Feasibility of shortening intravenous antibiotic therapy for bronchiectasis based on bacterial load: a proof-of-concept randomised controlled trial

Pallavi Bedi[1,4], Manjit K. Cartlidge[1,4], Yang Zhang[1], Kim Turnbull[2], Samantha Donaldson[1,2], Andrea Clarke[1,2], Jane Crowe[2], Kadiga Campbell[2], Catriona Graham[3], Ruzanna Franguylan[2], Adriano G. Rossi[1] and Adam T. Hill[1,2]

[1]MRC Centre for Inflammation Research, Queen's Medical Research Institute, Edinburgh, UK. [2]Royal Infirmary of Edinburgh, Edinburgh, UK. [3]Edinburgh Clinical Research Facility, University of Edinburgh, Western General Hospital, Edinburgh, UK. [4]P. Bedi and M.K. Cartlidge are joint first authors.

Corresponding author: Pallavi Bedi (drpallavibedi@gmail.com)

Shareable abstract (@ERSpublications)
In bronchiectasis, bacterial load-guided therapy is feasible in most exacerbations requiring intravenous antibiotic therapy https://bit.ly/33VIQuR

Cite this article as: Bedi P, Cartlidge MK, Zhang Y, *et al*. Feasibility of shortening intravenous antibiotic therapy for bronchiectasis based on bacterial load: a proof-of-concept randomised controlled trial. *Eur Respir J* 2021; 58: 2004388 [DOI: 10.1183/13993003.04388-2020].

This article has supplementary material available from erj.ersjournals.com

This article has an editorial commentary: https://doi.org/10.1183/13993003.01416-2021

Received: 4 Dec 2020
Accepted: 4 May 2021

Abstract

Background There is a lack of evidence to guide the duration of intravenous antibiotics for bronchiectasis exacerbations.

Aims The aim of this study was to assess whether it is feasible, based on bacterial load, to shorten intravenous antibiotics during exacerbations and whether 14 days of treatment is superior.

Methods We recruited participants requiring intravenous antibiotics for exacerbations. Participants were randomised into two groups: to receive antibiotics for 14 days (14-day group) or to have a shorter duration of treatment based on bacterial load (bacterial load-guided group (BLGG)). Bacterial load was checked on days 0, 7, 10, 14 and 21. If the bacterial load was $<10^6$ CFU·mL^{-1} on day 7 or day 10 in the BLGG, antibiotics were stopped the following day.

Results A total of 47 participants were in the 14-day group and 43 were in the BLGG. 88% of participants in the BLGG were able to stop antibiotics by day 8 and potentially 81% of participants in the 14-day group could have stopped antibiotics at day 8. There was a nonsignificant trend for increased clinical improvement by day 21 in the 14-day group compared to the BLGG. However, overall group data showed the median (interquartile range) time to next exacerbation was 27.5 days (12.5–60 days) in the 14-day group and 60 days (18–110 days) in the in BLGG (p=0.0034). In a Cox proportional hazard model, participants in the 14-day group were more likely to experience exacerbations (HR 1.80, 95% CI 1.16–2.80, p=0.009) than those in the BLGG, and those with mild bronchiectasis were less likely to experience exacerbations than patients with more severe bronchiectasis (HR 0.359, 95% CI 0.13–0.99, p=0.048).

Conclusions Bacterial load-guided therapy is feasible in most exacerbations requiring intravenous antibiotics. There was a nonsignificant trend for increased clinical improvement by day 21 with 14 days of antibiotics compared with bacterial load-guided therapy but paradoxically there was a prolonged time to next exacerbation in the BLGG.

Introduction

Bronchiectasis is characterised by chronic cough, daily sputum production and recurrent chest infections. Both the British Thoracic Society (BTS) and European Respiratory Society (ERS) [1–3] recommend the use of antibiotics to treat exacerbations. Studies by our group have previously demonstrated significant improvement in markers of airway inflammation using short-term treatment (14 days) with intravenous (*i.v.*) antibiotics and using longer-term treatment with 12 months of nebulised gentamicin [4]. These data provide strong evidence that antibiotic treatment can alter the underlying airway inflammation in

bronchiectasis, providing hope for improving clinical symptoms and the prognosis of the disease [4]. However, there are no randomised placebo-controlled studies evaluating the efficacy of antibiotics in exacerbations in adults. A randomised control trial performed by Bilton *et al.* [5] compared oral ciprofloxacin (in treatment doses) plus placebo to oral ciprofloxacin plus inhaled tobramycin. The addition of inhaled tobramycin led to an improved microbiological outcome but the inability to demonstrate an additional clinical benefit may have been due to emergent wheeze resulting from treatment.

Cohort studies by our research group [6–8] showed that those participants who needed *i.v.* antibiotic therapy according to the BTS guidelines 2010 [9] had a good clinical response. There was not, however, a control group that did not receive antibiotic therapy. In general, 14-day antibiotic courses are standard and should always be used in participants infected with *Pseudomonas aeruginosa* [1]. Shorter courses may suffice in participants with less severe bronchiectasis [1].

Several recent studies have demonstrated that long-term oral and inhaled antibiotics during the stable state improve clinical and patient-reported outcomes as well as increasing time to next exacerbation [10–13]. However, there is insufficient evidence to evaluate the efficiency of antibiotics during an exacerbation in bronchiectasis [1].

