Discharge of children affected by spinal muscular atrophy type 1 and type 2

[1]C. Di Pede, [2]C. Agosto, [1]S. Masiero, [2]F. Benini

[1]Department of Physical and Rehabilitation Medicine, Padua University, Italy
[2]Pediatric Palliative Care and Pain Service, Department of Women's and Children's Health, Padua University, Italy

Corresponding author: [1]C. Di Pede, Department of Physical and Rehabilitation Medicine, Padua University, Italy.
Email: chiaradipede@yahoo.it

Key points

Spinal muscular atrophy is a genetic neuromuscular disorder that affect children; it leads to severe hypotonia and swallowing difficulties; caregiver's training in the management of daily home care is crucial to guarantee a safe and early discharge at home of these children.

Abstract

Spinal Muscular Atrophy (SMA) is an inherited neuromuscular disease that leads to severe global hypotonia in children.

These patients are often known during critical episodes in the context of intensive care; they have a lot of special needs to satisfie at home.

A proper management of swallowing and feeding difficulties, together with a correct postural alignment are critical in this kind of children.

Granting a good quality of life should be the most important goal for these children and their family. Caregivers' training in the management of daily home care is crucial to guarantee a safe and early discharge at home.

Keywords. spinal muscular atrophy, swallowing, posture, daily home care, management, physiotherapy.

Introduction

Spinal muscular atrophy (SMA) is an inherited autosomal recessive neuromuscular disease caused by the deletion of the SMN1 gene (1), responsible for the production of the protein SMN (Survival Motor Neuron). The lack of production of this protein leads to the degeneration of motor neurons in the anterior horn of the spinal cord (second motor neuron) assigned to the control of the striated muscle, causing a progressive denervation, muscle wasting and weakness (2).

The muscle weakness is usually symmetrical and more proximal than distal; weakness in the legs is greater than in the arms. The severity of weakness generally correlates with the age of onset; the respiratory muscles are interested in a heterogeneous way, depending on the severity of the clinical form; in the most severe forms also oro-pharingo-laryngeal muscles can be involved, because of degeneration of bulbar neurons (3,4). The clinical presentation of the disease is heterogeneous; according to the international literature, SMA is classified into 4 forms, as reported in Table 1 (5,6)

<table>
<tr><th>SMA1
(never seats)</th><th>SMA2
(never walks)</th><th>SMA3
(stands and walks)</th><th>SMA4
(walks during adult years)</th></tr>
<tr><td>1A (more severe)</td><td rowspan="4">10 subgroups according to the functional level:
2.0 (more severe)
2.9 (milder)</td><td>3A (more severe)</td><td></td></tr>
<tr><td>1B</td><td>3B</td><td></td></tr>
<tr><td rowspan="2">1C (milder)</td><td rowspan="2">3C (milder)</td><td rowspan="2"></td></tr>
</table>

Table 1. Clinical presentation

Epidemiology

SMA has a global incidence of 1/6000-1/10000 (7,8) live births; the most serious forms account for the major part of the patients in charge to the Veneto Center for Paediatric Palliative Care in Padua.

SMA1 (non sitters)

It is the most severe form of SMA.

Type 1 patients have also been subclassified into types 1a (neonatal or antenatal onset), 1b (typical Werdnig-Hoffmann disease with onset after neonatal period), and 1c (later onset, better head control in supported sitting, mild feeding or respiratory difficulties during the first 6 months of life) (9,10).

SMA 1a occurs at birth or within the first month of life; from the motor point of view these patients have global hypotonia, with impossibility to perform even the slightest antigravitary movements; they present severe respiratory failure with collapse of the chest wall, abdominal balance and serious difficulties in feeding; they may have arthrogryposis, clubfoot and early multidistrectual muscle-tendon retractions. Life expectancy is generally less than 3 months (9).

SMA1b occurs between 1 and 3 months of age; we observe poor antigravitary movements of the limbs; head control is absent and respiratory failure occurs in the first months of life; also these children may show early muscle-tendon retractions and consequent skeletal deformities. The life expectancy without ventilatory support is usually 6-12 months (9,10).

