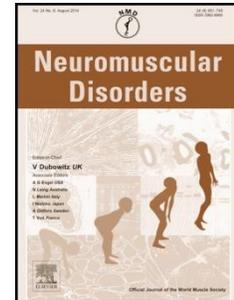


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Diagnosis and management of Spinal Muscular Atrophy: Part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics.

Short title : Diagnosis and management of SMA: Part 2

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## Highlights

- We report an update on standards of care recommendations for spinal muscular atrophy
- The paper provides a review of the recent literature
- Expert opinion is provided where there was not enough published evidence

## Abstract

This is the second half of a two-part document updating the standard of care recommendations for spinal muscular atrophy published in 2007. This part includes updated recommendations on pulmonary management and acute care issues, and topics that have emerged in the last few years such as other organ involvement in the severe forms of spinal muscular atrophy and the role of medications. Ethical issues and the choice of palliative versus supportive care are also addressed. These recommendations are becoming increasingly relevant given recent clinical trials and the prospect that commercially available therapies will likely change the survival and natural history of this disease.

Accepted Manuscript

## Introduction

This is the second part of a two-part document aimed at updating the standards of care recommendations published in 2007.[1] Included here is an update of some of the topics included in the earlier publication, such as respiratory management, but also topics that were only described briefly in the original publication, such as acute care, other organ involvement and ethical issues. Recent clinical trials[2, 3] and the approval in December 2016 by the United States Food and Drug Administration, and subsequently in May 2017 by the European Medicine Agency, of the first drug for SMA have led to include a review of 'medication' in order to provide the state of art on the medications that have been used in the last decade, and a brief update on the new therapeutic approaches that are becoming available. This update also takes into consideration how the impact of new therapies is changing the attitude of families and physicians towards a more proactive approach, especially in type 1 Spinal muscular atrophy (SMA). As with the first part, this update includes the results of dedicated working groups of experts in each topic, who, after a thorough review of the literature, used a Delphi analysis process to identify areas where evidence could be extrapolated from the literature and establish whether consensus could be reached among experts. Details of the methodology used are available in the first part and in a recent workshop report.[4]

## Pulmonary management

It is well known that spinal muscular atrophy has an impact on the respiratory system that is dependent in large part on the type of SMA or more precisely the severity of loss of muscle function.[5]

### NON-SITTERS

#### Assessment

The focus of the clinical assessment should be a physical examination (table 1). Screening non-sitters for respiratory failure should include assessment with pulse oximetry and capnography (end tidal CO<sub>2</sub> (EtCO<sub>2</sub>) or transcutaneous CO<sub>2</sub> (TcCO<sub>2</sub>)) when awake), and using sleep study or pneumogram with CO<sub>2</sub> recording when there is even minimal suspicion of hypoventilation. Data from the literature and expert opinion supports using a sleep study to confirm when a patient has sleep disordered breathing or respiratory failure and needs to use non-invasive positive pressure ventilation (NIV).[6]

Clinic visits are recommended initially for every 3 months for non-sitting patients with SMA.

#### Intervention

Over the last decade, the approach to treating the pulmonary manifestations of SMA has shifted from a reactive approach, of starting treatment to support airway clearance and ventilation only when there is a clear indication, to a proactive approach of introducing these therapies earlier in the disease process.[7] (Figure 1). A respiratory therapist should be involved to initiate and support assisted airway clearance and respiratory range of motion therapy.

*Airway Clearance:*

Manual chest physiotherapy combined with mechanical insufflation-exsufflation (e.g., Cough Assist® or VitalCough®) should be the primary mode of airway clearance therapy and should be made available to all non-sitters (table 1). Because of the importance of aggressive management of respiratory illnesses,[6, 8-12] airway clearance techniques should be introduced proactively in patients based on either clinical assessment of cough effectiveness or by measuring peak cough flow (not a routinely performed test in infants).[6] When initiating cough assist devices, the insufflation and exufflation pressures should be increased gradually to 30-40 cm H<sub>2</sub>O of positive or negative pressure, respectively,[10] or instead increasing to the maximal tolerated pressure.

In the absence of significant parenchymal lung disease with small airway obstruction and air trapping there is no significant risk of pneumothorax in using the cough assist. While there is the potential of aerophagia and gastric distention in using the cough assist, this risk and the subsequent risk of aspiration can be mitigated in GTube venting to prevent gastric distention.

While there are case reports suggesting the use of mechanical insufflation or NIV to help prevent chest wall distortion,[10, 13, 14] there was less consensus whether this is always a reasonable expectation and on the specifics of how to best accomplish this (supplementary table 1).

Oral suctioning with a mechanical suction pump and catheter is a critical part of airway clearance in non-sitters and should be used with any patient with an ineffective cough.

The high frequency chest wall oscillation (Vest) therapy does not improve clearance of secretions in the setting of an ineffective cough or improve clearance of secretions.

*Ventilation:*

Non-invasive positive pressure ventilation (NIV) should be used in all symptomatic infants,[8-10, 14, 15], and in non-sitters prior to signs of respiratory failure, to be “prepared” for respiratory failure, prevent/minimize chest wall distortion, and palliate dyspnea.

Continuous positive airway pressure (CPAP) should not be used to treat chronic respiratory failure, but may be used with caution temporarily to help maintain resting lung volume (functional residual capacity (FRC)) in younger patients who are unable to synchronize with the ventilator in NIV mode, and who are not markedly hypercapnic. This applies also to weak non-sitters. It should be recognized that CPAP may fatigue SMA patients and could interfere with weaning from full time use.

Interface selection and fitting to the patient by an experienced clinician is strongly recommended, as was using at least two comfortable interfaces with different facial contact points, and using a nasal interface initially. In non-sitters there is strong support for initiating NIV using clinical titration with focus on correcting gas exchange and reducing the work of breathing.

Tracheotomy ventilation is an option in selected patients in whom NIV is insufficient or fails, or if there is no effective interface for providing ventilation. This should be a decision focused individually on the clinical status, prognosis, and quality of life based on discussion with the family.

*Medications:*

Nebulized bronchodilators should be available if there is suspicion for asthma. Nebulized mucolytics, 3% or 7% hypertonic saline or dornase- $\alpha$  (Pulmozyme<sup>®</sup>) should not be used chronically as there is no evidence to support its use. Furthermore, if 3% or 7% saline is used beyond the therapeutic need it can thin secretions of normal viscosity thereby increasing secretion burden. Glycopyrrolate should be used with caution to treat hypersalivation with great care to adjusting the dose to attain the proper effect, and avoiding over drying of secretions, which may contribute to the development of mucus plugs. There was no consensus for the injection of botulinum toxin into the salivary glands or other methods to reduce production of oral secretions. Palivizumab should be given during RSV season as determined by regional RSV activity through the first 24 months of life, and influenza vaccination should be administered annually after 6 months of age. Gastroesophageal reflux should be searched for and treated when present.

