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

Title page

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

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ABSTRACT

Introduction
There is lack of evidence to guide duration of intravenous antibiotics for bronchiectasis exacerbations.

Aims
To assess whether it is feasible based on bacterial load to shorten intravenous antibiotics during exacerbations and whether 14days treatment is superior.

Method
We recruited participants requiring intravenous antibiotics for exacerbations. Participants were randomised into two groups to receive antibiotics for 14days or bacterial load guided group(BLGG). Bacterial load was checked on day 0/7/10/14/21. If bacterial load was $<10^6$cfu/ml on day7 or 10 in BLGG, antibiotics were stopped the following day.

Results
47 received 14days antibiotics and 43 were in BLGG. 88% of participants in the BLGG were able to stop antibiotics by day8 and potentially 81% could have stopped antibiotics at day8 in the 14day arm. There was a non-significant trend for increased clinical improvement by day21 with 14days compared to BLGG. However, overall group data showed the median (interquartile range) time to next exacerbation was 27.5(12.5-60)days in the group receiving antibiotics for 14days and 60(18-110)days in the in BLGG; p=0.0034. In Cox proportional hazard model, 14days was more likely to experience exacerbations (Hazard Ratio(95% CI)1.80 (1.16-2.80), p=0.009 compared to BLGG and those with mild bronchiectasis less likely to experience exacerbations than patients with more severe bronchiectasis (HR 0.359 (0.13-0.99), p=0.048).

Conclusion
Bacterial load guided therapy is feasible in most exacerbations requiring intravenous antibiotics. There was a non-significant trend for increased clinical improvement by day21 with 14day antibiotics compared with BLGG but paradoxically there was a prolonged time to next exacerbation in BLGG.

Introduction

Bronchiectasis is characterized by chronic cough, daily sputum production and recurrent chest infections. Both the British Thoracic Society and European Respiratory Society [1,2] recommend antibiotics be used to treat exacerbations. Studies by our group have previously demonstrated significant improvement in markers of airway inflammation using short-term (14 days) treatment with intravenous antibiotics and using longer-term treatment with 12 months of nebulized gentamicin [3]. These data provided strong evidence that antibiotic treatment can alter the underlying airway inflammation in bronchiectasis providing hope of improving clinical symptoms and the prognosis of the disease [3]. 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 [4] compared oral ciprofloxacin (in treatment doses) plus placebo to oral ciprofloxacin plus inhaled tobramycin. The addition of inhaled tobramycin led to 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 [5-7] showed that in those participants who needed intravenous antibiotic therapy according to the British Thoracic Society [BTS] guidelines 2010 [8], they had a good clinical response. There was, however, no control group that did not receive antibiotic therapy. In general, antibiotic courses for 14 days are standard and should always be used in participants infected with *P. aeruginosa* [1]. Shorter courses may suffice in participants with less severe bronchiectasis [1].

Recently there have been several studies that have demonstrated that long-term oral and inhaled antibiotics during the stable state have improved clinical and patient reported outcomes as well as increasing time to next exacerbation [9-12]. 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 intravenous 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 intravenous antibiotic treatment is superior to a shorter course. The hypothesis was that although it maybe feasible to stop antibiotic treatment early based on bacterial load reduction, there would be better clinical outcomes with 14 days intravenous antibiotic therapy compared with a bacterial load guided group. The National Clinical trials number for the study was NCT02047773.

METHODS

Study population

The authors recruited participants with an exacerbation requiring intravenous antibiotics. All were aged 18 years and over, had bronchiectasis confirmed on chest computed tomography and who were being followed up at the Bronchiectasis clinic in Royal Infirmary of Edinburgh, UK. Participants were given intravenous antibiotics (in our study all participants received Meropenem) for an exacerbation if they met the British Thoracic Society guidelines for administering intravenous antibiotics [1]. Meropenem (2g TDS) was the antibiotic of choice as it is broad spectrum and covers gram-positive and gram-negative bacteria including *Pseudomonas 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 analyzing the data. The plan was to add in intravenous colistimethate sodium (colomycin) if there was a clinical deterioration despite intravenous meropenem.