SMA 1c is characterized by an onset between three and six months of life; at least initially, these children have a partial head control and are able to perform some anti-gravitary movements of the limbs. The early onset of muscle-tendon retraction is a common occurrence. Life expectancy, in the absence of supportive interventions, is typically less than one year of life, but reaches 24 months and in some cases a stabilization of the clinical picture can be achieved after few years with proper ventilatory and nutritional support (9.10).

These children are often known during critical episodes in the context of intensive care; they have a lot of rehabilitative needs to satisfie at home; the priority is an early training of the caregivers with the aim of discharging them at home as soon as possible to ensure a better quality of life for the children and their family.

Swallowing and feeding

Swallowing and feeding difficulties are common in non sitters (11). The general hypotonia affects also the bulbar muscles involved in swallowing, causing weak suction and an important suction-breathing-swallowing incoordination. In addition to the difficulty in feeding by mouth, also the difficulty in managing saliva can occur; if saliva is not handled properly, it can be inhaled, especially during changing posture (11,12).

Poor head control may also be a factor in the development of feeding difficulties, precluding neck tuck or other compensatory postures to enhance the safety of swallowing (13). This dysfunction can cause aspiration pneumonias, which are the main cause of death in these patients (14).

Key symptoms of feeding difficulties include:

- prolonged mealtime;
- fatigue with oral feeding;
- poor weight gain;
- evident choking or coughing during or after swallowing;
- presence of recurrent pneumonias (15).

Clinical examination of the oropharyngeal apparatus and observation of the patient during the meal, are critical (11,12).

Videofluoroscopic swallowing study is indicated when dysphagia is suspected, in order to identify proper therapeutic strategies, such as adapted food texture and positioning (11, 12, 14).

Management of swallowing and feeding difficulties

Children suffering from the most severe forms of SMA1 (1a, 1b) show difficulties during suction and during swallowing since the first months of life, while children suffering from milder forms of SMA1 (1c), typically

preserve mechanism of sucking, experiencing the greatest difficulties when they are tired (11,16). In the latter category of patients, the weaning may take place in ways and times comparable to those we find in healthy children.

It's important to train parents to identify any "red flags": does the child sweat while eating? Does he/she seem tired while eating? Does he/she cough? Has he/she prolonged mealtime? (15).

If the child is breastfed, he/she should be gradually accustomed to the prone position, as it exposes the child to a lower risk of inhalation (Figure 1); if the baby is fed with baby bottles, small size baby bottles should be used, with a not too wide nipple hole, getting the baby used to position on the side or with the head turned to the side (17).

When oral feeding leads to excessive fatigue and to an increased risk of inhalation, starting enteral feeding is indicated. (18). Recent clinical studies suggest early placement of gastrostomy with the aim of ensuring an adequate caloric and idric intake and facilitate handling of the child during the acute phase of the disease (15). In clinical practice, nutritional supplementation via nasogastric tube is the first instance to start enteral feeding, with the aim of integrating the oral feeding, which has become no longer sufficient. It's important to train parents to early management of nasogastric tube and enteral feeding pump.

Posture and postural changes

The early training of parents to the proper positioning of their child is critical and has three main aims: to grant good breathing (minimizing the risk of inhalation of saliva / milk), to contain the onset of pain from musculoskeletal hypomobility and tendon retractions, to allow the child a social relationship as satisfying as possible.

The concept is that the more we can protect the body of the child through proper postural alignment, the more we can preserve residual motor functions and maintain effective ventilation (19).

It's essential to place the baby on special decubitus ulcer prevention devices (pearl millet pillows) (17) and to carry out posture changes at least every 2 hours.

The millet pillows are cotton pillows filled with millet seeds which have the purpose of supporting parts of the body that would otherwise be crushed on the support surface and contain the baby's body (17).

