Reviewers' comments:  
  
  
Reviewer #1: The manuscript PULMOE-D-18-00108 "Portuguese consensus document for the management of alpha-1-antitrypsin deficiency" by Mineiro et al is a state of the art narrative review of existing literature in this subject, and provide a general guidance and recommendations for the diagnosis and management of AATD that can be adopted by Portuguese clinicians.  
The subject is of utmost importance due to its severity and high level of underdiagnose and so, indicating the need to increase the knowledge of diagnosis criteria and treatment approach.  
  
I have no major suggestions, only minor suggestions:  
  
- Authors use several acronyms along the text, including: AAT, AATD, RCL, IEF, ER, NE, URTI, DBS, CT. To make it easier for readers, I suggest adding a list of acronyms.

* Agreed and done

- The manuscript does not include figures, for example, images. It might be interesting to include a CT image of panlobular emphysema, or to show CT examples on how to calculate densitometry parameters, for instance in Page 24, 5.1.2.2 Chest CT.

- We think that as the document is a diagnosis and management recommendation, we don’t think there is a necessity to include figures.   
  
- Page 4, line 45: "6 MWürzburg", instead of "6 Mwürzburg"

- Corrected  
  
- Page 4, line 46: "2 ZAugsburg", instead of "2 Zaugsburg"

- Corrected  
  
- Page 10, line 31: "A review published in 2010 summarizes information on the relationship between severe AATD, asthma, and COPD" (This statement needs a reference).

- Added (reference 75)  
  
- Page 14, line 1: "…that that…"

- Corrected  
  
- Page 15, line 18: "Therefore, AAT tests must be carried out preferably outside of these episodes." can be replaced by "Therefore, AAT tests must be carried out preferably outside these episodes."

- Agreed and replaced  
  
 - Page 15, line 38: "However, some patients may present normal or high AAT levels and little anti-elastase activity due to the fact that not every protein is active (oxidised, destroyed, or protein that is not capable of linking to neutrophils)" can be replaced by "However, some patients may present normal or high AAT levels and little anti-elastase activity due to the fact that not every protein is active (proteins might be oxidised, destroyed, or not capable of linking to neutrophils)".

- Agreed and replaced  
  
- Page 18, line 39 and page 25, line 30: Siiama and Siyama are written differently.

- Corrected to SIiyama  
  
- Page 22, line 20: Table 4: "Additional exams in the early stage…" instead of "Additional Exams in the early stage…"

- Corrected  
  
- Page 22, Table 4 and page 25, line 40 and page 26, line 6: authors should clarify what is FibroscanTM

- Agreed. We added to the text the following sentence: “FibroscanTM, a noninvasive technique using a probe with an ultrasound transducer and a mechanical vibrating device, exerts dynamic stress on the body surface to generate shear waves. The shear wave velocity can then be converted into liver stiffness, which is expressed in kilopascals. It may be used as an alternative to ultrasound to assess steatosis and liver fibrosis in patients with AATD.”  
  
- Page 23, line 12 and page 24, line 14: "hyperinflation" instead of "hyper-inflation".

- Corrected  
  
- Page 23, page 12: "… which translates into a decrease in forced vital capacity (FVC) and an increase in total lung capacity (TLC) and in residual volume (RV)", instead of "… which translates into a decrease in forced vital capacity (FVC) and an increase in total lung capacity (TLC) and a residual volume (RV)".

- Agreed and replaced  
  
- Page 23, line 48: This sentence is not accurate:  
"Patients suffering from AATD may hyperventilate while resting and their maximum voluntary ventilation may exceed 80% during mild exercise, which is an indication that ventilation may limit higher levels of exercise."  
I suggest authors to use this sentence instead:  
"Patients suffering from AATD deficiency may have increased respiratory rates while resting and their minute ventilation (VE) may exceed 80% of predicted maximum voluntary ventilation during mild exercise, which is an indication that ventilation may limit higher levels of exercise."

- Agreed and replaced  
  
- Page 23, line 53: Instead of "The 6-minute walk test assesses not only the cardiorespiratory function during exercise, but it is also important for determining the BODE index." It might be "The 6-minute walk test assesses not only the exercise functional capacity, but it is also important to estimate disease prognosis by calculating the BODE index.

- Agreed and replaced  
  
- Page 24, line 19: "intercostals" instead of "intercoastal"

- Corrected  
  
- Page 25, line 8: Please clarify "percentile 10 (P10) is the density value (HU) on which 10% of all pixels have low density, and, as a true density measure, this value will decrease as the emphysema worsens." Can authors give an example of a low-density value in Hounsfield Units?

- We don’t agree for the need to add na exemple as you ask. We replaced the sentence to make it more easily understandable: “The 10th percentile density (PD10) is derived from a histogram recording the densities in Hounsfield units (HU) of all lung voxels and is defined as the threshold value for which 10% of all lung voxels have a lower density. As a true density measure this value will decrease as emphysema worsens.”