Bronchiectasis severity

The severity of bronchiectasis was based on the Bronchiectasis Severity Index (BSI) [13].

Randomization and study design

The BTS and ERS guidelines recommend that intravenous 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 *Pseudomonas aeruginosa*) [1,2]. Exacerbations were defined as the presence of three or more of the following signs or symptoms for at least 24 hours: increased cough, increased sputum volume, increased sputum purulence, haemoptysis, increased dyspnoea, increased wheezing, fever (≥38°C) or malaise [1,2], The start date of this study predates the consensus definition of exacerbation by the European Respiratory Society [2]).

Random allocation sequence in block randomizations of four was done. Allocation was concealed in an envelope. Patients were either in the 14 days of intravenous Meropenem or bacterial load guided group (BLGG) of intravenous Meropenem therapy. In the bacterial load guided group, antibiotics were stopped early if the bacterial load was less than 10^6 cfu/ml on day 7 or day 10 (if not less that 10^6 cfu/ml at day 7). In the BLGG, all received a minimum of 7 days antibiotic therapy. No sputum was regarded as 0 cfu/ml and participants were eligible to stop antibiotics. Quantitative sputum microbiology analysis takes 24 hours and so in the BLGG, antibiotics were stopped therefore at day 8 if on day 7 the bacterial load was less than 10^6 cfu/ml and at day 11 (if bacterial load day 7 was 10^6 cfu/ml or greater but less than 10^6 cfu/ml on day 10).

Primary and Secondary outcomes
The primary outcomes of the study were: (i) Time to next exacerbation requiring oral or intravenous antibiotic therapy (dates were taken from the participant and confirmed from the General Practice records). [Time Frame: up to 1 year following intravenous antibiotics]. (ii) Proportion of participants that stopped antibiotics early in the bacterial load guided group [Time Frame: 14 days]. The proportion of participants where the authors could stop antibiotic treatment early guided by bacterial load either on day 8 or day 11 instead of usual day 14 course.

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

Place of administration of intravenous 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 intravenous antibiotics at our centre [5-7]. 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 is available in the online supplement.

Statistical Analysis
This was a proof of concept study. Based on national guidelines, study was powered on the expectation that 14 days was superior to shorter treatment. For prolonging time to next exacerbation by 28 days (thought to be a clinically significant prolongation), using 2 tailed, 5% level of significance, 80% power, 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 will recruit 45 participants per group, 90 participants in total. The authors planned to recruit at least 90 participants but randomisation was created for 120 participants. As recruitment was challenging, the study was stopped at 90 participants.
The authors analyzed the primary and secondary endpoint by intention-to-treat analysis. For demographic and clinical variables, the authors presented data as median (interquartile range IQR) for continuous variables and number (%) 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 (interquartile range) time to exacerbation. Further post hoc sub analyses of the data to calculate the time to next exacerbation was done by dividing the groups into those colonized by *Pseudomonas aeruginosa* (PA) and those with non pseudomonas (non PA) organisms. A multivariable Cox proportional hazards model was generated for time to next exacerbation with the following variables: treatment (14days, BLGG); baseline colonization with *Pseudomonas aeruginosa* (yes, no); high bacterial load greater than or equal to 10^6 colony forming units per ml (yes, no); Bronchiectasis Severity Index (mild 0-4, moderate 5-8 and severe 9 or more); hospitalization for the exacerbation (yes, no). The model was then repeated excluding the Bronchiectasis Severity Index as this also includes baseline colonization with *Pseudomonas aeruginosa*.

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

To compare the bacterial load difference within the groups, Wilcoxon signed rank test was used. Data was analyzed using SPSS version 25; significance was accepted with *P* values: $*P < 0.05$.

