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[Intervention Review]

Cough augmentation techniques for people with chronic neuromuscular disorders

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ABSTRACT

Background

People with neuromuscular disorders may have a weak, ineffective cough predisposing them to respiratory complications. Cough augmentation techniques aim to improve cough effectiveness and mucous clearance, reduce the frequency and duration of respiratory infections requiring hospital admission, and improve quality of life.

Objectives

To determine the efficacy and safety of cough augmentation techniques in adults and children with chronic neuromuscular disorders.

Search methods

On 13 April 2020, we searched the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, CINAHL, and ClinicalTrials.gov for randomised controlled trials (RCTs), quasi-RCTs, and randomised cross-over trials.

Selection criteria

We included trials of cough augmentation techniques compared to no treatment, alternative techniques, or combinations thereof, in adults and children with chronic neuromuscular disorders.

Data collection and analysis

Two review authors independently assessed trial eligibility, extracted data, and assessed risk of bias. The primary outcomes were the number and duration of unscheduled hospitalisations for acute respiratory exacerbations. We assessed the certainty of evidence using GRADE.

Main results

The review included 11 studies involving 287 adults and children, aged three to 73 years. Inadequately reported cross-over studies and the limited additional information provided by authors severely restricted the number of analyses that could be performed.

Studies compared manually assisted cough, mechanical insufflation, manual and mechanical breathstacking, mechanical insufflation-exsufflation, glossopharyngeal breathing, and combination techniques to unassisted cough and alternative or sham interventions. None of the included studies reported on the primary outcomes of this review (number and duration of unscheduled hospital admissions) or listed 'adverse events' as primary or secondary outcome measures.

The evidence suggests that a range of cough augmentation techniques may increase peak cough flow compared to unassisted cough (199 participants, 8 RCTs), but the evidence is very uncertain. There may be little to no difference in peak cough flow outcomes between alternative cough augmentation techniques (216 participants, 9 RCTs).

There was insufficient evidence to determine the effect of interventions on measures of gaseous exchange, pulmonary function, quality of life, general function, or participant preference and satisfaction.

Authors' conclusions

We are very uncertain about the safety and efficacy of cough augmentation techniques in adults and children with chronic neuromuscular disorders and further studies are needed.

PLAIN LANGUAGE SUMMARY

The safety and effectiveness of techniques to assist coughing in people with chronic neuromuscular disorders

Review question

We reviewed the evidence on the effectiveness and safety of techniques used to assist coughing in people with chronic neuromuscular disorders (cough augmentation techniques).

Background

People with neuromuscular disorders (nerve-related conditions that affect the muscles) may have difficulty coughing and clearing mucous from the airways, placing them at risk of choking, recurrent chest infections, and ongoing lung disease. Cough augmentation techniques, such as manually assisted cough, bagging (using a self-inflating bag commonly used for resuscitation), mechanical Cough Assist (a device that clears secretions by applying a positive pressure to the airway, then rapidly shifting to a negative pressure), 'frog' breathing (a method of breathing to help a person take in a bigger volume of air), and breathstacking (the person takes a number of sequential breaths in, stacking one breath on top of the other without breathing out in between breaths) aim to improve cough effectiveness, with the eventual aim of reducing the number or severity (or both) of chest infections, and improving the ability of people to perform daily activities (functional ability) and quality of life.

Methods

We carried out a wide database search for studies of cough augmentation techniques in adults and children with chronic neuromuscular disorders. We selected studies that assigned people to the treatment(s) or treatment order by chance, as this study type provides the best evidence.

Results and quality of the evidence

We found 11 studies with 287 people and several cough augmentation techniques. One study measured the long-term effects of treatment, but was only published as an abstract without enough information to accurately analyse the study findings. Many included studies had problems with how they were performed, how their findings were reported, or both, which made it difficult to fully interpret their results. None of the studies reported on the outcomes we thought were the most important for making decisions about the effectiveness and safety of cough augmentation techniques. For example, the studies did not report on the number or duration of unscheduled hospital admissions for chest infections, survival, functional ability, or quality of life. The safety of cough augmentation techniques could not be determined. Some studies suggested that cough augmentation techniques may be better than an unassisted cough, but the results are very uncertain. There was not enough evidence to show that any one technique was better than another in improving cough effort.

Conclusions and recommendation

The findings of this review provided insufficient information to make decisions about when and how to use cough augmentation techniques in people with chronic neuromuscular disorders. There is currently very low certainty evidence for or against the safety and effectiveness of cough augmentation techniques in people with chronic neuromuscular diseases and more studies are needed.

The evidence is up-to-date to 13 April 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Cough augmentation therapy compared with an alternative cough augmentation technique or combination of techniques for people with neuromuscular diseases

Cough augmentation compared with an alternative cough augmentation technique or combination technique

Patient or population: participants with chronic neuromuscular diseases

Settings: –

Intervention: cough augmentation

Comparison: alternative cough augmentation technique

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Alternative cough augmentation technique	Cough augmentation				
Number of unscheduled hospital admissions for 'maintenance therapy'	Not reported					
Duration of hospital stay (days) for 'rescue' therapy	Not reported					
PCF Follow-up: < 1 day ('rescue' and 'maintenance' therapy)	8 RCTs (198 participants) studied various cough augmentation techniques or combinations of techniques. <ul style="list-style-type: none"> Reported that MI-E, mechanical exsufflation, MAC, mechanical insufflation, manual and mechanical breathstacking, glossopharyngeal breathing, mechanical insufflation + MI-E, MAC + MI-E, and MAC + breathstacking may increase PCF above unassisted cough. 2 cross-over RCTs (26 participants) reported no change in PCF with MAC compared to unassisted cough. 1 cross-over RCT reported no difference in PCF with mechanical insufflation compared to unassisted cough (22 participants). 		—	198 (8 RCTs (7 cross-over, 1 parallel group))	⊕⊕⊕⊕ Very low ^a	Cough augmentation may improve PCF compared to unassisted cough, but the certainty of evidence was very low. See Table 1 for details.

	Repeated measures data were reported and could not be meta-analysed.				
Any adverse events	4 cross-over RCTs (64 participants) compared various cough augmentation techniques or combinations of techniques (including mechanical insufflation, mechanical exsufflation, MI-E, MAC, MAC + manual breath-stacking, MI-E + MAC, MAC + manual breathstacking, MAC + mechanical insufflation). <ul style="list-style-type: none"> 0 trials reported serious adverse events. 3 trials reported no adverse events occurred. In most trials it was unclear whether adverse effects were systematically investigated. 1 cross-over RCT (8 participants) reported fatigue as an adverse event, measured on a 10-point ordinal VAS. Fatigue was reported to increase from baseline in the MAC + M-IE group, with no change in the MAC group. No data were provided for the control group or the separate periods of cross-over. The mean postintervention fatigue score for both periods of the cross-over trial was 5.1 (SD 2.6). 	—	64 (4 cross-over RCTs)	⊕○○○ Very low ^b	We are unable to draw a conclusion as the certainty of evidence is very low. See Table 2 ; Table 3 for details.
Quality of life for 'maintenance' therapy	No study measured or reported quality of life.				
Participant preference or satisfaction for 'rescue' and 'maintenance' therapy	No study measured or reported participant preference or satisfaction.				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MAC:** manually assisted cough; **MI-E:** mechanical insufflation-exsufflation; **PCF:** peak cough flow; **RCT:** randomised controlled trial; **RR:** risk ratio; **SD:** standard deviation; **VAS:** visual analogue scale.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded three levels – twice for study limitations – all studies were at high risk of bias in at least one domain and unclear in several. Data were based on repeated (dependent) measurements from seven cross-over and one parallel-group RCTs. We also downgraded the evidence for imprecision – all studies had a small sample size, wide CI, or both. The outcome was measured less than one day after the intervention, rather than in the medium and long term as specified.

^bDowngraded three levels – twice for study limitations – all studies were at high risk of bias in at least one domain and unclear in several. Data were based on repeated (dependent) measurements from seven cross-over and one parallel-group RCTs. We also downgraded the evidence for imprecision – all studies had a small sample size.

Summary of findings 2. Cough augmentation therapy compared with standard care for people with neuromuscular diseases

Cough augmentation therapy compared with standard care for people with neuromuscular disease

Patient or population: participants with chronic neuromuscular diseases

Settings: –

Intervention: cough augmentation therapy

Comparison: standard care

Outcome	Summary of results	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Number of unscheduled hospital admissions for 'maintenance' therapy	No study reported the number of unscheduled admissions.			1 parallel-group RCT of manual breathstacking compared to standard care (67 participants) planned to measure these outcomes; however, only an abstract is available and data are not fully reported (Katz 2019).
Duration of hospital stay (days) for 'rescue' therapy	No study reported the duration of hospital stay.			Lack of quantitative data precludes assessment of precision.
Quality of life for 'maintenance' therapy	No study reported quality of life			
Peak cough flow for 'rescue' or 'maintenance' therapy	No study reported peak cough flow			
Any adverse events for 'rescue' and 'maintenance' therapy Follow-up: 2 years	1 parallel-group RCT reported that no adverse events had occurred during the 2-year study, but this outcome was not quantitatively reported and it was unclear how it was measured.	67 (1 study)	⊕○○○ Very low ^a	We are unable to draw a conclusion.
Quality of life for 'maintenance' therapy	No study reported quality of life.			1 parallel-group RCT of manual breathstacking compared to standard care (67 participants) planned to measure quality of life; however, only

an abstract is available and data are not fully reported (Katz 2019).

Participant preference or satisfaction for 'rescue' or 'maintenance' therapy No study measured or reported participant preference.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

^aDowngraded three times, twice for study limitations and once for imprecision. Data were from one parallel-group RCT, with high risk of performance and reporting bias. This outcome was not quantitatively reported and unclear how it was measured. Lack of quantitative data precludes assessment of precision but the trial was small (67 participants).

BACKGROUND

Description of the condition

A range of chronic neuromuscular disorders (NMDs) have been described in adults and children, including muscular dystrophies, congenital and metabolic myopathies, neuromuscular junction disorders, peripheral neuropathies, and anterior horn cell diseases (Gozal 2000). People affected by chronic NMDs are at risk of progressive respiratory insufficiency (breathing difficulties that worsen over time), primarily from a combination of respiratory muscle weakness and chest wall abnormalities (Boitano 2006; FINDER 2010; Gozal 2000; Panitch 2009).

Many people with NMDs experience progressive respiratory insufficiency with advancing age. Infants with NMDs generally have normal lungs and normal mucociliary clearance mechanisms at birth, although pulmonary mechanics may be affected from baseline, depending on the underlying NMD (Panitch 2017). Chest deformities may develop from infancy, particularly with severe forms of spinal muscular atrophy (SMA), because of respiratory muscle weakness and chronic paradoxical chest wall or abdominal movement during breathing (or both), in conjunction with an initially very compliant chest wall (Panitch 2009; Panitch 2017; Papastamelos 1996). Respiratory muscle weakness causes chronic shallow breathing; the inability to take a sufficiently deep breath to sigh or yawn, which is required to maintain full lung expansion; an ineffective cough with secretion retention; and progressive loss of lung compliance (Fauroux 2008; Panitch 2009; Panitch 2017). Progressive thoracic deformities such as scoliosis, kyphosis, and spinal rigidity, together with fibrosis of the intercostal muscles, may further impact on lung function with a progressive decrease in chest wall compliance and ultimately a restrictive pattern of respiratory disease (Fauroux 2008; Gozal 2000; Panitch 2009; Wang 2007). Bulbar weakness and glottic dysfunction, as typically seen in children with SMA type 1 and other severe NMDs, also impact on the ability to cough effectively as well as increasing the risks of aspiration (Boitano 2006; Chatwin 2018; Toussaint 2018).

An effective cough is essential to clear pulmonary secretions from the airways (Panitch 2017). If the cough is ineffective, as is often the case in people with chronic NMD and respiratory muscle weakness, short-term inability to clear secretions may lead to acute respiratory insufficiency and respiratory failure, while long-term retention of secretions leads to a vicious cycle of obstruction, infection, inflammation, increased work of breathing, recurrent acute respiratory tract infections, and ultimately chronic lung disease and respiratory failure (Chatwin 2018; Homnick 2007; Panitch 2017). Respiratory tract infection with altered sputum viscosity and volume, difficult or ineffective swallowing (dysphagia), and gastro-oesophageal reflux with chronic aspiration can all exacerbate secretion retention in people with NMD and respiratory muscle weakness (Farrero 2013; FINDER 2010; Iannaccone 2007).

An effective cough requires: a sufficiently deep inspiration; brief closure of the glottis with simultaneous contraction of expiratory respiratory muscles to increase intrathoracic pressure; and finally the abrupt opening of the glottis at the start of the expiratory phase to produce a rapid, forceful flow of air from the lungs (Boitano 2006; Chatwin 2018; Farrero 2013; Panitch 2017; Toussaint 2018). Any or all these phases may be affected in people with NMD (Bach 2003; Boitano 2006; FINDER 2010; Rokadia 2015).

Adults have a normal peak expiratory cough flow (PCF) range between 360 L/minutes and 1200 L/minutes (Anderson 2005; Leiner 1963; Mayer 2017; Tzeng 2000). Bach 1996 suggested that adults require a PCF greater than 160 L/minute for an effective cough. Furthermore, it has been suggested that adults with NMD require a PCF of more than 270 L/minute when well, to account for the expected decline in cough flows during intercurrent respiratory infections (Bach 1997). Cough augmentation may, therefore, be indicated if PCF falls below 270 L/minute in adults and adolescents with NMD (Toussaint 2018). In children with NMDs, an absolute PCF of less than 160 L/minute has been shown to be predictive of severe disease, but age or size-adjusted reference values are not available (Dohna-Schwake 2006). It must be noted that the normal range of PCF in young children is highly variable, with healthy children only able to achieve PCFs of 160 L/minute on the 5th percentile by six years of age (Bianchi 2008). Therefore, for children over the age of 12 years (when children attain adult PCF (Bianchi 2008)), use of the adult values of 160 L/minute and 270 L/minute PCF cut-offs may be appropriate (Hull 2012), but the corresponding levels in younger children are as yet unclear and this warrants further investigation.

Most episodes of respiratory failure in people with NMD are likely to be caused by ineffective coughing during intercurrent chest infections (Bach 2003; Boentert 2017; Chatwin 2018). The identification of the most effective, safe measures to optimise cough efficacy and promote secretion clearance is, therefore, vital to optimising pulmonary function, preventing morbidity, and improving the quality of life in people with chronic NMD (Toussaint 2018).

Description of the intervention

Many airway clearance techniques are used in clinical practice in people with chronic NMD. Some techniques aim to move secretions from the peripheral to the more central airways (secretion mobilisation techniques), while others aim to clear secretions from the central airways (cough augmentation techniques) (Chatwin 2018; Toussaint 2018). Secretion mobilisation and an effective cough are both needed for effective secretion clearance (Farrero 2013; FINDER 2010).

Manual techniques to assist peripheral secretion mobilisation in adults and children with chronic NMD include positioning, chest wall shaking, percussion and vibrations (Chatwin 2018; FINDER 2010; McCool 2006; Toussaint 2018; Wang 2007). Other secretion mobilisation techniques that have been suggested for people with NMD include the active cycle of breathing and forced expiratory techniques; autogenic drainage; positive expiratory pressure therapy; oscillatory positive pressure therapy; intermittent positive pressure breathing (IPPB); chest wall strapping; intrapulmonary percussive ventilation, and high-frequency chest wall oscillation (Anderson 2005; Bott 2009; Chatwin 2018; Douglas 1981; FINDER 2010; Hull 2012; Toussaint 2003; Toussaint 2018). Active breathing exercises, such as the active cycle of breathing and positive expiratory pressure therapy, are effort dependent and, therefore, may not be useful in people with severe respiratory muscle weakness (FINDER 2010; Hull 2012), unless concomitant ventilatory support is given (Chatwin 2018; Toussaint 2018).

Cough augmentation for proximal secretion clearance can be performed using manual or mechanical methods, alone or in combination, to support different components of the cough (Chatwin 2018; FINDER 2010; Panitch 2017; Toussaint 2018). These

may also be done in different body positions to optimise secretion clearance (Marques 2020). Techniques such as breath- or airstacking, glossopharyngeal breathing (GPB), and mechanical or manual single-breath insufflations (blowing air into the lungs), augment inspiration to achieve sufficient inspiratory lung volumes before a cough (Bott 2009; Chatwin 2018; Toussaint 2018). People can achieve lung insufflation using positive pressure devices including ventilators (invasively or non-invasively) and IPPB devices, with set pressure or volume limits, or both. They may achieve breathstacking independently (with glottic closure) or through use of an external self-inflating manual resuscitator bag with a one-way valve, if needed, to prevent air leak (Chatwin 2018; Toussaint 2018). For breathstacking, a person takes or receives multiple inspiratory breaths, without exhalation between breaths, until they achieve maximal insufflation capacity (MIC) (Bach 2007; Chatwin 2018; Marques 2014; Toussaint 2018). Thereafter, the individual releases the breath in a spontaneous or assisted forced expiratory manoeuvre or cough (Chatwin 2018; Marques 2014). MIC refers to the maximum tolerable inspiratory lung volume (Bach 2007; Chatwin 2018; Kang 2000). GPB or 'frog breathing,' which does not use any external equipment, requires the person with NMD to actively 'gulp' air into the lungs by opening and closing the glottis until MIC is reached (Bach 2007; Chatwin 2018; Nygren-Bonnier 2009; Toussaint 2018).

Mechanical exsufflation (forcible expulsion of air from the lungs by artificial means) and manually assisted cough (MAC), the latter achieved by manually compressing the thorax, abdomen, or both, aim to improve expiratory flow rates by rapidly increasing intrathoracic pressure (Anderson 2005; Chatwin 2018; FINDER 2010; Panitch 2017; Toussaint 2018).

Mechanical insufflation-exsufflation (MI-E) supports both insufflation and exsufflation, using a device that delivers a preset positive pressure into the airways for a set duration during inspiration (insufflation), immediately followed by an abrupt change to a preset negative exsufflation pressure, thereby simulating a cough with high expiratory flow rates (Anderson 2005; Chatwin 2018; Fauroux 2008; Morrow 2013; Panitch 2017; Toussaint 2018).

How the intervention might work

Both inspiratory and expiratory cough augmentation techniques aim to optimise cough efficacy by improving PCF when respiratory muscles are too weak to independently achieve sufficient flow rates for secretion clearance. The mechanism by which PCF is affected varies among different cough augmentation techniques (Chatwin 2018; Toussaint 2018).

Inspiratory cough augmentation techniques aim to augment inspiratory lung volumes to those required for an effective cough (MIC). By increasing inspiratory volume, these techniques enhance expiratory flow bias (creating higher expiratory than inspiratory air flow) during a spontaneous or assisted cough, thereby effectively mobilising and clearing secretions (Chatwin 2018). Inhaling a large volume of air before the compressive and expiratory phases of the cough optimises the length-tension relationship of expiratory muscles and may generate higher intrathoracic pressures and PCF (Boitano 2006; Chatwin 2018).

Expiratory cough augmentation techniques, whether manual or mechanical, aim to assist the weak expiratory muscles in

generating sufficient intrathoracic pressures thereby increasing the expiratory flow generated during the cough. The overall aim is to increase PCF enough to effectively clear secretions from the central airways (Boitano 2006; Chatwin 2018; Toussaint 2018).

Some investigators have suggested that combining inspiratory and expiratory cough augmentation techniques could optimise cough clearance in people with NMD (Boitano 2006; Chatwin 2018; Hull 2012; Toussaint 2018; Trebbia 2005).

Why it is important to do this review

Cough augmentation techniques are considered essential to prevent pulmonary morbidity and progression to respiratory failure in people with NMD (Bach 2003; Chatwin 2018). In addition, they prevent acute respiratory failure, improve work of breathing, and relieve distress caused by retained secretions in the short term. However, it is still unclear which technique(s) offer the greatest clinical benefit with the least risk of harm.

Any application of positive pressure to the airways carries a risk of complications including abdominal distention, discomfort, gastro-oesophageal reflux, cardiovascular effects such as changes in blood pressure and cardiac arrhythmia, and pneumothorax (Chatwin 2018; Homnick 2007; Morrow 2013; Toussaint 2018). Pneumothorax has been described in adults following the use of MI-E (Suri 2008), breathstacking (Westermann 2013), and long-term non-invasive positive pressure ventilation (Vianello 2004). There may be greater risk of barotrauma and volutrauma in infants and young children with NMD compared to older children or adults, considering their different respiratory anatomy and physiology. Application of positive pressure will affect the lungs differently according to, for example, lung volumes and respiratory system compliance and resistance, all of which vary with age and NMD condition (Gattinoni 2003; Gattinoni 2010). The effects of MAC may be altered by chest wall compliance, which is almost twice that of controls in infants with NMD (Papastamelos 1996), and may be substantially reduced in adults with NMD, particularly in the case of chest wall deformities (Gozal 2000; Panitch 2009). During MI-E specifically, applied insufflation volume is not usually measured in clinical practice, and a rapid swing to negative pressure follows insufflation. The combination of high applied tidal volume and atelectrauma (lung injury caused by repeated expansion and collapse of lung units) has been associated with lung injury in the context of invasive mechanical ventilation (Albuali 2007; Saharan 2010). The safety of MI-E and other insufflation techniques is unclear in this regard and warrants further research.

Some cough augmentation techniques recommended in international guidelines for the treatment of people with NMD require equipment or expertise that are not readily available in lower-resourced environments (Bott 2009; Chatwin 2018; FINDER 2004; McCool 2006; Rosière 2009; Toussaint 2018; Wang 2007; Wang 2010), while cheaper and more readily available techniques may be equally effective (Anderson 2005; FINDER 2010). Currently, people living with NMD and their caregivers generally manage their airway clearance according to perceived need, and clinical management is responsive to changes in the patient's condition (Toussaint 2018). The management approach also depends on availability of equipment and local expertise, which may vary substantially at a global level (Toussaint 2018). It is not yet clear what people with NMD and their caregivers prefer when considering the choice of cough augmentation technique, and this warrants investigation.

To advocate for the best and most appropriate treatment in different sociogeographical contexts, it is necessary to first determine which cough augmentation technique(s), dosages and frequencies are effective and safe for use in people with chronic NMD, using clinically relevant outcome measures.

OBJECTIVES

To determine the efficacy and safety of cough augmentation techniques in adults and children with chronic neuromuscular diseases.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), quasi-RCTs, and randomised cross-over trials. We considered quasi-RCTs (those in which participants were allocated using methods that were partly systematic, such as by case record number, date of birth, or alternation) were considered for inclusion, considering the likely paucity of high-level RCTs in the field. We included studies reported as full text and those published as abstract only. There were no language restrictions.

Types of participants

We included adults, adolescents, and children with a diagnosis of chronic NMD that may affect the muscles of respiration.

Owing to age-related changes in respiratory anatomy and physiology, we planned to stratify participants according to age. For the purposes of this review, 'infants' referred to children under the age of one year; 'children' from one to 13 years of age; and 'adolescents/adults' over the age of 13 years. We chose this cut-off, as peak cough flow normally reaches adult levels above 12 years of age (Bianchi 2008). We also planned to stratify participants according to whether the intervention was 'rescue' therapy (i.e. intercurrent acute chest infection in a person with chronic NMD) or maintenance therapy, where possible.

We excluded people with the following comorbidities/characteristics.

- Amyotrophic lateral sclerosis/motor neuron disease (ALS/MND), which is the focus of another review.
- Acute NMD with likelihood of resolution (e.g. Guillain-Barré syndrome).
- Spinal cord injuries.
- Neonates in the first month of life, as they are pathophysiologically and anatomically a unique patient group warranting a separate review.

We considered studies with mixed eligible and non-eligible population groups for inclusion, but only extracted data for participants meeting eligibility criteria for synthesis and analysis. Where separate data were not available, we contacted trial authors to obtain subgroup data. Where we could not obtain additional data, we presented results for all participants narratively, noting the mixed nature of the population.

Types of interventions

We included trials comparing any cough augmentation technique or combination of techniques, whether provided as maintenance therapy or for treatment of intercurrent respiratory tract infection, with no treatment (unassisted cough), alternative cough augmentation techniques, or combinations thereof. We allowed co-interventions if they were provided to each group equally.

Cough augmentation techniques included, but were not limited to, the following alone or in combination):

- manual or mechanical insufflation;
- air- or breathstacking;
- GPB ('frog' breathing);
- MI-E;
- mechanical exsufflation;
- and MAC.

Types of outcome measures

In formulating primary and secondary outcome measures, we differentiated between cough augmentation techniques used for 'rescue' therapy (e.g. during intercurrent respiratory exacerbations) and maintenance therapy.

In addition to the formal outcome measures listed below, we planned to informally include any valid measure of economic comparison between cough augmentation techniques relative to health outcomes.

The outcomes listed here were not eligibility criteria for this review, but rather outcomes of interest within included studies.

Primary outcomes

- Number of unscheduled hospital admissions for episodes of acute respiratory exacerbations over one year for 'maintenance' therapy.
- Duration of hospital stay (days) for 'rescue' therapy.

Secondary outcomes

- Peak cough flow (PCF) measured before and after intervention for 'rescue' therapy and measured over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' therapy.
- Any adverse events, including, but not limited to: pneumothorax, rib fractures, lung injury, aerophagia/abdominal distension, and death for both 'maintenance' and 'rescue' therapy.
- Measures of gaseous exchange (e.g. oxygen saturation in arterial blood (SaO₂) and expired carbon dioxide (CO₂; end tidal carbon dioxide; ETCO₂)) measured before and after the intervention for 'rescue' therapy, and measured over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' therapy.
- Pulmonary function measured by forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), vital capacity (VC), and peak expiratory flow rate (PEFR), over the short term (less than three months); medium term (between three months and one year); and long term (one year and longer), for 'maintenance' therapy. Where possible, values were presented

as percentages predicted according to age, gender, and height; or as Global Lung Function Initiative multiethnic norm-referenced Z score values (Quanjer 2012).

- Quality of life measured by any validated measure over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' therapy.
- Validated measures of function, including measures of perceived exertion, exercise tolerance, and motor function measured over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' therapy.
- Participant preference for, or satisfaction with, specific cough augmentation techniques, expressed as a proportion or percentage of the sample (preference) or any validated measure (satisfaction) for both 'rescue' and 'maintenance' therapy.

Search methods for identification of studies

Electronic searches

On 10 January 2019 and 13 April 2020, the Information Specialist searched the following databases.

- Cochrane Neuromuscular Specialised Register via the Cochrane Register of Studies (CRS-Web; [Appendix 1](#)).
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web; [Appendix 2](#)).
- MEDLINE OvidSP (1946 to 10 April 2020; [Appendix 3](#)).
- Embase OvidSP (1974 to 2020 Week 15; [Appendix 4](#)).
- Cumulative Index of Nursing and Allied Health Literature (CINAHL) EBSCOhost (1937 to 13 April 2020; [Appendix 1](#)).

We also searched the following trials registries.

- WHO International Clinical Trials Registry Platform (ICTRP; inaccessible on 13 April 2020; [Appendix 2](#)).
- US National Institutes for Health Clinical Trials Registry ([ClinicalTrials.gov](#); [Appendix 3](#)).

We searched all databases from their inception to the search date, and imposed no restriction based on language of publication, or by publication status (abstract only, 'in press,' 'grey' literature, full text, etc.).

Searching other resources

We searched reference lists of all primary studies and review articles for additional references. We also searched relevant manufacturers' websites for trial information and we searched for errata or retractions from included studies. We further performed handsearches for conference proceedings.

Data collection and analysis

Selection of studies

Using Covidence ([Covidence](#)), two review authors (BM and AH) independently screened titles and abstracts of all the studies identified from the search for inclusion criteria, and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve.' We retrieved the full-text study reports/publications, and two review authors (AH and LC) independently screened the full text and identified studies for inclusion, as well as identifying and recording reasons for exclusion of the ineligible studies. We

resolved any disagreement through discussion and planned, if required, to consult a third review author as arbiter (BM). We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram ([Moher 2009](#)).

Data extraction and management

We used a data extraction form for study characteristics and outcome data, which we piloted on one study in the review. One review author (BM) extracted study characteristics from included studies. We extracted data on:

- study design and setting;
- characteristics of participants (e.g. disease severity and age);
- eligibility criteria;
- intervention details;
- outcomes assessed;
- source(s) of study funding;
- conflicts of interest among investigators.

Two review authors (AH and LC) independently extracted outcome data from included studies. We noted in the [Characteristics of included studies](#) table if outcome data were not reported in a usable way, and planned to resolve disagreements by consensus or by involving a third review author if necessary (MT). One review author (BM) transferred data into Review Manager 5 ([Review Manager 2020](#)). A second author checked the outcome data entries (AH). Another review author (MZ) spot-checked study characteristics for accuracy against trial reports.

If reports required translation, it was planned that the translator would extract data directly using a data extraction form, or authors would extract data from the translation provided. Where possible a review author planned to check numerical data in the translation against the study report.

Assessment of risk of bias in included studies

Two review authors (LC and AH) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2020a](#)). We made summary assessments of the risk of bias for each important outcome (across domains) within and across studies comparing the same interventions. We resolved any disagreements by discussion or by involving another review author (BM) where necessary. We assessed the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded each potential source of bias as high, low, or unclear, and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We planned to summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for

different key outcomes where necessary. If information on risk of bias had been related to unpublished data or correspondence with an author, we planned to note this in the 'Risk of bias' table.

When considering treatment effects, we considered the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol, and reported any deviations in the 'Differences between protocol and review' section (Morrow 2018).

Measures of treatment effect

We planned to analyse all data for 'rescue' and maintenance therapy using cough augmentation techniques separately. We planned to analyse dichotomous data as risk ratios (RRs) and continuous data as mean difference (MD) when studies used the same scale, or standardised mean difference (SMD) for results across studies with outcomes that were conceptually the same but measured in different ways. We reported 95% confidence intervals (CI). Where studies reported standard errors of the means (SEMs), we planned to convert these to standard deviations (SDs) where possible. We entered data presented as a scale with a consistent direction of effect.

We planned to calculate a Peto odds ratio (Peto OR) and corresponding 95% CI for rare adverse events. In the case of statistically significant results, we planned to calculate the risk difference (RD) and 95% CI and the number needed to treat for an additional beneficial outcome or for an additional harmful outcome as appropriate.

We planned to undertake meta-analyses only where this was meaningful (i.e. where treatments, participants, and the underlying clinical questions were similar enough for pooling to be meaningful). We reported the types of cough augmentation techniques and different underlying conditions which could not be pooled separately (if the number of trials permitted).

We planned to describe skewed data reported as medians and interquartile ranges (IQRs).

Unit of analysis issues

We only included first-period data from cross-over trials for purposes of analysis, when sufficient data were available (Elbourne 2002; Higgins 2020b). Long-term studies with multiple repeated measures of outcome could be included, in which case we planned to define outcomes based on the specified time points (Higgins 2020b).

Where multiple trial arms were reported in a single trial, we planned to only include the treatment arms relevant to the review topic. If two comparisons (e.g. treatment A versus no treatment and treatment B versus no treatment) were combined in the same meta-analysis, we planned to follow guidance in Section 23.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* to avoid double-counting (Higgins 2020b). Our preferred approach was to halve the control group.

Dealing with missing data

We attempted to contact investigators or study sponsors to verify key study characteristics and obtain missing numerical

outcome data where possible (e.g. when a study was available as an abstract only; where only pooled data or estimates of results were presented; and where separate period data were not presented for cross-over studies). Where this was not possible, we considered the studies adequate if more than 85% of the participants were included in the outcome analysis or if fewer participants were analysed, but sufficient measures were taken to ensure or demonstrate that this did not bias the results. Where this was unclear, we planned to conduct an intention-to-treat analysis from extrapolated data. If we suspected that missing data may have introduced serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We planned to use the I^2 statistic to measure heterogeneity among the trials in each analysis. We planned to avoid the use of absolute cut-off values, but to interpret the I^2 statistic in relation to the size and direction of effects and strength of evidence for heterogeneity (e.g. P value from the χ^2 test, or CI for the I^2 statistic).

We planned to use the rough guide to interpretation as outlined in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017), as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

If we had identified substantial unexplained heterogeneity, we planned to report it and explore possible causes with prespecified subgroup analysis.

Assessment of reporting biases

If we had been able to pool more than 10 trials, we planned to create and examine a funnel plot to explore possible small-study biases.

Data synthesis

We were unable to pool more than one study in any meta-analysis due to inadequate presentation of results, as well as clinical and methodological heterogeneity. Where we could not source additional information, and there was insufficient information supplied, we reported the individual results as described in the original trials in qualitative, tabular, and narrative form. If the included trials had been similar enough to combine them, we would have performed a statistical pooling of effect measures using a random-effects model, as this is more conservative, and explore possible causes of heterogeneity by subgroup analyses if there were sufficient studies to do so. We reported the results for each review outcome measure and comparison separately, where possible. We compiled the review using Review Manager 5 (Review Manager 2020).

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

- Infants versus children.
- Children versus adolescents or adults, or both.

We planned to use the following outcomes in subgroup analyses.

- Number of hospital admissions over one year (for maintenance use).
- Duration of hospital stay (days) for 'rescue' use.

