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Mechanical insufflation-exsufflation use in neuromuscular disease: a single centre cohort study

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ABSTRACT

Introduction Mechanical insufflation-exsufflation (MIE) is a commonly used therapy to augment secretion clearance in individuals with neuromuscular disease. There are no clear evidence-based guidelines on the settings that should be used in different diagnostic groups and how they should be titrated. We report on the settings used in the largest cohort of individuals using domiciliary MIE in the literature.

Methods A retrospective observational study reporting on all individuals initiated on MIE for long-term domiciliary use at our centre, 2013–2019.

Results This study reports on 359 adults established on domiciliary MIE. The most common diagnostic groups were congenital neuromuscular disease (26%), spinal cord injury (23%) and amyotrophic lateral sclerosis (23%). Median age at initiation was 55 years. Median (IQR) insufflation pressure was 35 (30–40) cm H_2O and exsufflation pressure was 45 (40–50) cm H_2O. Inspiratory time was 2.5 (2.3–2.8) s, expiratory time was 2.7 (2.3–2.8) s, and pause between expiration and inspiration was 2.0 (1.2–2.0) s. Median (IQR) survival following the initiation of MIE was 66 (54–78) months. Increasing age and amyotrophic lateral sclerosis were significantly associated with shorter life expectancy, while the delivery of MIE via oronasal interface compared with tracheostomy was associated with longer life expectancy.

Conclusion This is the largest reported cohort of adults using domiciliary MIE. The most common groups using MIE were congenital neuromuscular disease, spinal cord injury patients and amyotrophic lateral sclerosis. The range of prescribed settings is narrow, reflecting the limited evidence base in this field and the need to better understand optimal targets for titration of different MIE settings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Our knowledge on the delivery of mechanical insufflation-exsufflation (MIE) in adults, and factors that are associated with survival, is limited.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that the range of MIE settings delivered to adults is very limited, despite a wide range of settings available. It provides further insights into factors that affect mortality at the time of MIE initiation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study demonstrates the need for further research to understand how to titrate MIE settings to achieve optimal secretion clearance. The study provides characteristics associated with worse survival, which can support clinical decision-making and prompt advanced care planning in high-risk individuals.

INTRODUCTION

Individuals with neuromuscular disease often develop respiratory muscle weakness which impairs secretion clearance.[1] A frequently used technique to augment secretion clearance in these individuals is mechanical insufflation-exsufflation (MIE) therapy. This involves the delivery of a positive pressure (insufflation) to recruit airways, followed by a negative pressure swing (exsufflation), aiming to augment the cough peak expiratory flow and thus clear airways of secretions.[2] While there are limited prospective data evaluating the patient-reported and physiological effects of MIE,[3] expert consensus highlights its importance in the management of individuals with neuromuscular disease and severely impaired respiratory function.[2]

Modifiable MIE parameters include the insufflation and exsufflation pressures, inspiratory and expiratory time, inspiratory rise time, number of individual coughs and cycles delivered and duration of pause between cycles. Despite the implementation of MIE in individuals with a cough peak expiratory flow <160 L/min in clinical practice,[2] there are no clear evidence-based guidelines on the settings these individuals should be established on and how they should be

titrated. Existing guidelines with recommendations about titrating MIE are based on expert consensus.[4–6] Importantly, there is growing interest in the effect of MIE on the upper airway.[7–11] An evidence-based method to titrate MIE settings to minimise upper airway closure has been published.[12] As a result of this variety in expert consensus-based guidelines, MIE practice varies both in the literature and clinically. Although an MIE titration protocol has been published, it is based mostly on the authors' clinical experience and judgement, rather than a physiological evidence base.[13] A single conference abstract has been identified reporting on the implementation of a titration protocol in the acute setting.[14] No studies have been identified reporting on the physiological or clinical effects of changing MIE parameters other than pressure in the domiciliary setting. Developing a better understanding of the use of different MIE parameters would be an early step towards the development of an evidence-based titration protocol. This study sought to report the characteristics of patients initiated on domiciliary MIE at a tertiary home ventilation centre and device settings. Furthermore, the study will investigate the relationship between patient and MIE device characteristics and survival.

METHODS

This was a retrospective observational study reporting on all individuals initiated on MIE therapy for long-term use at home at a tertiary ventilation centre between 1 January 2013 and 31 December 2019 (online supplemental table S1). The start date was chosen at this was when our institution's electronic medical record system was introduced, allowing data to be accessed with ease. The end date was chosen to avoid any impact of the COVID-19 pandemic on the number of individuals being initiated onto MIE. As a retrospective study of anonymised clinical data, our institution determined that ethical approval was not required. This study was registered as a clinical audit at our institution (reference number: 11051).

