Evidence for Beneficial Effect of Daily Use of Mechanical Insufflation-Exsufflation in Patients With Neuromuscular Diseases

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BACKGROUND: Daily application of mechanical insufflation-exsufflation (MI-E) is used increasingly in patients with neuromuscular diseases (NMDs) to prevent pulmonary congestion and thereby respiratory tract infections, although its beneficial effect remains uncertain. We, therefore, conducted a systematic review, registered in PROSPERO (CRD42020158278), to compile available evidence for daily MI-E use in subjects with NMDs and stable respiratory condition. METHODS: We performed a systematic comprehensive search of MEDLINE, Embase, CINAHL, and Web of Science up to December 23, 2021. We excluded articles studying the effect of MI-E in case of acute respiratory failure or infections and studies comparing different MI-E devices and settings. Studied outcomes were prevalence and severity of respiratory infections, lung function, respiratory characteristics, and patient satisfaction. We performed a meta-analysis using DerSimonian-Laird random effects model and assessed methodological quality by using the Alberta Heritage Foundation for Medical Research tool. RESULTS: A total of 3,374 records were screened, of which 25 were included, studying 608 subjects. One randomized controlled trial (RCT) found a trend toward reduced duration of respiratory infections compared to air stacking (AS) that was not statistically significant. Long-term effects on pulmonary function tests (PFT) results were reported in one RCT and one retrospective study, with mixed results regarding vital capacity. Most studies compared PFT results before and immediately after MI-E use. Meta-analysis showed an overall beneficial effect of MI-E on cough peak flow (CPF) compared to unassisted CPF (mean difference 91.6 L/min [95% CI 28.3–155.0], $P < .001$). Subject satisfaction was high, though possibly influenced by major bias. CONCLUSIONS: There is limited evidence available to support beneficial effects of daily use of MI-E in clinically stable subjects with NMDs, with the possible exception of increased CPF immediately after MI-E application. Lack of longitudinal studies preclude conclusions regarding long-term effects. The very limited data comparing MI-E to AS preclude comparisons.
Key words: neuromuscular diseases; airway clearance; medical devices; mechanical insufflation-exsufflation; home care; cough; adult; pediatrics. [Respir Care 2023;68(4):531–546.

Introduction

The primary cause of morbidity and mortality in patients with neuromuscular diseases (NMDs) is respiratory failure due to progressive respiratory muscle weakness.[1] Respiratory muscle weakness causes insufficient cough, thereby increasing the risk of recurrent respiratory tract infections (RTIs), resulting in hospital admissions and further lung function decline.[1-4]

To prevent pulmonary congestion, several consensus statements of respiratory care for children and adults with NMD recommend initiation of airway clearance techniques when cough is weak, that is, when cough peak flow (CPF) is < 270 L/min.[5-7] Airway clearance employs expiratory support (manually assisted cough) or inspiratory support (air stacking [AS] or glossopharyngeal breathing) or both (mechanical insufflation-exsufflation [MI-E]). MI-E uses positive pressure to promote maximal lung inflation followed by an abrupt switch to negative pressure to the upper airway. The rapid change from positive to negative pressure attempts to simulate the flow changes that occur during a cough, thereby assisting sputum clearance.[8] MI-E does not

require active cooperation and can, therefore, also be performed in patient groups that are more difficult to instruct, in particular young children or patients with intellectual impairment; however, it is also more expensive.[2,7,9]

Although expert opinion has facilitated the introduction of MI-E in individual patients or for specific indications,[2,7,10,11] reimbursement of MI-E may be complicated by the perceived scarcity of evidence for its efficacy. For this reason, we conducted a systematic literature review using a comprehensive search strategy to document evidence for regular, daily MI-E use in subjects with NMDs with stable respiratory status (ie, absence of RTIs). We were aware that studies on the most important outcome, that is, prevalence and severity of RTIs, were limited. For this reason, the studied outcome was the overall efficacy, including prevalence and severity of RTIs, pulmonary function tests (PFT) results, respiratory characteristics, and patient comfort and satisfaction.

Methods

For this systematic literature review, we followed the PRISMA guidelines.[12] The protocol was registered on PROSPERO (ID: CRD42020158278).

Search Strategy

We performed a systematic comprehensive electronic search of MEDLINE, Embase, CINAHL, and Web of Science from inception to December 23, 2021, using a detailed search. We used the following search items: "(mechanical insufflation exsufflation) OR (mechanical insufflation-exsufflation) OR (mechanical in-exsufflation) OR (mechanical in-exsufflator) OR (mechanical cough assistance) OR (cough assist) OR (cough assist therapy)." We purposely did not include outcome or NMD in the search, as this narrowed the search with risk of missing studies on this topic. No filters were applied to the search. We conducted handsearching of the reference lists of included articles.

Inclusion and Exclusion Criteria

We used the following criteria for inclusion: original research, English-language studies with data pertaining to clinically stable subjects (children or adults) with documented NMD. Clinically stable was defined as the absence of an RTI or acute respiratory failure at study enrollment. We excluded studies that used artificial lung or animal models, compared different MI-E devices or settings without an unassisted or other airway clearance comparator, or examined the effect of MI-E in acute respiratory failure or infection. We also excluded conference abstracts, reviews, editorials, letters, case reports, duplicate reports, and studies of which we could not access full text (even after contacting the authors).

Selection of Studies and Data Extraction

Two authors (EV and RW) independently screened titles and abstracts of all studies identified by the literature search. Studies for which at least one reviewer concluded that it possibly met the inclusion criteria were selected for full-text screening. Finally, all references of included research were checked for missing studies. Next, both authors independently extracted data from included studies to a standard form. Discrepancies in data interpretation were discussed until consensus. If necessary, we asked a third assessor (LVO) to resolve the discrepancy. We extracted the following data from each study for final analysis: study design, study objectives, years of study conduct, setting, subjects' age, underlying NMD, MI-E settings, and outcome.

Assessment of Quality

We assessed methodological quality of each study by using the tools developed by the Alberta Heritage Foundation for Medical Research: standard quality assessment criteria for evaluating primary research papers from a variety of fields (https://era.library.ualberta.ca/items/48b9b989-c221-4df6-9e35-af782082280e. *Accessed April 26, 2022*). For the quantitative studies, 14 items were scored depending on the degree to

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Supplementary material related to this paper is available at http://www.rcjournal.com.

