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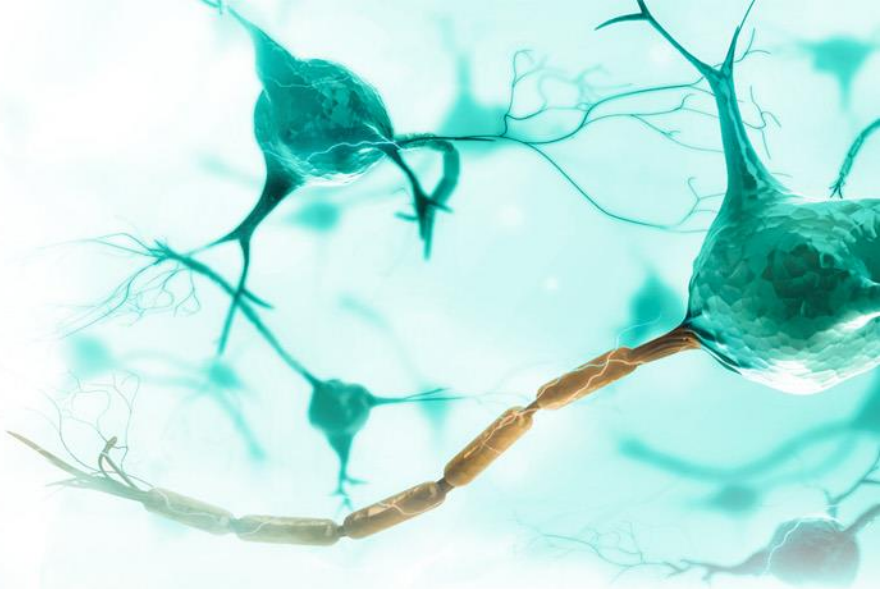

The 2017 Update of the Standard of Care Recommendations for Spinal Muscular Atrophy

Mercuri E, et al. Neuromuscul Disord. 2018;28:103-15.
Finkel RS, et al. Neuromuscul Disord. 2018;28:197-207.

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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

SMA, spinal muscular atrophy.

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

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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

SOC standards of care.

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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

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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.)

SMN, survival of motor neuron protein.

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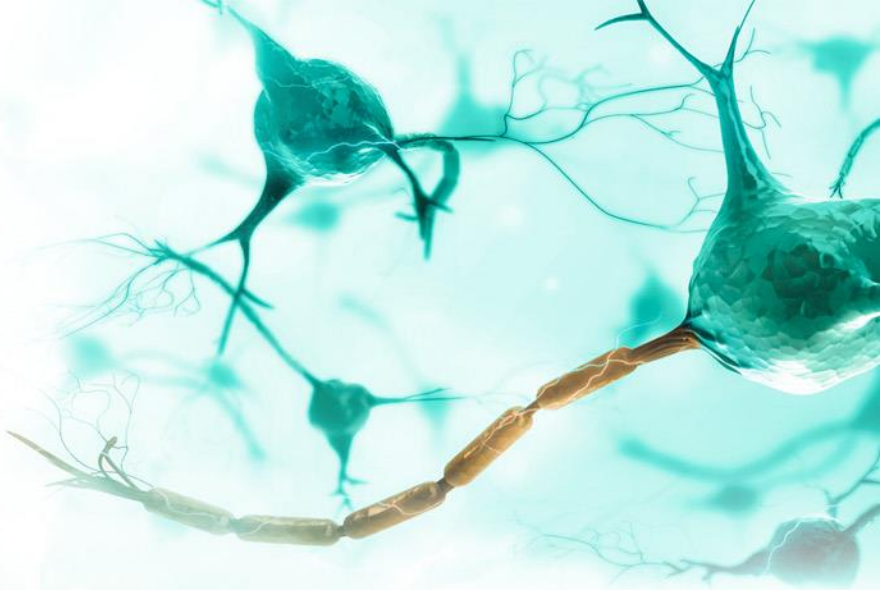