Patient and public involvement

Patients or members of the public were not involved in the design or delivery of this study.

Data collection

Participants were identified using our centre's database of all individuals who are provided with a medical device (ventilator or MIE) for use at home. During the period included in this study, all individuals were established onto MIE therapy using the Nippy Clearway device (Breas Medical). This device allowed delivery in manual, basic auto, time auto and triggered auto modes. It delivered pressures from 0 cm H_2O to 60 cm H_2O, insufflation (T_i) and exsufflation (T_e) times 0.5–5.0 s, pause time 0–5 s with a trigger of 1–5 cm H_2O. It allowed the addition of inspiratory and expiratory oscillations. Electronic medical records were interrogated to identify the cause of neuromuscular weakness, ventilatory support requirements, MIE interface, MIE settings, whether or not they had a gastrostomy in situ (used as a surrogate marker of bulbar weakness) and length of survival from the time of MIE initiation.

Data analysis

Data were assessed for normality both visually with histograms and using the Kolmogorov-Smirnov test.[15] Data are reported as mean±SD, median (IQR) or number (proportion). Normally distributed continuous variables were compared using the Student's t-test. The Mann-Whitney U test was used for unpaired non-parametric variables and the Wilcoxon matched-pair signed rank test for paired non-parametric variables. Differences between diagnostic groups were assessed using a one-way analysis of variance followed by a Tukey post hoc analysis. Differences between settings over time were assessed using a Kruskal-Wallis Test with Bonferroni correction. Survival curves were estimated using the Kaplan-Meier method. Life expectancy following the initiation of MIE between the diagnostic groups, and between individuals with and without a gastrostomy, was assessed using the log-rank test. A multivariate Cox proportional hazards model was used to estimate the estimated HR with a 95% CI. Multivariate regression analysis was performed using age at initiation of MIE, sex, diagnostic group (congenital neuromuscular disease as the reference group), presence of gastrostomy and MIE interface as variables. All statistical analyses were completed using IBM SPSS Statistics, V.28 (IBM Corp, New York, USA).

RESULTS

Between January 2013 and December 2019, 359 adults (66% male) were established on home MIE therapy (Nippy Clearway, Breas Medical) at our centre. Diagnoses leading to respiratory muscle weakness included congenital neuromuscular diseases (cNMDs; 26%), spinal cord injury (SCI 23%), amyotrophic lateral sclerosis (ALS; 23%), other inflammatory neuromyopathy (OIN; 7%), Guillain-Barre syndrome (GBS; 5%), acquired brain injury (ABI; 5%) and other (including critical care myopathy, spina bifida, poliomyelitis/postpolio syndrome and multisystem atrophy, 11%). Median age at initiation of MIE was 55 (40–68) years. Age by diagnostic group: cNMD (29 (20–48) years), SCI (58 (45–69) years), ALS (65 (57–72) years), GBS (66 (57–74) years), OIN (56 (49–69) years), ABI (40 (21–48) years) and other (61 (47–70) years). Among the cohort, 91% of individuals were receiving mechanical ventilation (57% overnight, 7% for 16–24 hours/day and 36% for 24 hours/day). The proportion of patients with gastrostomy in situ was 52%. The annual number of individuals initiated on MIE was 32 (2013), 54 (2014), 50 (2015), 74 (2016), 42 (2017), 53 (2018) and 70 (2019). MIE was delivered by the oronasal interface in 69% of patients and via tracheostomy in 31% of patients. MIE was delivered in manual

Table 1 MIE settings for each diagnostic group. Data are displayed as median (IQR)

	cNMD	SCI	ALS	GBS	OIN	ABI	Other
Insufflation pressure (cm H_2O)	35 (31–40)	38 (30–40)	35 (34–40)	35 (30–40)	40 (30–45)	35 (31–40)	40 (34–40)
Exsufflation pressure (cm H_2O)	45 (35–50)	45 (40–55)	48 (40–50)	40 (40–50)	48 (44–55)	48 (40–56)	45 (40–50)
Inspiratory time	2.5 (2.0–2.8)	2.5 (2.2–2.8)	2.8 (2.4–2.8)	2.8 (2.5–2.9)	2.8 (2.4–2.9)	2.7 (2.4–3.0)	2.5 (2.2–2.8)
Expiratory time	2.5 (2.0–2.8)	2.5 (2.3–2.8)	2.8 (2.5–2.8)	2.8 (2.2–2.9)	2.7 (2.3–2.9)	2.8 (2.5–2.9)	2.7 (2.3–3.0)
Pause	2.0 (1.0–2.0)	2.0 (1.6–2.2)	1.8 (1.2–2.0)	1.8 (1.6–2.2)	1.6 (1.2–2.0)	1.9 (1.7–2.3)	1.9 (1.2–2.2)

ABI, acquired brain injury; ALS, amyotrophic lateral sclerosis; cNMDs, congenital neuromuscular diseases; GBS, Guillain-Barre syndrome; MIE, mechanical insufflation-exsufflation; OIN, other inflammatory neuropathy; SCI, spinal cord injury.

mode in 44% and one of the automatic modes (basic, timed automatic, triggered automatic) in 56% of patients. Prescribed settings did not differ between diagnostic groups (table 1). Median insufflation pressure (P_{ins}) was 35 (30–40) cm H_2O and exsufflation pressure (P_{exs}) was 45 (40–50) cm H_2O. For patients using automatic mode, inspiratory time was 2.5 (2.3–2.8) s, expiratory time was 2.7 (2.3–2.8) s and pause between expiration and inspiration was 2.0 (1.2–2.0) s. P_{exs} was higher than P_{ins} (median difference 10 cm H_2O, p<0.0001). In patients receiving MIE via tracheostomy, P_{ins} (median difference 5 cm H_2O, p<0.001) and P_{exs} (median difference 5cm H_2O, p=0.009) were higher than in those patients receiving MIE via facemask. There was no difference in T_i, T_e pause between individuals receiving MIE via tracheostomy or facemask. P_{ins} was higher in patients with gastrostomy in situ, as a marker of bulbar weakness (median difference 3 cm H_2O, p=0.033). There was no correlation between age and prescribed settings. Over the course of this study, prescribed P_{ins}, T_i and T_e did not change. P_{exs} did change over time (p=0.014); however, post-hoc analysis demonstrated that this was due to an increase in P_{exs} in 2015 only. The pause delivered has increased over time from 1.5 (0.6–2.1) s in 2013 to 2.0 (1.8–2.2) s in 2018 (p=0.03). Median survival following initiation of MIE was 66 (54–78) months. The log-rank test demonstrated that survival was different between the diagnostic groups (χ^2=22.9, p<0.001, figure 1). Survival was shorter in individuals with a gastrostomy in situ (median survival 58 months), compared with those without (median survival 83 months, χ^2=7.3, p=0.007, figure 2). In the univariate Cox proportional hazard model, increasing age (HR 1.03 (1.02, 1.04), p<0.001), ALS diagnostic group (HR 5.57 (3.54, 8.76), p<0.001), other diagnostic group (HR 3.65 (2.15, 6.19), p<0.001) and those with gastrostomy in situ (HR 1.56 (1.13, 2.17), p=0.008) were significantly associated with shorter life expectancy from initiation of MIE. Male sex was associated with longer life expectancy