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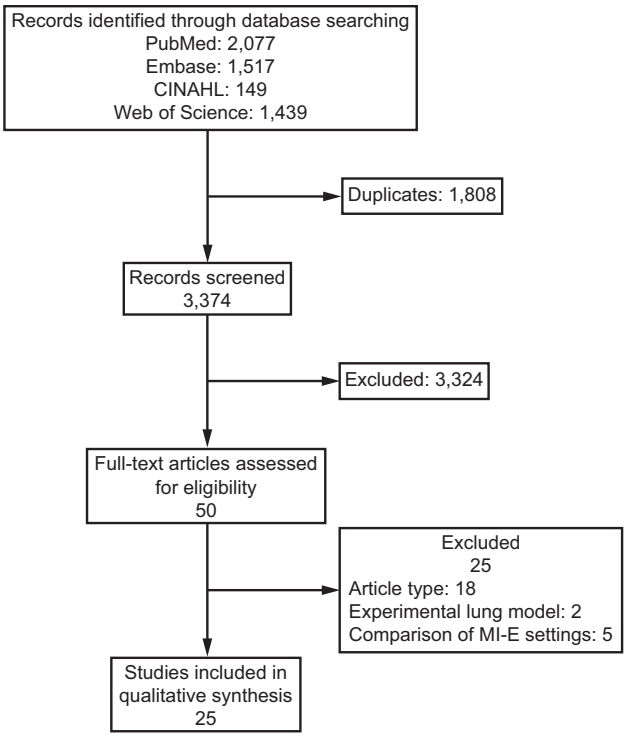

Fig. 1. Flow chart. MI-E = mechanical insufflation-exsufflation.

which the specific criteria were met (yes = 2, partial = 1, no = 0). Items not applicable to a particular study design were excluded from the calculation of the summary score. For the qualitative studies, 10 items were scored 0–2 points. A summary score was calculated for each paper by summing the total score obtained across relevant items and dividing by the total possible score.

Data Analysis

In case of multiple studies using the same comparison and outcome parameters, we performed a meta-analysis using DerSimonian-Laird random effects model to obtain overall pooled effect with 95% CIs. The mean (SD) in individual studies was estimated from those that were reported as median and interquartile range (IQR) by using the method described by Wan et al.[13] Because in amyotrophic lateral sclerosis (ALS) upper-airway closure may be present in the absence of or before the onset of bulbar symptoms,[14,15] we performed a subgroup analysis on studies without subjects with ALS. Heterogeneity of pooled data were assessed by using I^2 statistic. The I^2 statistic describes the percentage of total variation across studies due to true heterogeneity rather than chance. All analyses were performed using OpenMeta[Analyst] (http://www.cebm.brown.edu/openmeta). Data are not publicly available but available upon reasonable request.

Results

Study Selection

Totally, titles and abstracts of 3,374 records were screened (Fig. 1). After title and abstract screening, 50 articles were considered for full-text analysis. Twenty-five were excluded because they did not meet inclusion criteria. The remaining 25 studies were included in our review.[8,14-37]

Description of Included Studies

The characteristics of included studies are summarized in Table 1. Most studies were single-center cohort studies. A total of 608 subjects were studied, with a sample size range from 5–62 participants. Inclusion and exclusion criteria and study population varied significantly between studies. Fifteen studies included subjects with different NMD diagnoses.[17,20,24,27-32,33-37] Ten studies included a more homogeneous group of diagnoses, such as ALS (no. = 7),[14,15,20-22,24,25] Duchenne muscular dystrophy (no. = 2),[16,32] and both Duchenne muscular dystrophy and spinal muscular atrophy (no. = 1).[18] Study outcomes included respiratory-related events such as RTIs or hospital admissions (Table 2), PFT results (Table 3), respiratory characteristics (Table 4), laryngeal response (Supplementary Table 1, see related supplementary materials at http://www.rcjournal.com), and quality of life (Supplementary Table 2, see related supplementary materials at http://www.rcjournal.com).

Methodological Quality and Risk of Bias

Summary of quality assessment of the included studies is provided in the Supplementary Table 3 (see related supplementary materials at http://www.rcjournal.com). Median summary score was 0.85 (IQR 0.79–0.87). Blinding of investigator was only done in one study.[24] Control of confounding was limited in most studies. Sample size was limited in many studies and method of subject selection not always clearly described.[19,20,26,27] Supplementary Table 4 (See related supplementary materials at http://www.rcjournal.com) shows PRISMA 2020 checklists of this systematic review.

Respiratory-Related Outcomes

Respiratory-related outcomes were studied in 4 studies.[19,21,30,37] One randomized controlled trial (RCT) studied number and duration of RTIs and related hospital admissions because of RTIs in subjects with ALS, comparing AS and MI-E. This study reported a trend toward reduced duration of RTIs in the MI-E group but this was not

Table 1. Study Characteristics

Author, Year	Study Design	Year of Study	Follow-Up	Subjects, *N*	Age, y	Inclusion Criteria	Underlying Disease	Outcome	Adverse Events
Kim,[34] 2016	RCT	NS	Immediate effect	40 (and 16 healthy controls)	20.9 ± 7.2	Noninvasive ventilator dependent, familiar with MI-E, no RTI, no severe bulbar dysfunction	Mixed	PFT	0
Lacombe,[35] 2014	RCT	2012–2013	Immediate effect	14	21–68	No RTI < 1 mo, CPF < 3 L/s or P_{Emax} < 45 cm H_2O, no MI-E use	Mixed	PFT, PS	NS
Rafiq,[21] 2015	RCT	2009–2013	≥ 12 mo or till death	40 (21 AS and 19 MI-E)	Mean 64.1	Noninvasive ventilator dependent, no frontotemporal cerebral dysfunction	ALS	PFT, RTI, admissions, QOL, PS	0
Andersen,[14] 2017	Prospective patient control	2011–2013	Immediate effect	20 (and 20 healthy controls)	68.7 (control 66.9)	No tracheostomy, no RTI < 1 mo	ALS	Laryngeal response	NS
Chatwin,[8] 2003	Prospective patient control	NS	Immediate effect	22 (and 19 healthy controls)	Median 21 (10–56)	No AB < 1 mo, S_{pO_2} ≥ 90%, P_{ETCO_2} ≤ 7 kPa (52.5 mm Hg), no bulbar dysfunction	Mixed	PFT, PS	0
Mustfa,[20] 2003	Prospective patient control	NS	Immediate effect	47 (10 healthy controls)	NS	ALS (diagnosis according to El Escorial criteria)	ALS	PFT	NS
Sivasothy,[27] 2001	Prospective patient control	NS	Immediate effect	12 (and 8 COPD, 9 healthy controls)	27–73 (control 17–71)	Respiratory muscle weakness diagnosed by neurologist, no other respiratory disease	Mixed	PFT, respiratory characteristics	NS
Andersen,[15] 2018	Prospective observational	2011–2016	Median 17 (6–59) mo	13	50–83	No tracheostomy, no RTI < 1 mo	ALS	Laryngeal response	NS
Bach,[26] 1993	Prospective retrospective survey	NS	Survey:16. 4 y, PFT: immediate effect	*n* = 16 prospective, *n* = 46 survey	16–74	Ventilator dependent, PFT in patients within 2 h traveling	Mixed	PFT, respiratory characteristics, chest wall	0
Cesareo,[32] 2018	Prospective observational	NS	Immediate effect	20	Mean 20.8 ± 4.4	≥ 1 y MI-E use	DMD	PFT, respiratory characteristics, chest wall	NS
Fauroux,[33] 2008	Prospective observational	NS	Immediate effect	17	5–18	≥ 1 mo stable	Mixed	PFT, PS	0
		NS	Immediate effect	21	63.90 ± 15.75		Mixed	PFT	0

