Peer Review File
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Reviewer A:

Comment: Thank you for the opportunity to review this manuscript. The author performed a review on Indwelling pleural catheters infection.
The data is well known, there is nothing new or novel in the manuscript.
Reply: Thank you for this remark. As a review article, there was little emphasis placed upon describing novel findings, rather this manuscript represents a concise synthesis of already-available data.

Reviewer B:

The review by Sethi et al is well written and thought stimulating., on a topic of high clinical relevance. I have a few minor comments:
Comment 1: line 35: colonisation are Staphylococcus.....
Reply 1: Agreed

Comment 2: line 115: ? delete 'in' after 'significantly from'
Reply 2: Agreed

Comment 3: line 124: a word missing after 'segments of'
Reply 3: Agreed

Comment 4: line 140-143: is there postulation on why hepatic hydrothorax is associated with a much higher rate of deep infection (as compared to heart failure)?
Reply 4: A brief discussion surrounding the physiology underlying this observation has now been included.

Reviewer C:

This is an important topic that deserves additional study and attention. I do agree with your assertion in the paper that additional study is needed to support some of the claims surrounding IPC infection and colonization. I am supportive of this manuscript in that I think it can help guide clinicians who manage IPCs and their complications, though I would recommend caution with referencing unpublished data that has not been subject to peer review.

Some revisions I suggest:
Comment 1: (Grammar) In the abstract, line 35, would insert “are” between “colonization” and “Staphylococcus”
Reply 1: Agreed

Comment 2: (Grammar) Manuscript line 53, would remove “the presence of”; likewise,

in line 54, would remove “being experienced by a patient.”
Reply 2: Agreed

Comment 3: Lines 86-88 reference internal unpublished data. Will this data be published in the near future? Clarifying this will give readers greater confidence in the quality of this data.
Reply 3: Preliminary findings were presented at the BTS Winter Meeting, but the study is still in progress hence not yet published. I have added information indicating our progress through the study but would not like to commit to a date for publication prematurely. We anticipate completing the study in the next 12m, however this is subject to ongoing collection of IPCs.

Comment 4: Lines 93-94, see comment #3
Reply 4: As above

Comment 5: Line 118, I would soften the language to state “this suggests that once a biofilm is formed, …” given that biofilms on IPCs are hypothesized in the current work. I do agree that this mechanism is highly plausible
Reply 5: Agreed

Comment 6: Line 129, you reference the IPC cuff leading to closure of the tract within days of placement. Is there data that supports this? If so, would suggest citing that. I’m not aware of this, aside from manufacturer claims.
Reply 6: A timeframe of 1-2 weeks has been reported in patient information sheets. Despite this, I am unable to find a reference for this, and have therefore reworded this sentence to reflect this ambiguity.

Comment 7: Line 177, change “Bloods” to “Blood”
Reply 7: Agreed

Comment 8: Line 248, the BRICC study is mentioned in multiple spots along with citation to reference 12. It may be helpful to clarify if the BRICC study is referencing the same study as citation 12, and if 12 was just preliminary data from that larger study
Reply 8: Agreed, I have described the BRICC study in more detail, highlighting that it is preliminary data, where you have indicated in point 3.

Comment 9: The summary is concise and nicely written
Reply 9: Thank you

In summary, this is a well written and informative manuscript that adds value to the fund of knowledge regarding IPC complications. I look forward to seeing more work in this area.

Reviewer D:

Thank you for doing this very important work. The manuscript has broadly covered a

large area. I have made the following observations.

Comment 1: Abstract - Doesn't clearly set out the aims, key data/findings, and conclusions of the review. Could be improved to make this clearer.
Reply 1: I have rewritten the abstract to more clearly highlight this.