The aim of this study was to assess whether it is feasible based on bacterial load to shorten *i.v.* antibiotic treatment during bronchiectasis exacerbations from the standard 14 days recommended by the BTS and ERS guidelines. Additionally, the authors wanted to assess whether 14 days of *i.v.* antibiotic treatment is superior to a shorter course. The hypothesis was that although it maybe feasible to stop antibiotic treatment early based on a reduction in bacterial load, there would be better clinical outcomes with 14 days of *i.v.* antibiotic therapy compared with a bacterial load-guided therapy. The ClinicalTrials.gov identifier for the study is NCT02047773.

Methods

Study population

The authors recruited participants with an exacerbation requiring *i.v.* antibiotics. All were aged ⩾18 years, had bronchiectasis confirmed on chest computed tomography and were being followed up at the Bronchiectasis Clinic at the Royal Infirmary of Edinburgh, UK. Participants were given *i.v.* antibiotics (in our study all participants received meropenem) for an exacerbation if they met the BTS guidelines for administering *i.v.* antibiotics [1]. Meropenem (2 g three times a day) was the antibiotic of choice because it is broad spectrum and covers gram-positive and gram-negative bacteria, including *P. aeruginosa*, as well as anaerobes. In addition, it was the antibiotic of choice for participants with a penicillin allergy. This would also remove any confounding based on antibiotic class while analysing the data. The plan was to add *i.v.* colistimethate sodium (Colomycin) if there was a clinical deterioration despite *i.v.* meropenem.

Bronchiectasis severity

The severity of bronchiectasis was based on the Bronchiectasis Severity Index (BSI) [14].

Randomisation and study design

The BTS and ERS guidelines recommend that *i.v.* antibiotics should be considered when participants are particularly unwell, have resistant organisms or have failed to respond to oral therapy (this is most likely to apply to participants with *P. aeruginosa*) [1–3]. Exacerbations were defined as the presence of three or more of the following signs or symptoms for at least 24 h: increased cough, increased sputum volume, increased sputum purulence, haemoptysis, increased dyspnoea, increased wheezing, fever (⩾38°C) or malaise [1, 3]. The start date of this study predates the consensus definition of exacerbation by the ERS [3].

Patients were randomised using a random allocation sequence in block randomisations of four. Allocation was concealed in an envelope. Patients were either in the group receiving 14 days of *i.v.* meropenem or in the bacterial load-guided group (BLGG) of *i.v.* meropenem therapy. In the BLGG, antibiotics were stopped early if the bacterial load was $<10^6$ CFU·mL^{-1} on day 7 or on day 10 (if not $<10^6$ CFU·mL^{-1} on day 7). In the BLGG, all received a minimum of 7 days of antibiotic therapy. No sputum was regarded as 0 CFU·mL^{-1} and participants were eligible to stop antibiotics. Quantitative sputum microbiology analysis takes 24 h; therefore, in the BLGG, antibiotics were stopped on day 8 if the bacterial load was $<10^6$ CFU·mL^{-1} on day 7, and on day 11 if the bacterial load was $\geqslant 10^6$ CFU·mL^{-1} on day 7 but $<10^6$ CFU·mL^{-1} on day 10.

Primary outcomes

The primary outcomes of the study were 1) time to next exacerbation requiring oral or *i.v.* antibiotic therapy (dates were taken from the participant and confirmed from the general practice records) (time frame: up to 1 year following *i.v.* antibiotics); and 2) the proportion of participants in the BLGG in whom antibiotics could be stopped early, either on day 8 or day 11, instead of the usual 14-day course (time frame: 14 days).

Secondary outcomes

The secondary outcomes of the study were as follows. 1) Clinical recovery at day 21. Clinical recovery was defined as patients feeling better (quantitatively assessed using a ⩾4-point improvement in St George's Respiratory Questionnaire (SGRQ) [15] or a ⩾1.3-unit improvement in the Leicester Cough Questionnaire (LCQ)) [16, 17] and either a reduction in sputum purulence (purulent to mucopurulent, mucoid or no sputum; or mucopurulent to mucoid or no sputum [6]) or a ⩾50% reduction in 24-h sputum volume. The authors included a *post hoc* sub-analysis exploring using a ⩾4-point improvement in the SGRQ or a ⩾1.3-unit improvement in the LCQ. 2) Secondary safety end-points were measured on day 21 and included white cell count, C-reactive protein, forced expiratory volume in 1 s and forced vital capacity. 3) Antibiotic side effects (time frame: 14 days). 4) Any serious adverse events. Only other adverse events that led to a change or alteration of meropenem therapy were recorded.

Place of administration of i.v. antibiotics

Participants were administered domiciliary antibiotics if it was considered safe to do so. The authors have previously published on the safety and efficacy of *i.v.* antibiotics at our centre [6–8]. The remaining participants were admitted to hospital.

Consent

Lothian Research Ethics Committee gave consent for the study (13/SS/0198). All participants provided written consent for the study. Detailed study participant selection and study design are available in the supplementary material.

