Journal of Pulmonary & Respiratory Medicine

Fjaellegaard et al., J Pulm Respir Med 2016, 6:2
http://dx.doi.org/10.4172/2161-105X.1000337

Review Article Open Access

Non-antibiotic Inhaled Agents for Stable Non-CF Bronchiectasis in Adults - A Systematic Review

Katrine Fjaellegaard[1], Melda Dönmez Sin[1], Andrea Browatzki[2] and Charlotte Suppli Ulrik[1*,3]

[1]*Department of Pulmonary Medicine, Hvidovre Hospital, Denmark*
[2]*Department of Infectious Disease and Pulmonary Medicine, Nordsjællands Hospital, Denmark*
[3]*Institute of Clinical Medicine, University of Copenhagen, Denmark*

Abstract

Aim: Update on efficacy and safety of non-antibiotic therapy for stable non-cystic fibrosis (CF) bronchiectasis.

Methods: Systematic review based on the PRISMA-guidelines.

Results: Fifteen studies (1278 patients) fulfilled the inclusion criteria. Studies (n = 3) suggest that inhaled hypertonic saline may be beneficial in patients with non-CF BE, although possibly not superior to isotonic saline. The effect of hypertonic saline on QoL, lung function, and exacerbation rate has, at best, been inconsistent. Inhaled mannitol (n = 6) affects sputum characteristics, but with no significant effect on exacerbation rate, lung function, or sputum, although it may have an effect on QoL and time to first exacerbation. High-dose inhaled corticosteroids (ICS) (n = 4) reduce sputum volume and eosinophils, possibly due to concomitant asthma, but with no effect on sputum purulence and bacteriology, lung function and exacerbation rate, although it seems to have positive impact on QoL and respiratory symptoms. One study investigating add-on long-acting beta2-agonist to ICS (n = 40) reported an effect on QoL, but no effect on lung function or exacerbation rate.

Conclusion: Airway clearing techniques, including hypertonic saline and mannitol, and asthma controller medication may have beneficial effects in patients with non-CF BE, but only limited evidence suggests an effect on lung function and exacerbation rate.

Keywords: Non-cystic fibrosis bronchiectasis; Non-antibiotics; Maintenance therapy

Introduction

Non-cystic fibrosis (non-CF) bronchiectasis (BE) may be caused by a number of both lung and systemic diseases and a diagnosis of BE should be considered in patients with persistent symptoms like cough and sputum, dyspnoea and also in patients with unexplained haemoptysis. However, for decades BE has been regarded as an orphan disease, as a result of which the focus of both clinicians and researchers have diverted away from this condition. In recent years BE has attracted increasing focus as a disease with the potential for substantial morbidity. The increasing availability of high-resolution computed tomography (HRCT), the generally accepted golden standard for a diagnosis of BE, has also added to this development [1].

The pathophysiology of BE is characterised airway neutrophilia, a form of inflammation known to be relatively resitant to existing therapies, leading to abnormal destruction and dilation of bronchi and bronchioles [2], dysfunctional mucociliary clearance, and by that retention of secretions, repeated bacterial infections, chronic inflammation and progressive tissue destruction in a *vicious circle* [1-3].

The overall aim of the management of patients with non-CF BE is to reduce symptoms, maintain lung function and, not least, to prevent exacerbations and thereby improving the quality of life and long-term outcome [1]. However, the management strategy to reach these goals is not clearly defined, varies substantially between regions, and not least, unfortunately, there is limited evidence to guide treatment of patients with BE. A large number of questions related to best possible management, therefore, remain largely unanswered.

This aim of the present review is to provide an update on the current knowledge of the safety and, not least, efficacy of non-antibiotic inhaled therapy, including airway clearing techniques, in the management of adults with stable non-CF bronchiectasis.

Methods

The general principles of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [4,5] were adopted to perform this review. A series of systematic searches were carried out, last updated December 2015, using the database PubMed, EMBASE, Cochrane Controlled Trials Register, and Clinical Trials.gov, and was based on the following algorithm of MeSH terms: Non-CF bronchiectasis and bronchiectasis were searched alone and in combination with airway clearing techniques, mannitol, saline, hypertonic saline, corticosteroids, steroids, bronchodilators, asthma controller medication and non-steroid anti-inflammatories. The search was limited to English-language articles, and clinical trials published solely in abstract form were excluded because the methods and results could not be fully assessed.

