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Review article

Airway clearance techniques in neuromuscular disorders: A state of the art review

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ABSTRACT

This is a unique state of the art review written by a group of 21 international recognized experts in the field that gathered during a meeting organized by the European Neuromuscular Centre (ENMC) in Naarden, March 2017. It systematically reports the entire evidence base for airway clearance techniques (ACTs) in both adults and children with neuromuscular disorders (NMD). We not only report randomised controlled trials, which in other systematic reviews conclude that there is a lack of evidence base to give an opinion, but also include case series and retrospective reviews of practice. For this review, we have classified ACTs as either proximal (cough augmentation) or peripheral (secretion mobilization). The review presents descriptions; standard definitions; the supporting evidence for and limitations of proximal and peripheral ACTs that are used in patients with NMD; as well as providing recommendations for objective measurements of efficacy, specifically for proximal ACTs. This state of the art review also highlights how ACTs may be adapted or modified for specific contexts (e.g. in people

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with bulbar insufficiency; children and infants) and recommends when and how each technique should be applied.

1. Introduction

In healthy individuals, mucociliary clearance and cough mechanisms are effective and efficient in defending against secretion encumbrance, but these mechanisms may become ineffective if the systems malfunction and/or in the presence of excessive bronchial secretions. Mucus is transported under normal circumstances from the lower respiratory tract into the pharynx by cephalad-bias airflow and the mucociliary escalator mechanism [1].

An effective cough is essential to clear airway secretions from the more proximal airways [2]. For an effective cough one needs firstly to take a sufficiently deep breath in; the glottis needs to close briefly to allow an increase in intrathoracic pressure; followed by expulsive glottic opening together with abdominal contraction, which results in air being forcibly expelled [3]. This cough expiratory airflow can be measured and is known as peak cough flow (PCF). Individuals with weak or impaired inspiratory and/or expiratory muscles, with or without glottis closure issues (bulbar insufficiency, tracheostomy), will have decreased PCF.

Weakness of the inspiratory muscles leads to a progressive decrease in vital capacity (VC), but the lung volume changes that appear in some patients with neuromuscular disorders (NMD) are attributable to a combination of muscle weakness and alterations of the mechanical properties of the lungs and chest wall [4]. Reduced ability to cough leads to secretion retention, predisposing to progessive respiratory morbity. Severe bulbar dysfunction and glottic dysfunction most commonly occurs in patients with amyotrophic lateral sclerosis (ALS), spinal muscle atrophy (SMA) type 1, other rarer neuromuscular disorders such as x-linked myotubular myopathy and pseudobulbar palsy of central nervous system etiology [5]. Inability to close the glottis and vocal cords results in complete loss of the ability to cough and swallow. Difficulty swallowing liquids may result in pooling of saliva and mucus in the pharynx, especially in the valleculae and the pyriform sinuses. This results in the perception of excessive pharyngeal secretions, similar to post-nasal drip [6].

Alterations in alveolar ventilation, atelectasis, mucus plugging, and recurrent respiratory tract infections (RTI's), as a consequence of an ineffective cough; together with severe bulbar dysfunction, are the main causes of morbility and mortality in patients with NMD [7–9]. Recurrent RTI's lead to further respiratory muscle weakness, with a resulting vicious cycle of respiratory disease [10,11]. Hypoventilation and managing secretions are amongst the most important problems from patients' perspective [12] and present the respiratory physiotherapist with unique management challenges in the care of people with NMD. Despite the clear implications, the problem of managing secretions has received little attention in the care of patients with NMD.

Patients with NMD's are living longer [13–15]; and consequently we are seeing more complex ventilator dependent and independent patients. Respiratory physiotherapy is an essential part of the multidisciplinary management of these individuals, but owing to the inherent heterogeneity of the condition; the growing number of available airway clearance techniques (ACTs) and associated technological developments, it is challenging for physiotherapists to understand what assessments are required and what treatment options are available and appropriate for people with NMD.

As in other chronic disorders, the home organization of patients with chronic respiratory disorders is challenging and time consuming. The cost and availability of respiratory experts in primary care, the geographical location of patients, lack of engagmenet of general practioners (GP) and care coordination may lead to poor care quality and organization. Project “Leonardo” investigated the impact of a new care organization that included a partnership between patients, considered here as key members of their own health team, their GP and their dedicated care coordinator. This study suggested positive effects in terms of increasing patient health knowledge and autonomy, improved care collaboration, appropriate resource utilization and readiness to make changes in health behaviours. A similar project worth's investigation in the respiratory care of patients with NMDs [16].

In this state of the art review written by an expert group during the 228th European Neuromuscular Centre (ENMC) international workshop on ACT's in NMD, we aim to define ACTs using simple, common language to help patients and all members of their care team. ACTs will be classified into proximal (cough augmentation) and peripheral (secretion mobilizing) ACTs (Fig. 1). We further aim to provide standard

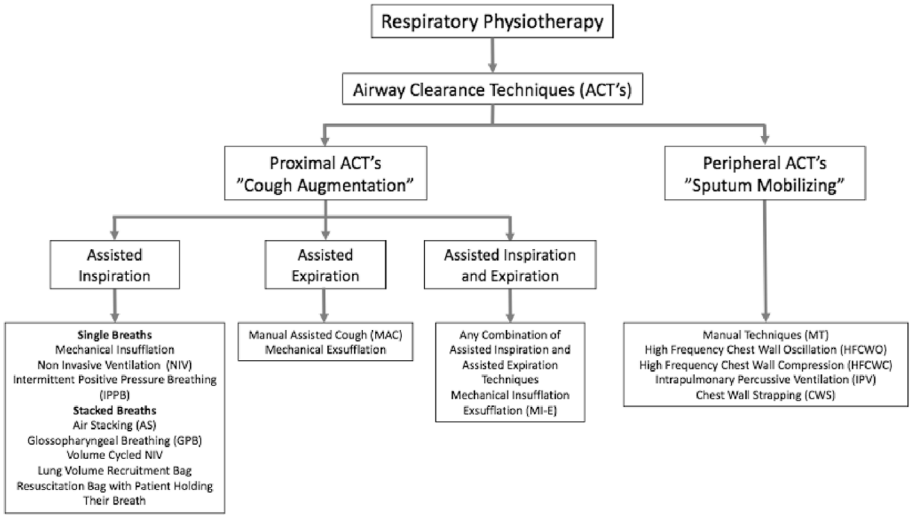

Fig. 1. Shows the classification of airway clearance techniques that are used in individuals with neuromuscular disease. Single breaths are defined as a breath given to the individual by the device followed by them exhaling or coughing. Stacked breaths are defined as multiple breaths in without the individual breathing out after the inspiration. Once the individual is close to their total inspiratory capacity they can actively or passively exhale, or cough. Mechanical insufflation is defined as an insufflation only provided by a positive pressure device. Mechanical exsufflation is defined as an exsufflation only provided by a mechanical insufflation-exsufflation (MI-E) device.