Statistical analysis

This was a proof-of-concept study. Based on national guidelines, the study was powered on the expectation that 14 days of treatment was superior to shorter treatment duration. For prolonging time to next exacerbation by 28 days (thought to be a clinically significant prolongation), using a two-tailed test, 5% level of significance, 80% power and a common standard deviation of 42 days [18], we would need a sample size of 37 participants per group. To allow for a 20% dropout, the authors recruited 45 participants per group, *i.e.* 90 participants in total. The authors planned to recruit at least 90 participants but randomisation was created for 120 participants. Because recruitment was challenging, the study was stopped at 90 participants.

The authors analysed the primary and secondary end-points by intention-to-treat analysis. For demographic and clinical variables, data are presented as median (interquartile range (IQR)) for continuous variables and n (%) for categorical variables, unless otherwise stated.

Time to next exacerbation is shown using a Kaplan–Meier survival curve with group comparisons using a log-rank statistic and presented with median (IQR) time to exacerbation. Further *post hoc* sub-analyses of the data to calculate the time to next exacerbation were done by dividing the groups into those colonised by *P. aeruginosa* and those with non-*Pseudomonas* organisms.

A multivariable Cox proportional hazards model was generated for time to next exacerbation with the following variables: treatment (14 days, BLGG); baseline colonisation with *P. aeruginosa* (yes, no); high bacterial load $\geqslant 10^6$ CFU·mL^{-1} (yes, no); BSI (mild 0–4, moderate 5–8, severe ⩾9); hospitalisation for the exacerbation (yes, no). The model was then repeated excluding the BSI because this also includes baseline colonisation with *P. aeruginosa*.

For the secondary end-points, a binomial test for the comparison of proportions was used to compare the proportion of participants with clinical improvement. The change from baseline to day 21 was calculated in each group and the differences compared in the group by Mann–Whitney U test.

To compare the bacterial load difference within the groups, Wilcoxon signed rank test was used. Data were analysed using SPSS version 25 (IBM Corporation); significance was accepted with p-values <0.05.

Results

A total of 114 participants were screened and 90 were recruited in the study. Participants were randomised into one of two arms of the study (figure 1). All 90 participants completed the study. The first patient was enrolled on January 16, 2014, and the last patient on November 9, 2018. Baseline characteristics of the study participants are shown in table 1. None of the patients was on hypertonic saline. However, all patients were recommended to practice twice-daily chest physiotherapy and continued to do so if they were in hospital.

Treatment

All patients received 2 g meropenem three times daily. Only one patient in this study (in the 14-day group) had a sample with subsequent meropenem resistance, but they showed a clinical response and so continued the meropenem and were given no additional antibiotics. No participant needed additional *i.v.* antibiotics to meropenem during the study.

Primary end-point

The median (IQR) time to next exacerbation was 27.5 days (12.5–60 days) in the group receiving antibiotics for 14 days and 60 days (18–110 days) in the BLGG (p=0.003). Figure 2a shows a Kaplan–Meier plot of the estimated time to next exacerbation.

For participants colonised with *P. aeruginosa*, the median (IQR) time to exacerbation was 24.5 days (16–58.5 days) in the 14-day group and 28 days (12.5–115.5 days) in the BLGG (p=0.110, figure 2b).

For participants colonised with non-*Pseudomonas* organisms, the median (IQR) time to exacerbation was 31.5 days (12–75 days) in the 14-day group and 60 days (30–114 days) in the BLGG (p=0.021, figure 2c).