To be included, studies had to meet all of the following criteria: 1) published in peer-reviewed journal, 2) inclusion of adults aged >18 years, 3) bronchiectasis diagnosed by high-resolution CT in non-CF patients, 4) report at least one of the following outcomes quality of life (QoL), dyspnoea, number of exacerbations, time to next exacerbation, forced vital capacity (FVC), forced expiratory volume in first second

***Corresponding author**: Charlotte Suppli Ulrik, Professor, Department of Pulmonary Medicine 253 Hvidovre Hospital, DK-2650 Hvidovre, Denmark, Tel: 4521623648; E-mail: csulrik@dadlnet.dk

Received February 28, 2016; **Accepted** April 27, 2016; **Published** April 29, 2016

Citation: Fjaellegaard K, Sin MD, Browatzki A, Ulrik CS (2016) Non-antibiotic Inhaled Agents for Stable Non-CF Bronchiectasis in Adults - A Systematic Review. J Pulm Respir Med 6: 337. doi:10.4172/2161-105X.1000337

(FEV_1), sputum production, sputum bacteriology, C-reactive protein (CRP), and white blood cell count (WBC), and 5) published after 1990; and not the following exclusion criteria: 1) Only physiotherapy, and 2) Treatment of exacerbated patients. Potential relevant papers to be included in the present review were assessed in detail by at least two of the authors.

A meta-analysis was not included in the present review, primarily due to the limited number of published clinical trials fulfilling the inclusion criteria within each therapy category.

Results

A total of 363 potential relevant papers were identified at the initial step, of which 269 papers were excluded as they did not meet the inclusion criteria. Of the remaining 94 papers, 72 papers were excluded (e.g. studies addressing either patients with chronic cough or exacerbation only) based on the predefined inclusion and exclusion criteria. Finally, 15 trials published in 15 papers (comprising a total of 1.278 subjects) were included in the present review. Participants in the included trials were stable, but symptomatic, and fulfilled the CT criteria for a diagnosis of non-CF bronchiectasis.

Airway Clearing Therapies

Inhaled hypertonic saline

Three studies, compromising 92 subjects, have examined the effect of inhaled hypertonic saline in patients with non-CF bronchiectasis (Table 1).

In a randomised, cross-over trial, Kellet et al. [6] investigated the effect of 7% hypertonic saline in 24 BE-patients with less than 10 g sputum daily. In random order, enrolled patients received all of the following treatments for a 4-week period: 1) active cycle breathing technique (ACBT), 2) nebulised terbutaline and ACBT, 3) nebulised terbutaline and isotonic saline, followed by ACBT or 4) nebulised terbutaline and 7% hypertonic saline, followed by ACBT once weekly; with double-blind administration of saline. A higher sputum weight was found on treatment with hypertonic saline (mean 5.3 g compared to 1.4 g, 2.8 g and 3.2 g, respectively; $p < 0.0001$) and in ease of expectoration (visual analog scale [VAS] 2.4 vs. 8.0, 7.7 and 5.2, respectively; $p < 0.0001$) compared with the other interventions; and, furthermore, also between hypertonic and isotonic saline ($p = 0.0005$). Significant differences between treatments were also found for FEV_1 ($p = 0.04$) and FVC ($p = 0.01$), but with no difference between hypertonic and isotonic saline ($p = 0.12$ and $p = 0.23$, respectively). The authors concluded that hypertonic saline is safe and effective as add-on to physiotherapy in selected patients. The most important study limitations include small sample size, short duration of treatment, and no reported measures of QoL.

In 2011, Kellet et al. [7] published a single-blind, cross-over trial, where patients were randomised to either inhaled 7% hypertonic (n = 14) or isotonic saline (n = 14) for 3 months or vice versa, with a 4-week wash-out between treatments. Treatment with 7% hypertonic saline significantly improved lung function (%change from baseline) compared to isotonic saline (FEV_1 %pred (15.1, 95% CI 8.2-22.0 vs. 1.8, 95% CI-8.9-10.7) ($p < 0.01$) and FVC %pred (11.2, 95% CI 8.6-13.9 vs. 0.7, 95% CI -7.4-8.9), ($p < 0.01$). QoL, assessed by the St George´s Respiratory Questionnaire (SGRQ), improved significantly in global score (-6.0 vs. -1.2, $p < 0.05$), but not significantly in subscales. Compared to the patients receiving isotonic saline, patients receiving hypertonic saline required significantly fewer courses of antibiotics per year (2.4 vs. 5.4, $p < 0.05$), and had fewer exacerbations per year (2.1 vs. 4.9, $p < 0.05$). The authors concluded that patients with non-CF BE benefit clinically from daily nebulised 7% hypertonic saline. However, larger, long-term, double-blind studies are required to establish the clinical efficacy, as important limitations of the study are small number of participants and single-blind design. Also, it is important to notice that an improvement was not found in all SGRQ subscales. Furthermore, extrapolation from observations during a 3-month study period to changes over a 12-month period might not be appropriate.