Fig. 2. Shows a lung volume recruitment bag (components from Intersurgical, distributed via Breas Medical, Stratford up on Avon, UK). Note the one-way valve at the top with arrows, which allows inspiration only.

definitions (online supplement 1) and recommendations for appropriate and objective outcome measurements of ACTs. Within the above classifications, a full description of each ACT, along with its physiological effects, evidence-base and limitations will be presented. This state of the art review also aims to highlight how ACTs may be adapted or modified for specific contexts (e.g. in people with bulbar insufficiency; children and infants) and recommends when and how each technique should be applied. A summary from each studies on the evidence for ACT's is in online supplements 2, 3 and 4.

2. Respiratory measurements for patients with NMD

The literature is overflowing with different terminologies for measures of efficacy of proximal ACT. The lack of common terminology and outcome measures limits the ability to compare outcomes and advance the understanding and development of these interventions. For previously defined volumes such as VC, we defer to the American thoracic society (ATS)/European respiratory society (ERS) definitions [17].

2.1. Insufflation capacity

2.1.1. Lung insufflation capacity (LIC)

The LIC, measured on exhalation, is the maximum, tolerable, externally assisted insufflation capacity that does not involve the patient holding their breath [18]. The “lower end” of the LIC is residual volume (RV) as per VC. The “upper end” of LIC is assisted inspiration, which may be provided using a bag valve mask; non-invasive ventilation (NIV) (typically volume pre-set ventilator mode), the inflation component of mechanical insufflation-exsufflation (MI-E), using an MI-E device or intermittent positive pressure breathing (IPPB).

2.1.2. Maximum insufflation capacity (MIC)

The MIC, measured on exhalation, is the maximum, tolerable, externally assisted insufflation capacity that is dependent on the patient being able to hold their breath. The “lower end” of a MIC is residual volume (RV) as per VC. The “upper end” of a MIC is assisted inspiration, which may be provided using glossopharyngeal breathing (GPB) [19], a bag valve mask with or without a one way valve (lung volume recruitment bag (LVR) (see Fig. 2), or a NIV device in a volume mode. With respect to MIC generation, this technique is also delivered by volume device and is typically not pressure limited or limited to a pressure of 40cmH_2O.

2.2. Peak cough flow (PCF)

Quantitative assessment of cough efficacy in NMD is typically made by measuring PCF, although in contrast with other spirometric measures [20], no internationally agreed testing guidelines are currently available. However, it has been suggested as a reliable measure in SMA [21]. PCF is typically measured using a hand-held flow meter as per peak expiratory flow rate monitoring for asthma [17] but may be measured with various devices including portable spirometers or calibrated pneumotachographs. Pneumotachographs have been suggested to be preferable due to their high sampling frequency and greater accuracy [22], although portable spirometers may provide satisfactory measurements at flows > 270 L/min [23]. PCF measurements from MI-E devices should only be taken as a trend as measurements are not calibrated. The Authors agreed with the following definition: PCF is the peak expiratory flow measured during cough. PCF may be assisted ($PCF_{assisted}$) or unassisted ($PCF_{unassisted}$). During $PCF_{unassisted}$, the patient is instructed to cough from their maximum, unassisted inspiratory lung volume (i.e. to take a deep breath in prior to coughing). During $PCF_{assisted}$ the patient is instructed to cough from their maximum, assisted inspiratory volume. This flow rate may be obtained from LIC (PCF_{LIC}) or MIC (PCF_{MIC}). The choice of measurement interface can affect PCF test performance and results. The Authors consensus view is that PCF testing in NMD should be performed using a facemask.

While the literature describing critical cut-off values for cough efficacy and the relationships of these critical values to clinical outcomes is incomplete, there are a number of broad, clinically accepted and often quoted PCF cut-off values. These include an able-bodied, normal adult range of 360–840 L/min, [24]; and evidence that a PCF of > 160 L/min is sufficient to eliminate airway debris and secretions following extubation and tracheostomy removal in adults [25]. Data from patients with Duchenne Muscular Dystrophy (DMD) suggests that a PCF exceeding 270–300 L/min is required when a patient is well in order to maintain PCF > 160 L/min and effectively clear secretions when unwell [26]. In the ALS population PCF < 255 L/min could predict the risk of ineffective spontaneous cough during a respiratory tract infection (RTI) [27]. Another study reported $aPCF_{unassisted}$ cut-off point of 2.77 L/s (166 L/min) predicted cough effectiveness [28]. Age adjusted PCF values have been published for children from the age of 4–18 years old [29] along with normal values for adults [30]. After the age of 12 years, PCF appears to be within the adult range, albeit at the lower limit [29]. In clinical practice, cough efficacy with mucus expectoration classically requires values above 160–200 L/min [31]. The Authors consider that these values represent the best-available cut-offs for clinical use until more robust data is produced. PCF remains the most common effect outcome measure of ACT in patients with MNDs [26,32,33].

Box 1 provides some recommendations for recording PCF, LIC and MIC measurements based on this group's expert consensus.

Box 1
Recommendations For Measurements.

- PCF should be measured at each clinic review
- LIC and MIC measurements can be made using any device appropriate for the recording of VC
- Either an oro-nasal mask or a mouthpiece with a nose clip may be used for measuring LIC or MIC. The same interface and circuit should be used for repeated measurements
- Bag valve mask circuits (resuscitation bags), lung volume recruitment circuits and preset volume cycle ventilators should have a pressure limit to prevent the potential risk of barotrauma
- A pneumotachograph provides the most accurate measure of PCF, especially for patients with PCF < 270 L/min. If unavailable a paediatric PEF meter is recommended
- PCF measurement should ideally be performed using an oronasal mask interface rather than a mouthpiece
- The same device should be used for repeated and longitudinal measures of PCF
- Values of PCF and volumes provided by MI-E devices should be used as an indicator of improvements or decline associated with the intervention

3. Proximal airway clearance techniques

Cough is the primary defense mechanism against foreign bodies in the central airways. Proximal ACTs are techniques that aim to augment the cough by assisting inspiration, expiration or both. They are often described as “cough augmentation” techniques, supporting or imitating a cough. The primary goal is to clear mucus from the larger airways by increasing PCF. Figure 3 presents the flow, volume and pressure profile of these techniques.

3.1. Assisted expiration

The aim of these techniques is to assist the expiratory muscles that are otherwise incapable of generating sufficient increases in intra-abdominal and intra-thoracic pressure and/or to increase the expiratory flow generated during the cough manoeuvre.

3.1.1. Manually-assisted cough (MAC)

A MAC uses either, or a combination of, a manual Heimlich/abdominal thrust manoeuvre and manual costo-phrenic compression [34] to increase expiratory airflow. Expiratory assistance may also be achieved by a self-induced thrust to the abdomen and/or chest from a stationary object such as a table [35].

