Hypertonic saline or carbocisteine in bronchiectasis: 2x2 factorial trial

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Abstract

Background: Bronchiectasis guidelines are inconsistent regarding the effectiveness of mucoactives and use varies geographically. Large trials are needed to assess safety and effectiveness.

Methods: CLEAR(NCT04140214) was a 2x2 factorial, randomized, open-label trial in patients with non-cystic fibrosis bronchiectasis with frequent pulmonary exacerbations (PEx) and reporting daily sputum production, at 20 UK sites. Current smokers and those with recent use of mucoactive treatments were excluded. Participants were randomized to standard of care (SOC) plus HTS (6%), SOC plus carbocisteine, SOC plus both HTS and carbocisteine, or SOC alone. The primary outcome was number of PEx over 52 weeks. Secondary outcomes were measures of disease-specific HRQoL, health impairment, time to next PEx, days antibiotics related to PEx, lung function, patient treatment preference, adherence to treatment and safety. Analysis used modified intention-to-treat (mITT) adjusted for site, prior antibiotic use, and current macrolides at baseline.

Results: 288 participants were recruited. No treatment interactions were found. The mean (95% confidence interval(CI)) adjudicated fully qualifying PEx count over 52 weeks was 0.76(0.58, 0.95) in the HTS group and 0.98(0.78, 1.19) in the no HTS group; adjusted mean difference (95% CI) -0.25(-0.57, 0.07), p=0.12. The mean (95% CI) adjudicated fully qualifying PEx over 52 weeks was 0.86(0.66, 1.06) in the carbocisteine group and 0.90(0.70, 1.09) in the no carbocisteine group; mean difference (95% CI) -0.04(-0.36, 0.28), p=0.81. Secondary outcomes appeared similar across the groups. AEs/SAEs incidence was low and comparable across groups.

Conclusion: In bronchiectasis patients, neither carbocisteine nor HTS significantly reduced mean PEx over 52 weeks.

Introduction

Bronchiectasis is characterized by chronic cough, sputum production, chest pain, and shortness of breath. These symptoms, together with recurrent pulmonary exacerbations (PEx), reduce quality of life and survival.[1,2]

Mucoactive drugs vary by mechanism of action, including expectorants that induce mucus expulsion through coughing (e.g. hypertonic saline (HTS)), mucoregulators that regulate mucosecration (e.g. carbocisteine), mucolytics that decrease mucus viscosity (e.g. N-acetylcysteine) and mucokinetics that enhance mucociliary movement (e.g. surfactants).[3] It is envisaged that these actions could disrupt the "bronchiectasis vicious vortex", decrease PEx frequency and severity, and ultimately slow disease progression.[4]

Some current guidelines[5] recommend mucoactive drugs plus airway clearance to enhance sputum expectoration in bronchiectasis. However, these guidelines rely on a 2014 systematic review reporting limited effectiveness of mucolytics for bronchiectasis, based on low quality evidence from four trials.[6] The European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) study found that 28.0% of 16,723 patients in 28 countries used mucoactive drugs (carbocisteine/N-acetycysteine (17.2%), nebulised HTS (8.6%)), and insufficient evidence of benefit is likely the primary reason for inconsistent use.[7] We performed a UK multicentre, 2x2 factorial, randomized open label trial of HTS (6%) and carbocisteine versus SOC over 52 weeks in patients with non-CF bronchiectasis.

Methods

Trial design

CLEAR was a UK multicentre, 2x2 full factorial, randomized open label trial in bronchiectasis with internal pilot to confirm recruitment rates, protocol compliance and data collection, and 52-week follow-up period.

Trial Oversight

The published trial protocol describes trial oversight[8]. Trial recruitment was paused during COVID and changes made on resumption including the requirement of ≥2 PEx relaxed to ≥1 PEx post-COVID, reduction of the sample size to provide 80% rather than 90% power, and to deliver visits remotely (further details in the revised protocol and Supplementary Appendix).

Data were collected by trial site investigators and analyzed independently by the Northern Ireland Clinical Trials Unit (NICTU). The manuscript was written by the authors according to Good Publication Practice guidelines and they critically reviewed drafts and decided to submit for publication. They vouch for data accuracy and completeness and adherence to the protocol. No confidentiality agreements were made that precluded the publication of trial findings. The funder had no role in designing the trial, analyzing data, writing the manuscript, or submission.

Belfast Health and Social Care Trust was trial Sponsor and the Chief Investigator took overall responsibility for trial conduct. The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice, and applicable regulatory requirements. North East - Tyne & Wear South Research Ethics Committee (approval no. 17/NE/0339) approved the study. All recruited participants provided written informed consent. An independent, external Data Safety Monitoring committee reviewed all adverse events (AEs) in an unblinded manner. A separate blinded independent panel adjudicated all reported PEx events, according to EMBARC criteria

for PEx[9] (Table S1 Supplementary Appendix). The trial was prospectively registered (ClinicalTrials.gov: NCT04140214).

