The 2017 Update of the Standard of Care Recommendations for Spinal Muscular Atrophy

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Educational Objectives

• Participants should be able to:
  – Implement the currently recommended algorithm for SMA diagnosis in daily clinical practice
  – Apply a multidisciplinary approach to the management of SMA according to the current best practices
  – Develop a comprehensive care plan in close cooperation with neurologists, physical therapists, respiratory therapists, and other members of the multidisciplinary team
  – Describe the key benefits of the first treatment approved for the management of SMA
Purpose of the Spinal Muscular Atrophy Standard of Care

• Supply an aspirational or optimal care guide
• Provide an opportunity to justify resource allocations
  – Illustrates the importance of multidisciplinary care
• Identify knowledge gaps and promotes future research
  – Illustrates both progress in evidence levels and unmet needs
• Provide a standard for research protocols
  – Minimizes variation, thus improving the accuracy and efficiency of clinical trials

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Practice Goals of the Spinal Muscular Atrophy Standard of Care

- Reduce the diagnostic odyssey for SMA patients
- Early identification of symptomatic individuals
- Anticipatory guidance on the natural history of the disease
- Proactive care for anticipated aspects of the disease, including pulmonary, nutritional, and orthopedic aspects
Standards of Care and the Changing Natural History of Spinal Muscular Atrophy

• Improved supportive care and newly approved drugs are altering SMA natural history and phenotype
  – These changes are likely to affect the use of guidelines over time

• The current SOC anticipates developments in care
  – Fundamentals of care will remain constant
Adaptation of Spinal Muscular Atrophy Subtype Classification to Functional Status

• SMA type classification is defined by age of onset and motor function
• The new SOC treats individuals based on current functional status, not on their subtype classification at diagnosis
  – Change from previous guideline
Further Changes From 2007 Guidelines

• Updated topics:
  – Pulmonary aspects
  – GI and nutritional aspects
  – Orthopedic aspects
  – Physical therapy and rehabilitation
  – Ethics and palliative care

GI, gastrointestinal.

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Further Changes From 2007 Guidelines

• New topics:
  – Acute care management
  – Medication
  – Other organ systems beyond motor neurons (SMN effect on muscle/GI systems etc.)
Diagnosis
Important Factors in the Diagnostic Processes

• Guidance for the evaluation of the hypotonic child has been updated
• Early diagnosis and treatment is critical to therapy success
• Pediatricians should send hypotonic “floppy” babies to a neurologist immediately

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Simple Diagnostic Signs for Pediatricians

- Weight bearing
  - A baby held under the armpits should attempt to bear weight with legs
- Head control
  - Head control should be reasonable by age 1 or 2 months, and should improve
- De-rotation of trunk
  - Rotation of the pelvis should cause rotation of the shoulder girdle, and vice versa

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The child must be seen within days

A highly reliable genetic test for SMA is available:
- 96% positive for infant with SMA
- 100% specific

If there is one copy of SMN1 (4%), further testing is required by a specialist (e.g. EMG)

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Other Testing and Screening Considerations

• *SMN2* copy number should be requested, as this is a strong prognostic biomarker for disease severity
• Early diagnosis is key for treatment efficacy and anticipatory care
• Newborn screening will facilitate more rapid presymptomatic diagnosis

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Multidisciplinary Care
The Importance of Multidisciplinary Care

- Parents have a central role at all stages, which is essential for holistic care and treatment compliance.
- Downstream complications of weakness (e.g., respiratory problems) are a very frequently experienced in the disease, and are major issues for care.
- Optimal coordination of multidisciplinary care is crucial.
- Multidisciplinary care must adapt to local resources.

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Physical Therapy
The Changing Role of Physical Therapy and Rehabilitation

• New treatment options are changing the phenotype
• The goal of physiotherapy is to promote optimal motor function as these phenotypic changes evolve
• The management of adult patients has to be considered
• Physiotherapy should: increase independent functioning and living; reduce pain; reduce the burden of disease

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The Changing Role of Physical Therapy and Rehabilitation

• Range of motion and positioning are key
• Exercise, orthoses, and weight-bearing for promotion of bone strength are also important
• Preventing contractures is a goal
• Finding experts regionally may be an issue for physical therapy
  – Travel to a specialist center followed by local implementation may be necessary

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Goals of Physiotherapy

• Promotion of well being and independent function is the goal of physical therapy for all Types of SMA
• In non-ambulant patients, the focus is on upper limb function e.g. with the help of assistive devices
• Patients should be encouraged to expect more from physical therapy
Orthopedic Care
Orthopedic Care, Growth, and Bone-Health Care

- Scoliosis remains a challenge, along with other deformations
- Major advancements have occurred since 2007 in growth-enabling surgeries
- Preventive care allows definitive spinal fusion surgery to be carried out later than was previously the case

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Orthopedic Care Algorithm

Clinical examination of the spine

Spinal X-ray

If > 15–20°: monitor

If >15-20°: thoracic bracing and monitor

> 50°: discuss surgery

Skeletally immature: consider growing rods, VEPTR, magnetic bars

In skeletally mature: spinal fusion

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VEPTR, vertical expandable prosthetic titanium rib.
Orthopedic Surgery and Intrathecal Access

• During spinal surgery the necessity for intrathecal access for novel SMA therapies (i.e. nusinersen) should be considered
  – Creating a lumbar window during surgery is one option

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Nutrition
Nutrition

• Nutrition is one of the most challenging areas for SMA care
• Optimal growth is difficult to assess using growth charts due to differences in muscle and bone mass
  – It is difficult to define what represents an over/undernourished child
• It is important to consider bone health, with a focus on vitamin D and calcium
• Care should be taken to prevent deficiencies in micronutrients