## SITTERS

## Assessment

The focus of the clinical assessment should be a physical examination supported by clinical assessment of cough function. For sitters and standers, there is consensus that all patients able to perform spirometry should do so during each visit.

There was no clear consensus on the value of peak cough flow measurement or when a sleep study should be performed in the management of sitters. A sleep study should always be performed, however, in symptomatic patients or when there is even a minimal suspicion of nocturnal hypoventilation to determine when a patient has sleep disordered breathing or respiratory insufficiency and needs to use bilevel NIV.[6]

Clinic visits are recommended, every 6 months for sitters.

## Intervention

### *Airway Clearance:*

Manual chest physiotherapy combined with mechanical insufflation-exsufflation (e.g., Cough Assist® or VitalCough®) should be made available to all patients with an ineffective cough. It should be introduced proactively in patients using either clinical assessment of cough effectiveness or by measuring peak cough flow.[6] The issues related to settings are similar to those described for non-sitters.

### *Ventilation:*

Similar to non-sitters, non-invasive positive pressure ventilation (NIV) should be used in all symptomatic patients.[8-10, 14, 15] The best approach is individualized to each patient's need and quality of life. A sleep study should be used to determine when a patient has sleep disordered breathing or respiratory failure and needs to use bilevel NIV, and to titrate settings.[6] (figure 1)

As reported for non-sitters, continuous positive airway pressure (CPAP), with rare exceptions, should not be used.

The need for tracheostomy ventilation is less frequent than in non-sitters but in some weak sitters bilevel NIV can be insufficient or fail. As for non-sitters this should be a decision based on clinical status and discussion with the family and patient, if age-appropriate.

### *Medications:*

Nebulized bronchodilators should be available if there is high suspicion for asthma or a clear clinical improvement after administration. Nebulized mucolytics should not be used

chronically. Annual influenza and pneumococcal immunizations should be administered per standard pediatric recommendations for patients with chronic neuromuscular conditions.

## WALKERS

### Assessment.

Most ambulant patients with SMA type 3 have normal pulmonary function, but with a small decline noted over a 4-year span in one natural history study. [5, 16] Nonetheless, the clinical assessment of these patients should include careful review of cough effectiveness with an upper respiratory infection, and search for any symptoms of sleep apnea or hypoventilation (snoring, arousals, morning headaches, daytime somnolence). The presence of any such concerns should prompt an assessment by a pulmonologist with consideration of pulmonary function testing and sleep study. Pre-operative assessment is also important.

### Intervention

No pro-active interventions are indicated for ambulant patients with SMA. Supportive care should be provided when there are specific concerns identified in the clinical assessment. Immunizations are the same as for Sitters.

Acute Care Management
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Acute care for children and adults with SMA expands upon the vigilant respiratory and multidisciplinary care recommended for outpatient management. Individuals affected by SMA are particularly vulnerable to acute respiratory decompensation, related to

community-acquired infections, aspiration, and impaired secretion clearance[1, 17, 18]. Baseline diffuse muscle weakness is often exacerbated during illness. Associated increased metabolic demands with insensible fluid losses necessitate additional consideration of appropriate nutritional support and avoiding fasting.[19-21] Acute hospitalization may be required to support those with SMA experiencing the range of routine illnesses (e.g., viral respiratory infection, gastroenteritis with dehydration, and appendicitis among other acute processes), unanticipated bone fracture management, labor and delivery for women with SMA, and scheduled surgical procedures (e.g., gastrostomy tube placement, femoral osteotomies, and spinal instrumentation along with other preventative strategies, supportive interventions, or symptom management). Extensive consideration is required, whether admission is planned or unanticipated at the individual's primary neuromuscular care hospital or other institution (table 2). The following considerations were devised mainly for non-sitters and sitters but some aspects may also be applied to weak ambulant type 3 children and adults who also often present some degree of respiratory impairment or nutritional issues and are at higher risk during acute illness (supplementary table 2).

#### *Assessment and management of acute illness at home*

Individualized anticipatory care plans should be developed and include review of vital signs (e.g., oxygen desaturation and tachycardia) and symptom parameters and prompting escalation of care with specific recommendations for airway clearance, ventilation, nutrition, hydration, antibiotics, and emergency contact measures (table 2).

Patient-specific protocols should be created based upon community resources, emergency medical services, and hospital capacity to provide for children and adults with SMA and other neuromuscular conditions.

When appropriate, families should be provided with homecare technology for monitoring respiratory function and providing related support, such as augmented secretion clearance, bilevel NIV to prevent hospitalization, and to optimize status prior to presentation. This equipment, when available, should be brought by the family for possible use during transport.

As part of the anticipatory care, discussions with families about the options for both chronic and acute respiratory care should occur early in the disease course and written anticipatory resuscitation statements prepared with the family should be available for any professional involved in the transport or in the emergency room. Similarly, families should have a list of medical needs and neuromuscular providers including pulmonology/respirology.

Criteria for presentation to emergency care should include severity of acute clinical signs and symptoms in relation to capacity and limitations of homecare technology and providers.

*Transport from home to a medical facility considerations and emergency department evaluation*

Hospitalization care considerations should include site or level of care, degree of illness, and goals of care including need for respiratory protocols, nutrition and hydration. Non-sitters and sitters should be triaged to tertiary care centers with SMA expertise. Presentation to the closest facility should be considered based upon the goals of care, distance from a tertiary facility, availability of pediatric transport team, and other aspects such as environmental considerations.

Engagement of the neuromuscular team providers during acute care is critical.

Emergency medical services should be provided by certified staff who have the capacity to provide the most appropriate level of ventilation and cardiac and respiratory life support.

Mode of transportation between home and acute care facility should be considered on a case-by-case basis involving the neuromuscular team.

#### *Medical care site/Hospital capacity considerations*

Respiratory assessment and support should be of highest priority[22-25] (table 3).

Management should include proactive measures including optimizing use of bilevel positive airway pressure (i.e., NIV, not CPAP) respiratory support with a backup respiratory rate (delivered via noninvasive measures, tracheostomy, or endotracheal tube) and augmented secretion clearance prior to empiric oxygen supplementation.

Oxygen supplementation should not be provided empirically in the absence of NIV or without monitoring CO<sub>2</sub> gas exchange. Oxygen supplementation should not be withheld, but weaned to minimal provision prior to extubation and not employed in lieu of positive pressure ventilatory support.