Comment 2: Line 29 - Infections can be difficult to diagnose - Suggest remove or modify. Pleural infections are the main complication being monitored for during follow up.
Reply 2: This sentence has now been revised

Comment 3: Line 32 - It is important to differentiate between infection and colonisation....
Reply 3: I have reworded this to reflect your suggestion

Comment 4: Line 53 - Definition of IPC infection should consider including "culture negative" pleural infections where there are clinical symptoms and signs of infection and other biochemical markers suggestive of infection but no microbial growth on culture. This is mentioned under deep infection in Table 1 but not under Definitions section of the text.
Reply 4: Thank you for this observation. I have included in the paragraph describing the microbiology of IPC infections as it ties in more smoothly with this section

Comment 5: Line 54-55 Consider rephrasing - Specify where is microbial growth - Skin, IPC, pleural fluid and simplify "in the absence of infective symptoms"
Reply 5: Agreed.

Comment 6: Line 56 - consider removing word "simply"
Reply 6: Agreed.

Comment 7: Line 63 - consider reversing order to keep consistency - superficial or deep
Reply 7: Agreed

Comment 8: Line 88: consider rephrasing "IPC colonization is common"
Reply 8: Agreed

Comment 9: Line 104 - 107: consider revising - May be better to say "S aureus and CoNS are the most commonly cultured organisms in IPC associated deep infection and IPC colonisation respectively".
Reply 9: Thank you, this is clearer.

Comment 10: Microbiology: Suggest commenting on Culture negative IPC infections
Reply 10: Agreed, as per your prior comment

Comment 11: Lines 117-118: Consider removing sentence once biofilm is formed it is difficult to clear without removing the IPC. This is not unequivocally proven.

Reply 11: In general terms, medical device infections associated with a biofilm can be difficult to manage without explanation of the device. I agree that this has not been demonstrated in IPCs as of yet, hence have moderated the language used to reflect that.

Comment 12: Line 136-138 Suggest rephrasing summary - the evidence for biofilm is not conclusive beyond doubt. Even though there may be some evidence to support deep IPC infections and colonisations have association with biofilm formation, one cannot necessarily conclude that biofilm is the primary reason for difficulty in clearance of infection or need for removal of the IPC.
Reply 12: This is a valid comment and I have rephrased this sentence.

Comment 13: Mechanism - No comments on bacterial virulence or strains.
Reply 13: At present, very limited assessment of the bacteria responsible for IPC infections has been undertaken, let alone an assessment of virulence factors. We have extensively discussed the bacterial species associated with infection. We are actually intending on conducting this study on the bacteria we have acquired from BRICC, and I have highlighted this in the script.

Comment 14: Line 156 consider repharsing - Index of suspicion for infection is high hence it is not as challenging as the author is trying to make it out.
Reply 14: I have softened the language used here.

Comment 15: Individual practices may vary but there is a role for performing a pleural ultrasound and sending off pleural fluid (via IPC) even when a superficial infection alone is suspected.
Reply 15: We have added a description of the use of USS

Comment 16: Line 162 Consider maintaining consistency of terms Deep IPC infection vs pleural infection
Reply 16: Agreed, I have implemented this suggestion at multiple points across the manuscript now.

Comment 17: Line 178 Consider adding role of performing blood cultures and discuss procalcitonin. Reply 17: Thank you, I have added both along with reference to suPAR.

Comment 18: Paragraph 188 and 194 - Incomplete without atleast discussing common antibiotics and regimens.
Reply 18: I had previously advised that these would be as per local protocols, and refined upon receipt of relevant microbiology. I have now added further details regarding which Abx would typically be considered

Comment 19: Line 192 Define treatment failure
Reply 19: Agreed

Comment 20: Paragraph starting line 205 - no mention of role of pleural ultrasound
Reply 20: This has now been included

Comment 21: There must be comments on the consequences or pitfalls of removal of IPC due to pleural infections
Reply 21: I have added an explanation of why we would prefer to avoid IPC removal.

Comment 22: Paragraph 232 - No mention of patient education, keeping IPC clean and dry, avoiding swimming
Reply 22: I have added this valid point.

