Reviewer’s report

Title: Soluble RAGE as a severity marker in community acquired pneumonia sepsis

Version: 1 Date: 23 June 2011

Reviewer: James Keith

Reviewer’s report:

This is an important and timely manuscript that seeks to investigate new biomarkers of severe sepsis occurring in CAP, especially CAP produced by H1N1 2009. Although it is a small study, I believe some important results were obtained.

I would like to suggest several Minor Essential revisions to the manuscript before publication.

First, I strongly suggest that you add another appropriate Figure with "box and whiskers" graphs comparing the descriptive statistics for your serologic markers and severity assessment scores between H1N1 2009 and non H1N1 2009 severe sepsis cases. I think this is important since almost 60% of the H1N1 cases developed ARDS and 50% of the mortality was also due to H1N1 infection. If this comparison proves to be interesting, you may want to edit Table 2 in a similar fashion.

Second, I believe numbers are transposed in Table 1, ARDS column, bottom 2 lines, where you list 5 cases of ARDS from seasonal influenza, but throughout the paper you say there were only 2 cases of seasonal influenza.

Third, I have suggested several spelling and grammatical edits to improve the manuscript:

page 2, line 5- ....death from infectious disease....
page 2, lines 11-12- to evaluate ......CAP-induced sepsis and determine....
page 2, line 16- Thirty evaluable patients....
page 3, line 5- Logistic regression modelling demonstrated....
page 4, line 13- ...impact on public health...
page 4, line 15 ...illnesses produced.....
page 4, line 17- delete “as far as”...
page 4, line 18- ...unit, and 14 to 46% of them died.
page 4, line 20- delete “They” and substitute Bautista et al. studied....pneumonia. More than.....
page 5, line 2- CAP; sepsis being....
page 5, line 12- ......designed a simpler prediction.....
page 6, line 3-4- by measuring inflammatory mediators that may participate....
When Angus....after presentation, with higher......

Further, there......

America. Clinical data......

Blood samples

The HMGB1 ELISA kit...

the RAGE....

A sample of whole blood, anticoagulated with EDTA, from each patient was used for flow cytometry analysis. One hundred microliters of whole blood were incubated with a rabbit anti-human RAGE antibody(Chemicon) for 15 minutes at room temperature.

...with the U Mann-Whitney....

This technique was used to find variables that predicted the ..... respiratory system, similar to criteria....

...this elevation approached statistical significance (P=0.058) when.....

Although there has been intense CAP ......

Despite identification of several recent molecules, such as....

...activation, which may be a predictor...

Angus et al. found that....

Gaini et al. also found...

CAP demonstrated an association....

One explanation for the elevated sRAGE levels could be an increased gene expression of RAGE in patients with sepsis. Since we know that RAGE....

...between groups. Larger studies will be necessary to investigate the role of these potential sepsis markers.

...patients as splice-variants of RAGE or shed variants of cell surface...

RAGE. In contrast to animal studies where a protective effect of sRAGE was seen, we found...

As we mentioned above, this could be the result of more shed variants of cell surface RAGE with inflammation. However, the ELISA we used does not differentiate between splice variants and the shed variants of RAGE.

during sepsis, diminishing its...

patients, and that the difference between survivors and nonsurvivors approached significance.

...possible marker of sepsis. Since

organ dysfunction score, SOFA, its application as an early
marker could be limited.

**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 am presently an employee of Pfizer Inc and hold shares of the company. Previously, I was an employee of Wyeth, now a wholly owned subsidiary of Pfizer, and conducted preclinical research concerning the role of RAGE in sepsis. I am co-author of 2 publications concerning RAGE in animal models of sepsis:
