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Combined Noninvasive Ventilation and Mechanical In-Exsufflator in the Treatment of Pediatric Acute Neuromuscular Respiratory Failure

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Summary. Objectives: The present study aims to evaluate the efficacy and complications of combined noninvasive ventilation (NIV) and assisted coughing by mechanical in-exsufflator (MIE) for acute respiratory failure (ARF) in children with neuromuscular disease (NMD). Methods: A prospective study was conducted in the pediatric intensive care unit. Children with NMD and ARF treated by combined NIV and MIE were included. Treatment success was defined as freedom from tracheal intubation during the hospital stay. Physiologic indices including PaO_2, $PaCO_2$, pH, and PaO_2/FiO_2 were recorded before and 12, 24 hr after the use of NIV/MIE. Results: Combined NIV/MIE was used in 15 NMD children (mean: 8.1 years, range: 3 months to 18 years) with 16 cases of ARF. There was no mortality in this cohort. Treatment success was achieved in 12 cases (75%), including six cases (38%) demanding "Do Not Intubate." ARF was due to pneumonia, with a mean baseline $PaCO_2$ of 73.2 $\pm$ 19.0 mmHg. In the success group, hypercarbia and acidosis improved after use of NIV/MIE for 24 hr ($PaCO_2$: 71.7 $\pm$ 18.6 mmHg vs. 55.8 $\pm$ 11.6 mmHg, $P < 0.01$; pH: 7.29 $\pm$ 0.07 vs. 7.38 $\pm$ 0.05, $P < 0.01$). All patients tolerated NIV/MIE well despite transient skin pressure sores in five cases. Conclusions: Combined NIV/MIE is a safe and effective approach to rapidly improve physiologic indices and decrease the need for intubation in NMD children with ARF. NIV/MIE provides a good alternative for those refusing intubation. **Pediatr Pulmonol. 2014; 49:589–596.** © 2013 Wiley Periodicals, Inc.

Key words: acute respiratory failure; neuromuscular disease; noninvasive ventilation; mechanical in-exsufflator.

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INTRODUCTION

Respiratory failure is the most common cause of death for children with chronic neuromuscular disease (NMD).[1] These children are at high risk of developing fulminant or repeated chest infections, which often precipitates acute respiratory failure (ARF) requiring admission to the pediatric intensive care unit (PICU).[2,3] In addition, ineffective airway clearance may further impair pulmonary function during infections, making neuromuscular respiratory failure the most common cause of prolonged ventilator dependency in the PICU.[1,4,5] Therefore, optimal management of ARF is critical to prevent mortality and morbidity of children with NMD.

Seventy percent of pediatric NMD patients will require intubation with ARF in the PICU.[2] However, such invasive approach often results in poor outcomes due to complications that can include ventilator-associated pneumonia, laryngeal edema, difficulties in extubation, and poor quality of life.[6–8] In addition, NMD patients or their parents often refuse intubation in the scenario of ARF.[9,10] In this regard, there is emerging evidence suggesting the role of noninvasive ventilation (NIV) as a first-line approach to ARF in adult patients with NMD.[11–13] However, data regarding the use of NIV as an alternative to intubation in NMD children with ARF is scarce.

In addition to NIV, recent clinical guidelines have recommended that a mechanical in-exsufflator (MIE), a device used for increasing cough flows and efficacy, be in the home care of NMD patients with impaired respiratory function.[14–16] MIE effectively mobilizes and clears airway secretions, since inadequate clearance of secretions in NMD patients is an important cause of exacerbation of ARF even with the support of NIV.[17,18] Some recent studies have indicated that, from the perspective of chronic respiratory care, the use of NIV combined with MIE can significantly decrease the need of hospitalization and ICU admission in NMD children.[19–21] However, the role of NIV combined with MIE in NMD children with ARF has not been established.

Thus, the purpose of this prospective study was to determine the feasibility and efficacy of a combined NIV/MIE approach for NMD children with ARF.