We planned to use the formal test for subgroup interactions in Review Manager 5 ([Review Manager 2020](#)). Owing to inadequate data, we were unable to conduct subgroup analyses, and this is recommended for future versions of the review.

Sensitivity analysis

We planned the following sensitivity analyses, but could not conduct them owing to insufficient data. This should be considered for future versions of this review.

- Repeat the analysis excluding unpublished studies (if there were any).
- Repeat the analysis excluding studies with high risk of bias (e.g. randomised versus quasi-randomised). We planned to rate studies at overall high risk of bias if there was a high risk of bias for one or more key domains ([Higgins 2020a](#)).
- In the case of including one or more very large study, repeat the analysis excluding these to determine to what extent they dominated the results.
- Repeat the analysis using different statistical models (fixed-effect versus random-effects).

Reaching conclusions

We based our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We avoided making recommendations for practice and our implications for research suggest priorities for future research and outline what the remaining uncertainties are in the area.

Summary of findings and assessment of the certainty of the evidence

We planned to create separate 'Summary of findings' tables for 'rescue' and 'maintenance therapy' using cough augmentation techniques, using GRADEpro GDT software, presenting the following outcomes.

- Number of unscheduled hospital admissions for episodes of respiratory exacerbations over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' therapy.
- Duration of hospital stay (days) for 'rescue' therapy.
- PCF measured before and after intervention(s) for 'rescue' and maintenance therapy and measured over the medium term

(between three months and one year) and long term (one year and longer) for maintenance therapy.

- Any adverse events measured over the short term, medium term (three months to one year), and long term (one year or longer) ('rescue' and maintenance therapy).
- Quality of life measured by any validated measure over the medium term (between three months and one year) and long term (one year and longer) (maintenance therapy).
- Participant preference for, or satisfaction with specific cough augmentation techniques ('rescue' and maintenance therapy), measured over the short term, medium term (three months to one year) and long term (one year or longer).

However, based on the included studies, we chose to rather present separate 'Summary of findings' tables for the comparison between cough augmentation technique(s) and alternative cough augmentation technique(s) and for the comparison between cough augmentation technique(s) and standard of care, for the above outcome measures.

Two review authors (BM and AH) independently assessed the certainty of the body of evidence (studies that contributed data for the prespecified outcomes) using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias). We used methods and recommendations described in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2017a](#); [Schünemann 2017b](#)). We resolved any disagreements by discussion or by involving another review author (LC) where necessary. We considered RCTs as high-certainty evidence if the five factors above were not present to any serious degree, but could downgrade the certainty to moderate, low, or very low. We downgraded evidence once if a GRADE consideration was present to a serious degree, twice if very serious, and three times based on several GRADE concerns. We justified all decisions to downgrade or upgrade the certainty of evidence using footnotes, and made comments to aid readers' understanding of the review where necessary.

RESULTS

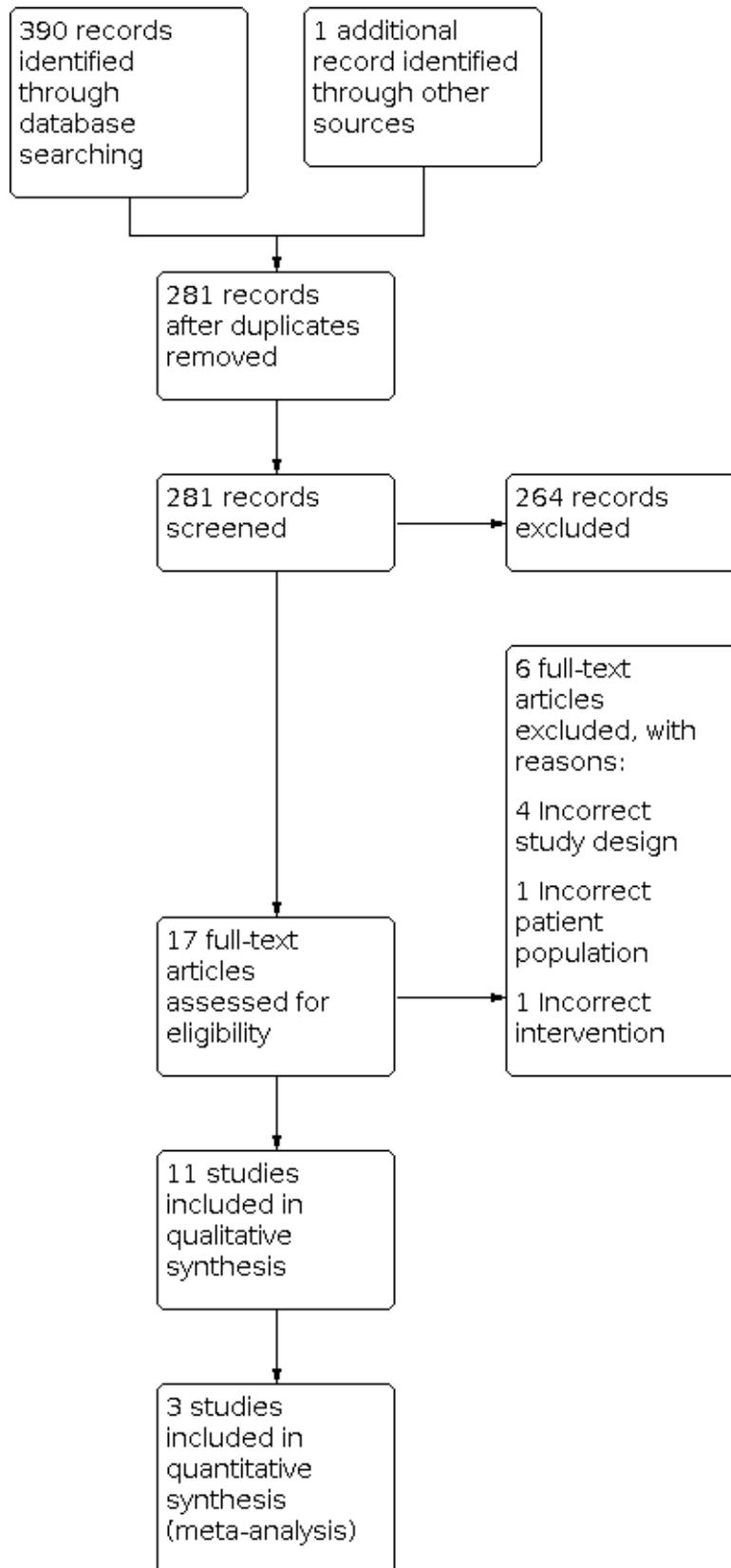
Description of studies

See [Characteristics of included studies](#), [Characteristics of excluded studies](#), and [Characteristics of ongoing studies](#) tables.

Results of the search

The literature search identified 390 papers (see [Figure 1](#) for study flow diagram): 20 from the Cochrane Neuromuscular Specialized Register, 142 from CENTRAL, 81 from MEDLINE, 55 from CINAHL, and 92 from EMBASE.

Figure 1. Study flow diagram.



From ClinicalTrials.gov, we identified 76 potentially relevant ongoing clinical trials and 64 ongoing trials from ICTRP, from which we identified five studies for possible inclusion in future reviews (NCT01518439; NCT02651805; NCT03355105; NCT04081116; PACTR201506001171421) (see [Characteristics of ongoing studies](#) table).

We identified one study through other methods, after reviewing the published study protocol ([Katz 2019](#)). After removing duplicates, we reviewed the titles and abstracts of 281 papers, and identified a further two duplicates in this process. We selected 17 studies for full-text review and excluded six of these studies, with reasons ([Bianchi 2014](#); [Kang 2000](#); [Silva 2012](#); [Toussaint 2003](#); [Toussaint 2009](#); [Winck 2004](#); see [Characteristics of excluded studies](#) table). Eleven studies met the inclusion criteria for the review ([Brito 2009](#); [Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Katz 2019](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#); [Toussaint 2016](#)).

Included studies

Ten included studies were full published articles ([Brito 2009](#); [Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#); [Toussaint 2016](#)), while one study was a congress abstract, with detailed methodology published on ClinicalTrials.gov ([Katz 2019](#)). Full details of the [Katz 2019](#) study results were not available, and attempts to contact the author were unsuccessful.

Region and setting

Three included studies were from the UK ([Chatwin 2003](#); [Chatwin 2009](#); [Sivasothy 2001](#)); three from Europe (two from France ([Del Amo Castrillo 2019](#); [Lacombe 2014](#)) and one from Belgium ([Toussaint 2016](#))); two from Canada ([Jenkins 2014](#); [Katz 2019](#)); one from Brazil ([Brito 2009](#)); one from Korea ([Kim 2016](#)); and one was from Chile ([Torres-Castro 2016](#)). Ten were short term (i.e. two days or less in duration) studies of the immediate effects of cough augmentation techniques in a hospital or clinic setting ([Brito 2009](#); [Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#); [Toussaint 2016](#)). One two-year study investigated the long-term effects of maintenance interventions performed outside the hospital setting ([Katz 2019](#)).

Study design

Two studies were prospective parallel-group RCTs ([Katz 2019](#); [Toussaint 2016](#)). [Toussaint 2016](#) was a single-centre, short-term trial of a single intervention (52 participants); while the study by [Katz 2019](#) was a long-term multicentre study conducted over two years (67 participants). [Katz 2019](#) further used a minimisation technique to allocate participants to intervention arms to ensure between-group matching. With minimisation, allocation of the next participant depends wholly or partly on the characteristics of participants already enrolled in the trial, with only the first participant being truly randomised ([Altman 2005](#)). Minimisation is considered a valid alternative to ordinary randomisation, and has the advantage of better balancing intervention groups, especially in smaller trials ([Altman 2005](#)). Sufficient data for analysis were available for [Toussaint 2016](#); however, the abstract of [Katz 2019](#) did not provide sufficient data for analysis.

Most studies were cross-over trials in which all participants received every intervention in random order, in a single session, with variable washout periods between interventions ([Brito 2009](#); [Chatwin 2003](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#)). One study was a randomised cross-over trial conducted over two days, in which eight participants were randomly assigned to receive MI-E for one treatment session and no MI-E for a second treatment session, with a reverse cross-over the following day ([Chatwin 2009](#)). Only the first part of [Jenkins 2014](#) was randomised, a second substudy involved systematically assigned interventions and, therefore, we did not include it in this review. [Torres-Castro 2016](#) and [Lacombe 2014](#) provided additional first-period data on request, which could be analysed. The remaining cross-over trials did not present separate first-period data, or make these data available, precluding meta-analysis ([Brito 2009](#); [Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Sivasothy 2001](#)).

Participants

Participants were adults and children (total 287) with a variety of NMDs ranging in age from three to 73 years. Four studies included adults only: [Lacombe 2014](#) included 18 adults aged 21 to 68 years; [Toussaint 2016](#) included 52 adults with a mean age of 25.3 (SD 5.1) years (27 participants) in the mechanical breathstacking group and 24.7 (SD 5.7) years (25 participants) in the manual stacking group; [Del Amo Castrillo 2019](#) included 20 adults aged 21 to 71 years; and [Sivasothy 2001](#) included four adults with respiratory muscle weakness and scoliosis secondary to NMD, aged 44 to 66 years. [Katz 2019](#) included 67 children and adolescents aged six to 16 years (median 11.4 years) and [Torres-Castro 2016](#) included 14 children and adolescents aged from nine to 18 years. The remaining studies had mixed child, adolescent, and adult populations: [Chatwin 2003](#) included eight children and adolescents aged 10 to 17 years, and 14 adults aged 18 to 56 years. [Chatwin 2009](#) included two children aged four and 12 years, and six adults aged 21 to 44 years. [Jenkins 2014](#) included 13 children and adolescents with NMDs aged four to 18 years, and one adult aged 19 years. [Kim 2016](#) did not report separate paediatric and adult data, but enrolled 40 participants with a mean age of 20.9 (SD 7.2) years. Similarly, [Brito 2009](#) included 28 participants over 10 years old (mean 20, SD 4 years), and did not report separate data for children, adolescents, and adults. Reports provided insufficient information to enable subgroup analysis for different age groups or comorbid conditions.

Conditions

Duchenne muscular dystrophy (DMD) was the most commonly reported condition (207 participants), with three studies only including participants with DMD ([Brito 2009](#); [Katz 2019](#); [Toussaint 2016](#)). The other studies included a range of NMDs including DMD ([Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#)); SMA (39 participants) ([Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#)); poliomyelitis or postpolio syndrome (six participants) ([Chatwin 2003](#); [Del Amo Castrillo 2019](#); [Sivasothy 2001](#)); congenital muscular dystrophy (CMD) (four participants) ([Chatwin 2003](#); [Lacombe 2014](#)); congenital myopathy (five participants) ([Chatwin 2009](#); [Kim 2016](#); [Torres-Castro 2016](#)); Becker muscular dystrophy (BMD) (three participants) ([Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Lacombe 2014](#)); gamma-sarcoglycanopathy (four participants) ([Del Amo Castrillo 2019](#));

Lacombe 2014); acid maltase deficiency (three participants) (Del Amo Castrillo 2019; Lacombe 2014), and other NMDs, including Ulrich Syndrome (two participants) and facio-scapulo-humeral muscular dystrophy, vacuolar myopathy, congenital fibre type disproportion (myopathy), limb girdle muscular dystrophy, Charcot-Marie-Tooth Type 1 disease, progressive muscular dystrophy, and myasthenia gravis (one participant each) (Del Amo Castrillo 2019; Jenkins 2014; Kim 2016; Lacombe 2014).

Two studies included comparative participant groups without NMD (Chatwin 2003; Sivasothy 2001), healthy controls (Chatwin 2003; Sivasothy 2001), or controls with chronic obstructive pulmonary disease (COPD) (Sivasothy 2001), which were not eligible for inclusion in this review. Therefore, we only included data for the groups of participants with NMD. Jenkins 2014 also included participants with other central nervous system (CNS) disorders (including cerebral palsy (two participants), and seizure disorder, spinal cord injury, Rett syndrome, encephalomalacia, hypoxic brain injury, Batten disease, and Cri-du-Chat syndrome (one participant each)), but did not provide separate data for participants with NMDs versus CNS disorders. Similarly, Torres-Castro 2016 included one participant with spinal cord injury, but it was not possible to analyse participants with NMD separately. Sivasothy 2001 included seven of eight participants in a non-scoliotic participant group with ALS; therefore, we did not include this group's data in the review. We only included and described data from the participant group with eligible NMD and scoliosis (four participants) in this review (Sivasothy 2001).

One study investigated participants admitted to hospital with acute respiratory tract infections, thereby receiving 'rescue' therapy (Chatwin 2009); while one other study investigated the effects of a two-year course of cough augmentation therapy as maintenance therapy (Katz 2019). Jenkins 2014 included both inpatients and outpatients but did not distinguish between results obtained with rescue and maintenance therapy. This study did not report participants' respiratory infection status, although participants requiring oxygen therapy were excluded (Jenkins 2014). Eight studies specifically investigated stable participants without intercurrent infection (Brito 2009; Chatwin 2003; Del Amo Castrillo 2019; Kim 2016; Lacombe 2014; Sivasothy 2001; Torres-Castro 2016; Toussaint 2016).

There were insufficient data to allow for subgroup analysis among different conditions, participant ages, and therapy circumstances ('rescue' or maintenance therapy).

Interventions

Studies compared cough augmentation techniques to alternative and combination techniques (Brito 2009; Chatwin 2003; Chatwin 2009; Del Amo Castrillo 2019; Kim 2016; Lacombe 2014; Sivasothy 2001; Torres-Castro 2016; Toussaint 2016); standard or conventional management (Katz 2019); spontaneous unassisted cough (Kim 2016); or sham interventions (Jenkins 2014). Ten studies reported a change in outcome measurements from baseline or preintervention unassisted cough to intervention-assisted cough, but unassisted cough in these studies was not a randomly assigned intervention (Brito 2009; Chatwin 2003; Chatwin 2009; Del Amo Castrillo 2019; Jenkins 2014; Katz 2019; Lacombe 2014; Sivasothy 2001; Torres-Castro 2016; Toussaint 2016). A summary of interventions and main results is presented in Table 2; Table 3; and

Table 4, and descriptions of the interventions are fully described in the Characteristics of included studies table.

Cough augmentation techniques included mechanical insufflation (Chatwin 2003; Del Amo Castrillo 2019; Sivasothy 2001); mechanical exsufflation (Chatwin 2003); MI-E (Chatwin 2003; Kim 2016; Lacombe 2014); MAC (Brito 2009; Chatwin 2003; Chatwin 2009; Sivasothy 2001); manual or ventilator-assisted breathstacking, or both (Brito 2009; Del Amo Castrillo 2019; Jenkins 2014; Katz 2019; Torres-Castro 2016; Toussaint 2016); GPB (Torres-Castro 2016); and breathstacking plus MAC (Brito 2009; Kim 2016); MAC plus MI-E (Chatwin 2009; Kim 2016; Lacombe 2014); and mechanical insufflation plus MAC (Del Amo Castrillo 2019; Lacombe 2014; Sivasothy 2001).

One RCT conducted over two years compared conventional treatment (which could have included chest physiotherapy or peripheral airway clearance techniques, or both; nutritional support; antibiotics; non-invasive ventilation (NIV) and systemic steroids) to conventional treatment plus twice daily lung volume recruitment/breathstacking, using a self-inflating resuscitation bag with a one-way valve (Katz 2019). Measures of adherence to the intervention were not reported (Katz 2019). One randomised cross-over trial conducted over two days compared standardised airway clearance therapy (with MAC and ventilator-assisted active cycle of breathing technique) with and without MI-E (Chatwin 2009). Ventilator tidal volumes and pressures applied for the thoracic expansion component of the active cycle of breathing technique and preinsufflation part of the cough were not reported (Chatwin 2009). Toussaint 2016 compared mechanical breathstacking using a home mechanical ventilator to manual breathstacking with a resuscitation bag. Del Amo Castrillo 2019 compared standard, mechanical breathstacking using a home ventilator to augmented mechanical insufflation using the ventilator's volumetric cough mode, which provides a programmable intermittent deep breath set at a percentage of the baseline tidal volume. Torres-Castro 2016 compared manual breathstacking (using a resuscitation bag and one-way valve) to GPB. Brito 2009 compared MAC to manual breathstacking (using a resuscitation bag) and manual breathstacking plus MAC; Chatwin 2003 compared baseline maximal unassisted cough to 1. standard "physiotherapy assisted cough;" 2. cough after supported inspiration by a non-invasive positive pressure ventilator (mechanical insufflation); 3. exsufflation-assisted cough with negative pressure initiated manually at end-inspiration; 4. insufflation-assisted cough using a mechanical in-exsufflator; and 5. mechanical exsufflation-assisted cough with negative pressure delivered immediately preceding the cough effort. Chatwin 2003 did not clearly describe the method of performing "standard physiotherapy-assisted cough," but we presumed it to include or be equivalent to MAC. Jenkins 2014 compared involuntary manual breathstacking using a self-inflating resuscitator bag and one-way valve, to sham breathstacking; Kim 2016 compared unassisted cough, MAC performed after manual breathstacking to maximal inspiratory capacity, MI-E and MI-E plus MAC; Lacombe 2014 compared mechanical insufflation (using a positive pressure ventilator) plus MAC, MI-E plus MAC and MI-E alone; and Sivasothy 2001 compared MAC alone to mechanical insufflation (delivered using an MI-E device) and to mechanical insufflation plus MAC.

Studies applied MAC using pressure to the abdomen (Chatwin 2009; Jenkins 2014; Kim 2016), chest (Brito 2009), or both

abdomen and chest (Sivasothy 2001); while Lacombe 2014 used abdominal, thoracic, or thoraco-abdominal compression according to participant comfort. Chatwin 2003 did not describe the therapist's hand position for "physiotherapy assisted cough," but, in the study's literature review, MAC is mentioned as forming part of standard physiotherapy treatment and we assumed that the techniques were equivalent (Chatwin 2003).

Studies applied insufflation-assisted cough mechanically using a non-invasive positive pressure ventilator (Chatwin 2003; Del Amo Castrillo 2019; Lacombe 2014) or MI-E devices (Sivasothy 2001). Ventilators used for insufflation were a bilevel positive airway pressure ventilator (BiPAP: Respironics Inc. Murraysville, North Carolina, USA or Breas Medical Sweden), with insufflation pressures titrated to participant comfort (Chatwin 2003); a ventilator equipped with volumetric cough mode (Astral 150, Resmed, Saint-Priest, France) (Del Amo Castrillo 2019); and an Alpha 200C ventilator (Air Liquide, France), set to provide IPPB with a low inspiratory trigger and gradually increased inspiratory pressure to the highest tolerated value, to a maximum of 40 cmH₂O, with inspiratory flow set according to patient comfort (Lacombe 2014). Sivasothy 2001 used a "CoughAssist" MI-E device (JH Emersen, Cambridge, Massachusetts, USA) to provide insufflation, in which two cycles of both insufflation and exsufflation (set at +20 cmH₂O/-20 cmH₂O) were followed by a third insufflation and maximal spontaneous cough, which was measured without assistance or exsufflation support (Sivasothy 2001).

Exsufflation-assisted cough was applied using a "CoughAssist" MI-E device (JH Emersen, Cambridge, Massachusetts, USA) with the negative pressure applied manually at the end of inspiration (Chatwin 2003). Exsufflation pressures were titrated for participant comfort and reported to have a mean of -15 (SD 9) cmH₂O (Chatwin 2003).

Five studies applied breathstacking using a manual resuscitation bag and face mask interface (Brito 2009; Jenkins 2014; Katz 2019; Torres-Castro 2016; Toussaint 2016). Brito 2009, Jenkins 2014, Katz 2019, and Torres-Castro 2016 specified use of a unidirectional valve during manual breathstacking. Brito 2009 and Jenkins 2014 applied three consecutive stacking breaths without exhalation before the maximum exhalation or cough, while Katz 2019 and Torres-Castro 2016 did not specify the required number of stacked breaths to reach maximal insufflation. Toussaint 2016 individualised the number of successive inspirations for each participant, but participants were typically instructed to take "two to three successive insufflations" without breathing out in-between. Jenkins 2014 applied sham breathstacking using the same technique as involuntary resuscitation bag breathstacking, but in the absence of a directional valve. Toussaint 2016 specified using a 2 L resuscitator bag (Resutator 2000, Dräger, Germany), while other studies did not specify the size of the resuscitator bag used.

Toussaint 2016 and Del Amo Castrillo 2019 applied mechanical breathstacking using volume-cycled home mechanical ventilators and nasal mask (Toussaint 2016) or face mask (Del Amo Castrillo 2019) interfaces. Del Amo Castrillo 2019 specified that consecutive inspiratory-hold insufflations were performed until participants felt their lungs were fully expanded or until the insufflation pressure plateau was 50 cmH₂O.

Two studies delivered mechanical insufflation/exsufflation-assisted cough using the CoughAssist device manufactured by JH Emerson Co (Cambridge, Massachusetts, USA) (Chatwin 2003; Lacombe 2014), and two studies used the Philips Respironics (Murraysville, Pennsylvania, USA) (Chatwin 2009; Kim 2016). All four studies reporting MI-E used a full-face mask interface (Chatwin 2003; Chatwin 2009; Kim 2016; Lacombe 2014). Insufflation pressures ranged from +15 (SD 3) cmH₂O (Chatwin 2003, titrated for patient comfort); through +20 cmH₂O (range 15 cmH₂O to 35 cmH₂O) (Chatwin 2009, titrated for patient comfort); up to +40 cm H₂O (Kim 2016; Lacombe 2014). Exsufflation pressures ranged from -40 cmH₂O (Kim 2016; Lacombe 2014); -20 cmH₂O (range -20 cmH₂O to -40 cmH₂O) (Chatwin 2009); to -15 (SD 9) cmH₂O (Chatwin 2003). Kim 2016 set the MI-E device to deliver \pm 40 cmH₂O pressures as standard, while Lacombe 2014 reported gradually increasing or decreasing insufflation/exsufflation pressures to the highest or lowest tolerated values. All studies used the MI-E device in manual mode (Chatwin 2003; Chatwin 2009; Kim 2016; Lacombe 2014). Chatwin 2003 and Lacombe 2014 did not describe insufflation/exsufflation and pause times, while Chatwin 2009 used an insufflation time of two seconds to four seconds and exsufflation time of four seconds to five seconds and Kim 2016 used an insufflation time of three seconds and exsufflation time of two seconds. Only Kim 2016 reported a three-second pause between cycles. Lacombe 2014 set insufflation flow (and therefore insufflation time) according to participant comfort. Chatwin 2003 and Lacombe 2014 did not describe the number of MI-E cycles delivered, while Kim 2016 applied five cycles of insufflation and exsufflation.

Torres-Castro 2016 included GPB, in which participants were instructed to perform successive air "swallowing" manoeuvres, until they achieved maximum volume.

Outcomes

Ten studies reported only short-term outcome measures of interventions, mostly in the context of single treatment sessions (Brito 2009; Chatwin 2003; Chatwin 2009; Del Amo Castrillo 2019; Jenkins 2014; Kim 2016; Lacombe 2014; Sivasothy 2001; Torres-Castro 2016; Toussaint 2016). Only one studies planned to report on this review's primary outcome measures (number of unscheduled hospital admissions and duration of hospital stay) in 67 participants; however, the results of this outcome measure were not reported in the published abstract and, therefore, could not be included in qualitative or quantitative analysis (Katz 2019). Although some studies reported our secondary short-term outcome measures of PCF and gaseous exchange, measured before and after intervention, we note that only one study measured them in the context of 'rescue' therapy, in eight participants (Chatwin 2009).

Objective outcomes measured in the included studies were: PCF (265 participants) (Brito 2009; Chatwin 2003; Del Amo Castrillo 2019; Katz 2019; Kim 2016; Lacombe 2014; Sivasothy 2001; Torres-Castro 2016; Toussaint 2016); FVC and time to reach a 10% decline in FVC (67 participants) (Katz 2019); physiological variables of heart rate (eight participants) (Chatwin 2009); transcutaneous oxygen saturation (31 participants) (Chatwin 2009; Jenkins 2014); transcutaneous carbon dioxide tension (PtcCO₂) (eight participants) (Chatwin 2009); respiratory rate (23 participants) (Jenkins 2014); cough expiratory volume and

peak value time (four participants) (Sivasothy 2001); treatment time (eight participants) (Chatwin 2009); oesophageal or gastric pressures (four participants) (Sivasothy 2001); tidal volume (23 participants) (Jenkins 2014); inspiratory or insufflation capacity (171 participants) (Del Amo Castrillo 2019; Katz 2019; Lacombe 2014; Torres-Castro 2016; Toussaint 2016); effective cough time (time with PCF of more than 3 L/second) (18 participants) (Lacombe 2014); maximal expiratory pressure (MEP) (119 participants) (Katz 2019; Toussaint 2016); maximal inspiratory pressure (MIP) (67 participants) (Katz 2019); and the number of insufflations to reach MIC (52 participants) (Toussaint 2016).

Subjective outcome measures were: scores on a visual analogue scale (VAS) for participant comfort (46 participants) (Chatwin 2003; Chatwin 2009; Del Amo Castrillo 2019; Lacombe 2014); distress (22 participants) (Chatwin 2003); breathlessness (eight participants) (Chatwin 2009); fatigue (eight participants) (Chatwin 2009); mood (eight participants) (Chatwin 2009); secretion production (eight participants) (Chatwin 2009); and cough effectiveness or strength (42 participants) (Chatwin 2003; Del Amo Castrillo 2019; Lacombe 2014). Chatwin 2009 (eight participants) measured auscultation score. Sivasothy 2001 asked four participants to report whether the intervention had aided, impaired, or had no effect on their cough. None of the included studies included standardised, valid measures of function, or participant preference.

Katz 2019 planned to measure health-related quality of life, using the Pediatric Quality of Life Inventory (PedQL) Score in 67 participants; however, this outcome was not reported in the published abstract.

None of the studies listed adverse events as a primary or secondary outcome. Chatwin 2003 (22 participants) and Sivasothy 2001 (four participants) reported there had been no adverse events. Kim 2016 (40 participants) reported that the interventions were "well tolerated." Chatwin 2009 (eight participants) reported fatigue as an adverse effect of MI-E.

It was unclear whether serious adverse events such as pneumothorax were systematically investigated in any of the studies.

Potential conflicts of interest

Chatwin 2009 disclosed a relationship with a healthcare company that manufactured ventilation equipment, although the nature of the relationship and the relevance to this study was unclear. Del Amo Castrillo 2019 disclosed a relationship with ResMed France, the company who manufacture the ventilator device with volumetric cough mode used in their study. The exact nature of the relationship was unclear. Katz 2019 declared relationships with a pharmaceutical company, but it was unclear whether these relationships would have constituted a source of bias. Jenkins 2014 and Brito 2009 declared their funding source, which, in both studies, was unlikely to constitute a conflict of interest. Chatwin 2003, Lacombe 2014, Sivasothy 2001, Torres-Castro 2016, and Toussaint 2016 did not declare funding sources or other potential conflicts of interest. Kim 2016 declared no financial conflicts of interests, but other interests were not declared.

Excluded studies

We excluded six studies (see [Characteristics of excluded studies](#) table): four due to incorrect study design (Bianchi 2014; Kang 2000; Toussaint 2009; Winck 2004); one because of the incorrect population (Silva 2012), and one did not describe a cough augmentation technique and we excluded it based on studying the incorrect intervention (Toussaint 2003).

Kang 2000 investigated the relationships between VC, MIC, and both unassisted and assisted PCF (using manual insufflation versus unassisted or spontaneous PCF in two groups of participants with MIC greater than or equal to their VC). The study was not designed to determine effectiveness of the cough augmentation interventions, and neither the allocation nor order of intervention was randomised.

Toussaint 2009 conducted a prospective cross-sectional observational study investigating three cough augmentation techniques (MAC, breathstacking, and breathstacking with MAC) in 179 clinically stable participants with a range of NMDs. Breathstacking as well as breathstacking plus MAC was only conducted in a subgroup of 60 participants receiving NIV.

Winck 2004 conducted a prospective observational study to evaluate the tolerance of three different MI-E pressures (+15 cmH₂O to -15 cmH₂O, +30 cmH₂O to -30 cm H₂O, and +40 cmH₂O to -40 cm H₂O) in a heterogeneous sample of people with NMD (seven participants), ALS (13 participants), and COPD (nine participants). Data for each participant group were provided separately. The MI-E pressures were increased systematically for each participant, without randomisation of order.

Silva 2012 studied the effect of MAC alone or in association with increased positive end-expiratory pressure (PEEP) and inspiratory time on peak expiratory flow and respiratory mechanics in mechanically ventilated participants diagnosed with head trauma, stroke, congestive heart failure, and ventilator-associated pneumonia. The study did not include participants with NMD.

Toussaint 2003 conducted a randomised cross-over study comparing mucous clearance techniques with and without intrapulmonary percussive ventilation (IPV), in eight participants with DMD (five with mucous hypersecretion). IPV is considered a peripheral airway clearance technique, not a proximal clearance (cough augmentation) technique, and we determined the intervention ineligible for this review.

Bianchi 2014 conducted a prospective observational study on 18 participants (aged 21.1 (SD 5.4) years) with muscular dystrophy, comparing unassisted PCF to augmented PCF using various interventions, including GPB; a self-induced thoracic or abdominal thrust (by independently manoeuvring a wheelchair into a table); assistant-delivered MAC; breathstacking; and combination techniques. There was no randomisation or allocation to different interventions or order of interventions, and this study was ineligible for inclusion in this review.

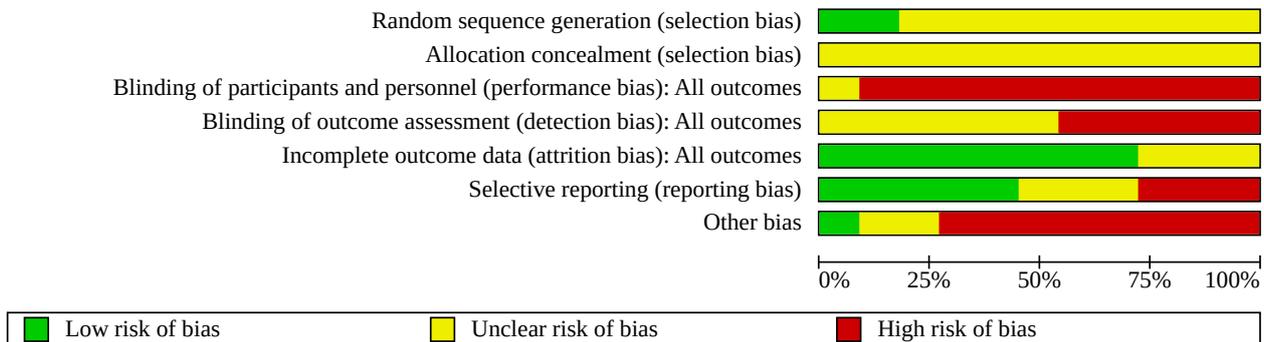
Risk of bias in included studies

See [Figure 2](#), [Figure 3](#), and the [Characteristics of included studies](#) table.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Brito 2009	?	?	-	-	+	-	-
Chatwin 2003	?	?	-	?	+	?	-
Chatwin 2009	?	?	-	?	?	-	-
Del Amo Castrillo 2019	?	?	-	-	+	+	-
Jenkins 2014	?	?	?	?	+	+	-
Katz 2019	?	?	-	?	?	-	?
Kim 2016	?	?	-	-	+	+	-
Lacombe 2014	?	?	-	?	+	?	-
Sivasothy 2001	?	?	-	?	+	?	-
Torres-Castro 2016	+	?	-	-	?	+	?
Toussaint 2016	+	?	-	-	+	+	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Eight studies provided no details about the method of randomisation (Brito 2009; Chatwin 2003; Chatwin 2009; Del Amo Castrillo 2019; Jenkins 2014; Kim 2016; Lacombe 2014; Sivasothy 2001). Katz 2019 used a minimisation technique, but provided no details of the minimisation methodology. Therefore, we judged these studies at unclear risk of bias for the generation of randomisation sequence. Toussaint 2016 conducted an RCT that randomised participants to receive one of the two interventions by means of a coin toss. Torres-Castro 2016 described using freely available software to generate random number lists. We judged these two studies at low risk of selection bias. None of the included studies described allocation concealment, leading to a judgement of unclear risk of selection bias for all included studies.

