Nebulized levofloxacin for chronic *Burkholderia cepacia* pulmonary infection in cystic fibrosis: A case report

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**A R T I C L E   I N F O**

Keywords:
Nebulized
Levofoxacin
*Burkholderia cepacia* complex
Cystic fibrosis
Inhaled antibiotics

**A B S T R A C T**

We present a patient with cystic fibrosis who used nebulized levofloxacin off-label to suppress chronic *Burkholderia cepacia* pulmonary infection. The patient was initially using tobramycin inhalation powder (TIP) off-label continuously for suppression of chronic *B. cepacia*; this was changed to alternating months of nebulized levofloxacin and TIP. Following initiation of nebulized levofloxacin, the patient had significant improvement in respiratory symptom burden and lung function (as measured by forced expiratory volume in 1 second [FEV1]), and a decrease in the frequency of pulmonary exacerbations. Further research is necessary to determine whether the benefits observed with nebulized levofloxacin in our patient translate to a larger population of patients with chronic *Burkholderia* spp. pulmonary infection.

1. Introduction

In cystic fibrosis (CF), viscous mucus production and impaired mucociliary clearance leads to chronic inflammation and infection in the lungs. *Burkholderia cepacia* complex (BCC) species are among the most pathogenic organisms for people with CF (PwCF); in particular, virulent strains of *Burkholderia cepacia* (geminovar III) in the IIIA subgroup have been associated with increased frequency of pulmonary exacerbations (PEx) and rate of lung function decline, as well as increased risk of mortality or lung transplantation [1–5]. Treatment of BCC species is complicated by inherent and acquired antimicrobial resistance [1]; to-date, no nebulized or inhaled antibiotic has demonstrated clinical benefit for suppression of chronic BCC pulmonary infection in PwCF [1,6,7].

Herein, we present a case of nebulized levofloxacin used for suppression of chronic *B. cepacia* (IIIA subgroup) pulmonary infection in a patient with CF, demonstrating a favorable clinical response.

2. Case presentation

The patient is a 34-year-old male with CF (genotype F508del/N1303K), moderate lung disease (forced expiratory volume in 1 second [FEV1] 56% predicted), chronic pulmonary infection with *B. cepacia* (IIIA subgroup) for upwards of 9 years, intermittent sputum growth of *Stenotrophomonas maltophilia*, and no growth of *Pseudomonas aeruginosa*. Co-morbidities include pancreatic insufficiency, chronic sinusitis, osteopenia, history of hemoptysis requiring bronchial artery embolization, and previous distal intestinal obstruction syndrome.

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https://doi.org/10.1016/j.rmcr.2022.101772
Received 4 July 2022; Accepted 6 November 2022
Available online 12 November 2022

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Despite optimization of maintenance pulmonary therapy with dornase alfa, nebulized 7% NaCl solution, and azithromycin, the patient continued to experience 4–6 PEx annually, with 2–3 requiring hospitalization. PEx management was historically complicated by intolerance of cotrimoxazole (rash) and meropenem (rash and transaminitis), both first-line alternatives for treating *B. cepacia*. Based on pilot study data indicating tobramycin inhalation powder (TIP) may decrease sputum bacterial density of BCC in PwCF [6], a trial of continuous use of TIP was initiated off-label in January 2020.

Although TIP subjectively reduced the patient’s respiratory symptoms, PEx frequency remained essentially unchanged, requiring 3 courses of oral (PO) antibiotics and 3 hospitalizations for intravenous (IV) antibiotics in the 13 months following TIP initiation. Based on previous favorable clinical response to oral levofloxacin, an off-label trial of nebulized levofloxacin was initiated in March 2021, to be used alternating monthly with TIP (subsequently replaced by tobramycin inhalation solution [TIS] due to better tolerance). Sensitivity of *B. cepacia* to levofloxacin is not routinely tested, but results available from the patient’s sputum culture and sensitivity in August 2020, December 2020, and December 2021 all reported resistance of *B. cepacia* to levofloxacin (minimum inhibitory concentration [MIC] was not evaluated). The patient performed weekly home spirometry as part of routine clinic follow-up, and completed the CF Questionnaire-Revised (CFQ-R) at baseline and monthly after initiation of nebulized levofloxacin.