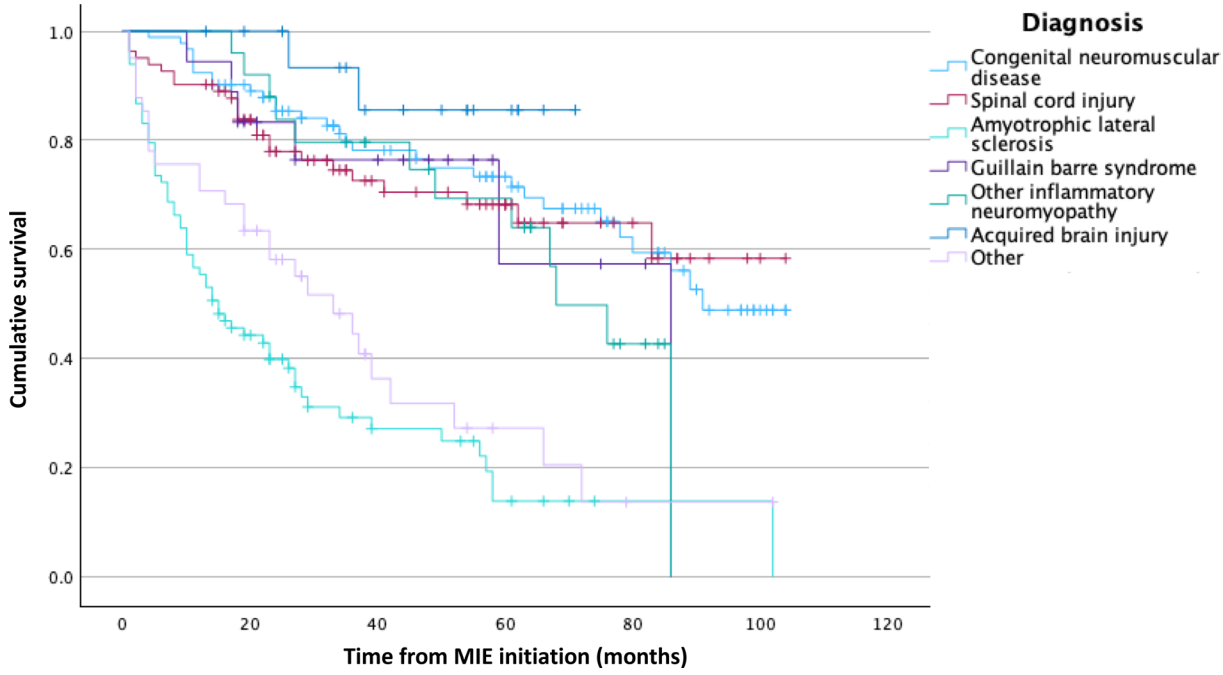

Figure 1 Kaplan-Meier curve displaying survival in months from the time of initiation of MIE. Different diagnostic groups are displayed as individual curves. MIE, mechanical insufflation-exsufflation.

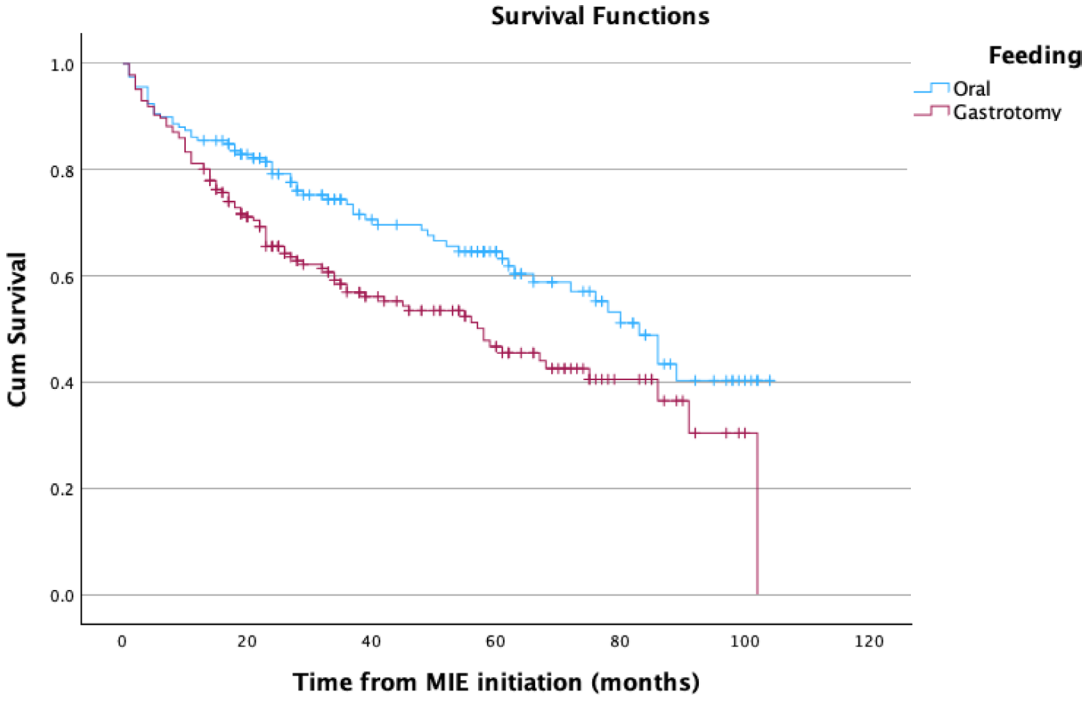

Figure 2 Kaplan-Meier curve displaying survival in months from the time of initiation of MIE. Survival is compared between individuals who had a gastrostomy with those who did not. MIE, mechanical insufflation-exsufflation.