Blinding

Considering the nature of cough augmentation interventions, it is highly unlikely that participant or clinician blinding would have been possible, leading to a high risk of performance bias in 10 studies (Brito 2009; Chatwin 2003; Chatwin 2009; Del Amo Castrillo 2019; Katz 2019; Kim 2016; Lacombe 2014; Sivasothy 2001; Torres-Castro 2016; Toussaint 2016).

Jenkins 2014 used a sham intervention as a control, but it was unclear if blinding was successfully achieved. Both involuntary breathstacking and sham interventions were performed in the same way except for the presence or absence of a valve. It was unclear if the masks looked identical, with a sham valve, or whether the valve was simply not added to the mask circuit for the sham intervention. Therefore, the risk of performance bias for participants was unclear. Considering therapists applying the intervention would likely have known whether a one-way valve was applied or not, we judged the risk of personnel (therapist) performance bias as high. Overall, therefore, we judged the risk of performance bias in Jenkins 2014 as unclear.

Owing to insufficient methodological information, it was unclear whether six studies blinded outcome assessors, which we judged at unclear risk of detection bias (Chatwin 2003; Chatwin 2009; Jenkins 2014; Katz 2019; Lacombe 2014; Sivasothy 2001). Five studies measured outcomes while investigators were performing the study interventions, and, therefore, outcome assessment could not have been blinded, leading to a high risk of detection bias

(Brito 2009; Del Amo Castrillo 2019; Kim 2016; Torres-Castro 2016; Toussaint 2016).

Incomplete outcome data

All participants completed the interventions, or were appropriately accounted for, in eight studies, leading to a judgement of low risk of attrition bias (Brito 2009; Chatwin 2003; Del Amo Castrillo 2019; Jenkins 2014; Kim 2016; Lacombe 2014; Sivasothy 2001; Toussaint 2016). In two studies, it was unclear whether all included participants completed all outcome measurements, as this was not explicitly stated in the text (Chatwin 2009; Katz 2019). In one study, three participants were excluded after screening, but the trial authors did not provide clear reasons for exclusion (Torres-Castro 2016). We judged the risk of attrition bias for these three studies as unclear (Chatwin 2009; Katz 2019; Torres-Castro 2016).

Selective reporting

We judged three studies at high risk of reporting bias (Brito 2009; Chatwin 2009; Katz 2019). Brito 2009 did not present all stated baseline measurements (SpO₂; expired CO₂) but fully reported the primary outcome of PCF. Chatwin 2009 presented no data for the primary physiological outcome measures of peripheral capillary oxygen saturation (SpO₂), heart rate, and PtcCO₂. In addition, the study only presented VAS scores for comfort, breathlessness, and mood as graphs, and we could not extract the data precisely. Katz 2019 presented selected outcome measures in the published abstract, while the published protocol presented several primary and secondary outcome measures that were not reported in the abstract. Efforts to obtain missing data for these studies were unsuccessful.

We judged three studies at unclear risk of reporting bias (Chatwin 2003; Lacombe 2014; Sivasothy 2001). Chatwin 2003 did not report separate VAS scores of patient comfort, distress, and strength of cough. Lacombe 2014 presented several outcome measures graphically, with specific values not reported for PCF, inspiratory capacity, and effective cough time. Sivasothy 2001 did not clearly describe the study's primary and secondary outcome measures and did not mention a trial registration number, so the review authors could not confirm the outcome measures by checking the predescribed protocol. The report did not present gastric and oesophageal pressures; however, the trial authors acknowledged this and ascribed it to a measurement problem owing to collapse of

balloons in the control groups. The trial authors did not fully report the subjective outcome measure of cough effectiveness, but simply stated that participants did not report any benefit of any assisted cough interventions. [Sivasothy 2001](#) fully reported other measured outcomes.

The other five studies reported all the prespecified primary and secondary outcome measures and we judged these studies at low risk of reporting bias ([Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Torres-Castro 2016](#); [Toussaint 2016](#)).

Other potential sources of bias

We judged one study at low risk of other biases ([Toussaint 2016](#)), and two studies at unclear risk ([Katz 2019](#); [Torres-Castro 2016](#)). [Torres-Castro 2016](#) did not explicitly identify primary and secondary outcomes and [Katz 2019](#) provided insufficient information to judge the risk of other biases. We judged eight studies at high risk of other bias, considering they were all short-term cross-over trials with no analysis of carry-over effect, and no separate period reporting in the primary publication ([Brito 2009](#); [Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#)). A short-term cross-over study design may not be the most appropriate for studies on conditions such as NMD, which require long-term follow-up. Also, none of these studies considered the potential confounder of learning effect on outcome measurement, and this may have influenced the results. 'Learning effect' refers to participants improving their ability to perform or co-ordinate the outcome assessment (e.g. PCF technique) through practice and learning, rather than showing an objective improvement in the actual outcome being measured. [Lacombe 2014](#) and [Torres-Castro 2016](#) provided separate baseline data for group allocation; for the other cross-over studies it was unclear whether groups were well balanced at baseline, or whether the groups were treated the same except for the intervention ([Brito 2009](#); [Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#)). Other potential confounders in studies included: presence of comorbid conditions ([Brito 2009](#); [Del Amo Castrillo 2019](#); [Katz 2019](#)); oral/bulbar control ([Chatwin 2003](#); [Jenkins 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#)); heterogeneity of included conditions or ages, or both ([Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Lacombe 2014](#); [Torres-Castro 2016](#)); and concomitant use of NIV ([Katz 2019](#); [Kim 2016](#)).

Effects of interventions

See: [Summary of findings 1](#) Cough augmentation therapy compared with an alternative cough augmentation technique or combination of techniques for people with neuromuscular diseases; [Summary of findings 2](#) Cough augmentation therapy compared with standard care for people with neuromuscular diseases

One study was a short-term RCT ([Toussaint 2016](#)), the main results of which are presented in [Analysis 1.1](#) and [Analysis 1.2](#). [Katz 2019](#) conducted a long-term RCT; however, the published abstract provided insufficient data. Attempts to contact the author were unsuccessful, and we could not perform any additional analysis.

Eight studies applied every intervention to every included participant in a single session, in random order ([Brito 2009](#); [Chatwin 2003](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#)). Therefore, each

participant received several interventions. None of these published reports presented individual responses to each intervention, which could have allowed secondary analysis. However, [Torres-Castro 2016](#) and [Lacombe 2014](#) provided additional individual data on request, allowing separate first-period analysis of one our secondary outcome measures, PCF ([Analysis 2.1](#); [Analysis 3.1](#); [Analysis 4.1](#); [Analysis 5.1](#)). Meta-analysis and pooling of the results of the remaining six studies was not possible, owing to the repeat counting that occurred, which would cause unit-of-analysis errors from the unaddressed correlation between the estimated intervention effects of multiple comparisons ([Higgins 2020b](#)). The two-day cross-over study by [Chatwin 2009](#) also did not report data separately for the two periods of the study, precluding inclusion in a meta-analysis. All the reported quantitative results of the included studies are presented in [Table 2](#); [Table 3](#); and [Table 4](#). The main results for studies comparing cough augmentation technique(s) with alternate cough augmentation technique(s) are summarised in [Summary of findings 1](#) and results for studies comparing cough augmentation technique(s) with standard of care are presented in [Summary of findings 2](#).

Cough augmentation therapy compared with alternative cough augmentation therapy

Ten studies compared cough augmentation therapies to alternative individual or combination cough augmentation therapies ([Brito 2009](#); [Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#); [Toussaint 2016](#)). See [Summary of findings 1](#).

Primary outcomes

1. Number of unscheduled hospital admissions for episodes of acute respiratory exacerbations over one year, for 'maintenance' therapy

No studies reported number of hospital admissions for episodes of acute respiratory exacerbations over one year, for 'maintenance use.'

2. Duration of hospital stay (days) for 'rescue' therapy

No studies reported duration of hospital stay (days) for 'rescue' use.

Secondary outcomes

1. PCF measured before and after intervention for 'rescue' therapy and measured over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' therapy

PCF was the most common outcome, measured in eight studies with 198 participants ([Brito 2009](#); [Chatwin 2003](#); [Del Amo Castrillo 2019](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#); [Toussaint 2016](#)). These studies reported the immediate effect on PCF of the cough augmentation techniques, whether for acute or maintenance use ([Summary of findings 1](#); [Table 1](#)). We considered the certainty of evidence for this outcome very low, downgrading twice for very serious study limitations (risk of bias) and once for imprecision (all studies had a small sample size, wide CIs, or both).

Manual versus mechanical breathstacking

[Toussaint 2016](#) compared PCF (the primary outcome) with mechanical breathstacking compared to manual breathstacking. The mean (\pm SD) PCF increased in the mechanical breathstacking group from 132 (SD 55) L/minute to 199 (SD 48 L/min) (within-group $P = 0.001$) compared to the manual breathstacking group, in which PCF increased from 125 (SD 52) L/min to 186 (SD 50 L/

min) (within-group $P < 0.001$). This study reported no evidence of a difference between the two intervention groups in the PCF change (between-group MD 6.00 L/minute, 95% CI -33.43 to 45.43; $P = 0.3$; 52 participants; [Analysis 1.1](#)). The conclusion of lack of difference between resuscitator bag and ventilator breathstacking on PCF was based on a low-certainty evidence, double downgraded as results were from a single study ([Toussaint 2016](#)), with substantial risk of bias due to lack of blinding of personnel, participants, or assessors; and unclear allocation concealment.

Glossopharyngeal breathing versus manual breathstacking

[Torres-Castro 2016](#) provided data for the first cross-over period, which could be analysed. This study compared PCF at baseline and after either GPB or breathstacking using a self-inflating resuscitator bag, in adults with DMD. In the first period of cross-over, mean PCF in the manual breathstacking group increased from 162.86 (SD 77.4) L/min to 235.71 (SD 125.01) L/min (MD 72.86 (SD 61.84) L/minute, 95% CI 15.67 to 130.05; within-group $P = 0.02$); while PCF in the GPB group increased from 167.14 (SD 42.71) L/min to 199.29 (SD 52.95) L/min (MD 32.14 (SD 26.44) L/min, 95% CI 7.69 to 56.59; within-group $P = 0.02$). There was no evidence of a difference in the change of PCF between groups (between-group MD -40.72, 95% CI -90.54 to 9.10; $P = 0.14$; 14 participants; [Analysis 2.1](#)). The conclusion that GPB and manual breathstacking have a similar effect on PCF was based very low-certainty evidence, triple downgraded based on data extracted from a single randomised cross-over study design ([Torres-Castro 2016](#)), with unclear allocation concealment, very small sample size, imprecision of results (wide CIs), and substantial risk of performance and detection bias.

MI-E versus mechanical insufflation plus MAC

[Lacombe 2014](#), in adults with a range of NMD, provided separate allocation data for the first period of cross-over, which could be analysed. The first period of cross-over reported increases from baseline with both MI-E and mechanical insufflation plus MAC. Mean PCF increased from 157.2 (SD 64.2) L/min (unassisted cough) to 210.6 (SD 52.8) L/min with MI-E alone (MD 53.4 (SD 51.0) L/min) and from 100.8 (SD 69) L/min to 225 (SD 83.4) L/min with mechanical insufflation plus MAC (MD 124.8 (SD 38.4) L/min). Mechanical insufflation plus MAC produced a greater change in PCF compared to MI-E alone (between-group MD 71.40 L/minute, 95% CI 18.08 to 124.72; $P = 0.009$; 11 participants; [Analysis 3.1](#)).

MI-E versus MI-E plus MAC

[Lacombe 2014](#) compared baseline unassisted PCF to PCF produced with MI-E and MI-E plus MAC. The study reported increases from baseline with both interventions. In the first period of cross-over, mean PCF increased from 157.2 (SD 64.2) L/min (unassisted cough) to 210.6 (SD 52.8) L/min with MI-E alone (MD 53.4 (SD 51.0) L/min) and from 104.4 (SD 41.4) L/min to 210.6 (SD 50.4) L/min with MI-E plus MAC (MD 106.2 (SD 50.4) L/min). There was a slightly greater increase in PCF with MI-E plus MAC compared to MI-E alone (between-group MD 52.80, 95% CI -0.32 to 105.92; $P = 0.05$; 14 participants; [Analysis 4.1](#)).

[Kim 2016](#) reported increased PCF with both MI-E and MI-E plus MAC compared to unassisted cough, in children and adolescents with DMD. The PCF generated with MI-E plus MAC was greater than with MI-E alone. Separate data for the two periods of cross-over were not available for analysis.

MI-E plus MAC versus mechanical insufflation plus MAC

In the first period of cross-over RCT, [Lacombe 2014](#) reported that mean PCF increased from 101 (SD 69) L/min (baseline unassisted cough) to 225 (SD 83) L/min with mechanical insufflation plus MAC (MD 124 (SD 38.4) L/min); and from 104 (SD 41) L/min to 211 (SD 50) L/min with MI-E plus MAC (MD 106 (SD 50.4) L/min). There was no evidence of a difference in the change in PCF from baseline between the MI-E plus MAC and mechanical insufflation plus MAC (between-group MD -18.60, 95% CI -34.46 to 71.66; $P = 0.49$; 11 participants; [Analysis 5.1](#)).

MAC versus mechanical insufflation

[Sivasothy 2001](#) reported no evidence of a change from baseline PCF measurement with MAC or mechanical insufflation in four adults with NMD and scoliosis, and no evidence of between-group differences. The very small sample size eligible for inclusion in this review limited the interpretation of these results. Separate data for the two periods of cross-over were not available for analytical purposes.

[Chatwin 2003](#) reported no evidence of a difference in PCF between "physiotherapy-assisted cough" (MAC) and mechanical insufflation-assisted cough using a non-invasive ventilator device in 22 participants. Moreover, there was no evidence of a difference between PCF with unassisted cough and either MAC or mechanical insufflation alone. Separate data for the two periods of cross-over were not available for analytical purposes.

MAC versus mechanical insufflation plus MAC

[Sivasothy 2001](#) reported no evidence of a change from baseline PCF measurement with MAC or MAC plus mechanical insufflation, in four adults with NMD and scoliosis. There was no evidence of a difference in PCF change between interventions. The very small sample size eligible for inclusion in this review limited the interpretation of these results. Separate data for the two periods of cross-over were not available for analytical purposes.

MI-E versus MAC

In 22 adults and children with NMD presenting with severe respiratory muscle weakness (MIP 25 (SD 16) cmH₂O; MEP 26 (SD 22) cmH₂O), [Chatwin 2003](#) reported that MI-E assisted cough produced a higher PCF than MAC, while only MI-E increased PCF significantly above baseline unassisted cough. Separate data for the two periods of cross-over were not available for analytical purposes.

MI-E versus mechanical exsufflation-assisted cough

In 22 adults and children with NMD and severe respiratory muscle weakness, [Chatwin 2003](#) reported that MI-E-assisted cough produced a higher PCF than exsufflation-assisted cough, while both interventions produced a higher PCF than unassisted cough. Separate data for the two periods of cross-over were not available for analytical purposes.

MI-E versus mechanical insufflation

[Chatwin 2003](#), in 22 participants, reported that MI-E-assisted cough produced a higher PCF than mechanical insufflation-assisted cough, while only MI-E increased PCF significantly above baseline unassisted cough. Separate data for the two periods of cross-over were not available for analytical purposes.

MI-E versus manual breathstacking plus MAC

Kim 2016 reported increased PCF with MAC plus breathstacking and MI-E, compared to unassisted cough, in 40 children and adolescents with DMD. The PCF generated with MI-E was significantly higher than with MAC plus breathstacking. Separate data for the two periods of cross-over were not available for analytical purposes.

MI-E plus MAC versus manual breathstacking plus MAC

Kim 2016 reported significantly increased PCF with both MAC plus breathstacking and MI-E plus MAC compared to unassisted cough in 40 participants. The PCF generated with the MI-E plus MAC produced greater PCF than manual breathstacking plus MAC. Separate data for the two periods of cross-over were not available for analytical purposes.

MAC versus manual breathstacking

Brito 2009 reported that, in 28 adults with DMD, PCF increased with MAC and manual breathstacking compared to unassisted cough. There was no difference between PCF generated with MAC compared to manual breathstacking. Separate data for the two periods of cross-over were not available for analytical purposes.

MAC versus manual breathstacking plus MAC

Brito 2009 reported that PCF increased with both MAC and MAC plus breathstacking, compared to unassisted cough, in 28 adults with DMD. PCF was higher when using manual breathstacking plus MAC compared to MAC alone. Separate data for the two periods of cross-over were not available for analytical purposes.

Manual breathstacking versus manual breathstacking plus MAC

In 28 adults with DMD, PCF increased significantly with both manual breathstacking and manual breathstacking plus MAC, compared to unassisted cough. PCF was higher when using manual breathstacking plus MAC compared to manual breathstacking alone (Brito 2009). Separate data for the two periods of cross-over were not available for analytical purposes.

Mechanical breathstacking versus mechanical insufflation

Del Amo Castrillo 2019 reported that, in 20 adults with NMD, both mechanical breathstacking (using a ventilator) and mechanical insufflation using a ventilator's volumetric cough mode were associated with an increase in PCF, but that mean PCF was higher with mechanical insufflation (using volumetric cough mode) than with mechanical breathstacking ($P < 0.01$). Data were presented graphically, and we could not extract data precisely from the figures provided. Attempts to contact the author for additional data were unsuccessful.

2. Any adverse events, including, but not limited to: pneumothorax, rib fractures, lung injury, aerophagia/abdominal distension, and death for both 'maintenance' and 'rescue' therapy

Chatwin 2009 recorded fatigue using a VAS, in eight adults and children with a range of NMD conditions, but did not report other adverse events. Reporting for the outcome measure of fatigue was, however, incomplete, with fatigue VAS values only reported for the intervention MAC plus MI-E, and there were no data for MAC alone (Chatwin 2009). In the latter group, fatigue was only reported as being not significantly different before to after intervention, while with MAC plus MI-E, mean fatigue VAS increased from 3.2 (SD 2.2) before the intervention to 5.1 (SD 2.6) after the intervention ($P =$

0.005; see Table 3). Separate data for the two periods of cross-over were not available for analytical purposes. The lack of comparable data makes meaningful conclusions difficult. The evidence was very-low certainty due to very serious study limitations and imprecision due to the small study size (eight participants).

None of the included studies specified adverse events as primary or secondary outcome measures, and six studies with 155 participants did not report on this outcome measure (Brito 2009; Del Amo Castrillo 2019; Jenkins 2014; Lacombe 2014; Torres-Castro 2016; Toussaint 2016). Chatwin 2003 (22 participants) reported that no adverse events occurred during the study, and that participants tolerated the interventions well. Kim 2016 (40 participants) also reported that all three interventions were "well tolerated" and Sivasothy 2001 (four participants) reported that no adverse events had occurred. Although the studies reported no serious adverse events, it was unclear whether these were systematically investigated. We downgraded the body of evidence for adverse effects three times to very-low certainty – twice for very serious study limitations and once for imprecision (see Summary of findings 1).

3. Measures of gaseous exchange measured before and after the intervention for 'rescue' therapy, and measured over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' therapy

None of the studies investigated the medium- or long-term effects of cough augmentation techniques on measures of gaseous exchange. Chatwin 2009 (eight participants) measured the short-term effects of interventions on physiological variables of heart rate, transcutaneous oxygen saturation, and PtcCO₂ in adults and children with NMD; however, this study did not provide separate data for the interventions. Instead it simply reported that there was no difference between intervention groups for these physiological parameters. Jenkins 2014 (23 participants) reported that there was no difference in the change of transcutaneous oxygen saturation from before to after manual breathstacking using a resuscitator bag compared to sham breathstacking (see Table 2).

4. Pulmonary function measured by FEV₁, FVC, VC, and PEF_R, over the short term (less than three months); medium term (between three months and one year), and long term (one year and longer) for 'maintenance' therapy

None of the studies reported pulmonary function.

5. Quality of life measured by any validated measure over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' use

None of the studies reported quality of life.

6. Validated measures of function, including measures of perceived exertion, exercise tolerance, and motor function measured over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' therapy

Chatwin 2009 measured the level of perceived breathlessness with MI-E plus MAC and MAC alone, using a 10-point VAS, in eight adults and children. The validity of the scale was not determined, and data were not presented for separate interventions. It was simply reported that there were no significant changes from baseline to after intervention (see Table 3).

7. Participant preference for, or satisfaction with, specific cough augmentation techniques, expressed as a proportion or percentage of the sample for both 'rescue' and 'maintenance' therapy

None of the studies reported participants preference or satisfaction.

8. Other outcome measures

We presented data for other outcome measures in [Table 2](#) and [Table 3](#).

8.1. Tidal volume

One study, with 23 participants, reported an increase in tidal volume from before to after intervention with manual breathstacking using a resuscitation bag ($P < 0.0001$) compared to a no change with sham breathstacking ([Jenkins 2014](#)). Authors did not report between-group significance levels, and as separate cross-over period data were not available, these could not be calculated.

8.2. Maximum inspiratory or insufflation capacity

Four studies measured maximal inspiratory or insufflation capacity in 104 participants ([Del Amo Castrillo 2019](#); [Lacombe 2014](#); [Torres-Castro 2016](#); [Toussaint 2016](#)).

8.2.1. Manual breathstacking versus mechanical breathstacking

[Toussaint 2016](#) reported that mean MIC achieved by participants performing manual breathstacking was 1.344 (SD 0.520) L compared to 1.481 (SD 0.477) L for those performing breathstacking using a ventilator (between-group MD 0.14 L, 95% CI -0.13 to 0.41; $P = 0.3$; 52 participants; [Analysis 1.2](#)). Therefore, there was no evidence of a difference between manual and mechanical breathstacking in achieved MIC.

8.2.2. Glossopharyngeal breathing versus manual breathstacking

[Torres-Castro 2016](#) reported the change from baseline VC to postintervention MIC. The published article reported that the median MIC achieved with manual breathstacking was 290 mL (IQR 168 to 567) greater than was achieved using GPB ($P = 0.002$); however, on analysing the provided separate first-period data, the MD in postintervention MIC between groups was calculated as 90 mL ($P = 0.76$). There was no evidence of between-groups difference in the MIC change from baseline to after intervention, with an MD from baseline to postintervention MIC in the breathstacking group of 435.0 (SD 364.5) mL compared to 454.29 (408.16) mL in the group receiving GPB (between-group MD 19.29 mL, 95% CI -386.09 to 424.67; $P = 0.9$; 14 participants; [Analysis 2.2](#)).

8.2.3. MI-E versus mechanical insufflation plus MAC

First-period data provided on request by [Lacombe 2014](#) compared mean inspiratory capacity between MI-E alone (1.55 (SD 0.34) L) and mechanical insufflation plus MAC (1.43 (SD 0.34) L). There was no evidence of a difference in inspiratory capacity achieved between interventions (MD -0.12 L, 95% CI -33.44 to 33.20; $P = 0.99$; 11 participants; [Analysis 3.2](#)).

8.2.4. MI-E versus MI-E plus MAC

[Lacombe 2014](#) provided first-period data for mean inspiratory capacity with MI-E alone (1.55 (SD 0.34) L) and MI-E plus MAC (1.39 (SD 0.43) L). There was no evidence of a difference in inspiratory

capacity achieved between the interventions (between-group MD -0.16, 95% CI -0.57 to 0.25; $P = 0.44$; 14 participants; [Analysis 4.2](#)).

8.2.5. Mechanical insufflation plus MAC versus MI-E plus MAC

First-period data for mean inspiratory capacity for mechanical insufflation plus MAC (1.43 (SD 0.34) L) and MI-E plus MAC (1.39 (SD 0.43) L) showed no evidence of difference between interventions (between-group MD 0.04, 95% CI -0.42 to 0.50; $P = 0.86$; 11 participants; [Analysis 5.2](#)) ([Lacombe 2014](#)).

8.2.6. Mechanical breathstacking versus mechanical insufflation

[Del Amo Castrillo 2019](#) reported no difference in inspiratory capacity between breathstacking using a ventilator compared to mechanical insufflation using the ventilator's volumetric cough mode in 20 participants ($P = 0.12$). Separate cross-over period data were not available, precluding analysis.

8.3. Minute ventilation

One study reported minute ventilation in 23 participants ([Jenkins 2014](#)). Minute ventilation increased from baseline with breathstacking using a manual resuscitation bag ($P < 0.001$) compared to a non-significant change with sham breathstacking. Authors did not report between-group significance levels, and, as separate period data were not available for the cross-over RCT, these could not be calculated.

8.4. Maximal expiratory pressure

[Toussaint 2016](#) reported that mean maximal expiratory pressure was 26 (SD 9) cmH₂O in the group receiving resuscitator bag breathstacking compared to 28 (SD 10) cmH₂O in those receiving ventilator breathstacking (MD 2.00 cmH₂O, 95% CI -3.16 to 7.16; 52 participants).

8.5. Cough expiratory volume

One study reported cough expiratory volume in four participants ([Sivasothy 2001](#)). Median cough expiratory volumes were not different between mechanical insufflation, MAC, and MAC plus mechanical insufflation. The small sample size and lack of separate period data limit interpretation of these results.

8.6. Respiratory rate

[Jenkins 2014](#) (23 participants) reported respiratory rate increased from 27 (SD 9.2) breaths/min to 28 (SD 10.6) breaths/min ($P < 0.05$) with manual breathstacking using a resuscitator bag compared to a non-significant change from 26 (SD 10.3) breaths/min to 26 (SD 10.4) breaths/min with sham breathstacking. Between-groups significance levels were not provided, and separate period data were not available, precluding analysis.

8.7. Heart rate

[Chatwin 2009](#) (eight participants) reported heart rate; however, although the trial authors reported that there were no differences in heart rate between standard airway clearance therapy with and without MI-E, data and significance levels were not reported. Attempts to obtain additional data were unsuccessful.

8.8. Effective cough time (time with PCF greater than 3 L/sec or greater than 180 L/min)

One study reported effective cough time in 18 participants (Lacombe 2014). Based on first-period data received from the author on request, the MD in effective cough time from baseline with MI-E alone was 54 (SD 95) ms; 93 (SD 111) ms with mechanical insufflation plus MAC; and 20 (SD 42) ms with MI-E plus MAC. Although the trial authors reported, based on the combined cross-over data, that the increase in effective cough time was smaller with MI-E alone than with both the combined techniques using MAC, on analysis of separate first-period data, there was no evidence of differences between any intervention: MI-E versus mechanical insufflation plus MAC (MD 39.0 ms, 95% CI -90.56 to 168.56; $P = 0.56$; 11 participants); MI-E versus MI-E plus MAC (MD -34.00 ms, 95% CI -110.95 to 42.95; $P = 0.39$; 11 participants); and mechanical insufflation plus MAC versus MI-E plus MAC (MD 73.00 ms, 95% CI -40.14 to 186.14; $P = 0.21$; 14 participants).

8.9. Peak value time (time from onset of expiratory flow to peak expiratory cough flow)

One study reported peak value time (Sivasothy 2001). In four participants, median peak value time was reported not to be significantly different between mechanical insufflation, MAC, and MAC plus mechanical insufflation. Separate first-period data were not available, precluding analysis.

8.10. Ability to perform breathstacking

One study compared the ability to breathstack using a resuscitator bag (manual breathstacking) compared with ventilator (mechanical) breathstacking (Toussaint 2016). There was no evidence of a difference in the ability to breathstack between groups, with 88% in the resuscitator bag group versus 89% in the ventilator group being able to perform the technique (RR 0.93, 95% CI 0.21 to 4.17; $P = 0.33$; 52 participants).

8.11. Number of insufflations to achieve MIC

Toussaint 2016 reported that a mean of 1.8 (SD 0.6) insufflations were required to reach MIC with manual breathstacking using a resuscitator bag compared to a mean of 2.6 (SD 0.6) insufflations with mechanical breathstacking using a ventilator (between-group MD 0.80 insufflations, 95% CI 0.47 to 1.13; $P < 0.001$; 52 participants).

8.12. Subjective outcome measures

One study reported auscultation score, measured using a 10-point VAS (eight participants) (Chatwin 2009). Auscultation VAS decreased significantly with both MAC ($P = 0.007$) and MAC plus MI-E ($P = 0.02$). Between-groups significance levels were not reported, and we could not obtain separate period data, precluding analysis.

Chatwin 2003 (22 participants) reported a combined outcome of comfort, distress, and cough strength. The trial authors reported that there were no changes from baseline in VAS results on a 10-point scale for any intervention (MAC, mechanical insufflation, mechanical exsufflation, or MI-E). Between-group significance levels were not reported, and we could not obtain separate period data, precluding analysis.

Chatwin 2009 (eight participants) reported participants' perceived presence of secretions, using a 10-point VAS, improved from before to after intervention with standard therapy including MAC ($P =$

0.03) and with standard therapy with MAC plus MI-E ($P = 0.03$). Between-group significance levels were not reported, and we could not obtain separate period data, precluding analysis.

Three studies (46 participants) reported participant comfort using a 10-point VAS (Chatwin 2009; Del Amo Castrillo 2019; Lacombe 2014). Chatwin 2009 (eight participants) presented results graphically only, and data could not be extracted from the figures. Lacombe 2014 (18 participants) reported no significant differences in subjective comfort between MI-E, mechanical insufflation plus MAC, and MI-E plus MAC, but did not present significance levels. Del Amo Castrillo 2019 (20 participants) reported no significant difference in comfort VAS between ventilator breathstacking and mechanical insufflation using the ventilator's volumetric cough mode.

Two studies (38 participants) reported subjective cough effectiveness (Del Amo Castrillo 2019; Lacombe 2014). Aggregate results from the cross-over study by Lacombe 2014 (18 participants) suggested a significant difference in perceived cough effectiveness between MI-E alone and MI-E plus MAC ($P < 0.05$, favouring MI-E plus MAC) and between mechanical insufflation plus MAC and MI-E alone ($P < 0.05$, favouring mechanical insufflation plus MAC). Median values provided for the first period of cross-over study by Lacombe 2014 (see Table 3), however, suggested a possible difference between MI-E and MI-E plus MAC, and no evidence of a difference between MI-E and mechanical insufflation plus MAC in perceived cough effectiveness (measured using a 10-point VAS). There were insufficient data to confirm the size or precision of the effect. Del Amo Castrillo 2019 (20 participants) reported no difference in perceived cough effectiveness with mechanical breathstacking compared to mechanical insufflation using volumetric cough mode ($P = 0.17$). Separate period data could not be obtained for this study, precluding analysis.

One study measured participant mood using a 10-point VAS (eight participants) (Chatwin 2009). The report only presented data graphically and results could not be extracted accurately from the figures. The study reported that no within-groups changes from baseline to after either intervention: standard treatment with MAC, or standard treatment with MAC plus MI-E. No between-group values or significance levels were reported, and attempts to obtain additional information were unsuccessful.

None of the studies provided cost-effectiveness analyses, and we could not evaluate it as part of this review.

Cough augmentation therapy compared to standard of care

One study, in 67 children and adolescents with DMD, compared twice daily manual breathstacking compared to standard care, over two years (Katz 2019). Reported outcomes are presented in Table 4 and Summary of findings 2.

Primary outcomes

1. Number of unscheduled hospital admissions for episodes of acute respiratory exacerbations over one year for 'maintenance' therapy

The study did not report number of hospital admissions for episodes of acute respiratory exacerbations over one year, for 'maintenance use.'

2. Duration of hospital stay (days) for 'rescue' therapy

The study protocol by [Katz 2019](#) included, as a secondary outcome measure, the number and duration of hospital admissions over two years in 67 participants. However, the published abstract did not present these outcome data. Attempts to contact the author were unsuccessful.

Secondary outcomes

1. PCF measured before and after intervention for 'rescue' therapy and measured over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' therapy

The study did not report PCF.

2. Any adverse events, including, but not limited to: pneumothorax, rib fractures, lung injury, aerophagia/abdominal distension, and death for both 'maintenance' and 'rescue' therapy

[Katz 2019](#) did not include adverse events as a primary or secondary outcome measure but reported that no adverse events had occurred (67 participants; very low-certainty evidence).