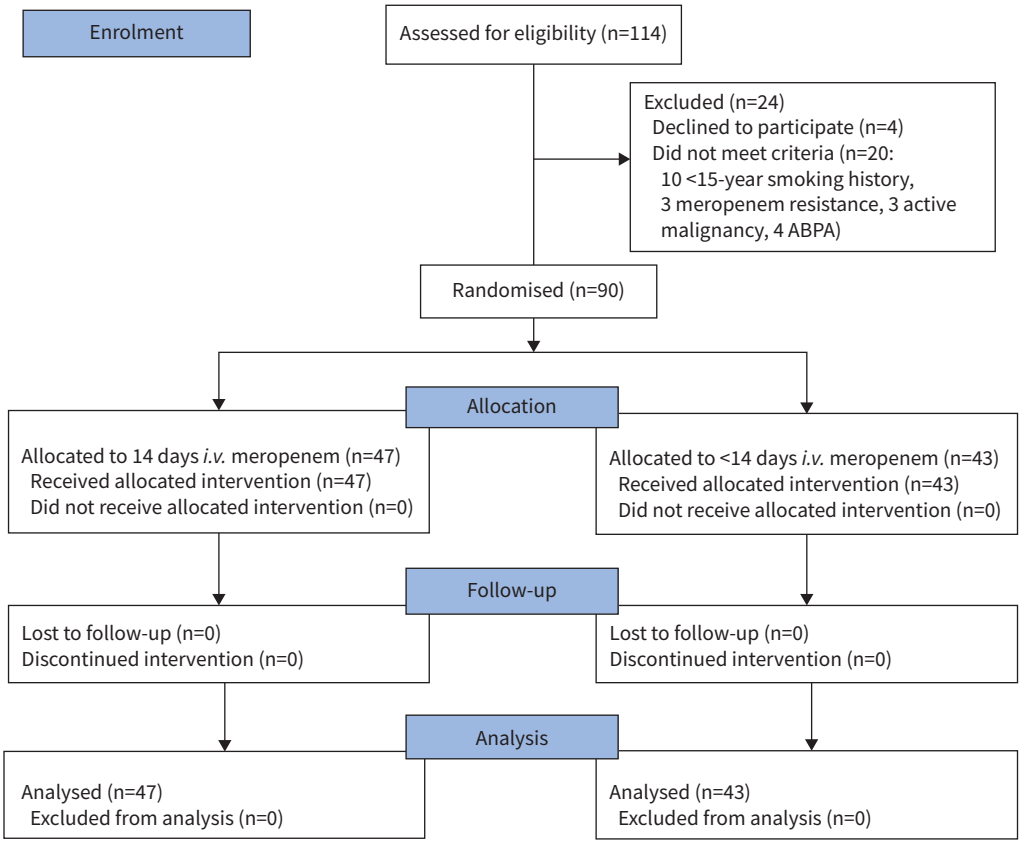

FIGURE 1 Consort diagram of participants recruited in the study. ABPA: allergic bronchopulmonary aspergillosis.

TABLE 1 Baseline demographics of study participants

Parameters	14-day group	BLGG
Subjects n	47	43
Age (years)	67 (59–74)	71 (61–77)
Gender		
Female	28 (60%)	24 (56%)
Male	19 (40%)	19 (44%)
Place of *i.v.* antibiotics		
Domiciliary	38 (81%)	28 (65%)
In hospital	9 (19%)	15 (35%)
Aetiology		
Idiopathic	25 (53%)	23 (53%)
Post infectious	14 (30%)	11 (26%)
ABPA	3 (6%)	1 (2%)
Immune defect	2 (4%)	5 (12%)
RA	2 (4%)	2 (5%)
PCD	1 (2%)	0
UC	0	1 (2%)
Comorbidities		
Asthma	27 (57%)	18 (42%)
COPD	10 (21%)	8 (19%)
GORD	3 (6%)	2 (5%)
WCC ($\times10^9\cdot L^{-1}$)	8.4 (6.1–10.3)	8.4 (6.6–9.8)
Neutrophils ($\times10^9\cdot L^{-1}$)	5.2 (4–7.7)	5.6 (3.9–7.2)
ESR ($mm\cdot h^{-1}$)	13 (6.5–30)	20 (8–33.7)
CRP ($mg\cdot L^{-1}$)	8.5 (3–26)	13 (4–23)
Colonised with *P. aeruginosa*	20 (43%)	17 (40%)
Long-term antibiotics	5 (10.6%)	6 (14%)
Long-term macrolides	1(2%)	2 (5%)
Incremental shuttle walk (m)	260 (167.5–450)	225 (120–352.5)
FEV_1 % predicted	61 (49.5–72)	71 (53–94)
FVC % predicted	81 (67.5–97)	83 (64–99)
BSI score	11 (7–15)	11 (7–15)
Mild	3 (6%)	3 (7%)
Moderate	11 (23%)	14 (33%)
Severe	33 (71%)	26 (60%)
LCQ (units)	10.8 (8.6–14.1)	10 (7.6–13.3)
SGRQ (units)	43.4 (31.5–62.4)	44.8 (27.9–65.9)

Data presented as median (interquartile range) or n (%), unless otherwise stated. BLGG: bacterial load-guided group; ABPA: allergic bronchopulmonary aspergillosis; RA: rheumatoid arthritis; PCD: primary ciliary dyskinesia; UC: ulcerative colitis; COPD: chronic obstructive pulmonary disease; GORD: gastro-oesophageal reflux disease; WCC: white cell count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BSI: Bronchiectasis Severity Index; LCQ: Leicester Cough Questionnaire; SGRQ: St George's Respiratory Questionnaire.

Cox proportional hazard model

Patients in the 14-day group were more likely to experience exacerbations (HR 1.80, 95% CI 1.16–2.80, p=0.009) compared to those in the BLGG. Patients with mild bronchiectasis were less likely to experience exacerbations than those with more severe bronchiectasis (HR 0.359, 95% CI 0.13–0.99, p=0.048). When excluding the BSI from the model, those in the 14-day group were more likely to experience exacerbations than those in the BLGG (HR 1.77, 95% CI 1.14–2.75, p=0.012).

Proportion of participants stopping/able to stop antibiotics early

On day 7, 84% of all participants (76 of 90) had a bacterial load $<10^6$ $CFU\cdot mL^{-1}$ and hence could have stopped antibiotics early. In the BLGG, 88% (38 of 43) stopped treatment on day 8; in the 14-day group, 81% (38 of 47) could have stopped but continued as per treatment allocation.

On day 10, 76% of all participants (68 of 90) had a bacterial load $<10^6$ $CFU\cdot mL^{-1}$ and hence could have stopped antibiotics early. In the BLGG, the remaining 12% of participants still on medication (five of 43) had their treatment stopped on day 11.