Results

A total of 114 participants were screened and 90 were recruited in the study. Participants were randomised into one of two 2 arms of the study (figure 1). All 90 participants completed the study. The first patient was enrolled on 16th January 2014 and the last patient on 9th November 2018. Baseline characteristics of the study participants are shown in Table 1. None of the patients were on hypertonic saline. However, all patients were recommended to practice twice daily chest physiotherapy and continued to do so if they were in hospital.

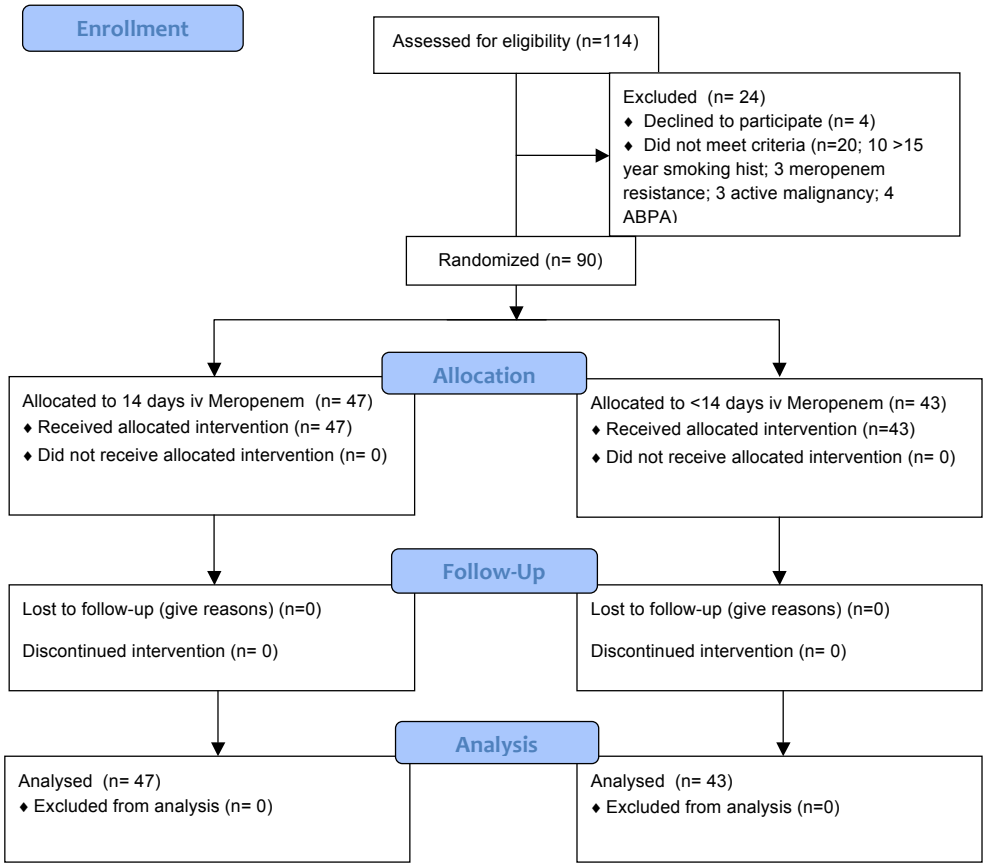

Figure 1. Consort diagram of participants recruited in the study.

Parameters	**14 day group (N=47)**	**Bacterial load guided group (N=43)**
Age (years) Median (inter quartile range)	67 (59- 74)	71 (61- 77)
Gender		
• **%Female**	28 (60%)	24 (56%)
• **Male**	19 (40%)	19 (44%)
Place of iv 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 (x10^9/L)	8.4 (6.1-10.3)	8.4 (6.6-9.8)
Neutrophils (x10^9/L)	5.2 (4-7.7)	5.6 (3.9-7.2)
ESR (mm/hr)	13 (6.5-30)	20 (8-33.7)
CRP (mg/L)	8.5 (3-26)	13 (4-23)
Colonized with *Pseudomonas aeruginosa*	20 (43%)	17 (40%)
On 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 **Mild** **Moderate** **Severe**	11 (7-15) 3 (6%) 11 (23%) 33 (71%)	11 (7-15) 3 (7%) 14 (33%) 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)