(Continued)

Table 1. Continued

Author, Year	Study Design	Year of Study	Follow-Up	Subjects, *N*	Age, y	Inclusion Criteria	Underlying Disease	Outcome	Adverse Events
Lalmolda,[36] 2019	Prospective observational					CPF < 160 L/min, ≥ 18 y, no tracheostomy, no contraindication for MI-E, good tolerance			
Meric,[16] 2017	Prospective observational	2014–2015	Immediate effect	9	18–30	No RTI < 1 mo, NIV,VC < 30%	DMD	PFT, respiratory characteristics, chest wall motion, PS	NS
Sancho,[22] 2004	Prospective observational	NS	Immediate effect	26	Mean 61	Consecutively referred, ALS, no antecedent lung disease, no significant kyphoscoliosis	ALS	PFT	NS
Santos,[23] 2017	Prospective observational	2013–2014	Immediate effect	47	Mean 41 ± 14	VC < 80%, no tracheostomy	Mixed	PFT	NS
Senent,[24] 2011	Prospective observational	NS	Immediate effect	16	63 (57–68)	No tracheostomy,> 2 mo home ventilation,no RTI < 1 mo,CPF < 270 L/min	ALS	PFT, PS	NS
Winck,[31] 2004	Prospective observational	2002–2003	Immediate effect	20 (and 9 COPD)	26–68	≥ 1 episode respiratory failure, ↓ S_{pO_2}, no AB < 1 mo, respiratory stable > 3 mo	Mixed (65% ALS)	PFT, respiratory characteristics, PS	0
Mahede,[37] 2015	Retrospective	2007–2011	Health records 25 y (1988–2012)	37	Mean 19.8 (1–59)	Home MI-E use	Mixed	ED presentations, hospital admission, PS	NS
Miske,[17] 2004	Retrospective	1998–2001	Median 13.4 mo (0.5–45.5 mo)	62	0.2–28.6	MI-E use at home (P_{Emax} < 60 cm H_2O, history of RTI/atelectasis, home ventilation)	Mixed	PS, QOL	1
Moran,[19] 2013	Retrospective	NS	Mean 2.3 y (1.2–4.9 y)	*n* = 10 child, *n* = 10 parent	1.4–18.1	MI-E use at home	Mixed	Respiratory-related hospital admission, PS, QOL	0
Stehling,[28] 2015	Retrospective	2009–2012	1–2 y before and after	21	5–27	VC < 30%, CPF < 160, NIV	Mixed	PFT	NS

(Continued)

Table 1. Continued

Author, Year	Study Design	Year of Study	Follow-Up	Subjects, *N*	Age, y	Inclusion Criteria	Underlying Disease	Outcome	Adverse Events
Veldhoen,[30] 2019	Retrospective	2005–2019	Up to 3 y before and after	37	Median 5.2 (2.7–12.4)	Children, daily use of MI-E at home	Mixed	RTI-related hospital admission, PS	1
Moran,[18] 2015	Qualitative study	NS	Single interview	11 ($n = 8$ parents, $n = 3$ children > 10 y)	4–18	0.5–10.0 y MI-E use	SMA and DMD	PS, QOL	NS
Siewers,[25] 2013	Qualitative study	2009–2010	No follow-up	$n = 5$ patients, $n = 3$ families $n = 3$ health professionals	43–81	ALS patients using MI-E with mask	ALS	PS, QOL	NS
Travlos,[29] 2016	Qualitative study	NS	Single interview	9 ($n = 3$ children $n = 3$ parents $n = 3$ physiotherapists)	6–8	5–15 y, > 6 mo MI-E use	Mixed	PS, QOL	NS

Data are presented as median (interquartile range) or mean (± SD) unless otherwise noted.
RCT = randomized controlled trial
NS = not specified
MI-E = mechanical insufflation-exsufflation
RTI = respiratory tract infection
0 = data on adverse events collected and not present
CPF = peak cough flow
P_{Emax} = peak expiratory pressure
PS = patient satisfaction
AS = air stacking
ALS = amyotrophic lateral sclerosis
AB = antibiotics
P_{ETCO_2} = end tidal carbon dioxide pressure
PFT = pulmonary function test
DMD = Duchenne muscular dystrophy
NIV = noninvasive ventilation
VC = vital capacity
ED = emergency department
QOL = quality of life
1 = data on adverse events collected and present
SMA = spinal muscular atrophy

Table 2. Outcome: Respiratory Tract Infections and Hospital Admissions

Outcome Studied	Study Reference	Study Design	Follow-Up	Results
RTI	Rafiq et al,[21] 2015	RCT: MI-E vs AS	≥ 12 mo or till death	Number of subjects with ≥ 1 RTI: 32% vs 33% ($P = .75$) No. of RTIs:19 vs 13 ($P = .93$) Mean duration RTI symptoms: 3.9 d vs 6.9 d ($P = .16$)
RTI-related admissions	Rafiq et al,[21] 2015	RCT: MI-E vs AS	≥ 12 mo or till death	No. of admissions: 6 vs 6 ($P = .64$) 32% vs 46% admissions of all RTIs ($P = .47$)
	Veldhoen et al,[30] 2019	Observational: before and after MI-E introduction	3 y before and 3 y after	No. of admissions/1,000 eligible d: 3.7 vs 0.9 ($P = .006$) No. of admission d/1,000 eligible d: 33.6 vs 2.7 ($P = .001$)
Respiratory-related hospital presentations				
Hospital presentation	Mahede et al,[37] 2015	Observational: before and after MI-E introduction	Total: 8 y After: mean 2.3 (0.1–4.0) y	ED presentation: RR 1.76 vs 1.00 ($P = .055$)
	Moran et al,[19] 2013	Observational: before and after MI-E introduction	Before: 12 mo	0–6 mo: 1.9 vs 1.4 ($P = .55$)
			After: mean 1.4 (0.3–3.8) y	0–12 mo: 2.9 vs 2.7 ($P = .86$)
Hospital admissions	Mahede et al,[37] 2015	Observational: before and after MI-E introduction	Total: 8 y After: mean 2.3 (0.1–4.0) y	RR 1.82 vs 1.00 ($P > .05$)
	Moran et al,[19] 2013	Observational: before and after MI-E introduction	Before: 12 mo	0–6 mo: 1.6 vs 1.1 ($P = .45$)
			After: mean 1.4 (0.3–3.8) y	0–12 mo: 2.0 vs 1.7 ($P = .69$)
Hospital length of stay	Mahede et al,[37] 2015	Observational: before and after MI-E introduction	Total: 8 y After: mean 2.3 (0.1–4.0) y	RR 2.83 vs 1.00 ($P > .05$)
	Moran et al,[19] 2013	Observational: before and after MI-E introduction	Before: 12 mo	Hospital: 0–6 mo: 39 d vs 9.3 d ($P = .04$)
			After: mean 1.4 (0.3–3.8) y	0–12 mo: 43.7 d vs 13.3 d ($P = .03$) ICU: 0–6 mo: 17.7 d vs 2.1 d ($P = .03$) 0–12 m:19.9 d vs 4.6 d ($P = .06$)