ABBREVIATIONS:

NIV	Noninvasive ventilation
MIE	Mechanical in-exsufflator
ARF	Acute respiratory failure
NMD	Neuromuscular disease
PICU	Pediatric intensive care unit
ABG	Arterial blood gas
BiPAP	Bilevel positive airway pressure
IPAP	Inspiratory positive airway pressure
EPAP	Expiratory positive airway pressure
SB	Spontaneous breathing
ST	Spontaneous timed
PRISM-III	Pediatric Risk of Mortality-III score
SMA	Spinal muscular atrophy
DMD	Duchenne muscular dystrophy
LGMD	Limb-girdle muscular dystrophy
CMT	Charcot–Marie–Tooth disease
MTPD	Mitochondrial trifunctional protein deficiency
DNI	Do not intubate

MATERIALS AND METHODS

Patients

We carried out a prospective and non-controlled study on children with NMD in a PICU of a university hospital from September 1, 2009, to July 31, 2012. The Institutional Review Board of Kaohsiung Medical University Hospital approved this study and informed consent was obtained from patients or guardians of patients.

Patients were included when they had previous diagnosis of NMD, confirmed with histopathological or/and genetic studies by an experienced pediatric neurologist (Y.-J. Jong), and when they required ventilatory support for ARF or postextubation ARF. The ARF was defined according to any of the following criteria: oxyhemoglobin saturation <90% with fractional concentration of oxygen in inspired gas (FiO_2) > 0.6, arterial blood gas (ABG) showing partial arterial oxygen (PaO_2) <60 mmHg, a ratio of PaO_2 to FiO_2 < 300, a partial arterial pressure of carbon dioxide ($PaCO_2$) ≥ 50 mmHg, or clinical symptoms or signs observed by the attending intensivist leading to the decision of ventilatory support. Episodes of pneumonia were defined as[1]: the presence of fever or leukocytosis[2]; positive signs perceived by physical examination[3]; purulent respiratory secretions; and[4] new onset infiltrate or consolidation on chest X-ray (CXR). Postextubation ARF was defined as the appearance of ARF within 24 hr after extubation. The exclusion criteria for this study included[1] profound bulbar weakness defined as absence of cough or gag reflex, or vocal cord paralysis[2]; cardiopulmonary collapse[3]; recurrent apnea[4]; un-drained pneumothorax[5]; multi-system failure[6]; a Glasgow Coma Scale score < 10; or[7] at-home using NIV or MIE prior to recruitment into this study.

Administration of NIV

NIV was delivered by bilevel positive airway pressure (BiPAP; Respironics, Murrysville, PA). Sedation was required for those who could not cooperate during the use of NIV. Drugs used for sedation included chloral hydrate (30–40 mg/kg q6–8h by orogastric tube or per rectal) or midazolam (0.1–0.15 mg/kg q6–8h iv bolus or 0.5–0.8 μg/kg/min iv infusion). The most optimal nasal or facial mask was chosen by a respiratory therapist and was

then gently positioned over the nasal bridge with minimal air leak. Skin damage was prevented by the application of colloid dressings (DuoDERM) on the different facial pressure points. Indication of intubation was mainly based on the attending intensivist's clinical decision determining poor tolerance and/or the progression of respiratory failure requiring endotracheal intubation (ETI).

In our PICU, the initial settings of BiPAP were[1]: inspiratory positive airway pressure (IPAP) 8–10 cmH_2O[2]; expiratory positive airway pressure (EPAP) 4–5 cmH_2O. Subsequently, the settings of BiPAP were rapidly adjusted within the first hour, to the point that the patient demonstrated good thoracic cage movement without paradoxical breathing. When applicable, IPAP was increased by an increment of 2 cm H_2O (maximum: 25 cm H_2O) to achieve an exhaled tidal volume of 5–6 ml/kg maintaining a $PaCO_2$ value < 55 mmHg, and pH > 7.3 and EPAP was adjusted in a range of 4–12 cmH_2O to maintain oxyhemoglobin saturation $> 94\%$ with a required $FiO_2 < 0.6$. All patients were set on spontaneous breathing (SB) or spontaneous timed (ST) mode of ventilation with a programmed backup rate set at 2 breaths/min less than the estimated baseline respiratory rate.