Patients

Eligibility Criteria

Eligible patients were adults (>18 years), with primary diagnosis of bronchiectasis (confirmed on CT), who experienced frequent PEx (≥2 in last year modified to ≥1 in last year post-COVID) and reported producing daily sputum. Key exclusion criteria were current smokers and those on mucoactive treatment within the past 30 days. For full inclusion/exclusion details, see Supplementary Appendix.

Setting

The trial was conducted in 20 UK hospitals (Table S2 Supplementary Appendix).

Randomization

Participants were randomized (1:1:1:1) using central randomization prepared by the trial statistician. Randomization was stratified by site, antibiotic use due to PEx in last year and current macrolides at baseline. Allocation sequence was concealed, but participants, clinicians and researchers were not blinded to treatment allocation in this open design, as it was deemed impractical to blind nebulization.

Interventions

The interventions and comparators for 52 weeks were: standard of care (SOC) plus twice-daily nebulized HTS (6%); SOC plus carbocisteine (750mg 3x/day until 8 weeks, then 750mg 2x/day); SOC plus combination HTS and carbocisteine; and SOC alone. HTS 6% was chosen pragmatically due to availability (7% is also available but with no evidence of any difference between these doses). Carbocisteine dosing of 750mg

3/day until 8 weeks, then 750mg 2/day was in accordance with the Summary of Product Characteristics. All participants allocated to HTS 6% used an eFlow rapid nebulizer (PARI Pharma GmbH) and passed a drug response assessment (DRA) (Figure S1, Supplementary Appendix). SOC was per British Thoracic Society guidelines for bronchiectasis[5] including airway clearance for all. Patients without a regular airway clearance regimen at baseline were taught active cycle of breathing techniques using standardized material.[10] All patients were given an action plan at baseline (reviewed every visit) regarding planning daily airway clearance in coordination with their allocated mucoactive therapy. Site training and procedures delivered are described in the Supplementary Appendix.

End points

The primary outcome measure was PEx count over 52 weeks. PEx was defined using EMBARC criteria[9] (Table S1 Supplementary Appendix). Respiratory Systemic Symptoms Questionnaire (RSSQ)[11] objectively collected signs and symptoms (including duration), required for EMBARC and was completed at all visits either over the telephone or onsite (unscheduled visit) when participants experienced PEx symptoms. Antibiotic rescue packs facilitated PEx management using defined criteria (Table S1 Supplementary Appendix). PEx end was the day all prescribed antibiotic treatment for that specific PEx was completed. Another RSSQ questionnaire was completed at that time.

Secondary outcome measures, collected primarily during onsite visits, were disease-specific HRQoL (respiratory symptoms domain of Quality of Life - Bronchiectasis (QoL-B)[12]: higher scores indicate better HRQoL, minimal clinically important difference (MCID) 8 points); health impairment (St Georges Respiratory Questionnaire

(SGRQ)[13]: lower scores indicate better HRQoL, MCID is 4 points); Euro Quality of Life 5-level (EQ-5D-5L)[14]: 5-dimension questionnaire plus visual analog scale (EQ-VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health), MCID has not been reported for bronchiectasis); time to next PEx, days antibiotics related to PEx, and lung function. Patient preference for treatment was assessed using the Treatment Satisfaction Questionnaire for Medication (TSQM)[15]: higher values indicate higher satisfaction. Adherence to trial treatment over 52 weeks was measured (see Supplementary Appendix for methods).

Safety was monitored to 30 days after last administration of study drug. PEx collected as a trial outcome were not reported as AEs (except those PEx between consent and randomization). All AEs and SAEs were assessed by the principal investigator or designee at each site for seriousness, causality and severity.

Statistical analyses

Sample Size

For mean PEx 52 weeks in the control group of 0.7 with standard deviation (SD) 0.9,[16] 162 participants overall are required to detect a mean between groups difference of 0.4 with 80% power using a two-sided type I error of 0.05. Whilst there is no clinical or biological rationale or expectation of any interaction between the two mucoactives, an informal decision was made to inflate by 50% to 243; assuming 15% dropout gave a required sample size of 288 participants.

