Peer Review File

Article information: https://dx.doi.org/10.21037/med-23-25

Reviewer A

Comment 1: The authors report their clinical review of the diagnosis and management of spontaneous pneumomediastinum. While they partly convey the importance of this clinical entity, their review is limited by an unclear methodology for gathering and evaluating source material. Several critical statements are inaccurate by incorrectly attributing source information.

Reply 1: Although we have presented more of a clinical systematic review rather than a Cochrane database review, we feel this is adequate and appropriate given the highly variable ways spontaneous pneumomediastinum can be evaluated and treated. In addition, we also performed a thorough PUBMED, systematic literature search by first and senior author, in which there is very little concrete evidence and/or data for one optimal evaluation algorithm and treatment plan for spontaneous pneumomediastinum. Our clinical review is based on the most recent uptodate literature in addition to the author's extensive experience in managing spontaneous pneumomediastinum for over 5 million insured members, 21 medical centers, and all of Northern California, we feel this is still a very important review for our readers. We as an integrated health system have also instituted our current algorithm presented in this manuscript as our standardized guideline for spontaneous pneumomediastinum management. We very much appreciate the feedback and have reviewed and updated sources a second time to provide to our knowledge clinically relevant and up to date material.
Changes in the text: Multiple throughout text as this is an overarching comment.

Comment 2: Abstract lines 23-47: Most of the abstract primarily states generic background information that would be more suitable for the background section of the manuscript. For a review such as this, a concise abstract with a more cogent description of the current state of knowledge and gaps in knowledge would strengthen the manuscript.

Reply 2: We thank you for the feedback and have shortened the abstract in favor of a more succinct and directed approach.
Changes in the text: Please see page 2, starting at line 25.

Comment 3. Lines 94-95. The authors state that "Best [sic] evidence guiding pneumomediastinum treatment comes from various case series and reports." While it is true that the best source data is from case series, there are a number of reviews on the topic that arguably provide the best cumulative evidence guiding pneumomediastinum treatment.

Reply 3: The reviewer's point is well-taken, and the line has been updated to clarify that the highest level source data is from case series along with multiple review papers. However, there are no meta-analyses or randomized controlled trials available regarding this topic. Additionally, we included both small and larger reviews of spontaneous pneumomediastinum and referenced in the text.

Changes in the text: Please see page 4, line 120.

Comment 4. Lines 100-103 state the objective of the manuscript, "This review aims to gather the current

evidence guiding isolated pneumomediastinum (pneumomediastinum without associated effusion) diagnosis and management, with respect to potential initiating event causing pneumomediastinum: the airways and lungs (i.e. coughing) versus the gastrointestinal tract (i.e. vomiting, retching).” This statement will confuse the readership. I think the authors mean to gather current evidence guiding diagnosis and management of spontaneous pneumomediastinum with respect to two scenarios: 1) when pneumomediastinum is secondary to spontaneous pneumomediastinum causes with no concern for esophageal rupture (e.g. cough, asthma) versus 2) cases where there is history possibly consistent with esophageal perforation (e.g. vomiting, retching), but still without esophageal perforation. However, the wording suggests the possibility of spontaneous pneumomediastinum from a GI source; to my knowledge this is not an entity that exists, except in cases of perforation.

Reply 4: Thank you for your clarification as to how this section in initial version of the manuscript may be confusing and/or misleading. We do indeed mean to distinguish between lower and higher concern for esophageal rupture based on history. These lines have been reworded to reflect this.
Changes in the text: Please see page 5, line 129-131.

Comment 5. Page 4, line 157: The phrase “ascertain for certain” is redundant.
Reply 5: Yes, we agree this is a typo and redundant. “For certain” has been removed.
Changes in the text: Please see page 7, line 183.

Comment 6. Page 4, lines157-160: The authors state that “The most likely cause of pneumomediastinum is due to alveolar rupture as a result from increased Valsalva pressure from prolonged coughing or vomiting/retching as compared to the less common tracheal/bronchial injury or esophageal perforation32.” I can find no report of the incidence of esophageal perforation to validate this statement in the referenced publication.

Reply 6: Thank you for highlighting this discrepancy. To make the statement more concise, the statement is instead revised to emphasize that primary spontaneous pneumomediastinum is indeed from alveolar rupture from intravalsalva forces such as coughing and/or retching and that this is more common than secondary causes of pneumomediastinum which are separate from our topic, with appropriate citation.
Changes in the text: Please see page 7, line 184.

Comment 7. Page 5, lines 183-186: The authors state, “In Song et al., 45 patients with spontaneous pneumomediastinum were studied, 90% underwent esophagogram, 31% bronchoscopy, and 2.2% endoscopy, and no injury was found. 24 Similar findings have suggested futility of extensive workups for most cases of spontaneous pneumomediastinum.10,33” These statements may confuse the reader. A case series of spontaneous pneumomediastinum is, of course, going to have negative esophagrams, bronchoscopies and endoscopies. However, the futility of extensive workup for “typical” spontaneous pneumomediastinum (e.g. after an asthma patient coughs) does not mean an extensive workup is f1utile for all cases of spontaneous pneumomediastinum. Although that’s not what the authors suggest, their wording may lead some readers to that conclusion.