In a 12-month, controlled, double-blind study, published by Nicolson et al. [8] in 2012, patients were randomised to either nebulized 0.9% saline (n = 20) or 6% saline (n = 20) twice daily. Both groups improved significantly in QoL ($p < 0.05$), assessed by SGRQ and Leicester Cough Questionnaire (LCQ), FEV_1 (mean 90 ml, 95% CI 11-169 ml; $p = 0.04$) and sputum colonisation (by 15%; $p < 0.05$). However, no significant differences were found between the groups in QoL, exacerbation rate, lung function or culture colonization. The authors, therefore, concluded that administration of hypertonic saline is not superior to isotonic saline in patients with non-CF bronchiectasis. However, the size of the study population is an important limitation.

Based on the available evidence, hypertonic saline is potentially beneficial in patients with non-CF BE, but is difficult to conclude whether it is superior to isotonic saline or not. None of the studies mentioned above observed a significant improvement in QoL compared to isotonic saline, which is the most important outcome to the patients, besides sputum volume. Nicolson et al. [8] could not confirm the improvement in lung function, reported by Kellet et al. [7], and the former study appears more valid due to the double-blind design and 12-months duration. However, further studies are needed to clarify a potential beneficial effect of hypertonic saline on lung function and, most important, QoL in patients with non-CF BE.

Mannitol

Six studies, in total including 846 subjects, in seven publications, have examined the effect of treatment with the osmotic agent mannitol in non-CF BE (Table 1).

In the first study, published by Daviscas et al. [9] in 1999, 11 patients received 300mg inhaled dry powder mannitol, resting nasal breathing (baseline) or no intervention (control) at 3 different visits in random order, although mannitol always preceded the control visit. Right lung mucociliary clearance (MCC) significantly increased after mannitol compared with both control (mean ± SD 34 ± 5% vs. 17 ± 4%; $p < 0.0001$) and baseline (34 ± 5% vs. 12 ± 4%, $p < 0.0001$) with no difference between control and baseline. No difference was found in cough or radio-aerosol deposition. The authors concluded that mannitol significantly increases mucociliary clearance. However, the interpretation is limited by few study participants and short treatment period.

In a further controlled study by Daviskas et al. [10] investigated the 24-hour effect of inhaled mannitol in eight patients. On day 1 and 3, clearance was measured without any intervention, whereas on day 2, clearance was measured 2 and 24 hours after administration of 400 mg mannitol. Treatment with mannitol significantly increased mucus clearance 75 min after treatment (whole right lung: 32 ± 6% vs. 10 ± 4%; $p < 0.005$) compared to day 1, whereas no significant difference was found at 24 hours. However, the 24-hour retention of mucus was significantly reduced, most likely due to the acute increase in clearance (whole right lung 58 ± 6 vs. 68 ± 6%, $p < 0.01$). No differences were found in lung function or cough. The authors conclude that mannitol increase mucus clearance acutely. Small number of patients and

treatment regimen are important limitations.

Daviskas et al. [11] published yet a controlled, clinical trial in 2005, where nine patients were treated with mannitol 400 mg once daily for 12 days with follow-up at day 12, 6+ and 10+. At the end of treatment, i.e., day 12, no change was observed in lung function apart from improvement in forced expiratory flow (FEF%pred) (mean ± SD 85 ± 13% vs. 91 ± 14%; $p < 0.05$) compared to baseline, although, not sustained at day 6+ and 10+. There was a significant improvement in QoL, measured by SGRQ, at day 12 (score decreased by 12±10 from a meanSD 49 ± 14 at baseline; $p < 0.01$). With regard to sputum characteristics, they found a significantly reduced wettability (51 ± 3 vs. 33.2 ± 2.4 degrees; $p < 0.0001$) and spinnability (11.8 ± 0.4 mm vs. 10.0 ± 0.2 mm; $p < 0.005$) after 12 days compared to baseline. Viscosity, elasticity, mucociliary transportability, haematology, sputum microbiology and arterial blood gases did not change significantly. Cough transportability was significantly increased after 12 days (26 ± 1 mm vs. 34 ± 3 mm; $p < 0.003$). There were no reports of adverse effects. The authors concluded that mannitol significantly improved health status after 12 days of treatment and this improvement was maintained for 10 days after end of treatment. In addition, it improved mucus hydration and cough transportability. However, the short treatment period and small number of participants limits the study.