3. Measures of gaseous exchange measured before and after the intervention for 'rescue' therapy, and measured over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' therapy

The study did not report measures of gaseous exchange.

4. Pulmonary function measured by FEV₁, FVC, VC, and PEFR, over the short term (less than three months); medium term (between three months and one year); and long term (one year and longer) for 'maintenance' therapy

[Katz 2019](#) measured change in FVC (as percentage predicted) over two years from baseline. Change in FVC among participants in the breathstacking group was 4.1% compared to 6.4% in the conventional treatment group (adjusted MD 2.0%, 95% CI -8.2 to 12.3; 67 participants). Sufficient data, including number of participants per group, separate allocation baseline data, and SD of the mean, were not available for analysis. This study also reported that the time to 10% decline in FVC% predicted was not significantly different between groups ($P = 0.5$) but did not provide data, precluding analysis. We may be able to include complete results from this study in analysis in updates of this review, if data become available.

5. Quality of life measured by any validated measure over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' therapy

[Katz 2019](#) planned to report health-related quality of life using the PedsQL 4.0. However, the published abstract did not report this outcome measure, and attempts to contact the author for additional data were unsuccessful. If data become available, we may be able to include health-related quality of life data in updates of this review.

6. Validated measures of function, including measures of perceived exertion, exercise tolerance, and motor function measured over the medium term (between three months and one year) and long term (one year and longer) for 'maintenance' therapy

The study did not report validated measures of function.

7. Participant preference for, or satisfaction with, specific cough augmentation techniques, expressed as a proportion or percentage of the sample for both 'rescue' and 'maintenance' therapy

The study did not report participant preference or satisfaction.

8. Other outcome measures

We presented data for other outcome measures in [Table 4](#).

[Katz 2019](#) included MIC, MEP, MIP, and the number and duration of outpatient oral antibiotic courses as additional outcome measures in the published protocol (67 participants). However, these data were not reported in the published abstract and attempts to contact the author were unsuccessful. Results from this study may be able to be included in updates of this review, if data become available.

DISCUSSION

Summary of main results

Eleven studies involving 287 children, adolescents, and adults, with a variety of NMDs, met this review's inclusion criteria. Sample sizes in individual studies ranged from four to 67 eligible participants; 10 studies were full-text articles and one was in abstract form.

Included studies compared a range of cough augmentation technique(s) to alternative interventions ([Brito 2009](#); [Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#)); standard care (control) ([Katz 2019](#)); unassisted cough ([Kim 2016](#)), or sham intervention ([Jenkins 2014](#)), for several outcome measures. Most studies compared intervention-assisted cough outcomes with preintervention or baseline measurements of unassisted cough ([Brito 2009](#); [Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Katz 2019](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#); [Toussaint 2016](#)). Only one study was of long-term duration, lasting two years ([Katz 2019](#)), but there were limited data presented in abstract format only. One study was a two-day cross-over trial ([Chatwin 2009](#)), while the remainder measured the immediate effects of single intervention sessions. Only two studies were prospective RCTs ([Katz 2019](#); [Toussaint 2016](#)), the remaining nine were short-term randomised cross-over trials ([Brito 2009](#); [Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#); [Jenkins 2014](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#)). Two cross-over studies provided first-period data ([Lacombe 2014](#); [Torres-Castro 2016](#)), which constitutes a major limitation of this review. The large number of inadequately reported results from cross-over studies, and the limited information provided by authors on request, severely restricted the number of analyses that could be performed.

Cough augmentation techniques aim to improve cough efficiency, with potential for both short- and long-term effects on pulmonary morbidity. During acute respiratory exacerbations, cough augmentation techniques aim to clear obstructed secretions to prevent the progression to respiratory failure, improve work of breathing and gaseous exchange, and potentially reduce the need for hospital admission and, if admitted, reduce the length of stay. In the longer term, regular use of cough augmentation is hoped to reduce the incidence or severity (or both) of respiratory tract infections requiring unscheduled hospitalisation. Although one long-term RCT planned to measure this review's primary outcome measures of number and duration of hospital admissions ([Katz 2019](#)), the published abstract of the study did not report these

outcomes and attempts to contact the author for additional data were unsuccessful, therefore, these data could not be included in this review. None of the other included studies measured or reported on this review's primary outcomes. Therefore, the evidence is very uncertain about the efficacy of any cough augmentation technique for reducing the number or duration (or both) of hospital admissions for respiratory exacerbations in people with NMD (see [Summary of findings 1](#); [Summary of findings 2](#)).

Clinically important secondary outcomes of this review were selected for their utility in measuring the safety of cough augmentation techniques and their effect on cough efficiency (PCF), gas exchange (oxygenation and carbon dioxide clearance), as well as objective and subjective measures of pulmonary and general function, quality of life, and participant preference or satisfaction. Only three studies provided sufficient data for analysis of one of this review's secondary outcome measures of PCF ([Lacombe 2014](#); [Torres-Castro 2016](#); [Toussaint 2016](#)). None of the included studies provided sufficient data for analysis of any of this review's other secondary outcome measures. Therefore, the evidence is very uncertain about the effect of cough augmentation techniques on measures of safety, gaseous exchange, pulmonary function, quality of life, general function, or participant preference or satisfaction.

Although four studies reported that no adverse events had occurred ([Chatwin 2003](#); [Katz 2019](#); [Kim 2016](#); [Sivasothy 2001](#)), none of the included studies listed "adverse events" as primary or secondary outcome measures. [Chatwin 2009](#) reported that fatigue increased in participants receiving MAC plus MI-E, with no change in fatigue in those receiving MAC alone; however, there were insufficient data for analysis ([Summary of findings 1](#)). The evidence is therefore very uncertain about the safety of any of the included cough augmentation interventions.

One RCT with 67 participants planned to measure the long-term effect of manual breathstacking on PCF ([Katz 2019](#)); however, this outcome measure was not reported in the published abstract and data could not be included in this review ([Summary of findings 2](#)).

Eight studies with 198 participants compared the PCF generated with various cough augmentation techniques to baseline unassisted cough, as a repeated measure for each participant ([Brito 2009](#); [Chatwin 2003](#); [Del Amo Castrillo 2019](#); [Kim 2016](#); [Lacombe 2014](#); [Sivasothy 2001](#); [Torres-Castro 2016](#); [Toussaint 2016](#)). All but two cross-over RCTs with small sample sizes ([Chatwin 2003](#); [Sivasothy 2001](#)), showed significant increases in PCF with cough augmentation therapy from baseline. However, "unassisted cough" in all studies, except for [Kim 2016](#), was measured at baseline or before intervention, and was not a randomly assigned control intervention. [Kim 2016](#) did not provide separate period data. Therefore, there is only very low-certainty evidence that manual and mechanical breathstacking; GPB; MI-E; mechanical exsufflation; MAC; MAC plus MI-E; MAC plus breathstacking; and mechanical insufflation may all increase PCF above unassisted cough ([Table 2](#); [Table 3](#); [Table 1](#)).

Based on one single-centre, short-term RCT (52 participants), with high risk of performance and assessor bias, and unclear allocation concealment ([Toussaint 2016](#)), there was low-certainty evidence that manual breathstacking using a resuscitation bag may result in little to no difference in PCF in the short-term, compared to

mechanical breathstacking (using a ventilator). Further results from RCTs are very likely to have an important impact on our confidence in the estimate of effect and are likely to change this estimate ([Table 1](#)).

Based on the results of the first-period data of one short-term, randomised cross-over study (14 participants) ([Torres-Castro 2016](#)), there may be little to no difference in the short-term outcome of PCF between GPB compared with manual breathstacking ([Table 1](#)). Considering the very small sample size of this single study, and high risk of performance and detection bias, we are very uncertain about this estimate, and sufficiently powered RCTs to compare the effects of these interventions on PCF are warranted.

Based on the first period results of one short-term, randomised cross-over study with small sample size (18 participants), very wide CIs, and substantial risk of performance and other biases ([Lacombe 2014](#)), there is very low-certainty evidence that, in adults with chronic NMD, mechanical insufflation plus MAC may improve PCF more than MI-E alone in the short term. The evidence suggests little to no difference in the change in PCF between MI-E plus MAC and mechanical insufflation plus MAC. We are very uncertain about these estimates, and further adequately powered RCTs are required to confirm or refute these results ([Table 1](#)).

Aggregate results of short-term cross-over trials, without provision of separate period data, reported little to no difference in PCF between MAC and manual breathstacking ([Brito 2009](#)), or among MAC, mechanical insufflation, and MAC plus mechanical insufflation ([Sivasothy 2001](#)). Higher PCF was reported with MI-E compared to mechanical exsufflation ([Chatwin 2003](#)) and MAC plus manual breathstacking ([Kim 2016](#)); with MAC plus manual breathstacking compared to either MAC or manual breathstacking individually ([Brito 2009](#)); with MAC plus MI-E compared to MI-E alone ([Kim 2016](#)) and MAC plus manual breathstacking ([Kim 2016](#)); and mechanical insufflation compared to mechanical breathstacking ([Del Amo Castrillo 2019](#)). Overall, the evidence suggests there may be little to no difference between alternate cough augmentation interventions in improving PCF ([Table 1](#)). The evidence for this is, however, very uncertain.

Two cross-over studies measured the short-term effect of interventions on gaseous exchange. [Chatwin 2009](#) reported there was no difference in transcutaneous oxygen saturation and PtcCO₂ between MAC and MAC plus MI-E; [Jenkins 2014](#) reported no difference in transcutaneous oxygen saturation between manual and sham breathstacking. One long-term RCT measured pulmonary function (FVC) ([Katz 2019](#)); however, there were insufficient data, precluding analysis. This study reported no change in FVC or change in the time to 10% decline in FVC between participants receiving manual breathstacking compared to standard care. One study planned to report the long-term effects of interventions on health-related quality of life ([Katz 2019](#)); however, no data were available. The evidence is therefore very uncertain about the effect of any cough augmentation technique on gaseous exchange or health-related quality of life.

Other outcome measures were variably reported in included studies. Based on aggregated reported results of three cross-over studies ([Chatwin 2003](#); [Chatwin 2009](#); [Del Amo Castrillo 2019](#)), and first-period data from one cross-over study (total 68 participants) ([Lacombe 2014](#)), there was no evidence of superior participant comfort with any cough augmentation technique.

Although no study reported participant preference, short-term perceived cough effectiveness was reported in the aggregate results of three cross-over studies with 42 participants (Del Amo Castrillo 2019; Lacombe 2014; Sivasothy 2001). Lacombe 2014 reported that perceived effectiveness was higher with MAC plus MI-E compared with MI-E alone. The potential greater efficacy of combined cough augmentation techniques compared with single techniques requires attention in future RCTs.

Four studies with 104 participants reported maximal insufflation or inflation capacity (MIC) (Del Amo Castrillo 2019; Lacombe 2014; Torres-Castro 2016; Toussaint 2016), with three studies (84 participants) providing sufficient data for analysis (Lacombe 2014; Torres-Castro 2016; Toussaint 2016). Based on these studies, there may be little to no difference in MIC with MAC, MI-E, and MAC plus MI-E; manual breathstacking versus GPB; mechanical versus manual breathstacking; or mechanical breathstacking versus mechanical insufflation (using volumetric cough mode).

Overall completeness and applicability of evidence

We identified 11 studies for inclusion in this review, nine of which were short-term cross-over studies of which only two provided separate first-period data for analysis. These methodological limitations substantially impact on the internal and external validity of this review. We found only one long-term trial for maintenance therapy; however, complete data were not available for inclusion in this review. None of the included studies reported clearly on the short- or long-term effects of cough augmentation interventions on clinically relevant outcomes of morbidity and safety, and this study could not, therefore, address the objective of this review in determining the efficacy and safety of cough augmentation techniques for adults and children with chronic NMD and respiratory muscle weakness. Furthermore, none of the studies compared different dosages or frequencies of application of any cough augmentation technique and the evidence is therefore very uncertain regarding optimal safe and effective prescription of cough augmentation techniques in people with NMD.

Participant numbers were generally small, with no possibility of subgroup analyses for different age groups or conditions. As seen in Table 2; Table 3; and Table 4, studies compared a variety of interventions, with variable techniques, and a wide range of outcome measures. Studies were conducted in Europe (three), the UK (three), Canada (two), Korea (one) and South America (two). External generalisability to other geographical regions and socioeconomic contexts cannot be determined. None of the studies provided any estimate of cost-effectiveness.

Quality of the evidence

Key limitations of included studies were: study design; small sample sizes; unreliable or clinically irrelevant outcome measures; and unclear to high risk of bias, specifically related to poorly reported methods of allocation concealment, randomisation sequence generation, insufficient blinding of participants and personnel, and insufficient reporting of data. The overall certainty of the evidence of included studies was low or very low, with most being short-term randomised cross-over trials, in which participants received two or more interventions in randomly assigned order, with undetermined and untested carry-over effects (Mills 2009) and, in all but three studies, insufficient information to allow data analysis. In several studies, the investigators compared

cough augmentation techniques and unassisted cough; however, unassisted coughing was not a randomly assigned controlled intervention except in one study (Kim 2016), and definitive conclusions regarding efficacy of interventions cannot therefore be made.

Cross-over study designs are considered suitable for evaluating interventions with a temporary effect in participants with stable or chronic conditions (Nolan 2016), and may, therefore, be appropriate for measuring outcome measures such as PCF, a secondary outcome of interest for this review. However, short-term cross-over designs are generally not the most appropriate for measuring longer-term health-related outcomes of chronic life-limiting and progressive conditions such as NMDs. The immediate effects of an intervention may not translate into longer-term benefit, and results of such studies must, therefore, be interpreted with caution. The decision to include cross-over trials in this review was based on the knowledge that this is the most common study design used among this population group, likely owing to various factors including the fact that NMDs are rare conditions, and generally a smaller overall sample size is needed for cross-over compared to parallel-group RCTs (Nolan 2016). In addition, well-conducted cross-over trials may yield more precise results than parallel-group designs, owing to lower variability with individual compared to between-participant responses (Elbourne 2002). The inability to pool or individually analyse data from most cross-over trials limits the validity of this review. It is not considered methodologically acceptable to simply treat cross-over trials as parallel-group RCTs for the purposes of systematic reviews and meta-analysis (Elbourne 2002).

Blinding of participants and research personnel is generally not possible for interventions such as cough augmentation techniques, increasing the risk of bias of studies. Limited available information regarding methodology (e.g. allocation concealment, washout periods, and randomisation sequence generation) further increased the risk of bias in included studies. The publications of all included cross-over trials presented results as though from parallel-group RCTs, and we judged the data unsuitable for meta-analysis (Elbourne 2002).

The body of evidence included in this review did not allow any clear conclusions to be reached regarding the efficacy or safety of cough augmentation techniques in people with chronic NMD.

Potential biases in the review process

There were no major deviations from the published protocol in conducting this review. Our literature search was comprehensive, and included searches for unpublished material through trial registration platforms and congress abstract reports. There were no geographical, time, or language constraints to this review. However, it is possible that some studies may have been overlooked, particularly if published in non-peer reviewed journals or presented at small or regional congresses. Further, we cannot control for inherent publication bias.

We contacted the corresponding authors of included studies, where appropriate, to obtain missing results or additional information but most did not respond and only one author was able to provide all the necessary information. We could not obtain missing data on the primary outcomes of this review, as measured by Katz 2019, and this may have substantially impacted on this review, which is

an unavoidable source of bias. We hope that these data will be available for future versions.

Agreements and disagreements with other studies or reviews

A previous Cochrane systematic review concluded that there was insufficient evidence for or against the use of MI-E as a cough augmentation technique in people with NMD, for efficacy and safety outcome measures (Morrow 2013). This review was also unable to present moderate or high certainty evidence for or against the safety or efficacy of either MI-E or any other cough augmentation technique in people with NMD. Further, the evidence from this review suggests there may be little to no difference between any alternate cough augmentation technique, for a range of short- or long-term outcome measures.

A previous 'state of the art' narrative review systematically reviewed the evidence-base for airway clearance techniques (including both peripheral and proximal techniques) in adults and children with NMD, including participants with ALS (Chatwin 2018). The review reported on all study designs, including case studies and retrospective audits. Chatwin 2018 suggested that all cough augmentation techniques, including MAC, single-breath assisted inspiration (manual insufflation), breathstacking, GPB, and MI-E effectively increase PCF, as is also suggested in this review, based on very low-certainty evidence. Chatwin 2018 also suggested that combining a technique augmenting inspiration with one that enhances expiration may further increase cough efficacy; however, this review demonstrated that the evidence for better cough efficiency with combination compared to single techniques is very uncertain and further research is warranted in this regard. Based largely on observational studies, Chatwin 2018 recommended using MI-E preferentially for weaker patients with NMD. This recommendation is not supported or refuted by the results of this review. The review by Chatwin 2018 was limited by the lack of defined review objectives, the inclusion of all study types, and the lack of a risk of bias or GRADE assessments for the included studies. Owing to the differing purpose, methodologies, and reporting, direct agreements or disagreements between reviews cannot be made.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review do not provide sufficient certainty of evidence to guide clinical practice, as we were unable to address important short- and long-term clinically relevant outcomes, including measures of safety. There is very low-certainty evidence that a range of cough augmentation techniques may increase peak cough flow (PCF) above that of unassisted cough; however, there is insufficient certainty of evidence to determine whether any one technique is superior to another technique or combination of techniques in this regard. The evidence is currently very uncertain about the safety and effectiveness of cough augmentation techniques in adults and children with chronic neuromuscular disease (NMD). Considering that respiratory decompensation in people with NMD may occur as a consequence of the inability to clear secretions during cough (Toussaint 2018), and given the very low-certainty evidence supporting the effect of cough augmentation techniques on PCF, practitioners may continue to implement this therapy in people with chronic NMD and respiratory

muscle weakness, as recommended previously (Chatwin 2018; Toussaint 2018). However, as there is no moderate or high certainty evidence for the superiority of any cough augmentation technique/s, the choice of techniques may take other factors into account, including cost, patient preference and ability, therapist knowledge and proficiency, and equipment availability. Further, there is insufficient evidence to inform safe and effective frequency or dosage of cough augmentation techniques in the management of people with respiratory muscle weakness caused by chronic NMD.

Implications for research

Further research is required to establish the safety and efficacy of cough augmentation techniques in people with NMDs, for both long-term maintenance use, and during respiratory exacerbations or acute obstructive episodes, for 'rescue' use. We need future studies to measure longer-term, clinically relevant outcomes that will inform the effects of interventions on morbidity, mortality, and health-related quality of life. We also need systematic reporting of adverse events to obtain safety data, and reporting on participant choice of techniques. Studies comparing dosage and frequency regimens would be useful in this regard. Choice of comparators would depend on local standard of care. Sham treatment or non-intervention controls may be difficult to support ethically over the long term, but comparative studies of different interventions could be ethically justifiable, as there is clearly equipoise between intervention types. Given the diversity of NMD and of age groups affected, we need studies that either focus on a specific age group or condition, or provide sufficient data for subgroup analyses in systematic reviews.

In terms of study design, long-term parallel-group RCTs provide the best evidence, but NMDs are rare and attaining sufficient sample size is often difficult. Researchers should therefore be encouraged to consider multisite collaborative studies to reach sufficient sample sizes for adequate power, and to allow meaningful subgroup analyses. It is particularly important to consider paediatric and adult data separately, owing to the anatomical and physiological differences between these participant groups, which likely translate into different safety and efficacy profiles.

For short- and medium-term outcomes such as immediate change in PCF, cross-over trials may be useful, as smaller samples may yield equivalent power to a parallel-group RCT. Importantly, comprehensive reporting of data from cross-over trials will allow for systematic review synthesis and analysis (Elbourne 2002; Nolan 2016). This includes providing full details on methods (including allocation concealment, sequence generation, washout periods, and carry-over effects) and either individual level data (including allocation information) or appropriately summarised, separate data for both periods (Elbourne 2002). Our findings support the recommendation that minimum standards for the transparent reporting of cross-over trials are urgently needed (Mills 2009), as currently the results of many of these trials are essentially lost, because they cannot be included in important meta-analyses to inform clinical practice.

Involvement of people living with or affected by NMDs when designing clinical trials can ensure that outcome measures and interventions are appropriate and responsive to their needs and experiences. Cost-effective analyses are also warranted to relate the potential benefits of interventions with financial, physical, and social costs or harms.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Brito 2009

Study characteristics

Methods	<p>Study design: prospective randomised cross-over trial comparing MAC, breathstacking, and MAC + breathstacking</p> <p>Study grouping: cross-over</p> <p>'Rescue' vs maintenance therapy: maintenance</p> <p>Ethics: ethical clearance provided by Federal University of São Paulo (UNIFESP) Research Ethics Committee (CEP 0775/06)</p>
Participants	<p>Baseline characteristics</p> <p>Separate data were not documented for group allocations in the first period of cross-over. Data were presented for all participants, who received all interventions.</p> <ul style="list-style-type: none"> • Sample size, n: 28 • Age in years, mean: 20 (SD 4) • FVC % predicted, mean: 29 (SD 12) • Bodyweight in kg, mean: 56 (SD 17) • Pronounced kyphoscoliosis, n: 17 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • DMD • Aged > 10 years • Receiving NIV (BiPAP) • FVC < 60% of predicted • Intellectual level sufficient to perform the manoeuvres <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Current acute infection • Other NMDs • Presence of nasogastric tube <p>Pretreatment</p> <ul style="list-style-type: none"> • Not applicable • All participants randomly received the various cough augmentation techniques
Interventions	<p>Intervention characteristics</p> <p>Baseline spontaneous MEE</p> <ul style="list-style-type: none"> • Participant positioning: sitting • Technique description: participants were asked to take a deep inhalation, after which PCF for spontaneous (unassisted) MEE was measured.

Brito 2009 (Continued)

Manual chest compression (MAC)

- Participant positioning: sitting
- Technique description: therapist placed external pressure on the rib cage by placing 1 hand over the posterosuperior region of the chest and 1 hand supported the anterior region of the chest at the inferior third of the sternum. The participant was instructed to inhale deeply (spontaneous maximal inspiratory effort), close their glottis and on exhalation therapist applied chest compression in the direction of the abdomen (down and inwards).

Breathstacking using a manual resuscitation bag

- Participant positioning: sitting. Participant's head was supported (to avoid hyperextension)
- Technique description: sequential insufflations were delivered using a manual resuscitation bag, with closed unidirectional valve (Moriya, São Paulo, Brazil) and a face-mask interface. The mask was fitted firmly to the participant's face to avoid air leaks. With each compression of the manual resuscitation bag, the participant was instructed to take a deep breath and hold it. With each subsequent compression of the manual resuscitation bag, the participant inhaled again, without releasing the air inhaled previously. 1 complete air stacking manoeuvre consisted of 3 insufflations without exhalation. After the third insufflation, the participant made a forced exhalation, and the PCF with maximal expiratory effort was measured.

Chest compressions (MAC) + breathstacking

- Participant positioning: sitting
- Technique description: breathstacking as described above followed by manual chest compression (MAC) as described above.

Outcomes

Separate first-period data were not presented, precluding analysis.

PCF

- Outcome type: continuous outcome
- Reporting: fully reported
- Unit of measure: L/min
- Technique description: all measurements were taken by the same examiner and with the participant in a sitting position. The PCF measurements were determined using a disposable cardboard mouth-piece attached to a peak flow meter (Mini-Wright AFS; Clement Clarke International, Essex, England), on MEE.
- Direction: higher was better

Adverse events: not reported

Identification

Funding source: financial support was provided by the Associação Fundo de Incentivo à Psicofarmacologia (AFIP, Association for the Incentive Funding of Psychopharmacology).

Conflict of interest statement: funding source declared and unlikely to constitute a conflict of interest.

Country: Brazil

Setting: outpatient clinic: Pediatric Sector of the Noninvasive Mechanical Ventilation Outpatient Clinic of the Psychobiology Department of the Sleep Institute at UNIFESP, Federal University of São Paulo

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Brito 2009 (Continued)

- Study design (cross-over trial) with undetermined carry-over effect
- Potential learning effect regarding techniques and improved co-ordination with performance of assessment techniques was not considered, and may have been a confounder.
- No washout period or time was mentioned.
- Comorbid conditions were not reported (potential confounding factors).
- No mention of standard therapy (how groups were treated throughout the study besides the intervention).
- Separate data for the first period of cross-over were not provided, and data could, therefore, not be included in meta-analysis.

Chatwin 2003
Study characteristics
Methods

Study design: prospective randomised cross-over trial, comparing MI-E to other cough augmentation techniques*

Study grouping: cross-over

'Rescue' vs maintenance therapy: maintenance

Ethics: local ethics committee approval. All participants, parents, or both, provided informed consent

Participants
Baseline characteristics

Separate data were not available for group allocations in the first period of cross-over. Data were presented for all participants, who received all interventions.

Neuromuscular disease group

- Total sample size, n: 22
- Age in years adult and paediatric population combined, mean: 25 (SD 13)
- Age in years paediatric population, mean: 14 (SD 2)
- Age in years adult population, mean: 32 (SD 13)
- Gender (male/female), n: 16/6
- Diagnosis paediatric population, n: SMA 3, DMD 3, CMD 2
- Diagnosis adult population, n: SMA 7, DMD 3, CMD 1, poliomyelitis 3
- Diagnosis total population, n: SMA 10, DMD 6, CMD 3, poliomyelitis 3
- Nocturnal NIPPV, n: 17
- Duration of nocturnal NIPPV in months, mean: 49 (SD 28)
- Courses of antibiotics for respiratory tract infections in preceding 12 months, n range: 2–6
- Poor cough, n (%): 22 (100)
- Severe scoliosis (Cobb angle > 40°), n: 11
- Spinal surgery, n: 11
- SNIP in cmH₂O for paediatric population, mean: 24.8 (SD 9.5)
- SNIP in cmH₂O for adult population, mean: 26.7 (SD 17.9)
- SNIP in cmH₂O for total population, mean: 26.0 (SD 14.8)
- Pmo,w in cmH₂O for paediatric population, mean: 21.5 (SD 10.0)
- Pmo,w in cmH₂O for adult population, mean: 31.2 (SD 30.5)
- Pmo,w in cmH₂O for total population, mean: 27.7 (SD 24.6)
- MIP in cmH₂O for paediatric population, mean: 22.7 (SD 14.3)
- MIP in cmH₂O for adult population, mean: 26.6 (SD 16.8)

Chatwin 2003 (Continued)

- MIP in cmH₂O for total population, mean: 25.3 (SD 15.4)
- MEP in cmH₂O for paediatric population, mean: 19.7 (SD 12.2)
- MEP in cmH₂O for adult population, mean: 29.9 (SD 25.8)
- MEP in cmH₂O for total population, mean: 26.5 (SD 21.9)
- FEV₁ in L for paediatric population, mean: 0.5 (SD 0.4)
- FEV₁ in L for adult population, mean: 0.9 (SD 0.7)
- FEV₁ in L for total population, mean: 0.8 (SD 0.6)
- FVC in L for paediatric population, mean: 0.7 (SD 0.5)
- FVC in L for adult population, mean: 1.1 (SD 0.9)
- FVC in L for total population, mean: 0.9 (SD 0.7)
- FEV₁/FVC in % for paediatric population, mean: 76.41 (SD 23.63)
- FEV₁/FVC in % for adult population, mean: 83.3 (SD 13.9)
- FEV₁/FVC in % for total population, mean: 80.7 (SD 17.3)
- SpO₂ in % for paediatric population, mean: 96 (SD 1)
- SpO₂ in % for adult population, mean: 96 (SD 2)
- SpO₂ in % for total population, mean: 96 (SD 1)
- PETCO₂ in kPa for paediatric population, mean: 5.6 (SD 0.4)
- PETCO₂ in kPa for adult population, mean: 5.7 (SD 0.9)
- PETCO₂ in kPa for total population, mean: 5.6 (SD 0.7)

Inclusion criteria (NMD group)

- Adults and children (all ages)
- History of recurrent chest infections or ineffective cough, or both
- Clinically stable

Exclusion criteria (NMD group)

- Use of antibiotics within 1 month prior to the research
- Resting SpO₂ < 90%
- PETCO₂ > 7 kPa
- Presence of severe bulbar dysfunction
- Previous history of pneumothorax

Age-matched controls

- Total sample size, n:19
- Recruited from staff and families
- Age in years adult and paediatric population combined, mean: 21 (SD 9)
- Age in years paediatric population, mean: 13.6 (SD 2.4) (SD 2)
- Age in years adult population, mean: 26(SD 8)
- SNIP in cmH₂O for paediatric population, mean: 95.8 (SD 19.2)
- SNIP in cmH₂O for adult population, mean: 92.3(SD 29.2)
- SNIP in cmH₂O for total population, mean: 93.8 (SD 24.9)
- Pmo,w in cmH₂O for paediatric population, mean: 113.3 (SD 41.0)
- Pmo,w in cmH₂O for adult population, mean: 145.2 (SD 51.)
- Pmo,w in cmH₂O for total population, mean: 131.7 (SD 48.6)
- MIP in cmH₂O for paediatric population, mean: 102.3 (SD 33.0)
- MIP in cmH₂O for adult population, mean: 103.5 (SD 33.2)
- MIP in cmH₂O for total population, mean: 103.0 (SD 32.2)
- MEP in cmH₂O for paediatric population, mean: 94.1 (SD 39.6)

Chatwin 2003 (Continued)

- MEP in cmH₂O for adult population, mean: 121.1 (SD 39.0)
- MEP in cmH₂O for total population, mean: 109.7 (SD 40.5)
- FEV₁ in L for paediatric population, mean: 2.8 (SD 1.3)
- FEV₁ in L for adult population, mean: 3.5 (SD 0.7)
- FEV₁ in L for total population, mean: 3.2 (SD 1.0)
- FVC in L for paediatric population, mean: 3.5 (SD 1.7)
- FVC in L for adult population, mean: 4.4 (SD 1.2)
- FVC in L for total population, mean: 4.0 (SD 1.5)
- FEV₁/FVC in % for paediatric population, mean: 79.9 (SD 7.6)
- FEV₁/FVC in % for adult population, mean: 80.8 (SD 9.2)
- FEV₁/FVC in % for total population, mean: 80.4 (SD 8.4)
- SpO₂ in % for paediatric population, mean: 97 (SD 1)
- SpO₂ in % for adult population, mean: 98 (SD 1)
- SpO₂ in % for total population, mean: 98 (SD 1)
- PETCO₂ in kPa for paediatric population, mean: 5.3 (SD 0.4)
- PETCO₂ in kPa for adult population, mean: 5.1 (SD 0.5)
- PETCO₂ in kPa for total population, mean: 5.2 (SD 0.5)

Inclusion criteria (controls)

- None provided

Exclusion criteria (controls)

- None provided

Pretreatment: no separate data were provided for the first period of cross-over, or for separate intervention order groups.

Interventions

For all participants, baseline unassisted cough was compared, in random order: to standard physiotherapy and assisted cough; cough after inspiration supported by NIPPV (BiPAP); exsufflation-assisted cough, with negative pressure initiated manually at end of inspiration; insufflation-assisted cough; and exsufflation-assisted cough with negative pressure delivered immediately preceding the cough effort.

Baseline unassisted cough

- Participant positioning: participant's preferred position, "usually seated."
- Technique description: 6 maximal unaided coughs, with rest periods in between. Primary outcomes of PCF and patient comfort were measured, as described above, after the intervention.

Standard "physiotherapy assisted cough"

- Participant positioning: participant's preferred position, "usually seated."
- Technique description: not described. Primary outcomes of PCF and patient comfort were measured, as described, after the intervention.

Cough after inspiration supported by a non-invasive positive pressure ventilator

- Participant positioning: participant's preferred position, "usually seated."
- Technique description: non-invasive positive pressure ventilator (BiPAP) used to support inspiration (Respironics Inc, Murrysville, Pennsylvania, USA or PV401, Breas Medical, Moinlucke, Sweden). Pressures titrated to patient comfort. Primary outcomes of PCF and patient comfort were measured, as described, after the intervention.

Exsufflation-assisted cough, with negative pressure initiated manually at end inspiration

- Participant positioning: participant's preferred position, "usually seated."

Chatwin 2003 (Continued)

- Technique description: using the mechanical in-exsufflator, described for PCF measurement, and a face mask interface ("Cough-Assist;" JH Emerson Co.; Cambridge, Massachusetts, USA); exsufflation pressure titrated for patient comfort and the negative (exsufflation) pressure initiated manually at the end of inspiration. Primary outcomes of PCF and patient comfort were measured, as described, after the intervention.

Insufflation-exsufflation-assisted cough

- Participant positioning: participant's preferred position, "usually seated."
- Technique description: using the mechanical in-exsufflator and a face mask interface ("Cough-Assist;" JH Emerson Co.; Cambridge, Massachusetts, USA). Insufflation was given using the manual mode during the inspiratory phase. Insufflation pressure was titrated for patient comfort. Negative exsufflation pressure was delivered immediately preceding the cough effort. Primary outcomes of PCF and patient comfort were measured, as described above, after the intervention.

Exsufflation-assisted cough with negative pressure delivered immediately preceding the cough effort

- Participant positioning: participant's preferred position, "usually seated."
- Technique description: using the mechanical in-exsufflator, described for PCF measurement, and a face mask interface ("Cough-Assist;" JH Emerson Co.; Cambridge, Massachusetts, USA); exsufflation pressure titrated for patient comfort and the negative (exsufflation) pressure applied immediately before the cough effort. Primary outcomes of PCF and patient comfort were measured, as described, after the intervention.

