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CASE REPORT

REVISED Case Report: Dual nebulised antibiotics among adults with cystic fibrosis and chronic *Pseudomonas* infection [version 2; referees: 1 approved, 2 approved with reservations]

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 Latest published: 28 Feb 2018, 6:2079 (doi: [10.12688/f1000research.13298.2](https://doi.org/10.12688/f1000research.13298.2))

Abstract

Pulmonary exacerbations in adults with cystic fibrosis (CF) and chronic *Pseudomonas aeruginosa* (Psae) infection are usually treated with dual intravenous antibiotics for 14 days, despite the lack of evidence for best practice. Intravenous antibiotics are commonly associated with various systemic adverse effects, including renal failure and ototoxicity. Inhaled antibiotics are less likely to cause systematic adverse effects, yet can achieve airway concentrations well above conventional minimum inhibitory concentrations. Typically one inhaled antibiotic is used at a time, but dual inhaled antibiotics (i.e. concomitant use of two different inhaled antibiotics) may have synergistic effect and achieve better results in the treatment of exacerbations. We presented anecdotal evidence for the use of dual inhaled antibiotics as an acute treatment for exacerbations, in the form of a case report. A female in her early thirties with CF and chronic Psae infection improved her FEV₁ by 5% and 2% with two courses of dual inhaled antibiotics to treat exacerbations in 2016. In contrast, her FEV₁ changed by 2%, -2%, 0% and 2%, respectively, with four courses of dual intravenous antibiotics in 2016. Baseline FEV₁ was similar prior to all six courses of treatments. The greater FEV₁ improvements with dual inhaled antibiotics compared to dual intravenous antibiotics suggest the potential role of using dual inhaled antibiotics to treat exacerbations among adults with CF and chronic Psae infection, especially since a greater choice of inhaled anti-pseudomonal antibiotics is now available. A previous study in 1985 has looked at the concomitant administration of inhaled tobramycin and carbenicillin, by reconstituting antibiotics designed for parenteral administration. To our knowledge, this is the first literature to describe the concomitant use of two different antibiotics specifically developed for delivery via the inhaled route.

Open Peer Review

Referee Status:

	Invited Referees		
	1	2	3
REVISED version 2 published 28 Feb 2018			
	↑		
version 1 published 01 Dec 2017			

- 1 **Tim Lee** , Leeds Teaching Hospitals NHS Trust, UK
- 2 **Freddy Frost** , Liverpool Heart and Chest Hospital, UK
Dilip Nazareth, Liverpool Heart and Chest Hospital, UK
- 3 **Theodore G. Liou** , University of Utah, USA

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Author roles: **Mann N:** Data Curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Murray S:** Data Curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Hoo ZH:** Data Curation, Formal Analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – Review & Editing; **Curley R:** Data Curation, Formal Analysis, Investigation, Methodology, Validation, Writing – Review & Editing; **Wildman MJ:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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REVISED Amendments from Version 1

As recommended by Dr Lee, we have:

1. clarified that colomycin 2MU thrice daily was given intravenously alongside intravenous Tazocin
2. clarified the location (home/hospital) for all treatment courses
3. clarified that the subject was also using nebulised dornase alfa throughout all treatment courses
4. provided objective adherence (I-neb data) during the dual nebulised antibiotics courses

As recommended by Drs Frost and Nazareth, we have:

1. mentioned the 2014 randomised cross-over trial of inhaled tobramycin in the introduction
2. clarified that "typically one inhaled antibiotic is used as a time" referred to chronic setting
3. described organisms isolated from her sputum in the prior-year, follow-up year and subsequent year (this was also recommended by Dr Liou)
4. clarified the location (home/hospital) for all treatment courses
5. clarified the use of adjunctive therapies

As recommended by Dr Liou, we have:

1. clarified which treatment courses were specifically for acute exacerbation - the 1st dual nebulised antibiotics course was for acute exacerbation (subject was symptomatic although %FEV₁ was relatively stable) and the 3rd intravenous antibiotics course was for acute exacerbation (4% absolute decline in FEV₁ from previous although there was no clear symptoms)
2. iterated the sentence in 2nd paragraph of "case report" to clarify the more intensive treatment during the follow-up year
3. provided more detailed results for sputum cultures
4. provided in generic name with first use of trademarked names for nebulised antibiotics, and only using generic name for intravenous antibiotics

We have explained in our response to Dr Liou's comments that we felt adequate history has been provided (especially in terms of age and genotype), and that we have already provided a gold-standard adherence measure in the form of adherence data captured using I-neb (a data logging nebuliser).

