Author's response to reviews

Title: Interstitial Lung Diseases In The Hospitalized Patient

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Author's response to reviews: see over
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Ursula D'Souza, PhD
Senior Editor
BMC Medicine

Dear Dr. D'Souza,

I write in response to reviewer’s comments regarding our manuscript entitled “Interstitial Lung Diseases In The Hospitalized Patient”. We are pleased with the favorable remarks from the reviewers and appreciate their comments as they have improved the content of manuscript. The manuscript has been revised in response to these comments. Summarized below are responses to their comments. In addition, the abstract has been revised consistent with the standards for your journal. Changes to the manuscript are highlighted green in the manuscript. Thank you once again for the careful consideration of our manuscript. We hope you find the current version suitable for publication.

Sincerely,

[Signature]

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Re: David Hansell’s comments for discretionary revisions:

1. The title and scope of the article is a little confusing – for example, the second sentence of the last paragraph of the Background (page 3) is ambiguous. It could be read as a) the patient just happens to be in hospital when their chronic ILD is first manifest or b) the patient will need to be admitted to hospital at the time their ILD first declares itself. This confusion could easily be attended to (and the title could probably be modified to give a better idea of the scope of the article).

   Response: We agree with this comment and have edited the MS on lines 60-61 to read: “In some instances patients need to be hospitalized during the first manifestation of, what ultimately proves to be, a chronic ILD”. The title has not been edited as we prefer the current title.

2. Suggest “an absence of ground-glass opacities” is omitted in the HRCT description of IPF/UIP (page 4, second paragraph) – in very few cases is there a complete dearth of ground-glass opacities.

   Response: We agree with this comment and have edited the MS on lines 74-75 to read: “a paucity of ground glass opacities”

3. Consider moving “characteristic” (third from last line, page 4), given that the changes are not specific to an acute exacerbation of IPF.

   Response: Characteristic was not removed from the sentence because the sentence would then read as if all HRCTs show new ground glass opacities, etc. This is incorrect.

4. The reversed halo sign is no longer regarded as particularly specific for organizing pneumonia (page 6, second paragraph), so consider rewording – other signs including a perilobular pattern/distribution are, in fact, more frequent and helpful in suggesting the diagnosis of organizing pneumonia.

   Response: A reference to the perilobular sign has been added to lines 130-131 in the MS: “Perilobular abnormalities (curved-like bands of parenchymal consolidation with blurred borders along the structures that surround the secondary pulmonary lobule)....”


   Response: This reference has been added to the MS.

6. The section on drug-induced ILD is commendably brief, but perhaps over-simplifies – for example: “clues to drug-induced ILD are that the onset of symptoms may correlate to time of first use”. Whilst this is generally true, the latent period between starting a drug and the onset of a related pneumonitis is hugely variable, and the authors may wish to make this point.

   Response: (although this relationship is variable and the latency period can be quite long) has been added to line 172 of the MS.
7. In the section on How are ILDs clinically differentiated in the hospitalized patient?, consider, in the second paragraph (page 9), changing to “pattern and distribution of abnormality on HRCT” – distribution being of at least equal importance in some hands/diseases.

    Response: “The text has been changed to: The pattern and distribution of abnormality on HRCT....”

Re: Katerina Antoniou’s comments:

General comments
The text should be subdivided according to the ILDs (for instance, IPF, CTD-ILDs (teasing out the characteristic of the most frequent forms), COP etc.) and try to ask the questions they have put for each one of these entities. It would be nice to read their opinion in the cases where guidelines or trials do not exist regarding the management of these entities as they come from a well-known referral center. Finally the authors should comment quite extensively on the presence of comorbidities, which can be a frequent cause of hospitalization of ILD patients. Acute pulmonary embolism, left heart disease, ischemic heart disease, arrhythmias due to hypoxemia.

    Response: The section “ILDs commonly requiring hospitalization” is subdivided by ILD. However, we prefer not ask questions for each ILD because there is overlap with the approaches for the topics being discussed. Asking questions for each ILD would greatly lengthen the MS.... An earlier version of the MS included more specific opinions for cases where guidelines do not exist. However, because a consensus could not be reached within our group re: these opinions, they were removed and opinions discussed more broadly..... Inclusion of a paragraph on comorbidities is an excellent suggestion, and one has been added to the MS.

Specific comment
1. Background, 2nd para: ‘Recently, a multidisciplinary panel of American Thoracic Society/European Respiratory Society (ATS/ERS) members published a revised classification of ILDs based on their clinical, radiologic, and histopathologic findings (1, 2). Ref number 1 does not fit with the sentence (they talk about the consensus). Please rephrase.

    Response: Reference 1 has been removed from the MS.

2. Background, 3rd para: Not all CTD-ILDs present acutely. Please be more specific.

    Response: The text has been revised to: “rapidly progressive or acute exacerbation of connective tissue disease-associated ILDs (CTD-ILD)” on lines 64 and 65 of the MS.

3. Acute manifestation: ‘Summarized below are clinical manifestations of ILDs that most commonly require hospitalization.’ I think the sentence is misleading. What follows describes different clinical entities with their own clinical manifestation. Please rephrase.
4. IPF and acute exacerbations: ‘Radiographically, a high resolution computed tomography (HRCT) of the chest in an IPF patient reveals bilateral subpleural reticulation, traction bronchiectasis, an absence of ground glass opacities and subpleural honeycombing.’ Absence of GGOs is not the only finding inconsistent with UIP/IPF pattern. The sentence is misleading. Please rephrase according to the 2011 statement published in AJRCCM and add the respective ref.