Implementation of MIE

In our PICU, MIE (CoughAssist, Cambridge, MA) was used to facilitate the expectoration of airway secretions in patients with NMD. The MIE was used by the nurses and respiratory therapists whenever the patients' oxyhemoglobin saturation decreased $< 94\%$, ventilator IPAP increased, or airway secretions increased. Use of the CoughAssist machine was according to the manufacturer's instructions. In brief, positive inspiratory pressures were established initially at 20 cmH_2O, and increased incrementally up to 40 cmH_2O, based on visual inspection of chest wall excursion and auscultation for bilateral adequacy of air entry. Negative pressures were set at 15 cmH_2O, and increased incrementally according to the patient's comfort and production of secretions up to 40 cmH_2O. The positive-pressure breath was delivered to the patient over 1–2 sec, while the negative exsufflation was delivered in 1–2 sec. The breaths were coordinated with the patient's own breath rate and rhythm. Three to five breaths were delivered followed by a period of rest before continuing, for a total of three to five cycles. Manual cough augmentation such as abdominal thrust was not routinely used with MIE in our PICU due to the concern of aggravating gastroesophageal reflux, which is common in NMD and might complicate ARF.

Interfaces included a mouthpiece or a facemask. Airway suctioning was performed at the end of each cycle and as needed during each rest period. Oxyhemoglobin saturations were monitored during the initial trial and as necessary during subsequent treatments. Supplemental oxygen was administered through the device as necessary to maintain oxyhemoglobin saturations of 94%.

Complications of NIV/MIE

Complications were recorded including CXR findings of pneumothorax or pneumomediastinum, and clinical features including gastric distension, aspiration, chest pain, or severe skin lesion on face caused by mask compression.

Data Collection and Outcome Measurement

Pediatric Risk of Mortality (PRISM)-III score upon PICU admission was recorded. During the PICU stay, standard monitoring was applied in all the patients, including blood pressure, heart rate (HR), respiratory rate (RR), and transcutaneous oxyhemoglobin saturation. Results of ABG were recorded prior to and 12, 24 hr after the use of NIV/MIE.

The outcome of each ARF case was divided into two groups: success or failure. Treatment success was defined as improvement of ARF and free from ETI or tracheostomy during the PICU stay. Treatment failure was defined by the eventual requirement of ETI or persistent dependence of mechanical ventilation requiring further tracheostomy during the PICU stay.

Statistic Analysis

Quantitative continuous variables were compared between groups by using Student t-test for parametric data or non-parametric Mann–Whitney's *U*-test when appropriate. Variables at different time points within the success or failure group were compared by repeated analysis of variance (ANOVA) with Tukey test for post hoc analysis. Data were presented as mean $\pm$ standard deviation (SD) and a *P*-values < 0.05 was considered significant. The statistical analysis was performed with the statistical package SPSS 15.0 for Windows (SPSS, Chicago, IL).

RESULTS

During the study period, we consecutively enrolled 15 eligible subjects (mean age: 8.1 years, range: 3 months to 18 years) with 16 cases of ARF in our PICU. The demographics and outcome of all patients are listed in Table 1. Among these patients, the diagnoses of NMD were: six spinal muscular dystrophy, two Duchenne muscular dystrophy, two congenital myopathy, one Leigh disease, one mitochondrial trifunctional protein deficiency (MTPD), one limb-girdle muscular dystrophy type 2I described in a previous case report,[22] and one Charcot–Marie–Tooth disease (CMTD) and one CMTD with demyelinating and infantile onset. Of note, five patients