Results are reported following CONSORT 2025,[17] and CONSORT Extension for Factorial Randomized Trials.[18,19]

The analyses involved two separate comparisons: participants allocated HTS versus those who were not allocated HTS (no HTS) and participants allocated carbocisteine versus those who were not allocated carbocisteine (no carbocisteine); each comparison was assessed with a type I error of 0.05, with no adjustment for multiple testing. No interactions were anticipated between HTS and carbocisteine; this was formally tested before testing these main comparisons. Descriptive summary measures were used, along with tabulation of the amount of missing data and standard approaches to detect patterns in missing data (visual inspection, calculation of proportions and assessment of the distribution of missing data). No missing outcome data were imputed. For the primary/safety outcomes, analyses were two-sided and tested at a significance level of p=0.05. Because the SAP did not include a provision for correcting for multiplicity when conducting tests for secondary endpoints or in subgroups, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

The primary analysis used a modified intention-to-treat (mITT) basis (participants with ≥1 post baseline efficacy assessment at week 8 or later). Groups were compared for the primary outcome (PEx over 52 weeks) and antibiotic use (days over 52 weeks) using Negative Binomial regression adjusted for site, antibiotic use for PEx in last year and current baseline macrolides. Continuous outcomes were adjusted for these same baseline factors. A post-hoc ITT analysis was used, including all randomized patients adjusted for follow up time, site, baseline macrolide use and baseline antibiotic use. For AEs, chi-square test (or Fisher's exact test if appropriate) were used. Risk Ratio (RR) and 95% confidence intervals (CI) were reported.

Results

Between June 27, 2018 and September 28, 2023, 288 participants were randomized (Figure 1, by comparison group; Figure S2, by treatment group). Baseline characteristics for the main comparisons are shown in Table 1 and Table S3 Supplementary Appendix. Overall, the baseline characteristics are similar, with slightly more females allocated to carbocisteine. Baseline characteristics pre-, during and post COVID-pandemic were similar (Tables S4, S5 and S6 Supplementary Appendix).

There was no evidence of treatment interaction between HTS and carbocisteine (p=0.60).

Primary and secondary outcomes are presented in Tables 2a & 2b, and Table S7a & S7b, Supplementary Appendix.

Primary Outcome.

There was no significant difference in the primary outcome, fully qualifying PEx 52 weeks, with either HTS or carbocisteine. The mean (95%CI) adjudicated fully qualifying PEx 52 weeks for HTS was 0.76 (0.58, 0.95) and for no HTS group was 0.98 (0.78, 1.19); adjusted mean difference (95% CI) -0.25 (-0.57, 0.07), p=0.12. The mean (95%CI) adjudicated fully qualifying PEx 52 weeks for carbocisteine was 0.86 (0.66, 1.06) and for no carbocisteine was 0.90 (0.70, 1.09); adjusted mean difference (95%CI) -0.04 (-0.36, 0.28), p=0.81.

Secondary analyses for adjudicated PEx (including fully qualifying, partially qualifying, other and missed) gave similar results (Table S8 Supplementary Appendix) as did a

post-hoc ITT analysis including all randomized patients (Table S9 Supplemental Appendix).

Secondary Outcomes

HRQoL results (QOL-B, SGRQ and EQ-5D-5L) in the HTS, no HTS, carbocisteine and no carbocisteine groups are shown in Table 2b, as are the time to next PEx, antibiotic days and lung function results. Kaplan-Meier curves for time to next PEx are shown in Figure S3, Supplementary Appendix. Although inferential testing was not performed, the results appeared to be similar in the HTS group and no HTS group, as well as in the carbocisteine and no carbocisteine groups.

Patient preferences for treatment (TSQM scores) and adherence for the HTS, no HTS, carbocisteine and no carbocisteine groups are shown in Tables S10, S11 and S12, Supplementary Appendix.

Safety outcomes

Hypertonic Saline

SAEs/AEs for the HTS and no HTS groups and specific categories related to study drug are shown (Table 3a). Total SAEs were not significantly different in the HTS (17 events, 16 patients) and no HTS (22 events, 19 patients) groups, relative risk (RR) 0.8 (0.4, 1.5), p=0.53. Total AEs were also not significantly different in the HTS (274 events, 100 patients) and no HTS (238 events, 94 patients) groups, RR 1.0 (0.9, 1.2), p=0.68. 69 AEs among 43 patients were reported as related to study drug in the HTS group and 22 events among 15 patients in the no HTS group. Specific categories of SAEs/AEs varied, with the highest rates of respiratory, thoracic, and mediastinal

disorders in both the HTS and no HTS groups (Table 3a and Table S13, Supplementary Appendix).

Carbocisteine

SAEs/AEs incidence and specific categories related to the study drug for carbocisteine and no carbocisteine are shown (Table 3b). Total SAEs were not significantly different in the carbocisteine (24 events, 20 patients) and no carbocisteine (15 events, 15 patients) groups, RR 1.3 (0.7, 2.5), p=0.37. Total AEs were also not significantly different in carbocisteine (284 events, 103 patients) and no carbocisteine (228 events, 91 patients) groups, RR 1.1 (1.0, 1.3), p=0.13. 63 AEs among 40 patients were reported as related to study drug in the carbocisteine group and 28 AEs among 18 patients in the no carbocisteine group. SAE/AE specific categories varied, with the highest rates of respiratory, thoracic, and mediastinal disorders in both carbocisteine and no carbocisteine. Gastrointestinal disorder AEs were higher (absolute number and number considered related) in the carbocisteine compared to no carbocisteine group (Table 3b and Table S14, Supplementary Appendix).

