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Neuromuscular Disorders 28 (2018) 103–115

www.elsevier.com/locate/nmd

Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care

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Received 3 September 2017; received in revised form 6 November 2017; accepted 13 November 2017

Abstract

Spinal muscular atrophy (SMA) is a severe neuromuscular disorder due to a defect in the survival motor neuron 1 (*SMN1*) gene. Its incidence is approximately 1 in 11,000 live births. In 2007, an International Conference on the Standard of Care for SMA published a consensus statement on SMA standard of care that has been widely used throughout the world. Here we report a two-part update of the topics covered in the previous recommendations. In part 1 we present the methods used to achieve these recommendations, and an update on diagnosis, rehabilitation, orthopedic and spinal management; and nutritional, swallowing and gastrointestinal management. Pulmonary management, acute care, other organ involvement, ethical issues, medications, and the impact of new treatments for SMA are discussed in part 2.
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Keywords: Spinal muscular atrophy; Care; Diagnosis; Orthopedic; Phisotherapy; Nutrition

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https://doi.org/10.1016/j.nmd.2017.11.005
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1. Introduction

Spinal muscular atrophies (SMA) include a group of neuromuscular disorders characterized by degeneration of alpha motor neurons in the spinal cord with progressive muscle atrophy, weakness and paralysis [1]. The most common form of SMA is due to a defect in the survival motor neuron 1 (*SMN1*) gene localized to 5q11.2-q13.3 [2]. It includes a wide range of phenotypes that are classified into clinical groups on the basis of age of onset and maximum motor function achieved: very weak infants unable to sit unsupported (type 1), non-ambulant patients able to sit independently (type 2), up to ambulant patients with childhood (type 3) and adult onset SMA (type 4).

In 2004 an International Conference established a committee of experts in SMA to create a consensus statement on SMA standard of care [3]. Different working groups were established, addressing different aspects of diagnosis and management, focusing on rehabilitation and orthopedic, pulmonary, nutritional and palliative care. Each group had two leaders, facilitating the work of other experts who were invited to participate. The Delphi technique [4] was used to explore consensus expert opinion and to identify topics where no consensus could be reached for which further study was needed.

A report of the SMA SOC consensus statement was published in 2007 [3]. The guidelines have been widely adopted by clinicians all over the world and were translated and promoted by patient advocacy groups and international neuromuscular networks such as TREAT-NMD. More recently, with the advent of clinical trials in SMA [5–8], the guidelines have also been used in protocols as a benchmark for care for recruitment and during participation in a clinical trial.

Over the last decade there has been increasing evidence of improvements in the natural history of all the SMA types [9–11]. Even in type 1, the most severe form of SMA, there has been an increase of survival as a result of a more proactive approach, following the introduction of non-invasive ventilation and enteral feedings, suggested in the original SOC recommendations [12,13]. These improvements are likely to be the result of the recommendations provided in the consensus statement and of new advances in care that are not always reflected in the existing literature.

In this paper we report an update of the consensus statement, following the need to include more recently published data and more generally advances in the topics addressed in the original version. New aspects, such as those related to acute and emergency care, medications or the involvement of other organs have also been added.

The need for an update has also been driven by the advent of clinical trials [14]. The approval of the first drug for SMA in December 2016 and promising early results from other clinical trials have changed the perspective of physicians and families who are now more willing to be proactive in the management of this disorder, especially in type 1.

2. Method

Nine topics were included in this update:1. Diagnosis and genetics; 2. Physical therapy and rehabilitation; 3. Orthopaedic care, growth and bone health care; 4. Nutrition; 5. Pulmonary care; 6. Acute care in the hospital setting; 7. Other organ system involvement; 8. Medication; 9. Ethics and palliative care.

For each topic, two leaders, in most cases one from Europe and one from the United States, were identified to head a working group inviting other clinicians with expertise in the topic and, when appropriate, at least one SMA patient or parent/caregiver. The choice of the participants in each subgroup was based on strict criteria, inviting the experts from all continents who had published on the specific topic, or had a large experience in the field and were part of national or international working groups.

A literature search identified all the relevant articles that were classified according to their consistency with the previous recommendations [3], or whether they included novel or contrasting findings.

Each working group (WG) had 2 preliminary conference calls, and at least 2 web-based Delphi rounds of inquiry. The first round of Delphi used open-ended questions to generate specific topics. The second round focused on the topics ranked the highest on the first round.

The review of the literature and the results of the first two rounds were analyzed and discussed in an in-person workshop where the leaders of all the working groups convened. The American Academy of Pediatrics guidelines for classifying recommendations for clinical practice [15] were used to analyze the results.

Within each working group, each topic was summarized as to where a) Consensus was reached with uniform opinion; b) Consensus was reached with a majority opinion, and with minority opinions mentioned; c) No consensus is reached and more work has to be performed.

Following the workshop, more rounds of Delphi were performed to further define some aspects requiring further definition, highlighted during the workshop. Details of the methodology used have been recently published in the workshop report [16].