TABLE 1—Demographic Data and Outcomes of Patients

Case	Age	Gender	Type of NMD	Cause of ARF	Presentation of ARF	PRISM-III	DNI	Type of NIV	Max. settings	Duration of NIV/MIE use	PICU stay (days)	Outcome
1[1]	16 years	M	DMD	Pneumonia	Hypercarbic, $PaCO_2$: 70.7 mmHg	5	Yes	BiPAP SB/ST mode	16/5 cmH_2O	4 days	8	Success
2[1]	18 years	M	DMD	Pneumonia	Hypercarbic, $PaCO_2$: 102.7 mmHg	9	Yes	BiPAP ST mode	22/5 cmH_2O	5 days	8	Success
3	3 years	M	Congenital myopathy	Pneumonia, postextubation ARF	Hypercarbic, $PaCO_2$: 68.9 mmHg	4	No	BiPAP ST mode	12/5 cmH_2O	20 days	27	Success
4	3 months	M	SMA type 1	Pneumonia, atelectasis	Hypercarbic, $PaCO_2$: 62.3 mmHg	10	Yes	BiPAP ST mode	14/4 cmH_2O	40 days	48	Success
5	10 months	F	SMA type 1	Pneumonia, atelectasis	Hypercarbic, $PaCO_2$: 56.0 mmHg	4	Yes	BiPAP ST mode	12/3 cmH_2O	22 days	32	Success
6	17 years	M	DMD	Pneumonia	Hypoxemic, PaO_2: 50 mmHg	15	Yes	BiPAP ST mode	22/5 cmH_2O	32 days	40	Success
7	4 months	M	SMA type 1	Pneumonia	Hypercarbic, $PaCO_2$: 59.0 mmHg	11	Yes	BiPAP ST mode	18/5 cmH_2O	30 days	41	Success
8	17 years	F	LGMD 2I	Pneumonia	Hypercarbic, $PaCO_2$: 94.0 mmHg	8	No	BiPAP SB/ST mode	20/5 cmH_2O	8 days	15	Success
9	7 years	F	CMTD	Pneumonia	Hypercarbic, $PaCO_2$: 58.0 mmHg	5	No	BiPAP ST mode	12/5 cmH_2O	5 days	10	Success
10	7 years	F	SMA type 2	Pneumonia	Hypercarbic, $PaCO_2$: 92.0 mmHg	10	No	BiPAP ST mode	14/5 cmH_2O	7 days	12	Success
11	16 years	F	SMA type 2	Pneumonia	Hypercarbic, $PaCO_2$: 60.0 mmHg	4	No	BiPAP SB/ST mode	14/5 cmH_2O	9 days	15	Success
12	13 years	F	CMTD	Pneumonia	Hypercarbic, $PaCO_2$: 91.9 mmHg	16	No	BiPAP ST mode	18/5 cmH_2O	5 days	7	Success
13	18 years	M	MTPD	Pneumonia	Hypercarbic, $PaCO_2$: 66.7 mmHg	9	No	BiPAP SB mode	12/5 cmH_2O	10 hours	21	Failure
14	4 years	M	Leigh disease	Pneumonia	Hypercarbic, $PaCO_2$: 85 mmHg	10	No	BiPAP ST mode	20/5 cmH_2O	16 hours	15	Failure
15	10 months	F	SMA type 1	Pneumonia	Hypercarbic, $PaCO_2$: 53.6 mmHg	3	No	BiPAP ST mode	18/5 cmH_2O	18 hours	41	Failure
16	2 years	F	Congenital myopathy	Pneumonia	Hypercarbic, $PaCO_2$: 105 mmHg	10	No	BiPAP ST mode	20/5 cmH_2O	26 hours	34	Failure

NMD, neuromuscular diseases; ARF, acute respiratory failure; PRISM-III, Pediatric Risk of Mortality-III score; DNI, do not intubate; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; DMD, Duchenne muscular dystrophy; SMA, spinal muscular atrophy; LGMD, limb-girdle muscular dystrophy; CMTD, Charcot–Marie–Tooth disease; MTPD, mitochondrial trifunctional protein deficiency; BiPAP, bilevel positive airway pressure; ST, spontaneous timed; SB, spontaneous breathing; CPAP, continuous positive airway pressure; M, male; F, female.

[1]Belong to the same patient.

(six cases) had specified "Do Not Intubate" request at admission of PICU.