The "table mat" is an important device to use especially when the baby is still small; it consists of a pad of foam glued to a board of plywood, on which you place the baby with millet pillows (17). The purpose is to allow parents to easily move the baby from one room to another while keeping him/her correctly positioned.

Let's see which are the possible postures for a child with SMA1, their indications and benefits:

- Supine posture (“relationship posture"): the baby can be maintained supine until he/she is able to manage the saliva, so that the care giver can look the baby in his/her eyes getting a rewarding relationship;
- Posture on the side (“play posture") (figure 2): when the baby experiences disconfort or difficuties in maintaining the supine position or when we want to allow him/her to manipulate small and light toys in a situation of reduced gravity, it's possible to place him/her on the side, so that saliva can easily come out from the mouth;
- Prone posture (“safety position”) (figure 3): it must be considered the safest posture for all children with SMA1, as it allows better ventilation of the lung bases and is always indicated during emergency situations; in this position the abundant secretions present in the pharynx can leak from the mouth and be sucked smoothly, avoiding that they invade the airways; the baby can be positioned with the help of the millet pillows or can be held in the arms supporting the abdomen and chest with the forearm, and supporting the head rotated 90° with the other hand, in order to enable him/her to observe the surrounding environment.

- It's important to preserve the head-trunk-pelvis axis during every postural change, considering the head as the point of "support" and the pelvis as the point of "hub".

Physiotherapy

Currently no studies address physical and occupational therapy as general therapies; reccomendations expressed in the Consensus Statement for Standar of Care in Spinal Muscular Atrophy (15) are followed in clinical practice.

In non sitters limited range of motion, head control, postural control and alignment, and progressive scoliosis are found.

In these patients it is important that parents are trained to daily perform global mobilization with the aim of preventing the onset of muscle-tendon contractures and consequent musculoskeletal deformities (upper and lower limbs, spine and rib cage). The baby should be mobilized several times a day, in particular just after awakening, before nocturnal sleep and after the bath.

Stretching exercises of the spine are of crucial importance and aim to maintain the spine flexible; one of the most used maneuvres of spine elongation is the so called "ferret maneuver" (17), which consists in the manual traction of the spine (figure 4).