The results were subdivided using the functional classification from the original consensus statement document. Considering that type 3 patients who lost ambulation share many aspects with type 2 patients, the two groups are collectively indicated as “sitters”, while the type 3 patients who are still ambulant are indicated as “walkers”. Type 1 patients are indicated as non-sitters.

2.1. SMA diagnosis

The diagnostic process for SMA has not changed since the original consensus statement paper [3] but more accurate information on the genetic background has become available.

Unless there are previous familial cases, the diagnostic process is generally prompted by the clinical signs. Clinically, these infants present with hypotonia, progressive symmetric

and proximal weakness affecting the legs more than the arms, sparing of the facial muscles but often with bulbar muscle weakness. There is also weakness of the intercostal muscles with relative sparing of the diaphragm, which results in the typical "bell-shaped" chest and paradoxical breathing pattern. Childhood onset is similarly characterized by hypotonia and proximal weakness, but with less prominent bulbar and respiratory findings.

In approximately 96% of patients, SMA is caused by homozygous absence of exons 7 and 8 of the *SMN1* gene, or, in some cases, only of exon 7 [2,17–20]. The majority of patients inherit the *SMN1* deletion from their parents; in 2% de-novo deletions in one of the 2 alleles have been described [21]. In 3–4%, other mutations in *SMN1* can be found, typically with an *SMN1* deletion on the other allele [22].

Population studies have indicated variations in the carrier frequency of *SMN1* deletions, with the Asians having the highest carrier frequency (2.4%) [23]. The SMN locus is part of a genomic inverted duplication region on human chromosome 5, which contains a paralogue gene, *SMN2*. *SMN2* is intact in all SMA patients. The *SMN2* copy numbers however can vary between 0 and 4 per chromosome 5 in the general population. SMA patients always carry at least 1 *SMN2* copy.

The diagnosis of SMA is based on molecular genetic testing. Genetic testing of *SMN1/SMN2* is highly reliable and it is first line investigation when the condition is suspected in a typical case (Fig. 1). In a typical presentation there is no need for a muscle biopsy.

EMG is also usually not needed in type 1 and 2 children; this investigation can help in more chronic forms in which the phenotype might be less striking. CK serum levels are usually normal or only mildly elevated in SMA; however few exception with markedly (10×) elevated levels are on record hence this test does not necessarily exclude the diagnosis [24].

The gold standard of SMA genetic testing is a quantitative analysis of both *SMN1* and *SMN2* using multiplex ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR) or next generation sequencing (NGS) [23,25–27]. Homozygous *SMN1* deletions can be identified also by PCR followed by restriction digest. This method is faster and is less expensive, and often readily available in any lab but does not allow quantification of *SMN1* or *SMN2* copy number. However, knowledge on *SMN1* copies is relevant for identification of heterozygous deletions whereas *SMN2* copies are important for prognosis and therapeutic approaches.

The absence of both full *SMN1* copies will provide diagnosis of SMA. If only 1 full copy is present and clinical phenotype is compatible with SMA, the remaining *SMN1* gene should be sequenced looking for other subtle mutations. If both full *SMN1* copies are present, a diagnosis of SMA is highly unlikely but the *SMN1* gene should be sequenced if there is a striking typical phenotype or consanguinity. If sequencing indicates an intact *SMN1* gene in the presence of a phenotype suggestive of SMA including also neurogenic EMG, other motor neuron diseases should be considered.

There was consensus that even if the number of *SMN2* copies is not essential to reach the diagnosis of SMA, this should be routinely assessed as it is an important factor influencing the severity of the SMA phenotype [26,28–30] (Supplementary Table S1).

The majority of type 1 SMA patients carry two *SMN2* copies, type 2 SMA and type 3a SMA patients (onset before the age of 3 years) three *SMN2* copies, type 3b SMA patients (age of onset after 3 years) four *SMN2* copies, and type 4 four to six copies [26,30]. Although there is a strong correlation between *SMN2* copies and severity of the disease, there are exceptions and in individual cases the number of *SMN2* copies may not predict the severity of the phenotype. This limitation should be