Among 16 ARF cases, 15 were ARF requiring immediate ventilatory support and one was postextubation ARF developing 1 hr after extubation. The cause of ARF was pneumonia in all episodes and two of them were complicated with atelectasis. Fifteen patients had ARF from hypercapnia and one patient from hypoxemia, with the initial mean $PaCO_2$ of 73.2 ± 19.0 mmHg (range: 54–105 mmHg). NIV was deployed by BiPAP in all cases. The mean duration of minimal NIV settings used in these patients was 28.1 ± 10.3 min. The mean duration of NIV/MIE administration was 11.9 ± 12.8 days (range: 10 hr to 40 days). The mean PICU stay was 23.4 ± 14.1 days (range: 7–41 days). There was no mortality during this cohort study.

All patients tolerated NIV and MIE well. Sedation by chloral hydrate or midazolam was required in four patients younger than 3 years old. The initial physical indices and outcomes were comparable between patients with and without sedation (data not shown). There was no major complication such as pneumothorax or gastric distension. The most common complication was skin irritation caused by NIV interfaces, including mild erosion or irritant dermatitis of nasal bridge in five cases. All these skin lesions healed completely with supportive care during the ICU stay and did not affect the use of NIV or MIE.

Primary Outcome—Success or Failure

In this cohort, there were 12 ARF cases (75%) in success group and four cases (25%) in failure group. Baseline demographics before initiation of NIV/MIE were comparable between these two groups (Table 2).

In the success group, both hypercarbia and acidosis resolved significantly 12 hr after initiation of NIV and MIE (Fig. 1). However, the PaO_2/FiO_2 ratio did not change significantly. As shown in Figure 2, the serial changes of CXR were evident in one patient in the success group (case 5). In the failure group, the mean time from start of NIV/MIE use to intubation was 17.5 ± 6.6 hr (range: 10–26 hr). Patients in the failure group were intubated based on the attending intensivist's clinical impression assuming NIV failure. The reasons for intubation in these patients were: poor tolerance to the mask (case 13); repeated seizures (case 14); poor tolerance and progressive hypercapnia ($PaCO_2$: from 53 to 72 mmHg; case 15); severe airway bleeding (case 16). At 12 hr after NIV use, three patients of this group before they were intubated had persistent hypercarbia and acidosis compared with data at baseline (pH: 7.21 ± 0.21 vs. 7.27 ± 0.08, $P = 0.67$; $PaCO_2$: 75.1 ± 26.7 mmHg vs. 67.2 ± 8.0 mmHg, $P = 0.65$). Nevertheless, all patients in the failure group (4/4) were extubated successfully during the same hospital stay with the mean duration of intubation of 22.8 ± 8.7 days (range: 15–34 days).

To analyze factors associated with NIV failure, we compared physiologic parameters between groups and found that patients in the failure group had lower RR decrease from initial RR at 3 hr (success: 11.3 ± 8.9 vs. failure: 5.7 ± 7.6, $P = 0.02$). In addition, patients in the failure group had higher RR and HR at 9 hr when compared to those in the success group (HR: 139 ± 5.0 vs. 126.5 ± 10.8, $P = 0.04$; RR: 34.8 ± 5.4 vs. 28.2 ± 4.7, $P = 0.03$).

All patients were discharged from the hospital without tracheostomy, with four children (five cases) free from the need of ventilatory support, eight patients requiring nocturnal use of NIV, and three infants of type I spinal muscular atrophy requiring continuous NIV/MIE support at home.

TABLE 2— Baseline Characteristics Between Patients With Different Outcomes[1]

	Success	Failure	*P*-value
Cases	12	4	—
Age (y/o)	9.6 ± 7.3	6.0 ± 7.5	0.4
PRISM-III	8.4 ± 4.2	8.0 ± 3.4	0.9
HR (bpm)	141.1 ± 16.8	138.0 ± 15.3	0.8
RR (b/m)	30.3 ± 8.1	33.8 ± 11.1	0.5
MAP (mmHg)	85.1 ± 26.8	91.7 ± 10.2	0.6
pH	7.29 ± 0.07	7.20 ± 0.17	0.1
$PaCO_2$ (mmHg)	71.7 ± 18.6	77.6 ± 22.4	0.6
PaO_2 (mmHg)	98.2 ± 43.4	112.4 ± 40.7	0.6
PaO_2/FiO_2	307.9 ± 208.1	397.9 ± 156.2	0.4
SpO_2 (%)	97.0 ± 2.5	95.3 ± 5.3	0.4

PRISM-III, Pediatric Risk of Mortality-III score; HR, heart rate; RR, respiratory rate; MAP, mean arterial pressure.
[1]Values are given as the mean ± SD, unless otherwise indicated.