Reply 7: We understand that this statements may be confusing and have reworded this section to emphasize that while the extensive workup should not be routinely performed for all patients, it may be essential in some patients.
Changes in the text: See page 8, 210-215

Comment 8. Page 5, lines 197-201: The authors quote “age less than forty years” as a low risk feature of pneumomediastinum features. There is no mention of "forty years" as an important demographic in the referenced articles.

Reply 8: While the referenced articles demonstrated a mean age of approximately 20 years in patients with pneumomediastinum, we agree they are not the best references for this demographic risk factor for pneumomediastinum. These citations have been removed and replaced with the study from Morgan et al. 2023 highlighting age greater than 40 as a high risk factor.

Changes in the text: Please see page 9, line 238-241.

Comment 9. Page 6, lines 239-242: The authors reference the low recurrence rate of spontaneous pneumomediastinum, but give no putative recurrence rate (a well known value) or mention of recent conflicting studies such as Kumeda et al.'s "Clinical features of recurrent spontaneous pneumomediastinum (2023)".

Reply 9: We agree that it would be prudent to include the recurrence rate established in the literature and reference Kumeda et al.'s contrastingly high recurrence rate. The text has been updated to include both these
Changes in the text: Please see page 10, lines 281-293.

Thank you for the opportunity to review your manuscript titled: "a clinical review of spontaneous pneumomediastinum, this topic is very interesting and has been discussed in the literature for many years; While most cases of spontaneous pneumomediastinum(sPMD) are benign and resolve without intervention, this is not often true for non-spontaneous PMD, which has a variety of other causes, including esophageal perforation, traumatic respiratory tract injury, and infection. Patients presenting with suspected sPMD are often worked up for esophageal perforation because such cases can rapidly lead to sepsis and death if not adequately treated in a timely manner. The recommended workup for sPMD includes esophagram or CT esophagram (CTE). Nonetheless, these cases, are very rarely found to have esophageal perforations on imaging and often are managed conservatively. We noticed that your review of the literature does not include a rising etiology as THC-induced pneumomediastinum which we recently published in from Frontiers of Surgery. I am not sure why and pneumopericardium is an indication for esophagram still can be associated with Macklin effect could be as part of the pneumomediastinum. Tension pneumopericardium is a different clinical scenario which mandate drainage or surgical intervention.
Can you define a better criterion for esophagram? What will be to supportive care and for how long?, how long do you recommend to admit the patient to the hospital? What will be your criteria for intervention, elevated white count, fever, other clinical changes?

Reply 9: We thank you for your point regarding THC-induced pneumomediastinum and included this as a rising etiology of spontaneous pneumomediastinum. We have included the Frontiers of Surgery paper as a reference as well. Additionally, we agree that pneumopericardium can still be associated with Macklin effect and thus have removed it from indications for esophagram. We discuss pneumopericardium and tension pneumopericardium separately.

We will define our criterion for esophagram to be pursued if any of the following are present: hemodynamic instability (tachycardia or hypotension), fever, leukocytosis, tachycardia, or persistent symptoms. Supportive care involves: no antibiotics, advancing diet as tolerated, and supplemental O2 if needed while admitted.

Regarding admission, there is limited literature as to whether to admit the patient and for how long. Given that much of the data is retrospective, the reported average length of stay has been reported for 2-4 days, but is not granular enough to elucidate the reason for admission (instability? Pain? Other?). However, many

of these case series speculate that admission may not be warranted given many patients have minimal intervention once spontaneous pneumomediastinum is diagnosed. While our thoracic surgery center currently has a protocol to discharge the patient with return precautions; we are currently studying this data and hope to report the results. However, given that there is no data on routine discharge, we recommend a clinical judgment on admission for observation versus discharge in each clinical scenario. Patients with risk factors for recurrence, including asthma, pain or other ongoing symptoms may warrant admission.

Changes in the text: See page page 3 line 102, page 8 lines 217-241and Figure 2.

Reviewer B

1. Please also indicate the **department** information of Affiliation 2. You should provide the affiliations of author including: name of department(s), unit, city and country.

The edited versions of the affiliations are:
Cynthia J Susai, MD[1]; Kian C Banks, MD[1]; Nathan J Alcasid, MD[1]; Jeffrey B Velotta, MD[2]

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2. Author Contributions section of this article is incomplete. Please provide author contributions in the following format:
(I) Conception and design:
(II) Administrative support:
(III) Provision of study materials or patients:
(IV) Collection and assembly of data:
(V) Data analysis and interpretation:
(VI) Manuscript writing: All authors.
(VII) Final approval of manuscript: All authors.
Note: 1. With VI and VII, "All authors" is obligatory, while the other credits are case-based.

The manuscript has been appropriately updated with the format for author contributions.

3. Please indicate running title in your title page. Please note that running title should be within 60 characters including spaces.
A running title "Spontaneous Pneumomediastinum" has been added to the title page.

4. Please enrich your Abstract to more than **200** words.
Thank you for your feedback; we have added more to our abstract to fully convey the aim and findings of our manuscript.

5. In the **main body** of your paper (except for Introduction and Conclusions sections), you should **discuss about the stren3gths and limitations of the review**. Please check and supplement this information.
We have supplemented this information; please see page 12-13 for these updates.

6. If applicable, please provide **editable** version of Figure 2 in Word/PPT format since it's a flow diagram.

The flow diagram is editable in Word; after a single click on the flow chart a “SmartArt Text” editor appears to edit wording.