RTI = respiratory tract infection
RCT = randomized controlled trial
MI-E = mechanical insufflation-exsufflation
AS = air stacking
ED = emergency department
RR = relative risk

statristically significant.[21] The other 3 were observational, pediatric studies comparing number of RTIs and respiratory-related hospital presentations years before and after introduction of MI-E[19,30,37] (Table 2). Veldhoen et al[30] ($n = 37$) showed a significant effect on admissions because of RTIs, with MI-E use. Moran et al[19] and Veldhoen et al[30] ($n = 47$) showed reduced hospital stay. However, meta-analysis was not possible due to the limited number of studies and different outcome measures.

Pulmonary Function Test Results

PFT results were reported in 16 studies (Table 3), with 2 investigating long-term effects.[21,28] Rafiq et al[21] conducted an RCT comparing AS and MI-E in subjects with ALS. The researchers found no between-group differences in vital capacity decline per month ($P = .47$) or CPF ($P = .43$).[21] In a retrospective observational study, Stehling et al[28] showed a significant beneficial effect of MI-E

Table 3. Outcome: Pulmonary Function Test Results

Outcome Studied	Study Reference	Study Design	MI-E Settings	Results
		Longer-term effect		
CPF/PEF	Rafiq et al,[21] 2015	RCT: AS vs MI-E, follow-up ≥ 12 mo or till death	≥ 2×/d, 3–5 I/E, ≥ +40/−40 cm H_2O	CPF ↓ 5.77 L/min/mo vs ↑ 0.9 L/min/mo ($P = .43$)
VC	Rafiq et al,[21] 2015	RCT: AS vs MI-E, follow-up ≥ 12 mo or till death	≥ 2×/d, 3–5 I/E, ≥ +40/−40 cm H_2O	VC ↓ 0.94%/mo vs 0.45%/mo ($P = .47$)
	Stehling et al,[28] 2015	Observational: 1–2 y before and after MI-E introduction: −2 vs −1 vs 0 vs 1 vs 2	10 min 3 × I/E +18/20 vs +40/−40 cm H_2O (mean +25/−25 cm H_2O)	0.88 vs 0.71 vs 0.5 vs 0.64 vs 0.65 L (year after introduction compared to before: $P <$ .002)
		Immediate effect		
Cough expiratory volume	Sivasothy et al,[27] 2001	Observational: unassisted vs manually assisted cough vs MI-E vs MI-E + manually assisted cough	3 × I/E +20/−20 cm H_2O	Without scoliosis: 0.5 vs 0.7 vs 0.6 vs 0.6 L ($P > .01$) With scoliosis: 0.9 vs 0.5 vs 0.7 vs 0.6 L ($P >$ .01)
Cough PEF	Bach et al,[26] 1993	Observational: unassisted vs MI-E	5 × I/E with maximum comfortable pressures (not quantified)	1.81 ± 1.03 L/s vs 7.47 ± 1.02 L/s
	Mustfa et al,[20] 2003	Observational: unassisted vs manually assisted cough vs MI-E	Not specified, except from maximal tolerated expiratory pressure	Manually assisted cough 11–13% ↑ ($P <$ .001); MI-E 26–28% ↑ ($P < .001$)
	Sivasothy et al,[27] 2001	Observational: unassisted vs manually assisted cough vs MI-E vs MI-E + manually assisted cough	3 × I/E +20/−20 cm H_2O	Without scoliosis: 104 vs 185 L/min vs 156 vs 248 L/min($P < .01$) With scoliosis: 288 vs 193 L/min vs 231 vs 362 L/min
CPF	Cesareo et al,[32] 2018	Observational: unassisted vs MI-E	5 × 5 I/E, pressures as at home (not quantified)	163 L/min vs 165 L/min ($P = .86$)
	Chatwin et al,[8] 2003	Observational: unassisted vs manually assisted cough vs NIV vs M-E vs MI-E	Pressures at patients comfort (mean mask pressure +15/−15 cm H_2O), cycles and applications not specified	169 vs 188 vs 182 vs 235 L/min ($P < .01$) vs 297 L/min($P < .001$)
	Kim et al,[34] 2016	RCT: unassisted vs AS + manually assisted cough vs MI-E vs MI-E + manually assisted cough	5 × I/E +40/−40 cm H_2O	96 vs 156 vs 177 vs 202 L/min ($P < .01$)
	Lacombe et al,[35] 2014	RCT: unassisted vs MI-E vs MI-E + manually assisted cough	No. of cycles and applications not specified, up to +40/−40 cm H_2O	Unassisted < MI-E ($P = .003$); MI-E < MI-E + manually assisted cough ($P = .030$)
	Lalmolda et al,[36] 2019	Observational: unassisted vs MI-E with +40/−40 cm H_2O vs MI-E with settings resulting in maximum CPF	Maximum pressures tolerated up to +40/−40 cm H_2O (increase with 10 cm H_2O in each step)	57 vs 198 vs 214 L/min($P < .005$) ALS bulbar: 57 vs 164 vs 189; non-bulbar 44 vs 243 vs 251

(Continued)