DISCUSSION

To our knowledge, this is the first study evaluating combined NIV/MIE as a first-line intervention of pediatric ARF in the ICU. Our results demonstrated that combined NIV/MIE was well tolerated and averted 75% of cases from endotracheal intubation, indicating that this is a feasible and effective approach to ARF in NMD children, even in those with no prior experience of using NIV. Another important finding of this study is that 38% of these cases were in the "Do Not Intubate" status, and all of these patients survived from this non-invasive approach, demonstrating that this is an effective strategy to prolong the survival of this subgroup of patients.

Recently, NIV and/or assisted coughing by MIE have been advocated as parts of the standard of care for chronic respiratory insufficiency for patients with NMD, such as Duchenne muscular dystrophy, spinal muscular atrophy,

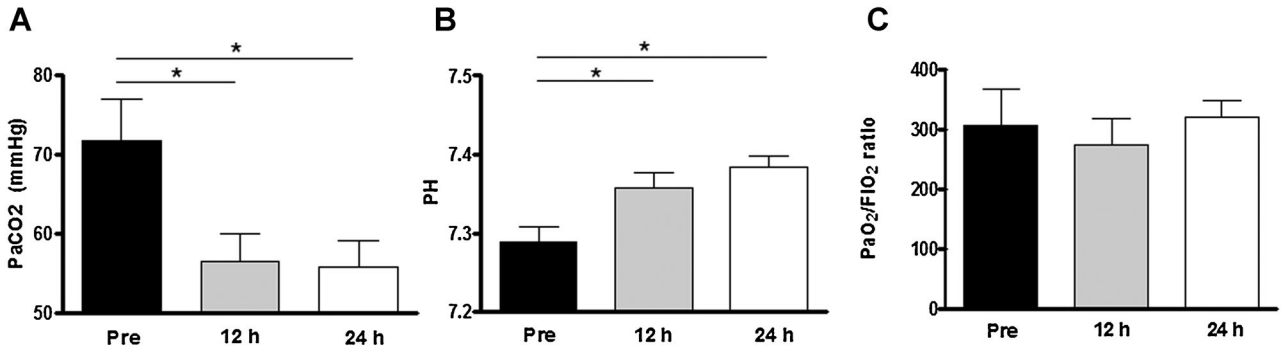

Fig. 1. Changes of physiologic indices over 24 hr after use of NIV/MIE in the success group. A: $PaCO_2$ level declined significantly as early as 12 hr after treatment. B: Acidosis improved after 24 hr of treatment. C: The PaO_2/FiO_2 ratio did not change significantly after treatment. $^*P < 0.001$.