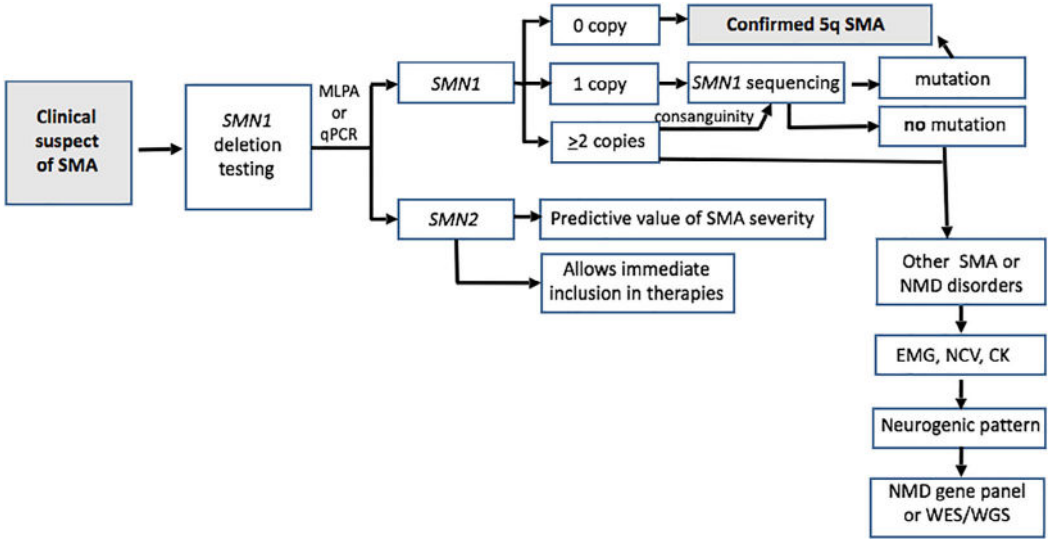


Fig. 1. Diagnostic algorithm for spinal muscular atrophy (SMA: spinal muscular atrophy; SMN1: survival motor neuronon 1; SMN2: survival motor neuron 2; NMD: neuromuscular disorders; EMG: electromyography; NCV: nerve conduction velocity; CK: creatine kinase levels; WES: whole exom sequencing; WGS: whole genome sequencing).



Fig. 2. Multidisciplinary approach.

mentioned when reporting the number of copies or counseling patients or their families.

Another reason for determining the number of *SMN2* copies is that this is currently used as a criterion for enrolment of patients into clinical trials [7,8].

Presence of *SMN1* but homozygous absence of *SMN2*, a genotype found in about 3–5% of control individuals, has no apparent phenotypic consequences [2,20]. The presence of at least one fully functional *SMN1* gene, as typically found in SMA carriers, is indeed sufficient to protect from SMA.

Genetic counseling is obviously important at the time of diagnosis, as is psychological support to the families, especially when a diagnosis of type 1 SMA is communicated.

2.2. Management: a multidisciplinary approach

A multidisciplinary approach is the key element in the management of SMA patients [1,3]. SMA is a complex disorder involving different aspects of care and professionals, and each of the aspects should not be dealt in isolation but as part of a multidisciplinary approach (Fig. 2). In the past families had to coordinate all the assessments and visits but it is now recommended that this should be coordinated by one of the physicians, generally the neurologist or pediatric neurologist, who is aware of the disease course and potential issues. This will allow to monitor the various aspects that are known to be part of the disease progression and, when possible, to provide anticipatory care.

2.3. Neuromuscular and musculoskeletal evaluation

Clinical assessment in SMA includes performing a physical examination, with a focus on the musculoskeletal system and related functional impairments. The choice of the assessments used will reflect the aspects that are more relevant for each level of severity (Supplementary Table S2).

These should include different means of assessments of strength and range of joint motion, relevant motor functional scales [31–35] and timed tests to monitor those aspects of function that reflect activities of daily living (Table 1).

These assessments should be performed routinely by trained examiners every 6 months, unless there are special circumstances requiring different follow up.

Regular monitoring of these aspects will allow to monitor possible changes over time, to identify aspects requiring intervention and response to intervention. The use of these assessments also allows to compare individual results to the trajectories of progression reported in recent studies [36,37].

2.4. Rehabilitation

Since the original consensus statement paper there has been increasing evidence that a proactive approach, including regular sessions of physical therapy (PT) may influence trajectories of progression. In a recent study on sitters and walkers, functional changes over 12 months were minimal in the whole cohort and the few outliers showing a more substantial loss of functional activities were often those with increase in their joint contractures, sudden scoliosis deterioration or excessive weight gain [36]. Other papers have reported the benefits of braces, orthoses and exercise [38–45] (Supplementary Table S3).

2.4.1. Non-sitters

The primary rehabilitation goals for non-sitters include: optimization of function, minimization of impairment, and optimizing tolerance to various positions (Table 1).

2.4.1.1. Stretching. This includes the use of orthoses and splints, active-assistive and passive techniques, supported supine/standing/standing frames and serial casting. Thoracic bracing is recommended for postural stabilization and to promote function. Cervical bracing is often used for head support particularly, as head control is often absent or not fully developed, to minimize risk of asphyxiation while upright.

Upper and lower limb orthoses are used to promote function and range of motion.

2.4.1.2. Positioning. Seating systems and postural supports should include supine positioning with rolls, beanbags, molded pillows or wedges. Custom and molded wheelchair seating systems as well as custom sleeping systems are recommended.

To promote mobility and transfers the use of strollers and power wheelchairs with recline/tilt options and adapted seating systems are recommended.

2.4.1.3. Mobility and exercise. To promote function, assistive technology and adaptive equipment are recommended. The use of eye tracking devices is also recommended to improve communication. Some non-sitters can participate safely in aquatic therapy with proper head and neck support and constant supervision.

2.4.1.4. Chest physiotherapy. Chest physiotherapy is an important part of the assessment and management. It is

Table 1
Rehabilitation assessment and intervention.

