improved the prediction of risk by the CURB65 score with regards to both adverse events and mortality in CAP and non-CAP-LRTI patients.
The study’s objective is clinically relevant, especially for its potential effects on triage decisions. The limitations of risk assessment tools (CURB65, PSI) on this question are evident. The combination of ProADM and the CURB65 score may provide for physicians an added level of confidence for treating low-risk cases (CURB65 0-1) as outpatients, and also help identify those patients with high risk based on CURB65 score who show however, a good prognostic (Figure 6 is very interesting in this regard).
The way it is written the study raises several questions and some points that should be addressed.
We thank the reviewer for important suggestions and constructive criticism, which has been addressed in the revised manuscript.

Major comments:
1- The study’s main problem is to have included cases of pneumonia together with cases with uncompensated COPD and also cases of bronchitis. The differences between these three diseases is very important conceptually, in addition they differ in their baseline characteristics, process-of-care and outcomes (Table 2).On the other hand, the number of non-CAP cases included is very low (379), with only 10 deaths found among them (thus their statistical impact is limited). This is enhanced by the fact that uncompensated COPD is not the same as bronchitis. The authors should concentrate their study on CAP and comment with lots of caution the results related to the non-CAP-LRTI group.
We agree that CAP and non-CAP-LRTI are different in terms of baseline characteristics and outcome. However, from a clinical perspective the presentation of CAP and non-CAP LRTI patients is usually very similar and the classification largely depends on evidence for an infiltrate on chest X-ray. This diagnostic test has well known limitations, especially in an older patient population with comorbidities such as chronic heart failure and COPD. In addition, it has been suggested that the development of a pulmonary infection is a continuum and in the majority a sequelae of a viral bronchitis. Tissue damage induced by viral acute bronchitis increases susceptibility for a bacterial superinfection of the pulmonary parenchyma, which defines CAP if an infiltrate is documented by chest X-ray. For this reason, we included the whole spectrum of LRTI, but also present our CAP results separately.
We have now added the following paragraph to the limitations: “Finally, since the number of patients was higher in the CAP than in the non-CAP-LRTI group and since our primary endpoint was mainly driven by the outcomes in the CAP group with relatively low mortality and adverse event rates in the non-CAP-LRTI group, the utility of the CURB65-A score for patients with non-CAP-LRTIs is less certain. The similar results of the algorithm in patients with and without CAP, however, are reassuring. Nonetheless, this heterogeneous but clinically important group of non-CAP-LRTI patients deserves particular attention in future studies testing the CURB65-A score.”

2- In the authors’ section for “any disease specific complications” the “adverse events” must be defined with greater precision. In particular, they need to show detailed information about the type and the number of those “specific complications”. They should also take into account that they are grouping under “adverse events” death, ICU admission and emphysema, among others. Including variables as different as death and for instance emphysema, in a composite end point is a limitation that should be noted. This limitation would imply that all comments related to results surrounding “adverse events” should be stated with extreme caution.

Thank you for pointing this out. All disease-specific complications are now stated in the manuscript: “…ie, persistence or development of pneumonia, lung abscess, empyema, and acute respiratory distress syndrome”. In the Results section under “Performance of CURB65 and ProADM overall and in CAP and non-CAP-LRTI” the type and number of all these adverse events are listed. Please note that there were no other disease-specific complications than empyema. The text states: “Overall, 12.2% of patients experienced an adverse event within 30 days of enrollment, including death (4.9%) and ICU admission (7.6%). Disease-specific complications - all of them empyema - occurred in 2.4% and only in CAP patients.”

We admit that there are inherent problems with composite endpoints even though they are becoming increasingly popular and accepted in many clinical trials. We added a paragraph in the discussion section on this: “In line with the original ProHOSP study (ref- Schuetz, 2009), we used a composite of adverse events defined as all-cause mortality, ICU admission, or any disease specific complications (i.e. empyema in all cases) as our primary endpoint. While this was done to incorporate clinically meaningful outcomes in light of sample size considerations, there are disadvantages of composite endpoints (ref-Ross, 2007), such as differences in the importance of each part of the composite. One may argue that while all-cause mortality is an objective endpoint, ICU admission depends in part on the experience of the physician in charge, critical-care bed availability and other “soft” factors; however, we displayed severity criteria within ProHOSP in order to standardize ICU admission. In addition, all adverse events were monitored by an independent data safety and monitoring board.”
3- Discussion, page 12, paragraph 3. The authors should discuss in more detail the apparent differences between their results and those found in reference 12. The differences are probably not so deep: Figure 5, B, CURB65 0-1 and ProADM categories, mortality rates 1.2%-0.5%-1.8%. Are there differences? What’s the p trend? It would also be useful to know the p trend for CURB65 2 and 3-5 categories.