3.1.1.1. Physiological effects. Compression of the abdomen causes a sudden increase in abdominal pressure; this causes the abdominal contents to push the diaphragm upwards, increasing expiratory airflow. Similarly, sudden thoracic compression causes air to be rapidly expelled, with acceleration of airflow towards the mouth. The technique involves the patient taking a spontaneous, or receiving an assisted, inspiration and at the start of the cough expiratory compression is applied. Care is taken to ensure that the direction of the compression is in line with the expiratory chest wall movement, i.e. down and in; with the exception of the techniques incorporating the Heimlich-type assist, when the abdominal pressure is up and in [36].

3.1.1.2. Limitations of the technique. MAC requires a cooperative patient, good coordination between the patient and care giver, and adequate physical effort and often frequent application by the therapist or family care giver. It may be ineffective in the presence of severe

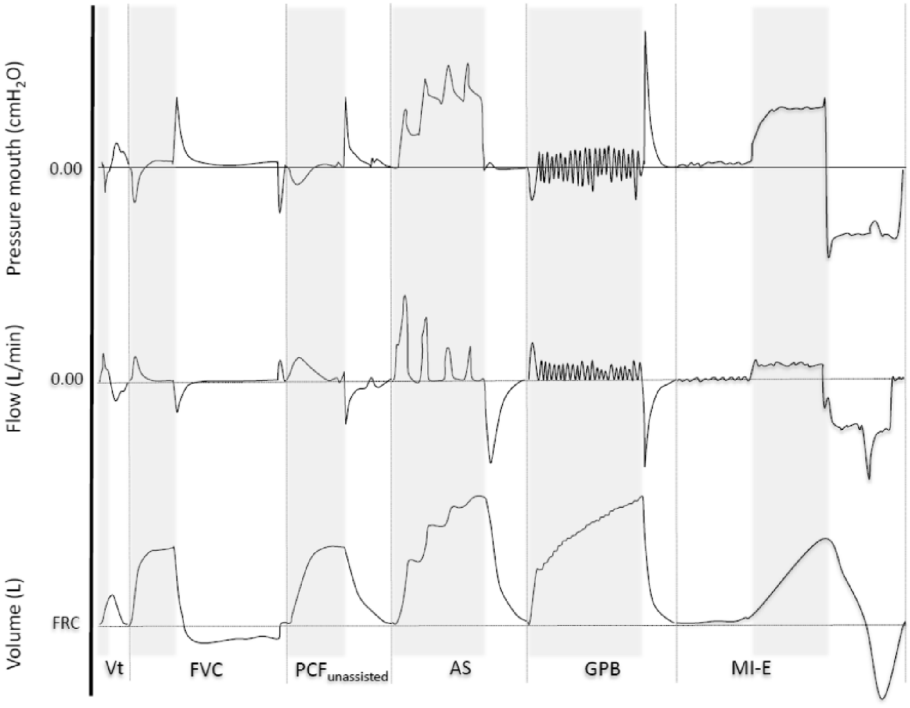

Fig. 3. Shows schematic flow, volume and pressure curves for respiratory patterns in proximal airway clearance techniques (ACT's). Pressures are illustrated as measured at the mouth and proximal ACT's are illustrated always followed by a single cough maneuver. The grey shading relates to the inspiratory component and the white to the expiratory component. Normal tidal volume (Vt), forced vital capacity (FVC), peak cough flow(PCF), air stacking (AS), glossopharyngeal breathing (GPB), mechanical insufflation-exsufflation (MI-E) and liters (L).

scoliosis [37]. Abdominal compressions should not be used for 1–1.5 h following a meal, however, chest compressions can be used to augment PCF at this time. Chest compression techniques must be performed with caution in the presence of osteoporotic ribs. Unfortunately, since it is not widely taught to health care professionals, MAC is underutilized [38]. Limits of effectiveness for the use of MAC in NMD have been reported when $PCF_{unassisted} \geq 140$ L/min, VC ≥ 1030 L or maximum expiratory pressure (MEP) ≥ 14cmH_2O, using MAC can augment PCF to > 180 L/min [34]. In patients with ALS (ALS), In ALS, the predictor of ineffective MAC was a MAC PCF below 169 L/min [28].

3.1.1.3. Evidence-base. Increases in PCF with a MAC have been reported [34,37,39–43]. However, greater effect on PCF has been shown by combining inspiratory and expiratory techniques [18,34,40]. Sancho and co-workers [27] reported in stable ALS patients that mean $PCF_{unassisted}$ 245 ± 87 L/min was required for a MAC to be effective during a RTI.

3.1.2. Exsufflation alone

This is when a MI-E device delivers negative pressure (exsufflation) alone via a full-face mask or catheter mount attached to an artificial airway.

3.1.2.1. Physiological effects. This aims to increase expiratory airflow during the cough maneuver.

3.1.2.2. Limitations of the technique. This technique has been minimally evaluated and the device is expensive.

3.1.2.3. Evidence base. Using exsufflation alone has been shown to increase PCF in adults with NMD [44] and in patients with ALS [45].

3.2. Assisted inspiration

Inspiration prior to coughing is limited in weak patients with NMD. Augmentation of inspiratory lung volumes, through assisted inspiration, is associated with increased PCF [46,47]. These techniques are relatively inexpensive methods of cough augmentation. Assisted inspiration may be either a *single breath inspiration* (e.g. inspiration, expiration, inspiration, expiration) or *stacked breath inspirations* (e.g. inspiration, inspiration, inspiration, expiration).

3.2.1. Single breath assisted inspiration

A single breath assisted inspiration is where the patient's inspiratory VC is augmented via a bag valve mask, NIV (in a preset pressure or preset volume mode) or IPPB device with a single breath via an oronasal mask or mouthpiece. The objective of this technique is to reach LIC. The patient is given a long deep breath in by the chosen device, after which they are instructed to cough (unassisted or with a MAC).

3.2.1.1. Physiological effects. Single breath assisted inspiration provides a single, sustained inspiratory flow that inflates the respiratory system to the maximal desired volume. Once this volume has been attained, a combination of static recoil and expiratory muscle recruitment provide for an increased expiratory volume or a PCF beyond that which can be obtained by an unassisted cough. LIC is an objective, quantifiable, reproducible measure that (inversely) correlates with glottic integrity the technique is indicative of ineffective glottic function [48].

3.2.1.2. Limitations of the technique. Although the technique can be delivered easily via a bag valve mask some centres will deliver the technique via a volume preset ventilator, IPPB device or insufflation from MI-E device, which has cost and resources implications. When using a bag valve mask to deliver the technique the correct size should be used for the age and size of the patient (i.e. infant (around 220–360 mls), child (around 650 mls) and adult > 1500 mls) along with the correct volume to be delivered.

3.2.1.3. Evidence base. Dohna-Schwake and co-workers [46] investigated the effects of a single breath assisted inspiration with an IPPB device. IPPB increased PCF. This effect was similar for both young (ages 6–10 years) and older patients (aged > 10 years). Trebbia and co-workers [43] measured VC and PCF during a single breath assisted inspiration with IPPB, MAC or both. Each technique improved VC and PCF as compared to baseline. Mellies and Goebel [49] performed lung insufflation using IPPB set to 30 and 40 mbar. The study included NIV dependent patients. IPPB increased VC and PCF. The highest individual PCF was achieved with insufflation at 27 mbar and volume at 924 ml, which was significantly below the MIC. Contrary to others the authors concluded that a submaximal insufflation is ideal for generating the best individual PCF, even in patients with severely reduced respiratory system compliance [49]. The BTS guideline recommends that assisted inspiration prior to coughing should achieve MIC and suggests these as effective methods of improving cough efficiency, which should be used when appropriate [50]. However, these guidelines were published before Mellies and Goebel's study [49].