Discussion

In this randomized trial, adding HTS or carbocisteine to standard treatment demonstrated no additional benefit. The consistencies between findings for HTS and carbocisteine suggest the proposed physiological effects of these mucoactives do not translate to clinical benefit for patients with bronchiectasis. The overall proportion of patients with any AEs/SAEs were similar, suggesting that these mucoactives may not cause substantial harm but there are associated costs and treatment burdens, which is important to consider absent benefits. Gastro-intestinal AEs were common in those taking carbocisteine. This is a known side effect of this drug and it did not persist.

Mucoactives are often prescribed early to target a reduction in PEx. Adherence to treatment plans decreases as the number and complexity of medications in treatment plans increase.[20] Therefore, CLEAR suggests that HTS or carbocisteine usage should be reconsidered in bronchiectasis. Low to moderate quality evidence suggests some benefit with mucoactives in COPD.[21,22]

CLEAR participants had similar baseline characteristics to large bronchiectasis registries and other large trials with regard to disease status, BSI, and HRQoL. The results are therefore likely generalizable (Table S15). However, social determinants of health, including sex, ethnicity and socioeconomic status, are linked to health outcomes in people with bronchiectasis and are therefore important to consider in terms of wider applicability of the CLEAR results. Although the randomized groups are balanced across key social determinants of health, and the study population seems to be representative of the general bronchiectasis population in terms of sex compared to all other recent trials,[23–25] it is less diverse in terms of ethnicity. This may mean that the impact of HTS or carbocisteine on patients with bronchiectasis in some ethnic groups may not be represented by CLEAR. Although there are no physiological reasons to suggest that the effect of these mucoactives may differ across ethnic groups, different health disparities could affect outcomes. We acknowledge that a positive recruitment strategy to ensure diversity was not implemented in the CLEAR trial. Targeted recruitment strategies are needed in bronchiectasis research to address barriers to participation and promote inclusivity.[26]

Strengths

Our primary outcome, PEx, ranks highly in the core outcome set for bronchiectasis,[27] despite a lack of clarity in the definition and specific criteria for recognising and

categorising PEx in clinical trials. This can contribute to the variation in number and duration of PEx among trials. In other conditions, Endpoint Adjudication Committees or Algorithms have been used for decision making about the primary endpoint.[25,28–30] The CLEAR trial used similar approaches, with documented decision-making and adjudication processes to ensure consistency and independence of PEx reporting. This helped ensure accurate evaluation of PEx and may help inform other trials relying on patient recall for PEx. Despite rigorous methodology and education, patients may self-select to take antibiotics (especially with easy access to rescue packs), potentially leading to overuse of antibiotics and impacting on the reporting of PEx. Some recent trials, such as ASPEN,[25] have used adjudication panels, which together with the use of electronic records may further optimize accurate data in future trials.

This trial used an open-label pragmatic design for practical and transparent intervention delivery supported by emerging evidence regarding the potential impact on applicability of using placebos and participant blinding in trials.[31] We also measured adherence (albeit we recognise the challenges with using self-reporting and returns of unused medication to assess adherence). In general, participants took their allocated medication during the trial, although adherence to the oral mediation (carbocisteine) was higher than to the nebulised medication (HTS), which reflects clinical practice.

Limitations

The CLEAR trial was conducted in the UK only. There were some differences in drop out numbers between the groups, which we postulate reflects the patient burden of the respective treatment groups. The study was designed with 80% power (after sample size was reduced) to detect the prespecified treatment differences in the overall population and did not have adequate power to assess differences in

subgroups. Although we recruited patients who produced daily sputum, we did not use inclusion criteria relating to the amount of sputum (e.g. a minimum daily amount) or difficulty clearing sputum; whether results would differ among subgroups according to these sputum characteristics is not known The investigation of those possibilities would require even larger studies than CLEAR. This trial focused on two specific mucoactives and there is a need to carefully assess the effects of other commonly used mucoactives, including different concentrations of HTS commonly in use, and also different mucoactives, such as N-acetylcysteine and guaifenesin, which are used in countries such as the USA and Canada, where carbocisteine is not available. Although this trial incorporated airway clearance, it did not assess airway clearance competency and so we are unclear of the impact airway clearance competency had on the results.

The CLEAR trial began before the COVID pandemic and continued through and beyond it. Active recruitment stopped during the pandemic (12th March 2020 to 1st November 2021) and the eligibility criteria were revised when recruitment re-started to account for the reduction in PEx that was observed during the pandemic. However, the annualised mean number of PEx in the standard of care group was similar before and after the pandemic, and similar to other trials,[25] suggesting that the findings of the CLEAR trial were not impacted by the pandemic or the change in inclusion criteria.