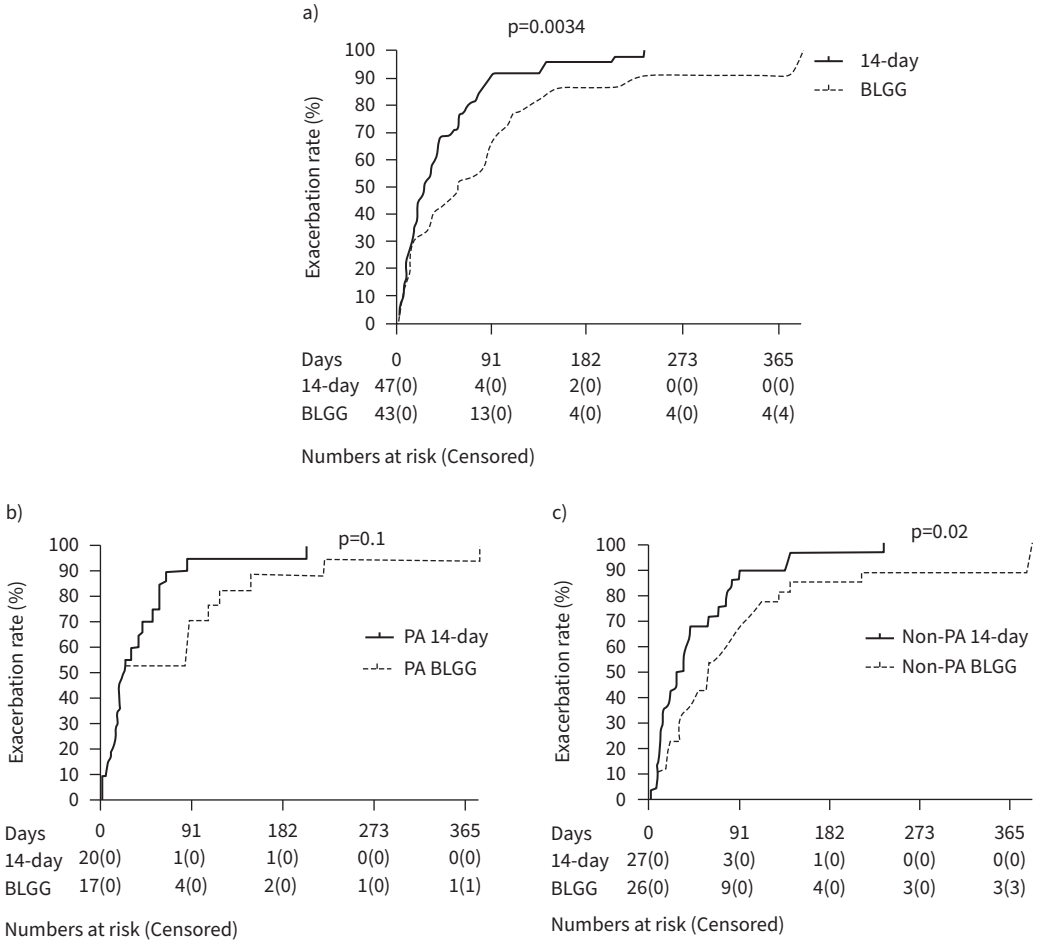

FIGURE 2 a) Kaplan–Meier plot to estimate the time to next exacerbation in the 14-day group and in the bacterial-load-guided group (BLGG); p=0.0034. b) Kaplan–Meier plot to estimate the time to next exacerbation comparison between participants colonised with *Pseudomonas aeruginosa* (PA) in the two groups; p=0.110. c) Kaplan–Meier plot to estimate the time to next exacerbation comparison between participants colonised with non-PA in the two groups; p=0.021.

Participants with exacerbations within 1 week of stopping antibiotics

In the 14-day group, seven of 47 participants had an exacerbation within 1 week of stopping antibiotics, with *P. aeruginosa* isolated from one patient and non-*Pseudomonas* organisms isolated from six patients. In the BLGG, three of 43 participants had an exacerbation within 1 week of stopping antibiotics, with non-*Pseudomonas* organisms isolated from all three. There was no evidence of a statistically significant difference in proportion (difference 7.9%, 95% CI −4.8–20.6, p=0.222).

Secondary end-points

Clinical recovery at day 21

In the 14-day group, 32% had a clinical recovery compared to 37% in the shorter arm. There was no evidence of a statistically significant difference in proportion (difference −5.3%, 95% CI −24.9–14.4, p=0.598, table 2).

In a *post hoc* analysis, clinical recovery was then analysed using quality of life questionnaires alone (⩾1.3 unit improvement in the LCQ or ⩾4 unit improvement in the SGRQ). For the whole group there was a nonsignificant trend for increased clinical improvement by day 21, with an improvement in 79% in the 14-day group compared with 60% in the BLGG (p=0.056). There was a similar trend for improved quality of life for patients with both *Pseudomonas* and non-*Pseudomonas* colonisation in the 14-day group compared with patients in the BLGG who had shortened treatment, but this did not reach statistical significance (table 2).

