Title: "Treatment of acute pancreatitis with protease inhibitors: an updated systematic review and meta-analysis."

Version: 1 Date: 13 October 2013

Reviewer: Anubhav Mittal

Reviewer's report:

Major Revisions

1. Why were trials where protease inhibitors given oral, intra-arterial or via intra-abdominal infusions excluded? Certainly the title of the paper does not suggest that the method of giving anti-protease therapy would be a limiting factors. The authors need to explain the reasons and also modify the title accordingly.

2. Why was the administration of FFP an exclusion factor?

3. Also exclusion criteria 11 seems very global and could introduce bias. The authors need to clarify which papers were removed due to this exclusion criteria and why?

4. One of the problems with studies in acute pancreatitis is that each RCT uses differing definitions of severity. This leads to misclassification of patients into mild, moderate or severe pancreatitis and makes any meta-analysis difficult. How did the authors deal with this problem? How many different definitions of severity were used in the 17 RCTs?

5. Outcome measures should be separated into primary and secondary.

6. GRADE – it was mentioned in the letter but where is the analysis? It would be nice to know how the body of evidence stacks up in terms of quality.

7. Not enough is made of the fact that protease therapy did reduce mortality with low heterogeneity in the subgroup of patients with severe acute pancreatitis. This needs to be discussed further. Perhaps antiprotease therapy is indicated in this subgroup of patients? A Forest plot would be helpful for this subgroup analysis.

8. The conclusion is nihilistic. There is recent animal research showing that perhaps targeting anti-proteases to mesenteric lymph may be a way forward. Certainly, there should be a paragraph in the discussion about where to from here? New directions in research should be discussed rather than shutting the door forever on this type of therapy.

Minor Revisions

The language and style of writing can be improved throughout the manuscript.
**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