Outcomes

Separate first-period data were not presented, precluding analysis.

PCF

- Outcome type: continuous outcome
- Reporting: fully reported
- Unit of measure: L/min
- Direction: higher was better
- Participant position: seated
- Technique description: measured by coughing into a tight-fitting, full-face mask (Mirage Full-face mask; ResMed, Abingdon, UK), connected by plastic tubing to a 41 cm long (3.5 cm internal diameter) metal tube, which was, in turn, connected to a Fleisch No. 4 pneumotachograph head (Fleisch, Lausanne, Switzerland) and an electrospirometer (GM Instruments, Kilwinning, UK). The pneumotachograph head was connected via ventilator tubing to a mechanical insufflator-exsufflator ("Cough-Assist;" JH Emerson Co.; Cambridge, Massachusetts, USA). Mask pressure was measured from a side port, with the mask secured to the participant's face to minimise air leak.

VAS comfort, distress, and perceived cough strength

- Outcome type: ordinal
- Reporting: individual VAS scores not presented, only mean overall VAS
- Unit of measure: ordinal scale 0–10
- Direction: higher was better

Adverse events: no adverse events reported and participants were reported to tolerate all interventions well.

Identification

Funding source: Jennifer Trust for Spinal Muscular Atrophy, UK (M Chatwin); Brompton Breathers Trust Fund, UK (patient expenses support); Cystic Fibrosis Trust, UK (E Ross); British Lung Foundation, UK (AH Nickol); Association Française Contre Les Myopathies, France (N Hart)

Conflict of interest: funding sources identified and unlikely to constitute a conflict of interests.

Country: UK

Setting: Sleep and Ventilation Unit, Royal Brompton Hospital

Chatwin 2003 (Continued)

Comments: no conflict of interest mentioned

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Notes

*The study was designed as a parallel non-randomised clinical trial comparing participants with NMD to 19 healthy, age-matched controls (parallel grouping). Only data from the prospective randomised cross-over trial within the NMD participant group was eligible for inclusion in this review.

We contacted the author who was unable to provide additional data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "...random order by coughs assisted by physiotherapy, noninvasive ventilation, insufflation and exsufflation, and exsufflation alone."</p> <p>Quote: "Initial assessment consisted of at least six maximal unaided coughs followed in random order by the cough intervention techniques;"</p> <p>Comment: the interventions in the NMD arm of the study were performed in random order to reduce bias. However, it is unclear how randomisation was performed and whether there were baseline differences between groups.</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: no information was provided. Unclear whether or how allocation concealment was maintained.</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Comment: participants and personnel would have been aware of group allocation, given the nature of the interventions. Those performing the interventions could not be blinded.</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>Comment: PCF was assessed during the cough assist and, therefore, was likely done by a non-blinded outcome assessor; however, this is not clear from the article. The outcome "comfort" was rated on a VAS scale by the participants, who were aware of the intervention they were given. There was no mention of whether the same assessor performed all measurements.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Comment: there were no missing data.</p>
Selective reporting (reporting bias)	Unclear risk	<p>Quote: "Following each intervention, the subjects rated comfort of intervention, distress and strength of cough produced (0: least; 10: most)."</p> <p>Comment: separate VAS scores for patient comfort, distress, and strength of cough were not reported; only 1 VAS result was presented, and it is unclear how this was calculated. It was stated that there was no significant change from baseline in results for comfort or distress of intervention on the VAS.</p>
Other bias	High risk	<p>Comment: the following factors placed the study at high risk of other bias.</p> <ul style="list-style-type: none"> • Study design (cross-over trial) with undetermined carry-over effect.

Chatwin 2003 (Continued)

- Potential learning effect with improved co-ordination and oral control when performing PCF measurements could be a confounder. No information about attempts to minimise the learning effect was provided.
- Unclear whether groups were treated equally.
- Separate data for the first period of cross-over were not available, and data could, therefore, not be used for meta-analysis.

Chatwin 2009
Study characteristics

Methods

Study design: 2-day randomised controlled cross-over trial comparing standard chest physiotherapy with and without MI-E

Study grouping: cross-over

'Rescue' vs maintenance therapy: rescue

Ethics: ethical clearance obtained. All participants, caregivers, or both, provided informed consent

Participants
Baseline characteristics

Separate period data for the cross-over trial were not available, therefore, overall baseline data were presented for the entire sample only.

Overall

- Sample size, n: 8
- Age in years, median: 21.5 (range 4–44)
- Gender (male/female) n: 6/2
- Diagnosis, n: DMD 4, SMA II 3, congenital myopathy 1
- C-reactive protein level in mg/L, median: 113 (range 13–321)
- White cell count in $\times 10^9$ cells/L, median: 14 (range 7–25)
- NIV use, n: 8 (nocturnal 4, occasional 1, > 23 hours/day 2, 20 hours/day 1)
- Difficulty clearing secretions, n: 8
- Duration NIV use in months, median: 19.5 (range 1–130)

Inclusion criteria

- Participants aged > 3 years admitted to Royal Brompton Hospital (adult and paediatric wards) with confirmed NMD and an acute respiratory infection.
 - * Acute respiratory tract infection determined by a participant presenting with ≥ 3 of the following:
 - decreased oxygen saturation < 94%;
 - sputum production (patient producing yellow or green secretions when normally has none);
 - increased shortness of breath (subjectively reported or increase in resting respiratory rate of > 5 breaths/min);
 - pyrexia (temperature > 38 °C);
 - signs of infection on chest x-ray (collapse or consolidation) or auscultation (presence of crackles in lung fields);
 - elevated C-reactive protein (> 5 mg/L) or white-cell count (> $\times 10^9$ cells/L).
- All participants used nocturnal NIV.

Exclusion criteria

- Pneumothorax
- Tracheostomy
- Severe bulbar weakness

Chatwin 2009 (Continued)

- Severe uncontrolled asthma
- Rapidly progressive chest infection with failure to control arterial blood gas tension using NIV
- Patients referred for weaning of NIV after intubation.

Pretreatment: cross-over study. Separate data were not provided for allocation groups at baseline or for the first period of cross-over.

Sputum growth/culture: 3 sputum cultures were positive

Chest x-ray: at baseline 5 participants presented with changes on chest x-ray

Interventions

Intervention characteristics

Participants received MI-E for 1 treatment session and no MI-E for the second treatment session, in a randomly assigned order, with reverse cross-over the following day.

Standard airway clearance therapy without in-exsufflation

- Technique description: modified ACBT on NIV with manual assisted cough (abdominal thrust): ACBT comprised: breathing control, 4 or 5 thoracic expansion exercises by changing settings on NIV to increase tidal volume and for preinsufflation part of cough, with or without manual chest physiotherapy techniques (clapping, shaking), breathing control, forced expiration technique. Expiration was performed with MAC.
- Patient position: not specified
- Frequency: twice a day (morning and afternoon). If evening treatments were required, conventional physiotherapy was provided. If treatment time was required "earlier" than standardised treatment, this was provided and further treatment times adjusted accordingly.
- Duration: minimum 30 min, after which participants were reassessed. If treatment was considered incomplete at 30 min (on reassessment), the session was continued (until fatigue or effective airway clearance or no more secretions). Additional time after 30 min was recorded.

Standard airway clearance therapy with in-exsufflation

- Technique description: similar to non-MI-E intervention ("standard care"), but with MI-E added (CoughAssist, Philips Respironics, Murrysville, Pennsylvania, USA) during the cough manoeuvre (manual mode), together with MAC. Settings were: +20 cmH₂O (range 15–35 cmH₂O) and exsufflation: –20 cmH₂O (range –20 cmH₂O to –40 cmH₂O). Insufflation time 2–4 s, exsufflation time: 4–5 s. A face mask interface was used for MIE.
- Patient position: not specified
- Frequency: twice a day (morning and afternoon). If evening treatments were required, conventional physiotherapy was provided. If treatment time was required "earlier" than standardised treatment, this was provided and further treatment times adjusted accordingly.
- Duration: minimum of 30 min, then reassessed. If treatment was incomplete at 30 min (reassessment), session was continued (until fatigue or effective airway clearance or no more secretions). Additional time after 30 min was recorded.

Outcomes

Separate first-period data were not presented, precluding analysis.

Transcutaneous oxygen saturation (SpO₂)

- Outcome type: continuous
- Reporting: not fully reported
- Unit of measure: %
- Direction: higher was better

PtcCO₂

- Outcome type: continuous
- Reporting: not fully reported
- Unit of measure: %

Chatwin 2009 (Continued)

- Direction: higher was worse

Treatment time after 30 min

- Outcome type: continuous
- Reporting: fully reported
- Unit of measure: min
- Direction: lower was better

Auscultation score

- Outcome type: ordinal, subjective (VAS)
- Reporting: fully reported
- Direction: lower was better

VAS for comfort, mood, breathlessness, fatigue, and presence of sputum

- Outcome type: ordinal, subjective (VAS) – separate scores for each item listed above
- Reporting: not fully reported – some data presented in figures only, no values or significance levels provided
- Direction: lower was better
- Evaluated 1–2 min before and 1–2 min after intervention

Adverse events: fatigue based on VAS; no other adverse events reported on.

Identification

Sponsorship source: partly sponsored by the Jennifer Trust for Spinal Muscular Atrophy, UK

Conflict of interest statement: disclosed a relationship with a healthcare company (Breas Medical) that manufactures ventilation equipment, although the nature of the relationship and the relevance to this study was unclear.

Country: UK

Setting: Royal Brompton Hospital (adult and paediatric wards), London

Comments: M Chatwin disclosed a relationship with Breas Medical, Molnlycke, Sweden; A Simonds had no conflicts of interest.

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Notes

Author was contacted for first-period baseline and outcome data; however, these data were not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "2-day randomized crossover treatment program." Quote: "Patients were randomized to group 1 or group 2." Comment: 2-day randomised cross-over trial; however, unclear how randomisation was performed.

Chatwin 2009 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: no information provided. Unclear whether or how allocation concealment was maintained.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and therapists performing the interventions could not feasibly have been blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: the assessor performing the auscultation and determining the auscultation score was blinded to allocation. No information provided regarding blinding of other outcome assessors. Potential high level of assessor bias for the outcome measure "treatment time."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear whether outcome data on all 8 included participants were presented. This was not explicitly mentioned in the text.
Selective reporting (reporting bias)	High risk	Comment: data were not presented for the primary physiological outcome measures of SpO ₂ , heart rate, and PtcCO ₂ . Other prespecified outcome measures were reported. VAS scores for comfort, breathlessness, and mood were only presented as graphs and data could not be extracted precisely.
Other bias	High risk	<p>Quote: "Airway clearance sessions were standardized to prevent treatment bias. Individuals had their randomized treatment at standardized times, as in other airway clearance studies."</p> <p>Quote: "Patients then continued to have treatment until they were fatigued or there were no longer any secretions produced."</p> <p>Comment: the following factors placed the study at high risk for other bias:</p> <ul style="list-style-type: none"> • Cross-over study design – this may not be the ideal study design for a condition such as NMD requiring long-term follow-up. • Sampling method used: purposive sampling, inclusion of all eligible participants at 1 centre or hospital. • No mention of whether order of group allocation influenced results (carry-over effect). • Separate data for the 2 periods of cross-over were not available, therefore, data could not be pooled in meta-analysis. • Treatment standardisation was in place, but this was not further defined. • A minimum duration of intervention was described, but the stopping rule of 'fatigue' was unclear and could have introduced bias for this outcome measure. • Discrepancy between decrease in secretions (depicted in Figure 2 of publication) with in-exsufflation after intervention and what was stated in the text on page 1477.

Del Amo Castrillo 2019
Study characteristics

Methods	<p>Study design: randomised, open, single-centre, cross-over study comparing breathstacking and mechanical insufflation using VCM, both using a home ventilator</p> <p>Study grouping: cross-over</p> <p>'Rescue' vs maintenance therapy: maintenance</p>
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Del Amo Castrillo 2019 (Continued)

Ethics: ethical clearance obtained. All participants or caregivers (or both) provided informed consent

Participants

Baseline characteristics (n = 20)

Separate data were not available for group allocations in the first period of cross-over. Data were presented for all participants who received all interventions.

- Age in years, median: 32 (IQR 26–50)
- Gender (male/female), n: 14/6
- Diagnosis, n: DMD 7; SMA 6; Ulrich syndrome 1; vacuolar myopathy 1; poliomyelitis 1; gamma-sarcoglycanopathy 2; BMD 1; acid maltase deficiency 1
- Duration of mechanical ventilation in hours n = 18 (2 not determined); median: 8 (IQR 8–10)
- Seated VC in %, median: 17 (IQR 14)
- Maximum inspiratory pressure in cmH₂O, median: 21 (IQR 15)
- Maximum expiratory pressure in cmH₂O, median: 21 (IQR 10)
- PCF in L/min, median: 176 (IQR 68)

Inclusion criteria

- Documented NMD
- Using home NIV with a volumetric mode
- No previous experience with cough-assistance techniques
- Aged > 18 years
- Haemodynamic stability
- Absence of acute respiratory tract infection in the past month
- PCF < 270 L/min or maximum expiratory pressure < 45 cmH₂O

Exclusion criteria

- Concomitant lung disease
- Respiratory infection on day of assessment
- Tracheostomy

Interventions

Intervention characteristics
Breathstacking

- Position: seated in usual wheelchair
- Duration: participants could rest between each cough, and total participation did not exceed 1 hour per person.
- Technique description: using a ventilator equipped with VCM (Astral 150, Resmed, Saint-Priest, France), a face-mask interface (Laerdal Medical, Limonest, France), and volumetric mode, participants performed consecutive inspiratory-hold insufflations until the lungs felt fully expanded, "producing a stretching sensation across the front of the chest, or until the insufflation pressure plateau was 50 cmH₂O. The first exhalation after a single augmented insufflation was used to cough. Care was taken to avoid leaks around the face masks during tests, and during coughing participants received "strong verbal encouragement."
- Repetitions: each test repeated ≥ 3 times

Mechanical insufflation using ventilator VCM

- Position: seated in usual wheelchair
- Duration: participants could rest between each cough, and total participation did not exceed 1 hour per person.
- Technique description: using a ventilator equipped with VCM (Astral 150, Resmed, Saint-Priest, France), a face-mask interface (Laerdal Medical, Limonest, France), and using volumetric mode, lungs were intermittently inflated with a volume greater than participants' baseline tidal volume (hyperinflation cycle): the intermittent deep breath began at 110% of baseline tidal volume, and increased

Del Amo Castrillo 2019 (Continued)

volitionally by 10% increments until the insufflated volume reached the highest tolerated value or 500% of baseline tidal volume or until maximum pressure reached 50 cmH₂O. Care was taken to avoid leaks around the face masks during tests, and during coughing participants received "strong verbal encouragement."

- Repetitions: hyperinsufflation cycle automatically repeated after 30 s of usual cycles. Each test was repeated ≥ 3 times.

Outcomes

Separate first-period data were not presented, precluding analysis.

Primary outcome measures

PCF

- Outcome type: continuous
- Reporting: not fully reported – data presented graphically only
- Unit of measure: L/min
- Technique description: PCF was measured during coughing after the participant was disconnected from the ventilator at the end of the augmented insufflation, to avoid resistance. The highest PCF value of 3 attempts was selected, if the difference did not exceed 10% of the other 2 values.

All measurements were taken with the participant in a sitting position. The PCF measurements were made using a pneumotachograph (Fleisch No. 4, Lausanne, Switzerland). Flow increases were linear at 600 L/min, therefore the volume measured during calibration with a syringe was not influenced by flows of 30–600 L/min. The flow signal was sampled at 1000 Hz and recorded using an analogue-numeric system (MP100, Biopac System, Goleta, California, USA) and its software (AcqKnowledge).

- Direction: higher was better

Inspiratory capacity

- Outcome type: continuous
- Reporting: fully reported
- Unit of measure: L
- Technique description: calculated as tidal volume delivered by the ventilator multiplied by the number of stacked breaths during breathstacking and as the delivered volume during VCM.
- Direction: higher was better

Secondary outcome measures

Subjective ratings of breathing comfort

- Outcome type: ordinal, 10-point VAS
- Reporting: fully reported
- Unit of measure: no units
- Technique description: at the end of each intervention the participant was asked to rate their breathing comfort from 0 to 10
- Direction: higher was better, scores range from 0 (I breathe very badly) to 10 (I breathe very well).

Subjective ratings of cough effectiveness

- Outcome type: ordinal, 10-point VAS
- Reporting: fully reported
- Unit of measure: no units
- Technique description: at the end of each intervention the participant was asked to rate their cough effectiveness from 0 to 10
- Direction: higher was better, scores ranged from 0, indicating a completely inefficient cough, to 10, indicating a fully effective cough.

Oxygen saturation and heart rate were recorded but not listed as primary or secondary outcome measures.

Del Amo Castrillo 2019 (Continued)

Adverse events: not reported

Identification

Sponsorship source: not stated

Conflict of interest: the authors disclosed a relationship with ResMed France, the company who manufacture the VCM ventilator device. The exact nature of the relationship was unclear.

Country: France

Setting: home ventilation unit of the medical ICU of the Raymond Poincaré Teaching Hospital, Garches, France

Comments: authors disclosed a relationship with ResMed, France

First author name: Del Amo Castrillo

Institution: Ms Del Amo Castrillo, Mr Lacombe, and Mr Bore were affiliated with the ICU at Hôpital Raymond Poincaré, AP-HP, Garches, France. Ms Vaugier and Dr Orlikowski were affiliated with Hôpital Raymond Poincaré, INSERM CIC 1429, Garches, France. Ms Falaize and Dr Prigent, and Dr Lofaso were affiliated with Service de Physiologie-Explorations Fonctionnelles, Hôpital Raymond Poincaré, AP-HP, Garches, France

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Notes

Study was approved by the French Ethics Committee (Comité de Protection des Personnes) of Saint-Germain-en-Laye, France, on 3 September 2015 (NCPP15031) and registered on ClinicalTrials.gov as NCT02847299.

Attempts to contact the trial author for additional data were unsuccessful.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "We used a randomized, open, single-center, crossover design..." Comment: method of randomisation not described.
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not mentioned in the article.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "One physiotherapist and one technician carried out the tests, prevented leakage and performing measurements." Comment: the same personnel conducted all interventions and measurements, and, therefore, it was highly unlikely that they would have been blinded. The nature of the interventions suggested that participants could not have been blinded to allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "One physiotherapist and one technician carried out the tests, prevented leakage and performing measurements." Comment: all outcome assessments were measured by the same technician, who could not feasibly have been blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcome measures were reported for all participants.

Del Amo Castrillo 2019 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: all primary and secondary outcome measures were fully reported.
Other bias	High risk	<p>Comment: the following factors placed this study at high risk of other sources of bias.</p> <ul style="list-style-type: none"> • Short-term cross-over study design – this may not be the ideal study design for a condition such as NMD requiring long-term follow-up. • There was no mention of whether order of group allocation influenced results (carry-over effect). • Separate data for the 2 periods of cross-over were not available, precluding analysis.

Jenkins 2014
Study characteristics

Methods	<p>Study design: RCT comparing IBS to sham intervention*</p> <p>Study grouping: cross-over</p> <p>'Rescue' vs maintenance therapy: both inpatients and outpatients were included, no differentiation made between rescue and maintenance therapy.</p> <p>Ethics: no information available regarding ethical review provided for the RCT. For the second, non-randomised study, approval by the University of Manitoba's Research Ethics Board was reported. Written informed consent was obtained from all caregivers, and assent was obtained from participants where applicable.</p>
Participants	<p>Baseline characteristics</p> <p>No separate data were provided for the first period of cross-over; therefore, aggregated data are provided for all participants, who underwent all interventions.</p> <ul style="list-style-type: none"> • Sample size, n: 23 • Age in years, mean: 11 (range 3–19) • Gender (male/female), n: 17/6 • Diagnosis, n: NMD disorders: DMD 8; SMA 1; facio-scapulo-humeral muscular dystrophy 1; congenital fibre type disproportion (myopathy) 1; BMD 1; limb girdle muscular dystrophy 1; Charcot-Marie-Tooth Type 1 disease 1. 9 children with other CNS disorders were also included, without separation of results: seizure disorder 1, cerebral palsy 2, spinal cord injury 1, Rett syndrome 1, encephalomalacia 1, hypoxic brain injury 1, Batten disease 1, and Cri-du-Chat syndrome 1. • Bodyweight in kg, mean: 43.8 (range 12–80) • Cognitively aware and able to communicate, n: 15 • Scoliosis, n: 12 • Spinal fusion surgery, n: 7 • Ambulatory, n: 5 • NIPPV at night, n: 7 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Aged > 1 year • Diagnosed with NMD • Admitted to Winnipeg Children's hospital <i>and</i> required chest physiotherapy for airway clearance <i>or</i> attended the Muscular Dystrophy Clinic at the Rehabilitation Centre for Children <i>or</i> Children's Hospital Physiotherapy (outpatient follow-up)

Jenkins 2014 (Continued)

Exclusion criteria

None indicated

Pretreatment

No separate group data reported

Interventions

Intervention characteristics

IBS

- Position: those in hospital were studied in different positions (depending on their ability to sit). Sitting position was preferred. All patients attending outpatient facilities were assessed in the sitting position. For the IBS manoeuvre, participants indicated when they felt that maximum stacking was reached.
- Duration: 15 s
- Technique description: 3 involuntary stacking interventions (IBS) were applied to each participant, using a resuscitator bag, mask interface, and a unidirectional valve. IBS was randomly interspersed with sham treatment (same intervention but without a 1-way valve). Prior to, and after each series of interventions, the mask was applied to each participant and 30 s of flow and pressure data were recorded.
- Repetitions: 3

Sham

- Position: those in hospital were studied in different positions (depending on their ability to sit). Sitting position was preferred. All the patients attending outpatient facilities were assessed in the sitting position.
- Duration: 15 s
- Technique description: 3 sham interventions were applied to each participant (using a resuscitation bag and mask without a valve); randomly interspersed with IBS manoeuvres. Prior to, and after each series of interventions, the mask was applied to the participant and 30 s of flow and pressure data were recorded.
- Repetitions: 3

Outcomes

Separate first-period data were not presented, precluding analysis.

Tidal volume

- Outcome type: continuous
- Unit of measure: mL
- Fully reported

Respiratory rate

- Outcome type: continuous
- Unit of measure: breaths/min
- Fully reported

SaO₂

- Outcome type: continuous
- Unit of measure: %
- Fully reported

Adverse events: not reported

Identification

Funding source: Children's Hospital Foundation of Manitoba and Health Sciences Centre Foundation, Winnipeg, Manitoba, Canada

Jenkins 2014 (Continued)

Conflict of interest: funding source declared and unlikely to constitute a conflict of interest.

Country: Canada

Setting: Winnipeg Children's Hospital for inpatients; Muscular Dystrophy Clinic at The Rehabilitation Centre for Children or Children's Hospital Physiotherapy for outpatient follow-up

Comments: some participants were unable to communicate verbally or follow instructions (due to age and cognition level). This study formed the basis of the Masters thesis by HML Jenkins.

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Notes

Attempts to contact corresponding author for first-period data were unsuccessful.

*This paper also reported on a second study, which was a "comparative study" of voluntary and supported, compared to IBS in 6 children and adolescents with DMD. Although the order of voluntary and IBS was randomised, all received supported breathstacking as the final intervention. Therefore, this study was an observational, non-randomised study, which did not qualify for inclusion in this review. Only data for the randomised cross-over trial are therefore presented.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This initial study of IBS followed a randomized cross over design. Inpatient subjects were assigned by blocked order randomization to two streams, either receiving the intervention or the sham in the morning and the reverse in the afternoon of the same day." Quote: "randomized cross over design." Quote: "assigned by blocked order randomization to two streams," Quote: "For each participant the sequence of interventions was randomized." Comment: randomised cross-over trial; however, no indication was given as to how randomisation was achieved.
Allocation concealment (selection bias)	Unclear risk	Comment: unclear how allocation concealment was maintained. No information was provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The sham trial was done to rule out the possible effects of the placement of a mask on the child's face and of the effect of dead space ventilation during the 1 min of recording time." Comment: unclear if blinding was successfully achieved. Both IBS and sham were performed in the same way except for the presence or absence of a valve. Unclear if the masks looked identical, with a sham valve, or whether the valve was simply not added to the mask circuit for the sham intervention. It is likely that the intervention would have "felt" different, and in that way could have unblinded participants. Some participants were not cognitively aware/could not communicate.
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: insufficient information to allow judgement. Not stated if the assessments were performed by the physiotherapists performing the interven-

Jenkins 2014 (Continued)

All outcomes		tions/sham or if they were performed by an independent assessor. If the assessor was present during the stacking manoeuvres to take the measurements, they would have been aware of the intervention (allocation).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Twenty-four children and adolescents participated in the study of IBS. Data from one patient were excluded due to a face mask leak. Twenty-three children, 15 inpatients and 8 outpatients, were included in the final analysis." Comment: it was mentioned that 1 participant's results were excluded due to a facial mask leak, and this was considered unlikely to have introduced bias. Data of 4 participants who could not breathstack were described in the text (e.g. all had a tidal volume lower than the dead space of the mask).
Selective reporting (reporting bias)	Low risk	Comment: all outcome measures described in the methods section were reported.
Other bias	High risk	Comment: the following factors placed the study at high risk for other bias. <ul style="list-style-type: none"> • Short-term cross-over study design, with unknown carry-over effect. A short-term cross-over design may not be appropriate to NMD, a condition that requires long-term follow-up. • The heterogeneity of neurological and neuromuscular conditions (including cerebral palsy, spinal cord injury, progressive muscular dystrophy, etc.) decreases the generalisability of the results, owing to differences in underlying pathology, upper motor and lower motor neuron involvement, progression of conditions, etc. • The mean of 3 trials was used for analysis, but the authors did not specify if there was a limitation on the variation between the 3 trials and the mean could, therefore, present skewed results if there a large variance/outliers were present. • Oral control/bulbar involvement may have influenced results, and this was not well considered. • No washout period was mentioned. • Learning effect with different procedures/interventions could have introduced bias, and was not accounted for. • Unclear whether the groups were similar at the start of the study. • Separate data were not available for the 2 periods of the study. Only pooled data per intervention were available and data could, therefore, not be used for meta-analysis. • Unclear whether groups were treated similarly throughout the study, as no information was available.

Katz 2019
Study characteristics

Methods	<p>Study design: multicentre 2-year RCT comparing LVR (breathstacking exercises) as an add-on to conventional treatment and conventional treatment alone*</p> <p>Study grouping: parallel-group assignment</p> <p>'Rescue' vs maintenance therapy: maintenance</p> <p>Ethics: no information regarding ethical review or informed consent was provided.</p>
Participants	<p>Baseline characteristics (entire sample, n = 67)</p>

Katz 2019 (Continued)

- Sample size, n: 67
- Age in years, median: 11.4
- Gender (male/female), n: 67/0
- Diagnosis, n (%): DMD 67 (100)
- Baseline FVC (% predicted), median: 85.5%
- Percentage ambulatory: 31.9%

Conventional treatment + LVR

No separate group data were presented

Conventional treatment

No separate group data were presented

Inclusion criteria

- Boys aged 6–16 years
- Diagnosed with DMD: confirmed by any of the following: muscle biopsy showing complete dystrophin deficiency; genetic test positive for deletion or duplication in the dystrophin gene resulting in an 'out-of-frame' mutation; or dystrophin gene sequencing showing a mutation associated with DMD.
- FVC \geq 30% predicted
- A caregiver willing to provide the therapy
- Fluency in English or French

Exclusion criteria

- Unable to perform pulmonary function tests or LVR manoeuvre, or both
- Presence of an endotracheal or tracheostomy tube
- Already using LVR or the Respironics in-exsufflator between and during respiratory infections, or both
- Known susceptibility to pneumothorax or pneumomediastinum
- Uncontrolled asthma or other obstructive lung disease
- Symptomatic cardiomyopathy (ejection fraction < 50%)

Interventions
Conventional treatment

This could have included:

- physiotherapy, consisting of percussion, active cycle of breathing, postural drainage, or a combination;
- nutritional support, consisting of oral or tube-fed dietary supplements;
- antibiotics (oral or intravenous), if there was evidence of respiratory infection;
- NIPPV, if there was evidence of nocturnal hypoventilation or sleep-disordered breathing;
- systemic steroids.

LVR (breathstacking)

Participants were instructed to use LVR (breathstacking) twice per day, using an inexpensive, portable self-inflating resuscitation bag containing a 1-way valve and mouthpiece. Details regarding the number of repetitions/sets per session were not provided.

Duration: 2 years

Outcomes
Primary outcome measures

- Relative decline in FVC (% predicted) over 2 years, measured according to American Thoracic Society standards, using the Stanojevic normative equations (time frame 2 years)

Secondary outcome measures

- Time to FVC decline of 10% of predicted (time frame 2 years)

Katz 2019 (Continued)

- Total number and duration of outpatient oral antibiotic courses, hospital and ICU admissions for respiratory exacerbations over 2 years
- Health-related quality of life over 2 years: measured biannually with Pediatric Quality of Life Inventory 4.0
- Change in unassisted PCF over 2 years
- Change in MIC over 2 years
- Change in MIP over 2 years
- Change in Pe max over 2 years

Other outcome measures

- Maximal and mean pressure achieved with LVR (cmH₂O) (time frame 2 years)
- Respiratory symptoms: assessed every 3 months by telephone and personnel interview at clinic visits. A self-report usage diary was given to participants to record daily activities to help with recall at the telephone follow-ups
- Satisfaction with LVR, as assessed every 3 months by telephone

Adverse events: not listed as a primary or secondary outcome in the published protocol, but were reported in the abstract. It is unclear what adverse events were monitored or recorded.

Identification

Funding source: Children's Hospital of Eastern Ontario

Conflict of interest: Craig Campbell declared a "Scientific Medical Advisor relationship with Biogen, Genzyme, PTC Therapeutics" and Sherri Katz disclosed a financial speaker relationship with Biogen.

Unclear how declared interests may have influenced the study.

Country: Canada

Setting: participants were recruited from 9 tertiary care paediatric hospitals across Canada. Interventions were conducted at the participants' homes.

Comments: none

First author name: Sherri Katz

Institutions: Canadian study sites listed on the protocol: Alberta Children's Hospital; Stollery Children's Hospital; BC Children's Hospital; McMaster University; London Health Sciences; Children's Hospital of Eastern Ontario; Holland Bloorview Kids Rehabilitation Hospital; SickKids Hospital; Hôpital Ste. Justine

Email: not provided

Address: not provided

Notes

*Information was sourced from a published abstract of findings as well as from ClinicalTrials.org. Adherence to all aspects of the published protocol could not be assessed based on the published abstract. No contact information was available on either the abstract or protocol; however, a current email address of the corresponding author was identified using "Google" search and she was contacted (unsuccessfully) for additional information.

Risk of bias

Bias

Authors' judgement

Support for judgement

Random sequence generation (selection bias)

Unclear risk

Quote: "multi-centre randomized controlled trial."

Quote: "Participants were allocated with a minimisation procedure to receive conventional treatment or conventional treatment plus twice daily lung volume recruitment exercises."

Katz 2019 (Continued)

		Comment: unclear whether the minimisation procedure biased the randomisation procedure, as there was insufficient methodological information.
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single (Investigator) blinding." Comment: no information provided regarding participant blinding; however, considering they were randomised to receiving breathstacking with standard care or standard care alone, blinding of participants seems unlikely to have been achievable.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: study was described as single blinded, but there was no description provided of how blinding was maintained.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Primary analysis was by intention to treat." Quote: "Multiple imputation was used to account for longitudinal missing data." Comment: there was no indication of dropout numbers or reasons for loss to follow-up.
Selective reporting (reporting bias)	High risk	Comment: published protocol listed numerous outcome measures. Only FVC, time to 10% decline in FVC, and adverse events (adverse events was not an a priori listed outcome measure) were reported in the published abstract.
Other bias	Unclear risk	Comment: insufficient detail provided in the description of interventions.