In 2008, Daviskas et al. [12] investigated a possible dose-dependent effect of mannitol on mucociliary clearance by administration of placebo and 160 mg, 320 mg, and 480 mg, respectively, of mannitol in random order to 14 patients on day 1-4, with day 5 as control. Whole right lung clearance over 45 min was 5 ± 1% and 11 ± 3%, respectively, at baseline and control day. It increased to 17 ± 4%, 23 ± 4% and 31 ± 5%, respectively, after 160, 320 and 480 mg mannitol (all comparisons $p < 0.001$, apart for 160 mg and control day). Furthermore, a significant greater clearance was found after 480 mg mannitol compared to 160 mg ($p < 0.001$). They concluded that the effect of mannitol on mucociliary clearance is dose-dependent. Given the small number of patients in the study, a larger confirmatory study seems appropriate.

In 2010, Daviskas et al. [13] investigated changes in physical properties of sputum at different doses of mannitol in the 14 patients enrolled in the above described study. At baseline, patients were either given no treatment, doing 100 repetitive voluntary coughs or administered additional mannitol, whereas no treatment was given at the control day. The solid content, surface tension and contact angle were significantly reduced after all doses of mannitol and after coughing alone compared to the controls ($p < 0.0001$), and, furthermore, also for adhesion ($p < 0.002$), elasticity and viscosity ($p < 0.0005$). The authors concluded, that the dose-dependent effect of mannitol was not explained by changes in physical properties.

In 2013, Bilton et al. [14] published a double-blind, placebo-controlled study, where patients were randomised to inhaled 320mg mannitol (n = 231) or placebo (n = 112) twice daily for 12 weeks, with visits at week 0 (baseline), week 6 and week 12. A significant change of 4.3 g in sputum weight was found between mannitol and placebo at 12 weeks (95% CI 1.6-7.0; $p = 0.002$). No change in sputum weight was found in the intervention group (-0.9 g, 95% CI -2.5 to -0.6; $p = 0.24$), compared to a reduction in the placebo group (-5.3 g, 95% CI -7.5 to -3.0; $p < 0.0001$). A statistical significant improvement in SGRQ from baseline was seen in both groups (-3.4, 95% CI -4.8 to -1.9; $p < 0.0001$ and -2.1, 95% CI -4.2 to -0.1; $p < 0.05$), but with no difference between the groups ($p = 0.3$). No significant differences were found in symptoms, measured by Bronchiectasis Symptoms Questionnaire (BSQ) and Leicester Cough Questionnaire (LCQ), antimicrobial use, exacerbation rate, lung function, exercise capacity, microbiology and anti-inflammatory markers, including IL-6, IL-8, TNF-alfa and human neutrophil elastase, in sputum or adverse events. The authors concluded that a larger controlled study would be required to investigate the effect of mannitol on exacerbations and antibiotic use. However, it should be noted that the change in SGRQ did reach the minimal clinical important difference.

Bilton et al. published in 2014 [15] a double-blind study comprising 461 patients with severe BE randomised to receive 400 mg (cases, n = 233) or 50 mg (controls, n = 228) inhaled mannitol twice daily for 12 months. No significant difference was found in number of exacerbations (annual rate 1.7 95% CI 1.5-1.9 and 1.8 95% CI 1.6-2.1, respectively; $p = 0.3$) between cases and controls. However, a significant difference was found in days to first exacerbation (165 vs. 124, $p = 0.02$) and in number of days on antibiotics (20 (95% CI 16-25) vs. 26 (95% CI 21-32), $p < 0.05$) between cases and controls. Furthermore, an improvement in QoL, assessed by SGRQ, was seen in both arms, but significantly higher in cases compared to controls (-11 (95% CI -13 to -9) vs. -9 (95% CI -10 to -7); $p < 0.05$). A reduction in 24-hour sputum weight was also seen in both arms, but again more so for the cases (6.6 g vs. 9.4 g, respectively; $p = 0.045$) compared with controls. No difference was found in lung function or hospital admissions. The authors conclude that inhalation of mannitol twice daily on patients with moderate to severe BE is safe and can improve QoL, increase time to first exacerbation and decrease duration of antibiotic treatment. The study is well conducted, however, it should be noticed that it only includes patients with severe BE and no placebo group. Furthermore, although statistically significant, the reported differences between the groups were relatively small, and might, therefore, be of limited clinical value.