Table 1. Baseline demographics of study participants. BSI= Bronchiectasis severity index; CRP= c reactive protein; ESR= erythrocyte sedimentation rate; ABPA= allergic bronchopulmonary aspergillosis; GORD= gastro oesophageal reflux disease; LCQ= Leicester Cough Questionnaire; PCD= Primary ciliary dyskinesia; RA= rheumatoid arthritis; SGRQ= St George's Respiratory Questionnaire; UC= ulcerative colitis; WCC= white cell count. Data presented as median (interquartile range) or number (percentage).

Treatment
All patients received Meropenem 2G three times daily. Only one patient in this study (in the 14-day arm) had a sample with subsequent meropenem resistance but clinically responded and so continued the meropenem and given no additional antibiotics. No participant needed additional intravenous antibiotic/s to meropenem during the study.

Primary end point
The median (interquartile range) time to next exacerbation was 27.5 (12.5-60) days in the group receiving antibiotics for 14 days and 60 (18-110) days in the BLGG; p=0.003. A Kaplan Meier plot of the estimated time to next exacerbation is shown in figure 2a.
For participants colonized with *Pseudomonas aeruginosa*, the median (interquartile range) time to exacerbation was 24.5 (16-58.5) days in the 14 day group and 28 (12.5-115.5) days in the BLGG, p=0.110; figure 2b.
For participants colonized with non-Pseudomonas organisms, the median (interquartile range) time to exacerbation was 31.5 (12-75) days in the 14 day group and 60 (30-114) days in the BLGG, p=0.021; figure 2c.