Diagnosis

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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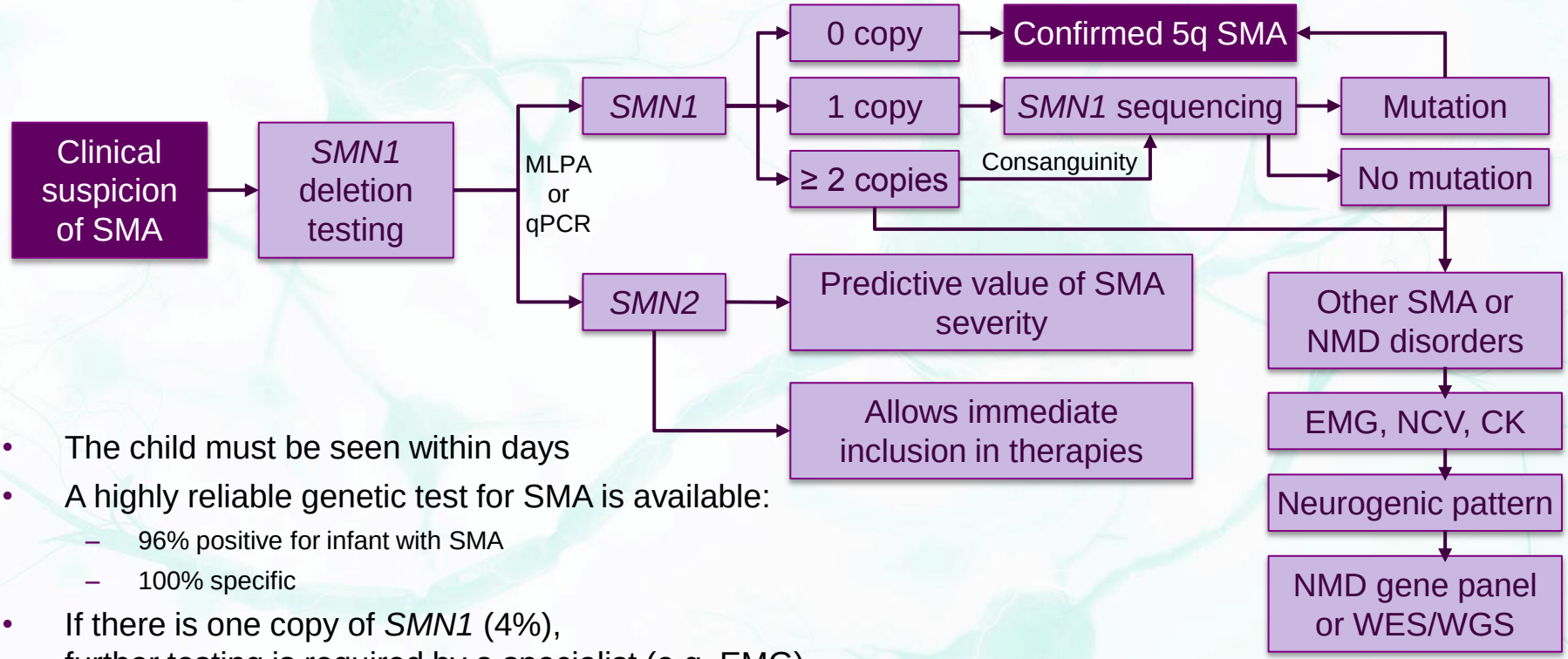
Diagnostic Algorithm



- 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)

Mercuri E, et al. Neuromuscul Disord. 2018;28:103-15.
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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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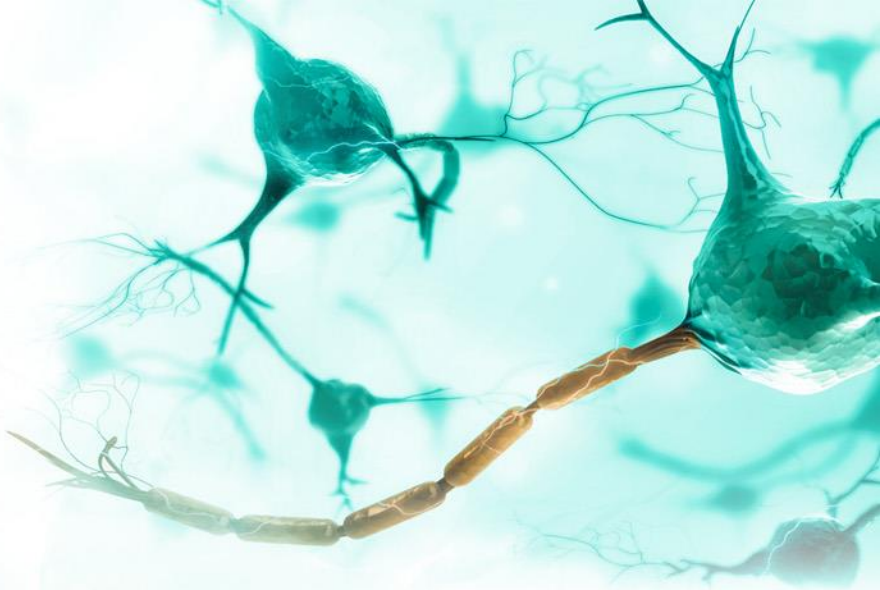