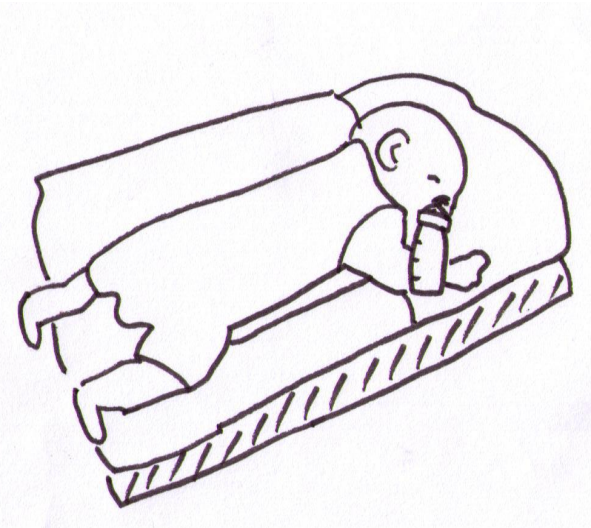

Figure 1

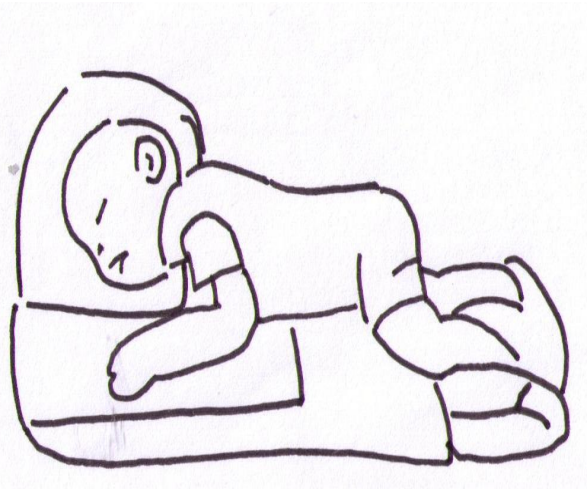

Figure 2

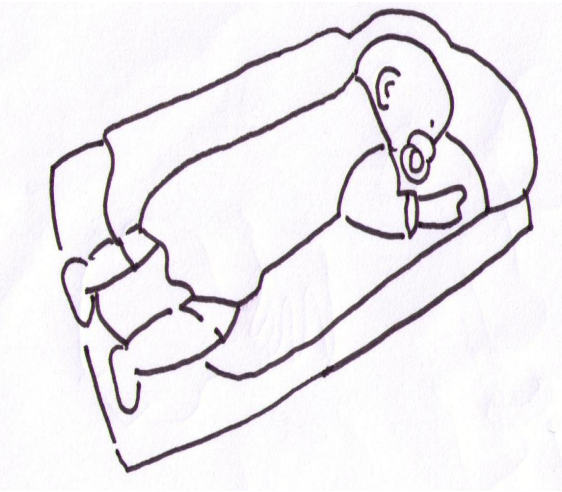

Figure 3

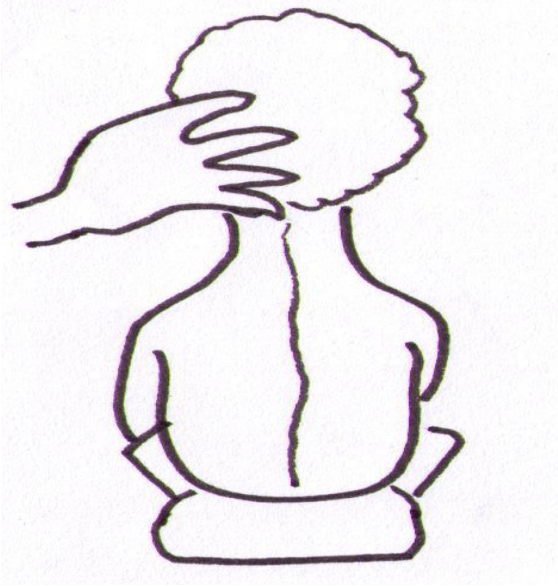

Figure 4

Chest physiotherapy

The main objectives of chest physiotherapy are: to maintain the rib cage elastic and prevent its deformity, to encourage secretions drainage and ensure their elimination (20). Airway clearance is very important in both acute and chronic management of all patients with spinal muscular atrophy.

Caregivers of these patients should learn to assist coughing in all patients with ineffective cough. These techniques include manually and mechanically assisted cough. Mechanical insufflation-exsufflation (Cough Machine) is widely accepted in management of neuromuscular diseases, combined with manually assisted cough manouvers (abdominal thrust); secretion mobilization techniques are also helpful and include chest physiotherapy and postural drainage. (21,22).

Oral suctioning can assist in secretion management after assisted coughing (15).

Aquatic therapy

Water is an ideal environment for children in general, and particularly in children with neuromuscular diseases (23); thanks to the anti-gravity force facilitating flotation, aquatic therapy allows children affected by SMA to perform exercises and movements in conditions of reduce gravity and in total safety.

As long as children are small it's possible to immerse them in hot water in the bathtub at home every day, taking advantage of the myorelaxant action of hor water; when they grow up, it's possible to set an appropriate rehabilitation program in aquatic environment (water temperature > 32-33 ° C), defining the individual needs and goals of the child.

SMA2 (sitters)

The second from of SMA is defined “intermediate”; these children have delayed motor milestones; some learn to achieve independent sitting, whereas others need help to sit up. The defining characteristic is an ability to maintain a sitting position unsupported.; independent ambulation is never achieved (15).

SMA 2 presents an extreme variability in its clinical manifestations and is therefore classified into ten subgroups, according to the classification of Dubowitz (5), based on the score obtained at the Hammersmith Functional Motor Scale (25,26).