	Assessment	Intervention	Care considerations
Non-sitters	Postural control Scoliosis Hip dislocation Sitting tolerance Chest deformities	*Positioning and Bracing* Daily use of seating systems, postural and positioning supports, thoracic bracing and cervical bracing for head support. Static thoracic bracing should have incorporated modifications for respiratory support including abdominal cutouts.	To be effective, orthoses should be applied for more than 60 minutes to overnight. Session duration for effective stretching and range of motion depends on specific patient needs, joints, and rehabilitation aims.
	Contractures (ROM, goniometry)	*Stretching* Daily use of orthoses for upper lower limb orthoses for stretching and to promote function and range of motion. Static orthoses Knee immobilizers and hand splints are recommended for positioning and stretching. AFOs and KAFOs can be used for stretching and positioning. TLSOs are used for positioning. Supported standing	The minimal frequency for stretching and range of motion is 3–5 times per week The minimal frequency for bracing to be effective is 5 times per week.
	Muscle weakness (Antigravity movements) Functional scales (CHOP INTEND) Motor development (HINE)	*Promote function and mobility* Use of seating and mobility systems Mobile arm supports to assist upper extremity function.	Recommend toys with switches, light weight rattles, Bath equipment, adapted beds, upper extremity assistive devices, as well as hoists (lifts), Environmental controls, and eye tracking devices for computers and communication, Strollers with recline and the ability to lay flat, power wheelchairs should have recline/tilt, adapted seating systems
Sitters	Postural control Foot and chest deformities Scoliosis and pelvic obliquity Hip dislocation	*Positioning and Bracing* Thoracic bracing is recommended for posture and to promote function. Cervical bracing is often used for head support for safety and transportation.	Orthoses should be worn for more than 60 minutes to overnight. The minimal frequency for bracing: 5 times/week.
	Contractures (ROM, goniometry)	*Stretching* Orthoses are used for the upper and lower limbs to promote function and ROM Regular stretching for segments known to be at risk for contractures: hip, knee and ankle, wrist and hand Knee immobilizers, KAFOs, and AFOs are recommended for positioning and standing. RGOs and KAFOs can be used for supported ambulation. TLSOs and hand splints are used for positioning.	Minimal frequency for stretching and ROM: 5–7 times/week When stretching or performing joint mobilization ensure joint segments are aligned throughout the treatment. Supported standing should be up to 60 minutes and minimal frequency is 3–5 times/week, optimal 5–7 times/week.
	Functional scales (HFMSE, RULM, MFM) Muscle weakness (Strength tests)	*Promote function and mobility* Use of seating and mobility systems. Use of gait training devices and mobility devices to promote supported ambulation Mobile arm supports to assist upper extremity function.	Exercise can have an effect on function, strength, ROM, endurance, ADLs, participation, and balance Recommend swimming, hippotherapy, and wheelchair sports. All sitters should have electric/power wheelchairs with custom postural support and seating systems The option to tilt and/or recline and a seat elevator is sometimes necessary in weaker patients. Lightweight manual wheelchairs or power assist wheels are ideal to promote self-propulsion in stronger patients.
Ambulant	Mobility Timed tests Measure of endurance (6MWT) Falls Functional scales (HFMSE, RULM) Muscle weakness (Strength tests)	*Promote function and mobility*	Recommend aerobic and general conditioning exercise for SMA walkers. Options include: Swimming, walking, cycling, yoga, hippotherapy, rowing, elliptical/cross-trainers. Exercise program should be designed and monitored by a physical or occupational therapist, familiar with SMA. Optimal duration for aerobic exercise: at least 30 minutes
	Contractures (ROM, goniometry)	*Stretching*	Minimal frequency: 2–3 times/week, optimal: 3–5 Maintain flexibility through active assisted stretching and include the use of orthoses according to specific needs.
	Postural control Scoliosis Hip dislocation	*Positioning and Bracing*	Recommend some form of balance exercise. Lower limb orthoses are used for posture and function at the ankle and knee, Thoracic bracing may be used to promote posture in sitting

ROM, range of motion; CHOP INTEND, Children Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurological Examination; AFOs, ankle foot orthosis; KAFOs, knee ankle foot orthosis; TLSOs, thoraco lumbo sacral orthosis; HFMSE, Hammersmith Function Motor Scale Expanded; RULM, Revised Upper Limb Module; MFM, Motor Function measure; 6MWT, 6 minute walk test; ADL, activities of daily living; SMA, spinal muscular atrophy.

particularly important to implement during illness or perioperative periods and as prophylaxis pulmonary management to promote airway clearance and improve ventilation. Manual techniques include percussion, vibration and positioning to promote postural drainage.

2.4.2. Sitters

The main objectives for rehabilitation in sitters are to prevent contractures and scoliosis, and maintain, restore or promote function and mobility.

2.4.2.1. Stretching. Modalities for stretching include techniques that can be achieved manually and through the use of orthoses, splints, active-assistive stretching, supported standing/standing frames and positioning techniques such as serial casting. Stretching modalities should be performed and/or supervised by physical or occupational therapists. Parents and caregivers should also be instructed in daily stretching activities.

Session duration for effective stretching depends on specific patient needs, joints, and rehabilitation aims.

2.4.2.2. Positioning. Thoraco-lumbar sacral orthoses are recommended for posture and to promote function. Cervical bracing is often used for safety and transportation. Static, dynamic and functional orthoses are used for positioning and standing and, when possible, for supported ambulation.