Following introduction of nebulized levofloxacin, the patient reported a subjective improvement in respiratory symptoms (mean end-of-month CFQ-R respiratory domain score of 100 points versus 41.5 points for levofloxacin versus tobramycin formulations). To compare clinical outcomes before and after initiation of nebulized levofloxacin, a 9-month radius was used, as exacafactor/tezacafor/ivacaftor (ETI) was commenced 9 months after nebulized levofloxacin when provincial funding was approved. PEx frequency decreased after initiation of nebulized levofloxacin, with only 1 course of PO antibiotics and 1 hospitalization for IV antibiotics required over the 9-month observation period, compared to 2 courses of PO and 3 hospitalizations for IV antibiotics in the 9 months prior to nebulized levofloxacin initiation. This translated to a decrease in antibiotic exposure from 105 antibiotic days per 9-month period pre-levofloxacin to 30 antibiotic days per 9-month period after starting alternating months of levofloxacin (Fig. 1a).

Following introduction of levofloxacin, the mean FEV1 was higher while receiving levofloxacin than during tobramycin use (2.29 L vs 2.22 L, mean difference 70 mL [95%CI: 16–124 mL, p = 0.007] by two-tailed Welch’s t-test) (Fig. 1b). This difference was preserved when stratifying to compare levofloxacin to TIP, and attenuated when comparing levofloxacin to TIS (Fig. 1c). No adverse effects were reported with nebulized levofloxacin.

![Figure 1](image_url)

**Fig. 1. Pulmonary function, antibiotic requirements, and symptom scores while on inhaled/nebulized antibiotics.** **Panel A:** Depiction of FEV1 measures (open circles) and antibiotic requirements (solid horizontal lines) pre- and post-introduction of inhaled levofloxacin (dashed vertical line). CFQ-R respiratory scores are represented by red-filled diamonds. **Panel B:** Following introduction of levofloxacin, FEV1 was higher during periods of levofloxacin use than tobramycin use (2.29 L vs 2.22 L, mean difference 70 mL [95%CI: 16–124 mL, p = 0.007]) by two-tailed Welch’s t-test. **Panel C:** FEV1 values remained significantly higher when comparing levofloxacin measurements to TIP (p = 0.0176) and not significantly higher than those taken during TIS use (p = 0.493) by post-hoc Dunn test with p-value adjustment by Benjamini-Hochberg method. CFQ-R = Cystic Fibrosis Questionnaire-Revised, FEV1 = forced expiratory volume in 1 second, IV-abx = intravenous antibiotics, Levo = levofloxacin, ns = not significant, PEx = pulmonary exacerbation, PO-abx = oral antibiotics, TIP = tobramycin inhalation powder, TIS = tobramycin inhalation solution. *p < 0.05, **p < 0.01.
3. Discussion

In this case report, off-label use of nebulized levofloxacin alternating months with TIS or TIP for chronic *B. cenocepacia* (IIIA subgroup) pulmonary infection in a patient with CF resulted in decreased PEx frequency and antibiotic exposure when compared to continuous TIP. Nebulized levofloxacin was also associated with improved patient-reported respiratory symptoms and quality of life as well as measured FEV₁ when compared to values recorded while using tobramycin during the prospective observation period.

Although a mean difference of 70 mL FEV₁, while on nebulized levofloxacin versus tobramycin formulations could be considered marginal, our patient experienced improvements in other aforementioned objective outcomes. Some of the difference in the patient's FEV₁ value may be explained by possible bronchoconstriction while receiving TIP, a recognized and relatively common side effect. Mean FEV₁ remained higher when using levofloxacin compared to TIS, though the difference was not statistically significant. Notably, the line of best fit for the patient's measured FEV₁ appeared higher during the 9 months of continuous TIP use (retrospective period) when compared to the 9-months of alternating levofloxacin/tobramycin (prospective observational period) (Fig. 1a), though the slope of change in FEV₁ was seemingly attenuated during the latter period.