- Page 26, line 15 and line 55: Both citations should be in "brackets"

- Added  
  
- Page 28, Table 5: In the column of "Primary Endpoint" some of the lines start with a "-"and others not. Please uniform all the table lines in using or not the "-"

- Corrected to none  
  
 - Page 28, Table 5: "FEV1 decline" instead of "FEV1 Decline". Please correct all the table accordingly.

- Corrected  
  
- Page 28, Table 5, line 7: "Lower FEV1 decline in the treated group with FEV1 35-49% of predicted value" instead of "Lower FEV1 decline in the group treated with FEV1 35-49% of predicted value"

- Corrected  
  
- Page 28, Table 5, lines 48 and 58: "Secondary endpoint" instead of "Secondary"

- Corrected  
  
- Page 29, Table 5, line 12: Chapman et al study… dose of augmentation therapy was not specified in the second column

- Added  
  
- Page 29, Table 5, line 18: "- No differences in the pulmonary function ~"   the phrase ends with a "~"

- Corrected  
  
- Page 29, Table 5: in the bottom of the table there should be a note: "NS - non significant"

- Added  
  
- Page 30, line 13: "Decisional cut-off" instead of "Decisional Cut-off"

- Corrected  
  
- Page 30, line 21: "Observational studies indicate a smaller decline in pulmonary function of  
patients undergoing therapy with airways obstruction within FEV1 31-65% interval or  
FEV1 35-49% of predicted value." Authors should clarify the difference of "FEV1 31-65% interval" and "FEV1 35-49% of predicted value", because both are % of predicted values, aren't they?

- These are two articles in which one studies a subgroup within FEV1 31-65% of predicted value and the other one studies a subgroup within FEV1 35-49% of predicted value. We replace the sentence to the following: “Observational studies indicate a smaller decline in pulmonary function of patients undergoing therapy with airways obstruction within FEV1 31-65% or FEV1 35-49% of predicted values”  
  
- Page 31, line 12: FEV1 should have the "1" underscript.

- Corrected  
  
- Page 31, line 27: "An integrated assessment of the findings in these two studies showed a significant reduction in the decline of lung density in treated patients, where -2.297 g/L  
(p=0.006) difference was found between groups."…and in line 41:" Lung density loss of 1.45 g/L/year was observed in the treated group vs. 2.19 g/L/year in the placebo group…" This is the first time in the manuscript where a measure of lung density is shown in g/L. How was it measured? These variable and unit should be clarified earlier in the text, maybe in the page 24, where calculation of densitometry parameters is referred.

- We added the following sentence: “Lung attenuation values (in HU) can be converted to lung tissue density values (g/l) by adding 1000 to the HU. For example, a 15th percentile density value of -950 HU equals a lung density of 50 g/l, meaning that 15% of the pixels/voxels have a density value below 50 g/l”. We added reference 125.  
  
- Page 31, line 46 and in Page 32, line 34:  "health-related quality of life" instead of: "Quality of Life".

- Corrected  
  
- Page 32, line 48: "Taking into account all these data" instead of "Taking into account all this data".

- Corrected  
  
- Page 33, line 19:  In the criteria for augmentation therapy: "- No selective immunoglobulin A deficiency". Authors should explain in the previous text, the reason for this exclusion.

- We added: “Selective immunoglobulin A (IgA) deficiency is a contraindication to treatment as augmentation therapy may contain small amounts of IgA. Hypersensitive or anaphylactic reactions with anti-IgA antibodies may occur in these patients, therefore, testing for this deficiency is recommended before initiating therapy”  
  
  
In References:  
  
- Page 37, line 18: Trends Mol Med. instead of "Trends in molecular medicine"  
  
- Page 37, line 28: "Arch Immunol Ther Exp" instead of "Archivum immunologiae et therapiae experimentalis."  
  
- Page 37, line 33: "Am J Respir Crit Care Med" instead of "American journal  
of respiratory and critical care medicine."  
  
Authors should correct all other references accordingly. Journals should be presented as abbreviations and the first letter is a capital letter. The only exception is the references 40 and others, where the journal Copd should be corrected as COPD.

- All corrected  
  
  
- Page 40, line 41: Ref 67: the 1 of FEV1 should be underscript

- Corrected  
  
- Page 40, line 51. Ref 70 is not correct: "Wencker M, Denker J, Konietzko N. Serial measurements of FEV1 over 12 years in a patient with alpha-1-protease inhibitor deficiency:influence of augmentation therapy and infections. Respiration; international review of thoracic diseases. 1994;61(4):195-8.  
Ver refs 125, 127, 139, 144."  
There are two journals: Respiration and International Review of Thoracic Diseases. The correct one is Respiration. Please erase the other.

- Corrected  
  
  
- Page 41, line 15: "Pulmonology Portuguese Society Bronchiectasis Study Group" instead of "Pulmonology Portuguese Society Bronchiectasis Study G."

- Corrected  
  
- Page 43, line 46: 124 "INVALID CITATION" - please clarify.

- Reference 124