At the strongest end of this category are those who can stand with a standing frame or long leg braces but are not able to walk independently (25).

Swallowing and feeding

Swallowing and feeding difficulties can often occur in sitters (27); the typical symptons related to these difficulties are:

- prolonged mealtimes;
- poor growth or weight loss;
- coughs during swallowing.

In these patients the main causes of these difficulties are due to:

Pre-oral phase:

- limited mouth opening due to reduced temporomandibular joint range of motion;
- difficulties in getting food to the mouth for self-feeding resulting from upper limbs weakness;

Oral phase:

- weak bite force;
- increased fatigue of the masticatory muscles;
- craniofacial deformities (including dental malocclusion, anterior open bite..)

Pharyngeal phase:

- pharyngeal muscles dysfunction;
- poor coordination of the swallow with airway closure. (27)

Poor head control may also be a factor in the development of feeding difficulties, precluding neck tuck or other compensatory postures to enhance the safety of swallowing. (13) In these children clinical examination of oropharyngeal structures that influence feeding efficiency and consideration of the effect of positioning and head control on feeding and swallowing are essential.

Videofluoroscopic swallow studies should be carried out after initial assessment if there are concerns about swallow safety and to identify proper therapeutic strategies. (11,12,14)

Management of swallowing and feeding difficulties

Specific treatments should aim at reducing the risk of aspiration during swallow and optimizing efficiency of feeding and promote enjoyable mealtimes. (15)

There is currently no supporting evidence that oral motor treatment programs impact safety or efficiency of oral feeding. (13)

Let's see some of the compensatory strategies to implement daily:

- Changing food consistency: a semisolid diet can be adopted to compensate for poor chewing and reduce length of mealtimes; thickened liquids may protect against aspiration of thin fluids. (13)
- Ensuring proper sitting position and use appropriate orthotic devices, if necessary, in order to enhance self-feeding ability and increase swallowing efficacy and efficiency. (11,12)
- Performing passive mobilization of the cervical spine and temporomandibular joint to prevent stiffness (13).
- Performing oral tactile stimulation with foods of different tastes and temperatures to strengthen the swallowing reflex (11,12).

According to international consensus optimal management requires proactive nutritional supplementation as soon as inadequate oral intake is recognized.

Physiotherapy

Contracture management and exercise are a major focus of treatment, with implementation of a regular stretching to preserve flexibility and prevent joint stiffness.

Regular exercise to maintain fitness should be encouraged and may include swimming, aquatic therapy, horseback riding, and adaptive sports. (15)

Chest physiotherapy

Most children with SMA2 don't have intrinsic lung disease that can limit the effectiveness of the mucociliary system in clearing secretions from the airways; otherwise respiratory muscle weakness results in limited cough strength that requires cough-augmentation therapy.

Manual cough augmentation can be administered by supporting either hyperinflation or forced expiration alone or by combining both therapies to improve cough strength. Manual hyperinflation can be administered by using a self-inflating resuscitator bag combined with a 1-way valve and a mouthpiece. (30)

Patients with weak inspiratory muscle strength and adequate expiratory muscle strength may be able to significantly increase cough flows to clear secretions with manual hyperinflation therapy alone. Patients with adequate inspiratory muscle strength and weak expiratory muscle strength may benefit from an abdominal thrust maneuver to improve peak cough flows. (31)

Manual hyperinflation may also be used as a maintenance therapy to maintain lung inflation by preventing atelectasis and improving chest wall compliance. A 2- or 3-times-daily regimen of 8 to 10 hyperinflation maneuvers with a 5-second breath hold at the end of each hyperinflation maneuver has been suggested as a maintenance therapy for pulmonary and chest wall compliance. (30)

Mechanical in-exsufflation (MIE) can be used to support limited cough function by combining pressure preset insufflation and exsufflation by means of a switch-activated reversible flow and an adjustable flow generator.

The CoughAssist device has been shown to produce a higher peak cough flow when compared with combined manual Cough Assist therapies alone. (32)

MIE is administered by using preset in-exsufflation pressures.