Conclusion

For participants with bronchiectasis, neither HTS nor carbocisteine significantly reduced the mean number of PEx over 52 weeks.

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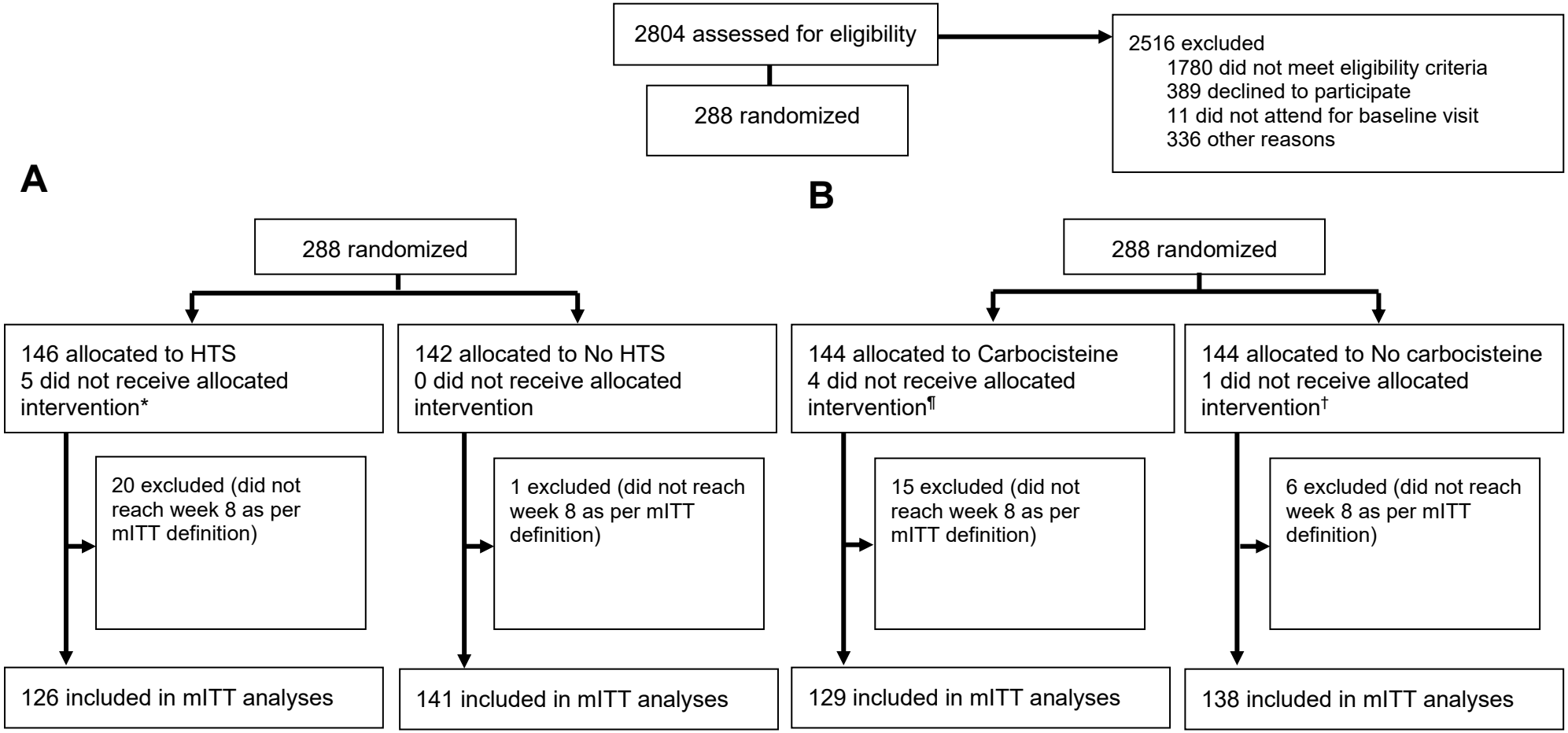

Figure 1 Trial Flow Diagram (by comparison)

(A) Hypertonic saline (HTS) vs no HTS (B) Carbocisteine vs no carbocisteine.

HTS group included participants randomized to HTS alone (n=73) and HTS and carbocisteine (n=73). The No HTS group included participants randomized to carbocisteine alone (n=71) and standard of care (n=71). Carbocisteine group included participants randomized to carbocisteine alone (n=71) and HTS and carbocisteine (n=73). The No carbocisteine group included participants randomized to HTS alone (n=73) and standard of care (n=71). Participants randomized to HTS completed a drug response assessment (DRA) as detailed in Figure S1. Figure S2 Supplementary Appendix provides a flow diagram for the four treatment groups. *n=1, complexity of study; n=3, failed DRA; n=1 no HTS dispensed at visit 1 (only carbocisteine dispensed). ¶n=3 failed DRA, n=1 no HTS dispensed at visit 1 (only carbocisteine dispensed). †n=1, complexity of study.