Table 3. Continued

Outcome Studied	Study Reference	Study Design	MI-E Settings	Results
				Non-ALS: 75 (dystrophies) and 95 (other NMDs) vs 186 (all non-ALS) vs 202 (all non-ALS)
	Sancho et al,[22] 2004	Observational: unassisted vs MI-E	No. of cycles and applications not specified, +40/−40 cm H_2O	4.47 L/s vs 3.75 L/s; baseline CPF < 2.7 L/s vs >2.7 L/s: after MI-E 2.79 L/s vs 4.12 L/s
	Senent et al,[24] 2011	Observational: unassisted vs max inspiration vs max inspiration + manually assisted cough vs manually assisted cough + AS vs manually assisted cough +NIV vs manually assisted cough + NIV (30 cm H_2O) vs MI-E	4–6 cycles, +40/−40 cm H_2O	84 (35–118) vs 79 (36–142) vs 104 (80–140) vs 284 (146–353) vs 212 (99–595) vs 233 (100–389) vs 488 (243–605) L/min
	Winck et al,[31] 2004	Observational: unassisted vs MI-E	3 × 6 I/E, +15/−15, +30/−30, +40/−40 cm H_2O	ALS: 170 L/min vs 200 L/min ($P < .005$)
				Other NMD 180 L/min vs 220 L/min ($P < .005$)
Expiratory reserve volume	Santos et al,[23] 2017	Observational: unassisted vs passive MI-E vs active MI-E	3 × I/E passive (+20, +30, + 40/−40 cm H_2O) and active +40/−40 cm H_2O	Passive: 5–24% ↑ ($P > .05$) Active: 7–32% ↑ ($P < .05$)
$FEF_{25–75}$	Bach et al,[26] 1993	Observational: unassisted vs MI-E	5 × I/E with maximum comfortable pressures (not quantified)	0.80 ± 0.59 L/s vs 0.91 ± 0.69 L/s
FVC	Bach et al,[26] 1993	Observational: unassisted vs MI-E	5 × I/E with maximum comfortable pressures (not quantified)	0.49 ± 0.37 L vs 0.54 ± 0.39 L
FEV_1/FVC	Bach et al,[26] 1993	Observational: unassisted vs MI-E	5 × I/E with maximum comfortable pressures (not quantified)	89.3 ± 12.5% vs 91.0 ± 8.2%
Inspiratory capacity	Cesareo et al,[32] 2018	Observational: unassisted vs MI-E	5 × 5 I/E, pressures as at home (not quantified)	0.73 L vs 0.67 L ($P > .5$)
	Lacombe et al,[35] 2014	RCT: unassisted vs MI-E vs MI-E+ manually assisted cough	No. of cycles not specified, up to + 40/−40 cm H_2O	Unassisted < MI-E ($P < .001$), unassisted < MI-E + manually assisted cough ($P < .001$), MI-E ≈ MI-E+ manually assisted cough ($P > .001$)
	Santos et al,[23] 2017	Observational: unassisted vs passive MI-E vs active MI-E	3 × I/E passive (+20, + 30, +40/−40 cm H_2O) and active +40/−40 cm H_2O	Passive: 18–23% ↑ ($P < .0001$); active: 23–31% ↑ ($P < .0001$)
Peak value time	Sivasothy et al,[27] 2001	Observational: unassisted vs manually assisted cough vs MI-E vs MI-E + manually assisted cough	3 × I/E + 20/−20 cm H_2O	Without scoliosis: 80 vs 118 vs 85 vs 75 ms ($P > .01$)
P_{Emax}	Meric et al,[16] 2017	Observational: unassisted vs MI-E	15 × I/E + 30/−30 cm H_2O	24 vs 22 vs 23 ($P > .05$)
P_{Imax}	Meric et al,[16] 2017	Observational: Unassisted vs MI-E	15 × I/E + 30/−30 cm H_2O	24 vs 22 vs 21 ($P > .05$)

(Continued)

Table 3. Continued

Outcome Studied	Study Reference	Study Design	MI-E Settings	Results
Sniff nasal inspiratory pressure	Fauroux et al,[33] 2008	Observational: unassisted vs MI-E with + 15/−15vs + 30/−30 vs +40/−40 cm H_2O	3 × 6 I/E, + 15/−15, +30/−30, +40/−40 cm H_2O	29 vs 30 vs 28 vs 31 cm H_2O
VC	Cesareo et al,[32] 2018	Observational: unassisted vs MI-E	5 × 5 I/E, pressures as at home (not quantified)	0.75 L vs 0.59 L ($P = .78$)
	Fauroux et al,[33] 2008	Observational: unassisted vs MI-E with + 15/−15vs + 30/−30 vs + 40/−40 cm H_2O	3 × 6 I/E, +15/−15, +30/−30, +40/−40 cm H_2O	1.04 vs 1.01 vs 1.00 vs 1.04 L
	Meric et al,[16] 2017	Observational: unassisted vs MI-E	15 × I/E +30/−30 cm H_2O	↑ 108% of unassisted ($P = .02$), after 1 h ↓ as unassisted
	Santos et al,[23] 2017	Observational: unassisted vs passive MI-E vs active MI-E	3 × I/E passive (+20, + 30, +40/−40 cm H_2O) and active +40/−40 cm H_2O	Passive: 16–22% ↑ ($P < .0001$); active: 23–28% ↑ ($P < .0001$)

MI-E = mechanical insufflation-exsufflation
CPF = cough peak flow
PEF = peak expiratory flow
RCT = randomized controlled trial
AS = air stacking
VC = vital capacity
NIV = noninvasive ventilation
ALS = amyotrophic lateral sclerosis
NMD = neuromuscular disease
$FEF_{25–75}$ = forced mid-expiratory flow
P_{Emax} = peak expiratory pressure
P_{Imax} = maximal peak inspiratory pressure