Mean in-exsufflation pressures of 30 cwp with a range of insufflation of 15 to 40 cm H2O

and exsufflation of 20 to 50 cmH2O have been suggested for the application of MIE for pediatric patients.

It's suggested to perform 4-5 cycles of insufflation-exsufflation followed by spontaneous breathing (or mechanical ventilation).

The CoughAssist device can also be used to apply hyperinflation therapy. A twice-per-day treatment regimen using manual insufflation cycles of 5 to 6 seconds at 50 cmH2= can be applied to prevent atelectasis and improve chest wall compliance.

It'important a proper training of the caregiver and the child to guarantee the efficacy of this therapy. (15)

In children with severe thoracic deformities and poor rib cage compliance, chest pain from stretching of the musculo-skeletal structures may arise from the use of the machine. The effectiveness of MIE may be limited in patients with a weak or enlarged tongue that may block exsufflation flow. (30)

Skin care in SMA 1-2

Proper care of the skin is essential in this kind of patients who are at high risk of developing decubitus lesions because of reduced mobility.

In particular, in children who use oro-nasal or nasal masks for non invasive ventilation, bedsores are frequently found right where the interface lays (usually forehead and nose).

If redness appears, a different mask must be used in the following days, to prevent contact on the same area; it's also advisable to apply special barrier creams on the red area in order to prevent ulceration.

Orthotics

Motor physiotherapy is not sufficient to prevent and contain the onset of muscle-tendon retractions and consequent skeletal deformities (15); custom made orthoses and special adaptive aids must be used during the day and during the night, if well tolerated, with the aim to contain skeletal deformities and delay the surgical option as soon as possible.

In selecting and fabricating an orthosis for patients with spinal muscular atrophy, it is important that rehabilitation physician, orthotist, therapist, and family work together to ensure that the appropriate orthosis is fabricated and allows wearers to meet their functional goal. (15).

Custom made orthoses and aids must be early proposed to the child and his/her family:

- Thoracic-lumbar-sacral orthoses (TLSO; ex. Cheneau brace) with/without head support with an abdominal cutout to allow appropriate diaphragmatic excursion and access to gastrostomy tubes where present (figure 5). Spinal orthoses may be used for postural support, but there is insufficient evidence to support delayed curve progression. (15) The use of the brace while sitting promotes a better head control and allows the children to take advantage of the residual strenght of the upper limbs to manipulate small and light objects, control a power wheelchair with special interfaces, use personal computers and touch screen devices to communicate, play and at school.
- Ankle-foot orthoses (AFO): to wear during the day to prevent foot flexors retraction (figure 6).
- Knee- ankle- foot orthoses (KAFO): to wear during the night rest to prevent knee flexors retraction (figure 7) or for standing/assisted ambulation with a walker for patients with sufficient strength.
- Hip-Knee-ankle-foot orthoses (HKAFO): for standing (figure 8).
- Upper extremity or hand orthoses: to use during the night rest to correct postural deviations.
- Upper extremity orthotics with mobile arm supports or slings augment active range of motion and functional abilities.
- Postural seat units can be used in different situations (at home, inside the car, in a stroller , in a wheelchair…) to guarantee a better posture.

A standing frame or a mobile stander should be early considered to promove the upright position, respecting

basic criteria as body alignment and comfort. Some SMA1 children who are able to maintain a sufficient head-trunk control with support and all SMA2 children can early experience autonomy on a wheelchair. Evaluations for manual and power wheelchair may be conducted as early as 18 to 24 months of age. The following wheelchair types are more frequently proposed:

- manual ultralight wheelchair (figure 9): for very young children (1.5 -5 years), to move in indoor environments;
- manual light wheelchair (figure 10): for children who preserve a reasonable upper limb function , to move in indoor and outdoor environments;
- power wheelchair (figure 11): for children with minimal upper limb function; thanks to adapted interfaces (proper joysticks, table control systems, chin/foot/breath control systems...) they can easily drive the wheelchair and experience independence.