(HR 0.69 (0.49, 0.97), p=0.032). In the multivariate Cox proportional hazard model, increasing age (HR 1.02 (1.01, 1.03), p<0.001) and ALS diagnostic group (HR 2.88 (1.66, 5.00), p<0.001) were significantly associated with shorter life expectancy, while MIE via oronasal interface compared with via tracheostomy was associate with longer life expectancy (HR 0.62 (0.42, 0.93), p=0.02). Male sex was not associated with longer survival in the multivariate analysis.

DISCUSSION

To our knowledge, this is the largest report of adults receiving domiciliary MIE in the published literature. These data highlight that the most common diagnostic groups that are prescribed long-term MIE include cNMD, SCI and ALS. Despite a wide range of potential settings that the MIE device can deliver, individuals were prescribed a narrow spectrum of insufflation and exsufflation pressures, as well as inspiratory, expiratory and pause times. From the time of MIE initiation, shorter life expectancy was associated with increasing age and ALS, while delivery of MIE via oronasal interface was associated with longer life expectancy.

Two studies reporting on MIE use in the home in adults have been identified, one from London[16] and the other from Switzerland.[17] Median age in this study was 50 years, similar to that reported in the Swiss cohort. The other UK cohort reported a median age of 33 years; this can be explained by the different proportions of diagnostic groups in the datasets. This cohort includes equal proportions of cNMD (26%), SCI (23%) and ALS (23%), whereas Chatwin and Simonds' included a high proportion of individuals with cNMD (52%) and lower proportion of individuals with SCI (5%) and ALS (13%).[16] The predominance of cNMD in their dataset is likely to have resulted in a lower median age of initiation, as respiratory muscle weakness tends to develop at a younger age than in ALS, while SCI is a condition that can affect all ages. As there is no expected difference in populations in the different areas served by the two centres, the different patient populations likely represent different referral patterns and specialisation between the units.

There were also differences in the delivery of MIE. While 96% of individuals in the UK cohort[16] and 95% of individuals in the Swiss cohort[17] received MIE using an automatic mode, only 56% of our cohort did. During the period of the study, the titration of MIE was conducted by physiotherapists with experience in home ventilation and was delivered to optimise subjective secretion clearance as judged by the practitioner. There was no formal titration protocol or objective assessment conducted of the final titration outcome. Therefore, despite the intended individualised process, the delivered MIE settings may represent the judgement of the individual practitioner based on their knowledge, experience and interpretation of the available data. It is therefore difficult to identify why so many more patients in our cohort received MIE via manual mode without further qualitative work involving the relevant practitioners. Prescribed settings also differed with the UK and Swiss cohorts. Both centres delivered lower P_{ins} and P_{exs} than the data reported in this study. Interestingly, the Chatwin and Simonds cohort involved a preset algorithm for titrating pressures, whereas our data suggest a subjective individual practitioner approach, which may explain the difference in pressures delivered. Equally, individuals

in our cohort received longer inspiratory and expiratory times, compared with the other published data (1.5 s and 2.0 s, respectively). When comparing with the Chatwin and Simonds cohort, this may reflect that their practice also includes delivery of MIE to the paediatric population, and so lower pressures reflect increased caution when delivering MIE to children. A study reporting on MIE use solely in children reported lower pressures at younger ages.[18] Alternatively, it may reflect reduced chest compliance in adult populations leading to a requirement for higher pressures to achieve adequate inspiratory volumes in our population. In addition, the Swiss cohort included a higher proportion of individuals with diagnoses that tend to develop respiratory muscle weakness at a younger age and so may reflect MIE settings that were prescribed when the patient was younger. Despite the differences in settings delivered between the datasets, they all demonstrate a narrow range of settings prescribed to individuals with respiratory muscle weakness. This seems at odds with the individualised settings promoted both in published guidance and local policies. This may reflect the limited evidence base and understanding of the impact of changing settings, as highlighted by a UK survey, although in the intubated population[19] with both a protocolised titration algorithm and a subjective practitioner-judged process resulting in a 'one size fits all' prescribing of MIE,[20] which is also reflected in the lack of variation in settings prescribed between different diagnostic groups (table 1). These data may also indicate what was accepted as 'standard' practice during the years included, and therefore how our clinicians practised. The range of pressure delivered at our centre was clustered around 40 cm H_2O. Historically, MIE pressures were targeted at +40 mm Hg and −40 mm Hg and these were erroneously translated into +40 cm H_2O and −40 cm H_2O in the newer generation of MIE devices.[21] This was reflected in physiological studies that appear to use +40/−40 cm H_2O as the initiating pressure, with only upwards titration.[22 23] Protocols of clinical studies also tended to involve delivering MIE at pressures of +40/−40 cm H_2O.[24–26] The widespread use of pressure settings of +40/−40 cm H_2O in the literature in years preceding and during the cohort included in this study may have influenced our practitioners. More recent expert-based titration guidelines have recommended initiating MIE at lower pressures, starting at 15 cm H_2O or 20 cm H_2O.[4 16] These guidelines may result in different practices at our centre in the coming years. In fact, a protocol introduced more recently at our centre, which aims to titrate MIE settings against peak cough flow, has demonstrated a wider range of pressures being delivered.[14] With emerging data about the impact of MIE on the upper airway, and differences between patients who suffer from bulbar weakness and those who do not,[7 10 27 28] the importance of tailoring treatment to the individual is becoming increasingly apparent. This may translate into different settings being delivered to patients from diagnostic groups particularly at risk of bulbar weakness, such as ALS. In order to fully understand the decision-making rationale around prescribing MIE settings, particularly in the context of these recently published guidelines and the increasing awareness of the effect of MIE on the upper airway, a qualitative study interviewing clinicians initiating and titrating MIE would be useful.