TABLE 2 Predefined recovery (⩾1.3 unit improvement in LCQ or ⩾4 unit improvement in SGRQ and reduction in sputum purulence or ⩾50% reduction in sputum volume) and *post hoc* analyses (⩾1.3 unit improvement in LCQ or ⩾4 unit improvement in SGRQ) of quality of life measures in the groups

Day 21	14-day group	BLGG	Difference (95% CI)	p-value
Predefined recovery	15/47 (32%)	16/43 (37%)	−5.3% (−24.9–14.4%)	0.598
***Post hoc* analysis**				
All participants	37/47 (79%)	26/43 (60%)	18.2% (−0.5–37.0%)	0.056
Pseudomonas	15/20 (75%)	10/17(59%)	16.2% (−13.9–46.3%)	0.293
Non-*Pseudomonas*	22/27 (81%)	16/26 (62%)	19.9% (−3.8–43.7%)	0.100

Data presented as n/N (%). BLGG: bacterial load-guided group; LCQ: Leicester Cough Questionnaire; SGRQ: St George's Respiratory Questionnaire.

Quantitative sputum microbiology

The quantitative sputum microbiology is available in the supplementary material. In the 14-day group, there was a significant reduction in bacterial load compared to baseline on day 7 (p<0.0001), day 10 (p<0.0001) and day 14 (p=0.008) but not day 21 (p=0.061) (figure 3a). Similarly, in the BLGG, there was a significant reduction in bacterial load compared to baseline on day 7 (p<0.0001), day 10 (p<0.0001) and day 14 (p=0.005) but not day 21 (p=0.311) (figure 3a). There was no statistical difference between the two groups at any given time point (figure 3a).

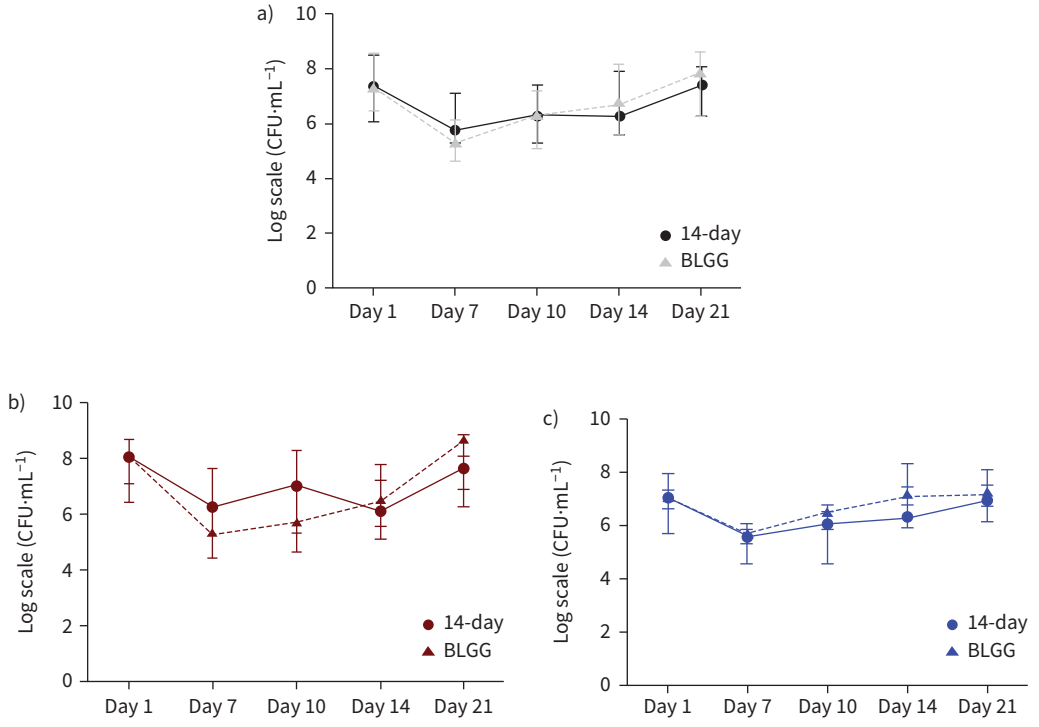

FIGURE 3 a) Change in sputum microbiology from baseline to day 21 in the 14-day group and bacterial load-guided group (BLGG) for all participants. There was a significant reduction in bacterial load in both groups at time points day 7, day 10 and day 14 but not at day 21, compared to baseline. b) Change in *Pseudomonas* sputum microbiology from baseline to day 21 in the 14-day group and BLGG. There was no significant difference in the quantitative sputum microbiology at any of the given time points between the two groups. c) Change in non-*Pseudomonas* sputum microbiology from baseline to day 21 in the 14-day group and BLGG. There was no significant difference in the quantitative sputum microbiology at any of the given time points between the two groups. Mann–Whitney U test used to compare the difference in change in microbiology at the different time points. Graphs represent median (IQR). CFU: colony-forming units.

Participants colonised with *P. aeruginosa*

In the 14-day group, those with *P. aeruginosa* colonisation had a significant reduction in bacterial load compared to baseline on day 7 (p=0.004) and day 14 (p=0.011) but not day 21 (p=0.912) (figure 3b). In the BLGG, those with *P. aeruginosa* colonisation had a significant reduction in bacterial load compared to baseline on day 7 (p=0.003) but not on day 14 (p=0.312) or day 21 (p=0.442) (figure 3b). There was no statistical difference on comparison of quantitative sputum microbiology between the two groups at any given time point.

