Author’s response to reviews

Title: Implementation of a Successful Eradication Protocol for Burkholderia Cepacia Complex in Cystic Fibrosis Patients

Authors:

Bryan Garcia (bryangarcia25@gmail.com)
Jacque Carden (jlcarden@uabmc.edu)
Dana Goodwin (dgoodwin@uabmc.edu)
Tim Smith (tasmith@uabmc.edu)
Amit Gaggar (agaggar@uabmc.edu)
Kevin Leon (kleon@uabmc.edu)
Veena Antony (Vantony@uabmc.edu)
Steven Rowe (srowe@uabmc.edu)
George Solomon (gsolomon@uabmc.edu)

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Author’s response to reviews:

In response to BMC Pulmonary reviewers and specific reviews regarding our article titled “Implementation of a Successful Eradication Protocol for Burkholderia Cepacia Complex in Cystic Fibrosis Patients” (PULM-D-17-00532):

Thank you for your time in reviewing our manuscript. We appreciate your reviews and recommendations. We have addressed each review individually within the edited version of our manuscript and we have provided responses to specific reviews below. We hope that your editorial staff will find these responses sufficient but we are happy to provide any further insight into our manuscript as needed.

Sincerely,

George M. Solomon, MD (Corresponding Author)
Reviewer 1:

The paper reads well and is appropriately concise. The conclusions you have drawn are supported by your data and you have outlined the limitations of them clearly in the discussion. The eradication protocol itself, while aggressive, is also clearly described. I think it would be beneficial to include a column in Table 1 stating which pathogen each antibiotic targets, to make it clear that you are using tobramycin (and presumably azithromycin) to target PA and not BCC.

Thank you for your appraisal of our article. Based on your recommendation we have included an additional column in table 1 identifying the rationale for utilization of each antibiotic discussed. Our institution routinely places all patients on thrice weekly azithromycin for anti-inflammatory effect so long as they do not have a contraindication to this (ie co-infection with an NTM). All patients in our eradication protocol were colonized with PsA in addition to Bcc. These patients were previously maintained on every-other-month inhaled tobramycin. Inhaled tobramycin and intravenous tobramycin have both been shown to have significant anti-Bcc activity as well as anti-PsA activity and thus these antibiotics were chosen in addition to the Bcc-specific antibiotic trimethoprim-sulfamethoxazole. Similarly, Ceftazidime has efficacy against both PsA and Bcc.

I would also be interested to know how many of your patients were on long term azithromycin and inhaled tobramycin in each group prior to the study, and during the study in the case of the 'control' group.

Thank you for this recommendation, we have included this data in the results section under the “Outcome following Bcc eradication” subsection-

“All patients in both groups were maintained on thrice weekly oral azithromycin therapy for anti-inflammatory effect. In addition, all patients placed on Bcc eradication were previously colonized with PsA and were maintained on every-other-month inhaled tobramycin. Three of the four control patients were previously maintained on inhaled tobramycin for this reason.”
If the data is available, time to first exacerbation would also be a helpful endpoint.

We agree this is an important endpoint and have included this as well as number of exacerbations in the results section under the “Outcome following Bcc eradication” subsection. During the one-year follow up period the eradication group experienced a mean number of exacerbation of 1.66 ± 0.42 versus 3.25±1.0 by the control group (p=0.166). The mean time to first exacerbation was 230 ± 24.55 in the eradication group versus 88 ± 27.6 in the control group (p=0.009).

Reviewer 2:

The article by Garcia et al reports the successful eradication of new isolates of Burkholderia cepacia complex (Bcc) in 6 adult patients with cystic fibrosis. Changes in lung function (FEV1) and nutrition (BMI) are compared to a group of patients with chronic Bcc infection. Changes in FEV1 and BMI are also shown for the 6 patients who underwent Bcc eradication.

Given the paucity of data on Bcc eradication in patients with CF, the details of the eradication regimen and the outcomes in these 6 patients warrants publication. However, I do not think the comparison to the 'control' group adds anything and the importance of this comparison is overstated in the paper. The controls were likely to have chronic Bcc infection and therefore cannot fairly be compared to those with a new isolate of Bcc. The comparison is made even less relevant by only having 4 subjects in the control group.

Thank you for your appraisal of our paper. We agree there exists a paucity of data on the topic of Bcc eradication efficacy and outcomes in CF patients. Complicating this matter is the heterogeneity of clinical courses experienced by patients ranging from spontaneous clearance to colonization and asymptomatic infection to rapid fulminant “cepacia syndrome”. No prior study has reported on the effect early Bcc eradication compared to chronic colonization. Although the number of patients in the study is small, it provides early evidence that chronic colonization is associated with increased morbidity.

We agree there are concerns with the control group. However, since no prior study has included a cohort of CF patients with chronic Bcc infection we feel it is important to provide some form of control for the purpose of comparison with the understanding that this control group represents a small set of case controls. We discuss further the limitations of this control group in the discussion section and comment on the appropriate interpretations of this data in light of the limitations.
Additional comments:

Page 6 Line 4. Were patients with any previous Bcc isolates excluded from inclusion or only those who previously isolated the same genomovar.

Thank you for this comment, we feel the previous draft was not clear in its description of inclusion. We have amended the manuscript to:

“Beginning January 2012 through June 2015, patients were placed on the eradication protocol if they were found to have a sputum culture isolate positive for newly acquired Bcc. Patients who were known to have chronic airway colonization by Bcc were treated with guideline-based standard of care (15).”

Page 6 Line 9. How long had subjects been free from Bcc for? i.e. Did the author review the Paediatric culture data?

All Bcc positive cultures were considered newly acquired if the patient did not have a sputum culture positive in the two years prior to their first positive isolate. Following eradication protocol, all patients remained Bcc free during the one-year follow up period. To make this clearer we have adjusted the text as follows:

“Beginning January 2012 through June 2015, patients were placed on the eradication protocol if they were found to have a sputum culture isolate positive for newly acquired Bcc which had not been isolated from sputum during the two prior years. Patients who were known to have chronic airway colonization by Bcc were treated with guideline-based standard of care (15).”

Page 6 Line 29. It should not read 'All patients' as only 6/7 were started on eradication

Thank you for this recommendation, we agree and have amended the manuscript to read-

“Patients included in the eradication group following sputum culture isolation of newly acquired Bcc were placed on the eradication protocol (Table 1). “

Page 8 Line 15. More details need to be given about the 3/7 'controls' that were not reported. Losing 2/7 (29%) to follow up over 12 months seems high, further details should also be given as to why the control had an uncertain diagnosis of CF - if a patient is seen in the CF clinic and isolates BCC in their sputum - the diagnosis does not sound uncertain

The authors agree that losing 2/7 patients to follow up is not ideal however we were not able to include them due to lack of follow up despite their severe illness. The third patient was identified as having atypical CF. The manuscript has been amended to better address this review-
“Of these seven control patients, two patients were not included due to inadequate clinic follow up. A third patient with Bcc colonization was not included due to identification of only one CF causing mutation despite genetic sequencing. These patients were excluded from further analysis.”


We agree this is a valuable alternative protocol and have included this in the discussion:

“Alternative protocols in pediatric patients with newly isolated Bcc have been described with some success and have utilized similarly aggressive regimens combining inhaled and intravenous Tobramycin, Ceftazidime and Temocillin (18). The patients described by that series were not complicated by chronic PsA co-infection. An additional case-series described utilizing combination inhaled amiloride and tobramycin with eradication of initial colonization in 3 of 4 patients but was unsuccessful in chronically infected patients (19, 20).”