See referee reports

Introduction

Cystic fibrosis (CF) is a genetic condition whereby ~80% of mortalities are primarily due to lung disease¹. People with CF are prone to recurrent respiratory infections (termed 'pulmonary exacerbations'), which leads to progressive lung damage and respiratory failure². This is especially so after *Pseudomonas aeruginosa* (Psaе) is acquired³.

Although there is a lack of evidence for best practice in treating exacerbations among adults with CF and chronic Psaе infection⁴, two weeks of dual intravenous antibiotics are generally used for synergistic effect^{4,5}. The European CF Society recommend against using inhaled antibiotics to treat exacerbations, due to concerns that increased mucus plugs during exacerbations may prevent antibiotics from reaching smaller airways⁵.

There is scant research on using inhaled antibiotics to treat exacerbations. A Cochrane review in 2012 found only four relevant studies, with inadequate sample sizes to demonstrate efficacy⁶. Subsequently, a randomised cross-over trial among 20 adults with CF and pulmonary exacerbation in 2014 demonstrated longer time to next exacerbation with nebulised compared to intravenous tobramycin (all participants received intravenous colistin as the second antibiotic)⁷. A large observational study in North America found that ~24% of exacerbations are treated with inhaled antibiotics⁸. Inhaled antibiotics have several advantages. Systemic adverse effects e.g. allergic reactions, gastrointestinal manifestations, ototoxicity and renal failure are common with intravenous antibiotics^{9,10} but rare with inhaled antibiotics¹¹. Higher antibiotic concentrations within the airways are achieved via inhaled route, which may be beneficial in overcoming resistance¹². Inhaled route also overcomes difficulties associated with venous access.

For long-term suppressive therapy, typically one inhaled antibiotic is used at a time, and someone on multiple inhaled antibiotics would alternate between those antibiotics¹¹. Of the five existing trials looking at inhaled antibiotics for acute exacerbation, only one study with 18 participants concomitantly administered two inhaled antibiotics (tobramycin and carbenicillin)⁶. Yet dual inhaled antibiotics (i.e. concomitant use of two different inhaled antibiotics) may have synergistic effect, thus achieve better results. We report on an adult with CF and chronic Psaе infection who achieved good results when treating exacerbations using dual inhaled antibiotics.

Case report

A Caucasian female in her early thirties with F508del/Class I mutation, pancreatic insufficiency and CF related diabetes also fulfilled the Leeds criteria¹³ for chronic Psaе infection. Only Psaе (Liverpool epidemic strain sensitive only to colistin) was cultured from all 12 sputum samples in the previous year. Despite high objective adherence to nebulised dornase alfa 2.5mg once daily and alternating colistin (Promixin®) Imegaunit twice daily/tobramycin (TOBI®) 300mg twice daily (82.9% two years ago, 96.3% in the previous year; measured with an I-neb®), stable BMI around 23.1 and reasonable glycaemic control (HbA1c 47 in month 1 of the follow-up period), there was a trend of declining %FEV₁. Her annual best FEV₁ was 47%, 44% and 42% over the previous three years. There was no evidence of allergic bronchopulmonary aspergillosis (ABPA) or other CF complications compromising her %FEV₁.

In month one, Promixin® was also switched to nebulised Aztreonam (AZLI®) 75mg thrice daily. She had two courses (28 days) of intravenous antibiotics throughout the previous year. She agreed to three-monthly intravenous antibiotics in the follow-up year to try halt the FEV₁ decline. She had 14 days of home intravenous piperacillin/tazobactam 4.5g thrice daily and intravenous colistin 2megaunit thrice daily in month one (%FEV₁ improved from 38% to 40%), and again in month 4 (%FEV₁ declined from 40% to 38%).

She felt less well with increased sputum volume and dyspnoea at the start of month six. Her %FEV₁ was 39%. She agreed to try 14 days of concomitant nebulised AZLI[®] 75mg thrice daily and TOBI[®] 300mg twice daily at home (nebulised dornase alfa was continued) as treatment for acute exacerbation. She used 69/70 (98.6%) of her nebuliser doses over the 14 days (note that TOBI[®] twice daily = 4 doses via I-neb[®] and AZLI[®] could not be administered via I-neb[®]). Her %FEV₁ improved to 45% at day 7 and 44% at day 14. Her symptoms resolved by day 14.