Figure 5

Figure 6

Figure 7

Figure 8

Figure 9

Figure 10

Figure 11

The role of play in SMA1-2

Play is one of the best ways to explore the world and the interpersonal relationships, to develop motor and cognitive skills; it's clear that play has a critical role also in SMA children.

Every child has the right to experience the joy of play; choosing the appropriate toys is essential, complying the child's motor difficulties and avoiding him/her to experience the frustration of not being able to use them because they are too big, too heavy...

Different categories of toys are available:

- Commonly available toys suitable to be used by children with severe muscle weakness (for newborns: inflated balloons, rag dolls to slip on the fingers, gyms with objects hanging low enough to be reached, bright rattles... for children 1-3 years: soap bubbles, clay, finger crayons; for preschool children: highlighters, crayons to connect to the wheelchair base, stensils; for age school children: racetracks, make up, videogames...)
- Commonly available and easily adaptable toys: puzzle with small magnets for easy positioning.
- Adapted toys, specially designed to meet specific needs: battery toys connected to external sensors which allows facilitated activation (figure 12).

Figure 12

Conclusions

SMA children require a special care; granting a good quality of life should be the most important goal for these children and their family.

Caregivers' training in the management of daily home care is crucial to guarantee a safe and early discharge at home.

Disclosure

The authors declare that they have no competiting interests.

References

1. Lefebvre S, Burglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell 1995; 80: 155-165.
2. Farrar MA, Kiernan M. Spinal muscula Atrophy. In: Encyclopaedia of life sciences. Chichester: John Wiley & sons, Ltd; 2011.
3. Munsat TL. The spinal muscular atrophies. Current Neurology. St Louis, Mo: Mosby; 1994; 325-367.
4. Mannaa M, Kalra M, Wong B, Cohen A, Amin RS.

Survival probabilities of patients with childhood spinal muscle atrophy. Journal of clinical neuromuscular disease 2009; 10:85-89.

5. Dubowitz V. Chaos in the classification of SMA: a possible resolution. Neuromuscular disorders 1995; 5:3-5.
6. Merlini L, Granata C, Dubowitz V. Current Concepts in childhood spinal muscular atrophy. Wien; New York :Springer-Verlag; Bologna: Aulo Gaggi Editore, 1989.
7. Pearn J. The gene frequency of acute Werdnig-Hoffman disease (SMA type 1): a total population survey in North-East England. J Med Genet 1973; 10: 260-265.
8. Pearn J. Incidence, prevalence and gene frequency studies of chronic childhood spinal muscular atrophy. J Med 1978; 15: 409-413.
9. Bertini E, Burghes A, Bushby K, et al. 134th ENMC International Workshop: Outcome Measures and Treatment of Spinal Muscular Atrophy, 11-13 February 2005, Naarden, the Netherlands. Neuromuscul Disord. 2005; 15:802-816.
10. Dubowitz V. Very severe spinal muscular atrophy (SMA type 0): an expanding clinical phenotype. Eur J Paediatr Neurol. 1999; (3): 49 – 51.
11. Willig TN, Paulus J, Lacau-Saint-Guily J, et al. Swallowing problems in neuromuscular disorders. Arch Phys Med Rehab. 1994;75:1175-1181.
12. Tilton AH MM, Khoshoo V. Nutrition and swallowing in pediatric neuromuscular patients. Semin Pediatr Neurol. 1998; 5:106-115.
13. Houston KD, Buschang PH, Iannaccone ST, Seale NS. Craniofacial morphology of spinal muscular atrophy. Pediatr Res. 1994; 36:265-269.
14. Grunebaum M, Nutman J, Nitzan M. The pharyngo-laryngeal deficit in the acute form of infantile spinal muscular atrophy (Werdnig-Hoffmann disease). Pediatr Radiol. 1981; 11:67-70.
15. Ching H. Wang, Richard S. Finkel, Enrico S. Bertini, Mary Schroth, Anita Simonds, Brenda Wong, Annie Aloysius, Leslie Morrison, Marion Main, Thomas O. Crawford, Anthony Trela and Participants of the International Conference on SMA Standard of Care. Consensus Statement for Standard of Care in Spinal Muscular Atrophy. J Child Neurol 2007; 22:1027.
16. Granger MW, Buschang PH, Throckmorton GS, Iannaccone ST. Masticatory muscle function in patients with spinal muscular atrophy. Am J Orthod Dentofacial Orthop. 1999; 115:697-702.
17. Mastella C, Ottonello GC: La cura del corpo del bambino nella vita quotidiana. In: SMA1 Abita con noi. Print LAb S.r.l – Spazio Aperto S.c.a.r.l. Buccinasco 2009, pp 71 – 107.
18. Birnkrant DJ, Pope JF, Martin JE, et al. Treatment of type I spinal muscular atrophy with noninvasive ventilation and gastrostomy feeding. Pediatr Neurol. 1998; 18:407-410.
19. Hough JL, Johnston L, Brauer SG, Woodgate PG, Pham TMT, Schibler A. Effect of body position on ventilation distribution in preterm infants on continuous positive airway pressure. Pediatr Crit Care Med 2012; 13: 446 – 451.
20. Bush A, Fraser J, Jardine E, et al. Respiratory management of the infant with type 1 spinal muscular atrophy. Arch Dis Child. 2005;90:709-711.
21. Chatwin M, Ross E, Hart N, et al. Cough augmentation with mechanical insufflation/exsufflation in patients with neuromuscular weakness. Eur Respir J. 2003; 21:502-508.
22. Finder JD, Birnkrant D, Carl J, et al. Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. Am J Respir Crit Care Med. 2004; 170:456-465.
23. Plecash AR, Leavitt BR. Aquatherapy for neurodegenerative disorders. J Hungtington disease 2014; 3:5-11.

