

Peer Review File

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Reviewer A

The first case indicates that the used endobronchial valves were not only well tolerated by the patient with AD-HIES, but also did not provoke the development of parapneumonic purulent complications.

The second case struck with its uniqueness as it describes how postoperative complications can be corrected/ resolved without reoperation (“which further worsens their pulmonary compromise”) if one is persistent in the installation of endobronchial valves in six segmental bronchi for the treatment of Persistent Air Leaks Associated with Autosomal Dominant Hyper-IgE Syndrome.

Reply: No request for revisions is noted. Thank you for your summary of our report.

Changes in the text: None

Reviewer B

Thank you for your work reporting these cases and a well-written article.

I only have minor comments:

1) Please explain why these patients were not considered (or accepted) for surgical management given their young age, especially the 2nd case which was a post-operative patient

Reply: Thank you for the question. In the past, repeated surgeries were frequently performed in AD-HIES patients after air leaks developed from their lung surgeries due to the intrinsic poor healing. Unfortunately, lung surgeries frequently did not correctly the air leak quickly and led to further lung tissue loss, infection and more prolonged air leaks. Therefore, we have been focused on finding alternatives to lung surgery, which the endobronchial valves provided for these individuals. We further clarify this point.

Changes in the text: See Introduction on page 3. “In this subgroup, definitive treatment has been difficult without additional surgery, which has led to more lung tissue lost, and further worsened their pulmonary compromise.”

2) Recommend altering the conclusion paragraph. It includes strengths and limitations which should be in the discussion

Reply: Thank you for this observation, and we agree.

Changes in the text: See the Conclusions section on page 6.

Strengths and limitations are moved into the Discussion section above as the last sentences. “Strengths of this report are the availability of the entirety of clinical information prior to and post-placement, including relevant genetic data. It also provided a brief overview of the utility of EBV in this unique and challenging patient population. Shortcomings include the description of only two cases.”

For additional clarity, we moved our comment about need for prospective study to Conclusions section as the final sentence. “Our experiences suggest that EBV should be considered in the first-line during management of PAL, but more prospective studies are needed in AD-HIES patients.”

3) Please reconsider (or alter) Table 1 (Timeline) if truly required - it could either be summarised in the text OR explained via the Table rather than repeating similar points. Please revise Air-leak development at Day 5 in Case 1 as an air-leak develops with any pneumothorax.

Reply: Thank you for this suggestion about the Table and noticing the mistake about air leak leading to pneumothorax. While it is true that the Table (timeline) contains redundant information from text, the graphical layout may be preferred by some readers who are looking for highlights similar to the Key Findings box. In keeping with our intent to maximize communication and readability, we would hope to keep the Table.

Changes in the text: (in Table) Patient 1 Air leak Recurred: Hospital Day 5

Reviewer C

Interesting case report. The procedure is not new, nevertheless I think it is worth to publish due setting of Hyper-IgE syndrome

Reply: No request for revisions is noted. Thank you for your comment of our report.

Changes in the text: None

Reviewer D

Thank you for the\is interesting case series.

I have several comments

- It is interesting to note that endobronchial valves were used as a temporarizing measure. However, in the literature, endobronchial valves work best if there is minimal collateral ventilation. There

are a few ways - The Chartis pulmonary assessment system or looking at the CT to see fissure integrity. How did the team do so? The methods described in lines 129-141 is an attempt to determine the site of the PAL, rather than looking at the lack of collateral ventilation. I wonder whether the second set of EBV was required because there was collateral ventilation.

Reply: Thank you for raising this concern. We agree that these EBV valves perform well when collateral ventilation is minimal or non-existent specifically in context of COPD/emphysema therapy. Patient 2 illustrates the complexity of the wound healing deficits in patients with AD-HIES. This patient likely had collateral ventilation by inferring from our difficulty in precise localization of a single airway contributing to PAL. The lung scarring and wound healing associated with AD-HIES is very complex and not similar to the physiology of COPD patients. And of course, identifying the airway(s) contributing to PAL is different from identifying regions of lungs with hyperinflation. Furthermore, the preoperative CT scan appearance would not reliably reveal lung fissures especially as this patient had surgery to remove a large symptomatic giant pneumatocele. Since we used Olympus Spiration EBV, the Chartis System would not apply to us since it is a proprietary device for use with Zephyr valves.

Changes in the text: None (please see reply to your similar suggestion to mention about this issue in Discussion section).

- The authors had highlighted the possible complications of EBV. But those were in the setting of COPD and on occasions, pneumothorax. If this is related to bacterial infections, was there anything done to deal with the risks involved with surrounding infection? Including infection of the EBV? Was prolonged antibiotics given as a precautionary measure? This is particularly so as the authors had highlighted that AD-HIES patients frequently suffer from recurrent infections, empyema and possible surgeries.

Reply: Thank you for this important question. It is true these patients are at increased risk of infection and that was a significant concern of ours. These patients are typically on suppressive antibiotics for *Staphylococcus aureus*, which was continued. Also, both patients received antibiotics for suppression of their airway colonizing Gram negative bacilli while the EBVs were in place.

Changes in the text:

An addition sentence was added about this to each case description.

(page 4, patient 1) “Intravenous antibiotics were then changed to oral antibiotics covering the infecting *Staphylococcus aureus* and *Pseudomonas aeruginosa*.”

(page 5, patient 2) “Intravenous antibiotics targeting the airway colonizing *Escherichia coli* and *Pseudomonas aeruginosa* that were continued through the PAL were changed to oral suppression.”

In the Discussion section (page 6) the following sentence was added: “The EBV were well tolerated in these AD-HIES patients, and no progressive infections were noted, although

suppression of the airway colonizing pathogens were continued while the EBV were in place due to the patients' immune compromised state."

- It may be relevant to discuss how EBV application in such cases differ from what is routinely described in literature. There are several resources to refer to on this ie *Pulm Ther* 2023;9:49-69.

Reply: We interpret this suggestion to be related to your point raised above when inquiring about measures of success for EBV placement (as commonly known for COPD patients). Thank you for suggesting a recent timely review article of approved indications for EBV.

Changes in the text: See new sentence in Discussion section on page 6.

"Although, unlike the multiple patient trials that have defined the clinical scenarios for successful deployment of EBV in COPD, PAL physiology is different and not yet rigorously studied in EBV trials."

Add new reference {5}_Li, A., Lee, P. Which Endoscopic Procedure to Use and in What Patient? Valves, Coils, Foam, and Heat in COPD and Asthma. *Pulm Ther* **9**, 49–69 (2023). <https://doi.org/10.1007/s41030-022-00208-6>.

Updated reference list to total of 6 articles.