She felt well but her %FEV₁ declined to 39% during her next clinic review at the end of month seven. She went on another 14-day course of home intravenous piperacillin/tazobactam 4.5g thrice daily and intravenous colistin 2megaunit thrice daily as treatment for acute exacerbation. At day 14, her %FEV₁ remained 39%. Another 14-day course of home concomitant nebulised AZLI[®] and TOBI[®] was started in month 8 (nebulised dornase alfa was continued). She used 66/70 (94.3%) of her nebuliser doses over the 14 days (note that TOBI[®] twice daily = 4 doses via I-neb[®] and AZLI[®] could not be administered via I-neb[®]). Her %FEV₁ improved to 41% at day 7 and day 14, despite developing viral coryzal symptoms at day 12. With 14 days of hospital IV piperacillin/tazobactam 4.5g thrice daily and intravenous tobramycin 480mg once daily in month 11, her %FEV₁ improved from 39% at day 1 to 41% at day 14. She received intensive physiotherapy during her in-patient stay in month 11 which may contribute to some of the %FEV₁ improvement but received no other adjunctive therapies (e.g. corticosteroid) during all treatment courses. All her inhaled therapies were continued during dual intravenous antibiotic courses.

During the follow-up year, only Psae (Liverpool epidemic strain sensitive only to colistin) was cultured from all eight sputum samples. During the subsequent year, only Psae (Liverpool epidemic strain sensitive only to colistin) was cultured from all nine sputum samples.

Discussion

In this case, %FEV₁ improvement following acute treatment of exacerbations with dual inhaled antibiotics at home (mean 3.5% over two courses) was somewhat higher than with dual intravenous antibiotics (mean 0.5% over four courses), despite similar baseline %FEV₁ and one of the intravenous antibiotics courses was delivered in hospital. The %FEV₁ improvement also occurred despite severe background lung disease (high resolution CT in month eight showed extensive bronchiectasis and baseline %FEV₁ was ~40%).

Although she reported symptomatic improvement during her first dual inhaled antibiotics course, we did not formally measure symptomatic responses to treatments with a validated tool.

The sample size is too small for null hypothesis significance testing, and regression to the mean is potentially a threat to our results. Our results are nonetheless intriguing and suggest that dual inhaled antibiotics could potentially have a role in treating exacerbations among adults with CF and chronic Psae infection. With the increasing number of inhaled anti-pseudomonal antibiotics available, e.g. nebulised levofloxacin¹⁴, different combinations of concomitant inhaled antibiotics can be used in the future for synergistic effect.

Like all medications, there are adverse events associated with inhaled antibiotics. There is a case report of acute respiratory distress syndrome potentially due to inhaled colistin¹⁵. However, localised adverse events with inhaled antibiotics are usually mild, e.g. bronchoconstriction which tends to resolve spontaneously within hours or can be controlled by pre-dosing with nebulised bronchodilator¹¹.

High adherence to inhaled therapies probably contributed to the good clinical response from dual inhaled antibiotics observed in this case. Real-world adherence with long-term inhaled antibiotics among adults with CF is only 35–50%^{16,17}. Someone who is already struggling with a single inhaled antibiotic is unlikely to cope with dual inhaled antibiotics, thus may derive less benefit. However, adherence to short-term drug regimen tends to be higher¹⁸. Adults with CF might be able to summon adequate self-regulation during a 14-day dual antibiotics course to really focus on their nebuliser use¹⁹.

In conclusion, the %FEV₁ improvements observed in this case report provide anecdotal evidence that dual inhaled antibiotics could potentially be a treatment option for exacerbations among adults with CF and chronic Psae infection. Given the lack of good quality evidence regarding optimum exacerbations treatments and the theoretical advantages of using inhaled antibiotics, this warrants further investigations.

Consent

Written informed consent for publication of her clinical details was obtained from the patient.

Data availability

No data is associated with this article.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Open Peer Review

Current Referee Status:



Version 2

Referee Report 01 March 2018

doi:10.5256/f1000research.15356.r31266



Tim Lee 

Regional Paediatric Cystic Fibrosis Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK

I thank the authors for revising the manuscript. My previous comments have been addressed and I support publication.

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Referee Report 08 February 2018

doi:10.5256/f1000research.14431.r29543



Theodore G. Liou 

Department of Internal Medicine, University of Utah, Salt Lake City, UT, USA

This is a case report of a patient with CF during a 6 month period during which she was treated with multiple antibiotics in several regimens that seemed to differ with each treatment episode.

The introduction is well written and informative. The case history itself raises many questions. There are fewer details of the patient's baseline history than desired. The lack of a specific age is not typical for case reports. It would be nice to know whether her genotype was F508del homozygous or heterozygous with a second, preferably identified, mutation. The report of high adherence of the patient is open to doubt because of the poor track record of clinicians detecting non-adherence in an accurate way, and confirmation of the degree of adherence, perhaps with a medication possession report, would be helpful.