3.2.2. Stacked breaths assisted inspiration

Stacked breaths assisted inspiration is where the patient has repeated inspirations without breathing out until they reach their MIC. Various techniques can be used to achieve this (Figs. 1 and 2). Techniques include: GPB, air stacking (AS) via a bag valve mask or a lung volume recruitment circuit (this has a one-way valve to restrict exhalation) (see Fig. 2) or a preset volume cycled ventilator.

GPB also known as auto or self-air-stacking or frog breathing. It increases inspiratory capacity (IC) by pumping air into the lung using the mouth, tongue, pharynx and larynx to compensate for the weakness of the inspiratory muscles [19]. AS increases inspiratory capacity by providing a series of breaths in, without the patient breathing out in-between. The patient is instructed to either take a deep breath in first, and then the inspiratory capacity is augmented via a series of breaths in without the patient breathing out, until they feel full of air. Or the patient is passively provided with a series of breaths without breathing out. Once the patient is close to their total lung capacity (TLC), the patient is instructed to cough with or without a MAC.

3.2.2.1. Physiological effects. As with the single breath techniques, the stacked breath techniques aim to inflate the respiratory system to the maximal desired volume, thereby increasing the inspiratory capacity. During AS, significant gas compression occurs and absolute lung volumes can be estimated by simultaneous measurements of chest wall volume changes, changes in lung volume and pressure variation at the airways opening [51].

3.2.2.2. Limitations of the technique. Glottic function may limit some techniques, although a one-way valve may mitigate this to some extent. If the patient is unable to perform stacked breath techniques then a single assisted inspiration should be performed.

3.2.2.3. Evidence base. In a large group of patients, MIC/VC difference correlated with the difference between $PCF_{unassisted}$ and $PCF_{assisted}$ [47]. The greater the MIC/VC difference, the greater the PCF. The lower the VC, the greater the percent increase in MIC and $PCF_{assisted}$ [47]. Jenkins et al. [52], investigated 23 children's ability to learn AS using a LVR circuit (Fig. 2); eight of whom had some degree of learning difficulty. Only four participants were unable to effectively AS. PCF after AS was

also greater in those patients with greatest muscle weakness [52]. In patients with SMA and congenital muscular dystrophy (CMD), AS has also been shown effective, however AS was more effective in the absence of scoliosis [53]. AS was evaluated in patients with DMD, where 94.9% of patients could AS and the ability to increase expiratory volume was better via AS than with GPB [54]. Maximal insufflations are extremely important to increase PCF in adult patients who have VCs of < 1500 ml [47]. The acute effects of AS on PCF and chest wall compartmental volumes were evaluated in patients with ALS and healthy controls at 45° head up. PCF_{MIC} and chest wall compartmental inspiratory capacity significantly increased in both groups ($P < 0.001$) [55].

Specific evidence base is also available for GPB. Nygren-Bonnier and co-workers [56] evaluated the ability of children with SMA type II to learn GPB. 45% of children learned the technique and increased their VC and PCF. Bach et al. [54], found GPB could be learned in 27% of patients with DMD. Although GPB was considered inferior to AS in terms of the ability to be taught, both techniques increased lung volumes and PCF. The haemodynamic effects of GPB in people with cervical spinal cord injury (SCI) showed that if GPB is performed correctly, the risks of clinically significant haemodynamic changes are low, although syncope may still occur [57]. The experiences of GPB were perceived as a possibility to make a difference in one's life by improving respiratory function, both immediately and for the future [58].

3.3. Assisted inspiration and expiration

3.3.1. Assisted inspiration combined with MAC

A very useful way to assist both inspiration and expiration consists in combining assisted inspiration (one or multiple breaths) with a MAC. The combination of those cheap techniques is very common in the practice [25,34,40,41,50].

3.3.1.1. Physiological effects. This technique combines the physiological effects of inflating the respiratory system to its desired volume with the compression of the abdomen or chest to increase expiratory airflow in conjunction with a greater inspiratory capacity. This therefore has the capacity to increase PCF further.

3.3.1.2. Limitations of the technique. As one would expect, combining techniques can increase reliance on carers. The lower limit of effectiveness for AS plus MAC was best predicted by VC > 340 mL [34].

3.3.1.3. Evidence base. Bianchi et al. [35], showed that GPB combined with self-induced thoracic or abdominal thrust was as effective as AS and MAC in wheelchair-dependent patients with NMD. The authors suggest that independently assisted cough via GPB plus table thrust should be utilized where possible [35]. Studies have found the greatest improvement in PCF occurred when combining assisted inspiration (via AS, mechanical insufflation or IPPB) with a MAC [18,40,43] and the greatest change in PCF was in the weakest patients [18]. Therefore, it is recommended that AS be used with a MAC to achieve the greatest improvement in PCF.

3.3.2. Mechanical insufflation-exsufflation (MI-E)

MI-E devices deliver a deep inspiration to the lungs (insufflation) followed immediately (10 ms) by a deep expiration (exsufflation), by applying sequentially positive and negative pressure swings via a full-face mask or catheter mount attached to an artificial airway. The insufflation aims to “fill” the lungs and the exsufflation aims to “empty” the lungs of air. The rapid switch from positive to negative pressures aims to simulate the airflow changes that occur during a normal cough, potentially assisting secretion clearance [59]. Theoretically, MI-E compensates both for weak inspiratory and expiratory capacities. It is possible to coordinated the glottic closure and opening to MI-E cycles when instructed to cough [60,61]. Setting the MI-E device involves adjustment of the positive and negative pressures, the inspiratory, expiratory and pause times (seconds) and the inspiratory flow rate (L/min). One MI-E treatment usually consists of several phases of coughing and rest periods. These cycling periods are repeated several times or until secretions are substantially expelled [59]. An additional MAC can be provided during exsufflation (usually in weaker patients).

3.3.2.1. Physiological effects of MI-E. Studies have reported increases in PCF with low pressures [45,62–64] whilst others have reported efficacy with high pressures [7,65–69]. Studies evaluating proximal ACT's showed MI-E to increase PCF [39,44,70] with MI-E superior to other techniques [44,45,71] and the greatest change in PCF occurring in the weakest patients [45], with the exception of Lacombe and co-workers [72] who found that in stronger patients MI-E did not produce the greatest change in PCF. One possible explanation for the difference in pressures reported could be related to the baseline strength of the patient groups. As spontaneous cough strength declines, there may be a need to increase pressures to improve expiratory flow, however optimal MI-E dosage and frequency has not been determined. Fauroux and co-workers [70], showed in children, who received insufflation and exsufflation at different pressure settings without them coughing, an insufflation pressure of $+40 cmH_2O$ and exsufflation pressures of -40 cmH_2O achieved mean PCFs of about 120 L/min. This suggests that higher pressures may clinically be required in weaker patients. Hov and co-workers [73], found by survey that the provision of MI-E to children in Europe that younger children were set up with lower pressures than older. However, there was wide variation in settings prescribed. Indeed, current practice is to start with low pressures and to build up pressure until efficacy is achieved. Titration of settings is often to improve audibility of the cough or to an objective increase in PCF measurement on the device.