Based on the available evidence, inhalation of mannitol twice daily appears safe and can improve mucociliary clearance, reduce surface tension, wettability, spinnability and solids. The effect is dose-dependent, but this is not explained by changes in the physical sputum properties. No effect has been documented on exacerbation rate, lung function, 24-hour sputum production, sputum microbiology, and sputum or systemic inflammatory markers. However, there is some evidence for an effect on QoL and time to first exacerbation. In order to draw valid conclusions, long-term, well-designed studies, however, are clearly needed to confirm the findings in the few studies studies published so far.

Anti-asthma Therapy

Inhaled corticosteroids

Five randomised, double-blind, placebo-controlled studies, including 300 subjects in total, have evaluated the effect of inhaled corticosteroids in patients with stable non-CF BE (Table 2).

In 1992, Elborn et al. [16] published a cross-over study, where 20 patients were randomised to either beclomethasone diproprionate 750 µg twice daily or placebo for 6 weeks and then vice versa. A small, but statistically significant increase in FEV_1 was observed on treatment with beclomethasone compared to placebo (mean [95% confidence interval (95% CI)] 2.3l (1.2-4.8) vs. 2.2l (1.2-4.4), $p = 0.03$) at end of the treatment period. Compared with placebo, patients on active treatment also had a significant decrease in mean daily sputum production (mean (95% CI) 22.3 g (0-68) vs. 27.3 g (9-95), $p = 0.003$) and in cough, as assessed by a visual analogue scale [VAS], (mean (95% CI) 48 (22-72) vs. 43 (17-68), $p = 0.02$) whereas no difference was observed in FVC, wheezing or dyspnoea (VAS). The authors concluded, that high dose beclomethasone reduced daily sputum production and might reduce

Treatment	Hypertonic saline			Mannitol						
Study/Author	Kellet et al. [6]	Kellet et al [7]	Nicolson et al. [8]	Daviskas et al. [9]	Daviskas et al. [10]	Daviskas et al. [11]	Daviskas et al. [12]	Daviskas et al. [13]	Bilton et al. [14]	Bilton et al. [15]
Design	Randomised, cross-over	Randomised, placebo-controlled, single-blind, cross-over	Open-label Randomised	Randomised, case-control	Non-randomised, un-blinded	Controlled, un-blinded	Controlled, un-blinded	Controlled, un-blinded	Randomised, placebo-controlled, double-blind	Randomised, case-control
No. of subjects	24	28	40	11	8	9	14	14	343	461
Therapy	7% Nebulized	7% Nebulized	6%, Nebulized daily	Inhalation 300 mg	Inhalation, 400 mg	Inhalation, 400 mg o.d.	Inhalation, 160 mg, 320 mg or 480 mg	Inhalation 635 mg	Inhalation 320 mg b.i.d.	Inhalation, 400 mg, 50 mg b.i.d.
Duration of treatment	Once	3 months (4 week wash-out)	12 months	Once	Once	12 days	Once	Once	12 weeks	12 months
Primary outcome	Sputum	Lung function	QoL and cough	Mucociliary clearance	Mucus clearance	QoL (sgrq)	Mucus clearance	Sputum characteristics	Sputum weight and qol (sgrq)	Exacerbations
Sputum weight	Improvement								Improved	Some improvement
Mucus clearance				Improvement	Improvement		Improvement			
FEV_1	No change	Improvement	No change		No change	No change			No change	No change
FVC	No change	Improvement			No change	No change			No change	No change
QoL		Some improvement	No change			Improvement			No change	Improvement
Exacerbations		Improvement							No change	No change
Admissions										No change
Antibiotic use		Improvement							No change	Improvement
Colonies			No change						No change	
Adverse events						No change			No change	

Table 1: Overview of the studies investigating the effect of airway clearing therapies for patients with stable non-cystic fibrosis bronchiectasis.