24. Pini A, Ghezzo A. Atrofia muscolare spinale tipo I o grave (Malattia di Werdnig – Hoffmann). In: Dopo la diagnosi. Il monitoraggio delle malattie neuromuscolari ad esordio in età evolutiva. Pini A, Ghezzo A. Alberto Perdisa eds. 2007; pp 102 – 103.
25. Main M, Kairon H, Mercuri E, Muntoni F. The Hammersmith functional motor scale for children with spinal muscular atrophy: a scale to test ability and monitor progress in children with limited ambulation. Eur J Paediatr Neurol. 2003; 7:155 - 159 .
26. Mercuri E, Messina S, Bertini E, et al. Reliability of the Hammersmith functional motor scale for spinal muscular atrophy in a multicentric study. Neuromuscul Disord. 2006; 16: 93 – 98.
27. Messina S, Pane M, De Rose P, Vasta I, Sorleti D, Aloysius A, Sciarra F, Mangiola F, Kinali M, Bertini E, Mercuri E. Feeding problems and malnutrition in spinal muscular atrophy type II. Neuromuscular Disorders 2008; 389–393.
28. Jenkins HM, A. Stocki, D. Kriellaars, H. Pasterkamp. Breath Stacking in Children With Neuromuscular Disorders. Paediatric Pulmonology 2014; 49:544-553.
29. Tzeng AC, Bach JR. Prevention of pulmonary morbidity for patients with neuromuscular disease. Chest 2000;118:1390–1396.
30. Louis J. Boitano. Equipment Options for Cough Augmentation, Ventilation, and Noninvasive. Pediatrics 2009;123;S226.
31. Kirby N, Barnerias MS, Siebens AA. An evaluation of assisted cough in quadriparetic patients. Arch Phys Med Rehabil. 1966; 47:705–710.
32. Fiona CE Moran, Alicia Spittle, Clare Delany, Colin F Robertson and John Massie. Effect of home mechanical in-exsufflation on hospitalisation and life-style in neuromuscular disease: A pilot study. Journal of Paediatrics and Child Health 2013; 49:233–237.