Author's response to reviews

Title: A Study of Empyema Thoracis And Role of Intrapleural Streptokinase in its Management

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The Editor,
BMC Infectious Diseases

Sub: Revision of the manuscript titled “A Study of Empyema Thoracis And Role of Intrapleural Streptokinase in its Management”

Dear Sir

Thank you very much for considering our manuscript entitled “A Study of Empyema Thoracis And Role of Intrapleural Streptokinase in its Management” for publication in your esteemed journal. The thorough review by the esteemed reviewers has indeed helped us to improve the manuscript immensely.

Kindly find enclosed the point-by-point reply to each of the comments by both the reviewers.

I look forward to your reply.

Thank you
Sincerely

Amit Banga MD, DNB
First Reviewer (Dr G Simpson)

1. **Comment**: Unfortunately the clinical and laboratory details do not adequately separate the groups treated with streptokinase from those treated simply by intercostal drainage and so no useful conclusions can be drawn as to whether streptokinase improved outcome, even allowing for the fact that the controls were historical so that other aspects of management may have changed.

   **Response**: All co-authors agreed entirely with the comments of the esteemed reviewer regarding this deficiency in the preparation of the manuscript. In the original manuscript, Table 1 was prepared for the whole study group as a single cohort, to provide a descriptive analysis of the patients with empyema thoracis seen in the last 6 years at our institute. But, in light of the reviewer’s comments, it was felt that presenting the data by splitting the study group into IPSTK and non-IPSTK would be far more useful. We are pleased to comply with the suggestion and have modified the results as well as revised the Table 1 to compare the clinical and laboratory profile of the two groups.

2. **Comment**: The empyemas are described as chronic but the duration of symptoms had a huge range from three days to three years and again it would be helpful to separate the patients into those presenting early and those with truly chronic empyemas. The same sort of strictures apply to the patients with tuberculous effusions.

   **Response**: Again, all co-authors fully agreed with the respected reviewer’s suggestion. In the revised Table 1, the two groups have been compared for the median duration of the history of illness, incidence of chronic empyema (history more than 4 weeks), signs of volume loss and incidence of tubercular empyema. This definitely appears to have helped to bring out the message of the study in a better way.

3. **Comment**: With regard to the tuberculous effusions it is certainly surprising that there were no confirmatory bacteriological cultures of TB and the diagnosis was made purely on radiological features suggestive of pulmonary tuberculosis. It is certainly possible that at least some of these patients had bacterial empyemas and coincidental scars of old pulmonary TB. It would also be of interest to know whether the patients with presumed tuberculous empyemas improved simply with tuberculosis treatment.

   **Response**: All co-authors concur with the reviewer’s comment regarding the rates of bacteriological cultures of TB. During our clinical practice also we have felt all along that it was rare to isolate AFB from patients suspected as having tubercular empyema. It is totally paradoxical of what has been reported from the west. We admit that, as of now, it is difficult to determine a plausible reason for the same. Nonetheless, we would like to submit that the same trend has been reported from most of the other centers from our country, as has been highlighted in the ‘discussion’ section (page 11, para 1).

   The esteemed reviewer is justified in raising the question of reliability of diagnosis of tubercular etiology. Although one can never be absolutely sure regarding the etiology until and unless a micro-organism is isolated in a culture medium, because of the sheer number of cases of tuberculosis, that are seen in the Indian subcontinent and especially at our center, we have good exposure to cases with pulmonary lesions secondary to tuberculosis. As has been highlighted in the manuscript (page 8, para 2),
diagnosis of tubercular etiology was reached only when pulmonary parenchymal lesions that are typical of active pulmonary tuberculosis, such as soft fibro-parenchymal lesions and/or cavitary lesions in apical regions of the lung, were seen. In addition, a majority of these patients also had the typical rim-enhancing type of mediastinal lymphadenopathy, which is extremely unlikely to be due to a bacterial etiology. Also, in all these patients the type and duration of history of the present illness and other corroborative evidence (such as mantoux test), as is the standard protocol at our center, were used to reach the diagnosis of tubercular empyema. Therefore, we firmly believe that all the patients labeled as tubercular empyema did, in fact, have active tuberculosis. Unfortunately, the data regarding the response to treatment in the patients started on ATT is not available.

4. **Comment**: In the Background, on page 3, I think it is going too far in saying that open surgical drainage has been replaced by VATS, particularly in the more chronic empyemas.
   **Response**: It was not intended to come out the way this statement eventually comes out in the manuscript. We accept the error on our part and have modified the statement in the revised manuscript.

5. **Comment**: The authors state that fibrinolytic agents make the pus thinner. This is incorrect and it has now clearly been shown that fibrinolytics have no effect on pus viscosity. It seems that fibrinolytics can work only by breaking down loculation and the reduced pus viscosity noted as far back as Sherry and Tibbett’s 1949 report was attributable to the streptococcal DNase present in their impure preparation.
   **Response**: We are extremely thankful to the esteemed reviewer for raising this valid and pertinent objection regarding a glaring error on our part. We also appreciate the thorough review of the manuscript by the reviewer. We acknowledge our mistake and would like to withdraw the statement both in ‘introduction’ and ‘discussion’ section.