Response: The text has been edited to: “Radiographically, a high resolution computed tomography (HRCT) of the chest in an IPF patient reveals bilateral subpleural reticulation, traction bronchiectasis, a paucity of ground glass opacities and subpleural honeycombing” and the reference added.

5. IPF and acute exacerbations: ‘Patients may be hospitalized at the time IPF is first recognized, often when the patient has an intercurrent infection, or may suffer an acute exacerbation of their disease (AE-IPF).’ It is not always possible to distinguish infection from AEIPF and if it was would that make any difference? Please comment and refer to Huie TJ, et al. Respirology. 2010;15:909-17.

Response: The text has been edited to: In some instances AE-IPF may be due to a secondary cause, such as an intercurrent infection, in up to one-third patients In some instances AE-IPF may be due to a secondary cause, such as air pollution, microaspiration, or an intercurrent infection in up to one-third patients on lines 83-84. The Huie reference has been added.

6. IPF and acute exacerbations: ‘AE-IPF is characterized by acute worsening of respiratory symptoms, typically over several weeks, accompanied by new lung opacities on chest imaging(11). The characteristic HRCT of the chests hows new ground glass opacities with or without consolidation overlying the typical radiographic changes of IPF (11).’ I believe that the definition of AEIPF should be corrected as well as the ref. One of the authors is also the first author of the statement of AEIPF published in 2007 in AJRRCM. Please rephrase.

Response: The text has been edited to: “AE-IPF is characterized by new or worsening of respiratory symptoms, typically less than 30 days, accompanied by new lung opacities on chest imaging” on lines 87-89.

7. Connective tissue disease-associated ILDs (CTD-ILD): ‘NSIP and UIP are the most common radiologic and histopathologic patterns found in patients with CTD.’ Please be more specific. In which CTD UIP and NSIP is more predominant and add that OP is the most predominant in antisynthetase syndrome. Please rephrase and add refs.

Response: These points are now included in the revised text on lines 104-107 “NSIP is the most common radiologic and histopathologic patterns found in patients with SSc or PM/DM, a UIP pattern is most common in patients with rheumatoid arthritis, and NSIP with or without overlapping areas of OP is most commonly found in antisynthetase syndrome”.
8. Cryptogenic organizing pneumonia (COP): ‘Pathological predictors of unfavorable outcome are co-existent lung fibrosis, which suggest the organizing pneumonia is not present in isolation.’ The meaning of the sentence is not clear. Please rephrase.

Response: The text has been edited on lines 139-140; “….organizing pneumonia is not present in isolation but rather a feature of a more dominant ILD pattern such as NSIP.”

9. Please comment also for the presence of perilobular pattern in HRCT which is characteristic of OP. Add refs.

Response: A reference to the perilobular sign has been added to lines 130-131 in the MS: “Perilobular abnormalities (curved-like bands of parenchymal consolidation with blurred borders along the structures that surround the secondary pulmonary lobule).”

10. What is the Role of Bronchoscopy? The role of BAL is not clear. Does it add in terms of diagnosis and treatment? Please discuss the role in AEIPF and in AECTD-ILD (rule out/confirm infection or AECTD-ILD and treat accordingly)

Response: The text has been edited on lines 224-225 to “. BAL can be used in patients with acute ILD or AE-IPF to exclude lung infection by bacterial culture and PCR for viruses.”. In addition, there is discussion regarding the use to rule out infection in CTD-ILD patients on lines 227-231. Lines 233-235 discuss the use of BAL as a diagnostic tool to screen for AEP.

11. What pharmacologic treatments should be administered? ‘Nevertheless, clinical experience suggests that patients with specific interstitial lung diseases improve with corticosteroid treatment. ILDs that appear to be steroid responsive are COP, AEP, some cases of connective tissue disease-associated interstitial lung disease and drug induced ILDs.’ Please be more precise. In SSc-ILD it is not recommended to use high doses of steroids. Therefore the sentence may be misleading for non experts in the field.

Response: The text has been edited on lines 266-267 to “(importantly, high doses of corticosteroids is not recommended in SSc-ILD”). Lines 261-264 now make the point that “. Due to the challenge in differentiating lung infection from an acute presentation of ILD or acute exacerbation of preexisting ILD, treatment with broad-spectrum antibiotics should be considered in all patients.”

12. What pharmacologic treatments should be administered? ‘The use of cytotoxic medications should be carefully considered in these patients, especially given data showing that corticosteroids and azathioprine are associated with worse outcomes in IPF patients or patients with other forms of DAD (40). Cytotoxic agents are definitely not recommended in the treatment of IPF and AEIPF and their use should not be carefully considered as stated. In few cases iv steroids could be used but most of times without effect. Please comment on the use of broad-spectrum antibiotics in patients with acute deterioration of IPF.

Response: the lack of utility of cytotoxic agents is more strongly emphasized in the revised text on lines 279-281. “. Because of reports that azathioprine is associated with worse outcomes in IPF patients or patients with other forms of DAD, the use of cytotoxic medications should not be used for management of these patients”.