The multidisciplinary team (neuromuscular and respiratory) should be contacted to assist with acute care protocols, involving the physician, generally the neurologist or pediatric neurologist, who is aware of the disease course and potential issues.[26, 27] Family should be involved.[28, 29]

As reported in the Nutritional Care Section, during acute illness, fasting should be avoided to prevent metabolic acidosis, hyper/hypoglycemia or fatty acid metabolism abnormalities [20, 21, 30-32]. Adequate hydration and electrolyte balance are imperative.

Attention should be paid to the risk of aspiration, when orally feeding a weaker child during illness.

Criteria establishing the threshold for endotracheal intubation should be established taking into account several factors including limited neck and mandibular mobility, and positioning restrictions and patient and family preference.

Extubation criteria and procedure should be established (see supplementary table 3).

There is no clear evidence to support empiric use of antibiotics or volume resuscitation (except for sepsis management in the general population) during acute illness or to guide viral testing or other diagnostics. For these issues, providers should consider presentation characteristics, the presence of indwelling devices and history of recent surgical interventions, and recurrent antibiotics.

Integration of physical and occupational therapy, psychosocial services, speech-language pathologist, palliative care services and Endocrinology consultants can contribute to other aspects of care such as skin care or bone fracture risk.

#### *Hospital Discharge considerations*

Discharge planning should begin shortly after admit to identify goals with the patient/family, inpatient team, and primary care providers. Planning should consider threshold for discharge, need to augment outpatient services, follow-up care, and indications for urgent re-hospitalization. Threshold for discharge based on medical status will depend on the comfort and skill of family and outpatient medical care team.

*Preprocedural screening[33], anesthesia / sedation consideration[34, 35] and pain management*

Polysomnograms, and nutritional assessment may be considered as part of a pre-anesthetic evaluation. Cardiology screening is not recommended, unless there is a concern for cardiac dysfunction in older individuals or conditions unrelated to SMA. Difficult airway status should be considered based upon mandibular contractures, limited neck mobility, positioning restrictions and other factors. A low threshold for deferring elective/non-emergent sedation/anesthesia should be considered during intercurrent illness across all SMA Types. Opiate-based analgesia should be considered as part of routine post-procedural management with anticipation of providing appropriate NIV and cough assistance.

Regional analgesia may be considered for all SMA Types and may allow for lower amounts of systemic analgesics with subsequent effects on respiratory drive and intestinal motility. Practical consideration must be taken into account when evaluating for epidural catheter placement in context of pre-existing scoliosis. Monitoring during procedural sedation and anesthesia should include capnography to complement oximetry, as apneic or hypopneic oxygenation should be avoided.

Additional recommendations not addressed in the Delphi survey include consideration of delivery of novel gene-targeted therapies and other interventions for individuals with SMA. For example, provision of repeated intrathecal drug therapies such as recently approved antisense oligonucleotides will require extensive planning for developmentally appropriate and safe care, including procedural sedation, interventional radiology support, and potential orthopedic considerations. The anticipated emergence of gene replacement with viral vectors and other disease/symptom modifying agents may also require extensive acute care supports. Understanding that the natural history of this condition and recognized phenotypes will be altered should prompt all providers (acute,

chronic, hospital-based, or community) to engage accordingly in informed discussions and adjustment of the acute care paradigm.

#### Medication, Supplements and Immunizations

Until recently no drug treatment had proved to be able to influence the disease course of SMA. A Cochrane review published in 2012 reported six randomized placebo-controlled trials on treatment for SMA using creatine, phenylbutyrate, gabapentin, thyrotropin releasing, hydroxyurea and combination therapy with valproate and acetyl-L-carnitine[36, 37]. None of these studies showed statistically significant effects on the outcome measures in participants with SMA types 2 and 3. Others have reported using other possible therapeutic approaches, such as albuterol, a beta-adrenergic agonist that showed promising functional improvements in open label studies [38] [39].

Despite the lack of evidence from randomized placebo-controlled trials, some of these drugs, especially albuterol, are often used in some countries in clinical practice in sitters and ambulant patients.

Antibiotics or medications/supplements for bone health, such as vitamin D and calcium and bisphosphonate, or drugs for gastroesophageal reflux, were recommended but with the exceptions of vitamin D, were rarely used prophylactically, and were mainly used if needed/deficient. These are discussed in the sections dedicated to bone health and nutrition. Annual influenza and pneumococcal immunizations, as reported in the pulmonary section, were strongly recommended.

At the time the consensus process was completed, none of the drugs involved in clinical trial had completed the regulatory process and were commercially available. Nusinersen

(Spinraza™), an antisense oligonucleotide that had completed phase 3 clinical trials in both type 1 and type 2 SMA,[3, 40, 41] received recent approval both by the United States Food and Drug Administration and by the Agency for Medicines Agency in Europe for the treatment of all SMA types and has become commercially available in several countries. While the early patient and family clinical outcomes have been very favourable, because it is intrathecally administered, there is a required institutional infrastructure to provide administration and post-procedural monitoring in a reliable way. In addition the cost of the medication has made long term insurance company approval uncertain.

Olesoxime, a neuroprotective drug, has completed a phase 3 trial in patients with type 2 and 3 SMA, but the primary endpoint was not met. Secondary endpoints and sensitivity analyses indicate that olesoxime might maintain motor function in patients with SMA [42]. Other approaches, such as small molecules aiming to increase SMN protein level or *SMN1* gene replacement using viral vector, are also being used in clinical trials with promising preliminary results [43] and in the next few years the scenario is likely to rapidly change.

#### Other Organ System Involvement

SMA is primarily a motor neuron disease but the deficient SMN protein is ubiquitously expressed in all cells throughout fetal and post-natal development. [44-46] Therefore, there is ongoing discussion as to what extent other tissues might be affected in patients with SMA. Several animal models and some case reports or small case series report involvement of other organ systems, such as peripheral nerve, brain, muscle, heart, vasculature, and pancreas (for review see [47-50]). While the involvement of other tissues might have implications for therapeutic approaches, only a minority of patients with SMA shows clear clinical manifestation of other organ involvement.

Hemodynamically relevant cardiac defects have been reported in very severely affected infants with SMA type 1. Recent reviews of the literature [50, 51] identified a number of cases with congenital heart defects such as atrial or ventricular septal defects. All of these patients showed the severe neonatal onset, also indicated as type 0, with respiratory distress at birth. They all had only a single copy of *SMN2*. [51] In long-term survivors with type 1 SMA receiving ventilatory support, 15 of 63 patients (24%) had severe, symptomatic bradycardia, suggesting a possible concomitant autonomic dysfunction. [52]

Cardiac involvement in contrast is much less frequent in types 2 and 3 SMA. There are some reports of heart rate abnormalities in type 3 SMA. [53, 54] Recent studies performed in type 2 and 3 SMA, suggested that there is no need for regular cardiac surveillance in type 2 and type 3 patients as it is highly unlikely that these patients will develop obvious clinical, ECG or echocardiographic signs of cardiomyopathy [33, 55].