Supported standing is important to facilitate lower extremity stretching but also to promote bodily functions and bone health, enable upright participation, and promote spine and trunk posture.

2.4.2.3. Mobility and exercise. All sitters should have electric/power wheelchairs with custom postural support and seating systems. Assessments for power wheelchair mobility can begin before 2 years of age [46]. Lightweight manual wheelchairs or power assist wheels are ideal to promote self-propulsion in stronger patients. Exercise programs and activities that encourage muscle activation should be encouraged since it can have an effect on maintaining and improving function, strength, range of motion, endurance, balance, activities of daily living, and participation in school, social activities and occupation. Recommended exercise for sitters include aquatic therapy, concentric and eccentric exercise and aerobic and general conditioning exercise with and without resistance.

2.4.2.4. Chest physiotherapy. Similar to non-sitters, chest physiotherapy is an important part of the assessment and management to implement, especially I the weak type 2, both as prophylaxis and during illness or perioperative periods. Manual techniques are similar to those reported for non-sitters.

2.4.3. Walkers

The main objectives for rehabilitation in walkers are to maintain, restore or promote function, mobility, and adequate joint range, and improve balance and endurance.

2.4.3.1. Exercise/activity programs. The exercise programs will include many of the suggestions used for sitters. In addition, some form of balance exercise, both, dynamic and static forms, should also be part of an exercise program.

2.4.3.2. Stretching and range of motion. Modalities of stretching and range of motion include: passive stretching and active-assistive techniques. Lower limb orthoses are mainly used for maintaining flexibility, posture and function at the ankle and knee. Thoracic bracing is not typically used during walking as it may adversely affect ambulation ability and limit effective compensatory strategies but, when needed, may be used to promote posture in sitting.

2.4.3.3. Mobility. To ensure functional independence, lightweight manual wheelchairs or power assist wheels are recommended when endurance is limited. Similarly, electric/power wheelchairs or powered scooters may also be considered to facilitate independent mobility over longer distances.

2.5. Orthopedic management

2.5.1. Spine deformity management

2.5.1.1. Non-sitters. Until now, because of their limited survival, spinal management was rarely discussed as a possible option in non-sitters, unless they had stable respiratory and nutritional function [3,47]. Specific rigid braces allowing stable sitting position may be used, provided they do not compromise pulmonary function (Fig. 3). Supine Cobb angle or that obtained in the sitting position using a trunk brace may be used in their follow up [47]. The advent of new therapies leading to increased survival and overall functional improvements [7,8], is rapidly changing the scenario of spinal management in these patients.

2.5.1.2. Sitters.

2.5.1.2.1. Assessment. Scoliosis is still highly prevalent in children with SMA 1 and 2, with incidence of 60–90% and initial presentation in early childhood [1,48]. The hypotonic spinal curves continuously progress through childhood. Thoracic kyphosis also develops in most patients to a variable degree.

Inspection of the spine should be conducted as part of the routine clinical examination. When kyphoscoliosis is suspected on forward bend test in sitting or standing posture, anterior-posterior and lateral projection spine radiographs should be performed in the most upright position independently attainable by the patient (i.e. sitting in children who can sit independently, standing in SMA 3) to define and quantify the extent of spinal deformity in both coronal and sagittal planes. For SMA 1 and 2 patients, scoliosis >20° should be monitored every 6 months until skeletal maturity and yearly after skeletal maturity. Management with spinal orthoses is often advocated to support the hypotonic trunk and treat scoliosis >20°, especially in a child with significant growth remaining [42,49]. There was no consensus on the type of brace to be used, as both rigid and soft spinal thoracolumbar orthoses were recommended.

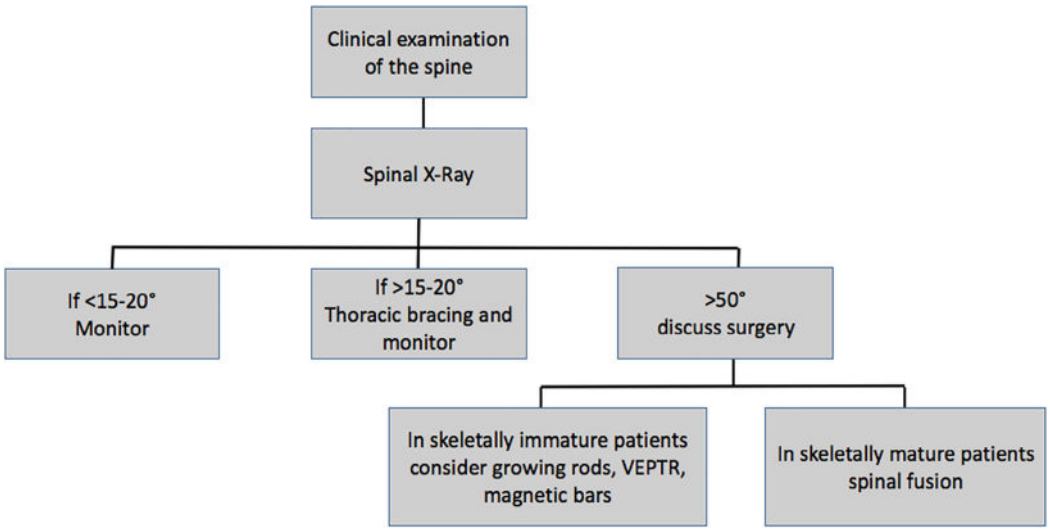


Fig. 3. Spine deformity management (VEPTR: Vertical Expandable Prosthetic Titanium Rib).