Table 4. Outcome: Respiratory Characteristics

Outcome Studied	Study Reference	Study Design	MI-E Settings	Results
Minute ventilation	Fauroux et al,[33] 2008	Observational: unassisted vs MI-E with +15/−15 vs +30/−30 vs +40/−40 cm H_2O	3 × 6 I/E +15/−15, +30/−30, +40/−40 cm H_2O	6.3 vs 5.9 vs 6.2 vs 6.3 L/min ($P > .05$)
	Winck et al,[31] 2004	Observational: unassisted vs MI-E +15/−15 vs +30/−30 vs +40/−40 cm H_2O	3 × 6 I/E +15/−15, +30/−30, +40/−40 cm H_2O	ALS: 8.5 vs 8.9 vs 9.8 vs 10.6 L/min ($P > .05$) Other NMD: 12.7 vs 11.4 vs 10.4 vs 11.4 L/min ($P > .05$)
P_{ETCO_2}	Fauroux et al,[33] 2008	Observational: unassisted vs MI-E with +15/−15 vs +30/−30 vs +40/−40 cm H_2O	3 × 6 I/E +15/−15, +30/−30, +40/−40 cm H_2O	39.9 vs 38.0 vs 37.7 vs 37.8 mm Hg ($P < .001$)
P_{tcCO_2}	Meric et al,[16] 2017	Observational: unassisted vs MI-E	15 x I/E, +30/−30 cm H_2O	48 vs 47 vs 49 (after 1 h) ($P > .05$)
PEF/MF	Winck et al,[31] 2004	Observational: unassisted vs MI-E +15/−15 vs +30/−30 vs +40/−40 cm H_2O	3 × 6 I/E +15/−15, +30/−30, +40/−40 cm H_2O	ALS: 1.54 vs 1.51 vs 1.54 vs 1.54 ($P > .05$) Other NMD: 1.55 vs 1.54 vs 1.55 vs 1.52 ($P > .05$)
PIF/MF	Winck et al,[31] 2004	Observational: unassisted vs MI-E +15/−15 vs +30/−30 vs +40/−40 cm H_2O	3 × 6 I/E +15/−15, +30/−30, +40/−40 cm H_2O	ALS: 1.38 vs 1.45 vs 1.44 vs 1.43 ($P > .05$) Other NMD: 1.45 vs 1.47 vs 1.43 vs 1.40 ($P > .05$)
Respiratory comfort	Fauroux et al,[33] 2008	Observational: unassisted vs MI-E with +15/−15 vs +30/−30 vs +40/−40 cm H_2O	3 × 6 I/E +15/−15, +30/−30, +40/−40 cm H_2O	73 vs 75 vs 76 vs 83/100 ($P = .02$)
Breathing frequency	Cesareo et al,[32] 2018	Observational: unassisted vs MI-E	5 × 5 I/E +15/−15 to +45/−45 cm H_2O	24 vs 19/min ($P = .001$)
	Fauroux et al,[33] 2008	Observational: unassisted vs MI-E with +15/−15 vs +30/−30 vs +40/−40 cm H_2O	3 × 6 I/E +15/−15, +30/−30, +40/−40 cm H_2O	26 vs 27 vs 26 vs 26/min ($P > .05$)
	Meric et al,[16] 2017	Observational: unassisted vs MI-E	15 x I/E +30/−30 cm H_2O	21 vs 19 vs 23/min (after 1 h) ($P > .05$)
RSBI	Cesareo et al,[32] 2018	Observational: unassisted vs MI-E	5 × 5 I/E +15/−15 to +45/−45 cm H_2O	Unassisted > MI-E ($P = .007$)
	Meric et al,[16] 2017	Observational: unassisted vs MI-E	15 × I/E +30/−30 cm H_2O	66 vs 61 vs 84 (after 1 h) ($P < .05$)
Oxygen saturation	Fauroux et al,[33] 2008	Observational: unassisted vs MI-E with +15/−15 vs +30/−30 vs +40/−40 cm H_2O	3 × 6 I/E +15/−15, +30/−30, +40/−40 cm H_2O	97.1 vs 96.6 vs 96.5 vs 96.4 ($P > .05$)
	Meric et al,[16] 2017	Observational: unassisted vs MI-E	15 × I/E +30/−30 cm H_2O	97 vs 97 vs 97 (after 1 h) ($P > .05$)
	Winck et al,[31] 2004	Observational: unassisted vs MI-E +15/−15 vs +30/−30 vs +40/−40 cm H_2O	3 × 6 I/E +15/−15, +30/−30, +40/−40 cm H_2O	ALS: 94 vs 95 vs 95 vs 98% ($P < .005$) Other NMD: 94% vs 96% vs 95% vs 98% ($P < .005$)
Subjective scores				
Borg score	Meric et al,[16] 2017	Observational: unassisted vs MI-E	15 × I/E +30/−30 cm H_2O	1.16 vs 1.33 vs 1.61 (after 1 h) ($P > .05$)

(Continued)

Table 4. Continued

Outcome Studied	Study Reference	Study Design	MI-E Settings	Results
	Winck et al,[31] 2004	Observational: unassisted vs MI-E +15/−15 vs +30/−30 vs +40/−40 cm H_2O	3 × 6 I/E +15/−15, +30/−30, +40/−40 cm H_2O	ALS: 2.0 vs 1.0 ($P > .05$) Other NMD: 2.00 vs 0.75 ($P < .05$)
Cough comfort	Senent et al,[24] 2011	Observational: unassisted vs max inspiration vs max inspiration + manually assisted cough vs manually assisted cough +AS vs manually assisted cough +NIV vs manually assisted cough + NIV (30 cm H_2O) vs MI-E	4–6 cycles, +40/−40 cm H_2O	5 (4–7) vs 5 (5–7) vs 7 (5–7) vs 6 (5–8) vs 8 (7–8) vs 6 (5–7) vs 7 (3–8) ($P > .05$)
Cough efficacy	Senent et al,[24] 2011	Observational: unassisted vs max inspiration vs max inspiration + manually assisted cough vs manually assisted cough +AS vs manually assisted cough +NIV vs manually assisted cough + NIV (30 cm H_2O) vs MI-E	4–6 cycles, +40/−40 cm H_2O	4 (2–7) vs 6 (4–7) vs 7 (4–8) vs 7 (5–8) vs 7 (6–8) vs 6 (5–7) vs 8 (6–8) ($P > .05$)
V_T	Cesareo et al,[32] 2018	Observational: unassisted vs MI-E	5 × 5 I/E +15/−15 to +45/−45 cm H_2O	Unassisted ≈ MI-E($P > .05$)
	Fauroux et al,[33] 2008	Observational: unassisted vs MI-E with +15/−15 vs +30/−30 vs +40/−40 cm H_2O	3 × 6 I/E +15/−15, +30/−30, +40/−40 cm H_2O	0.27 vs 0.27 vs 0.27 vs 0.28 L ($P > .05$)
	Meric et al,[16] 2017	Observational: unassisted vs MI-E	15 × I/E +30/−30 cm H_2O	316 vs 310 vs 275 (after 1 h) mL ($P > .05$)
	Winck et al,[31] 2004	Observational: unassisted vs MI-E +15/−15 vs +30/−30 vs +40/−40 cm H_2O	3 × 6 I/E +15/−15, +30/−30, +40/−40 cm H_2O	ALS: 408 vs 390 vs 408 vs 494 mL ($P > .05$) Other NMD: 468 vs 460 vs 440 vs 588 mL ($P > .05$)

MI-E = mechanical insufflation-exsufflation
ALS = amyotrophic lateral sclerosis
NMD = neuromuscular disease
P_{ETCO_2} = end tidal carbon dioxide pressure
P_{tcCO_2} = transcutaneous partial pressure of carbon dioxide
PEF/MF = peak expiratory flow to mean expiratory flow ratio
PIF/MF = peak inspiratory flow to mean inspiratory flow ratio
RSBI = rapid shallow breathing index
V_T = tidal volume
NIV= noninvasive ventilation

comparing vital capacity one year before and one year after MI-E introduction in a group with mixed NMDs.