Participants colonised with non-*Pseudomonas* organisms

In the 14-day group, those with non-*Pseudomonas* colonisation had no significant reduction in bacterial load compared to baseline on day 7 (p=0.521), day 14 (p=0.111) or day 21 (p=0.731) (figure 3c). Similarly, in the less than 14-day group, those with non-*Pseudomonas* colonisation had no significant reduction in bacterial load compared to baseline on day 7 (p=0.312), day 14 (p=0.222) or day 21 (p=0.924) (figure 3c). There was no statistical difference on comparison of quantitative sputum microbiology between the two groups at any given time point.

Secondary safety end-points at day 21

The change in clinical parameters from baseline to 21 days was calculated for both subgroups. The authors then calculated if there was a significant difference between the changes in the two groups (table 3).

Serious adverse events

There were no adverse events that led to a change or alteration in meropenem therapy and no serious adverse events (30-day mortality, anaphylaxis, change of antibiotic, drug rashes, *i.v.* line sepsis, pneumothorax secondary to midline or meropenem resistance) that led to a change of antibiotic therapy. All participants were able to complete the study as per the study protocol.

Discussion

The majority of participants had moderate to severe bronchiectasis and all participants met the BTS guidelines for those requiring *i.v.* antibiotics. The groups were wall matched, with similar numbers with *P. aeruginosa* colonisation between the groups.

Intravenous meropenem was used because this has broad antimicrobial coverage, including *P. aeruginosa*. Because *Pseudomonas* may not be cultured using culture-based standard microbiology, but can be picked up using molecular methods, the authors thought it would be useful to cover for *P. aeruginosa* in those patients who met the criteria for *i.v.* antibiotics. A standardised antibiotic was selected, rather than using antibiotics chosen based on the patients' previous microbiology results. This avoided having to wait at least 48 h for a result from culture-based microbiology and avoided the need to potentially have to change antibiotics. Because this was a single-centre study, we chose *i.v.* meropenem for these reasons, and did not use multiple antibiotics that would have made the analysis difficult. There was no need to change the meropenem in any patients in this study and no need to augment with other *i.v.* antibiotics.

The decision to shorten treatment was based on a bacterial load of $<10^6$ CFU·mL^{-1}. This was based on a study by Chalmers *et al.* [4] in which the authors showed that $\geqslant 10^6$ CFU·mL^{-1} led to airway inflammation. Higher bacterial load is associated with activation of a secondary neutrophilic host response

TABLE 3 Secondary end-points as calculated at baseline and day 21 in both arms of the study

Change from baseline to day 21	*P. aeruginosa* colonisation		p-value	Non-*Pseudomonas* colonisation		p-value
	14-day group	BLGG		14-day group	BLGG	
Subjects n	20	17		27	26	
FEV_1 % predicted	4 (−1–6.5)	2.5 (−4.5–16)	0.321	−2 (−5–2)	−0.5 (−8–7.3)	0.321
FVC % predicted	4.5 (−6–12)	10 (−5–13.5)	0.632	−2 (−15–7)	4.5 (−3.5–7.8)	0.330
WCC ($\times 10^9 \cdot L^{-1}$)	−0.1 (−1.3–2.4)	0.9 (−1.1–2.3)	0.710	0.3 (−0.3–2.5)	0.5 (−0.5–2.3)	0.546
CRP (mg·L^{-1})	−2 (−19.5–2.5)	1 (−6.3–24.8)	0.050	4.5 (0–18.5)	0 (−12.8–14.5)	0.950
ISWT (m)	0 (−80–42.5)	30 (−20–120)	0.223	30 (−20–120)	25 (−7.5–70)	0.314

Change was calculated and Mann–Whitney U tests were used for all comparisons of differences between the two groups. BLGG: bacterial load-guided group; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; WCC: white cell count; CRP: C-reactive protein; ISWT: incremental shuttle walk test.

[4, 18], thus lower bacterial loads are thought to comprise commensals as opposed to pathogens [4]. This was the rationale for stopping antibiotics when bacterial load was $<10^6$ CFU·mL^{-1}.

By day 7, stopping antibiotics on this basis was achievable in 88% of the BLGG and potentially would have been suitable in 81% of the 14-day group. The data showed that the bacterial load was reduced with antibiotic therapy, but when the antibiotic therapy stopped, the bacterial load rose and by day 21 there was no significant change from baseline. Despite this, only 11% needed further antibiotic therapy within 1 week of stopping antibiotic therapy.