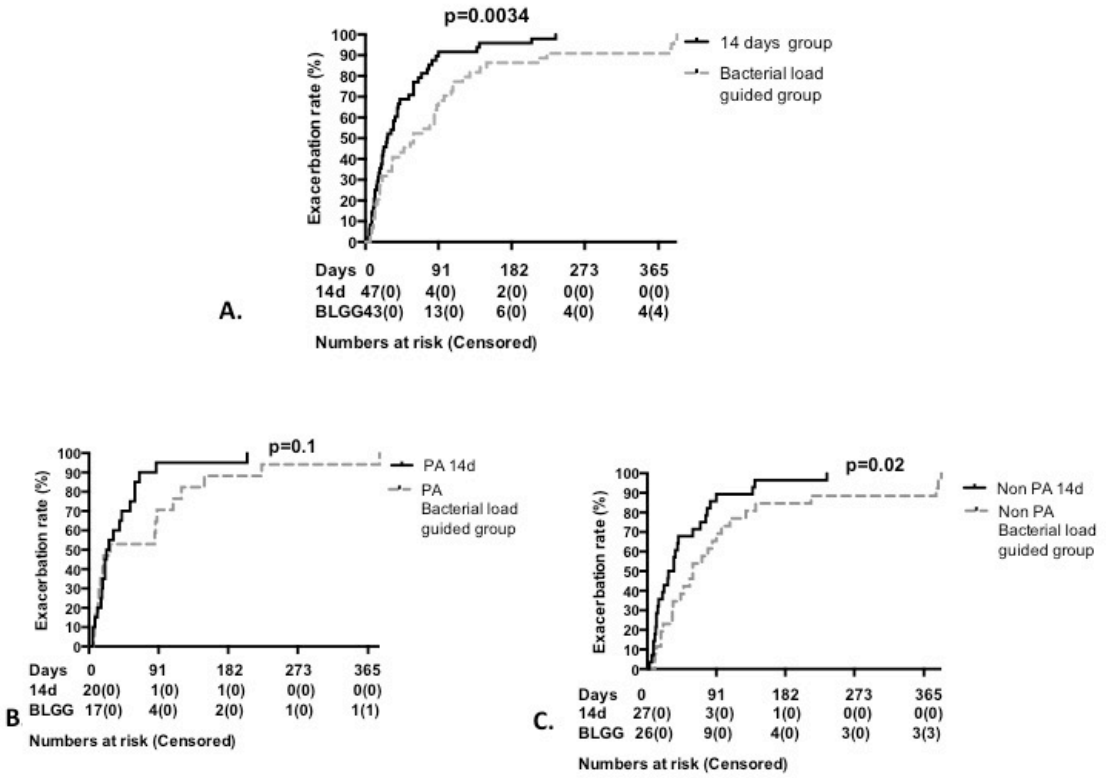

Figure 2a. Kaplan Meier plot to estimate the time to next exacerbation in the 14-day group and in the BLGG; p=0.0034.
Figure 2b. Kaplan Meier plot to estimate the time to next exacerbation comparison between participants colonized with PA in the two groups; p=0.110.
Figure 2c. Kaplan Meier plot to estimate the time to next exacerbation comparison between participants colonized with non-PA in the two groups; p=0.021.

Cox proportional hazard model
14days treatment are more likely to experience exacerbations (Hazard Ratio (HR) (95% CI) 1.80 (1.16-2.80), p=0.009 compared to those on BLGG and those with mild bronchiectasis less likely to experience exacerbations than patients with more severe bronchiectasis (HR 0.359 (0.13-0.99), p=0.048). Taking out Bronchiectasis Severity Index, only the found that those with 14days treatment are more likely to experience exacerbations compared to those on BLGG (Hazard Ratio (95% CI) 14days 1.77 (1.14-2.75), p=0.012).

(ii) Proportion of participants stopping/able to stop antibiotics early
On day 7, 84% (76/90) of all participants had a bacterial load $<10^6$ cfu/ml and hence could have stopped antibiotics early.
In the BLGG, 88% (38/43) stopped on day 8 and in the 14day arm 81% (38/47) could have stopped but continued as per treatment allocation.

On day 10, 76% (68/90) of all participants had a bacterial load $<10^6$ cfu/ml and hence could have stopped antibiotics early.
In the BLGG, the remaining 12% (5/43) of participants still on medication were stopped at day 11.

(iii) Participants exacerbating within 1 week of stopping antibiotics
In the 14 day group, 7 of 47 participants had an exacerbation within 1 week of stopping antibiotic of which 1 patient isolated *Pseudomonas aeruginosa* and 6 isolated non *Pseudomonas aeruginosa* organisms. In the BLGG, 3 of 43 participants had an exacerbation within 1 week of stopping antibiotic and all participants isolated non *Pseudomonas aeruginosa* organisms. 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
(i) 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 analyzed using Quality of life questionnaires alone (1.3 Unit or more improvement in LCQ OR 4 Unit or more improvement in SGRQ). For the whole group there was a non-significant trend for increased clinical improvement by day21 with 14day (79%) compared with 60% for BLGG; p=0.056. There was a similar trend for improved quality of life in both Pseudomonas and non Pseudomonas participants with 14 day therapy compared with the BLGG that had shortened treatment, but this did not reach statistical significance, table 2.

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

Table 2. Predefined recovery (1.3 Unit or more improvement in LCQ or 4 Unit or more improvement in SGRQ and reduction in sputum purulence or ≥50% reduction in sputum volume) and post hoc analyses (1.3 Unit or more improvement in LCQ or 4 Unit or more improvement in SGRQ) of quality of life measures in the groups. LCQ= Leicester Cough Questionnaire; SGRQ= St George's Respiratory Questionnaire.

(ii) Quantitative sputum microbiology

The quantitative sputum microbiology is available in the online supplement S1. In the 14 day group, compared to baseline, there was a significant reduction in bacterial load on day 7 ($p < 0.0001$), day 10 ($p<0.0001$), day 14 ($p=0.008$) but not day 21 ($p=0.061$); figure 3a. Similarly, in the BLGG, compared to baseline, there was a significant reduction in bacterial load on day 7 $p < 0.0001$), day 10 ($p<0.0001$), 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.