Fourteen studies examined the effect of MI-E on PFT results before and immediately after application of MI-E.[8,17,21,23-25,27,28,33-37] Two RCTs compared MI-E to unassisted maneuvers, including MI-E with and without the addition of manually assisted cough.[34,35] Both studies showed increased CPF after MI-E application.[34,35] Kim et al[34] also compared MI-E with and without manually assisted cough to AS with manually assisted cough ($n = 40$) and found that MI-E alone improved CPF significantly more than AS with manually assisted cough. MI-E used in conjunction with manually assisted cough improved CPF even further.[34]

Lung function outcomes varied in 12 observational studies.[8,17,21,23-25,27,28,32-34] Five studies were unique in studying a specific outcome.[16,23,26,27,33] Three studies explored inspiratory capacity comparing unassisted maneuvers to MI-E with and without manually assisted cough.[23,32,35] The immediate effect on CPF was studied in 8 studies: CPF after MI-E was compared to unassisted CPF,[8,22,24,31,34-36] CPF after manually assisted cough,[8,24] CPF after AS with manually assisted cough,[24,34] and CPF after MI-E with manually assisted cough.[34,35] We contacted the corresponding author of the study by Lacombe et al[35] to obtain the exact values of means and range of CPF, allowing us to include this study in the meta-analysis.

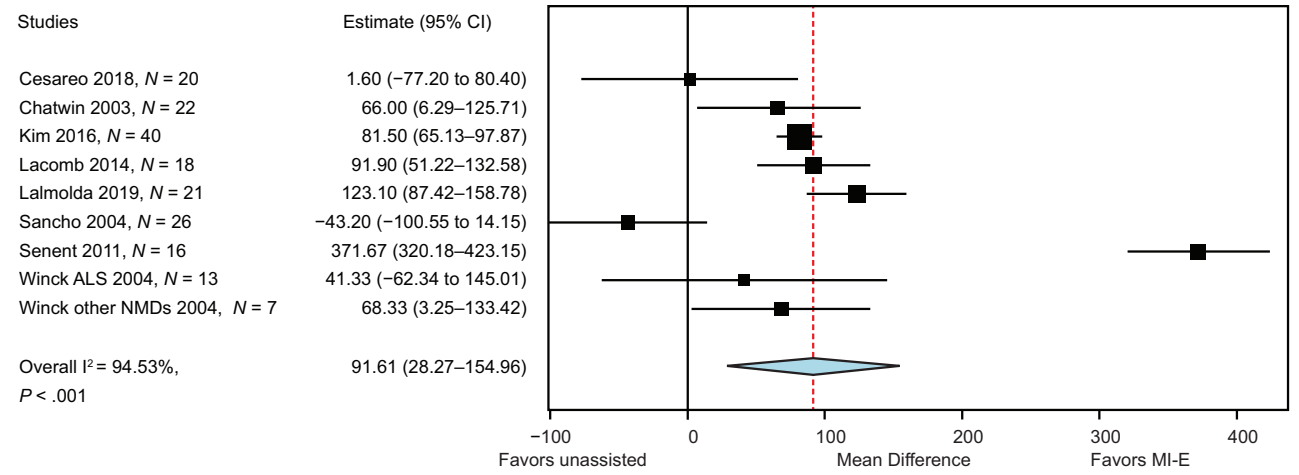

Fig. 2. Meta-analysis. Cough peak flow (CPF) after mechanical insufflation-exsufflation (MI-E) versus unassisted CPF. ALS = amyotrophic lateral sclerosis, NMD = neuromuscular disease.

Meta-analysis showed an overall beneficial effect of MI-E on CPF compared to unassisted CPF (mean difference 91.61 [95% CI 28.3–155.0] L/min, $P < .001$) (Fig. 2). There was considerable heterogeneity regarding the effects on CPF across 8 studies ($I^2 = 0$ 95%, $P < .001$). Subgroup analysis on 6 studies after the exclusion of studies on ALS showed similar effects on CPF (mean difference 83.1 [95% CI 59.4–106.7] L/min, $P < .001$) (Supplementary Fig. 1, see related supplementary materials at http://www.rcjournal.com). Moderate heterogeneity was observed across these 6 studies ($I^2 = 48\%$, $P = .09$).

Respiratory Parameters

There were mixed results for respiratory parameter outcomes between studies (Table 4). There was no significant effect on oxygen saturation in all[16,33] but one study.[31] Meric et al[16] found no changes in transcutaneous CO_2 levels, whereas Fauroux et al[33] found improved end-tidal CO_2. Data on breathing frequency after MI-E application were also conflicting.[16,32,33] Only one study observed a statistically significant reduction in breathing frequency.[32] None of the studies showed a significant effect on tidal volume comparing unassisted maneuvers to MI-E.[16,31,32,33] The rapid shallow breathing index, which is the ratio of breathing frequency and tidal volume, increased significantly immediately after MI-E application in one study[32] and 1 h after MI-E use in another study.[33]

Laryngeal Response

Andersen et al[14,15] found upper-airway closure from a variety of mechanisms during MI-E treatment in subjects with ALS and recommended customized MI-E settings to prevent this problem. (Supplementary Table 1).

Patient Satisfaction

Satisfaction of subjects and caregivers was reported in 7 studies[17-19,21,25,29,30] (Supplementary Table 2). Subject satisfaction was generally high. In nearly all cases, treatment with MI-E was perceived as a valuable improvement of subjects' health by managing the disease at home, preventing hospital admissions, and maintaining social participation.

Discussion

This systematic review shows that there is limited evidence for efficacy of daily use of MI-E in clinically stable subjects with NMDs, with the possible exception of increased CPF immediately after MI-E application. Little research has shown the superiority of MI-E compared to other airway clearance therapy. Only one RCT showed a superior effect of MI-E on CPF compared to AS and manually assisted cough. Unfortunately, there is no evidence on long-term efficacy, implying that additional studies are needed.

Since RTIs are the primary cause of acute respiratory deterioration and hospital admission in patients with NMDs, the most clinically relevant, long-term outcome of MI-E is a reduction in the number, duration, and severity of these infections.[4] Reducing respiratory-related infections would most likely have an important impact on patient/caregiver quality of life and may reduce health care costs.[38-40] However, there is only one RCT that compared AS and MI-E using the number of RTIs as an outcome measure. This study included subjects with ALS and reported a possible trend toward a reduction of these events but this was not statistically significant.[21] However, the study had a small sample size and may not be generalizable to other NMDs. The reported effect may have been more pronounced if this RCT included subjects with other NMDs. Previous studies

cautioned about possible counterproductive effects of MI-E in subject with ALS if high pressures and no individualized settings were used.[14,15] The difference in effect between study populations with and without inclusion of subjects with ALS was not supported by the forest plots in our results (Fig. 2 and Supplementary Fig. 1). This may be explained by the sample size, which was 43% more if all studies were included in the meta-analysis ($n = 183$) compared to study analyses without subjects with ALS ($n = 128$). Observational studies were of limited quality, and confounding factors preclude a conclusion regarding the effect of MI-E on RTIs.

