Isolation of *Burkholderia cepacia* complex in adults with primary ciliary dyskinesia

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To the Editor:

The *Burkholderia cepacia* complex (BCC) is a group of Gram-negative opportunistic pathogens, encompassing 22 distinct species, characterised by inherent broad-spectrum antibiotic resistance [1]. BCC is widely recognised for its propensity to colonise the airways of individuals with cystic fibrosis (CF) and can cause acute infections among people with granulomatous diseases or immunodeficiency, and in those in intensive care or on mechanical ventilation [2–4].

In CF, chronic colonisation with BCC can be associated with a more rapid decline in lung function and worse clinical outcome, and in some cases, it can lead to rapid uncontrolled deterioration, resulting in the so-called cepacia syndrome [2, 5, 6]. While there is limited evidence on eradication strategies, regimens including a combination of oral, intravenous and nebulised antibiotics are used [7, 8].

Primary ciliary dyskinesia (PCD) is a rare, heterogeneous group of genetic disorders characterised by dysfunction of motile cilia, leading to impaired mucociliary clearance and recurrent, chronic infections of the upper and lower respiratory tract. Patients with PCD often present with chronic airways colonisation with pathogens similar to those identified in CF, such as *Staphylococcus aureus*, *Haemophilus influenzae* and *Pseudomonas aeruginosa* [9–11]. However, there have been no reports of BCC infection or colonisation in individuals with PCD [9, 10].

In our cohort of 110 adults with PCD, two (1.8%) were found to be chronically colonised with BCC. Both cases had a confirmed diagnosis of PCD, as evidenced by the presence of biallelic pathogenic mutations and diagnostic ciliary function studies. CF and immunodeficiency had been previously ruled out as comorbidities.

Case 1 was a 35-year-old woman who had been under regular follow-up with our service for 4 years. During the COVID-19 lockdown period she reported an increase in the frequency of exacerbations despite shielding measures, limited social interactions and good adherence to airway clearance techniques (ACT). At her first in-person review after the lockdown (8-months interval from previous), a sputum sample was taken and BCC (Taxon K strain) was isolated and subsequently confirmed in a repeated sample. Lung function had minimally declined but chest radiograph did not show any consolidation or significant interval change compared to the previous image. A 6-weeks course of systemic antibiotics (3 weeks of intravenous piperacillin/tazobactam and oral minocycline, followed by 3 weeks of oral cotrimoxazole and minocycline) according to the sensitivities of the isolated strain was initiated as eradication. Despite this, microbiological clearance was not achieved and the patient continued to chronically culture BCC. No other pathogens were isolated at the same time. Lung function improved significantly with an increase in forced expiratory volume in 1 s (FEV_1) from 91% of the predicted valure prior to BCC isolation to 104% after the BCC eradication attempt. The number of exacerbations reduced, although this may reflect the addition of low-dose azithromycin therapy, which was initiated at the same time.

Case 2 was a 30-year-old woman who had been under the care of our service for 5 years and experienced a gradual decline in lung function, with FEV_1 decreasing from 68% to 60% of predicted. She also reported increased cough and sputum production, despite maintaining good adherence to ACT. Chest radiograph did not show any new consolidation or significant interval change compared to previous imaging. Sputum

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***Burkholderia cepacia* complex can be isolated in individuals with PCD. Extended microbiological analysis of respiratory samples can maximise the chances of isolation. Registry studies will help assessing the impact of these pathogens on long-term outcomes.** https://bit.ly/3xSHCD9

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sample, sent 6 months after the previous one, revealed the growth of BCC genomovar I, which was confirmed on repeated samples. Eradication treatment was initiated with a 6-weeks course of systemic antibiotics (3 weeks of intravenous meropenem and oral minocycline, followed by 3 weeks of oral minocycline) according to sensitivities. Microbiological clearance was not achieved and BCC continued to be intermittently isolated over the following 2 years. Lung function showed significant improvement and remained stable, with the FEV_1 increasing from 60% to 79% of predicted after the eradication attempt. No pulmonary exacerbations occurred in the 12 months preceding and following the initial isolation of BCC. However, further antibiotic courses were commenced in the second year after isolating BCC, as part of eradication therapy of new growths of methicillin-resistant *S. aureus* and *P. aeruginosa*.