As reported in the part on nutritional care, occasional cases of pancreatic dysfunction including diabetes and alterations in glucose metabolism have been reported in SMA patients. [56] Hyperleptinemia has been identified in SMA patients with types 1, 2 and 3. [57] Mitochondrial dysfunction has been described in patients and human neuronal cell lines. [21, 58, 59]

There was consensus among the experts that specific surveillance testing for other organ involvement should generally be based on clinical symptoms and is thus not necessary in most patients. Possible exceptions are the exclusion of cardiac defects in severely affected infants with SMA type 1 and monitoring glucose metabolism in all types of SMA. Despite immobilisation of many patients with SMA prophylactic anticoagulation is not deemed necessary in the absence of additional risk factors.

As intrathecal administration of nusinersen principally targets motor neurons[40], concerns have arisen that other non-central nervous system tissues may subsequently demonstrate symptoms or signs of dysfunction due to deficiency of SMN protein. Motor impairment may be alleviated while other symptoms arise. It is recommended that patients treated with nusinersen be monitored for these potential systemic concerns.

#### Ethical Considerations

The application of palliative care along with its attendant ethical challenges was the focus of an international interdisciplinary group that included clinicians, bioethics researchers, parents and patient representatives, and pediatric palliative care specialists.

The previous version of the standards of care guidelines[1] highlighted the lack of consensus and the controversies on palliative versus interventional approaches. In the absence of therapy a number of families perceived the interventional approach, especially tracheostomy, as placing quality of life in conflict with duration of life, prolonging suffering rather than relieving the burden of disease.[26, 52, 60, 61] The previous committee reached consensus that while there was no moral imperative to any therapy, there was a deep responsibility to present care options in a fair and balanced manner, providing accurate information that the choice for palliative or interventional supportive care was not an exclusive binary choice.

The update of the literature review provided little additional hard evidence and no consensus regarding standards of palliative care as applied to SMA[62-65]. The working group was, therefore, still unable to establish a consensus for palliative care and could only acknowledge the substantive ethical issues that must attend care decisions in the context of SMA, now

also in the light of the most recent therapeutic approaches. The group identified 3 key areas for future analysis; 1) The concept of palliative care as applied to SMA, 2) Patient management and decision-making, 3) Managing expectations.

Although the concept of palliative care has been defined and re-interpreted many times there is a need to regard this as an ongoing reflexive process especially when applied to contexts like SMA that are not static[66]. SMA in all of its degrees of severity does not fit a model of a condition with a relentlessly ingravescent course.[67, 68] The recent availability of new therapies has created substantial reasons to hope for changes in prognosis, but several issues are in need of further clarification before a move to a standard for palliative care in SMA can be achieved.[40, 41] notably, the need to address the meaning of palliative care for the SMA community. Despite recent trends that have emphasized the role of palliative care to focus upon improving quality of life, with a point of entry well 'upstream' within the disease trajectory, there is still an association of palliative care with end of life care. There is therefore a need to support a change of culture, which sees palliative care as having a role alongside the treatment of chronic debilitating conditions that have a long prognosis. A key challenge is thus to dismiss the dichotomous model, which sets active treatment against palliative care in favour of a model of complementarity. Ethical challenges will doubtless still persist, requiring both clinical evidence and good judgment to manage. One such concern is the challenge of managing the burden of care when the 'therapeutic ratio' between side-effects and benefits must be balanced. A second is managing the phases of transition across the disease trajectory, points at which advancing disease signals a transition in favour of palliative care and the cessation of life-extending treatments.[69] The challenge of managing expectations in this fluid context, especially where expectations are shaded by many and conflicting opinions, adds further complexity to the task of establishing a standard of care.

Resource limitations and cultural differences need also to be considered especially as variable access to resources across the globe will mean that inequalities are inevitable.

New issues about the choice of palliative care in patients enrolled in clinical trials are also emerging[70]. A recent survey among physician investigators, clinical evaluators, and study coordinators from different countries endorsed the concept that having a predefined degree of nutritional and ventilation support was warranted in this context.

## Conclusions

Spinal muscular atrophy presents with a diverse range of phenotypes of motor impairment and related comorbidities. Effective and efficient management of the patient with SMA requires coordination of multiple clinical specialists to address both current concerns and anticipated ones. These updated standard of care considerations have been developed to provide current expert opinion on necessary care and, where appropriate, optimal management. When reviewing the results, we were surprised by the discrepancy between the literature and the Delphi analysis. Although many advances in multiple aspects of care have been made, and these had a tremendous impact on survival and onset and severity of complications, the literature reporting evidence was scanty. Very few studies provided a level of evidence based on an appropriate design and most papers reported clinical observations and small series. In contrast, despite the paucity of evidence based recommendations, for each topic there was a large expert consensus on many components of SMA care. For many aspects, such as the introduction of early spinal surgery or of cough machine support, most, and often all the experts were convinced of the impact of these recommendations on changing natural history. In these cases it was felt that although large randomised studies would have been preferable to assess more systematically their efficacy, the impact on

natural history before and after their introduction was sufficient to recommend their inclusion in common practice. While this lack of evidence based papers makes it difficult to obtain an accurate estimate of the level of efficacy of individual aspects of care, the unequivocal and recent improvements in survival in type 1 and in the onset of progression in all SMA types validate the impact, collectively, of implementing these interventions.

The ultimate goal of these guidelines is to strive continually to improve quality of life and reduce burden of disease for these patients. While many of these considerations are technology driven, they all begin with a focus on a patient's clinical symptoms and signs and related risk factors. Recommendations are now based upon the current functional status of the patient: non-sitter, sitter and walker. Patient and parental autonomy and ethical dimensions must be respected. These guidelines should thus be applied with attention to individual patient concerns and complexities rather than as strict doctrine. Individual probative issues to consider include patient age, general medical status and extent of supportive care, local availability of clinical expertise, extent of health care provisions, and new treatment options. With the emergence of the first approved medication for treatment of patients with SMA, it is particularly important to meld optimal care with treatments that fundamentally alter the natural history of the disease. This effort identified questions that remain in many areas of supportive care for patients with SMA and will prompt future research. Further research is also needed on other aspects, such as psychiatric and emotional health, or on other aspects related to optimization of daily functioning. As the great majority of the aspects of care are related to the most severe phenotypes that have pediatric onset, further work is also needed to address issues related to the older population, including teenagers and adults. Further work is also needed to identify new models to support families

and physicians to improve local care and reduce the number of visits and admission to tertiary care centers.