Treatment	Inhaled corticosteroids (ICS)					ICS plus long-acting β_2-agonist
Study	Elborn et al. [16]	Tsang et al. [17]	Tsang et al. [18]	Martínez-García et al. [19]	Hernando et al. [21]	Martínez-García et al. [22]
Design	Randomised, double-blind, placebo-controlled, cross-over	Randomised, double-blind, placebo-controlled	Randomised, double-blind, placebo-controlled	Randomised, double-blind, placebo-controlled	Randomised, double-blind, placebo-controlled	Randomised, double-blind, active comparator
No. of subjects	20	24	86	93	77	40
Therapy	Beclomethasone diproprionate 750 µg b.i.d.	Fluticasone 500 ug b.i.d.	Fluticasone 500 µg b.i.d.	Fluticasone propionate 250 µg or 500 µg b.i.d.	Budesonide 400 µg b.i.d.	Formoterol/budesonide, 18/640 µg or budesonide, 1.600 µg b.i.d.
Duration of treatment	6 weeks	4 weeks	52 weeks	26 weeks	26 weeks	12 weeks
Primary outcome	Sputum characteristics	Sputum characteristics	Clinical response	Clinical response	Clinical response	Clinical response
Sputum weight	Improvement	No change	Improvement	No change		No change
FEV_1	Improvement	No change	No change	No change	No change	No change
FVC	No change	No change	No change	No change	No change	No change

QoL	No change		No change	No change	No change	Improvement
Exacerbations			No change	No change	No change	No change
Admissions					No change	
Antibiotic use		No change				
Bacterial colonies		No change		No change		

Table 2: Overview of studies investigating the effect of anti-asthma therapy for the treatment of patients with stable non-cystic fibrosis bronchiectasis.

airflow obstruction. Important limitations of the study are the small number of patients, the narrow age range (30-65 years), and the high likelihood that at least some of the patients also had asthma.

In 1998, Tsang et al. [17] reported on the effect of high-dose inhaled fluticasone dipropionate in a study, where patients were randomised to either 500 μg fluticasone twice daily (n = 12) or placebo (n = 12) for four weeks. No significant difference was found between the groups in spirometry, 24-hour sputum volume, *P. aeruginosa* density or overall bacterial density. However, the fluticasone-group had a significant decrease in levels of IL-1β (8.21 pg/ml vs. 4.01 pg/ml; p = 0.03), IL-8 (18.31 pg/ml vs. 6.91 pg/ml; p = 0.02) and LTB4 (3.17 pg/ml vs. 1.62 pg/ml; p = 0.01), but not in TNF-α. The authors concluded that high dose fluticasone effectively reduced sputum inflammatory indices in BE. The study is limited by its small size and the short treatment period, as well as the significant age difference between the two groups (43 ± 11 vs. 57 ± 11 years, respectively; p = 0.01), but patients with known asthma were excluded. Furthermore, the observed significant decrease in inflammatory markers did not have impact on patient-related outcomes.

In 2005, Tsang et al. [18] repeated the study in a larger scale, as 86 patients were equally randomised to either 500μg fluticasone twice daily (n = 43) or placebo (n = 43) for 12 months. The fluticasone group were more likely to have improvement in 24-hour sputum volume than the placebo group (OR 2.5, 95% CI 1.1-6.0, p = 0.03), whereas no difference was observed in spirometry, exacerbation rate, sputum purulence score or respiratory symptoms. A subgroup analysis revealed a better response to fluticasone in patients with 24-hour sputum volume <30 mL (p = 0.04), exacerbation rate ≤2/year (p = 0.04) and sputum purulence score >5 (p = 0.03). However, these subgroup analyses must be interpreted with caution, as they were not pre-specified.

In 2006, Martínez-García et al. [19] also evaluated the effect of fluticasone in a study, where patients without asthma were randomised to either placebo (n = 28), fluticasone 250 μg (n = 29) or fluticasone 500 μg (n = 29) twice daily for 6 months (data collection after 1, 3 and 6 months). Patients on high-dose fluticasone had a significant improvement in dyspnea, measured by transition dyspnoea index (TDI) compared to baseline, after 1, 3 and 6 months of treatment (1.03, p = 0.04; 1.28, p = 0.01 and 1.24, p = 0.02, respectively), daily sputum production (-9.7 ml, p = 0.001), cough (-24%, p = 0.01 after 6 months) and use of rescue bronchodilator compared to baseline (p = 0.01). Furthermore, this group also had a significant improvement in health status, as measured by SGRQ, after 3 months (45.5 vs. 40.5, p = 0.01) and after 6 months (45.3 vs. 35.3; p = 0.005) compared to baseline, whereas no change was observed in pulmonary function, number or severity of exacerbations or sputum microbiology. As expected, local side effects were more common in patients on high-dose fluticasone (p = 0.04). No persistent significant improvements were observed for patients treated with placebo or 250 μg fluticasone twice daily. The authors concluded that fluticasone 500μg twice daily significantly improves HR-QoL. However, the systemic effect of high dose inhaled fluticasone must be taking into consideration [20].