Table 1 Baseline Characteristics at trial entry (All Participants, by comparison)

Baseline Characteristics		Comparison Group			
		HTS	No HTS	Carbocisteine	No Carbocisteine
		n=146	n=142	n=144	n=144
Sex	Male	60 (41.1%)	57 (40.1%)	49 (34.0%)	68 (47.2%)
	Female	86 (58.9%)	85 (59.9%)	95 (66.0%)	76 (52.8%)
Age (years)		65.3 (13.6)	66.1 (12.3)	66.6 (13.1)	64.9 (12.9)
Ethnicity	White	142 (97.3%)	136 (95.8%)	137 (95.1%)	141 (97.9%)
	Asian/ Asian British	2 (1.4%)	1 (0.7%)	2 (1.4%)	1 (0.7%)
	Indian	0 (0.0%)	2 (1.4%)	1 (0.7%)	1 (0.7%)
	Chinese	0 (0.0%)	2 (1.4%)	1 (0.7%)	1 (0.7%)
	Black/ African/ Caribbean/ Black British	2 (1.4%)	1 (0.7%)	3 (2.1%)	0 (0.0%)
Cigarette Use	Never Smoked	87 (59.6%)	91 (64.1%)	86 (59.7%)	92 (63.9%)
	Ex-Smoker				
	Cigarettes	57 (39.0%)	49 (34.5%)	57 (39.6%)	49 (34.0%)
	Pipe	3 (2.1%)	2 (1.4%)	1 (0.7%)	4 (2.8%)
E-cigarette use	Never vaped	142 (97.9%)	140(98.6%)	139(97.2%)	143(99.3%)
	Ex-vaper	3 (2.1%)	1 (0.7%)	4 (2.8%)	0 (0.0%)
	Current vaper	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.7%)
Height (cm)		166.0 (9.1)	165.6 (9.9)	164.1 (9.7)	167.6 (8.9)
Weight (kg)		77.4 (17.2)	75.7 (17.3)	73.2 (17.4)	80.0 (16.4)
BSI Score		7.0 (3.3)[1]	7.8 (3.2)[2]	7.5 (3.1)[3]	7.3 (3.4)
FACED Score		2.0 (1.5)[4]	2.3 (1.4)[2]	2.2 (1.4)[2]	2.0 (1.5)
Use of airway clearance		108 (74.0%)	111 (78.2%)	112 (77.8%)	107 (74.3%)

Baseline Characteristics		Comparison Group			
		HTS	No HTS	Carbocisteine	No Carbocisteine
		n=146	n=142	n=144	n=144
Sputum Colour	Mucoid	46(31.7%)	36(25.5%)	45(31.7%)	37(25.7%)
	Mucopurulent	72(49.7%)	80(56.7%)	72(50.7%)	80(55.6%)
	Purulent	27(18.6%)	25(17.7%)	25(17.6%)	27(18.8%)
Pseudomonas Colonization#		16(11.0%)[1]	20(14.1%)	17(11.9%)[5]	19(13.2%)
Colonization with other organisms*		37(25.5%)[1]	39(27.5%)	34(23.8%)[5]	42(29.2%)
QoL-B Respiratory symptoms		62.4(17.5)	58.8(18.7)	59.4(18.9)	61.8(17.4)
SGRQ total score		42.5(19.5)[4]	45.9(19.7)[6]	43.8(19.5)[7]	44.6(19.7)[2]
EQ-5D-5L utility score		0.75 (0.24)[1]	0.72 (0.28)[2]	0.74 (0.25)	0.73 (0.27)[3]
Number of antibiotics in the year prior to study start		3.3 (1.9)	3.5 (2.1)	3.5 (1.9)	3.3 (2.1)
Number of PEx in the year prior to study start		3.4 (2.1)	3.6 (2.1)	3.5 (2.0)	2.5 (2.1)
Completed a washout of mucoactives prior to trial entry‡		23 (15.7%)	23 (16.2%)	19 (13.2%)	27 (18.8%)