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## References

- [1] Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol* 2007;22(8):1027-49.
- [2] Kissel JT, Elsheikh B, King WM, Freimer M, Scott CB, Kolb SJ, et al. SMA valiant trial: a prospective, double-blind, placebo-controlled trial of valproic acid in ambulatory adults with spinal muscular atrophy. *Muscle Nerve* 2014; 49(2):187-92.
- [3] Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med* 2017;377:1723-1732.
- [4] Finkel RS, Sejersen T, Mercuri E, Group ESWS. 218th ENMC International Workshop:: Revisiting the consensus on standards of care in SMA Naarden, The Netherlands, 19-21 February 2016. *Neuromusc Disord* 2017;27:596-605.
- [5] Samaha FJ, Buncher CR, Russman BS, White ML, Iannaccone ST, Barker L, et al. Pulmonary function in spinal muscular atrophy. *J Child Neurol* 1994;9(3):326-9.
- [6] Hull J, Aniapravan R, Chan E, Chatwin M, Forton J, Gallagher J, et al. British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. *Thorax* 2012;67(Suppl 1):1-40.
- [7] Lemoine TJ, Swoboda KJ, Bratton SL, Holubkov R, Mundorff M, Srivastava R. Spinal muscular atrophy type 1: are proactive respiratory interventions associated with longer survival? *Ped Critical Care Med* 2012;13:e161-5.
- [8] Bach JR, Baird JS, Plosky D, Navado J, Weaver B. Spinal muscular atrophy type 1: Management and outcomes. *Pediatr Pulmonol* 2002; 34:16-22.
- [9] Bach JR, Saltstein K, Sinqee D, Weaver B, Komaroff E. Long-Term Survival in Werdnig Hoffmann Disease. *Am J Phys Med Rehabil* 2007; 86:339-345.
- [10] Schroth MK. Special Considerations in the Respiratory Management of Spinal Muscular Atrophy. *Pediatrics* 2009; Suppl 4: S245-S249.
- [11] Gregoretti C, Ottonello G, Chiarini Testa MB, Mastella C, Ravà L, Bignamini E et al. Survival of Patients With Spinal Muscular Atrophy Type 1. *Pediatrics* 2013; 131: e1509-e1514.
- [12] Chiarini Testa MB, Paglietti MG, Pavone M, Schiavino A, Pedace C, Cutrera R. Respiratory problems in spinal muscular atrophy in the paediatric age group. *Paed Child Health*. 2009; 34: S123-S126.
- [13] Bach JR, Bianchi C. Prevention of Pectus Excavatum for Children with Spinal Muscular Atrophy Type 1. *Am J Phys Med Rehabil* 2003; 82: 815-819.
- [14] Ward S, Chatwin M, Heather S, Simonds AK. Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. *Thorax* 2005;60:1019-24.
- [15] Petrone A, Pavone M, Testa MBC, Petreschi F, Bertini E, Cutrera R, Noninvasive Ventilation in Children with Spinal Muscular Atrophy Types 1 and 2, in *Am J Phys Med Rehabil* 2007. p. 216-221.
- [16] Kaufmann P, McDermott MP, Darras BT, Finkel RS, Sproule DM, Kang PB, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. *Neurology* 2012;79:1889-97.
- [17] Hull J, Aniapravan R, Chan E, Chatwin M, Forton J, Gallagher J, et al. British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. *Thorax* 2012;67 Suppl 1:i1-40.

- [18] Sansone VA, Racca F, Ottonello G, Vianello A, Berardinelli A, Crescimanno G, et al. 1st Italian SMA Family Association Consensus Meeting: Management and recommendations for respiratory involvement in spinal muscular atrophy (SMA) types I-III, Rome, Italy, 30-31 January 2015. *Neuromusc Disord* 2015;25:979-89.
- [19] Zolkipli Z, Sherlock M, Biggar WD, Taylor G, Hutchison JS, Peliowski A, et al. Abnormal fatty acid metabolism in spinal muscular atrophy may predispose to perioperative risks. *European journal of paediatric neurology : EJPN* 2012;16:549-53.
- [20] Orngreen MC, Zacho M, Hebert A, Laub M, Vissing J. Patients with severe muscle wasting are prone to develop hypoglycemia during fasting. *Neurology* 2003;61:997-1000.
- [21] Crawford TO, Sladky JT, Hurko O, Besner-Johnston A, Kelley RI. Abnormal fatty acid metabolism in childhood spinal muscular atrophy. *Ann Neurol* 1999;45:337-43.
- [22] Khirani S, Bersanini C, Aubertin G, Bachy M, Vialle R, Fauroux B. Non-invasive positive pressure ventilation to facilitate the post-operative respiratory outcome of spine surgery in neuromuscular children. *Eur Spine J* 2014;23 Suppl 4:S406-11.
- [23] Ottonello G, Mastella C, Franceschi A, Bosticco D, Wolfler A, Pedemonte M, et al. Spinal muscular atrophy type 1: avoidance of hospitalization by respiratory muscle support. *Am J Phys Med Rehabil* 2011;90:895-900.
- [24] Bach JR, Niranjana V, Weaver B. Spinal muscular atrophy type 1: A noninvasive respiratory management approach. *Chest* 2000;117:1100-5.
- [25] Vianello A, Corrado A, Arcaro G, Gallan F, Ori C, Minuzzo M, et al. Mechanical insufflation-exsufflation improves outcomes for neuromuscular disease patients with respiratory tract infections. *Am J Phys Med Rehabil* 2005;84:83-8.
- [26] Hardart MK, Burns JP, Truog RD. Respiratory support in spinal muscular atrophy type I: a survey of physician practices and attitudes. *Pediatrics* 2002;110:e24.
- [27] Geevasinga N, Ryan MM. Physician attitudes towards ventilatory support for spinal muscular atrophy type 1 in Australasia. *J Paed Child health* 2007;43:790-4.
- [28] Graham RJ, Pemstein DM, Curley MA. Experiencing the pediatric intensive care unit: perspective from parents of children with severe antecedent disabilities. *Crit Care Med* 2009;37:2064-70.
- [29] Ottonello G, Mastella C, Franceschi A, Lampugnani E, Moscatelli A, Punch F, et al. Parental role in the Intensive Care Unit for children affected by Werdnig Hoffmann disease. *Minerva Pediatr* 2010;62:147-51.
- [30] Davis RH, Godshall BJ, Seffrood E, Marcus M, LaSalle BA, Wong B, et al. Nutritional practices at a glance: spinal muscular atrophy type I nutrition survey findings. *J Child Neurol* 2014;29:1467-72.
- [31] Tein I, Sloane AE, Donner EJ, Lehotay DC, Millington DS, Kelley RI. Fatty acid oxidation abnormalities in childhood-onset spinal muscular atrophy: primary or secondary defect(s)? *Pediatr Neurol* 1995;12:21-30.
- [32] Bruce AK, Jacobsen E, Dossing H, Kondrup J. Hypoglycaemia in spinal muscular atrophy. *Lancet* 1995;346:609-10.
- [33] Bianco F, Pane M, D'Amico A, Messina S, Delogu AB, Soraru G, et al. Cardiac function in types II and III spinal muscular atrophy: should we change standards of care? *Neuropediatrics* 2015;46:33-6.