Participants colonized with Pseudomonas aeruginosa

In the 14 day group, in those colonized with PA, compared to baseline, there was a significant reduction in bacterial load on day 7 ($p=0.004$) and day 14 ($p=0.011$) but not day 21 ($p=0.912$); figure 3b solid red line. In the BLGG, in those colonized with PA, compared to baseline, there was a significant reduction in bacterial load on day 7 ($p=0.003$) but not on day 14 ($p=0.312$) or day 21 ($p=0.442$); figure 3b broken red line. There was no statistical difference on comparison of quantitative sputum microbiology between the two groups at any given time point.

Participants colonized with non Pseudomonas organisms

In the 14 day group, in the non PA participants, compared to baseline, there was no significant reduction in bacterial load on day 7 ($p=0.521$), day 14 ($p=0.111$) or day 21 ($p=0.731$); figure 3c solid blue line. In the less than 14 day group, in the non PA participants, compared to baseline, there was no significant reduction in bacterial load on day 7 ($p=0.312$), day 14 ($p=0.222$) or day 21 ($p=0.924$); figure 3c broken blue line. There was no statistical difference on comparison of quantitative sputum microbiology between the two groups at any given time point.

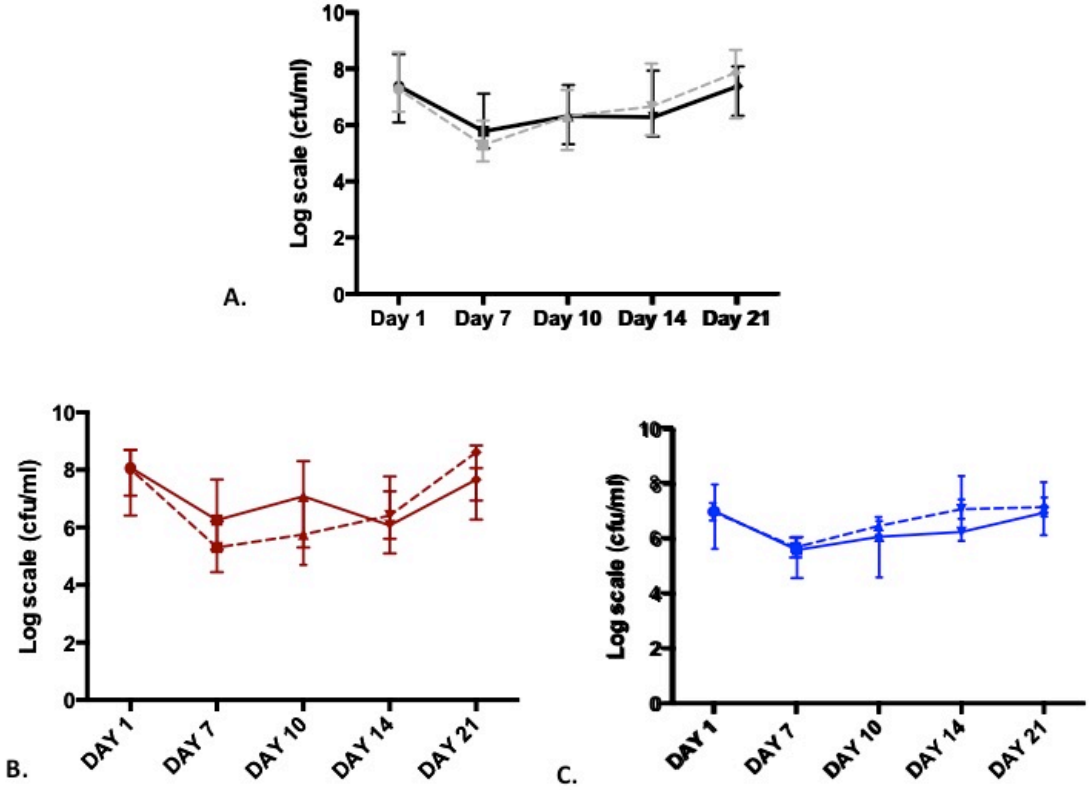

Figure 3a. Change in sputum microbiology from baseline to day 21 in the 14 day group, (solid black line) and bacterial load guided group (broken grey line), all participants. Significant reduction in bacterial load in both groups at time points day 7, day 10 and day 14 but not at day 21, compared to baseline.
3b. Change in Pseudomonas sputum microbiology from baseline to day 21 in the 14 day group, (solid red line) and bacterial load guided group (broken red line). No significant difference in the quantitative sputum microbiology at any of the given time points- between the two groups.
3c. Change in non Pseudomonas sputum microbiology from baseline to day 21 in the 14 day group, (solid blue line) and bacterial load guided group (broken blue line). 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).

Secondary safety endpoints at day 21

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

Change from baseline to day 21 (D21-D0)	**14 day group**	**BLGG**	**p value**	**14 day group**	**BLGG**	**p value**
	PA N=20	**PA N= 17**		**Non PA N=27**	**Non PA N= 26**	
%predicted FEV_1	4 (-1-6.5)	2.5 (-4.5-16)	0.321	-2 (-5-2)	-0.5 (-8-7.3)	0.321
