Author’s response to reviews

Title: Luminal lactate in acute pancreatitis - Validation and relation to disease severity.

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Author’s response to reviews:

Dear Mr Mark Andrew Cardinez and Dr Derek O’Reilly,

With this cover letter, we will submit the revised manuscript entitled, “Luminal lactate in acute pancreatitis - Validation and relation to disease severity.” for your evaluation. We would like to express our gratitude to the referees for their careful and constructive criticism. Based the comments, questions and suggestions by the referees, we have made changes of the manuscript. A detailed response to each issue is described herein. We do hope that with the review the manuscript has gained priority and interest high enough to be considered as published in the Journal.

Editor’s Comments:

In particular the conclusions need to be consistent with the limitations of the study. Luminal lactate did not predict severity.

Re: Thank you for the comment. We do agree. Accordingly, we have modified the end of the abstract: ‘Rectal luminal lactate concentration at the time of hospital admission did not predict the severity of pancreatitis.’

Editorial requirements:

1. Figure cropping.
Re: Now according to instructions.

2. Blank pages.
Re: removed.

Reply to the evaluation by the second referee

Professor Basil Ammori pointed out 3 things.

1. The authors' hypothesis was that luminal lactate on admission predicts severity of acute pancreatitis, yet their conclusion does not refer to this at all. That luminal
lactate did not predict severity needs to be stated. Moreover, the patients were not classified into mild and severe attacks and no method of classification was adopted. This shortcoming needs to be addressed.

Re: Thank you for pointing out shortcomings of the first version of the manuscript.

Page 2, we added to the abstract “Rectal luminal lactate concentration at the time of hospital admission did not predict the severity of pancreatitis.”

Page 12 in the Discussion, we modified the conclusions accordingly. Now it reads: “We conclude that rectal luminal lactate concentrations were associated with luminal O2 tension. Contrary to our hypothesis, a single rectal luminal lactate concentration at the time of hospital admission was not predictive for the severity of pancreatitis nor did it predict the clinically relevant complications or length of hospital stay. The L-lactate analyzer used adds potentially another confounding factor to the interpretation of the results.”

Severity of the pancreatitis: we would like to refer to Abid GH et al 2007 and Al-Bahrani et al 2008 when stating that we chose not to use Ranson score as severity marker of the disease. Instead we did use SOFA score as severity marker at the hospital admission and the days 3, 5 and 7. We have tested the association of the highest SOFA per patient to rectal luminal lactate at the admission. This is now more clearly pointed out. In addition, as described previously in the aforementioned reports, the length of hospital stay and hydration.

We added to the methods:

‘In addition, we measured Sepsis-related Organ Failure Assessment (SOFA score) at the first, third, fifth and seventh day of hospitalization. The clinically relevant complications (pseudocyst, abscess, drainage, necrotic pancreatitis, open necrosectomy) were recorded.’

‘Primary and secondary end points

The primary endpoint was rectal luminal lactate level and Sequential Organ failure Score (SOFA). More precisely, we chose not to use Ranson Score as severity marker. Instead we used sequential organ failure assessment (SOFA) for severity depiction during the hospital stay as reported earlier (Ammori 2007, 2008).

Secondary endpoint were: 1. laboratory measurements, 2. time between debut of symptoms at the hospital admission, hydration (total volume infused intravenously prior to rectal), and the length of hospital stay 3. need of intensive care and hospital mortality.’

We also wish to point out that indeed we wanted to emphasize the very limitation of the trial by stating already in the first paragraph of the Discussion that: ‘The main finding of our study was that a single rectal lactate measurement during the first 24 hours after hospital admission was not associated with the severity of illness or length of hospital stay, and that rectal luminal lactate did not predict the
severity of acute pancreatitis. However, this material consisted of a cohort of unselected consecutive patients with acute pancreatitis of whom only eight had clinically relevant complication.'

2. The authors overstate their conclusion "The association between rectal luminal lactate and oxygen tension indicates that luminal lactate is a marker mucosal anaerobiosis." In fact, that association was weak with an r^2=0.3. This gives little support to the conclusion statement. This needs to be discussed.

Re: With least square method we read R^2 value of 0.3226, which turns to R 0.57. This in turn translates in fact to p=0.005 through Pearson’s test (normal distribution checked). We do acknowledge the very limitation of the trial so that the n-value is low and in particular high luminal lactate was detected on in the minority of the patients. However, would certainly rely on the results as they are and read the statistics as they are. The reader of course decides for him/herself whether the results support the conclusions.

We Changed/add to results:
‘Dialysate lactate concentrations were correlated with dialysate PO2 (R=-0.57, p= 0.005) (Figure 1). Hydration intravenously prior to rectal lactate measurement was not correlated to rectal lactate concentration (R=-0.52, p=0.79). Dialysate concentrations of lactate at the hospital admission was not correlated with duration of symptoms before hospital admission (R=-0,30, p=0,13), laboratory measurements, SOFA score (table1), hospital length of stay (*R= -0,07, p=0,7), need for intensive care or mortality. SOFA score per patient per day ranged from 0 to 6 over the length of hospital stay. Overall, SOFA score did not increase during hospitalisation medians being 2(1-3), 1(1-2) and 1(0-2) on the 3th, 5th and 7th day of hospitalisation. The highest SOFA score per patient was not correlated with the rectal lactate at the admission (R=0.034, p=0.12).’

3. “The 'Primary and secondary end point parameters" should be replaced with "Primary and secondary endpoints".

Re: Duly acknowledged. Page 6, the three sentences were this occurs were deleted from the word “parameters”.

Reviewer 1. Highest sofa score was 3.

Re: Please allow us to further clarify the message: The range of total SOFA scores per patient per day varied from 0 to the highest 6. This is now clearly stated in the manuscript.

On the other hand, as pointed out by the reviewer the conclusions drawn from this patient population with limited severity of illness needs to be addressed. We now added to the Discussion:
‘The obvious limitation of the present investigation is the limited number of severe acute pancreatitis cases with only one of the patients needing intensive care. We cannot rule out the possibility of erroneously negative finding. On the other hand, eight patients developed clinically significant complication occurrence
of which none was associated with high rectal luminal lactate concentration at the hospital admission.’

In addition two different methods of lactate analysis yielded different results.

Re: Indeed, we find this as an important finding to alert the other researchers to this potential pitfall when comparing results obtained through different analyzers.

The reviewer recommends major compulsory revisions to weaken the aims.

Re: We do agree with this reviewer. However, as we designed the trial we did have the numbers based on which we presumed that mortality should be a relevant end point. The mortality was then, to our greatest surprise zero. We do accept the notion that other parameters are needed. Therefore we have made an attempt to strengthen the impact/importance of secondary endpoints. SOFA, highest SOFA, SOFA range, hydration and clinically relevant complications are emphasized. Please see the changes throughout the manuscript.

We appreciate the comments from the reviewers. Thank you for reviewing our manuscript.

Sincerely,
Lauri Pynnönen, BM
Jyrki Tenhunen, MD, PhD