In a double-blind, parallel group, placebo-controlled study from 2012, Hernando et al. [21] randomised patients (no asthma) to inhaled budesonide 400 μg (n = 37) or placebo (n = 33) twice daily for 6 months. Fewer eosinophils (% cell difference) was found in sputum in patients treated with budesonide compared to placebo (-0.2 vs. 1.7, p = 0.02), whereas no significant improvements were found in QoL, number of exacerbations or admissions, sputum microbiology or lung function. The clinical importance of the difference in sputum eosinophils is, therefore, questionable.

In conclusion, there is some evidence that high-dose inhaled corticosteroids reduce sputum volume and eosinophils in sputum, although the effect on eosinophil counts points to concomitant asthma, and, more importantly, no effect has been shown on sputum purulence or bacteriology, number of exacerbations or lung function. Although an outcome in only 3 of 4 studies, ICS may have positive impact on QoL and respiratory symptoms.

Fixed combination therapy with inhaled corticosteroid and long-acting β_2-agonist

Only one study comprising 40 patients have investigated the effect of fixed combination therapy with inhaled corticosteroids and long-acting β_2-agonist in non-CF BE has been published (Table 2).

In 2012, Martínez-García et al. [22] published a randomised, double-blind, parallel-group trial where patients were treated with budesonide 800 μg twice daily for three months, then allocated to either same dose of budesonide (n = 20) or budesonide 640 μg plus formoterol 18 μg (n = 20) twice daily for 3 months. Patients on combination therapy, in comparison with the single treatment group, had significant improvements in dyspnoea (TDI 1.39 vs. 0.1; p < 0.001), cough-free days (15% vs. 3%; p = 0.02), use of rescue β_2-agonist (-3.2 vs. -0.2; p < 0.001). Compared to baseline, only the combination therapy group showed a clinical significant improvement in QoL, measured by SGRQ (-5.3 units; p = 0.006). No significant differences were found in spirometry, sputum or exacerbation rate. The authors concluded that combination therapy with ICS and LABA is more effective than high-dose budesonide treatment. However, before valid conclusions can be drawn, there is a clear need for larger clinical trials on the effect of combination therapy in order to establish efficacy and safety.

Discussion and Conclusions

Several studies addressing the treatment of stable patients with non-CF BE with non-antibiotic inhaled agents have, although often based on relatively small studies, reported positive impact on a number of relevant outcome measures for a number of different treatment modalities. However, within each of the treatment categories, the reported observations have to a large extent been inconsistent, and, in order to permit valid conclusions to be drawn it is clear that further, large-scale trials are needed in this group of patients.

For airway clearing therapies, there is, based on the available studies, no clear evidence whether inhalation of hypertonic saline is superior to inhalation of isotonic saline or not. However, as this treatment is

often well-tolerated and, compared to treatment with e.g. antibiotics, the issue of bacterial resistance is likely to be non-existing. It is possible that treatment with inhaled hypertonic saline may be useful in patients without heavy bacterial load or in combination with antibiotic therapy.

Mannitol may increase sputum clearance, improve QoL and decrease use of antibiotics in exacerbations. However, there is very limited evidence for an improvement in lung function and exacerbation rate, so, although, it may potentially be a beneficial and, not least, safe treatment option for these patients, more and long-term studies with large number of patients are needed before valid conclusions can be drawn with regard to the efficacy of inhaled mannitol for the treatment of non-CF BE.

Based on the available evidence, monotherapy with inhaled corticosteroids cannot be recommend as maintenance therapy for non-CF BE, since there is no convincing evidence of an effect on lung function, QoL, number of exacerbations, number of admissions or sputum production. However, if the patient has concomitant COPD or asthma, inhaled corticosteroids may be indicated for the treatment of that component of the patient's airway disease. Furthermore, it should also be acknowledged that the number of studies addressing the effect of anti-asthma therapy in patients with stable non-CF BE is limited, not least when it comes to studies excluding patients with co-existing asthma or COPD.

In conclusion, the present systematic review of non-antibiotic inhaled therapy for stable non-CF BE revealed a limited amount of evidence for these therapeutic options, although some promising observations have been reported. There is, therefore, clearly an urgent need for high-quality, randomised, placebo-controlled, long-term studies in order to clarify the tolerability and efficacy of these therapies. In future clinical trials, it may be very helpful to include the disease-specific questionnaire QOL-B V3.0 [23] and stratify for disease severity [24], when evaluating the effect of therapy on outcomes of interest, including quality of life, in this group of patients.