Mean (SD) (or median [IQR] if appropriate) presented for continuous variables and no. (%) for all categorical variables. If n is different to the total n per group (due to missing data): [1]for 145 participants; [2]for 140 participants; [3]for 141 participants; [4] for 144 participants; [5]for 143 participants; [6]for 139 participants; [7]for 142 participants. ‡If a potential participant was prescribed HTS, carbocisteine or other mucoactives for the treatment of their BE prior to recruitment to the trial, the potential participant and physician may have decided to discontinue their current treatment in order to be able to participate. Informed consent was taken and the baseline visit/confirmation of eligibility completed at least 30 days after the patient started a washout from HTS, carbocisteine or other mucoactive. #Chronic colonization is defined by the isolation of *Pseudomonas aeruginosa* in sputum culture on 2 or more occasions, at least 3 months apart in a 1 year period. *Chronic colonization is

defined by the isolation of potentially pathogenic bacteria in sputum culture on 2 or more occasions, at least 3 months apart in a 1 year period. BSI: Bronchiectasis Severity Index; FACED: FEV1, age, chronic colonization, extension, dyspnoea; QoL-B, Quality of Life- Bronchiectasis (higher scores indicate better HRQoL, minimal clinically important difference (MCID) is 8 points); SGRQ, St George's Respiratory Questionnaire (lower scores indicate better HRQoL, MCID is 4 points); EQ-5D-5L, Euro Quality of Life 5-level (comprises a 5-dimension questionnaire and a visual analog scale (EQ-VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health).

Table 2a Primary outcome, mITT population

	HTS	No HTS	Mean difference (95% CI)	p-value	Carbocisteine	No Carbocisteine	Mean difference (95% CI)	p-value
Primary outcome*								
Mean number of pulmonary exacerbations (PEx) over 52 weeks †	0.76 (0.58, 0.95)	0.98 (0.78, 1.19)	-0.25 (-0.57,0.07)	0.12	0.86 (0.66, 1.06)	0.90 (0.70, 1.09)	-0.04 (-0.36, 0.28)	0.81

Table 2b Secondary outcomes, mITT population

	HTS	No HTS	Mean difference (95% CI)	Carbocisteine	No Carbocisteine	Mean difference (95% CI)
Secondary outcomes						
HRQoL						
QoL-B Respiratory symptoms § ||	59.8 (57.0, 62.6) n=106	60.5 (57.9, 63.1) n=106	-0.7 (-4.6, 3.1)	60.0 (57.2, 62.8) n=106	60.3 (57.7, 62.9) n=123	-0.3 (-4.2, 3.5)

SGRQ § ||	42.5 (39.9, 45.0) n=103	42.7 (40.4, 45.1) n=121	-0.3 (-3.8, 3.2)	42.8 (40.2, 45.3) n=105	42.5 (40.1, 44.9) n=119	0.3 (-3.2, 3.8)
EQ-5D-5L § ||	0.73 (0.68, 0.78) n=106	0.72 (0.67, 0.77) n=122	-0.01 (-0.06, 0.08)	0.75 (0.70,0.80) n=106	0.70 (0.65, 0.75) n=122	0.05 (-0.02, 0.13)
Time to next PEx (days) post randomisation ¶**	256.5 (229.4, 283.6)	239.2 (214.7, 263.7)	0.80 (0.56, 1.14)	244.8 (219.2, 270.4)	249.8 (224.0, 275.6)	1.17 (0.83, 1.67)
Number of days of antibiotics related to exacerbations over 52 weeks§	18.9 (13.3, 24.6)	21.7 (15.5, 27.8)	-0.14 (-0.5, 0.3)	19.6 (13.8, 25.3)	21.2 (15.1, 27.2)	-0.08 (-0.5, 0.3)
Lung function (change from baseline)						
FEV_1 (L) §	-0.01 (-0.10, 0.08) n=65	-0.02 (-0.10, 0.06) n=85	0.01 (-0.1, 0.1)	-0.003 (-0.09, 0.09) n=70	-0.03 (-0.12, 0.05) n=80	0.03 (-0.09, 0.2)
FEV_1 (% pred) §	1.6 (-1.9, 5.2) n=62	-0.0 (-3.1, 3.1) n=81	1.6 (-3.1, 6.4)	1.6 (-1.9, 5.1) n=65	-0.05 (-3.2, 3.1) n=78	1.7 (-3.2, 6.5)

FVC (L) §	-0.0 (-0.11, 0.11) n=84	-0.06 (-0.16, 0.03) n=65	0.06 (-0.08, 0.2)	-0.02 (-0.13, 0.08) n=69	-0.05 (-0.15, 0.05) n=80	0.02 (-0.1, 0.2)
FEF_{25-75} §	-1.3 (-3.0, 0.3) n=62	-0.4 (-1.9, 1.0) n=78	-0.9 (-3.2, 1.4)	-0.6 (-2.3, 1.0) n=63	-1.0 (-2.5, 0.5) n=77	0.4 (-1.9, 2.7)

Mean (95% CI) presented.*Results from negative binomial regression presented. † Fully qualifying PEx as classified by an independent panel§ adjusted for macrolide use, antibiotic use and site|| adjusted for baseline scores. ¶ Hazard ratio (95% CI) presented rather than mean difference. **Included all fully qualifying adjudicated PEx and included all participants (those with and without a PEx (without have been censored at the upper end of the week 52 window i.e. day 379. If n is different to the total n per group (due to missing data), n is reported. FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow between 25-75% of FVC; QoL-B, Quality of Life- Bronchiectasis (higher scores indicate better HRQoL, minimal clinically important difference (MCID) is 8 points); SGRQ, St George's Respiratory Questionnaire (lower scores indicate better HRQoL, MCID is 4 points); EQ-5D-5L, Euro Quality of Life 5-level (comprises a 5-dimension questionnaire and a visual analog scale (EQ-VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health). NB: 95% CIs are unadjusted for multiplicity and not for inferential use.