Comment 23: Table 1 Consider swapping column 1 and 2
Reply 23: Agreed

Comment 24: Figure 2 Reference 15 is for IPC related pleural infections not all infections. consider clarifying
Reply 24: Agreed

Reviewer E:

Thank you for the opportunity to read, review and critique this interesting piece of work.

My comments are as follows:

Comment 1: Line 83: Bacteria were grown from the intra-thoracic portion of the IPC, do you theorise that the tunnelled segment may host a different microbiome or that it may be sterile, will studying this help elucidate mechanisms of transmission of infection?
Reply 1: I have changed the word 'intra-thoracic' to 'internal'. The details of the BRICC study are probably beyond the scope of this paper, but by 'intrathoracic' I intended to describe segments proximal to the cuff. This interesting question that you raise should be addressed by the study in due course.

Comment 2: Line 109: Has the presence of a bacterial biofilm on IPCs ever been categorically demonstrated through empirical experimental data (eg electron microscopy, or other modalities), or does this remain theoretical? Human studies have not yet been performed to study this.
Reply 2: There are some animal studies which have demonstrated biofilm production upon pleural catheter surfaces.
(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9597695/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7576012/) This is well established in other contexts, such as urinary, vascular, dialysis catheters

Comment 3: Line 124 Typo: Incomplete sentence
The 'Bacteria Responsible for IPC Infection and Colonisation' (BRICC) study has 122 collected infected IPCs following removal from patients and demonstrated that the bacteria are 123 present on cultured segments of

Reply 3: I have rewritten this sentence

Comment 4: Line 136: Has biofilm formation been implicated in deep IPC related infections, or is this more often observed in colonisation alone (because if in the former, and given it is almost impossible to eliminate a biofilm, how do we reconcile the fact that most IPC infections can be managed with antibiotics and free drainage, without the need to remove the IPC, 'treat through the IPC') Most deep infections end in pleurodesis and IPC removal. The infected IPCs we have collected have bacteria on them. Some of the IPC 'infections' which resolve without treatment may actually colonization. Furthermore, IET is hypothesized to work by eliminating biofilms and this may be how it works in IPC infection. There is clearly a lot more work needed to be done to understand the role of biofilms in IPC infection which we plan to undertake in the near future.
Reply 4: We have added a sentence to clarify this.

Comment 5: Line 177 Typo: Missing closing brackets
(e.g. white cell count and C-reactive protein 177 levels
Reply 5: I have corrected this

Comment 6: Is there any role for 16s or other forms of NGS testing for Microbiology in the pleural fluid drawn from IPCs, how about Procalcitonin as a more specific marker for infection vs colonisation?
Reply 6: I have added some information regarding procalcitonin, but as colonization is not expected to be associated with an elevated WCC/ CRP, I would not describe it as better able to distinguish between infection and colonization.

Comment 7: In practice, can you outline what the clinical significance of IPC colonisation is, presumably when patients are well, IPC pleural fluid MCS is never sent therefore one doesn't ever discover the presence of colonisation. Whereas if one is unwell with symptoms only possibly suggestive of pleural infection, are we suggesting that CoNS from pleural fluid drawn from the IPC may be safely ignored?
Reply 7: This is a valid point, but unfortunately, we lack data to suggest this outright. Certainly, CoNS are over-represented in colonization versus infection, but this is inadequate to make this suggestion. I have added this ambiguity into the paragraph entitled 'Future Directions'.

Comment 8: Line 230: "However, this is confounded by the co-existing medical problems in 230 patients with IPC"
Shouldn't the mortality rate be greater due to co-existing medical problems in IPC patients compared to standard pleural infection patients? Or did you mean something different?

Reply 8: Apologies for the ambiguity here. I have rewritten this sentence to reflect my intended meaning. I wanted to point out that deaths may be attributed to the underlying disease (for which the IPC was sited) rather than an infection.