Kim 2016
Study characteristics

Methods	<p>Study design: randomised controlled cross-over trial comparing unassisted cough and cough augmentation using MAC, MIE, and MIE + MAC.</p> <p>Study grouping: cross-over</p> <p>'Rescue' vs maintenance therapy: maintenance</p> <p>Ethics: all 40 participants provided written informed consent. Ethical approval was obtained from the local ethics committee (no reference number provided).</p>
Participants	<p>Baseline characteristics</p> <p>Separate period data were not provided for the cross-over trial; therefore, only overall sample data were reported.</p> <ul style="list-style-type: none"> • Total sample size, n: 40 • Age in years, mean: 20.9 (SD 7.2) • Gender (male/female), n: 37/3 • FVC in mL, mean: 667.4 (SD 313.4) • FVC % predicted value, mean: 17.9 (SD 10.2) • MIP in cmH₂O, mean: 19.5 (SD 10.2) • MIP% predicted value, mean: 19.1 (SD 10.3)

Kim 2016 (Continued)

- MEP in cmH₂O, mean: 25.3 (SD 19.6)
- MEP% predicted value, mean: 16.0 (SD 12.7)
- Diagnosis, n: DMD 20, SMA 13, progressive muscular dystrophy 5, myasthenia gravis 1, congenital myopathy 1

Inclusion criteria

- Stable NMD
- Receiving NIV
- Familiar with the use of MIE device at time of enrolment

Exclusion criteria

- Pneumonia or another intercurrent respiratory infection
- Cognitive impairment
- Severe bulbar dysfunction
- Tracheostomy status

Interventions

Intervention characteristics

Unassisted cough

- Participant positioning: semi-recumbent or sitting (60° to 90° from supine)
- Technique description: participants were asked to cough as forcefully as possible through the CoughAid (at the same time the pushing bar was pressed to allow air flow through the device)
- Washout after intervention: 10 min

Manual thrust (MAC) following manual breathstacking

- Participant positioning: semi-recumbent or sitting (60–90° from supine)
- Technique description: maximal breathstacking was performed with an Ambu-bag (attached to the connection part of the CoughAid) up to MIC. Thereafter, the participant was asked to cough (while pushing bar was pressed) and MAC (abdominal thrust) was applied.
- Washout after intervention: 10 min

MI-E

- Participant positioning: semi-recumbent or sitting (60° to 90° from supine)
- Technique description: MI-E device (CoughAssist, Respironics) was connected to the CoughAid, insufflation pressure of +40 cmH₂O and exsufflation pressure of –40 cmH₂O were applied. 5 cycles were performed using the manual mode (to correlate with patient's inspiratory and cough efforts). Insufflation time 3 s, exsufflation time 2 s, with a 3 s pause between cycles. On the 5th application, the participant was asked to perform a maximal voluntary cough into the CoughAid. A face mask interface was used.
- Washout after intervention: 10 min

MI-E + manual thrust

- Participant positioning: semi-recumbent or sitting (60° to 90° from supine)
- Technique description: similar to MI-E technique, with the addition of an abdominal thrust (MAC) being applied during the cough manoeuvre.
- Washout after intervention: 10 min

Outcomes

Separate first-period data were not presented, precluding analysis.

PCF

- Outcome type: continuous
- Units: L/min

Kim 2016 (Continued)

- Measurement technique: the Cough Aid technique was used to measure PCF, using a 1-way valve connected to the MI-E or Ambu-bag; and a "pushing bar" which is pressed manually during cough to allow air to exit through the device. A commercial flow analyser test system with the Cough Aid device (Certifier FA, TSI Inc, Shoreview, Minnesota, USA) was used to measure PCF.
- Fully reported

Adverse events: not reported. All 3 cough augmentation techniques were reported to be "well tolerated."

Identification	<p>Sponsorship source: none mentioned</p> <p>Conflict of interest: declared no financial conflicts of interests, but other interests were not declared.</p> <p>Country: Korea</p> <p>Setting: not specifically stated</p> <p>Comments: seemed to have been in an outpatient setting; however, the exact setting was unclear.</p> <p>First author name: Sun Mi Kim</p> <p>Corresponding author: Dr Seong-Woong Kang</p> <p>Institution: Yonsei University College of Medicine</p> <p>Email: kswoong@yuhs.ac</p> <p>Address: Department of Rehabilitation Medicine, Gangnam Severance Hospital, Rehabilitation Institute of Neuromuscular Disease, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea</p>
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Notes	<p>Attempts to contact authors for first-period data were unsuccessful.</p> <p>A new device was used for measurement of PCF (CoughAid), and authors indicated that it accurately measured PCF in people with ALS. However, the article referred to the effectiveness of the CoughAid as a cough augmentation device, not as a measurement device for PCF. Therefore, the validity of this device was unclear.</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...following an MIC maneuver, MI-E, and MI-E in combination with manual thrust, with a 10-minute washout period between conditions. The order of the PCF measurements was randomized." Quote: "randomized crossover single-center controlled trial," Comment: randomised cross-over trial with randomisation of order of cough augmentation techniques. However, the method of randomisation was unclear.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to allow judgement (method of concealment not described).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: neither participants nor personnel could feasibly be blinded to cough augmentation intervention allocation.
Blinding of outcome assessment (detection bias)	High risk	Comment: same staff performing the cough intervention also performed the assessment; there was no attempt to blind outcome measurement.

Kim 2016 (Continued)

All outcomes		However, it noted that inter-rater (0.98) and intra-rater (0.99) reliability for measuring the primary outcome of PCF was high.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no attritions, and all participants performed all interventions. There were no dropouts or loss to follow-up.
Selective reporting (reporting bias)	Low risk	Comment: the primary outcome measure of PCF was fully reported. No secondary outcome measures were defined.
Other bias	High risk	<p>Comment: the following factors placed the study at high risk for other bias.</p> <ul style="list-style-type: none"> • Short-term cross-over study design, which may not be appropriate for a condition such as NMD, which requires long-term follow-up. • Undetermined carry-over effect. • The authors acknowledged the following limitation: some participants individually showed better PCF values with MAC following MIC, than with MI-E alone. Presenting aggregated mean values may have obscured individual variation. It would have reduced bias to present between subject variability. • The use of NIV (diurnal, nocturnal, or both) was not specified, which is a potential confounder. • Mean change in PCF was not compared among different interventions, rather the absolute values obtained with the interventions were reported. • The CoughAid device was reported to be valid and reliable in ALS; however, the cited study was not aimed at determining validation/accuracy of measurement, and the population (ALS vs other NMD), also differed. Therefore, the validity of the device in measuring PCF in the general NMD population was unclear. • The results sections and descriptions of statistical analytical methods were limited. • No separate data were available for each period of cross-over study, and data were, therefore, unable to be pooled for meta-analysis. • Unclear if patients were treated equally between the different arms of the study, in terms of standard management. • No distinction could be made between the various conditions (DMD, SMA, etc.) or age groups (adolescents and adults). • No washout period was described. • Learning effect may have influenced the results.

Lacombe 2014
Study characteristics

Methods	<p>Design: randomised controlled cross-over trial comparing mechanical insufflation + MAC, MI-E, and MI-E + MAC</p> <p>Group: cross-over</p> <p>'Rescue' vs maintenance therapy: maintenance</p> <p>Ethics: approved by hospital's ethics committee. Patients provided written informed consent before participating. Registered on ClinicalTrials.gov (NCT01518439).</p> <p>Time frame: March 2012 to June 2013</p>
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Lacombe 2014 (Continued)

Additional comments on methodology: open, single-centre, randomised (block size of 6) cross-over study

Participants

The author provided baseline separate group allocation data for the first period of cross-over on request.

Baseline characteristics
Entire sample

- Sample size, n: 18
- Age in years, median: 28.5 (IQR 24.0–38.0)
- Gender (male/female), n: 13/5
- Diagnosis, n: DMD 9; BMD 1; acid maltase deficiency 2; SMA 2; congenital MD 1; gamma-sarcoglycanopathy 2; Ulrich syndrome 1
- Duration of mechanical ventilation during the day in hours/day, median: 10 (IQR 8–13.5)
- VC, in %, median: 11.5 (IQR 8–22)
- MIP in cmH₂O, mean: 15.05 (SD 6.06)
- MEP in cmH₂O, median: 12 (IQR 10–16)
- PCF in L/min, mean: 124.2 (SD 60.6)
- IPPB pressure in cmH₂O, median: 39 (IQR 35–840)

Mechanical insufflation + MAC

- Sample size, n: 4
- Age in years, median: 30.5 (IQR 4.25)
- Gender (male/female), n: 2/2
- Diagnosis, n: DMD 2; congenital MD 1; gamma-sarcoglycanopathy 1
- Mechanical ventilation duration in hour/day, median: 16.5 (IQR 13.5)
- VC seated in %, mean: 18.5 (SD 5)
- MIP in cmH₂O, mean: 14.5 (SD 7.75)
- MEP in cmH₂O, mean: 9 (SD 7)
- PCF in L/min, mean: 100.8 (SD 69.0)
- IPPB pressure in cmH₂O, mean: 37.5 (SD 6.25)
- MI-E pressure in cmH₂O, mean (SD): N/A

MI-E

- Sample size, n: 7
- Age in years, median: 31 (IQR 18.5)
- Gender (male/female), n: 5/2
- Diagnosis, n: DMD 3; BD 1; SMA 1; gamma-sarcoglycanopathy 1; acid maltase deficiency 1
- Mechanical ventilation duration in hour/day, median: 8 (IQR 1.5)
- VC seated in %, mean: 22 (SD 16)
- MIP in cmH₂O, mean: 20 (SD 8)
- MEP in cmH₂O, mean: 16 (SD 29.5)
- PCF in L/min, mean: 157.2 (SD 64.2)
- IPPB pressure in cmH₂O, mean (SD): N/A
- MI-E pressure in cmH₂O, mean: +33 (SD 4.5)/–38 (SD 3)

MI-E + MAC

- Sample size, n: 7
- Age in years, median: 25 (IQR 7.5)
- Gender (male/female), n: 6/1

Lacombe 2014 (Continued)

- Diagnosis, n: DMD 4; SMA 1; acid maltase deficiency 1; Ulrich syndrome 1
- Mechanical ventilation duration in hour/day, mean: 10 (SD 2.25)
- VC seated in %, mean: 8 (SD 2.5)
- MIP in cmH₂O, mean: 15 (SD 4.5)
- MEP in cmH₂O, mean: 11 (SD 3.5)
- PCF in L/min, mean: 104.4 (SD 41.4)
- IPPB pressure in cmH₂O, mean (SD): N/A
- MI-E pressure in cmH₂O, mean: +35 (SD 6.5)/-40 (SD 3.5)

Inclusion criteria

- Confirmed/documentated NMD
- Cough assist naive (inexperienced)
- Aged > 18 years
- Haemodynamically stable
- Absence of acute respiratory infection (bronchial congestion) 1 month prior to study
- PCF < 3 L/sec (180 L/min) (threshold for statutory healthcare insurance coverage in France and Belgium) or MEP < 45 cmH₂O
- Presence of NIV

Exclusion criteria

None specified

Pretreatment

Baseline VC was considerably different among participant groups, with the lowest value recorded in the MI-E + MAC group. This suggests there may have been baseline differences in participant groups, which may have influenced the outcomes.

Interventions
Mechanical insufflation + MAC

Position: seated in wheelchair

Technique description: insufflation was provided by an Alpha 200 C ventilator (Air Liquide, Antony, France). Participants started IPPB insufflation with an inspiratory effort, then allowed the insufflation to continue passively until the selected inspiratory pressure was reached in about 5 s. The lowest inspiratory trigger was chosen to facilitate the start of insufflation. Inspiratory pressure (insufflation) with IPPB was increased gradually to the highest tolerated value, or 40 cmH₂O. Inspiratory flow was set to maximise participant comfort.

Once target inspiratory pressure was reached, 1 physiotherapist removed the IPPB circuit to avoid resistance while coughing. At the same time, MAC (compression to the abdomen, thorax, or both, participant and on cough efficiency as perceived by the participant and physiotherapist.

Interface: IPPB was applied using a face mask, chosen to fit each participant individually.

MI-E

Participant position: seated in wheelchair

Technique description: MI-E was performed using the CoughAssist device (JH Emerson Co., Cambridge, Massachusetts, USA) in manual mode. After each insufflation, a physiotherapist delivered the exsufflation while simultaneously asking the participant to cough. Inspiratory and expiratory pressures were increased/decreased gradually to the highest/lowest tolerated values, up to +40 cmH₂O for inspiratory pressure and down to -40 cmH₂O for expiratory pressure. Insufflation flow adjustment (high or low insufflation flow) was set according to participant comfort.

Interface: MI-E was applied using a face mask, chosen to fit each participant individually.

MI-E + MAC

Lacombe 2014 (Continued)

MI-E and MAC interventions as described above.

Outcomes

Separate first-period data were not presented, precluding analysis.

Primary objective outcome

PCF

- Outcome type: continuous
- Unit of measure: L/min
- Measurement: unassisted cough effort. All tests were repeated ≥ 3 times. The highest PCF value was used for analysis (if the difference did not exceed 10% of the other 2 values). Flow was measured making use of a Fleisch No. 4 Pneumotachograph
- First-period data fully reported on request

Secondary objective outcomes

Effective cough time: time with PCF > 3 L/s or 180 L/min

- Outcome type: continuous
- Unit of measure: ms
- Not fully reported (presented graphically only)

Inspiratory capacity

- Outcome type: continuous
- Unit of measure: L
- Not fully reported (presented graphically only)

Secondary subjective outcomes

Comfort ratings

- Outcome type: ordinal
- Unit of measure: VAS (0 – "I breathe very badly" to 10 – "I breathe very well")
- Fully reported

Subjective cough effectiveness

- Outcome type: ordinal
- Unit of measure: VAS (0 – completely inefficient cough to 10 – fully effective cough)
- Fully reported

Adverse events: not reported

Identification

Sponsorship source: no declaration of funding source

Conflict of interest: not declared

Country: France

Setting: home ventilation unit of the medical ICU, Raymond Poincare Teaching Hospital, Garches

Comments: registered on ClinicalTrials.gov (NCT01518439)

Author name: Matthieu Lacombe was the primary author; Prof F Lofaso is the contact author

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Lacombe 2014 (Continued)

805, Hôpital Raymond Poincaré, AP-HP, Garches; EA 4497, Université de Versailles Saint-Quentin-en-Yvelines, Versailles, France"

Notes	Separate baseline data and postintervention data for first-period group allocation were provided by author on request.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: cross-over trial during which cough assist techniques were applied in random order; however, it was unclear how randomisation was performed.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information was provided to determine if participants/physiotherapists involved in the study could have foreseen the cough augmentation technique allocated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: it would not be possible for participants and those implementing the cough augmentation techniques to be blinded to the cough augmentation used. 3 physiotherapists (MLa, LDAC, and AB) were involved in interventions and assessments. For each participant, 2 physiotherapists were needed for the intervention: 1 for using the device and 1 for MAC manoeuvres. The same physiotherapist performed the different cough techniques for a single participant. In addition, the same technician (MLe) performed the measurements.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: unclear whether the outcome assessor was blinded to group allocation, but seems likely that blinding would not have been possible.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no incomplete data in the study report.
Selective reporting (reporting bias)	Unclear risk	Comment: primary outcome measure of PCF and secondary outcomes of effective cough time and inspiratory capacity were only presented graphically, with no specific values provided. Subjective secondary outcome measures of comfort and cough effectiveness (VAS) were fully reported.
Other bias	High risk	Comment: the following factors placed the study at high risk of other bias. <ul style="list-style-type: none"> • Cross-over study design, which may not be appropriate for a condition such as NMD, which requires long-term follow-up. • Undetermined carry-over effect. • Learning effect, fatigue, and the variety of NMD included could have affected outcomes (potential confounders). • Standardisation of interventions were not ensured, with techniques adapted for participant comfort.

Sivasothy 2001
Study characteristics

Methods	Study design: randomised controlled cross-over trial comparing 3 cough augmentation techniques: MAC; mechanical insufflation, and mechanical insufflation with MAC* Study grouping: cross-over
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Sivasothy 2001 (Continued)

'Rescue' vs maintenance therapy: maintenance

Ethics: no mention of ethical clearance/number. All participants provided informed consent prior to participation.

Participants

Baseline characteristics*

Respiratory muscle weakness participant group – with scoliosis (separate data not presented for 2 periods of cross-over trial)

- Sample size, n: 4
- Diagnoses, n: previous poliomyelitis 2; DMD 1; SMA 1
- Age in years, median: 57 (range 44–66)
- Gender (male/female), n: 3/1
- MIP in cmH₂O, median: 37 (range 30–49)
- MIP % predicted, median: 41 (range 37.6–50.7)
- MEP in cmH₂O, median: 51 (range 17–62)
- MEP % predicted, median: 42 (range 36.4–67.3)
- FEV₁ in L, median: 0.8 (range 0.65–1.25)
- FEV1 % predicted, median: 33 (range 28.4–40.4)
- FVC in L, median: 1.5 (range 0.7–1.75)
- FVC % predicted, median: 35 (range 15–42.9)
- PEF in L/min, median: 225 (range 220–240)
- PEF % predicted, median: 47 (range 45.7–66.7)
- MVV in L/min, median: 33 (range 21–44)
- MVV % predicted, median: 24 (range 17.0–33.8)

Inclusion criteria

- Static inspiratory and expiratory maximal mouth pressures < 70% predicted
- Respiratory muscle weakness diagnosed by a neurologist: subdivided based on presence of thoracic scoliosis diagnosed on physical examination and spinal x-rays with a Cobb angle > 70°

Exclusion criteria

- Presence of other respiratory disease

Respiratory muscle weakness participant group - without scoliosis

- Sample size, n: 8
- Diagnoses, n: amyotrophic lateral sclerosis 7; Becker's muscular dystrophy 1
- Age in years, median: 63 (range 27–73)
- Gender (male/female), n: 8/0
- MIP in cmH₂O, median: 15 (range 11–22)
- MIP % predicted, median: 14 (range 11.9–24.9)
- MEP in cmH₂O, median: 22 (range 16–35)
- MEP % predicted, median: 19 (range 11.7–27.6)
- FEV₁ in L, median: 0.73 (range 0.48–1.8)
- FEV1 % predicted, median: 19 (range 13.6–43.9)
- FVC in L, median: 0.83 (range 0.55–1.57)
- FVC % predicted, median: 18 (range 13–42.0)
- PEF in L/min, median: 123 (range 68–150)
- PEF % predicted, median: 24 (range 13.1–31.9)
- MVV in L/min, median: 26 (range 16–35)
- MVV % predicted, median: 17 (range 11.1–27.8)

Sivasothy 2001 (Continued)

Inclusion criteria

- Respiratory muscle weakness diagnosed by a neurologist: subdivided based on absence of thoracic scoliosis on physical examination and spinal x-rays with a Cobb angle $<70^{\circ}$

Exclusion criteria

- Presence of other respiratory disease

Chronic obstructive pulmonary disease group (COPD)

- Sample size, n: 8
- Diagnoses, n: COPD 8
- Age in years, median: 65 (range 52-74)
- Gender (male/female), n: 3/5
- MIP in cmH₂O, median: 37 (range 18-91)
- MIP % predicted, median: 44 (range 18.5-93.3)
- MEP in cmH₂O, median: 84(range 52-167)
- MEP % predicted, median: 94 (range 74.7-194.3)
- FEV₁ in L, median: 0.95 (range 0.35-1.1)
- FEV1 % predicted, median: 37 (range 13.4-44.2)
- FVC in L, median: range 1.8 (range 0.77-2.75)
- FVC % predicted, median: 66 (range 24.5-84.9)
- PEF in L/min, median: 212 (range 110-270)
- PEF % predicted, median: 51 (range 24.9-66.7)
- MVV in L/min, median: 33 (range 19-60)
- MVV % predicted, median: 32 (range 16.7-66.1)

Inclusion criteria

- Fulfilled the American Thoracic Society criteria for the diagnosis of COPD

Exclusion criteria

- None described

"Normal" volunteers

- Sample size, n: 9
- Diagnoses, n: healthy 9
- Age in years, median: 27 (range 17-71)
- Gender (male/female), n: 4/5
- MIP in cmH₂O, median: 99 (range 59-137)
- MIP % predicted, median: 115 (range 87-151)
- MEP in cmH₂O, median: 126 (range 104-239)
- MEP % predicted, median: 118 (range 83-228)
- FEV₁ in L, median: 3.8 (range 1.7-4.2)
- FEV1 % predicted, median: 98(range 88.3-120.1)
- FVC in L, median: 4.6 (range 2.1-5.9)
- FVC % predicted, median: 100 (range 78.3-120.8)
- PEF in L/min, median: 444 (range 410-633)
- PEF % predicted, median: 103(range 86.9-140)
- MVV in L/min, median: 128 (range 75-195)
- MVV % predicted, median: 107 (range 71-115)

Inclusion criteria

Sivasothy 2001 (Continued)

- "normal" subjects
- non-smokers

Exclusion criteria

- history of respiratory, neuromuscular or cardiovascular disease

Pretreatment

No data were presented for different allocation groups at baseline; neither were separate data presented for the 2 periods of cross-over.

Interventions

Intervention characteristics
MAC

Participant position: semi-recumbent

Technique description: performed by an experienced physiotherapist. Manual thoracoabdominal compression during the expulsive phase of the maximal voluntary cough. Hand position was optimised for participants with scoliosis by placing the hand used for thoracic compression on the hyperinflated hemithorax.

Washout time: ≥ 5 min was allowed between each cough manoeuvre.

Mechanical insufflation

Participant position: semi-recumbent

Technique description: performed with an in-exsufflator (JH Emerson Co, Cambridge, Massachusetts, USA) set to give 20 cmH₂O inspiratory and -20 cmH₂O expiratory pressure. 2 in-exsufflation cycles were delivered and after the third insufflation, the participant was asked to make a maximal voluntary cough without the assistance of negative pressure.

Washout time: ≥ 5 min was allowed between each cough manoeuvre.

Mechanical insufflation with MAC

Participant position: semi-recumbent

Technique description: the 2 techniques above were combined but the technique was not described separately.

Washout time: ≥ 5 min was allowed each cough manoeuvre.

Outcomes

Separate first-period data were not presented, precluding analysis.

Maximal peak cough expiratory flow (PCF)

- Outcome type: continuous
- Unit of measure: L/min
- Measurement technique: a face mask (Hans Rudolf) was attached directly to a 4.5 cm pneumotachograph (PK Morgan), deriving PCF and CEV using an electric transducer and integrator.
- Fully reported

CEV

- Outcome type: continuous
- Unit of measure: L
- Measurement: maximal volume recorded using face mask and pneumotachograph (as described above).
- Fully reported

Sivasothy 2001 (Continued)

Peak value time

- Outcome type: continuous
- Unit of measure: ms
- Measurement: time from onset of expiratory flow to peak cough expiratory flow.
- Fully reported

Oesophageal and gastric pressures (as proxies to pleural and abdominal pressure)

- Outcome type: continuous
- Unit of measure: cmH₂O
- Measurement: using balloon manometry (PK Morgan)
- Not fully reported

Subjective cough effectiveness

- **Outcome type:** categorical/ordinal
- **Unit of measure:** participants were asked if the assisted cough technique had aided, impaired, or had no effect on their cough.
- Not fully reported

Adverse events: reported as none having occurred.

Identification

Sponsorship source: no sponsorship source declared.

Conflict of interest: not declared

Country: UK

Setting: setting of data collected not well described, assumed to be the Respiratory Support and Sleep Centre/Papworth Hospital and 9 healthy volunteers that participated.

Comments: none

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Notes

Attempts to contact the author for additional data were not successful.

*This study was reported as a non-randomised clinical trial of parallel groups (healthy controls; 1 group with chronic obstructive pulmonary disease and 2 groups with NMD and respiratory muscle weakness – 1 with and 1 without scoliosis). Only data from the cross-over component of the trial within the NMD group was eligible for inclusion in this review. The group with NMD and without scoliosis was further excluded, because 7/8 participants had ALS, an excluded condition in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "To exclude bias the order of the treatments was randomised for each subject." Comment: unclear how randomisation was performed.
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment was not described.

Sivasothy 2001 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: neither participants nor personnel were blinded to intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: unclear whether the outcome assessors were blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were accounted for, no dropouts or missing data.
Selective reporting (reporting bias)	Unclear risk	Comment: from the methods section, it was unclear which were the study's primary and secondary outcome measures. There was no trial registration number mentioned so we could not check the predescribed protocol. Gastric and oesophageal pressures were not presented due to the collapse of the balloons in the control groups. The subjective outcome measure of cough effectiveness was not fully reported, it was simply stated that participants did not report any benefit of any assisted cough interventions.
Other bias	High risk	<p>Quote: "All subjects practised with both manually assisted cough and mechanical."</p> <p>Quote: "All subjects practised coughing while the face mask was adjusted to minimise air leaks. An investigator held the subject's cheeks..."</p> <p>Comment: the following factors placed this study at high risk of other bias.</p> <ul style="list-style-type: none"> • Short-term cross-over trial design – this may not be the optimal study design for a condition such as NMD, which requires long-term follow-up. • Unclear carry-over effect. • Separate period data were not provided for the cross-over trial; therefore, data could not be pooled for meta-analysis. • There was no information on whether groups were treated equally, besides the intervention assigned. • Participants practised all the cough augmentation techniques prior to the implementation of interventions and the assessment of PECE, CEV, PVT; therefore, learning effect might also influence the outcome. • Holding the cheeks of the patients could affect the outcomes, e.g. PCF (no mention of bulbar control) – this is a possible confounder.

Torres-Castro 2016
Study characteristics

Methods	<p>Study design: prospective randomised cross-over study comparing air (breath) stacking and glosopharyngeal breathing</p> <p>Study grouping: cross-over</p> <p>'Rescue' vs maintenance therapy: maintenance</p> <p>Ethics: informed consent was obtained from participants. Ethical approval was obtained from the Ethics Committee for Research Involving Human Beings, Faculty of Medicine, University of Chile.</p> <p>Additional information: the author provided selected separate period data on email request.</p>
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Torres-Castro 2016 (Continued)

Participants

Baseline characteristics
Overall sample data

- Sample size, n: 14
- Age in years, median: 12.5 (range 9–18)
- Age at diagnosis in years, mean: 9.9 (SD 3.4)
- Gender (male/female), n: 8/6
- Duration of NIV in months, mean: 25.6 (SD 8.7)
- FVC in mL, mean: 1529 (SD 517)
- FVC % predicted, mean: 62.2 (SD 31.9)
- FEV1 in mL, mean: 1243 (SD 502)
- FEV1 percentage of reference value, mean: 64.1 (SD 31.4)
- FEV₁/FVC, mean: 82.7 (SD 15.5)
- MIP in cmH₂O, mean: 57.5 (SD 10.8)
- MIP % predicted, mean: 57.9 (SD 13.9)
- MEP in cmH₂O, mean: 40.7 (SD 22.2)
- MEP % predicted, mean: 31.5 (SD 21.3)
- PCF in L/min, median: 175 (IQR 130–200)
- Use of wheelchair, n (%): 14 (100)
- Diagnoses, n: DMD 7, SMA type II 3, nemaline myopathy 2, spinal cord injury 1, centronuclear myopathy 1
- Receiving nocturnal NIV in bilevel mode, n (%): 14 (100)

First-period baseline data, as provided by author on request
Breathstacking

- Sample size, n: 7
- Height in cm, mean: 152.29 (SD 9.59)
- Age in years, mean: 12.29 (SD 1.6)
- Gender (male/female), n: 5/2
- VC in mL, mean: 1392.86 (SD 458.83)
- PCF in L/min, mean: 162.86 (SD 77.40)

Glossopharyngeal breathing

- Sample size, n: 7
- Height in cm, mean: 147.57 (SD 18.32)
- Age in years, mean: 11.71 (SD 3.55)
- Gender (male/female), n: 4/3
- VC in mL, mean: 1284.29 (SD 453.28)
- PCF in L/min, mean: 167.14 (SD 42.71)

Inclusion criteria

- Diagnosis of NMD
- Aged 5–18 years
- Without respiratory exacerbation in past 30 days
- No prior use or knowledge of breathstacking or glossopharyngeal breathing techniques
- Ability to understand instructions
- Signed consent to participate

Exclusion criteria

- Tracheostomy

Torres-Castro 2016 (Continued)

- incomplete glottis closure (measured during insufflation manoeuvre)

Interventions

Intervention characteristics

Air/ breathstacking

- Participant positioning: seated in wheelchair
- Technique description: participants were first trained in the execution of the technique for 10 min. A manual resuscitation bag (maximum capacity 1600 mL) was used to provide insufflations (LIFESAVER model 5345, Hudson, Temecula, California, USA), connected to a corrugated tube with an internal diameter of 22 mm, a 1-way valve, and a pipette. A chest physiotherapist insufflated the participant during the inspiratory phase, requesting that they inspire as much air as possible.
- Washout after intervention: 40 min between interventions, which were all performed on the same day.
- Repetitions: 3 measurements of the technique were performed, and the highest reading recorded.
- Rest periods: participants rested for 5 min between each assessment.

Glossopharyngeal breathing

- Participant positioning: seated in wheelchair
- Technique description: participants were first trained in the execution of the technique for 10 min. The participant was instructed to perform successive manoeuvres of "swallowing air" until the maximum volume achieve was maintained.
- Washout after intervention: 40 min between interventions, which were all performed on the same day.
- Repetitions: 3 measurements of the technique were performed, and the highest reading recorded.
- Rest periods: participants rested for 5 min between each assessment.

Outcomes

Primary and secondary outcomes were not explicitly identified.

Baseline VC and postintervention MIC

- Outcome type: continuous
- Unit of measure: L
- Measurement: baseline VC and postintervention MIC were evaluated using a portable ventilometer device (FERRARIS Wright MK 8, Louisville, Colorado, USA). VC and MIC were measured by taking a maximal inspiration followed by a maximal expiration.
- Direction: higher was better
- Reporting: fully reported

PCF

- Outcome type: continuous
- Unit of measure: L/min
- Measurement: PCF was assessed at baseline, and after interventions, with the participant in the seated position, using a peak flow meter (MiniWright, Clement Clarke International, Essex, England) and mask interface. Participants were instructed to cough as hard as possible into the flowmeter connected to his/her mouth. For an evaluation to be considered repeatable, ≥ 3 efforts were required, with a difference $\leq 10\%$ and the highest value was recorded as the PCF.
- Direction: higher was better
- Reporting: fully reported

Adverse events: not reported

Identification

Sponsorship source: no sponsorship source declared.

Conflict of interest: no conflict-of-interest statement presented.

Country: Santiago, Chile

Setting: domiciliary NIV programme recipients, in the participants' own homes

Torres-Castro 2016 (Continued)

Comments: authors declared no competing interests exist.

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Address: not provided

Notes Additional separate-period baseline and outcome data were provided by author on request.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "To minimize the risk of bias, the order of execution of each cough assistance technique was performed randomly for each participant." Quote: "Randomization was performed by a free software (for www.randomization.com) specifically designed for generating random number lists."
Allocation concealment (selection bias)	Unclear risk	Quote: "To minimize the risk of bias, the order of execution of each cough assistance technique was performed randomly for each participant." Comment: the article did not describe whether or how allocation concealment was achieved.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "A chest physiotherapist insufflated the patient during the inspiratory phase." Quote: "The protocol was implemented in the patients' homes by a trained chest physiotherapist." Comment: the chest physiotherapist was physically performing the insufflation interventions; therefore, it would be impossible to blind them. Similarly, the participants could not feasibly be blinded to allocation considering the nature of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "A chest physiotherapist insufflated the patient during the inspiratory phase." Quote: "The protocol was implemented in the patients' homes by a trained chest physiotherapist." Quote: "Baseline PCF assessment was performed with the patient seated and with a respiratory physiotherapist monitoring the seal between the entire surface of the mask and the flowmeter to avoid any leakage." Comment: the baseline, intervention, and outcome assessments seem to have been performed by the same physiotherapist, who could not have been blinded to intervention allocation.
Incomplete outcome data (attrition bias)	Unclear risk	Comment: 3 participants were excluded after screening, but clear reasons for exclusion were not provided.

Torres-Castro 2016 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	Comment: all outcome measures listed in the protocol were reported.
Other bias	Unclear risk	Comment: the following factors placed this study at unclear risk of other bias. <ul style="list-style-type: none"> • Short-term cross-over study, which might not be the optimal study design for a chronic condition such as NMD. • Primary and secondary outcomes were not explicitly identified.