Sancho and co-workers [74] reported airway closure in adults with bulbar ALS with exsufflation pressures of -40 cmH_2O evaluated with a CT scan. They did not examine what happens with insufflation. Andersen and co-workers [60] recently showed the same phenomenon with video-recorded flexible transnasal fibre-optic laryngoscopy during MI-E in all ALS subjects regardless of bulbar symptoms, but in addition they observed laryngeal collapse during insufflation in all subjects with bulbar symptoms [60]. The implication for clinicians is that bulbar ALS patients are unlikely to benefit from high pressures as they have predisposition to upper airway collapse. This has not been reported in patients with other NMD.

Bench studies have added to this evidence base, although results may not be generalizable to clinical practice. High insufflation and exsufflation ($+50$ cmH_2O to -50 cmH_2O) pressures were required through endotracheal tubes and tracheostomies to produce high expiratory flows. The smaller the tube, the higher the resistance and the higher the pressures required to generate effective expiratory flows [75]. In a paediatric lung model an insufflation time of > 1 s was required for equilibration between insufflation pressure and alveolar pressure. Longer exsufflation time did not significantly change mean expiratory flows. Higher insufflation and exsufflation pressures both increased mean expiratory flow, but greater exsufflation pressures had a more substantial increase on mean expiratory flow [76]. One study in an adult lung model showed set pressures of 40 to -40 cmH_2O with an insufflation time of 3 s, and exsufflation time of 2 s was required to generate an exsufflation flow of 294 L/min [77]. The authors concluded that increasing insufflation times may be more effective than exsufflation times in improving expiratory flows.

Recommendations for children who use MI-E for airway clearance are that they should be given long enough periods of rest during treatment sessions to prevent respiratory muscle fatigue due to coughing. Also at the end of a treatment session with MI-E it is important to complete the session with an insufflation to leave an appropriate functional residual capacity [50]. MI-E is reported safe to use

in small children in a post op setting, e.g. by gastrostomy surgery [78].

Long-term VC was shown to increase with regular use of MI-E, supporting the suggestion that regular use of MI-E in people with NMD may contribute to the release of thoracic contractures [79]. Kim and co-workers [41], showed improvements in PCF with MI-E but greater increases in PCF were attained with the addition of a MAC to MI-E.

Newer MI-E devices have the option to add high frequency oscillations (HFO) during insufflation, exsufflation or both. Sancho and co-workers [69] found that HFO in addition to insufflations, exsufflation and in combination did not have an effect on PCF in medically stable subjects with ALS.

3.3.2.2. Limitations of the technique. Patient reported complications of MI-E use in adults are rare and MI-E treatments are usually well tolerated [18,32,50,68,70]. However, reported side effects include abdominal bloating, pneumothorax [80], nausea, bradycardia, tachycardia, and abdominal distention [42]. Children have also reported thoracic wall discomfort and crying and agitation in response to treatment with MI-E [64].

A major limitation is the cost and/or reimbursement of the devices. There are also discrepancies in the availability in the acute and long-term settings. In some middle and low-income countries MI-E devices are not available.

MI-E can be difficult to perform in very young infants who are not able to have a minimal cooperation and who are not able to relax and accept being “insufflated” during the MIC maneuver. Should the technique be ineffective at this time there is no reason not to try as the child gets older.

Lacombe et al. [72], suggested that the combination of MI-E to MAC is useless in patients whose $PCF_{assisted}$ with an insufflation technique and MAC exceeds 5 L/s (300 L/min). In patients with ALS, the predictor of effective MI-E was MI-E assisted PCF of 177 L/min [28].

Andersen and co-workers [60] evaluated upper-airway malfunction in patients with ALS during MI-E. Hypopharyngeal constriction during exsufflation was observed in all subjects, most prominently in patients with ALS and bulbar symptoms. This severely obstructed the airflow and limited the efficacy of the treatment. They concluded that individually customized settings can prevent airway obstruction and thereby improve and extend the use of non-invasive MI-E. Settings that can help these patients are triggered insufflation, decreasing the inspiratory flows and pressures and allowing a longer insufflation time in order to allow equilibrium of pressure from the device to the lungs.

3.3.2.3. Evidence base. Experts suggest that using MI-E in very weak patients is a priority. However, few trials have studied the limits of effectiveness of MI-E, or its efficacy and safety in the long-term [32,50]. MI-E in a protocol with MAC, oximetry feedback, and home use of NIV was shown to effectively decrease hospitalizations and respiratory complications and mortality in a program for patients with ALS [67].

Short-term studies [32,44,71,74], or bench studies [75] or feasibility in case reports [62], have suggested that MI-E improves PCF's enough to aid mucus clearance. The addition of MI-E may reduce the frequency of pneumonia [64] and the treatment time when added to MAC [81]. MI-E appeared to be as well tolerated as other cough augmentation techniques [32,68,70]. However, these studies did not report on mortality, morbidity, quality of life, or serious adverse events [32]. When MI-E was compared to AS over a 12-month period there was no difference in episodes of RTIs; days of antibiotic; mean duration of symptoms per RTI or hospitalization. However, a major confounder of the study was that it was significantly underpowered [82].

Because extubation failure can be a significant problem for patients with NMD, the use of MI-E in ICU has been evaluated. Strategies that can prevent the development of respiratory failure after extubation and the need for reintubation are necessary. Proximal ACTs and NIV are approaches that may be useful to address extubation failure [66].

Conventional management of respiratory secretions in patients with artificial airways is suctioning via a catheter. With routine suctioning, secretions in peripheral airways are not directly removed [83]. Moreover, suctioning can lead to serious complications [84]. In contrast, when MI-E is attached to an artificial airway it may clear secretions from both lungs along with the central airways. Garstang et al. [85], found that MI-E through tracheostomy tube was significantly less irritating, less painful, less tiring and less uncomfortable than endotracheal suctioning in patients with traumatic SCI.

The effects of MI-E via tracheostomy with inflated cuffs were compared to suctioning in patient with ALS. MI-E was deemed more effective in eliminating airway secretions than tracheal suctioning. Pulse oximetry (SpO_2), peak inspiratory pressure, mean airway pressure and work of breathing improved significantly with MI-E sessions. Patients found MI-E more effective and more comfortable than suctioning [86]. Different studies have reported on the effectiveness and security of MI-E in patients, mainly with ALS, on long-term invasive mechanical ventilation through a tracheostomy tube, particularly when MI-E is applied through un-cuffed tracheostomy tubes [87,88].