BCC is a group of Gram-negative pathogens belonging to the heterogeneous genus *Burkholderia*. The taxonomy is complex and continues to evolve, with the BCC being now classified into species that are genomically different but phenotypically similar, named genomovars. These include *Burkholderia multivorans* and *Burkholderia cenocepacia*, which typically colonise the airways of individuals with CF, with 4.2% of the population being chronically colonised, and can negatively affecte morbidity and mortality [2, 6, 12]. In contrast, it has rarely been reported in individuals with non-CF bronchiectasis [13]. To the best of our knowledge, this represents the first documented instance of isolation and colonisation with BCC in adults with PCD.

Standard sputum cultures can fail to identify CF-associated pathogens such as BCC and as a result, may underestimate the prevalence of this species in individuals with PCD. Sputum analysis in our cohort of PCD patients is undertaken using the same standard as used when processing CF sputum. As such, the laboratory uses a range of selective media to enhance the recovery of BCC and other CF-associated pathogens. Any organism isolated on the BCC-selective agar is identified to the species level using matrix-assisted laser desorption–ionisation time-of-flight mass spectrometry and if this indicates the possibility of BCC, further characterised in-house using 16S PCR before being submitted to a reference laboratory (Public Health England, Colindale, UK) for final confirmation of BCC species by *recA* sequencing. These led to the isolation of *BCC* Taxon K, a relatively newly identify member of the group, and of the type strain *B. cepacia* (genomovar I) in our patients.

Like the routine approach for initial isolation of BCC in CF and in line with the BEAT-PCD recommendations [7–9], eradication treatment was commenced in both patients with a prolonged course of systemic antibiotics tailored to the sensitivities of the isolated strains. Both patients displayed significant clinical improvement following antibiotic therapy for attempted eradication and this improvement was sustained over time, although microbiological clearance was not achieved. This suggest that isolation of BCC in these patients might have been a contributing factor to an acute clinical deterioration but does not seem to be associated with medium-term adverse effects in individuals with PCD. It is also plausible that in response to the isolation of this pathogen, the requirement for a hospital admission and a prolonged course of antibiotics, our patients improved their concordance to standard treatment of bronchiectasis and, in particular, to ACT, which in turn could have contributed to their clinical stability [14].

Presently, there is no evidence to support an early eradication approach in PCD and the current BEAT-PCD recommendation [9] to treat irrespective of symptoms is based on expert consensus and extrapolation of data related to CF. Without longitudinal data on the implication of infection with BCC in a larger number of individuals with PCD, it is not possible to predict whether these patients will follow the same trajectory as individuals with CF colonised with BCC. However, it is important to note that the genomovars isolated in our patients are different to those most frequently described in individuals with CF [6, 12] and this might play a part on the medium-long term of the infection. A recent case report detailed the successful use of nebulised aztreonam for eradicating BCC in two individuals with non-CF bronchiectasis [13]. However, we elected to tailor the antimicrobial regimen based on the sensitivities of the isolated strains. This decision led us to forego nebulised antibiotic treatment for our patients, as the strains demonstrated resistance to colomycin and aminoglycosides.

To date, we have not observed any instances of BCC transmission among individuals with PCD under our care. Our clinic adheres to a rigorous segregation policy during patient visits. Both patients in this report had relatives also affected by PCD who have not experienced any BCC growth to date. This suggests that in our patients, the acquisition of BCC was more likely related to environmental infection rather than person-to-person transmission within their social and familial circles.

In conclusion, BCC can colonise the airways of individuals with PCD. Therefore, it is crucial to maintain the practice of extended analysis of sputum samples using similar methodologies as applied to CF, in line

with the BEAT-PCD recommendations, and continuing to have specialist microbiology input to maximise the likelihood of isolating these pathogens. Future registry studies could provide valuable insights into assessing the actual prevalence of this pathogen among people with PCD and the long-term impact of chronic BCC colonisation. These studies would also be instrumental in addressing strategies for attempting eradication in this patient group, including the use of nebulised antibiotics as a potential tool in eradicating this pathogen in people with PCD.

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