

Peer Review File

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Reviewer A

Comment 1

Primary outcome is defined as "successful healing": can you define that more in details?

Reply 1

Thank you for this valid and important comment. Successful healing was defined vaguely and mostly non-standardised in most studies reviewed, with the most common criteria being 'infection resolution' or 'chest wall closure'. We have adjusted the paper to include the definitions used by the authors of the various articles we reviewed by adding "This outcome was heterogeneously defined in the studies analysed, ranging from reduced systemic signs of infection and negative cultures (14) to 50% reduction in empyema cavity and reduced infectious signs (15), to clean cavity and ability to perform thoracic closure (16, 17). The other studies did not have clearly defined success surrogates" on page 6 of the manuscript. Additionally, we have added the definition used by the authors of the review by adding "While outcomes were defined heterogeneously or sometimes not defined clearly at all in the studies analysed, a successful treatment outcome was defined by the authors of this review as discharge from hospital with a closed thoracic wound without the need for antibiotic therapy, re-intervention or renewed drain placement" on page 15.

Comment 2

118 patients had previous OWT: was the VAC applied at the same of the OWT?

Reply 2

We agree that this needs to be further clarified, therefore we have specified this in the manuscript, adding "Some authors applied vacuum sponge systems at the same time as OWT creation (17, 25, 28), while others applied the vacuum sponge several days after initial OWT creation (16, 24)" on page 11.

Comment 3

In patients who did not have a OWT, can you specify how the VAC therapy was applied?

Reply 3

We have specified how VAC therapy without OWT was carried out on page 12, addind "In these cases, the vacuum dressings (black polyurethane ester dressing) were applied using Alexis wound retractors without the need for an OWT or rib resection". We thank the reviewer for suggesting this valid change in the manuscript.

Comment 4

Were any of the patients discharged home with a VAC system in place?

Reply 4

We have added this additional information on page 12: “4 studies with a total of 13 patients performed vacuum therapy in ambulatory settings”.

Comment 5

Do the paper state how often the sponge needed changing?

Reply 5

Table 4 clarifies the number of sponge changes in the studies which were reviewed.

Reviewer B**Comment 1**

In the treatment of empyema, the disease-focused in this paper, the condition of patients with empyema, ideally, should be evaluated using the same criteria, such as the Karnofsky-Index or/and the RAPID score. Then, appropriate treatment methods should be sought and applied, and the outcomes should be evaluated using the same criteria as much as possible. Such recommendations are strongly encouraged in the conclusion.

Of course, as the authors state, it would be best if a prospective randomized clinical trial could be performed. However, it is difficult to conduct a prospective randomized clinical trial to evaluate a heterogeneous patient population. As the next best solution, we hope that the aforementioned recommendations will be presented in this paper.

Reply 1

We unreservedly agree that the RAPID score and Karnofsky Index should be used when performing treatment triage for patients suffering from pleural empyema, and we have added this as a point of criticism that the studies which exist when analysing patients with this condition often do not even include these parameters. We have added this point to the end of the discussion to add emphasis to the importance of the comments raised by the reviewer, and we have included the original publication for the RAPID score by Rahman et al. in the citations. Adjustments were made on page 18, where we have added “The authors of this paper believe that the condition of patients with pleural empyema should be clearly analysed and documented using a validated scoring system such as the Karnofsky Performance Index and/or the RAPID score. The RAPID score has been shown to accurately predict treatment outcomes in patients with pleural empyema (39). Improvements in the RAPID score and/or Karnofsky Performance Index should also be used to evaluate the treatment outcomes”.

I have several questions before the acceptance of this paper. I would appreciate your help in improving the paper and responding to my questions.

Comment 2

The main goal of intrathoracic vacuum therapy is to eliminate or minimize the empyema space. The empyema space is reduced by the expansion of the remaining lungs. In this sense, empyema space reduction after pneumonectomy is very difficult because there are no lungs to reduce the empyema space; open window thoracostomy (OWT) after pneumonectomy may lead to worsening of the contralateral lung expansion and possibly worsening of right heart failure. Therefore, empyema after pneumonectomy should be analyzed as a special issue. I would appreciate the authors' opinions.

Reply 2

We thank the reviewer for raising these extremely important points. We had initially considered excluding patients with post-pneumonectomy empyema for similar reasons but had come to the conclusion that all intrathoracic vacuum therapy regardless of origin of empyema would be included in this review. However, the pathophysiological mechanisms of empyema cavity space reduction are certainly different in patients with post pneumonectomy empyema, and we have adjusted the manuscript on page 4, adding “An exception are patients with post-pneumonectomy empyema, where no lung tissue remains to fill the empyema cavity” and on page 5 “In post pneumonectomy patients, OWT may also impair the re-expansion of the contralateral side and lead to worsening right heart failure”, to highlight this.