Toussaint 2016
Study characteristics

Methods	<p>Study design: prospective RCT comparing a single session of air (breath) stacking using a resuscitator bag (manual breathstacking) compared to a home ventilator (mechanical breathstacking).</p> <p>Study grouping: parallel-group</p> <p>'Rescue' vs maintenance therapy: maintenance</p> <p>Ethics: informed consent was obtained from patients before recruitment. Approval obtained from the Ethics committee at the institution (Inkendaal Rehabilitation Hospital).</p> <p>Additional information: participants were randomly allocated to 1 of 2 interventions; there was no control group where participants received no intervention. This study was conducted over 2 years (January 2012 to December 2013).</p>
Participants	<p>Baseline characteristics</p> <p>Overall</p> <ul style="list-style-type: none"> • sample size, n: 52 • Age in years: ventilator and resuscitator bag groups were reported separately, but not as a whole (n = 52); mean (SD) was not provided • Body mass index in kg/m², mean (SD): not provided • FVC in mL, mean (SD): not provided • FVC % predicted, mean (SD): not provided • MEP in cmH₂O, mean (SD): not provided • PCF in L/min, mean (SD): not provided • Manually assisted PCF in L/min, mean (SD): not provided • NIV tidal volume in mL, mean: 720 (SD 90) • Mouthpiece intermittent positive pressure ventilation use, n: 35 • Ventilator-free time within a 24-hour period, in hours, mean (SD): not provided • NIV duration in years, mean: 8.2 (SD 5.2) • Ventilator respiratory rate in cycles/min, mean: 22.2 (SD 4.2) <p>Mechanical breathstacking</p> <ul style="list-style-type: none"> • Sample size, n: 27 • Age in years, mean: 25.3 (SD 5.1) • Body mass index in kg/m², mean: 17 (SD 6.5) • FVC in mL, mean: 809 (SD 555) • FVC % predicted, mean: 17 (SD 10) • MEP in cmH₂O, mean: 18.3 (SD 10.9)

Toussaint 2016 (Continued)

- Cough peak flow in L/min, mean: 132 (SD 55)
- MAC peak flow in L/min, mean: 210 (SD 55)
- NIV tidal volume in mL, mean: 716 (SD 88)
- Mouthpiece intermittent positive pressure ventilation use, n: 19
- Ventilation-free time within a 24-hour period in hours, mean: 7.2 (SD 6.3)
- NIV duration in years, mean (SD): not provided
- Ventilator RR in cycles/min, mean (SD): not provided

Manual breathstacking

- Sample size, n: 25
- Age in years, mean: 24.7 (SD 5.7)
- Body mass index in kg/m², mean: 17.1 (SD 6.6)
- FVC in mL, mean: 807 (SD 495)
- FVC % predicted, mean: 16 (SD 8)
- MEP in cmH₂O, mean: 17.7 (SD 7.5)
- Cough peak flow in L/min, mean: 125 (SD 52)
- MAC peak flow in L/min, mean: 205 (SD 52)
- NIV tidal volume in mL, mean: 724 (SD 92)
- Mouthpiece intermittent positive pressure ventilation use, n: 16
- Ventilation-free time within a 24-hour period in hours, mean: 7 (SD 5.5)
- NIV duration in years, mean (SD): not provided
- Ventilator RR in cycles/min, mean (SD): not provided

Inclusion criteria

- Adults with DMD aged > 18 years
- Requiring NIV (all received volume cycle ventilation)
- Followed up at the Neuromuscular Excellence Centre and Centre for Home Mechanical Ventilation, Inkendaal Rehabilitation Hospital in a 2-year period.

Exclusion criteria

- Inability to perform lung function tests
- Tracheostomy in situ
- Prior formal training in breathstacking
- Respiratory instability (defined as acute respiratory failure)

Pretreatment: demographics, lung function values, and ventilation parameters were similar between the 2 groups (no statistically significant difference between groups, Table 1 of publication).

Interventions

Intervention characteristics
Mechanical breathstacking

- Participant position: sitting
- Technique description: number of successive insufflations required for each participant to optimise their technique was individualised. Air stacking was performed using a volume-cycled home mechanical ventilator and nasal mask interface, with parameters unchanged from those used for participant's nocturnal NIV. Instructions were tailored to the participant but an example of a provided explanation was, "Let your lungs fill with air from the ventilator/bag. Once this insufflation has finished, hold your breath and don't breathe out. Another insufflation will be delivered. Try to stack 2 or 3 of these successive insufflations. When your lungs feel like they're fully expanded, cough."
- Measurement: after performing the breathstacking technique to maximal insufflation, participants coughed into a mask (held by therapist), without additional manual assistance or abdominal compression.

Manual breathstacking

Toussaint 2016 (Continued)

- Participant position: sitting
- Technique description: number of successive insufflations required for each participant to optimise their technique was individualised. Air stacking was performed by an experienced physiotherapist, using a using a 2 L resuscitator bag (Resutator 2000, Drager, Lubeck, Germany) via a full face mask interface. Instructions were tailored to the participant as per 'mechanical breathstacking' above.
- Measurement: after performing the breathstacking technique to maximal insufflation, participants coughed into a mask (held by therapist), without additional manual assistance or abdominal compression.

Outcomes

Able to perform breath/airstacking

- Outcome type: dichotomous (yes/no)

Number of insufflations to maximal insufflation capacity

- Outcome type: continuous
- Direction: higher was better

Breathstacking-assisted PCF (primary outcome measure)

- Outcome type: continuous
- Unit of measure: L/min
- Measurement technique: measured using a heated Fleisch No. 2 Pneumotachometer (Metabo, Lausanne, Switzerland), the best of 3 trials was recorded.
- Direction: higher was better

Maximal insufflation capacity

- Outcome type: continuous
- Unit of measure: mL
- Measurement technique: measured using a heated Fleisch No. 2 Pneumotachometer (Metabo, Lausanne, Switzerland), the best of 3 trials was recorded.
- Direction: higher was better

MEP following breathstacking

- Outcome type: continuous
- Unit of measure: cmH₂O
- Measurement technique: recorded from total lung capacity
- Direction: higher was better

Adverse events: not reported on

Identification

Sponsorship source: not mentioned

Conflict of interest: no conflict-of-interest statement presented

Country: Belgium

Setting: Neuromuscular Excellency Centre and Centre for Home Mechanical Ventilation Inkendaal Rehabilitation Hospital

Comments: –

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Toussaint 2016 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "Participants were allocated by coin toss to a single session of either air stacking via home ventilator or air stacking via a resuscitator bag at a routine clinical visit."</p> <p>Comment: randomisation to intervention was determined by coin toss (air stacking with ventilator or resuscitator bag), therefore, selection bias was low.</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: no information provided regarding allocation concealment.</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Comment: participants and therapists were not blinded to treatment. All participants were trained in both air stacking techniques, before randomisation was implemented. However, it was not possible to blind participants to the techniques that were used.</p>
Blinding of outcome assessment (detection bias) All outcomes	High risk	<p>Comment: a blinded outcome assessor gathered baseline data prior to group allocation. However, the postintervention outcome assessment seemed to have been done by the attending therapist, who was not blinded to group allocation. The best of 3 values was recorded and standardised assessment guidelines were followed, but insufficient information was provided about who performed the assessments. As with blinding of participants and staff, it would have been difficult to blind the person assessing PCF, as they would have been aware of intervention allocation and air stacking technique. Other measures such as FVC and MEP were routinely assessed at the centre.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Comment: all participants allocated to a group were assessed in the group, with no loss to follow-up/missing data. Eligibility criteria were clear. 6 participants could not perform breath stacking (as defined by the study) and the number was too small to make a comparison between the 46 that could perform the procedure and those that could not. There was full transparency of the research process and alignment with the protocol.</p>
Selective reporting (reporting bias)	Low risk	<p>Quote: "primary outcome measure was air stacking-assisted cough peak flow."</p> <p>Quote: "Lung volume was recorded from a maximal effort unassisted breath (FVC) and following an air stacking-assisted breath (maximum insufflation capacity). Maximal expiratory pressure (P Emax) was recorded from total lung capacity as per American Thoracic Society/European Respiratory Society guidelines."</p> <p>Quote: "no difference in air stacking-assisted cough peak flow between groups."</p> <p>Quote: "P.001). Similarly, there were comparable expired volumes between techniques, with maximum insufflation capacity values greater than spontaneous FVC in both groups (mean within group change: 672)."</p> <p>Quote: "difference in maximum insufflation capacity between groups (Table 2)."</p> <p>Quote: "Table 2. Comparison of Air Stacking via Ventilator Versus via Resuscitator Bag."</p> <p>Comment: all outcome measures reported in the methods section were analysed and presented in the results section (Table 2 and in text). The study</p>

Toussaint 2016 (Continued)

protocol was well described regarding study procedure, participants, and outcome measures (reproducible) and all the specified outcomes were reported in the prespecified way.

Other bias	Low risk	<p>Quote: "Able to perform air stacking, n (%) 24/27 (89) 22/25 (88) NS [not significant]"</p> <p>Comment: the following factors placed the study at low risk of other bias.</p> <ul style="list-style-type: none"> • Groups well matched at baseline. • Number of participants unable to perform breathstacking was similar between groups.
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ACBT: active cycle of breathing technique; ALS: amyotrophic lateral sclerosis; BiPAP: bilevel positive airway pressure; BMD: Becker muscular dystrophy; CEV: cough expiratory volume; CMD: congenital muscular dystrophy; CNS: central nervous system; CO₂: carbon dioxide; DMD: Duchenne muscular dystrophy; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; IBS: involuntary breathstacking; ICU: intensive care unit; IQR: interquartile range; IPPB: intermittent positive pressure breathing; LVR: lung volume recruitment; MAC: manually assisted cough; MD: mean difference; MEE: maximal expiration effort; MEP: maximal expiratory pressure; MI-E: mechanical insufflation-exsufflation; MIC: maximal inspiratory or insufflation capacity; MIP: maximum inspiratory pressure; min: minute; n: number of participants; MVV: maximal voluntary ventilation; N/A: not available; NIPPV: non-invasive positive pressure ventilation; NIV: non-invasive ventilation; NMD: neuromuscular disease; PCF: peak cough flow; PEF: peak expiratory flow; PEFr: peak expiratory flow rate; PETCO₂: end-tidal carbon dioxide tension; Pmo,w: maximal pressure within the mouth; PtcCO₂: transcutaneous carbon dioxide tension; PVT: peak value time; RCT: randomised controlled trial; RR: risk ratio; s: second; SaO₂: oxygen saturation in arterial blood; SD: standard deviation; SMA: spinal muscular atrophy; SNIP: sniff nasal inspiratory pressure; SpO₂: peripheral capillary oxygen saturation; VAS: visual analogue scale; VC: vital capacity; VCM: volumetric cough mode; COPD: chronic obstructive pulmonary disease

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bianchi 2014	Incorrect study design: prospective observational study.
Kang 2000	Incorrect study design: observational study design.
Silva 2012	Incorrect patient population: mechanically ventilated people diagnosed with head trauma, stroke, congestive heart failure, and ventilator-associated pneumonia. No participants with NMD.
Toussaint 2003	Incorrect intervention: intrapulmonary percussive ventilation, which is a peripheral airway clearance technique and not a cough augmentation technique.
Toussaint 2009	Incorrect study design: prospective cross-sectional observational study.
Winck 2004	Incorrect study design: prospective observational study.

NMD: neuromuscular disease.

Characteristics of ongoing studies [ordered by study ID]

NCT01518439

Study name	Instrumental and manual Increase of cough[sic] in neuromuscular patients (OPTICOUGH)
Methods	Open monocentric randomised cross-over study
Participants	People with NMD with cough inefficiency in a stable respiratory state on recruitment

NCT01518439 (Continued)

Interventions	<p>Mechanical insufflation: Alpha 200 inspiratory capacity increased with a constant pressure device: Alpha 200 (presume mechanical insufflation)</p> <p>Mechanical insufflation + physiotherapy: Alpha 200 combined with physiotherapy – inspiratory capacity is increased with the use of constant pressure device (Alpha 200) combined with the manual pressures techniques to increase cough by the physiotherapist (presume mechanical insufflation + MAC)</p> <p>MI-E: CoughAssist – increased inspiratory capacity and mechanical exsufflation with the use of insufflation-exsufflation device (Cough Assist)</p> <p>MI-E + MAC: CoughAssist + physiotherapy – increased inspiratory capacity and mechanical exsufflation with the use of insufflation-exsufflation device (Cough Assist) + the "manual pressures techniques" (presume MAC) to increase cough by the physiotherapist (MI-E + MAC)</p> <p>MAC: physiotherapist manual pressures techniques to increase cough applied by the physiotherapist (presumed MAC alone)</p>
Outcomes	<p>Primary outcome measures</p> <ul style="list-style-type: none"> • Cough flow obtained from the combination of mechanical and manual cough assistance techniques (presume PCF) <p>Secondary outcome measures</p> <ul style="list-style-type: none"> • Duration of efficient PCF (> 180 L/min) for each cough assistance technique • Respiratory comfort (VAS) • Subjective evaluation of cough efficiency (VAS) • Respiratory comfort (Borg dyspnoea scale)
Starting date	January 2012
Contact information	<p>Contact: Helene Prigent, helene.prigent@rpc.aphp.fr</p> <p>Contact: Sandra Pottier, sandra.pottier@rpc.aphp.fr</p> <p>Principal investigator: Helene Prigent, MD, PhD</p> <p>Subinvestigator: Frederic Lofaso, MD, PhD</p> <p>Subinvestigator: David Orlikowski, MD, PhD</p>
Notes	Attempts to contact the corresponding investigators were unsuccessful.

NCT02651805

Study name	Mechanical insufflator-exsufflator to control mucus hypersecretion in patients in palliative care – a feasibility study
Methods	RCT
Participants	Hospitalised palliative care patients with mucous hypersecretion
Interventions	MI-E vs usual care
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Study feasibility assessed by verifying the recruitment rates, acceptability of the patients and hospital staff.

NCT02651805 (Continued)

Secondary outcomes

- Incidence of treatment-emergent adverse events (safety and tolerability) (assessed between start of intervention and 30 min after end of intervention). Assessed by the number of times an event with change in physiological parameters occurred during the intervention (heart rate > 150 bpm or < 50 bpm; systolic blood pressure > 200 mmHg or < 80 mmHg; decrease of 5% or higher in pulse oximetry; haemoptysis).
- Effect size of palliative outcome scale (between immediately after the inclusion and in the final assessment (24 hours after inclusion). This is a quality-of-life multidimensional scale in patients in palliative care.
- Effect size of discomfort due to hypersecretion (immediately before the first intervention and 10 min after the first intervention). Assessed using a numeric scale (0–10).
- Effect size of discomfort due to the therapy (10 min after the first intervention). Assessed using a numeric scale (0–10)
- Effect size of time until the next intervention (at the end of the 24-hour period). The moment immediately after the first intervention until the time a new intervention is required.
- Effect size of number of interventions during 24 hours (at end of 24-hour period). The number of interventions will be verified in the patient's records.

Starting date	February 2016
Contact information	Juliano Ferreira Arcuri, Universidade Federal de Sao Carlos, Brazil
Notes	Attempts to contact the corresponding investigator were unsuccessful.

NCT03355105

Study name	Comparison of two methods of adjusting mechanical in-exsufflation in neuromuscular adult patients (EXSUFLOW)
Methods	Bicentric, prospective cross-over, randomised, open-label trial
Participants	50 adults with stable NMDs
Interventions	<p>Objective adjustment of the MI-E Pe and evaluation of cough effort: the Pes will be progressively increased starting from -20 cmH₂O with 10 cmH₂O increments. 3 cough efforts will be performed for each level, until obtaining a 10% of area under the curve decrease or a PCF decline of ≥ 10% over last 2 levels, and without exceeding -70 cmH₂O. The selected setting will be the one allowing the largest PCF without presence of collapse. An intermediate bearing between 2 bearings may be tested to approach an optimum adjustment threshold < 5 cmH₂O.</p> <p>Subjective adjustment of the MI-E Pe and evaluation of cough effort: the Pes will be gradually increased from -20 cmH₂O, with 10 cmH₂O increments up to a maximum of -70 cmH₂O. The selected level will be the one selected both by the patient and the "clinician" therapist and considered as making it possible to obtain the most effective cough according to the return of the patient.</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • AUC flow volume (at baseline). The primary endpoint is the AUC flow volume during the cough expiratory phase. To compare the cough effectiveness obtained according to the current modalities of the MI-E Pe setting to that resulting from an adjustment based on the analysis of the flow-volume curve. <p>Secondary outcomes</p> <ul style="list-style-type: none"> • PCF • Association between the PCF generated and subjective criteria

NCT03355105 (Continued)

- Subjective therapist cough effectiveness (VAS)
- Subjective participant cough effectiveness (VAS)
- Respiratory comfort (VAS)

Starting date	28 November 2017
Contact information	Contact: Frédéric LOFASO, MD, PhD: f.lofaso@aphp.fr Contact: Aurélien BOREÉ: kines.widal3@rpc.aphp.fr
Notes	Attempts to contact corresponding authors were unsuccessful.

NCT04081116

Study name	Mechanical insufflation-exsufflation in children with NMD and weak cough
Methods	Randomised controlled, single-group assignment; quadruple-blinded cross-over trial
Participants	100 children aged 6 months to 18 years Inclusion criteria <ul style="list-style-type: none"> • Diagnosed NMD • Aged < 18 years • Established use (> 3 months) of MI-E • Reduced PCF < 270 L/min (when > 12 years) or < 5th percentiles for PCF (when 4–12 years) • Clinical indication (difficulty clearing secretions, audible weak cough, history of pneumonia, or frequent or prolonged respiratory tract infections). Exclusion criteria <ul style="list-style-type: none"> • Age < 6 months • Obstructive lung disease (hyperinflation or emphysema on x-ray)
Interventions	3 MI-E settings will be tested on the same day, in random order: <ul style="list-style-type: none"> • experimental: symmetric settings (high pressures/fast rate) • experimental: asymmetric settings ($P_i < P_e/T_i > T_e$) • sham comparator
Outcomes	Primary outcomes <ul style="list-style-type: none"> • PCF in the MI-E circuit (time frame: 30 min). Recording of maximal value produced by the MI-E device during cough • Participant-reported comfort (time frame: total time use 30 min). Comfort rated on a VAS (0–100) where 100 is very uncomfortable and 0 is very comfortable Secondary outcomes <ul style="list-style-type: none"> • Transcutaneous carbon dioxide level (time frame: maximal time use is 30 min): trend measurement of carbon dioxide during data collection • Transcutaneous oxygen saturation (time frame: maximal time use is 30 min): trend measurement of peripheral oxygen during data collection • Heart rate (time frame: total max 30 min (during 3 MI-E trials): trend measurement of heart rate during data collection

NCT04081116 (Continued)

- Participant-reported efficacy (time frame: the VAS is recorded after each of the 3 trials. Total time use 30 min). Efficacy rated on a VAS (0–100) where 100 is not efficient at all and 0 is very efficient.

Starting date	1 January 2019
Contact information	Brit Hov (MSc); +4723015667; uxbrov@ous-hf.no Vegard Hovland (PhD); +4722118765
Notes	Study still recruiting until end 2023.

PACTR201506001171421

Study name	The effect of mechanical insufflation-exsufflation (MI-E) (and inspiratory muscle training) on clinical outcomes and health-related quality of life in paediatric and adolescent patients with neuromuscular diseases presenting with respiratory muscle weakness: a multi-centre trial
Methods	RCT with parallel-group assignment
Participants	<p>Children with NMD, aged 5–18 years</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> Documented diagnosis of any congenital or paediatric/adolescent NMD People admitted to hospital for acute respiratory infections or respiratory complications (or both) such as increased work of breathing, respiratory muscle fatigue, orthopnoea, retention of secretions/inability to clear secretions, decreased PEF <p>Exclusion criteria</p> <ul style="list-style-type: none"> Unstable vital signs such as resting arterial SpO₂ < 90% or PETCO₂ > 7 kPa (or both) on the day of recruitment. If the vital signs should stabilise within the following 48 hours, patients will be reconsidered for inclusion Patients who are terminally ill Bullae emphysema Scoliosis > 100° (La Place's Law) Inability to co-operate/follow basic instructions Previous history of a pneumothorax/ pneumo-mediastinum Recent (< 6 months) barotrauma or thoracic/abdominal surgery Patient that present with cardiac failure (confirmed by a physician). Patient participating in the IMT study would not be eligible for the MI-E study, as this might influence their reaction to MI-E treatment as well as their clinical outcomes. Patients who are unable to co-operate/comply with the cough assist technique(s)
Interventions	<p>Standard management with bi-daily MI-E (using Nippy Clearway CoughAssist device) during hospital admission (Pi/Pe 10–30 cmH₂O; 4 sets consisting of 5 breaths, 1–2 min of rest between sets)</p> <p>Standard management with bi-daily MAC (thoracic compressions) during hospital admission</p>
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> Duration of hospital stay Requirement for ventilatory support Oxygen requirement <p>Secondary outcomes</p>

PACTR201506001171421 (Continued)

- Disease severity scale
- Vital signs: respiratory rate, heart rate, oxygen saturation, blood gases if available (PaO₂, PaCO₂ and FiO₂)
- Pulmonary function tests (baseline to discharge)
- Cough efficacy (PECF) (measured at baseline and discharge)
- Comfort of breathing (VAS) (measured daily)
- Comfort of cough augmentation technique (MAC vs MI-E) (VAS) (measured at first and last intervention)

Starting date	July 2016
Contact information	Anri Human; anrihuman@gmail.com Brenda Morrow (PhD); brenda.morrow@uct.ac.za
Notes	Only the MI-E arm (and not the IMT intervention) of this study would potentially be eligible for inclusion in updates of this review. The PACT site states that the study has not started recruiting; however the study has enrolled participants but is temporarily halted owing to feasibility issues. Data are not yet available for analysis.

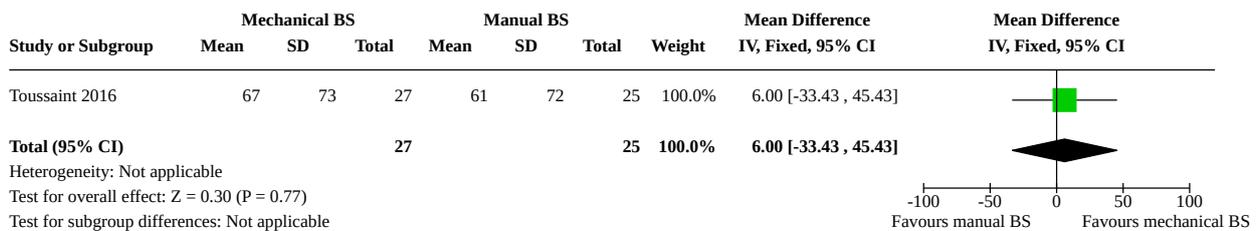
AUC: area under the curve; bpm: beats per minute; FiO₂: fraction of inspired oxygen; IMT: inspiratory muscle training; MAC: manually assisted cough; MI-E: mechanical insufflation-exsufflation; min: minute; NMD: neuromuscular disease; PaCO₂: partial pressure of carbon dioxide; PACT: Pan African Clinical Trials; PCF: peak cough flow; Pe: exsufflation pressure; PECF: peak expiratory cough flow; PETCO₂: end-tidal carbon dioxide tension; Pi: insufflation pressure; RCT: randomised controlled trial; SpO₂: peripheral capillary oxygen saturation; Te: time for exsufflation; Ti: time for insufflation; VAS: visual analogue scale.

DATA AND ANALYSES

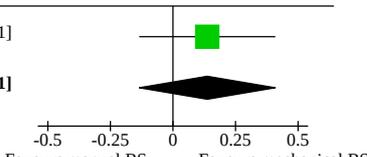
Comparison 1. Manual versus mechanical breathstacking (BS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Peak cough flow	1	52	Mean Difference (IV, Fixed, 95% CI)	6.00 [-33.43, 45.43]
1.2 Maximal insufflation capacity	1	52	Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.13, 0.41]

Analysis 1.1. Comparison 1: Manual versus mechanical breathstacking (BS), Outcome 1: Peak cough flow



Analysis 1.2. Comparison 1: Manual versus mechanical breathstacking (BS), Outcome 2: Maximal insufflation capacity

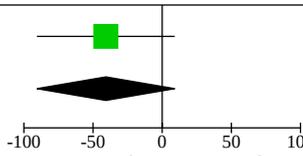
Study or Subgroup	Mechanical BS			Manual BS			Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Toussaint 2016	1.481	0.477	27	1.344	0.52	25	100.0%	0.14 [-0.13, 0.41]	
Total (95% CI)			27			25	100.0%	0.14 [-0.13, 0.41]	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable

Comparison 2. Glossopharyngeal breathing (GPB) versus manual breathstacking (BS)

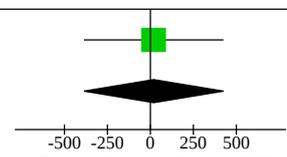
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Peak cough flow	1	14	Mean Difference (IV, Fixed, 95% CI)	-40.72 [-90.54, 9.10]
2.2 Inspiratory capacity	1	14	Mean Difference (IV, Fixed, 95% CI)	19.29 [-386.09, 424.67]

Analysis 2.1. Comparison 2: Glossopharyngeal breathing (GPB) versus manual breathstacking (BS), Outcome 1: Peak cough flow

Study or Subgroup	GPB			BS			Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Torres-Castro 2016	32.14	26.44	7	72.86	61.84	7	100.0%	-40.72 [-90.54, 9.10]	
Total (95% CI)			7			7	100.0%	-40.72 [-90.54, 9.10]	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.60 (P = 0.11)
Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2: Glossopharyngeal breathing (GPB) versus manual breathstacking (BS), Outcome 2: Inspiratory capacity

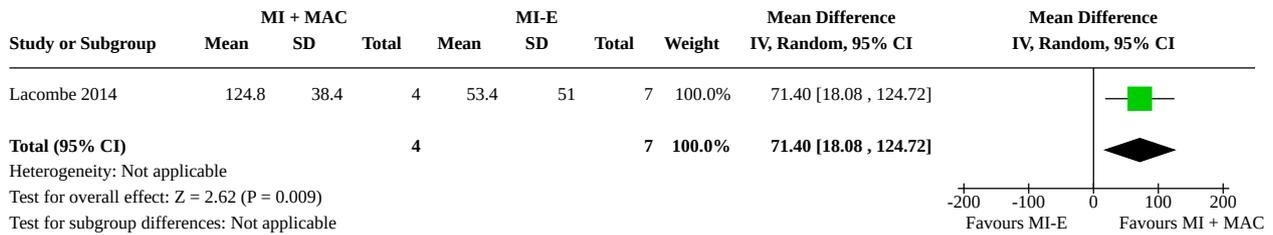
Study or Subgroup	GPB			BS			Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Torres-Castro 2016	454.29	408.16	7	435	364.5	7	100.0%	19.29 [-386.09, 424.67]	
Total (95% CI)			7			7	100.0%	19.29 [-386.09, 424.67]	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable

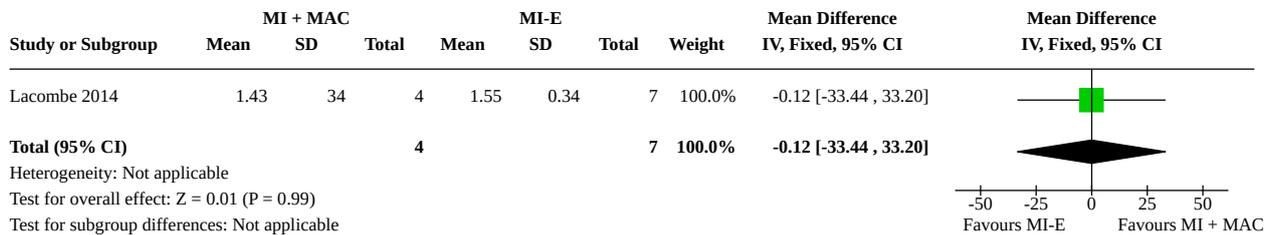
Comparison 3. Mechanical insufflation-exsufflation (MI-E) versus mechanical insufflation (MI) plus manually assisted cough (MAC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Peak cough flow	1	11	Mean Difference (IV, Random, 95% CI)	71.40 [18.08, 124.72]
3.2 Inspiratory capacity	1	11	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-33.44, 33.20]

Analysis 3.1. Comparison 3: Mechanical insufflation-exsufflation (MI-E) versus mechanical insufflation (MI) plus manually assisted cough (MAC), Outcome 1: Peak cough flow



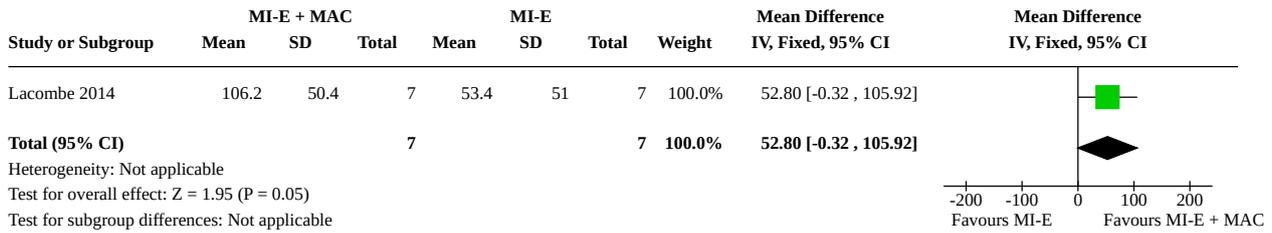
Analysis 3.2. Comparison 3: Mechanical insufflation-exsufflation (MI-E) versus mechanical insufflation (MI) plus manually assisted cough (MAC), Outcome 2: Inspiratory capacity



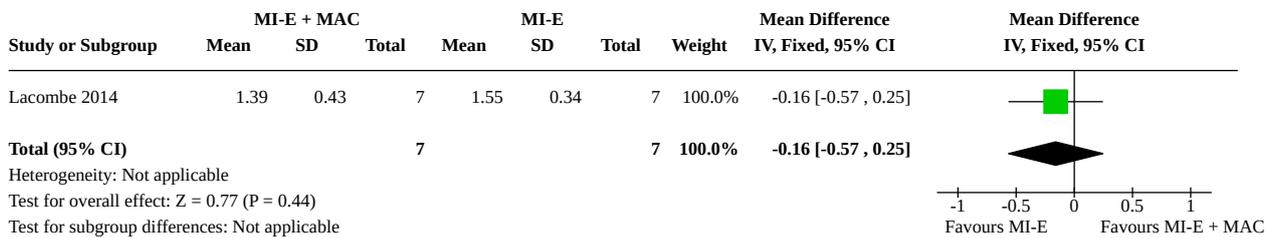
Comparison 4. Mechanical insufflation-exsufflation (MI-E) versus mechanical insufflation-exsufflation (MI-E) plus manually assisted cough (MAC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Peak cough flow	1	14	Mean Difference (IV, Fixed, 95% CI)	52.80 [-0.32, 105.92]
4.2 Inspiratory capacity	1	14	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.57, 0.25]

Analysis 4.1. Comparison 4: Mechanical insufflation-exsufflation (MI-E) versus mechanical insufflation-exsufflation (MI-E) plus manually assisted cough (MAC), Outcome 1: Peak cough flow



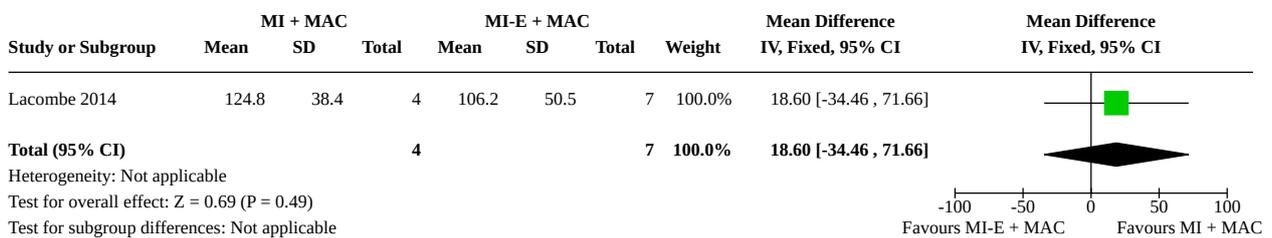
Analysis 4.2. Comparison 4: Mechanical insufflation-exsufflation (MI-E) versus mechanical insufflation-exsufflation (MI-E) plus manually assisted cough (MAC), Outcome 2: Inspiratory capacity



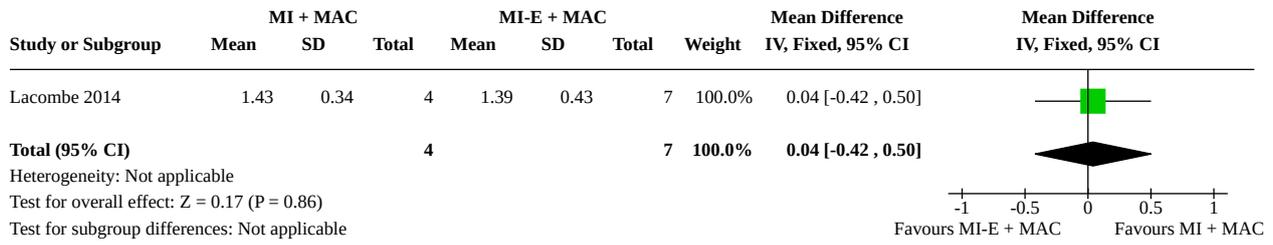
Comparison 5. Mechanical insufflation (MI) plus manually assisted cough (MAC) versus mechanical insufflation-exsufflation (MI-E) plus MAC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Peak cough flow	1	11	Mean Difference (IV, Fixed, 95% CI)	18.60 [-34.46, 71.66]
5.2 Inspiratory capacity	1	11	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.42, 0.50]

Analysis 5.1. Comparison 5: Mechanical insufflation (MI) plus manually assisted cough (MAC) versus mechanical insufflation-exsufflation (MI-E) plus MAC, Outcome 1: Peak cough flow



Analysis 5.2. Comparison 5: Mechanical insufflation (MI) plus manually assisted cough (MAC) versus mechanical insufflation-exsufflation (MI-E) plus MAC, Outcome 2: Inspiratory capacity



ADDITIONAL TABLES

Table 1. Summary of findings: cough augmentation therapy, short-term outcomes – details of PCF by comparison

Mean difference in PCF post intervention-baseline (L/min)							
Comparison (experimental vs control/al- ternative ther- apy/sham therapy)	Summary of results	Illustrative comparative risks		Relative ef- fect (95% CI)	No of partici- pants (studies)	Certainty of the evidence (GRADE)	Comments
		Control/com- parator	Experimental				
Manual breathstacking vs mechanical breathstacking Follow-up: < 1 day	No evidence of a difference be- tween manual and mechanical breathstacking in the change of PCF.	The mean PCF difference in the comparison group was 67 (SD 73) L/min	The mean PCF difference in the experimen- tal group was 61 (SD 72) L/ min	MD 6.00 (-33.43 to 45.43)	52 (1)	⊕⊕⊕⊕ Low ^a	Based on 1 short-term RCT with high risk of performance and detection bias and unclear allocation concealment (Tous- saint 2016).
Glossopharyn- geal breath- ing vs manual breathstacking Follow-up: < 1 day	No evidence of a difference between glos- sopharyngeal breathing and manual breath- stacking in the change of PCF.	The mean PCF difference in the comparison group was 72.86 (SD 61.84) L/min	The mean PCF difference in the experimen- tal group was 32.14 (SD 26.44) L/min	MD -40.72 (- 90.54 to 9.10)	14 (1)	⊕⊕⊕⊕ Very low ^b	Based on first-period data from 1 cross- over RCT with unclear allocation conceal- ment, very small sample size, imprecision of results (wide CI), and substantial risk of performance and detection bias (Tor- res-Castro 2016).
Mechanical in- sufflation + MAC vs MI-E Follow-up: < 1 day	Mechanical in- sufflation + MAC produced a greater change in PCF com- pared to MI-E alone.	The mean PCF difference in the comparison group was 53.4 (SD 51) L/min	The mean PCF difference in the experimen- tal group was 124.8 (SD 38.4) L/min	MD 71.40 (18.08 to 124.72)	11 (1)	⊕⊕⊕⊕ Very low ^c	Based on first-period data of 1 cross-over RCT with very small sample size, impreci- sion of results (wide CIs), and substantial risk of performance and other biases (La- combe 2014).
MI-E + MAC vs MI-E Follow-up: < 1 day	No clear evi- dence of a dif- ference be- tween MI-E + MAC compared to MI-E alone in the change in PCF.	The mean PCF difference in the comparison group was 53.4 (SD 51) L/min	The mean PCF difference in the experimen- tal group was 106 (SD 50.4) L/ min	MD 52.80 (-0.32 to 105.92)	54 (2)	⊕⊕⊕⊕ Very low ^c	Analysis based on first-period data of 1 randomised cross-over study with very small sample size (n = 14), imprecision of results (wide CIs), and substantial risk of performance and other biases (Lacombe 2014).