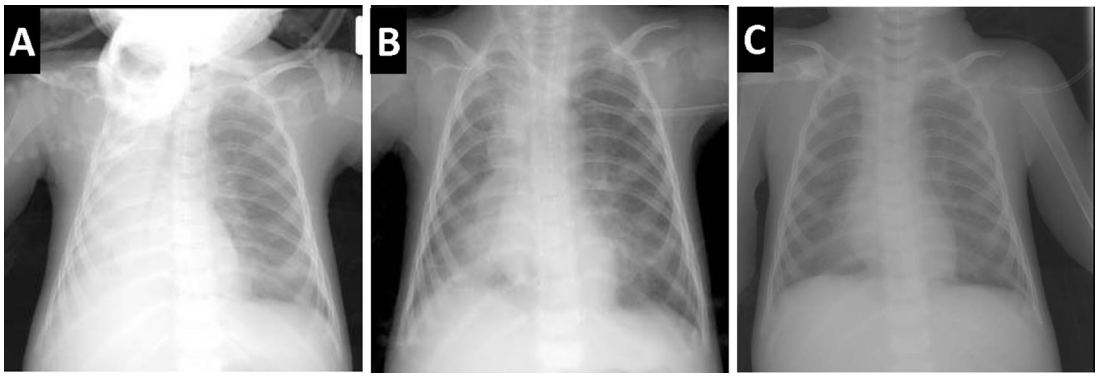

Fig. 2. Serial changes of chest radiographs in a 10-month-old patient of type I spinal muscular atrophy with the request of "Do Not Intubate" (case 5). A: Initial chest radiograph showed severe atelectasis of the right lung caused by pneumonia. B: A significant improvement was found after the use of NIV/MIE for 24 hr with residual pneumonia and relief of atelectasis. C: A near-total resolution was shown on day 15.

congenital muscular dystrophies and congenital myopathies.[14–16,23] A previous study evaluating this approach in adults demonstrated a similar success rate of 79.2% in averting intubation in 17 patients with NMD.[24] Of note, these patients were managed in the respiratory ward but not in the ICU, with milder disease severity as demonstrated by less hypercarbia than our patients (mean $PaCO_2$: 49 mmHg vs. 72 mmHg) at the presentation of ARF. Recently, Essouri et al.[25] reported a large-scale study of 114 pediatric patients and suggested NIV as a first-line therapy for ARF in the PICU setting. However, they did not use MIE and excluded patients with excessive airway secretions.

The major rationale of using MIE during NIV application for children with NMD is that difficulty mobilizing their secretions is often present in these patients because of weakness of the bulbar, inspiratory or expiratory muscles. Even though effects of MIE have not been previously studied in the setting of ARF, its physiologic benefits have been recently shown in both children and adults with NMD who are in the stable state.[26,27] Intriguingly, a previous study showed that cough flow could be augmented by MIE in both healthy subjects and adult patients with amyotrophic lateral sclerosis.[27] That study also demonstrated that MIE was more effective than manual cough assistance and that the greatest improvements were in patients with the weakest coughs, suggesting its important role in the patient population of NMD. Another reason to justify the use of MIE during NIV is that, as shown in the present study, most ARF cases in patients with NMD are caused by pneumonia, with copious secretions and/or atelectasis.[28] As such, a combined NIV/MIE approach can not only facilitate clearance of airway secretions at the time of chest infections but also provide positive pressure support to relieve the atelectasis. Furthermore, conventional

management by oropharyngeal suction may be inadequate for secretion clearance and can lead to failure of NIV treatment or even preclude the application of NIV due to the need for frequent suctioning.[29,30] However, tracheal collapse may be a concern in patients younger than 6 months of age receiving MIE, even though we did not observe such complication in our patients.

Although there is high-level evidence in the literature to support the use of NIV in general pediatric patients with ARF, data regarding its use in children with NMD is scarce. To our knowledge, there is only one previous study describing the outcome of NIV use in NMD children with ARF.[31] That study had only 10 patients and some had central nervous system diseases rather than true NMD. In addition, MIE was not used and the presentations of ARF in that study were mostly hypoxic rather than hypercarbic. Similar to that study, our patients with NIV failure were intubated early (within 26 hr), suggesting that early clinical improvement is critical.

Limitations of this study primarily relate to its small sample size. Nevertheless, this is the largest cohort study of ARF of NMD children in the ICU to date. Another limitation is the lack of control group in the present study. However, given there is no downside to initiate this noninvasive therapy, it is unethical to randomize these patients, especially in the DNI population. There is also a theoretical risk of aspiration, but risk benefit favors early NIV/MIE use. Additionally, one patient in our failure group was sedated and it is possible that this could have depressed respiratory drive and rendered NIV less effective. Lastly, the outcome may be confounded by the factor that most of intubations in this study occurred on clinical grounds rather than by objective criteria.

CONCLUSIONS

This study found that the majority of children with NMD and ARF from pneumonia were managed with NIF/MIE and not intubated. This combination provides an effective alternative, especially for those patients that are DNI.

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