PFT results are an important surrogate outcome measure, as studies in subjects with Duchenne muscular dystrophy suggest that vital capacity is a valuable predictor of susceptibility to RTIs, need for respiratory support, and survival.[7] Long-term effects on lung-function were reported in 2 studies. An RCT[21] found no significant improvement in vital capacity after MI-E introduction, whereas a retrospective observational study[28] showed significant vital capacity improvement. The studies that reported PFT results immediately after application of MI-E suggest direct improvement of lung volumes[17,24,27,36] but no change in respiratory muscle strength.[16,33] It is unclear how long these immediate, mainly beneficial, effects of MI-E application last.

Most studies showed no significant immediate effect on respiratory parameters.

Although, probably at least partly influenced by selection and study bias, the qualitative studies reported high subject satisfaction of MI-E. This is important, especially when evidence for beneficial effect is limited. Qualitative research involving studies with NMDs is very important, including the subject's choice of technique and health-related quality of life.[10]

The included studies had clear limitations. We identified and included only 3 RCTs in our analysis.[22,35,36] Results from other included studies should be interpreted with caution due to the retrospective nature of these studies on respiratory-related hospital admissions and RTIs, which render them susceptible to potential flaws and bias. Most prospective observational studies only described the immediate effect on PFT results but did not assess longer-term outcome. Forced maneuvers during lung function testing prior to MI-E application may have resulted in lung volume recruitment, thereby underestimating the effect of MI-E.[41] On the other hand, respiratory muscle fatigue may underestimate the effect of MI-E.[42] In our meta-analysis on the effect of MI-E on CPF, we combined absolute CPF measurements obtained with different devices. Different measurement devices perform variably, leading to potentially substantial inaccuracy in CPF measurements.[43]

NMDs are a large and heterogeneous group of diseases. This heterogeneity, the variation in clinical characteristics (type and severity of disease, affected respiratory muscle groups, age, scoliosis deformity), the small sample sizes, and varying MI-E settings preclude definite conclusions. Inclusion of predominantly subjects with ALS limits generalizability and may even have resulted in underestimation of beneficial effects. In addition to the 2 studies on laryngeal response,[14,15] 5 other studies exclusively included subjects with ALS,[20-22,24,25] and in 3 studies the majority of included subjects with NMDs consisted of those with ALS.[27,31,36] The RCT by Kim et al[21] that did not show a statistically significant effect on the number and duration of RTIs only included subjects with ALS.

Rarity of NMDs complicates the inclusion of larger numbers of subjects, particularly single-center studies. Future research on MI-E should ensure increased statistical power. Due to the heterogeneity of subjects, interventions, and outcome measures, we could only perform a meta-analysis on effect on CPF.

Adherence to treatment was not described in any study, whereas it is possible to check MI-E use for the preceding months in most, if not all, MI-E devices. Blinding of the researcher, although possible, was very uncommon. Blinding of the subjects was not possible but may have caused a placebo effect in some studies. Subjects naïve to MI-E treatment may have a different response to treatment than subjects who regularly use MI-E. Being an experienced or naïve user of MI-E was not specified in many studies. In addition, the technical and methodological information was often very limited. In studies comparing different airway clearance techniques or different settings of MI-E, the order of treatments was not always specified nor the use or length of pauses between treatments. Some qualitative studies did not describe the selection process of subjects for inclusion, which complicates the interpretation of subject satisfaction and the possibility of bias. On the other hand, patient-reported outcome measures are important. The reported subject satisfaction because of prevention of hospital admissions was confirmed by observational studies.[19,30,37] Only a limited number of studies reported adverse events (Table 1). Evaluation of the benefits alone, without evaluation of harm, is likely to bias conclusions about the net efficacy or effectiveness of the intervention.[44] The current review was restricted to English-language articles. Publication bias cannot be excluded as beneficial effects of MI-E are more likely to be published. No studies looked at the total costs of different airway clearance therapies, including the purchase and maintenance of the device, hospital visits, and admissions.

Reproducibility and transparency of reported results are ensured by our methodology. The broad search strategy has reduced the chance of incomplete overview of studies. We included 25 studies, considerably more than recent reviews. A Cochrane review on cough-augmenting therapy included 11 trials, with minority including data on MI-E.[10] A systematic review on MI-E use in subjects with NMDs published a few years ago included 12 studies published before 2015.[45] We cannot draw conclusions on the longer-term effects of MI-E. The results of this systematic review help to identify knowledge gaps regarding the use of MI-E. High-quality

controlled studies, preferably RCTs, are required not only to study the longer-term effects of daily MI-E use on the most clinically relevant outcomes measures including RTIs or hospital admissions but also to compare different airway clearance techniques. Long-term RCTs provide the best evidence, as observational studies are prone to potential confounders, such as concomitant use of ventilatory support, disease progression, and introduction of (gene modifying) treatments. We would advise a follow-up of at least 2 years to reduce seasonal influence on results and to be able to study the longer-term effects on lung function. RTIs are difficult to define, and the decision to start antibiotic treatment and to admit a patient are prone to subjectivity. Also, the decision and ability to admit a patient are highly variable between different countries and health systems. PFT results may be an alternative outcome because it may predict susceptibility to RTIs, need for respiratory support, and survival. Because some countries do not reimburse MI-E, we also suggest studying total cost of care as an outcome measure. Future studies should focus on NMDs such as Duchenne muscular dystrophy, other muscular dystrophies, congenital myopathies, and spinal muscular atrophy. These studies should be performed separately from studies in subjects with ALS given the fact that in this disease upper-airway closure may be present in the absence of (or before the onset of) bulbar symptoms.[14,15] Also, ALS is a more rapidly progressive condition in most patients, making long-term trials more difficult. Additional studies or subgroup analyses are needed to identify patient subgroups in whom MI-E has superior effect compared to other airway clearance therapy, allowing future patient selection for MI-E treatment. Optimal MI-E settings need to be investigated and most likely should be individualized to obtain maximal beneficial effects and avoid adverse effects.

Conclusions

At this moment, there are very limited data available to analyze the effect of MI-E on RTIs or respiratory-related admissions. Although MI-E has an immediate beneficial effect on CPF, evidence on longer-term lung function improvement is lacking. In subjects with ALS, upper-airway closure is described after MI-E application, even prior to the onset of bulbar symptoms, necessitating individualized approach to therapy. Qualitative studies describe high subject satisfaction.

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