2.5.1.2.2. Surgical intervention. Bracing is palliative and unable to halt progression of spinal deformity [49,50]. As a result, spinal instrumentation is frequently indicated to preserve trunk balance in sitting, re-align the distorted thorax to facilitate respiratory function and improve overall quality of life [50–55]. The decision to surgically instrument the spine is predicated mainly on curve magnitude (i.e. major curve Cobb angle ≥50°) and rate of progression (≥10° per year). Other factors, such as decreasing respiratory function, parasol rib deformity, hyperkyphosis and adverse effects on functional mobility, pelvic obliquity, and trunk imbalance should also be considered. Pulmonary function tests should be considered as part of the pre-operative evaluation to determine surgical risk and post-operative respiratory management.

There was consensus that surgical treatment of spine deformity should be delayed until after the age of 4 years (Supplementary Table S4).

In skeletally *immature* patients younger than 8 to 10 years, "growth-friendly" instrumentation, that stabilizes and improves spinal deformity, but allows for continued spine growth should be considered [3,50,52,56–60]. To decrease the need for repeated surgery, magnetically controlled growing rods have recently been advocated [61] as an alternative to traditional growing rods that require sequential surgical lengthenings [62–65]. For children between the ages 8 to 12 years, there was variability in practice among members of the expert panel; the surgical approach depended on clinical variables, especially skeletal maturity and spine growth remaining. In nearly skeletally mature patients 12 years of age or older, definitive posterior spine fusion using dual rod, multi-segmental constructs should be implemented with or without extension to the pelvis, depending on whether the pelvis is part of the scoliotic curve [66]. While there were no published studies on how to accommodate for intrathecal access in patients undergoing spinal instrumentation, there was consensus that one or two mid-lumbar levels should be left unexposed in the midline to accommodate intrathecal access, necessary for the administration of recently approved drugs such as nusinersen, and antisense oligonucleotide which does not cross the blood brain barrier. Conversion of growth-friendly instrumentation to definitive posterior spine fusion should be decided on a case-by-case basis.

2.5.1.2.3. Chest deformity, thoracic insufficiency and pulmonary health. As a consequence of poor trunk and thoracic muscular support, children with SMA have an increased incidence of thoracic insufficiency, the result of scoliosis and distortion of the rib cage [50,67]. Collapse of the ribs (similar to closing an umbrella) contributes to "parasol rib" deformity [53,54,67–69]. Retrospective study of children with hypotonic scoliosis treated with either rib- or spine-based growth-friendly instrumentation systems have shown poor efficacy in ameliorating parasol rib deformity or increasing thoracic volume, and therefore are not recommended [67].

2.5.1.2.4. Hip instability. Hip instability is common in patients with SMA [3,50,55,70]. Several older studies recommended against surgical repair, noting that surgically treated hips tended to re-subluxate or dislocate, and that hip pathology rarely caused pain [3,50,55,70]. However, these studies failed to reflect modern surgical techniques and did not evaluate young adult and middle-aged patients. Unilateral and bilateral hip instability should be surgically managed only in patients with significant pain.

2.5.1.2.5. Contractures. Contractures are common in patients with SMA as a result of decreased range of motion, prolonged static positioning, and agonist-antagonist muscle imbalance [50,71,72]. Functionally and symptomatically, contractures can lead to pain and inhibit function in patients

with SMA [24,42–46,71–75]. Conservative management of joint contractures has been discussed in the rehabilitation section [24,42–46]. Surgical management of contractures of the upper or lower extremities should be considered when they cause pain or impair function.

2.5.1.2.6. Management of fractures. Owing to disuse, osteoporosis and low vitamin D levels, fragility fractures are common in children with SMA 1 and 2. Closed treatment with cast immobilization is generally recommended for non-ambulatory patients, but prolonged cast immobilization (>4 weeks) that aggravates muscle wasting and disuse osteoporosis should be avoided. Ambulatory patients with long bone fractures of the lower extremities and non-ambulatory patients with hip fractures generally benefit from surgical stabilization using intramedullary rods or bridging fracture plates to restore immediate bone stability to allow early range of motion of the extremity and to promote accelerated fracture healing.

2.6. Nutritional management, swallowing and gastrointestinal dysfunction

The main topics covered include swallowing dysfunction and dysphagia, weight control and gastrointestinal dysfunction (Table 2).

Table 2
Nutritional assessment and intervention.