MI-E is increasingly used in the home management of both adults and children with NMD. A survey of patients with NMD using MI-E at home showed 46% used MI-E daily and 27% weekly. One third of patients had used MI-E to resolve a choking episode and 88% agreed that home MI-E had improved their/their child's overall respiratory health. One third reported negative features using MI-E, which were related to the size and weight of the device and the requirements to administer the device [89]. Poor adherence was identified as the major barrier to effective use [90]. The positive impacts included greater ability to manage the child's health, including avoidance of hospital admissions. Negative impacts were greatest for parents who were sole operators of the device, including a frequently disrupted lifestyle [91]. Siewers et al. [92], investigated home use of MI-E in ALS. They concluded that health professionals need to take into account individual and social aspects of implementing MI-E in the home environment. Proper instruction and practical training and confidence in how to use the device, and trust and continuity among careers are important factors for successful implementation [92].

3.4. Recommendations regarding proximal airway clearance

The Adult BTS guidelines [93] recommend that MI-E should be considered in the following: in SCI, if simpler techniques fail to produce an adequate result; in bulbar patients who are unable to AS; in any patient who remains unable to increase PCF to an effective level with other strategies and where cough effectiveness remains inadequate with MI-E alone, it is recommended that MI-E be combined with a MAC.

The Pediatric BTS guidelines [50] recommend that MI-E should be considered in the following: in very weak children; those with bulbar insufficiency, and those who cannot cooperate with MAC or AS, or in whom these methods are not effective [50]. MI-E should ideally be available in the acute setting in all hospitals that treat children with NMD as an alternative method of ACT, with the purpose of preventing deterioration and the need for intubation and mechanical ventilation [50].

Contrary to the above suggestions, a more recent Cochrane review reported that more randomised controlled trials were warranted and reported the lack of robust evidence supporting the use of MI-E in people with NMD [32]. Considering the large evidence base outside randomised controlled trials for the use of MI-E, some clinicians believe it would be unethical to randomise NMD patients not to receive a MI-E device in a clinical trial, where MI-E is available as standard practice. In

Box 2
Recommendations For The Use Of Mechanical Insufflation-Exsufflation (MI-E).

- MI-E is the treatment of choice for the weaker group of patients with NMD
- Face masks should be used when using MI-E in patients without an artificial airway
- Inspiratory and expiratory timing/pressures should be individualized with progressive build-up of pressure until efficacy is achieved
- Higher expiratory than inspiratory pressures are advisable
- Patients with ALS are likely to benefit from lower pressures, triggered insufflation and longer insufflation time
- MI-E is possible through tracheostomy tubes, with higher pressures for smaller tube diameters
- Complete the session with an insufflation to leave an appropriate functional residual capacity in weaker patients or children
- In ICU, MI-E maybe as a useful technique to prevent re-intubation
- MI-E may be considered in the weaker children with bulbar insufficiency, and those who cannot cooperate with MAC or AS or in whom these methods are not effective

the context of lower income countries, where access to MI-E devices is limited or non-existent, randomised clinical trials might be ethically permissible to inform local practice guidelines, and for the purposes of advocacy.

Box 2 highlights the recommendations from the authors of this review for MI-E.

4. Peripheral airway clearance techniques

Peripheral ACTs aim to improve ventilation, loosen secretions and enhance mucus transport from peripheral airways to the central airways (12th generation of the bronchial tree and above) with higher expiratory than inspiratory airflows (called biased expiratory flow) [94]. These include: manual techniques (MT), high frequency chest wall oscillations (HFCWO), or compression (HFCWC), intrapulmonary percussive ventilation (IPV) and chest wall strapping (CWS). See Figure 4 for the flow, volume and pressure profile of these techniques. Peripheral ACT do not necessarily require the patient's co-operation [95]. The use of these techniques is possible in infants, children and adults, even in the presence of a tracheostomy and/or bulbar failure or intellectual impairment (See Table 1). This review will not include positive expiratory pressure (PEP) and oscillatory PEP devices as patients with NMDs generally cannot generate sufficient expiratory flow for the technique to be effective and we therefore do not recommend these devices for patients with NMD.

4.1. Manual techniques

Manual techniques consist of chest percussion and vibrations or shaking. This is performed using a hand, fingers or facemask and is generally well tolerated and widely used in babies, small children and in patients unable to cooperate with therapy. Chest vibrations consist of a rapid extra-thoracic force at the beginning of expiration, followed by oscillatory compressions until expiration is complete [96].

4.1.1. Physiological effects

The compression and oscillation applied to the chest are believed to aid secretion clearance via increasing peak expiratory flow to move secretions towards the large airways for clearance via suction or a cough [97].

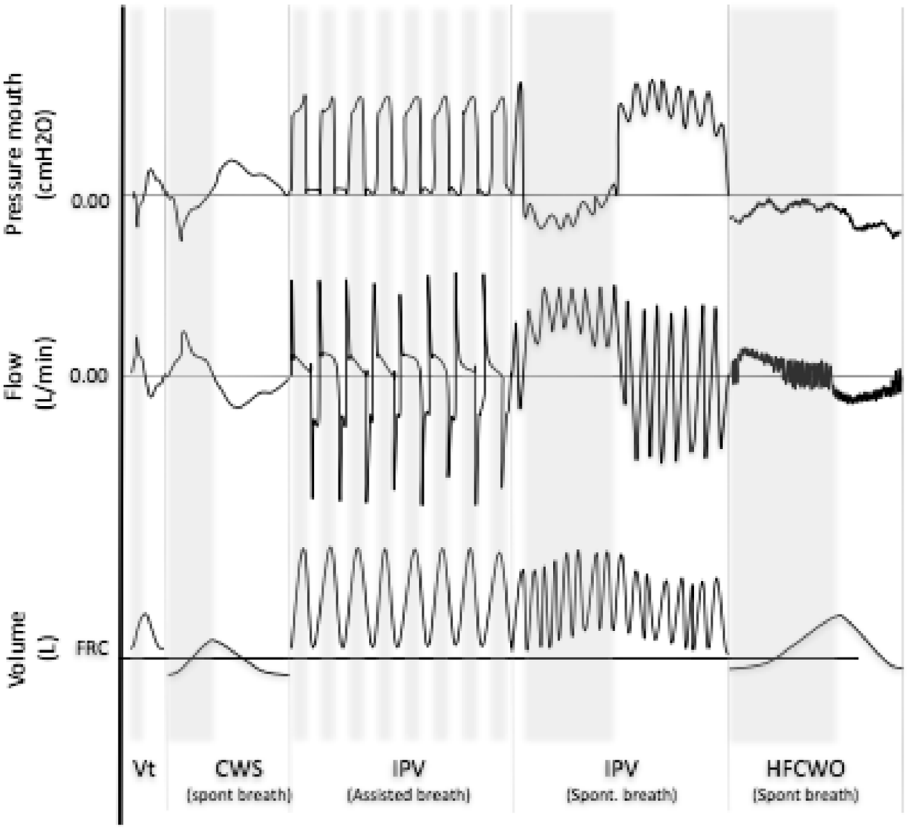

Fig. 4. Shows schematic flow, volume and pressure curves for respiratory patterns in peripheral airway clearance techniques (ACT's). Pressures are illustrated as measured at the mouth. The grey shading relates to the inspiratory component and the white to the expiratory component. Normal tidal volume (Vt), chest wall strapping (CWS), intrapulmonary percussive ventilation (IPV), high frequency chest wall oscillation (HFCWO).

