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ScienceDirect

Neuromuscular Disorders 28 (2018) 197–207

www.elsevier.com/locate/nmd

Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics

Richard S. Finkel [a,1], Eugenio Mercuri [b,1,*], Oscar H. Meyer [c], Anita K. Simonds [d], Mary K. Schroth [e], Robert J. Graham [f], Janbernd Kirschner [g], Susan T. Iannaccone [h], Thomas O. Crawford [i], Simon Woods [j], Francesco Muntoni [k], Brunhilde Wirth [l], Jacqueline Montes [m], Marion Main [k], Elena S. Mazzone [b], Michael Vitale [n], Brian Snyder [o], Susana Quijano-Roy [p], Enrico Bertini [q], Rebecca Hurst Davis [r], Ying Qian [s], Thomas Sejersen [t] for the SMA Care group

[a] *Nemours Children's Hospital, University of Central Florida College of Medicine, Orlando, USA*
[b] *Paediatric Neurology Unit, Catholic University and Centro Clinico Nemo, Policlinico Gemelli, Rome, Italy*
[c] *Division of Pulmonology, The Children's Hospital of Philadelphia, Philadelphia, USA*
[d] *NIHR Respiratory Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust, London, UK*
[e] *Division of Pediatric Pulmonary, Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, American Family Children's Hospital, Madison, Wisconsin, USA*
[f] *Division of Critical Care, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, USA*
[g] *Department of Neuropediatrics and Muscle Disorders, Medical Center, Faculty of Medicine, University of Freiburg, Germany*
[h] *Division of Pediatric Neurology, Departments of Pediatrics, Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center and Children's Medical Center, Dallas, USA*
[i] *Department of Neurology, Johns Hopkins University, Baltimore, USA*
[j] *Policy Ethics and Life Sciences Research Centre, Newcastle University, Newcastle, UK*
[k] *Dubowitz Neuromuscular Centre, UCL Great Ormond Street Institute of Child Health & Great Ormond Street Hospital, London, UK*
[l] *Institute of Human Genetics, Center for Molecular Medicine and Institute for Genetics, University of Cologne, Germany*
[m] *Department of Rehabilitation and Regenerative Medicine and Neurology, Columbia University Medical Center, New York, USA*
[n] *Department of Orthopaedic Surgery, Columbia University Medical Center, New York, USA*
[o] *Department of Orthopaedic Surgery, Children's Hospital, Harvard Medical School, Boston, USA*
[p] *Assistance Publique des Hôpitaux de Paris (AP-HP), Unit of Neuromuscular Disorders, Department of Pediatric Intensive Care, Neurology and Rehabilitation, Hôpital Raymond Poincaré, Garches, Hôpitaux Universitaires Paris-Ile-de-France Ouest, INSERM U 1179, University of Versailles Saint-Quentin-en-Yvelines, France*
[q] *Unit of Neuromuscular & Neurodegenerative Disorders, Dept of Neurosciences & Neurorehabilitation, Bambino Gesù Children's Research Hospital, Rome, Italy*
[r] *Intermountain Healthcare, University of Utah, Salt Lake City, USA*
[s] *SMA Foundation, New York, USA*
[t] *Department of Women's and Children's Health, Paediatric Neurology, Karolinska Institute, Stockholm, Sweden*

Received 4 September 2017; received in revised form 6 November 2017; accepted 13 November 2017

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.

Keywords: Spinal muscular atrophy; Care; Pulmonary; Acute; Nutrition

* Corresponding author. Pediatric Neurology, Catholic University, Largo Gemelli 8, Rome 00168, Italy.
E-mail address: eumercuri@gmail.com (E. Mercuri).
[1] Both first authors.

https://doi.org/10.1016/j.nmd.2017.11.004
0960-8966/

1. 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 toward 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].

2. 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].

3. Non-sitters

3.1. 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 CO2 (EtCO2) or transcutaneous CO2 (TcCO2)) when awake), and using sleep study or pneumogram with CO2 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.

3.2. 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]. (Fig. 1). A respiratory therapist should be involved to initiate and support assisted airway clearance and respiratory range of motion therapy.

3.3. 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 exsufflation pressures should be increased gradually to 30–40 cm H2O of positive or negative pressure, respectively [10], or instead increase them 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 S1).

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.

3.4. 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

Table 1
Pulmonary assessment, intervention and management recommendations.