%predicted FVC	4.5 (-6-12)	10 (-5-13.5)	0.632	-2 (-15-7)	4.5 (-3.5-7.8)	0.330
WCC ($x10^9$/L)	-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)	-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

Table 3. Secondary end points as calculated at baseline and day 21 in both arms of the study. Change was then calculated and Mann Whitney U tests were used for all comparisons of differences between the two groups.

CRP= c reactive protein; FEV_1= Forced Expiratory volume in 1 sec; FVC= Forced vital capacity, ISWT= Incremental Shuttle walk test; WCC= white cell count.

Serious adverse events

There were no adverse events that led to a change or alteration of meropenem therapy and no serious adverse events (30-day mortality, anaphylaxis, change of antibiotic, drug rashes, intravenous line sepsis, pneumothorax secondary to midline or meropenem resistance that led to needing 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 British Thoracic Society guidelines for those requiring intravenous antibiotics. The groups were wall matched, with similar numbers with *Pseudomonas aeruginosa* between the groups.

Intravenous meropenem was used as this has broad anti-microbial coverage including *Pseudomonas aeruginosa*. It is recognized that Pseudomonas may not be cultured using culture based standard microbiology but picked up using molecular methods, so thought to be useful to cover for *Pseudomonas aeruginosa* in those that met the criteria for intravenous antibiotics. The authors chose to use a standardized antibiotic rather than antibiotics chosen on their previous microbiology. This averts the complication of waiting at least 48 hours for a result from culture based microbiology and avoids the need to change antibiotics if needed. As this was a single centered study, we chose intravenous meropenem for these reasons, and not use multiple antibiotics that would make analysis difficult. There was no need to change the meropenem in all patients in this study and no need to augment with other intravenous antibiotics.

Shortening treatment was based on a bacterial load of $<10^6$ cfu/ml. This was based on a study done by Chalmers et al, where the authors showed that 10^6 cfu/ml or greater led to airways inflammation. Higher bacterial load is associated with activation of a secondary neutrophilic host response [18,3]. Hence lower bacterial loads were thought to be commensals as opposed to being pathogenic [3]. Hence the rationale for stopping antibiotics when bacterial load was $<10^6$ cfu/ml.