6. **Comment**: The references quoted in this section seem to have been misnumbered.
   **Response**: The correction in the numbering of the references has been corrected.

7. **Comment**: In the Methods, I found the dose of streptokinase confusion. I assume 2.5 lac IU means 250,000 IU. The description of the repeat dosage schedule given towards the bottom of page 5 is confusing.
   **Response**: Yes, 2.5 lac IU implies 250,000 IU. We have re-framed the description regarding the repeat dose of streptokinase. To summarize, we instilled 750,000 IU (split in to three doses at 0, 12 and 24 hrs) every alternate day to accomplish a mean dose of 375,000 IU per day.

8. **Comment**: It would also be helpful to know whether or not the intercostal tubes placed for drainage were placed under imaging and whether more than one drainage tube was required and also for how long drainage had been performed before streptokinase was used in the group receiving streptokinase.
   **Response**: We are glad that this point was raised as we routinely place intercostal tubes under ultrasound guidance except in cases where there is a large free collection. The same has now been elaborated in the manuscript (page 5, para 2, line 5). It is also correct that depending on the requirement (if the tube was lying in an area of
collection that had been drained, and there was another large separate collection) more than one tube was inserted. Although we always make an attempt to start IPSTK instillation as soon as possible, there is almost always a minimum time period of 4-5 days before the instillation is begun. This has to do with the logistics at our institute. Once a diagnosis of empyema is confirmed and chest tube is inserted, we have to ask for a date for CECT chest (which is not available on demand except for emergency cases). Since this process takes 4-5 days, all cases in the present series were on chest tube drainage alone for 4-5 days before streptokinase instillation was initiated. The same has been mentioned in the manuscript (page 11, para 2, line 7).

9. **Comment**: In the Results section, as mentioned above, there is little to be drawn from the clinical and laboratory data unless these are separated as suggested above. 
**Response**: As mentioned in the response to 1st comment we have modified the presentation of the results in the revised manuscript.

10. **Comment**: The microbiological results are slightly surprising. Apart from a failure to grow *Mycobacterium tuberculosis* the predominance of Gram negative organisms is unusual. The commonest organisms are of course in the Streptococcus anginosissrillieri group and these are not mentioned. 
**Response**: We have acknowledged the unusually poor isolation rates of *Mycobacterium tuberculosis* in the present as well as earlier studies done in Indian setting. Regarding the predominance of gram-negative organisms, we would beg to differ on this issue. We would like to submit that the finding of the present study regarding the microbiology are in concurrence with many recent studies where gram negative organisms have been found to be the commonest organisms among the aerobes. The same has been concluded in the recent BTS guidelines on the management of pleural infection (Davies *et al* Thorax 2003; 58: ii18-ii28). Lack of demonstration of *Streptococcus* group of organism appears to be related to the local sensitivity patterns of these organisms. It has been reported that the resistance of *Streptococcus* group of organisms to the penicillin group of antibiotics is still not very high in Indian setting, especially in comparison to the western data. This could be responsible for these organisms being rarely responsible for causing complicated para-pneumonic effusion / empyema in our setting.

11. **Comment**: As far as treatment goes, it is not clear why metronidazole was the commonest antibiotic used. Aminoglycosides are generally regarded as not helpful in treating empyema as penetration into the pleural space is poor and the drugs are inactivated by the low pH’s found in empyema fluid. 
**Response**: The widespread use of metronidazole in our study groups has to do with the management protocol at our center. Whenever anaerobic organisms are suspected, metronidazole is the preferred agent for anaerobic cover. We also appreciate the valid comment of the reviewer regarding the use of aminoglycosides in the patients. We would like to submit that many patients would have received these drugs for other indications such as underlying pneumonia. Also, most of the patients admitted to our center are from low socio-economic strata and are not able to afford costly drugs such as cephalosporins and the same are not available freely in the hospital supply. In most of these cases, aminoglycosides would be given for providing gram-negative coverage. The same has now been elaborated in the manuscript.
12. **Comment:** The main outcome measure is the increased pus drainage seen after instillation of streptokinase. Unfortunately this is now known to be meaningless as streptokinase itself stimulates secretion of pleural fluid. It would be helpful to have some objective description of radiological improvement in the various groups as well as details of hospital stay and so on. The only quoted difference between the streptokinase and the non-streptokinase groups is for surgical decortication which was not significant. In page 10 it is stated that surgical procedures were reduced in the patients receiving streptokinase, although this was not significant.