Table 1
Practical Aspects of Peripheral ACT's.

	Does the patient need to co-operate with the technique? (Y/N)	Is the technique possible when patient is fatigued? (Y/N)	Is it possible to do the technique in conjunction with ventilator support? (Y/N)	Can the technique be applied to infants? (Y/N)	Can the technique be applied to children? (Y/N)	Can the technique be applied to patients with tracheostomy (Y/N)	Can the technique be applied to patients with bulbar failure (Y/N)	Length of treatment (minutes)
Manual Techniques	N	N	Y	Y	Y	Y	Y	5 each lung area to be treated
HFCWO	N	N	Y	Y	Y	Y	Y	10–30
HFCWC	N	N	Y	N*	Y	Y	Y	10–30
IPV	N	Y	Y	Y	Y	Y	Y	30 with mask 5 with mouthpiece
CWS	N	N	Y	Y	Y	Y	Y	Unclear

High frequency chest wall oscillation (HFCWO); high frequency chest wall compression (HFCWC); intrapulmonary percussive ventilation (IPV); chest wall strapping (CWS); yes (Y); no (N). As with all peripheral airway clearance techniques (ACT's) in individuals with neuromuscular disorders it is essential to ensure effective proximal ACT's, to prevent secretion retention in the central airways. IPV may provide ventilator support if set correctly. *Manufactures recommendation is in children > 3 years old. In patient who require ventilator support these techniques should be used in conjunction with ventilator support.

4.1.2. Limitations of the technique

Care should be taken in infants not compress below airway closing volume or effective flow will be compromised. The lack of clear physiological effects and evidence base represent the limitations of manual techniques in NMD.

4.1.3. Evidence base

There is no evidence base for the use of manual techniques in NMD. However, manual techniques are widely used by professionals to help mobilise secretions.

4.2. Instrumental techniques

4.2.1. High frequency chest wall oscillations (HFCWO)/high frequency chest wall compression (HFCWC)

HFCWC provides compression of the chest wall at frequencies that are similar to the resonant frequency of the lung, between 5 and 20 Hz [98], via an air pulse generator that delivers intermittent positive airflow into the jacket. As the jacket expands compressing the chest wall, it produces a transient/oscillatory increase in airflow in the airways vibrating the secretions from the peripheral airways toward the mouth and can be used in conjunction with ventilator support.

HFCWO also provides compression of the chest wall at frequencies that are similar to the resonant frequency of the lungs via a negative pressure ventilator attached to a cuirass. As the ventilator delivers negative pressure the air is sucked into the lungs. When the negative pressure ceases the patient breathes out. The device has the ability to deliver high frequency intermittent negative pressure on top of the patients spontaneous or NIV supported breathing. This also produces a transient/oscillatory increase in airflow in the airways vibrating the secretions from the peripheral airways toward the mouth.

Starting settings for this device are a frequency of 5 Hz building up to 10–15 Hz. There have been no studies evaluating treatment times or frequencies in NMD. Therefore, treatments are individualized or based on manufactures pre-set programs. Often treatments in NMD are around 5 min stages or until the patient feels the need to cough.

4.2.1.1. Physiological effects. There is no evidence regarding the physiological effects of chest wall oscillations. An intuitive explanation of the physiologic effects on mucus clearance relates to generation of air-liquid shear forces [59]. The eccentric flow pattern (higher expiratory flow than inspiratory flow) may promote transport of secretions centrally. There is also some evidence that high frequency oscillations reduce mucus viscosity [99].

4.2.1.2. Limitations of the technique. These devices should be used in combination with ventilator support, in patients who are ventilator-dependent. The major limitation of this technique in patients with NMD is that proximal ACT's are still needed to clear secretions from the central airways. There is also the potential to mobilise a vast amount of secretions into the central airways, with the potential to precipitate a respiratory arrest. Therefore, it is essential to have equipment readily available to clear secretions from the airway [50,100]. The devices are also expensive compared to other methods of ACT's.

4.2.1.3. Evidence base. Yuan and co-workers [101] investigated HFCWC in patients with NMD. Data suggest safety, tolerability, and better compliance with HFCWC compared with “standard chest physiotherapy”. Crescimanno and Marrone [102] suggested that HFCWC is easy to use and accepted by patients with NMDs. They showed improvements in their clinical and radiological condition and suggested it was helpful for patients with scoliosis in whom conventional respiratory physiotherapy is not possible. HFCWC has been shown to decrease the work of breathing and decrease the sensation of breathlessness in with ALS and a sub-group showed a decreased rate of FVC decline [103]. More recently, Lechtzin and co-workers [104] evaluated the impact of HFCWC on healthcare use in patients with NMD. Total medical costs decreased after initiation of HFCWC along with inpatient admission costs and pneumonia costs. However, whilst it looks like HFCWC decreases RTI's in NMD, no data was provided on adherence or use. A case report of HFCWO of a child with SMA type 1 suggested the device was safe and the authors concluded that the increase in ventilator free time was attributed to improved secretion clearance [105].

4.2.2. Intrapulmonary percussive ventilation (IPV)

IPV is delivered via an IPPB pneumatic device. IPV delivers air to the lungs at frequencies of 100–300 cycles per minute at peak pressures from 10 to 40 cmH_2O. IPV superimposes high-frequency bursts of gas on top of the patient's own respiration. This creates a global effect of internal percussion of the lungs, which promotes clearance from the peripheral bronchial tree. The high frequency airflow pulsates to expand the lungs, vibrate and enlarge the airways. This potentially delivers air to the distal lung units, beyond accumulated secretions. IPV is reported to improve airway clearance and lung function in patients with NMDs [106].

4.2.2.1. Physiological effects. The physiological effects of IPV have been studied *in vitro* [107]. Increasing frequency increases positive end-expiratory pressure (PEEP) and percussion (i.e. the peak of pressure), but decreases ventilation. Increasing inspiratory/expiratory (I/E) time increases PEEP and decreases percussion. Increasing pressure increases PEEP and ventilation. Higher expiratory than inspiratory flows are always produced by IPV, favouring proximal secretion mobilisation [107].