References

1. Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group (2010) British Thoracic Society guideline for non-CF bronchiectasis. Thorax 65 Suppl 1: i1-i58.
2. Cohen M, Sahn SA (1999) Bronchiectasis in systemic diseases. Chest 116: 1063-1074.
3. Sidhu MK, Mandal P, Hill AT (2015) Developing drug therapies in bronchiectasis. Expert Opin Investig Drugs 24: 169-181.
4. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clinical research ed) 339: b2700.
5. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed) 339: b2535.
6. Kellett F, Redfern J, Niven RM (2005) Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis. Respir Med 99: 27-31.
7. Kellett F, Robert NM (2011) Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. Respir Med 105: 1831-1835.
8. Nicolson CH, Stirling RG, Borg BM, Button BM, Wilson JW, et al. (2012) The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 106: 661-667.
9. Daviskas E, Anderson SD, Eberl S, Chan HK, Bautovich G (1999) Inhalation of dry powder mannitol improves clearance of mucus in patients with bronchiectasis. Am J Respir Crit Care Med 159: 1843-1848.
10. Daviskas E, Anderson SD, Eberl S, Chan HK, Young IH (2001) The 24-h effect of mannitol on the clearance of mucus in patients with bronchiectasis. Chest 119: 414-421.
11. Daviskas E, Anderson SD, Gomes K, Briffa P, Cochrane B, et al. (2005) Inhaled mannitol for the treatment of mucociliary dysfunction in patients with bronchiectasis: effect on lung function, health status and sputum. Respirology 10: 46-56.
12. Daviskas E, Anderson SD, Eberl S, Young IH (2008) Effect of increasing doses of mannitol on mucus clearance in patients with bronchiectasis. Eur Respir J 31: 765-772.
13. Daviskas E, Anderson SD, Young IH (2010) Effect of mannitol and repetitive coughing on the sputum properties in bronchiectasis. Respir Med 104: 371-377.
14. Bilton D, Daviskas E, Anderson SD, Kolbe J, King G, et al. (2013) Phase 3 randomized study of the efficacy and safety of inhaled dry powder mannitol for the symptomatic treatment of non-cystic fibrosis bronchiectasis. Chest 144: 215-225.
15. Bilton D, Tino G, Barker AF, Chambers DC, De Soyza A, et al. (2014) Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. Thorax 69: 1073-1079.
16. Elborn JS, Johnston B, Allen F, Clarke J, McGarry J, et al. (1992) Inhaled steroids in patients with bronchiectasis. Respir Med 86: 121-124.
17. Tsang KW, Ho PL, Lam WK, Ip MS, Chan KN, et al. (1998) Inhaled fluticasone reduces sputum inflammatory indices in severe bronchiectasis. Am J Respir Crit Care Med 158:723-727.
18. Tsang KW, Tan KC, Ho PL, Ooi GC, Ho JC, et al. (2005) Inhaled fluticasone in bronchiectasis: a 12 month study. Thorax 60: 239-243.
19. Martinez-Garcia MA, Perpina-Tordera M, Roman-Sanchez P, Soler-Cataluna JJ (2006) Inhaled steroids improve quality of life in patients with steady-state bronchiectasis. Respir Med 100: 1623-1632.
20. Lipworth BJ (1999) Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med 159: 941-955.
21. Hernando R, Drobnic ME, Cruz MJ, Ferrer A, Suñé P, et al. (2012) Budesonide efficacy and safety in patients with bronchiectasis not due to cystic fibrosis. Int J Clin Pharm 34: 644-650.
22. Martinez-Garcia MA, Soler-Cataluna JJ, Catalan-Serra P, Roman-Sanchez P, Tordera MP (2012) Clinical efficacy and safety of budesonide-formoterol in non-cystic fibrosis bronchiectasis. Chest 141: 461-468.
23. Quittner AL, O'Donnell AE, Salathe MA, Lewis SA, Li X, et al. (2015) Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. Thorax 70: 12-20.
24. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, et al. (2014) The bronchiectasis severity index. An international derivation and validation study. Am J Respir Crit Care Med 189: 576-585.

Citation: Fjaellegaard K, Sin MD, Browatzki A, Ulrik CS (2016) Non-antibiotic Inhaled Agents for Stable Non-CF Bronchiectasis in Adults - A Systematic Review. J Pulm Respir Med 6: 337. doi:10.4172/2161-105X.1000337