	Assessment	Intervention	Care considerations
Non-sitters	Video Fluoroscopic Swallow Study shortly after diagnosis and when suggested by clinical signs suggestive of dysphagia (weak suck, fatigue, humid voice, pneumonias) Difficulties with feeding (pocketing, jaw contractures, increased mealtimes) Nutritional analysis of food records/feeding regimen Longitudinal anthropometrics Acute care monitoring 25 Hydroxy-vitamin D labs and Body Composition and Bone density Constipation	If swallow study is passed, consider referral to specialist for feeding therapy/modification For failure of a swallow study or for growth failure, for proactive care, place nasojejunal tube until a Gastric-tube can be placed with Nissen fundoplication. A dietitian should adjust caloric, fluid, macronutrient, micronutrient intake and timing of feeds. Nutrition labs may be indicated. Minimize fasting during acute care to less than 6 hours. Provide adequate fluid intake during illness. Monitor electrolyte levels and correct as needed. Monitor glucose levels to correct hypo/hyperglycemia. Provide adequate calcium, vitamin D intakes for bonehealth. Adequate hydration. Use of bowel regulation medications.	Determine appropriate calorie needs based on growth. Standardized growth charts are a good tool to track growth trends, but optimally, should be used with other body composition measurement tools to assess appropriate growth. For optimal care, recommend evaluation by a dietitian every 3–6 months for younger children and annually for older children/adults. Evaluation is especially important for those on specialized diets.
Sitters	Assessment of symptoms of dysphagia/aspiration/Difficulties with feeding Video Fluoroscopic Swallow Study if suggested by clinical signs suggestive of dysphagia. Nutritional analysis of food records/feeding regimen Longitudinal anthropometrics (height, weight, OFC) Nutrition labs may be indicated. Acute care monitoring Glucose metabolism labs 25 Hydroxy-vitamin D labs and Body Composition and Bone density (DXA) Constipation	If safe to swallow, refer to specialist for feeding therapy/modification. If failed swallow or interventions are not sufficient place nasofeeding tube as indicated prior to placement of a long term Gastric feeding tube. For growth failure, provide supplemental nutrition products. Referral to dietitian for increasing calories with nutrient dense foods. Adjust caloric, fluid, macronutrient, and micronutrient intake based on growth and intake. Limit calorie intake in overweight individuals and maximize nutrient intake. Minimize fasting during acute care. Appropriate fasting time depends on prior nutritional status and nature of acute event. Provide adequate fluid intake during illness. Monitor electrolyte levels and correct as needed. Monitor glucose levels to correct hypo/hyperglycemia. Indicated for individuals with increased body fat or other prediabetic symptoms. Adequate calcium, vitamin D intake. Diets rich in fiber are recommended to promote gastric motility and reduce constipation. Adequate fluid is needed with increased fiber intakes. Bowel regulation medication may be indicated.	At minimum, recommend evaluation by a dietitian shortly after diagnosis and for concerns of under/over nutrition. For optimal care, recommend evaluation by a dietitian every 3–6 months for younger children and annually for older children/adults. Evaluation is especially important for those on specialized diets.
Ambulant	See dietitian for concerns of over/under nutrition Nutritional analysis/monitoring if underweight or overweight Longitudinal anthropometrics (height, weight, OFC). Glucose metabolism labs 25 Hydroxy-vitamin D labs	Provide macro/micronutrient intakes based on guidelines for a healthy sedentary individual. Limit calories as indicated to prevent obesity. Minimize fasting during acute care Indicated for individuals with increased body fat or other prediabetic symptoms Provide adequate calcium, vitamin D intakes for bonehealth if needed	

For all SMA types regular assessments of growth are important and an expert nutritionist should be involved to promote an appropriate diet, monitoring not only weight but also fluid, macronutrient, and micronutrient intake, especially calcium and vitamin D intake for bone health [76–78]. SMA-specific growth charts are not yet available. Secondary to altered body composition in SMA [79–81], experts are divided in the use of standardized growth charts alone to monitor appropriate growth, but they may be helpful to monitor trends.

In all types it is important to ask and document details regarding GI symptoms such as presence of gastroesophageal reflux, constipation, use of bowel regulatory agents, delayed gastric emptying, and vomiting.

Over the last few years there has also been increasing evidence of possible metabolic abnormalities in SMA patients such as metabolic acidosis, abnormal fatty acid metabolism, hyperlipidemia, hyperglycemia, hypoglycemia, and muscle mitochondria defects [82–84]. Perturbations of glucose metabolism and pancreatic development have been reported in SMA mice [85–89]. Glucose metabolism abnormalities were later confirmed in some obese SMA patients [90,91] and pancreatic differences confirmed in deceased SMA 185.

2.6.1. Non sitters

2.6.1.1. Assessment. Safe swallowing is one of the most important aspects to consider for a non-sitter (Supplementary Table S5). Bulbar dysfunction can result in aspiration and pulmonary infections. A full modified barium swallow fluoroscopic study is recommended shortly after diagnosis and, if the initial test is normal, closely monitored to detect possible early signs of feeding difficulties. Contracture of the masseter muscles often develops in patients by one year of age and limits the opportunity for oral feeding. This may be a limiting factor for patients treated with nusinersen who demonstrate improvement in bulbar muscle strength.