- [34] Norton JA, Roy FD, Mahood JK. Preservation of motor evoked potentials under anesthesia in children with spinal muscular atrophy type II undergoing spinal deformity surgery. *J Clin Neurophysiol* 2013;30:382-5.
- [35] Graham RJ, Athiraman U, Laubach AE, Sethna NF. Anesthesia and perioperative medical management of children with spinal muscular atrophy. *Paediatr Anaesth* 2009.
- [36] Bosboom W, Vrancken AF, van den Berg LH, Wokke JH, Iannaccone ST. Drug treatment for spinal muscular atrophy types II and III. *Cochrane Database Syst Rev* 2009:CD006282.
- [37] Wadman RI, Bosboom WM, van der Pol WL, van den Berg LH, Wokke JH, Iannaccone ST, et al. Drug treatment for spinal muscular atrophy type I. *Cochrane Database Syst Rev* 2012;4:CD006281.
- [38] Kinali M, Mercuri E, Main M, De Biasia F, Karatza A, Higgins R, et al. Pilot trial of albuterol in spinal muscular atrophy. *Neurology* 2002;59:609-10.
- [39] Pane M, Staccioli S, Messina S, D'Amico A, Pelliccioni M, Mazzone ES, et al. Daily salbutamol in young patients with SMA type II. *Neuromusc Disord* 2008;18:536-40.
- [40] Chiriboga CA, Swoboda KJ, Darras BT, Iannaccone ST, Montes J, De Vivo DC, et al. Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. *Neurology* 2016;86:890-7.
- [41] Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet* 2016;388:3017-3026.
- [42] Bertini E, Mercuri E, Muntoni F, Kirschner J, Reid C, Lusakowska A, et al. Olesoxime SMA Phase 2 Study Investigators. Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomised, double-blind placebo controlled phase 2 trial. *Lancet Neurol* 2017;16(7):513-522.
- [43] Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *N Engl J Med* 2017;377:1713-1722.
- [44] Coovert DD, Le TT, McAndrew PE, Strasswimmer J, Crawford TO, Mendell JR, et al. The survival motor neuron protein in spinal muscular atrophy. *Hum Mol Gen* 1997;6:1205-14.
- [45] Tizzano EF, Cabot C, Baiget M. Cell-specific survival motor neuron gene expression during human development of the central nervous system: implications for the pathogenesis of spinal muscular atrophy. *A J Pathol* 1998;153:355-61.
- [46] Pellizzoni L, Kataoka N, Charroux B, Dreyfuss G. A novel function for SMN, the spinal muscular atrophy disease gene product, in pre-mRNA splicing. *Cell* 1998;95:615-24.
- [47] Hamilton G, Gillingwater TH. Spinal muscular atrophy: going beyond the motor neuron. *Trends Mol Med* 2013;19:40-50.
- [48] Shababi M, Lorson CL, Rudnik-Schoneborn SS. Spinal muscular atrophy: a motor neuron disorder or a multi-organ disease? *J Anat* 2014;224:15-28.
- [49] Shababi M, Habibi J, Yang HT, Vale SM, Sewell WA, Lorson CL. Cardiac defects contribute to the pathology of spinal muscular atrophy models. *Hum Mol Genet* 2010;19:4059-71.

- [50] Lorson CL, Rindt H, Shababi M. Spinal muscular atrophy: mechanisms and therapeutic strategies. *Hum Mol Genet* 2010;19:R111-8.
- [51] Rudnik-Schoneborn S, Heller R, Berg C, Betzler C, Grimm T, Eggermann T, et al. Congenital heart disease is a feature of severe infantile spinal muscular atrophy. *J Med Gen* 2008;45:635-8.
- [52] Bach JR. Medical considerations of long-term survival of Werdnig-Hoffmann disease. *Am J Phys Med Rehabil* 2007;86:349-55.
- [53] Takahashi N, Shimada T, Ishibashi Y, Sugamori T, Hirano Y, Oyake N, et al. Cardiac involvement in Kugelberg-Welander disease: a case report and review. *A J Med Sci* 2006;332:354-6.
- [54] Elkohen M, Vaksmann G, Elkohen MR, Francart C, Foucher C, Rey C. [Cardiac involvement in Kugelberg-Welander disease. A prospective study of 8 cases]. *Arch Mal Coeur Vais* 1996;89:611-7.
- [55] Palladino A, Passamano L, Taglia A, D'Ambrosio P, Scutifero M, Cecio MR, et al. Cardiac involvement in patients with spinal muscular atrophies. *Acta Myol* 2011;30:175-8.
- [56] Bowerman M, Swoboda KJ, Michalski JP, Wang GS, Reeks C, Beauvais A, et al. Glucose metabolism and pancreatic defects in spinal muscular atrophy. *Ann Neurol* 2012;72:256-68.
- [57] Kolbel H, Hauffa BP, Wudy SA, Bouikidis A, Della Marina A, Schara U. Hyperleptinemia in children with autosomal recessive spinal muscular atrophy type I-III. *PloS one* 2017;12:e0173144.
- [58] Acsadi G, Lee I, Li X, Khaidakov M, Pecinova A, Parker GC, et al. Mitochondrial dysfunction in a neural cell model of spinal muscular atrophy. *J Neurosci Res* 2009;87:2748-56.
- [59] Xu CC, Denton KR, Wang ZB, Zhang X, Li XJ. Abnormal mitochondrial transport and morphology as early pathological changes in human models of spinal muscular atrophy. *Dis Models Mech* 2016;9:39-49.
- [60] Bach JR. Threats to "informed" advance directives for the severely physically challenged? *Arch Phys Medicine Rehab* 2003;84:S23-8.
- [61] Sakakihara Y. Ethical attitudes of Japanese physicians regarding life-sustaining treatment for children with severe neurological disabilities. *Brain Dev* 2000;22:113-7.
- [62] Roper H, Quinlivan R, Workshop P. Implementation of "the consensus statement for the standard of care in spinal muscular atrophy" when applied to infants with severe type 1 SMA in the UK. *Arch Dis Child* 2010;95:845-9.
- [63] Cuisset JM, Estournet B, French Ministry of H. Recommendations for the diagnosis and management of typical childhood spinal muscular atrophy. *Revue neurologique* 2012;168:902-9.
- [64] Mitchell I. Spinal muscular atrophy type 1: what are the ethics and practicality of respiratory support? *Paed Resp Reviews* 2006;7 Suppl 1:S210-1.
- [65] Garcia-Salido A, de Paso-Mora MG, Monleon-Luque M, Martino-Alba R. Palliative care in children with spinal muscular atrophy type I: What do they need? *Palliative & supportive care* 2015;13:313-7.
- [66] Woods S, Death's Dominion: ethics at the end of life. *Facing Death Series*, ed. Clark D. 2007: Open University Press.