The key portion of the history detailing treatments with various antibiotics, regimens and dosing routes is interesting but lacks some key details. It is not entirely clear what triggered the more intensive 6 months. There is reference to symptoms and signs often associated with acute exacerbations, the introduction seems to focus at least in part on exacerbations, and the discussion refers to "acute treatment of exacerbations," but the patient's course is not described in a way as to identify when pulmonary

exacerbations were specifically diagnosed or treated. This detracts from helping readers understand the circumstances for which different treatments were initiated.

In the discussion, the authors discuss the possible effects of dual inhaled antibiotics, but I find it difficult to associate such use with a superior outcome even on an anecdotal basis because many drugs and regimens were employed in response to what seems to have been multiple clinical situations during the 6-month case history period.

I think the report could be improved by providing more patient history prior to the 6-month period of focus, better assessment of her level of adherence, clear definition of pulmonary exacerbation as used in this patient's case and clearer description of triggers for different treatments as well as more precise descriptions of outcomes. An additional outcome to consider including would be the results of subsequent bacterial cultures and any changes in resistance patterns.

A study of dual inhaled antibiotics compared to intravenous would be of interest. However, there are likely to be many barriers and difficulties developing a generally usable protocol. Some mention of these barriers might be helpful to explain why such a study has not been done.

Finally, to help readers in areas of the world where trade names are not the same or the medications are not available, Promixin, Azli, Tobi, Tazocin and Coly-Mycin should be identified by their generic names in addition to the trademarked names. It would be better, I think, if they were referred to by their generic names in preference to the trade names.

Is the background of the case's history and progression described in sufficient detail?

No

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: Dr Liou discloses that he is supported by grants from the National Institutes of Health/National Heart Blood and Lung Institute, the Ben B. and Iris M. Margolis Family Foundation of Utah, the Cystic Fibrosis Foundation, and funds from the Claudia Ruth Goodrich Stevens Endowment Fund. During the last three years, the Cystic Fibrosis Center at the University of Utah has received funds to conduct clinical trials from Cystic Fibrosis Foundation Therapeutics, Inc, the Foundation of the National Institute of Health, Gilead Sciences, Inc, Laurent Pharmaceuticals, Nivalis Therapeutics, Inc, Novartis, Proteostasis Therapeutics, Inc, Savara Pharmaceuticals and Vertex Pharmaceuticals. None of the clinical trials were related to the case reported here. Dr Liou is holder with colleagues at the U of Utah of a provisional patent for a novel polyketide antibiotic that is in pre-clinical research and development.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 08 Feb 2018

Zhe Hui Hoo, University of Sheffield, UK

We thank Dr Liou for the review and we will iterate the case report taking into account the comments.

In Sheffield whereby we only provide care for around 200 adults with CF, we only have a female adult with her exact age (in years) and her F508del/Class I mutation. Thus, to maintain the anonymity of the patient (which was the basis on which she provided consent), we could only provide an approximate age and specify that she was heterozygous for F508 mutation in the first sentence of the 'case report' section. In any case, whether the patient is 30 years of age or 33 years of age (which is the age range we consider to sit within 'early thirties') is irrelevant to the conclusion of the case report or to the interpretation of her FEV1. By stating that she has a Class II mutation (i.e. F508del) and Class I mutation in the first sentence of the 'case report' section, we have also specified that she has 'severe genotype' according to the definition of Castellani et al. J Cyst Fibros 2008, 7:179-196.

In Sheffield, we measure nebuliser adherence using I-neb (as specified in the second sentence of the 'case report' section). Electronic data capture is generally considered the 'gold standard' measure for adherence and MPR is not a "better assessment of adherence" compared to electronic data capture. The study by Siracusa et al. J Cyst Fibros 2015;14:621-6 have demonstrated that MPR data may be unreliable. In that study, ivacaftor adherence according to electronic data capture was only around 60% but MPR suggested adherence of 84%. There was also no correlation between adherence data captured using electronic data capture and MPR. Since we have provided EDC adherence data, we do not think MPR data will add further information regarding her adherence.

We will clarify the trigger for the more intensive treatment period and clarify which of the treatment was used to treat an acute exacerbation. We will also provide results for her subsequent bacterial cultures and any changes in resistance patterns.

A small study using dual nebulised antibiotics has been done in 1985, as identified by the 2012 Cochrane review. We agree that any study for the treatment of pulmonary exacerbation is challenging. The STOP program in the US appears to be making breakthroughs in starting to define best practices in the treatment of pulmonary exacerbations, suggesting that such studies are difficult but not impossible to execute.

Competing Interests: No competing interests were disclosed.