Our tertiary centre initiates 53 (42–70) adults onto MIE annually, with an increasing number year on year. This represents 47 (42–62)% of the patients with neuromuscular conditions initiated on non-invasive ventilation.[29] This will allow other centres to make budgetary predictions for the number of individuals they may set up each year. The out of proportion increase in 2016 is explained as our service took over the care of a large number of individuals living with ALS from another centre in that year.

Rose *et al*[30] reported 12-month survival from initiation of MIE as 78%, which is similar to the 12-month survival in our cohort of 82%. The association of ALS and increased age with shorter survival after initiation of MIE is unsurprising. Increasing age was a risk factor for mortality identified by Rose *et al*.[30] The association of MIE delivered by oronasal interface and longer survival may be explained by the adjustment for ALS in the multivariate regression model, particularly as this was not identified in the univariate model. A very small proportion of individuals living with ALS at our centre receive tracheostomies in line with UK practice; thus, the rapid progression of respiratory failure in this cohort will have had effect on the univariate model analysing the MIE interface.

A limitation of this dataset is that it did not include individuals who were initiated on MIE before 2013. This is because our electronic record system was introduced in 2013. As a retrospective study, we were limited to the information that was historically entered into the electronic record system. Although the process of data entry into the electronic record is part of our centre's standard operating procedure, it is at the same risk of data error as other registry studies.[31] As a single centre, the findings are limited to practice at our centre, which may not be representative of other long-term ventilation centres. An important limitation was that MIE usage was not recorded at our centre; this would have been useful to understand the pattern of use in the patients in this cohort. This would have provided more granularity on 'real world' domiciliary MIE use, compared with prescribed regimens. Additionally, the lack of adherence data makes inferences about clinical impact of MIE use less robust as pattern of use could not be confirmed. We reported on the presence of a gastrostomy as a surrogate marker of bulbar weakness, because in patients with neuromuscular disease, gastrostomy insertion is for clinically significant dysphagia. The use of a surrogate marker for bulbar weakness was necessary because our centre did not systematically document the assessment of bulbar function in the electronic health record. There is a possibility that the presence of a gastrostomy did not accurately represent individuals with bulbar weakness, but we believe that this approach is justified, given the importance of bulbar weakness in MIE delivery.

In summary, this is the largest reported cohort of adults using domiciliary MIE. The most common diagnostic groups receiving MIE were congenital neuromuscular diseases, spinal cord injury and amyotrophic lateral sclerosis. The range of prescribed settings for MIE is narrow, despite an

individualised approach to device titration, reflecting the limited evidence base in this field. Although the addition of MIE to a patient's package of care suggests significant respiratory muscle weakness and risk of infections, median survival is approximately 5 years from initiation of MIE. These data reflect the current practice of MIE delivery at a specialist centre and highlight the need to better understand the optimal targets for titration and the impact of different MIE settings on patient-reported outcomes and on long-term mortality.

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Contributors The study was designed by NMS, CA and PM. The literature search was completed by NMS, GK and SM-S. Data collection was completed by NMS, CA, MM and NW. Data were analysed by NMS, GK, SM-S, CA and PM. NMS, GK, SM-S, CA, SSh, MR, SSr, E-SS, RD'C, MM, NW, NH and PM contributed to manuscript preparation and manuscript review. PM is the guarantor of this study.

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