- [67] Chung BH, Wong VC, Ip P. Spinal muscular atrophy: survival pattern and functional status. *Pediatrics* 2004;114:e548-53.
- [68] Farrar MA, Vucic S, Johnston HM, du Sart D, Kiernan MC. Pathophysiological insights derived by natural history and motor function of spinal muscular atrophy. *J Ped* 2013;162:155-9.
- [69] Lovgren M, Sejersen T, Kreicbergs U. Parents' Experiences and Wishes at End of Life in Children with Spinal Muscular Atrophy Types I and II. *J Ped* 2016;175:201-5.
- [70] Finkel RS, Bishop KM, Nelson RM. Spinal Muscular Atrophy Type I: Is It Ethical to Standardize Supportive Care Intervention in Clinical Trials? *J Child Neurol* 2017;32:155-160.
- [71] American Academy of Pediatrics Steering Committee on Quality I, Management. Classifying recommendations for clinical practice guidelines. *Pediatrics* 2004;114:874-7.

Figure 1: Respiratory clinical algorithm.

(REM: rapid eye movements; NREM, non REM; FVC: forced vital capacity)

Table 1. Pulmonary assessment, intervention and management recommendations.

	Assessment	Intervention	Care considerations
NON-SITTERS	<p>Physical examination Assessment of hypoventilation (End tidal CO<sub>2</sub>)</p> <p>Sleep study or pneumograms in all symptomatic patients or to determine if a patient needs to initiate NIV</p> <p>Clinical assessment of gastroesophageal reflux</p>	<p>Support airway clearance Oral suctioning Physiotherapy/respiratory therapy should be implemented immediately: Manual chest therapy Cough insufflator /exufflator</p> <p>Support ventilation with bilevel NIV in symptomatic patients</p> <p>Nebulized bronchodilators in patients with asthma or a positive bronchodilator response</p> <p>Customary immunizations, palivizumab through 24 months, influenza vaccination annually after 6 months of age</p>	<p>Assessments should be performed at least every 3 months initially, then every 6 months Supporting airway clearance with oronasal suctioning, Physiotherapy/respiratory therapy and cough assist is critical to all non sitters with ineffective cough</p> <p>Ventilation should be started in all symptomatic patients. Some experts recommend to use it before documented respiratory failure to palliate dyspnea. This should be judged on individual basis</p> <p>NIV should be initiated observing the patient clinically for adequate gas exchange or during a sleep study.</p> <p>NIV interfaces should be fitted by skilled physiotherapists selecting two interfaces with different skin contact points.</p> <p>Mucolytics should not be used chronically</p>
SITTERS	<p>Physical examination</p> <p>Spirometry (when possible depending on age and cooperation)</p> <p>Sleep study or pneumograms in all patients with even minimal suspicion of symptoms of nocturnal hypoventilation</p> <p>Assessment of gastroesophageal reflux</p>	<p>Support airway clearance Physiotherapy/respiratory therapy should be implemented immediately: Manual chest physiotherapy Cough insufflator /exufflator</p> <p>Support ventilation with bilevel NIV in symptomatic patients</p> <p>Nebulized bronchodilators in patients with suspicion of asthma</p> <p>Customary immunizations, annual influenza and pneumococcal vaccination</p>	<p>Assessments should be performed every 6 months</p> <p>Supporting airway clearance is critical to all patients with ineffective cough</p> <p>Ventilation should be started in all symptomatic patients. Some experts recommend using it during acute respiratory illnesses to facilitate discharge.</p> <p>NIV should be initiated during a sleep study or observing the patient clinically for adequate gas exchange.</p> <p>NIV interfaces should be fitted by skilled physiotherapists selecting two interfaces to alternate skin contact points.</p> <p>Mucolytics should not be used chronically</p>
AMBULANT	<p>Clinical examination with review of cough effectiveness and detailed search for signs of nocturnal hypoventilation</p>	<p>Supportive care when needed</p> <p>Customary Immunizations, annual influenza and pneumococcal vaccination</p>	<p>Evidence of weak cough or recurrent infections or suspicion of nocturnal hypoventilation should prompt referral to a pneumologist</p>

Table 2. Acute care goals, intervention strategies and management

recommendations: home care and transportation

HOME CARE SETTING	<p>Individualized anticipatory care plans should be developed and outline:</p> <ul style="list-style-type: none"> <li>• airway clearance,</li> <li>• ventilation,</li> <li>• nutrition,</li> <li>• hydration,</li> <li>• antibiotics,</li> <li>• emergency contact measures</li> </ul> <p>General assessment and review of signs and symptoms</p> <p>Criteria/thresholds for presentation to emergency care</p> <p>Communication for EMS and acute care providers</p>	<p>Augmented secretion clearance, bilevel NIV, and oxygen supplementation should be provided to prevent hospitalization and/or optimize status prior to presentation</p> <p>Local emergency services should be made aware of the individual's needs in advance.</p> <p>Respiratory assessment and support should be of highest priority independent of hospitalization indication</p> <p>Criteria should include severity of clinical signs and symptoms in relation to capacity of homecare providers (nursing and family), limitations of homecare technology (support and monitoring)</p> <p>Families should have a summary of medical needs, list of primary providers, care protocols, and written anticipatory resuscitation statement available.</p>
COMMUNITY FIRST RESPONDERS/ TRANSPORTATION	<p>Community first responders</p> <p>Modality of transportation</p> <p>EMS triage</p> <p>Hospital level</p> <p>Personal medical equipment during transport</p>	<p>EMS should be provided by staff with advanced cardiac life support or equivalent certification and who have the capacity to provide noninvasive and transtracheal ventilation for Types I and II individuals.</p> <p>Mode of transportation between home and acute care facility should be considered on a case-by-case basis</p> <p>Presentation to the closest facility should be considered based upon the individual's degree of illness, distance from a tertiary care facility, availability of pediatric transport team, environmental considerations, and goals of care.</p> <p>Children and young adults with SMA I or II should be hospitalized at a tertiary care center, whether scheduled or emergent.</p> <p>The family should bring home equipment (e.g., NIV, cough assist device, mask interfaces, suction machine, oximeter, gastrostomy adaptors) for use during transport</p>