Referee Report 30 January 2018

doi:10.5256/f1000research.14431.r30297



• **Freddy Frost**  , **Dilip Nazareth**

Liverpool Heart and Chest Hospital, Liverpool, UK

Mann *et al* report an interesting case demonstrating that inhaled antibiotics may be useful for the treatment of acute pulmonary exacerbations in CF. The authors accurately describe the background and much of the evidence relating to the use of inhaled antibiotics in acute exacerbations including the Cochrane review of 2012. However, the Cochrane review preceded the most recent clinical trial in this field. The study demonstrated and discussed both pulmonary and renal benefits for nebulized tobramycin in the treatment of exacerbations and the authors should consider including it in the introduction. ¶

In the fourth paragraph it should be clarified whether “typically one inhaled antibiotic is used at a time” refers to the routine practice in the chronic setting or previous studies in the acute setting.

The case itself is well described however the authors may wish to consider including some relevant extra information. Firstly, had the patient cultured any other organisms aside from *P. aeruginosa* in their sputum in the preceding 12 months? Secondly, were all the treatments completed at home or in the inpatient setting? Differing settings with increased physiotherapy input as an inpatient could theoretically account for some of the differences. Finally, were other adjunctive therapies such as oral corticosteroids used in the management of each exacerbation.

The discussion is balanced and recognises the limitations of the case as well as potential adverse events related to nebulised therapy. Overall, this is an interesting case worthy of publication and we wholeheartedly agree with the authors that this is a management strategy that warrants further investigation.

References

1. Al-Aloul M, Nazareth D, Walshaw M: Nebulized tobramycin in the treatment of adult CF pulmonary exacerbations. *J Aerosol Med Pulm Drug Deliv.* 2014; **27** (4): 299-305 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the background of the case’s history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 30 Jan 2018

Zhe Hui Hoo, University of Sheffield, UK

We thank Drs Frost and Nazareth for the review and very useful comments which will guide our revision of the case report.

We will include 2014 pilot study of nebulised vs IV tobramycin in the 'Introduction'. We will also alter the 4th paragraph of the 'Introduction' to clarify that the first sentence was referring to inhaled antibiotics in chronic settings whilst the second sentence referred to inhaled antibiotics in acute settings.

We will include the extra information relating to microbiology results, clarify the treatment setting (all treatments were at home except for the last course of IV antibiotics in month 11) and clarify the use of any adjunctive therapies.

Competing Interests: No competing interests were disclosed

Referee Report 04 January 2018

doi:[10.5256/f1000research.14431.r29445](https://doi.org/10.5256/f1000research.14431.r29445)



Tim Lee 

Regional Paediatric Cystic Fibrosis Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK

This is a useful case report highlighting the potential for treating certain pulmonary exacerbations in people with cystic fibrosis with inhaled antibiotics. The background is well written. References are appropriate and balanced.

The case is well described and the adherence data prior to the exacerbations is helpful. The clinical response in terms of FEV1 is well reported and favourable by comparison to response to iv therapy.

Paragraph 2 of the "Case Report" section should in my view more clearly specify that the colomycin 2MU three times a day was given **intravenously** rather than nebulised alongside the intravenous Tazocin for 14 days in month 1 and month 4, given the overall title of the case report and the similar iv/nebulised dosages for colomycin. It would also be instructive to know whether the intravenous antibiotics were administered at home or in hospital.

In paragraphs 3 and 4 of the "Case Report" section, it would be useful to know if the subject was also taking nebulised dornase alpha during this period, i.e. was she achieving six nebulised therapies per day? Also, if available, adherence measures during these 2 week pulses of inhaled dual antibiotic therapies would be useful, as many clinicians do have concerns that this intensity of nebulised medications may be difficult to achieve for many people with CF, despite the good clinical response seen here.

The conclusions, acknowledgements of limitations, are all well written and appropriate. In summary this case report is valuable and will be of interest to the CF community. I support publication but would recommend the clarifications I have suggested are considered.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 04 Jan 2018

Zhe Hui Hoo, University of Sheffield, UK

We thank Dr Lee for the review and very useful comments which will guide our revision of the case report.

We will clarify in Paragraph 2 (and 4) of the "Case Report" section that colomycin 2MU thrice daily was given intravenously, and likely for tobramycin 480mg once daily (in paragraph 4).

We will also clarify the Paragraphs 2 and 3 of the "Case Report" section that once daily nebulised dornase alfa was continued throughout the dual nebulised antibiotics; and report the total number nebuliser doses taken during the 2 week pulses of dual inhaled dual antibiotic therapies.

Competing Interests: No competing interests were disclosed.

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