Table 1. Summary of findings: cough augmentation therapy, short-term outcomes – details of PCF by comparison (Continued)

		Study reported significantly higher PCF with MI-E + MAC compared to MI-E alone	N/A				The second study was a cross-over RCT with high risk of performance, detection and other bias (Kim 2016). Separate period data were not reported, precluding analysis and assessment of precision.
MI-E + MAC vs mechanical insufflation + MAC	There was no evidence of a difference in PCF change between MI-E + MAC and mechanical insufflation + MAC.	The mean PCF difference in the comparison group was 124.8 (SD 38.4) L/min	The mean PCF difference in the intervention groups was 106 (SD 50.4) L/min	MD 18.60 (-34.46 to 71.66)	11 (1)	⊕⊕⊕⊕ Very low ^c	Based on the first-period data of 1 randomised cross-over study design with very small sample size, imprecision of results (wide CIs), and substantial risk of performance and other biases (Lacombe 2014).
MAC vs mechanical insufflation	We were unable to draw a conclusion.	Both studies reported no evidence of a difference in PCF between interventions.	N/A		26 (2)	⊕⊕⊕⊕ Very low ^c	Based on 2 cross-over RCTs with small sample sizes (Chatwin 2003: n = 4; Sivasothy 2001: n = 22). Separate period data were not reported or available, precluding analysis and assessment of precision.
Mechanical insufflation + MAC vs MAC	We were unable to draw a conclusion.	Reported no evidence of a difference in PCF between interventions.	N/A		4 (1)	⊕⊕⊕⊕ Very low ^c	Based on 1 cross-over RCT with 4 participants eligible for this review (Sivasothy 2001). Separate period data were not reported or available, precluding analysis and assessment of precision.
MI-E vs MAC	We were unable to draw a conclusion.	MI-E reported to produce a higher PCF than MAC.	N/A		22 (1)	⊕⊕⊕⊕ Very low ^c	Based on 1 cross-over RCT with 22 participants (Chatwin 2003). Separate period data were not reported or available, precluding analysis and assessment of precision.
MI-E vs mechanical exsufflation	We were unable to draw a conclusion.	MI-E reported to produce a higher PCF than mechanical exsufflation.	N/A		22 (1)	⊕⊕⊕⊕ Very low ^c	Based on 1 cross-over RCT with 22 participants (Chatwin 2003).

Table 1. Summary of findings: cough augmentation therapy, short-term outcomes – details of PCF by comparison (Continued)

Follow-up: < 1 day						Separate period data were not reported or available, precluding analysis and assessment of precision.
MI-E vs mechanical insufflation	We were unable to draw a conclusion.	PCF reported to be higher with MI-E than with mechanical insufflation.	N/A	22 (1)	⊕⊕⊕⊕ Very low ^c	Based on 1 cross-over RCT with 22 participants (Chatwin 2003).
Follow-up: < 1 day						Separate period data were not reported or available, precluding analysis and assessment of precision.
Manual breathstacking + MAC vs MI-E	We were unable to draw a conclusion.	PCF reported to be higher with MI-E than with MAC + breathstacking.	N/A	40 (1)	⊕⊕⊕⊕ Very low ^c	Based on 1 cross-over RCT with 40 participants (Kim 2016).
Follow-up: < 1 day						Separate period data were not reported or available, precluding analysis and assessment of precision.
MI-E + MAC vs manual breathstacking + MAC	We were unable to draw a conclusion.	PCF reported to be higher with MI-E + MAC than with MAC + breathstacking.	N/A	40 (1)	⊕⊕⊕⊕ Very low ^c	Based on 1 cross-over RCT with 40 participants (Kim 2016).
Follow-up: < 1 day						Separate period data were not reported or available, precluding analysis and assessment of precision.
MAC vs manual breathstacking + MAC	We were unable to draw a conclusion.	PCF reported to be higher with manual breathstacking + MAC than with MAC alone.	N/A	28 (1)	⊕⊕⊕⊕ Very low ^c	Based on 1 cross-over RCT with 28 participants (Brito 2009).
Follow-up: < 1 day						Separate period data were not reported or available, precluding analysis and assessment of precision.
Manual breathstacking vs manual breathstacking + MAC	We were unable to draw a conclusion	PCF reported to be higher with manual breathstacking + MAC than with manual breathstacking alone.	N/A	28 (1)	⊕⊕⊕⊕ Very low ^c	Based on 1 cross-over RCT with 28 participants (Brito 2009).
Follow-up: < 1 day						Separate period data were not reported or available, precluding analysis and assessment of precision.
Mechanical breathstacking vs mechanical insufflation	We were unable to draw a conclusion.	PCF reported to be higher with mechanical insufflation compared to mechanical breathstacking. Not quantitatively reported.	N/A	20 (1)	⊕⊕⊕⊕ Very low ^c	Based on 1 cross-over RCT with 20 participants (Del Amo Castrillo 2019).

Table 1. Summary of findings: cough augmentation therapy, short-term outcomes – details of PCF by comparison (Continued)

Follow-up: < 1 day

Data were presented graphically only and could not be precisely extracted from figures provided.

Separate period data were not reported or available, precluding analysis and assessment of precision.

CI: confidence interval; **MD:** mean difference; **MAC:** manually assisted cough; **MI-E:** mechanical insufflation-exsufflation; **min:** minute; **n:** number of participants; **N/A:** not available; **PCF:** peak cough flow; **RCT:** randomised controlled trial; **SD:** standard deviation.

^aDowngraded twice because results come from a single short-term RCT at high risk of bias.

^bDowngraded three times based on a single randomised cross-over study design with very small sample size, imprecision of results (wide CIs), and high risk of performance and detection bias.

^cDowngraded three times based on a single randomised cross-over study design with very small sample size, imprecision of results (wide CIs), and substantial risk of performance and other biases.

Table 2. Study results grouped by outcome measures and interventions – cough augmentation therapy compared to alternative individual cough augmentation therapies

Outcome measure	Unassisted cough	MI	ME	MI-E	MAC	Manual BS	Mechanical BS	Sham BS	GPB	Between-group comparison
PCF (L/min)	Chatwin 2003 (n = 22)									
	Mean (95% CI)									
	169 (129 to 209) ^a	182 (147 to 217)	235 (186 to 284)	297 (246 to 350)	188 (146 to 229)	—	—	—	—	ME vs unassisted cough: P < 0.01 MI-E vs unassisted cough: P < 0.001 MI-E vs ME: P < 0.001
	Toussaint 2016 (n = 52)									
	Mean ± SD baseline to after intervention									
	—	—	—	—	—	125 ± 52 to 186 ± 50; P < 0.001; n = 25	132 ± 55 to 199 ± 48; P = 0.001; n = 27	—	—	P = 0.33

Table 2. Study results grouped by outcome measures and interventions – cough augmentation therapy compared to alternative individual cough augmentation therapies (Continued)

Del Amo Castrillo 2019 (n = 20)										
Median/IQR										
176/68 ^a	Data not reported	—	—	—	—	Data not reported	—	—	—	<p>P < 0.001 comparing MI to baseline (favouring MI)</p> <p>P < 0.001 comparing MI to BS (favouring MI)</p> <p>P = 0.004 comparing BS to baseline (favouring BS)</p>
Torres-Castro 2016 (n = 14)										
MD ± SD (95% CI) baseline to after intervention ^b										
—	—	—	—	—	72.86 ± 61.84 (15.67 to 130.05); P = 0.02	—	—	32.14 ± 26.44 (7.69 to 56.59); P = 0.018	—	P = 0.14
Transcutaneous oxygen saturation (%)	Jenkins 2014 (n = 23)	Mean ± SD before to after intervention								
—	—	—	—	—	96 ± 3.2 to 96 ± 3	—	96 ± 3.6 to 96 ± 2.5	—	—	NS
Tidal volume (mL)	Jenkins 2014 (n = 23)	Mean ± SD before to after intervention								
—	—	—	—	—	277 ± 131 to 310 ± 148; P < 0.001	—	303 ± 141 to 289 ± 128; NS	—	—	Significance levels not reported
Maximum inspiratory or insufflation capacity (L or mL)	Toussaint 2016 (n = 52)	mean ± SD, L								

Table 2. Study results grouped by outcome measures and interventions – cough augmentation therapy compared to alternative individual cough augmentation therapies (Continued)

	—	—	—	—	—	1.344 ± 0.520; n = 25	1.481 ± 0.477; n = 27	—	—	Mechanical vs manual BS: MD 0.14, 95% CI – 0.13 to 0.41; P = 0.3
	Del Amo Castrillo 2019 (n = 20)									
	median (IQR), L									
	—	1.630	—	—	—	—	1.320	—	—	P = 0.12
		(1.247 to 1.870)					(1.085– 1.755)			
	Torres-Castro 2016 (n = 14)									
	MD between baseline vital capacity and postintervention maximum inspiratory capacity ^b									
	mean ± SD (95% CI), mL									
	—	—	—	—	—	435.0 ± 364.5 (98.61 to 772.82); P = 0.02	—	—	454.29 ± 408.16 (76.80 to 831.77); P = 0.03	MD 19.29, 95% CI – 386.09 to 424.67; P = 0.93
Minute ventila- tion (L/min)	Jenkins 2014 (n = 23)									
	Mean ± SD before to after intervention									
	—	—	—	—	—	6.8 ± 3.1 to 8.0 ± 3.5; P < 0.001	—	7.4 ± 4.9 to 6.9 ± 3.3; NS	—	Significance levels not reported
Maximal expira- tory pressure (cmH ₂ O)	Toussaint 2016 (n = 52)									
	Mean ± SD									
	—	—	—	—	—	26 ± 9	28 ± 10	—	—	P = 0.45
Respiratory rate (breaths/ minute)	Jenkins 2014 (n = 23)									
	Mean ± SD before to after intervention									

Table 2. Study results grouped by outcome measures and interventions – cough augmentation therapy compared to alternative individual cough augmentation therapies (Continued)

	–	–	–	–	–	27 ± 9.2 to 28 ± 10.6; P < 0.05	–	26 ± 10.3 to 26 ± 10.4; NS	–	Significance levels not reported					
Ability to per- form breath stacking (%)	Toussaint 2016 (n = 52)					88	89	–	–	P = 0.9					
Number of in- sufflations to maximal insuf- flation capacity (n)	Toussaint 2016 (n = 52) Mean ± SD					1.8 ± 0.6	2.6 ± 0.6	–	–	P < 0.001					
Comfort, dis- tress, and strength of cough (VAS 10-point score)	Chatwin 2003 (n = 22) Mean (95% CI)					5.4 (4.5 to 6.3) ^a	5.8 (4.8 to 6.8) (NS)	6.9 (5.3 to 7.0) (NS)	7.3 (6.6 to 8.0) (NS)	5.9 (5.2 to 6.7) (NS)	–	–	–	–	Separate VAS scores not presented Significance levels not reported
Comfort (VAS 10-point score)	Del Amo Castrillo 2019 (n = 20) Median (IQR)					–	6.4 (5.2 to 7.6)	–	–	–	–	6.5 (3.9– 7.4)	–	–	P = 0.31
Subjective cough effective- ness (VAS 10- point score)	Del Amo Castrillo 2019 (n = 20) Median (IQR)					–	6.0 (4.85 to 8.2)	–	–	–	–	6.2 (5.1– 7.1)	–	–	P = 0.17

BS: breathstacking; CI: confidence interval; GPB: glossopharyngeal breathing; IQR: interquartile range; PCF: peak cough flow; MAC: manually assisted cough; MD: mean difference; ME: mechanical exsufflation; MI: mechanical insufflation; MI-E: mechanical insufflation/exsufflation; min: minute; n: number of participants; NS: not significant; SD: standard deviation; VAS: visual analogue scale.

^aBaseline value – not a randomly assigned control.

^bUsing raw first-period data provided by the author on request.

Table 3. Study results grouped by outcome measures and interventions – comparison of individual and combination cough augmentation therapies with alternative individual and combination interventions

Outcome measure	Unassisted cough	MI	MI-E	MAC	Manual BS	MAC + MI	MAC + manual BS	MAC + MI-E	Between-group differences
PCF (L/min)	Sivasothy 2001 (n = 4)								
	Median (range)								
	288 (175 to 367) ^a	231 (148–597)	—	193 (185–287)	—	362 (218–440)	—	—	NS
	Brito 2009 (n = 28)								
	Mean ± SD								
	171 ± 67 ^a	—	—	231 ± 81	225 ± 80	—	292 ± 86	—	Manual BS vs unassisted cough: P < 0.001
	Manual BS vs MAC: NS								
	MAC + BS vs unassisted cough: P < 0.001								
	MAC vs MAC + BS: P < 0.05								
	Manual BS vs MAC + BS: P < 0.05								
<hr/>									
Lacombe 2014 (n = 18)									
Mean ± SD									
—	—	Absolute value ^b : 210.6 ± 52.8	—	—	Absolute value ^b : 225 ± 83.4 MD from baseline ^b :	—	Absolute value ^b : 210.6 ± 50.4 MD from baseline ^b :	Comparison of MDs (intervention – baseline): MI + MAC vs MI-E alone: MD 71.4, 95% CI 18.08 to 124.72); P = 0.009	

Table 3. Study results grouped by outcome measures and interventions – comparison of individual and combination cough augmentation therapies with alternative individual and combination interventions (Continued)

			MD from baseline ^b : 53.4 ± 51.0; n = 7				124.8 ± 38.4; n = 4		106.2 ± 50.4; n = 7	MI-E + MAC vs MI-E alone: MD 52.8, 95% CI -0.32 to 105.92; P = 0.05 MI-E + MAC vs MI + MAC: MD -18.6, 95% CI -71.61 to 34.41; P = 0.49
<hr/>										
	Kim 2016 (n = 40)									
	Mean ± SD									
	95.7 ± 40.5	—	177.2 ± 33.9	—	—	—	—	155.9 ± 53.1	202.4 ± 46.6	MAC + manual BS vs unassisted cough: P < 0.01 MI-E vs unassisted cough: P < 0.01 MI-E vs MAC + manual BS: P < 0.01 MI-E + MAC vs unassisted cough: P < 0.01 MI-E + MAC vs MAC + manual BS: P < 0.01 MI-E + MAC vs MI-E alone: P < 0.01
<hr/>										
Transcutaneous oxygen saturation	Chatwin 2009 (n = 8)									
	Mean									
(%)	—	—	—	Data not reported	—	—	—	—	Data not reported	NS difference in group means
<hr/>										
Transcutaneous carbon dioxide tension	Chatwin 2009 (n = 8)									
	Mean									
(%)	—	—	—	Data not reported	—	—	—	—	Data not reported	NS difference in group means
<hr/>										
Maximum inspiratory or insufflation capacity	Lacombe 2014 (n = 18)									
	mean ± SD									

Table 3. Study results grouped by outcome measures and interventions – comparison of individual and combination cough augmentation therapies with alternative individual and combination interventions (Continued)

(L)	—	—	1.55 ± 0.34 ^b ; n = 7	—	—	1.43 ± 0.34 ^b ; n = 4	—	1.39 ± 0.43 ^b ; n = 7	Comparison of means: MI-E vs MI + MAC: MD -0.12, 95% CI -33.44 to 33.20; P = 0.99 MI-E vs MI-E + MAC: MD -0.16, 95% CI -0.57 to 0.25; P = 0.44 MI+ MAC vs MI-E + MAC: MD 0.04, 95% CI -0.42 to 0.50; P = 0.86
Cough expiratory volume (L)	Sivasothy 2001 (n = 4) Median (range)								
(L)	0.9 (0.5–1.1) ^a	0.7 (0.3–1.3)	—	0.5 (0.41–1.01)	—	0.6 (0.4–1.01)	—	—	NS
Heart rate (beats per minute)	Chatwin 2009 (n = 8) Not specified								
(L)	—	—	—	Data not reported	—	—	—	Data not reported	NS
Effective cough time (ms)	Lacombe 2014 (n = 18) Mean ± SD								
(L)	—	—	Absolute value ^b : 70 ± 79 MD from baseline ^b : 54 ± 95; n = 7	—	—	Absolute value ^b : 93 ± 111 MD from baseline ^b : 93 ± 111; n = 4	—	Absolute value ^b : 22 ± 47 MD from baseline ^b : 20 ± 42; n = 7	MI-E vs MI + MAC: MD 39.0, 95% CI -90.56 to 168.56; P = 0.56 MI-E vs MI-E + MAC: MD -34.00, 95% CI -110.95 to 42.95; P = 0.39 MI + MAC vs MI-E + MAC: MD 73.00, 95% CI -40.14 to 186.14; P = 0.21
Peak value time (ms)	Sivasothy 2001 (n = 4) Median (range)								

Table 3. Study results grouped by outcome measures and interventions – comparison of individual and combination cough augmentation therapies with alternative individual and combination interventions (Continued)

	44 (40–50) ^a	45 (30–60)	–	50 (35–55)	–	50 (45–120)	–	–	NS
Treatment time after 30 minutes (min)	Chatwin 2009 (n = 8) Median (range)			17 (0–35)	–	–	–	0 (0–26)	P = 0.03
Auscultation score (VAS 10-point score)	Chatwin 2009 (n = 8) MD ± SD before to after intervention			3.4 ± 2.0 to 2.3 ± 2.2; P = 0.007	–	–	–	2.9 ± 1.9 to 1.8 ± 2.0; P = 0.02	Significance level not reported
Secretions (VAS 10-point score)	Chatwin 2009 (n = 8) MD ± SD before to after intervention			4.4 ± 2.5 to 3.0 ± 1.4; P = 0.03	–	–	–	4.0 ± 2.2 to 1.7 ± 0.4; P = 0.03	Significance level not reported
Comfort (VAS 10-point score)	Chatwin 2009 (n = 8) Baseline to after intervention			Data not reported (NS)	–	–	–	Data not reported (NS)	Data presented graphically only. Significance level not reported
	Lacombe 2014 (n = 18) Median (IQR)			Original report: 6.4 (5.5 to –7.0)	–	Original report: 7.0 (6.0–8.5) b5.9 (1.15)	–	Original report: 6.6 (5.8–8.0) b6.8 (.7)	NS

Table 3. Study results grouped by outcome measures and interventions – comparison of individual and combination cough augmentation therapies with alternative individual and combination interventions (Continued)

*b*5.7 (0.9)

Subjective cough effectiveness	Sivasothy 2001 (n = 4)								
(VAS 10-point score)	Not reported*	Not reported	—	Not reported	—	Not reported	—	—	Participants did not report benefit of any intervention.
	Lacombe 2014 (n = 18)								
	Median (IQR)								
	—	—	Original report: 6.4 (4.8–8.2)	—	—	Original report: 8.3 (7.2–9.0)	—	Original report: 8.5 (6.2–9.0)	Original report: MI-E + MAC vs MI-E: P < 0.05
			<i>b</i> 7.2 (2.4)			<i>b</i> 7.1 (0.8)		<i>b</i> 8.0 (1.95)	MAC + MI vs MI-E: P < 0.05
Breathlessness	Chatwin 2009 (n = 8)								
(VAS 10-point score)	—	—	—	Data not reported (NS)	—	—	—	Data not reported (NS)	Data presented graphically only. Significance level not reported
Mood	Chatwin 2009 (n = 8)								
(VAS 10-point score)	—	—	—	Data not reported (NS)	—	—	—	Data not reported (NS)	Data presented graphically only. Significance level not reported
Fatigue	Chatwin 2009 (n = 8)								
(VAS 10-point score)	—	—	—	Data not reported (NS)	—	—	—	3.2 ± 2.2 to 5.1 ± 2.6	Incomplete reporting. Significance level not reported

Table 3. Study results grouped by outcome measures and interventions – comparison of individual and combination cough augmentation therapies with alternative individual and combination interventions *(Continued)*

(P = 0.005)

BS: breathstacking; CI: confidence interval; GPB: glossopharyngeal breathing; IQR: interquartile range; PCF: peak cough flow; MAC: manually assisted cough; MD: mean difference; ME: mechanical exsufflation; MI: mechanical insufflation; MI-E: mechanical insufflation/exsufflation; min: minute; n: number of participants; NS: not significant; SD: standard deviation; VAS: visual analogue scale.

^aBaseline value – not a randomly assigned control.

^bUsing raw first-period data provided by the author on request.

Table 4. Study results grouped by outcome measures and interventions – cough augmentation therapy compared to standard care

Outcome measure	Study identifier Sample size Data presentation	Unassisted cough	Manual BS	Standard care	Between-group differences
Number and duration of unscheduled hospital and ICU admissions	Katz 2019 n = 67 Units not specified	—	Not reported	Not reported	No results reported
Unassisted PCF	Katz 2019 n = 67 Units not specified	—	Not reported	Not reported	No results reported
Health-related quality of life	Katz 2019 n = 67 Pediatric Quality of Life Inventory score	—	Not reported	Not reported	No results reported
FVC	Katz 2019 n = 67 Median % predicted	85.5 (entire cohort) ^a	4.1% change	6.4% change	Adjusted MD 2.0, 95% CI -8.2 to 12.3
Time to 10% decline in FVC	Katz 2019 n = 67 Not reported	—	Data not reported	Data not reported	Manual BS vs standard care: P = 0.5
Maximal inspiratory or insufflation capacity	Katz 2019 n = 67 Units not specified	—	Not reported	Not reported	No results reported
MEP	Katz 2019 n = 67 Units not specified	—	Not reported	Not reported	No results reported
MIP	Katz 2019 n = 67 Units not specified	—	Not reported	Not reported	No results reported
Number and duration of outpatient oral antibiotic courses	Katz 2019 n = 67	—	Not reported	Not reported	No results reported

Table 4. Study results grouped by outcome measures and interventions – cough augmentation therapy compared to standard care (Continued)

Units not specified

BS: breathstacking; CI: confidence interval; FVC: forced vital capacity; ICU: intensive care unit; MD: mean difference; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; n: number of participants; PCF: peak cough flow.

^aBaseline value – not a randomly assigned control

APPENDICES

Appendix 1. CINAHL (EBSCOhost) search strategy

Monday, April 13, 2020 8:49:22 AM

CINAHL Plus with Full Text

S30 S29 Limiters – Exclude MEDLINE records 55

S29 S18 AND S28 102

S28 S19 OR S20 OR S21 OR S22 OR S27 284

S27 S25 AND S26 103

S26 breath* or resp* 1,091,462

S25 S23 OR S24 90 117

S24 "manual insufflation" 4

S23 mechanical N4 (insufflation or exsufflation) 117

S22 "frog breath*" 1

S21 "glossopharyngeal breath*" 25

S20 "breath stack*" or "air stack*" 48

S19 assist* N2 cough* 167

S18 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 1,529,197

S17 ABAB design* 162

S16 TI random* or AB random* 364,861

S15 (TI (cross?over or placebo* or control* or factorial or sham? or dummy)) or (AB (cross?over or placebo* or control* or factorial or sham? or dummy)) 734,319

S14 (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment* or preventive or therapeutic)) and (TI (trial*) or AB (trial*)) 280,652

S13 (TI (meta?analys* or "systematic review*")) or (AB (meta?analys* or "systematic review*")) 98,430

S12 (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*)) and (TI (blind* or mask*) or AB (blind* or mask*)) 55,477

S11 PT ("clinical trial" or "systematic review") 224,844

S10 (MH "Factorial Design") 1,352

S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies") 464,917

S8 (MH "Meta Analysis") 49,933

S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison") 120

S6 (MH "Quasi-Experimental Studies") 14,347

S5 (MH "Placebos") 13,662

S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies") 49,848

S3 (MH "Clinical Trials+") 317,588

S2 (MH "Crossover Design") 21,101

S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample") 114,917

Appendix 2. ICTRP Platform search strategy

ICTRP was not accessible at the time of update search on 13 April 2020.

Advanced search

Intervention: (cough AND assist) OR (assisted coughing) OR (breath stacking) OR (air stacking) OR (mechanical exsufflation)

Recruitment status: ALL

Appendix 3. ClinicalTrials.gov search strategy

Advanced Search

Study type: Interventional (Clinical Trials)

Intervention/treatment: (Cough AND Assist) OR Assisted Coughing OR Breath Stacking OR Air Stacking OR Mechanical Exsufflation

76 Studies Found

Appendix 4. Embase (OvidSP) search strategy

Database: Embase <1974 to 2020 Week 15>

Search Strategy:

1 crossover-procedure.sh. (62746)

2 double-blind procedure.sh. (171274)

3 single-blind procedure.sh. (38496)

4 randomized controlled trial.sh. (598106)

5 (random* or crossover* or cross over* or placebo* or (doubl* adj blind*) or allocat*).tw,ot. (1760750)

6 trial.ti. (296091)

7 controlled clinical trial/ (463970)

8 or/1-7 (2085723)

9 exp animal/ or exp invertebrate/ or animal.hw. or non human/ or nonhuman/ (27204367)

10 human/ or human cell/ or human tissue/ or normal human/ (20829599)

11 9 not 10 (6444888)

12 8 not 11 (1854230)

13 limit 12 to (conference abstracts or embase) (1561015)

- 14 (assist* adj2 cough*).mp. (503)
15 (breath stack* or air stack*).mp. (147)
16 glossopharyngeal breath*.mp. (77)
17 frog breath*.mp. (2)
18 (mechanical adj4 (insufflation or exsufflation)).mp. (296)
19 manual insufflation.mp. (11)
20 18 or 19 (307)
21 (breath* or resp*).mp. (8827319)
22 20 and 21 (258)
23 or/14-17,22 (810)
24 13 and 23 (92)
25 remove duplicates from 24 (92)

Appendix 5. Cochrane Neuromuscular Specialised Register via the Cochrane Register of Studies (CRS-Web) search strategy

- 1 assist* NEAR2 cough* AND INREGISTER 13
2 "breath stack*" or "air stack*" AND INREGISTER 7
3 "glossopharyngeal breath*" AND INREGISTER 0
4 "frog breath*" AND INREGISTER 0
5 mechanical NEAR4 (insufflation or exsufflation) AND INREGISTER 10
6 "manual insufflation" AND INREGISTER 0
7 #5 OR #6 10
8 breath* OR resp* AND INREGISTER 2723
9 #7 AND #8 10
10 #1 OR #2 OR #3 OR #4 OR #9 20

Appendix 6. CENTRAL via the Cochrane Register of Studies (CRS-Web) search strategy

- 1 assist* NEAR2 cough* AND CENTRAL:TARGET 7 9
2 "breath stack*" or "air stack*" AND CENTRAL:TARGET 46
3 "glossopharyngeal breath*" AND CENTRAL:TARGET 1
4 "frog breath*" AND CENTRAL:TARGET 0
5 mechanical NEAR4 (insufflation or exsufflation) AND CENTRAL:TARGET 51
6 "manual insufflation" AND CENTRAL:TARGET 0
7 #5 OR #6 51
8 breath* or resp* AND CENTRAL:TARGET 538201
9 #7 AND #8 46
10 #1 OR #2 OR #3 OR #4 OR #9 142

Appendix 7. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) ALL <1946 to April 10, 2020>

Search Strategy:

-
- 1 randomized controlled trial.pt. (503706)
 - 2 controlled clinical trial.pt. (93614)
 - 3 randomi#ed.ti.ab. (613469)
 - 4 placebo.ab. (206754)
 - 5 drug therapy.fs. (2194104)
 - 6 randomly.ab. (330921)
 - 7 trial.ab. (501216)
 - 8 groups.ab. (2032325)
 - 9 or/1-8 (4703106)
 - 10 exp animals/ not humans.sh. (4689538)
 - 11 9 not 10 (4080041)
 - 12 (assist* adj2 cough*).mp. (273)
 - 13 (breath stack* or air stack*).mp. (77)
 - 14 glossopharyngeal breath*.mp. (64)
 - 15 frog breath*.mp. (5)
 - 16 (mechanical adj4 (insufflation or exsufflation)).mp. (180)
 - 17 manual insufflation.mp. (8)
 - 18 16 or 17 (188)
 - 19 (breath* or resp*).mp. (6507692)
 - 20 18 and 19 (161)
 - 21 or/12-15,20 (482)
 - 22 11 and 21 (81)
 - 23 remove duplicates from 22 (81)

HISTORY

Protocol first published: Issue 11, 2018

Review first published: Issue 4, 2021

CONTRIBUTIONS OF AUTHORS

Conception of the review: BM, MZ, AH, LC, AA, MT.

Design of the review: BM, MZ, AH, LC, AA, MT.

Co-ordination of the review: BM.

Search and selection of studies: BM, AH, LC.

Extraction of data: BM, AH, LC.

Assessment of risk of bias: BM, AH, LC.

Data analysis: BM.

Interpretation of results: BM, MZ, AH, LC, AA, MT.

Assessment of certainty: BM, AH.

Writing of the review: BM wrote the review and MZ, AH, LC, AA, and MT reviewed and contributed to the manuscript.

DECLARATIONS OF INTEREST

BM: has no particular conflict of interest to declare in respect of this review. She received an equipment grant from the University of Cape Town, which supported the purchase of a "Nippy" mechanical In-exsufflation device as well as an unconditional donation of consumables for this device from Bakoni Medical company for an ongoing clinical trial of MI-E ([PACTR201506001171421](#)). BM is principal investigator of this trial, which may be eligible for inclusion in later versions of this review, in which case, she will recuse herself from that data extraction and analysis.

AA: is a specialist (paediatric critical care) physician and manages patients with a variety of conditions. He has no particular conflicts of interest to declare in respect of this review.

MZ: is a specialist (paediatric pulmonology) and manages patients with a variety of conditions, including NMD. He has no particular conflicts of interest to declare in respect of this review.

AH: as student investigator of the ongoing [PACTR201506001171421](#) trial, AH was also a recipient of an equipment grant from the University of Cape Town, which supported the purchase of a Nippy mechanical In-exsufflation device as well as an unconditional donation of consumables for this device from Bakoni Medical company. This trial may be eligible for inclusion in later versions of this review, in which case, she will recuse herself from that data extraction and analysis.

LC: is a physiotherapist and lecturer. She has no conflicts of interest to declare in respect of this review.

MT: is the first author of a study included in this review ([Toussaint 2016](#)), as well as two excluded studies ([Toussaint 2003](#); [Toussaint 2009](#)); however, he did not participate in any methodological or analytical processes related to these studies. He has no other conflicts of interest to declare in respect of this review.

SOURCES OF SUPPORT

Internal sources

- University of Cape Town, South Africa
Salary

External sources

- None received, UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no other major deviations from the published protocol of this review ([Morrow 2018](#)).

We had planned to create separate 'Summary of findings' tables for 'rescue' and 'maintenance therapy' using cough augmentation techniques; however, considering the lack of data, we instead presented two separate 'Summary of Findings' tables for the comparison between cough augmentation technique(s) and alternative cough augmentation technique(s) and for the comparison between cough augmentation technique(s) and standard of care. All predetermined outcome measures were presented in the 'Summary of findings' tables, for 'rescue' and 'maintenance' therapy.

NOTES

This review will partially supersede 'Mechanical insufflation-exsufflation for people with neuromuscular disorders' ([Morrow 2013](#)).