(NIV: non-invasive ventilation (bi-level positive air way pressure, not continuous

positive airway pressure; EMS: emergency medical services, SMA: spinal muscular

atrophy)

Table 3. Acute care goals, intervention strategies and management

recommendations: Hospital, and sedation/anesthesia. ( NIV: non-invasive ventilation (bi-level positive air way pressure, not continuous positive airway pressure; SMA: spinal muscular atrophy)

HOSPITAL	<p>Goals of care</p> <p>Respiratory Care Protocols</p> <p>Augmented secretion clearance</p> <p>Respiratory support in the Emergency Room</p> <p>Role of the consultant team</p> <p>Endotracheal intubation</p> <p>Extubation criteria</p>	<p>Goals of care, including resuscitation status, health care proxy (when age appropriate), indications and role of tracheostomy tubes, and other interventions, should be specified prior to the need for acute care. If not, the consultant teams should be engaged to facilitate discussion with the acute care team and family.</p> <p>Early and aggressive respiratory protocols should be implemented. Emphasis should include proactive measures, noninvasive supports use of positive pressure and augmented secretion clearance prior to empiric oxygen supplementation</p> <p>Augmented secretion clearance should be the priority during acute respiratory illness</p> <p>Noninvasive respiratory supports should be instituted early</p> <p>Oxygen supplementation should not be provided empirically in the absence of bilevel NIV.</p> <p>Acute care providers should contact consultant providers (e.g., neuromuscular, respiratory) to assist with acute care protocols.</p> <p>Threshold for endotracheal intubation should be established at the outset of an admission. Difficult airway status should be considered based upon mandibular contractures, limited neck mobility, positioning restrictions and other factors.</p> <p>If pulmonary consolidation was demonstrated on radiograph, re-expansion should be established prior to extubation. NIV should be implemented as transitional support following extubation. Oxygen supplementation should be weaned to minimal provision prior to extubation and not employed in lieu of positive pressure ventilation.</p>
SEDATION AND ANESTHESIA	<p>Pre-anesthetic / sedation evaluation</p> <p>Pre-anesthetic studies</p>	<p>Sedation and anesthesia should be provided at a tertiary care center familiar with SMA management</p> <p>Consultation with respiratory providers, consultant team, and an anesthesiologist familiar with SMA should be obtained prior to sedation or general anesthesia.</p> <p>Discussions should include options of noninvasive and invasive airway support.</p> <p>A low threshold for deferring elective / non-emergent sedation/anesthesia should be considered during intercurrent illness across all SMA Types.</p> <p>Cardiology screening, polysomnograms, and nutritional assessment might be considered as part of</p>

	<p>Sedation/anesthesia</p> <p>Post-sedation and anesthesia management</p> <p>Analgesia provision</p>	<p>a pre-anesthetic evaluation</p> <p>Respiratory supports (i.e., NIV and cough assist) might be introduced prior to sedation and anesthesia to optimize pre-procedural standing and for desensitization.</p> <p>A monitored setting should be considered Monitoring should include capnography.</p> <p>Aggressive secretion clearance measures (cough assist when intubated and extubated) should be integral to post-anesthetic care.</p> <p>Excessive oxygen supplementation in lieu of positive pressure and extubation to NIV should be avoided.</p> <p>Opiate-based analgesia should be considered as part of routine post-procedural management. Regional analgesia might be considered for all SMA Types.</p>
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Supplementary table 1: Pulmonary care and recommendations: The American Academy of Pediatrics guidelines for classifying recommendations for clinical practice [71] was used as the basis for determining the aggregate evidence quality for all the working groups. B represents data from randomized controlled trials or diagnostic studies with minor limitations or overwhelmingly consistent evidence from observational studies; C represents observational studies (case control and cohort design); and D represents expert opinion, case reports, and reasoning from first principles. The level of consensus of the acute care working group is listed as strong, moderate, divided or lack of consensus. The estimated degree of impact of implementing the recommended intervention is listed as high, mid or low.

Supplementary table 2: Acute care topics and recommendations.

(EMS: emergency medical services; NMD: neuromuscular disease)

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Pulmonary	Oscar Henry Mayer (USA) Anita Simonds (UK)	Jonathan Finder (USA) Richard Kravitz (USA) Hemant Sawnani (USA) Richard Shell (USA) Nanci Yuan (USA) Brigitte Fauroux (France) Uwe Mellies (Germany) Renato Cutrera (Italy) Dominic Fitzgerald (Australia)
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Other organ system involvement	Susan Iannaccone (USA) Janbernd Kirschner (Germany)	Enrico Bertini (Italy) Anne Connolly (USA) Basil Darras (USA) Darryl De Vivo (USA) Eduardo Tizzano (Spain) Richard Finkel (USA)

		<p>Rick Hall (USA)  Eugenio Mercuri (Italy)  Petra Neitzel (Germany)  Sabine Rudnik (Austria)  Ulrike Schara (Germany)  Eugene Schneider (USA)  Andreas Schwersenz (Germany)</p>
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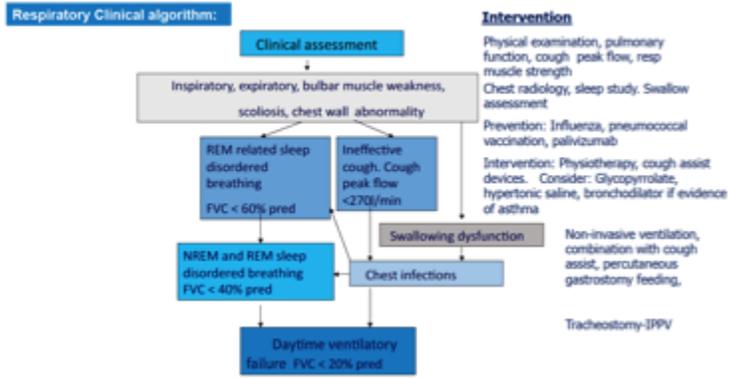


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