Parameters of IPV devices can be set as follows: in order to obtain

the highest peaks of pressure, high frequency and short inspiration times are recommended [95]. However, lower frequencies and higher pressures are required when patients need assisted ventilation. Lower pressures and higher frequencies should be set for infants and children. Again, pressures may be increased to obtain normal oxygen saturation and carbon dioxide levels in ventilator dependent patients, such as those with SMA type 1. The length of IPV session is related to patient comfort. With face masks, patients cannot tolerate IPV ventilation longer than 1 or 2 consecutive minutes. However, the use of nasal interface increases comfort and allows sessions of 15 min or longer [108]. Co-operation from the patient is not required with IPV. IPV is especially useful in patients with NMDs and acute respiratory failure. The use of IPV is possible with artificial airways such as an endotracheal tube or tracheostomy. IPV is also possible in association with mechanical ventilation [109].

4.2.2.2. Limitations of the technique. Devices may not be readily available in some countries and are also expensive. Other important limitations are the lack of evidence on adequate settings of parameters and the need for intensive training for professionals to build experience enough to be able to set parameters in different clinical conditions. Finally, IPV devices may hyperventilate patients when there is no control of arterial carbon dioxide during titration, in children in particular.

4.2.2.3. Evidence base. Preventive use of IPV has been suggested useful to prevent pulmonary infections in adolescents with NMDs who have impaired ability to clear secretions. Antibiotic use was lower, and the hospital stay was shorter [110]. IPV has also been shown to improve persistent pulmonary consolidation and appeared to be a safe and effective therapy for these patients who have difficulty mobilizing sputum and who do not respond to conventional therapeutic techniques [100]. In tracheostomised hypersecretive DMD patients, the addition of IPV enhanced secretion clearance and was a safe technique [111]. Bidiwala and co-workers [112] compared IPV to HFCWC in complex patients with a tracheostomy. They found that IPV was a superior treatment compared to HFCWC as it was associated with a significant decline in hospitalizations, decreased RTIs, decreased antibiotic, bronchodilator and steroid use. The authors concluded that IPV could be more effective and beneficial in providing airway clearance in specific subsets of the medically complex pediatric population.

4.2.3. Chest wall strapping (CWS)

CWS is the restriction of the chest wall through the application of elastic material around the thorax. Strapping via CWS passively lowers the functional residual capacity (FRC) without using expiratory muscles. This has been demonstrated to be beneficial for lung secretion clearance [113]. The principles and physiological effects of CWS are similar to that of Autogenic Drainage [114].

4.2.3.1. Physiological effects. The single most important physiologic change consists of the significant increase in maximal expiratory flow (+47–88%) for the same lung volume during CWS, thus augmenting the gas-liquid interactions. The enhancement in airflow is in particular attributed to by a higher conductance (+24–43%) and improved lung elastic recoil (+39–144%). The latter is expected to dilate small airways, which in turn may facilitate mucus transport [113,115–120]. However, the benefits of these physiological changes may be overwhelmed in NMD as CWS has been associated with a significant decrease in tidal volume (± 25%).

4.2.3.2. Limitations of the technique. The strapped thorax diminishes pulmonary system compliance while work of breathing and dyspnoea increase. In order to prevent this risk, the technique is widely carried out on ventilatory support [115].

4.2.3.3. Evidence base. There is no evidence regarding deflation and strapping to mimic breathing at a low lung volume as in the airway clearance technique, autogenic drainage (deflation). However, physiological arguments and clinical experience advocate for using CWS which induces breathing at low lung volumes, increases lung elastic recoil and increases maximal expiratory flows [121–123].

4.3. Recommendations regarding peripheral airway clearance

An expert report suggests that IPV and HFCWO/HFCWC may be recommended but lacks evidence, as for other ACT [124]. Various ACT modalities, including IPV, may be used effectively, either alone or in combination. IPV appears safe, even in infants who require airway clearance assistance. To date, however, criteria for children are lacking to determine when such modalities should be used and which are the most effective [124]. The Paediatric BTS guidelines suggest that oscillatory techniques should be considered in children who have difficulty mobilizing secretions or who have persistent atelectasis, despite use of other airway clearance techniques [50]. AARC clinical practice guidelines [125] contradicts the BTS guidelines and suggests that oscillatory techniques cannot be recommended due to insufficient evidence. The BTS guidelines on airway clearance techniques in the spontaneously breathing adult [93] highlight that “The ATS consensus statement on the management of patients with DMD [126] concludes there is also insufficient evidence to make any firm recommendations on the use of IPV with self-ventilating patients, but that the use of airway clearance devices dependent on a normal cough is likely to be ineffective without the concurrent use of other proximal ACT's. Therefore, other techniques, alone or in combination, may be required to clear secretions once mobilized centrally following intrapulmonary percussive ventilation. Further research is required to evaluate the safety and efficacy of IPV in the care of patients with NMD.” Box 3 highlights the recommendations from the authors of this state of the art review for peripheral ACT's, taking into account all the evidence published since these guidelines and non-randomized controlled trials. It is acknowledged that oscillatory devices are expensive and may not be readily available.

Box 3
Reccomendations for Peripheral ACT's.

- Peripheral ACT should be commenced before and after clearing any secretions from the upper airway with proximal ACT's
- Peripheral ACT's do not require physical or intellectual patient co-operation
- Peripheral ACT's is possible in infants, children and adults, even in the presence of a tracheostomy and/or bulbar failure
- Deflation by CWS strapping, is promising and worth evaluating in a clinical trial
- MT should be considered as a treatment option
- In the ventilatory dependent patient, peripheral ACT should be used in combination with ventilator support

ACT: airway clearance technique; IPV: intrapulmonary percussive ventilation; HFCWO: high frequency chest wall oscillations; CWS: chest wall strapping; MT: manual techniques.

5. Limitations of this state of the art review

Our main limitation is that this review was not performed as a systematic review for each technique because it was performed during a meeting gathering 21 international experts. For that reason, the current recommendations could be biased or incomplete. However, a summary of the studies can be found in the online supplement, 2, 3 and 4.

6. Conclusion

In this state of the art review we recommend that PCF is routinely measured in patients with NMD. PCF and MIC measurments can be used to evaluate the efficay of proximal ACTs, however PCF measurements from MI-E devices may not be accurate and should be used to establish a trend only. By splitting ACTs into peripheral and proximal ACTs we have described treatment options for patients with NMD. For proximal ACTs, we recommend MAC and assisted inspirations, as single breaths, AS and GPB, in patients with higher PCF. These techniques can be combined to futher increase efficacy. MI-E appears to be very effective in patients with lower PCF's (< 160 L/min). MI-E should be considered in weak children and those who cannot cooperate with MAC or AS or in whom these methods are not effective. Titration should be individualized and is possible with patients with ALS, with appropriate modifications. MI-E is widely considered an essential tool in the resolution of acute respiratory failure in patients with NMD, but is rarely needed for stable patients with intact bulbar function who can AS to maximum lung volumes and close the glottis against high pressures with an abdominal thrust. However, even in stable patients it may be advisable to use MI-E routinely, where available, in order to stay in practice so they can apply it in an effectively during respiratory tract infections. Peripheral ACTs: MT, HFCWC, HFCWC, IPV and CWS may be effective in patients with NMD and should be considered according to availability and local expertise in patients to mobilise the secretions prior to proximal ACTs.

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Appendix A. Supplementary data

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