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Pulmonary Care
Pulmonary Care

• Pulmonary care is also extremely challenging
• Major issues include:
  – Ineffective airway clearance, due to reduced cough efficiency (cough-assist machines are highly effective)
  – Increased sleep hypoventilation (BiPAP may be effective, but is not available everywhere)
  – Increased aspiration, which must be prevented
• Physical examination and assessment of sleep remains key

BiPAP, Bilevel Positive Airway Pressure.
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Clinical assessment

- Inspiratory, expiratory, bulbar muscle weakness, scoliosis, chest-wall abnormality

- REM-related sleep-disordered breathing
  - FVC < 60% predicted

- NREM- and REM-related sleep-disordered breathing
  - FVC < 40% predicted

- Ineffective cough
  - Cough peak flow < 270/min

- Swallowing dysfunction

- Chest infection

- Day time ventilatory failure
  - FVC < 20% predicted

FVC, forced vital capacity;
NREM, non-rapid eye movement;
REM, rapid eye movement.

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Pulmonary Care

- Paradoxical breathing due to muscle weakness might be at the root of later chest deformity
  - Early preventative BiPAP has been suggested to avoid chest deformity
  - This remains an area of controversy in need of further research

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The Acute Care Setting

- Key topics are pulmonary management and nutritional support
- Perioperative fasting is not an option
  - Caloric support and fluid balance have to be provided throughout procedures
- Anticipation, and the presence of a pulmonologist, is a requirement to manage expected admissions
  - Consider difficult airways and how these should be managed

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The Acute Care Setting

- Anticipation of complications, and presence of a care plan, are important for unexpected admissions
  - Parents should have a care plan and know what can be achieved at home
  - Equipment should be brought from home
  - A hospital with optimal care options should be chosen (pulmonary team present), if possible

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Medication
Pulmonary Medication

• There has been a reduction in the use of inhaled antibiotics with better pulmonary management

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SMN-Enhancing Agents: Nusinersen

- Nusinersen is the first approved drug for treating SMA
- It increases the amount of functional SMN protein
- It slows or stops degeneration
  - Early intervention is important
  - Functional improvement observed through development
- The magnitude of benefit depends on the time of intervention
Nusinersen

• Nusinersen is FDA approved for all ages and for all SMA classifications
  – Adults are expected to benefit from the treatment but clinical data is limited; robust outcome measures for adult patients are lacking
• Multidisciplinary care remains important
• Due to costs, access to the drug may be restricted in some regions

FDA, US Food and Drug Administration.

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Effect of Nusinersen on Phenotype

- Improvements in function associated with treatment are blurring the Type classification system.
- Improvements can occur asynchronously:
  - The most marked and rapid improvements are those in motor function.
  - Delayed or different levels of improvement may be occurring simultaneously in pulmonary and bulbar functions.
  - An infant with Type I SMA will not have a Type II phenotype after treatment but will have a new phenotype.

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Other Emerging Treatment Options in Clinical Trials

• Two classes of treatment options:
  – SMN-enhancing therapies (small molecules, gene therapy)
  – Downstream modifying drugs targeting e.g. the muscle
• Combination therapies might prove beneficial
Other Emerging Treatment Options in Clinical Trials

• Oral SMN-enhancing therapies that might have a systemic effect in other tissues are under investigation
• Gene therapy targeting SMN production is currently being tested in clinical trials

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Current and Future Prospects in SMA Management
Changing Outlook

• In 2007, infants with Type I SMA had a disease with an unmodifiable downward trajectory
  – SOC guidelines required a balance of burden of care and gain in quality of life

• In the changed landscape of the 2017 SOC, this care balance still remains a key consideration, though prospects are considerably brighter

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Palliative Care

• Palliative care must be integrated into all levels of SMA therapy
  – All treatment has a level of burden, which must not exceed what can be achieved

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Changing Outlook

• New therapies are disease-modifying, they are not cures
  – The considerations for patient care have been modified, not changed completely
  – Managing parental expectations is a challenge
  – Care, consideration, and a patient-/parent-focused approach remain key

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Newborn Screening and Early Treatment Initiation

• Early treatment appears to be a major factor in disease modification with novel and emerging therapies
• SMA newborn screening can be conducted early, particularly in regions with screening programs in place
• Consideration is required into how to manage asymptomatic infants with SMA
  – Sensitivity is required in breaking the news to parents with seemingly well infants
Newborn Screening and Early Treatment Initiation

- Alternative management plans for infants with different SMN2 copy numbers will likely be necessary
  - It has been suggested that SMN-enhancing therapy should be considered quickly in those with ≤ 3 copy numbers
  - Treatment for those with 4 copies, who are often asymptomatic for long periods, will need to be guided by future experience to balance the burden of treatment with potential efficacy reductions caused by delay

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Newborn Screening and Early Treatment Initiation

- Approval of newborn screening is anticipated in the USA
- In countries outside the USA, the presence of current newborn screening programs will likely be key
  - SMA screening can be added to SCID testing at a relatively low cost
  - Addition of SMA screening alone is costly
- Availability of treatment is likely to be a significant consideration

SCID, severe combined immunodeficiency.

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Key Messages

• There is an important role for the SOC guidelines for symptomatic, and possibly also for presymptomatic, patients
• In patients treated with novel therapies, the role of the SOC guidelines regarding all aspects of multidisciplinary care is likely to change and evolve with the changing phenotype of SMA