	Assessment	Intervention	Care considerations
Non-sitters	Physical examination Assessment of hypoventilation (End tidal CO2) Sleep study or pneumograms in all symptomatic patients or to determine if a patient needs to initiate NIV Clinical assessment of gastroesophageal reflux	Support airway clearance Oral suctioning Physiotherapy/respiratory therapy should be implemented immediately: Manual chest therapy Cough insufflator/exsufflator Support ventilation with bilevel NIV in symptomatic patients	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 Ventilation should be started in all symptomatic patients. Some experts recommend using it before documented respiratory failure to palliate dyspnea. This should be judged on individual basis NIV should be initiated in observing the patient clinically for adequate gas exchange or during a sleep study. NIV interfaces should be fitted by skilled physiotherapists selecting two interfaces with different skin contact points.
		Nebulized bronchodilators in patients with asthma or a positive bronchodilator response Customary immunizations, palivizumab through 24 months, influenza vaccination annually after 6 months of age	Mucolytics should not be used long-term
Sitters	Physical examination Spirometry (when possible depending on age and cooperation) Sleep study or pneumograms in all patients with even minimal suspicion of symptoms of nocturnal hypoventilation Assessment of gastroesophageal reflux	Support airway clearance Physiotherapy/respiratory therapy should be implemented immediately: Manual chest physiotherapy Cough insufflator/exsufflator Support ventilation with bilevel NIV in symptomatic patients	Assessments should be performed every 6 months Supporting airway clearance is critical to all patients with ineffective cough Ventilation should be started in all symptomatic patients. Some experts recommend using it during acute respiratory illnesses to facilitate discharge. NIV should be initiated during a sleep study or observing the patient clinically for adequate gas exchange. NIV interfaces should be fitted by skilled physiotherapists selecting two interfaces to alternate skin contact points.
		Nebulized bronchodilators in patients with suspicion of asthma Customary immunizations, annual influenza and pneumococcal vaccination	Mucolytics should not be used long-term
Ambulant	Clinical examination with review of cough effectiveness and detailed search for signs of nocturnal hypoventilation	Supportive care when needed Customary immunizations, annual influenza and pneumococcal vaccination	Evidence of weak cough or recurrent infections or suspicion of nocturnal hypoventilation should prompt referral to a pneumologist

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.

3.5. Medications

Nebulized bronchodilators should be available if there is suspicion for asthma. Nebulized mucolytics, 3% or 7% hypertonic saline or dornase-α (Pulmozyme®) should not be used long-term 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 adjust the dose to attain the proper effect, and avoid 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.

4. Sitters

4.1. 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.

5. Intervention

5.1. 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.

5.2. 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]. (Fig. 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.

5.3. 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 long-term. Annual influenza and pneumococcal immunizations should be administered per standard pediatric recommendations for patients with chronic neuromuscular conditions.

6. Walkers

6.1. 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.

6.2. 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.

6.3. Acute care management

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

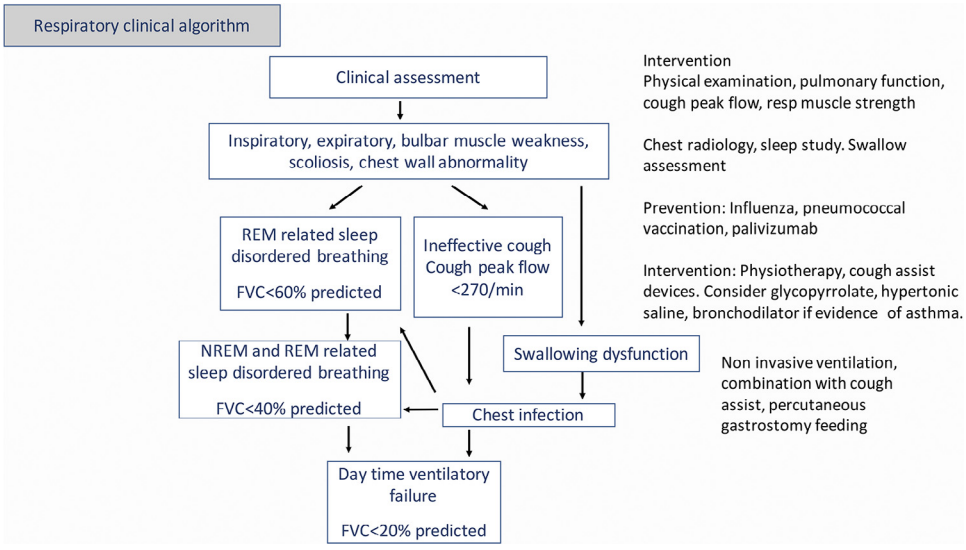

Fig. 1. Respiratory clinical algorithm.
(REM: rapid eye movements; NREM, non-REM; FVC: forced vital capacity)

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 S2).