**Response:** We appreciate the concerns of the esteemed reviewer regarding the outcome parameters reported in the present study. We agree that the study quoted by the reviewer that was published in the year 1993, did raise some concerns regarding the validity of estimation of pus drainage after instillation of streptokinase as an outcome parameter. Nonetheless, we would like to submit our concerns regarding the validity of extrapolation of the results of this single animal study (done in rabbits) to humans. Even the authors of this study do not claim that all the increase in pleural fluid drainage in the streptokinase group was due to stimulation of pleural fluid secretion. In addition, the findings have not been supplemented by further studies, animal or human, since then. We would also like to submit that stimulation of pleural fluid secretion by streptokinase is unlikely to result in drainage of pus, which was what was seen in most of the patients in the present study. The breakdown of pockets of loculations with consequent expansion of the underlying lung was consistently seen, as was the case with a couple of patients whose CT chest are presented in figure 2. Finally, in spite of concerns regarding possible effect of stimulation of pleural fluid secretion by streptokinase, an overwhelming number of studies, even after 1993, have been reporting and continue to report the drainage of pleural fluid as an outcome parameter. Although the parameter may not be a composite marker of success of streptokinase therapy and some of the increase in fluid drainage may occur due to stimulation of secretion, the drainage is likely to correlate well with the amount of lysis of loculations in the pleural cavity. In view of these facts, we would like to believe that the comment that ‘estimation of pleural fluid drainage is meaningless’ is a little bit harsh. Nonetheless, we do acknowledge that other outcome parameter should be compared between the two groups to conclusively demonstrate the efficacy of streptokinase therapy. Unfortunately, serial radiographs/CT scoring was not available for the patients but we did follow up all patients radiologically to assess the response to streptokinase treatment. Typically patients showed consistent response with lysis of loculations and preservation of the lung function. The same had been mentioned in the first version of the manuscript in ‘results’ section (First version page 8, para 1; second revised version page 8, para 2). Regarding the rates of decortication, we would like to believe that in spite of fairly long study duration, the relatively small sample size compromised the ‘power’ of the study. We could not clearly demonstrate superiority of streptokinase therapy over conservative approach. Nonetheless, the trend was towards reduction in need of surgery and the rate of decortication was almost three times among the patients who did not receive streptokinase.

13. **Comment:** The discussion on page 11 about the mechanism by which fibrinolytic agents work, needs to be revised in view of the light of data on viscosity referred above
**Response:** The revision has been carried out.

14. **Comment:** Table 1 is probably superfluous unless the streptokinase and non-streptokinase groups are separated.
   **Response:** Various clinical and laboratory parameters for the two groups have been now compared in Table 1.

15. **Comment:** The information in Table 2 could probably simply be given in the text
   **Response:** We have removed Table 2 and the information has been added in the text in the results section (page 8, para 1)

16. **Comment:** In Table 3, I think the quoted success rates would not really be claimed by the authors of the papers quoted and this column should be removed. Furthermore, the labeling is incorrect in that figures in parenthesis denote the reference number and the number of patients in each study is given in a separate column.
   **Response:** We have complied by the suggestion of the esteemed reviewer and have removed the success rates. The labeling error has also been corrected.
Second Reviewer (Dr Akhil Bidani)

1. **Comment**: The authors use the word “pus”, which has never been well characterized quantitatively in the literature. The usual context is of thick purulent fluid, which could be better characterized by its viscosity, density, cell count, protein content and other measures of cellular debris. Clearly, the character of a purulent drainage from an empyema changes over time, and when is not thick enough to be “pus”.  
   **Response**: An enlightening comment by the esteemed reviewer. All co-authors were in total concurrence with the reviewer and agree that the character of the purulent drainage varies over time especially when patients receive streptokinase instillation. We are happy to make the correction and have changed over the term from ‘pus’ to ‘pleural fluid’ in the revised manuscript.

2. **Comment**: The authors should have given the precise composition (neutrophil count or %) rather than merely the total cell count. Was pH of the fluid measured?  
   **Response**: We have now added the pleural fluid neutrophil counts in addition to the total count in the revised Table 1. Unfortunately, pleural fluid pH data for the patients included was not available.

3. **Comment**: Was the purulent materials sent for anaerobic cultures as well?  
   **Response**: We always send pleural fluid for anaerobic cultures in cases with empyema. This is especially true in cases where clinical suspicion is there, such as cases with underlying aspiration pneumonia or those with foul smelling pleural fluid. But, anaerobes could not be isolated in any of the patients included in the present study cohort.

4. **Comment**: The authors indicate that one patient had a broncho-pleural fistula. Should that be a relative contra-indication for the use of thrombolytics?  
   **Response**: As per the standard management protocol at our center, none of the patients with a broncho-pleural fistula received streptokinase instillation.

5. **Comment**: It would have been useful to know the specific antibiotics used in these patients.  
   **Response**: We have elaborated the antibiotics used in the patients in the ‘results’ section (page 8, para 3).