We appreciate this suggestion to describe the differences to the study by Huang in more detail and added the following in the results:

“In patients with high CURB65 classes, increasing ProADM levels indicated increasing risk of adverse events and of mortality (p for trend 0.03 and p=0.09, respectively, in CURB65 class 2; and p for trend <0.001 and p=0.02, respectively, in CURB65 classes 3-5). In low-risk patients (CURB65 classes 0-1) increasing ProADM levels provided no additional information on mortality risk (p for trend: 0.98), but indicated significantly increased risk of adverse events (p for trend: 0.008).”

and discussion section: “Our data confirm the additional prognostic gain from ProADM with significant increases in adverse events and in mortality in the high CURB65 classes. Similarly, in our study patients with low CURB65 classes (0-1) had low mortality with ProADM tertiles providing no additional information quoad vitam. However, increasing ProADM tertiles were associated with significantly increased risk of adverse events even in the low risk CURB65 classes.”

We calculated p for trends for figures 5A and 5B, which are listed in the results section (see above).

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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

Title: Enhancement of CURB65 score with proadrenomedullin (CURB65-A) for outcome prediction in lower respiratory tract infections: Derivation of a clinical algorithm

Version: 1 Date: 4 January 2011
Reviewer: Gavin Barlow

Reviewer's report:

The article is well presented and with a few exceptions highlighted below is in good English.

We appreciate the reviewer’s concerns and suggestions to improve the clarity of our manuscript.

Major Compulsory Revisions

1. You have presented observational data that shows the potential for proADM to add something to the CURB65 score with respect to clinical decision making, but, as far as I can see (and I apologise if I have missed something), no comparative data are presented showing that the addition of proADM to CURB65 statistically significantly improves classical test performance characteristics (I presume it does, but it would be nice to see these data). Some data are presented in Table 2 (i.e. AUC of CURB65 and proADM for adverse events and mortality), but I think readers would value some expansion of this, for example, AUC of CURB65-proADM for adverse events and mortality (and statistical comparisons with either/or used alone) and other classical performance characteristics.

We agree and now present data on the prognostic performance of CURB65 alone as compared to CURB65 with ProADM in a separate paragraph; of note, ProADM significantly improved the CURB65 score for mortality and adverse event prediction overall, and in CAP and non-CAP-LRTI patients. This is stated in the results section as follows: “When adding ProADM to the CURB65 score in a joint logistic regression model, the combined model showed a significant improvement of the CURB65 score alone for mortality prediction and adverse event prediction in ROC statistics. The AUC of the combined model in the overall cohort was 0.81 (95%CI: 0.77-0.86) for mortality prediction and 0.74 (95%CI: 0.70-0.79) for adverse event prediction (p<0.0001 compared to CURB65 score for both comparisons). For CAP patients, the respective AUCs were 0.80 (0.73-0.86; p<0.00001) and 0.73 (0.68-0.78; p<0.00001); for non-CAP LRTI patients the AUCs were 0.88 (0.81-0.95; p<0.05) and 0.76 (0.67-0.85; p<0.01).”

2. Table 3 - I think it would be useful to expand this to include the same data for CURB65 and pro-ADM used alone (and in combination as is currently presented). As above, this would provide readers with more data allowing comparison of the proposed score with each of the components used alone.

We expanded Table 3 as suggested by the reviewer.

Minor Essential Revisions

1. The following sentences do not make sense (to me!): a) P4 ProADM is one of the prototype “hormokines” which have characteristics as well of hormones as of cytokines and are…; b) P11 …while daily also decisions have to take into account other adverse outcomes…

Thank you for pointing out this unclear paragraph, which we modified: “ProADM is a “hormokine”, characterized by a hormone-like behavior in non-inflammatory conditions when it is produced only by endocrine cells; and a cytokine-like behavior in septic conditions when it is ubiquitously hyper-expressed.”
2. In the paragraph discussing weaknesses, I think it is important to more overtly point out that this is not a validation study. CURB65-proADM needs to be prospectively validated in another cohort of patients and/or, as you do point out, shown to add something to clinical practice in an intervention study.

We agree that this was not a validation study. We modified the conclusions of the abstract which now state: “Additional prospective cohort or intervention studies need to validate this score and demonstrate its safety and efficacy for the management of patients with LRTI.”

3. In my own hospital, many of the low CURB65/low proADM patients cannot go home due to social (or similar) reasons. In fact, many are admitted because they (and society!) cannot cope with a relatively minor illness at home (i.e. admitted for nursing than medical reasons). I suspect the situation is better in Switzerland, but I think this problem should be more overtly discussed than currently (i.e. that the potential for discharging patients may be less well achieved than might be expected because of such reasons).

We concur with the importance of non-medical (including societal) factors and have expanded this in the limitations section: “In some settings these non-medical factors might be even more important and lead to reduced effectiveness of the algorithm. We are currently planning an intervention study with a multidisciplinary risk assessment including these factors to assess the efficacy of the CURB65-A score and the real-life effectiveness of the interdisciplinary triage algorithm.”

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

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'