Table 3a Safety Outcomes for total SAEs/AEs and categories of SAEs/AEs related to study drug (HTS vs. no HTS)

		No. Events		No. Participants			
		HTS	**No HTS**	**HTS**	**No HTS**	**RR (95% CI)**	**p-value**
				N=146	N=142		
AEs, SAEs and SUSARs	**Total SAEs**	**17**	**22**	**16 (11.0%)**	**19 (13.4%)**	**0.8 (0.4, 1.5)**	**0.53**
	Related to study drug	**1**	**0**	**1 (0.7%)**	**0 (0.0%)**		
	Respiratory, thoracic and mediastinal disorders	**1**	**0**	**1 (0.7%)**	**0 (0.0%)**		
	Related to study drug and unexpected	**0**	**0**	**0 (0.0%)**	**0 (0.0%)**		
	Total AEs*	**274**	**238**	**100 (68.5%)**	**94 (66.2%)**	**1.0 (0.9, 1.2)**	**0.68**
	Related to study drug	**69**	**22**	**43 (29.5%)**	**15 (10.6%)**		
	Eye Disorders	3	0	2 (1.4%)	0 (0.0%)		
	Gastrointestinal Disorders	24	14	17 (11.8%)	11 (7.6%)		
	General	2	1	2 (1.4%)	1 (0.7%)		
	Infections and Infestations	1	0	1 (0.7%)	0 (0.0%)		
	Nervous System Disorders	2	1	2 (1.4%)	1 (0.7%)		

		No. Events		No. Participants			
		HTS	No HTS	HTS	No HTS	RR (95% CI)	p-value
				N=146	N=142		
	Respiratory, thoracic and mediastinal disorders	35	3	27 (18.8%)	1 (0.7%)		
	Skin and subcutaneous tissue disorders	1	3	1 (0.7%)	3 (2.1%)		
	Vascular disorders	1	0	1 (0.7%)	0 (0.0%)		
	Total Deaths	**0**	**2**	**0 (0.0%)**	**2 (1.4%)**		
	Related to study drug	**0**	**0**	**0 (0.0%)**	**0 (0.0%)**		

*Secondary outcome

Table 3b Safety Outcomes for total SAEs/AEs and categories of SAEs/AEs related to study drug (Carbocisteine vs. no carbocisteine)

		No. Events		No. Participants			
		Carbocisteine	No Carbocisteine	Carbocisteine	No Carbocisteine	RR (95% CI)	p-value
				N=144	N=144		
AEs, SAEs and SUSARs	**Total SAES**	**24**	**15**	**20 (13.9%)**	**15 (10.4%)**	**1.3 (0.7, 2.5)**	**0.37**
	Related to study drug	**1**	**0**	**1 (0.7%)**	**0 (0.0%)**		
	Respiratory, thoracic and mediastinal disorders	1	0	1 (0.7%)	0 (0.0%)		
	Related to study drug and unexpected	**0**	**0**	**0 (0.0%)**	**0 (0.0%)**		
	Total AEs*	**284**	**228**	**103 (71.5%)**	**91 (63.2%)**	**1.1 (1.0, 1.3)**	**0.13**
	Related to study drug	**63**	**28**	**40 (27.8%)**	**18 (12.5%)**		
	Eye Disorders	3	0	2 (1.4%)	0 (0.0%)		
	Gastrointestinal Disorders	32	6	23 (16.0%)	5 (3.5%)		
	General	2	1	2 (1.4%)	1 (0.7%)		
	Infections and Infestations	0	1	0 (0.0%)	1 (0.7%)		
	Nervous System Disorders	3	0	3 (2.1%)	0 (0.0%)		

		No. Events		No. Participants			
		Carbocisteine	**No Carbocisteine**	**Carbocisteine**	**No Carbocisteine**	**RR (95% CI)**	**p-value**
				N=144	N=144		
	Respiratory, thoracic and mediastinal disorders	18	20	15 (10.4%)	13 (9.0%)		
	Skin and subcutaneous tissue disorders	4	0	4 (2.8%)	0 (0.0%)		
	Vascular disorders	1	0	1 (0.7%)	0 (0.0%)		
	Total Deaths	**1**	**1**	**1 (0.7%)**	**1 (0.7%)**		
	Related to study drug	**0**	**0**	**0 (0.0%)**	**0 (0.0%)**		

*Secondary outcome