Comment 3

It is assumed that interstitial pneumonia causes contractile changes in the lungs that are resistant to the reduction of the empyema space. The authors would like to receive input on the impact of the presence or absence of interstitial changes after treatment of pyothorax.

Reply 3

We thank the reviewer for pointing this out. Similarly, to the poor reporting of the performance status of the patients treated with intrathoracic vacuum therapy, the studies included in this review included heterogeneous patient groups with empyema due to postoperative complications or pneumonia. A differentiation of the outcome of patients with interstitial pneumonia versus patients without pneumonia was unfortunately not possible. However, we do believe that the vacuum therapy may soften the empyema capsule and subsequently lead to a reduction in volume of the empyema cavity independent of interstitial changes. This is a debatable point, and we have included these new aspects in the discussion by adding “The heterogeneous patient cohorts across all analysed studies also makes it difficult to assess the quality of treatment for different causes of empyema. For example, interstitial pneumonia may lead to contractile changes in the lungs, inhibiting their re-expansion needed for reduction of the empyema cavity. Further studies should focus on patients with just one cause of empyema to allow an analysis of more homogeneous patient groups. However, the tissue softening of the empyema capsule through vacuum therapy may lead to a reduction of the empyema cavity independent of interstitial lung changes” on page 19 of the manuscript.

Comment 4

Is it correct to assume that the mini-vacuum technique does not require a rib resection? If so, it would be a benefit to the patient in terms of pain relief and minimal destruction of the ossiculothorax. I would like to hear the authors' opinions.

Reply 4

This is indeed correct. We have clarified this on page 12 by adding “In these cases, the vacuum dressings (black polyurethane ester dressing) were applied using Alexis wound retractors without the need for an OWT or rib resection”, and on page 17, “This means that a rib resection is not necessary, possibly leading to pain relief and higher levels of patient comfort”.

Comment 5

How are the authors treating empyema after the time of writing this paper? If you could give us a brief flowchart of this process, it would be helpful in actual practice.

Reply 5

The authors are currently performing and will soon publish another study highlighting our treatment algorithm for patients with pleural empyema and include a new treatment modality. As this is currently still in the validation phase, we hope that our next paper will shed light on these new treatment modalities.

Comment 6

Is it possible to utilize vacuum therapy in an outpatient setting? I would like to hear your opinions.

Reply 6

This is a very valid point and we thank the reviewer for bringing this up. We would like to refer to our answer to Comment 4 of Reviewer A.

Comment 7

The success rate of empyema treatment is used as the endpoint in this manuscript, but what is the definition of success? Is it a condition that does not require antibiotic therapy or wound disinfection? I would appreciate your opinion.

Reply 7

The authors agree that this was not adequately addressed in the initial version of the manuscript. Please refer to the reply to Comment 1, Reviewer A.

Comment 8

Are there differences in treatment difficulties among different bacterial species? What about the impact of treatment with steroids or other immunosuppressive drugs? The opinions of the authors would be greatly appreciated.

Reply 8

The reviewer raises another extremely interesting point. Our research group is currently investigating separate sub-species of bacterial infections as well as the impact of immunosuppressive drugs in pleural empyema and hope to publish

evidence on this soon.

Reviewer C

The authors present an excellent review on the application of NPWT in thoracic empyema. This is a relatively understudied treatment and definitely is contemporary. The authors rightly point out that the evidence of this technology is poor but given the circumstances by which these patients present, it is unlikely a randomized trial will ever take place. The authors adhere to the PRISMA guidelines and have summarized and synthesized the literature effectively. I would make a few minor suggestions to improve the paper:

Comment 1

The primary outcome is rate of successful healing of the empyema. This is a bit vague and should be better defined. What constitutes successful healing? No further interventions required? No readmissions?

Reply 1

The authors agree that this was not adequately addressed in the initial version of the manuscript. Please refer to our reply to comment 1, Reviewer A. We thank the reviewer for this valuable suggestion.

Comment 2

In the tables length of stay differences are described as difference from the control. This is not necessary, it would be better to simply state the LOS in each group and provide an interquartile range (IQR). The p-values for all analysis should also be provided in the tables. The confidence intervals are provided which is good.

Reply 2

We agree that this would and overall numeric value would better represent the LOS, unfortunately these data were not provided in the meta-analysis from which the tables are taken. The same applies for p-values. Following suggestions by a further reviewer, we have removed the tables 6 and 7 from the manuscript and added them as an appendix. We hope that this improves the readability of the paper.

Reviewer D

Congratulations on this interesting and important systematic review. It brings an important analysis of the most recent option in the treatment for these complex patients.

My only suggestion is to remove tables 6 and 7 which bring Vats and thoracic drainage as comparators because certainly, the population for these procedures is quite different from the population selected for the OWT and/or vacuum therapy.

Reply

We thank the reviewer for this suggestion. We have removed the tables from the document and added them as an appendix.