An important consideration when interpreting the observed results in this case is the potential impact of the coronavirus disease (COVID-19) pandemic. Specifically, CF registry data indicates a decline in PEx frequency and need for IV antibiotics for PEx in 2020 when compared to 2019 [8,9]; it is speculated that isolation and decreased exposure to common viruses during the pandemic likely contributed to this observation. However, our patient's PEx frequency was essentially unchanged during the early phase of the pandemic despite self-isolation; it was not until initiation of nebulized levofloxacin that his PEx frequency decreased.

Another important consideration is the potential for antimicrobial resistance developing after repeat exposure to nebulized levofloxacin. Treatment of chronic *P. aeruginosa* pulmonary infection in PwCF with three 28-day cycles on/off nebulized levofloxacin (total 24 weeks) has previously been reported to result in a numerical increase in prevalence of *P. aeruginosa* isolates resistant to levofloxacin, though these changes were reported to not be statistically significant [10]. Similarly, up to six 28-day cycles on/off nebulized levofloxacin did not result in a significant change in the proportion of levofloxacin isolates with an MIC greater than the 1 mcg/mL or 2 mcg/mL breakpoints for *P. aeruginosa* established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical Laboratory Standards Institute (CLSI), respectively [11]. Such evidence is not available for BCC species. Despite available culture and sensitivity results for our patient indicating *B. cenocepacia* resistance to levofloxacin both before and after initiation of nebulized levofloxacin, he still experienced objective clinical benefit from this. This finding is in keeping with evidence suggesting that antimicrobial testing *in vitro* is not reliably predictive of antimicrobial treatment response *in vivo* in PwCF [12]. Therefore, even if long-term use of nebulized levofloxacin does indeed affect antimicrobial sensitivity and MIC, it may not translate into a negative impact on clinical outcomes.

Unlike chronic infection with *P. aeruginosa*, for which the use of inhaled and nebulized antibiotics is an established standard of care in PwCF [13,14], nebulized or inhaled antibiotics have not demonstrated clinical benefit for chronic BCC pulmonary infection in PwCF. In a pilot trial involving 10 patients with CF and chronic BCC pulmonary infection, 28 days of TIP decreased sputum bacterial density by 1.4 log (CFU/mL), but there was no significant change in percent predicted FEV₁ (ppFEV₁) [6]. Continuous TIP for approximately 14 months only improved subjective symptom burden in our patient; it did not improve objective clinical outcomes such as lung function or PEx frequency. Moreover, aztreonam for inhalation solution (AZLI) was compared to placebo in a randomized controlled trial in 100 patients with CF and chronic *Burkholderia* spp. infection; after 24 weeks of continuous use, AZLI did not demonstrate benefit over placebo for any of the outcomes, including ppFEV₁ and PEx frequency [7].

To-date, nebulized levofloxacin has not been studied for treatment of chronic BCC in PwCF. In an in vivo mouse model of chronic BCC infection, 4 days of aerosolized levofloxacin reduced bacterial counts by at least 1 log CFU for all 5 strains of *Burkholderia* spp. studied [15]. Although change in sputum bacterial density was not assessed in our patient, our data suggest that introduction of nebulized levofloxacin significantly improved respiratory symptom burden and FEV₁, and also decreased the frequency of PEx and hospitalizations. Importantly, these improvements were achieved before initiation of ETI.

4. Conclusion

Given the potential negative outcomes associated with chronic pulmonary infection with *B. cenocepacia* in PwCF [2–5], the observed outcomes in this case report suggest use of nebulized levofloxacin as suppressive therapy warrants further consideration. In the era of CFTR-modulator therapy, adequately powered randomized controlled trials examining the effectiveness of inhaled levofloxacin in PwCF will be challenging, meaning reports such as ours will provide rare, but compelling insights into possible adjunctive therapeutic interventions for patients chronically infected with BCC species.

Funding

The authors report no funding for this work. Dr. Franciosi is supported by a Michael Smith Foundation for Health Research Trainee Award (#RT-2020-0493). Dr. Quon is supported by a Michael Smith Foundation for Health Research Scholar Award (#16414).

Declaration of competing interest

The authors have no potential or actual conflicts of interest to declare.
Acknowledgements

We would like to thank the patient for his approval to share his clinical data for this case report.

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