By day 7, this was achievable in 88% of the bacterial load guided group and potentially would have been suitable in 81% of the 14-day group. The data showed that the bacterial load 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 bacterial load guided group prolonged time to next exacerbation. In sub-analysis, this remained statistically significant for non Pseudomonas patients only. In the Cox regression analysis, the independent variables explored were 14d treatment, baseline colonization with *Pseudomonas aeruginosa,* high bacterial load greater than or equal to 10^6 colony forming units per ml, Bronchiectasis Severity Index (mild 0-4, moderate 5-8 and severe 9 or more) and hospitalization for the exacerbation as these parameters were thought to have an influence on time to next exacerbation. 14day treatment was the independent variable that increased the hazard of exacerbation whereas milder bronchiectasis severity is associated with a reduced hazard. The authors would like to highlight that participants recorded the time to exacerbation needing antibiotic therapy and GP records confirmed all. This is however subjective when participants felt unwell again. It is not clear why shortened treatment was beneficial and this remains speculative. As participants are chronically infected, shortened treatment may resolve the infection and have less impact on the microbiome. The longer treatment of 14days may have a greater impact on the microbiome and resurgence of pathogens may have a greater impact compared with shortened treatment. Hence this could be a possible explanation for a quicker relapse.

In support of this, there was increased *S. maltophilia* isolation following 14 days intravenous antibiotic therapy compared with the bacterial load guided group (14day group baseline 2.1% but 19.1% at day 21; bacterial load guided group baseline 2.3% but 4.6% at day21). It is not known whether the *S. maltophilia* was a driver to needing a further antibiotic course early or merely a reflection of more prolonged broad spectrum intravenous antibiotics in the 14day group. A previous study of *S. maltophilia* revealed chronic isolation was associated with the number of intravenous antibiotic courses in the year before and after the first isolation and with the absence of *Pseudomonas aeruginosa* colonization and had more exacerbations and more need of intravenous 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 or none had active allergic bronchopulmonary aspergillosis. The exacerbations were all deemed bronchiectasis exacerbations by the treating physician/s for those that had comorbid asthma or COPD 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 when analysing health-related quality of life questionnaires alone, highlighting issues when assessing sputum purulence and 24 hour sputum volume as endpoints. Both the LCQ and SGRQ have been shown to be useful questionnaires assessing response to intravenous antibiotic therapy [15,16]. In this analysis, there was a non-significant trend for increased clinical improvement by day21 with 14day compared with bacterial load guided group. It is difficult to interpret if the patients felt ‘safer’ when given 14 days antibiotics. As this was not a blinded study, it was not possible to give ‘placebo’ to the bacterial load guided group 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 or alteration of meropenem therapy. Clinical safety end points showed that despite stopping antibiotics early in the bacterial load guided group, 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 CRP reduction in the 14day versus bacterial load guided group arm, but just failed to reach statistical significance ($p=0.050$). Overall, this didn’t influence time to next exacerbation, but may party explain the improved trend for clinical improvement reported in the 14day group. This shows that it is safe to stop antibiotics earlier than the current day practice of 14days. Although more patients in the bacterial load guided therapy received treatment in hospital, this was entirely based on patient’s clinical status requiring hospital admission or unsuitability of 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 NHS laboratories measure qualitative bacteriology as opposed to the combined qualitative and quantitative microbiology. Additionally limitation of using a single antibiotic in this study is that it may limit the generalizability of the results to other, more frequently used, antibiotic regimens. The

original plan was to recruit 120 patients to allow more sub-analysis, but stopped at 90, as recruitment was challenging being a single centred study, taking over 4 years.

Conclusion

Bacterial load guided therapy is feasible in most exacerbations requiring intravenous antibiotic therapy. There was a non-significant trend for increased clinical improvement by day21 with 14day antibiotics compared with BLGG but paradoxically there was a prolonged time to next exacerbation in the BLGG. From the Cox proportional hazard model, those with 14days treatment are more likely to experience exacerbations and those with mild bronchiectasis less likely to experience exacerbations.

Contribution of authors:

PB contributed to experimental design, interpreted the data and wrote the manuscript.
MKC contributed to collecting the data and performing experiments.
YZ contributed to performing the experiments.
KT, SD, AC, JC, KC collected data, performed the patient interventions, provided domiciliary antibiotic service and performed the experiments.
CG is the statistician for this study and did the statistical analysis.
RF contributed to collecting data.
AGR contributed to experimental design, interpretation of data and writing of the manuscript.
ATH provided the experimental design, interpretation of data and writing of the manuscript.

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