6.4. 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.

Table 2
Acute care goals, intervention strategies and management recommendations: Home care and transportation.

Home care setting	Individualized anticipatory care plans should be developed and outline: • airway clearance, • ventilation, • nutrition, • hydration, • antibiotics, • emergency contact measures	Augmented secretion clearance, bilevel NIV, and oxygen supplementation should be provided to prevent hospitalization and/or optimize status prior to presentation Local emergency services should be made aware of the individual's needs in advance.
	General assessment and review of signs and symptoms	Respiratory assessment and support should be of highest priority independent of hospitalization indication
	Criteria/thresholds for presentation to emergency care	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)
	Communication for EMS and acute care providers	Families should have a summary of medical needs, list of primary providers, care protocols, and written anticipatory resuscitation statement available.
Community first responders transportation	Community first responders	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.
	Modality of transportation	Mode of transportation between home and acute care facility should be considered on a case-by-case basis
	EMS triage	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.
	Hospital level	Children and young adults with SMA I or II should be hospitalized at a tertiary care center, whether scheduled or emergent.
	Personal medical equipment during transport	The family should bring home equipment (e.g., NIV, cough assist device, mask interfaces, suction machine, oximeter, gastrostomy adaptors) for use during transport.

(NIV: non-invasive ventilation (bi-level positive air way pressure, not continuous positive airway pressure); EMS: emergency medical services, SMA: spinal muscular atrophy).

6.5. 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.

6.6. 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 CO2 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].

Table 3
Acute care goals, intervention strategies and management recommendations: Hospital, and sedation/anesthesia.

Hospital	Goals of care	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. Oxygen supplementation should not be provided empirically in the absence of bilevel NIV.
	Respiratory Care Protocols	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.
	Augmented secretion clearance	Augmented secretion clearance should be the priority during acute respiratory illness.
	Respiratory support in the Emergency Room	Noninvasive respiratory supports should be instituted early.
	Role of the consultant team	Acute care providers should contact consultant providers (e.g., neuromuscular, respiratory) to assist with acute care protocols.
	Endotracheal intubation	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.
	Extubation criteria	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.
Sedation and Anesthesia	Pre-anesthetic/sedation evaluation	Sedation and anesthesia should be provided at a tertiary care center familiar with SMA management. Consultation with respiratory providers, consultant team, and an anesthesiologist familiar with SMA should be obtained prior to sedation or general anesthesia. Discussions should include options of noninvasive and invasive airway support.
	Pre-anesthetic studies	A low threshold for deferring elective/non-emergent sedation/anesthesia should be considered during intercurrent illness across all SMA types. Cardiology screening, polysomnograms, and nutritional assessment might be considered as part of a pre-anesthetic evaluation Respiratory supports (i.e., NIV and cough assist) might be introduced prior to sedation and anesthesia to optimize preprocedural standing and for desensitization.
	Sedation/anesthesia	A monitored setting should be considered. Monitoring should include capnography.
	Post-sedation and anesthesia management	Aggressive secretion clearance measures (cough assist when intubated and extubated) should be integral to post-anesthetic care. Excessive oxygen supplementation in lieu of positive pressure and extubation to NIV should be avoided.
	Analgesia provision	Opiate-based analgesia should be considered as part of routine post-procedural management. Regional analgesia might be considered for all SMA types.

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

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 S3).

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.

6.7. Hospital discharge considerations

Discharge planning should begin shortly after admission 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.

6.8. 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.

7. 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 hormone, 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 with the exception of vitamin D, rarely used prophylactically, and 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 favorable, because nusinersen 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.

8. 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 show 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 types 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 of glucose metabolism in all types of SMA. Despite immobilization 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.

9. 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], including 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 favor 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. Second is managing the phases of transition across the disease trajectory points at which advancing disease signals a transition in favor 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 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.

10. 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, 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 and 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 randomized 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 in improving quality of life and reducing 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 admissions to tertiary care centers.

Acknowledgements

The authors thank the European Neuromuscular Consortium (ENMC), TREAT-NMD, SMA Europe, SMA support UK, SMA Foundation, Cure SMA and the Italian Telethon for their support.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2017.11.004.

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