Optimal nutritional management includes longitudinal evaluation of weight and length and dietary analysis. In type 1 patients, masticatory muscle weakness, dysphagia and respiratory problems are responsible for reduced calorie intake and risk of undernutrition. Additionally, increased work of breathing may increase energy expenditure and caloric requirements, further increasing the risk of undernutrition.

2.6.1.2. Intervention. For proactive care following a failed swallow study or growth failure, placement of a short-term nasogastric or nasojejunal tube is recommended until long term gastrostomy tube can be placed. There was no unanimous consensus but many experts prefer that Nissen fundoplication be performed in conjunction with gastrostomy tube placement secondary to decreased gastrointestinal motility, reflux, and increased pressure related to respiratory treatments [92] (Supplementary Table S6).

There is less consensus on the effect of the type of diet [12]. Consensus is divided on the use of the Amino Acid diet, a diet based on elemental formula [83,93]. Experts agreed that diet type and administration should be based on individual tolerance. Adequate hydration as well as bowel regulating agents, probiotics, and motility medications are recommended to ease symptoms of constipation and gastrointestinal dysmotility.

Regarding nutritional aspects during acute care in non-sitters, it has been strongly suggested that fasting should be avoided to prevent including metabolic acidosis, fatty acid metabolism abnormalities, and hyper/hypoglycemia [82,83,93–95]. Divided expert opinion suggests that nutrition including a protein source should be provided within 6 hours during acute episodes. Adequate hydration and electrolyte balance is imperative during illness.

2.6.2. Sitters

2.6.2.1. Assessment. For optimal care, nutrition evaluations are recommended after diagnosis and periodically, every 3–6 months for younger children and annual evaluations afterwards.

Chewing difficulties and fatigue with eating, are frequent in sitters [96,97]. Safe swallowing and risk of aspiration are also a concern. A history of choking or coughing episodes with feeds should be investigated and monitored with swallow studies.

Feeding evaluations are also recommended for possible feeding modifications/occupational therapy in order to swallow safely and eat effectively.

Longitudinal measures of weight and length in conjunction with body composition measures are recommended to promote appropriate growth.

Evaluation for obesity as well as glucose metabolism abnormalities may be recommended for overweight sitters. Some experts suggest that sitters with SMA should be evaluated for possibility of obesity/overfat at BMI greater than the 25th percentile [91].

Evaluation of fluid and fiber intake is recommended for frequent constipation.

2.6.2.2. Intervention. In a case series study 37% of sitters have growth failure and require intervention [96]. Feeding tubes are commonly used in this population for supplementary nutrition rather than total nutrition and suggestions for feeding tubes and GI surgical recommendations depend on the individual situation.

Sitters may be at risk for being overweight/obese as they grow older secondary to the reduction in physical activity due to weakness and altered body composition [80,91]. Concerns for overweight include reduced mobility and risks for related comorbidities including risk of metabolic syndrome [86,93].

Diet is variable in sitters. Calories, protein, fat and carbohydrate, are initially estimated using common standardized equations [98] and should be adjusted as appropriate growth and labs indicate. There is lack of consensus on the use of the amino acid diet and no data to support the use of synthetic amino acid as opposed to intact protein in patients with SMA.

Based on experience and case studies [93–95] experts recommend that fasting times should be limited during acute circumstances and electrolyte and fluids should be monitored and repleted as indicated.

Depending on severity of constipation, fiber intake, probiotics, and bowel regulating agents may be used to improve symptoms.

2.6.3. Walkers

In this population, swallowing dysfunction and feeding difficulties are rare. A dietitian/nutrition evaluation is recommended if there are nutritional issues. The largest nutritional concerns for walkers with SMA is the risk of obesity and overweight as this can reduce mobility and may increase risk of obesity-related comorbidities such as metabolic syndrome, high blood pressure, and diabetes.

2.6.3.1. Bone health. It has been recognized that SMN has a specific role in the metabolism of the bone interacting with osteoclast stimulatory factor osteoclast stimulatory factor [99]. Therefore, the high incidence of osteopenia and fractures in SMA patients may not be simply attributed to muscle weakness and lack of exercise [76,100,101]. Periodic Dual energy x-ray absorptiometry analysis (DEXA) to monitor bone density in patients with SMA, is recommended yearly. There was consensus among experts that Vitamin D blood levels and intake should be monitored at least annually and supplements should be given in the presence of low levels or of osteopenia. In the case of frequent fracture, review may be given to use of bisphosphonates.

3. Conclusions

The recommendations reported in this first part provide an overview of what should be considered standard of care for SMA. The paper highlights the importance of a multidisciplinary approach and of the role of the neurologist/pediatric neurologist in coordinating, together with the families, the various aspects of care.

In all the aspects of care included, there was often not enough published evidence and the recommendations were the results of what was available from the literature and experts' opinion, following a well-established Delphi method to classify consensus and appropriateness of assessments and interventions. The working groups identified the aspects that constitute optimal care but considering that some of the recommendations may not be easily applicable in centers or countries with less resources, an effort was made to identify assessments or interventions that constitute the *minimal care* that families should expect to find in any neuromuscular centre.

The second part of the two-part paper will focus on other aspects of care, such as pulmonary and acute care, involvement of other organs, medications and ethical issues.

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.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2017.11.005.

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