Surprisingly, the BLGG had prolonged time to next exacerbation. In a sub-analysis, this remained statistically significant only for patients with non-*Pseudomonas* colonisation. In the Cox regression analysis, the independent variables explored were 14 days of treatment, baseline colonisation with *P. aeruginosa*, high bacterial load $\geqslant 10^6$ CFU·mL^{-1}, BSI (mild 0–4, moderate 5–8, severe $\geqslant$9) and hospitalisation for the exacerbation because these parameters were thought to influence the time to next exacerbation. 14 days of treatment was the independent variable that increased the hazard of exacerbation, whereas milder bronchiectasis severity was associated with a reduced hazard. The authors would like to highlight that participants recorded the time to an exacerbation needing antibiotic therapy, and general practitioner records confirmed this. It was, however, subjective when participants felt unwell again. It is not clear why the shortened treatment was beneficial and this remains speculative. Because participants are chronically infected, shortened treatment may resolve the infection and have less impact on the microbiome. The longer treatment of 14 days may have a greater impact on the microbiome and resurgence of pathogens may have a greater impact compared with shortened treatment. This could be a possible explanation for a quicker relapse. In support of this, there was increased *Stenotrophomonas maltophilia* isolation following 14 days of *i.v.* antibiotic therapy compared to within the BLGG (14-day group: baseline 2.1%, day 21 19.1%; BLGG: baseline 2.3%, day 21 4.6%). It is not known whether the *S. maltophilia* drove the early need for a further antibiotic course or whether this was merely a reflection of more prolonged broad-spectrum *i.v.* antibiotic use in the 14-day group. A previous study of *S. maltophilia* revealed that chronic isolation was associated with the number of *i.v.* antibiotic courses in the year before and after the first isolation and with the absence of *P. aeruginosa* colonisation, as well as being associated with more exacerbations and more need of *i.v.* antibiotics in the year after the first isolation [19].

The authors note that although asthma was a comorbidity present in both groups (57% in the 14-day group and 42% in the BLGG), none of these patients had poorly controlled asthma, none were on disease-modifying treatment and none had active allergic bronchopulmonary aspergillosis. The exacerbations were all deemed bronchiectasis exacerbations by the treating physician for those who had comorbid asthma or chronic obstructive pulmonary disease and no patient received adjunctive oral corticosteroids for the exacerbation.

The predefined clinical recovery criteria led to low clinical recovery in both arms but much better results when analysing health-related quality of life questionnaires alone, highlighting issues when assessing sputum purulence and 24 h sputum volume as end-points. Both the LCQ and SGRQ have been shown to be useful questionnaires for assessing the response to *i.v.* antibiotic therapy [16, 17]. In this analysis, there was a nonsignificant trend for increased clinical improvement by day 21 within the 14-day group compared with the BLGG. It is difficult to interpret whether the patients felt "safer" when given 14 days of antibiotics. Because this was not a blinded study, it was not possible to give a placebo to the BLGG to make up the total duration of antibiotics to 14 days in this group.

There were no antibiotic-related adverse events in either of the study arms that led to a change of or alteration in meropenem therapy. Clinical safety end-points showed that despite stopping antibiotics early in the BLGG, there was no statistically significant difference in change in the measured parameters compared to those receiving antibiotics for 14 days. There was a trend for increased C-reactive protein reduction in the 14-day group *versus* the BLGG, but this failed to reach statistical significance (p=0.050). Overall, this did not influence time to next exacerbation, but may partly explain the improved trend for clinical improvement reported in the 14-day group. These results show that it is safe to stop antibiotics earlier than the current practice of 14 days. Although more patients in the BLGG received treatment in hospital, this was entirely based on patient's clinical status requiring hospital admission or unsuitability for receiving domiciliary antibiotics. No serious adverse events were recorded in either arm of the study.

Limitations

The authors acknowledge that this is a single-centre study and that this is not a placebo-controlled trial. Most National Health Services laboratories measure qualitative bacteriology as opposed to the combined

qualitative and quantitative microbiology. Additionally, the limitation of using a single antibiotic in this study is that it may limit the generalisability of the results to other, more frequently used, antibiotic regimens. The original plan was to recruit 120 patients to allow more sub-analyses, but recruitment stopped at 90 because of the challenge of recruiting participants in a single centre, which took over 4 years.

Conclusion

Bacterial load-guided therapy is feasible in most exacerbations requiring *i.v.* antibiotic therapy. There was a nonsignificant trend for increased clinical improvement by day 21 within the 14-day group compared with the BLGG but paradoxically there was a prolonged time to next exacerbation in the BLGG. From the Cox proportional hazard model, those with 14 days of treatment are more likely to experience exacerbations and those with mild bronchiectasis are less likely to experience exacerbations.

This study is registered at ClinicalTrials.gov as NCT02047773. Data will be available to researchers whose proposed use of the data has been approved by an independent review.

Author contributions: P. Bedi contributed to experimental design, interpreted the data and wrote the manuscript. M.K. Cartlidge contributed to collecting the data and performing experiments. Y. Zhang contributed to performing the experiments. K. Turnbull, S. Donaldson, A. Clarke, J. Crowe and K. Campbell collected data, performed the patient interventions, provided domiciliary antibiotic service and performed the experiments. C. Graham is the statistician for this study and carried out the statistical analysis. R. Frangulyan contributed to collecting data. A.G. Rossi contributed to experimental design, interpretation of data and writing of the manuscript. A.T. Hill provided the experimental design, interpretation of data and writing of the manuscript.

Conflict of interest: P. Bedi has nothing to disclose. M.K. Cartlidge has nothing to disclose. Y. Zhang has nothing to disclose. K. Turnbull has nothing to disclose. S. Donaldson has nothing to disclose. A. Clarke has nothing to disclose. J. Crowe has nothing to disclose. K. Campbell has nothing to disclose. C. Graham reports grants from the Scottish Office, during the conduct of the study. R. Frangulyan has nothing to disclose. A.G. Rossi has nothing to disclose. A.T. Hill has nothing to disclose.

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