Multidisciplinary Care

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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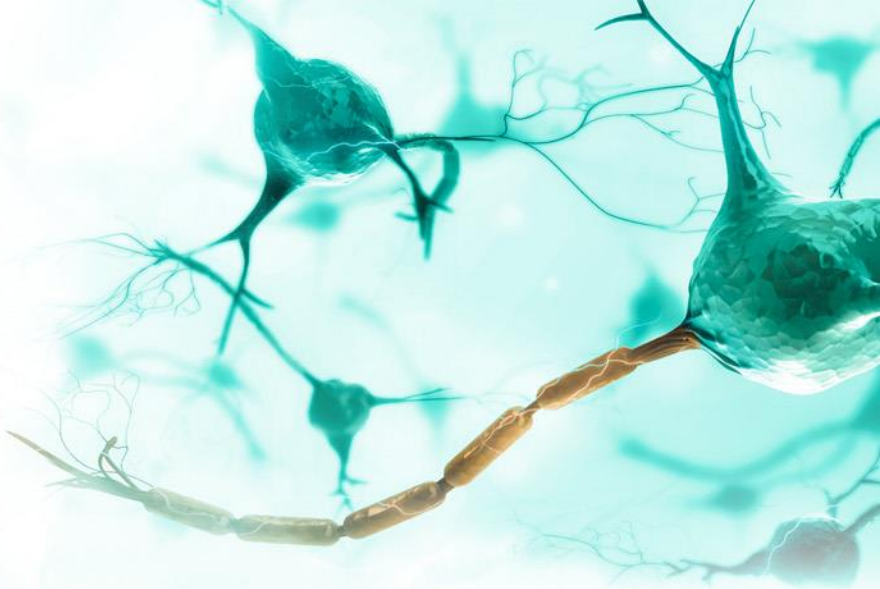

Physical Therapy

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

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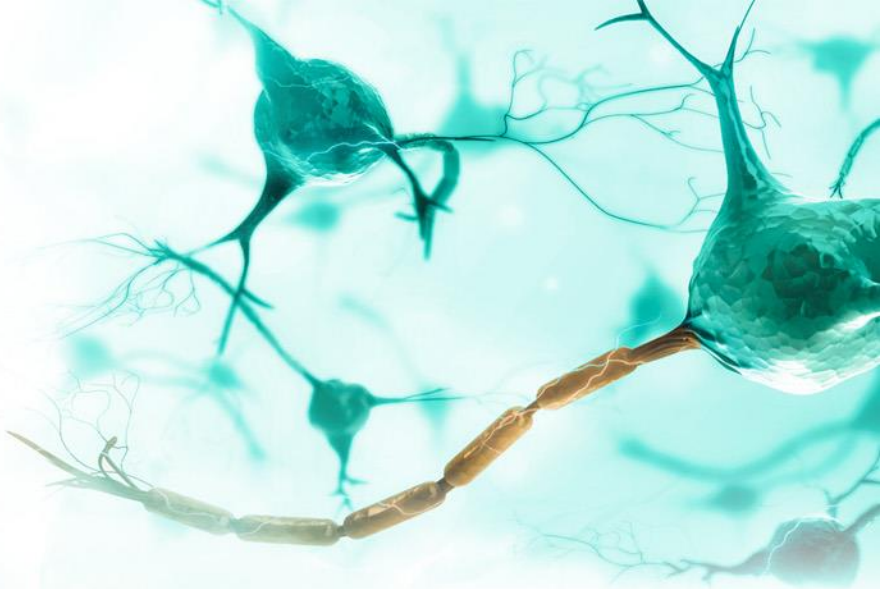

Orthopedic Care

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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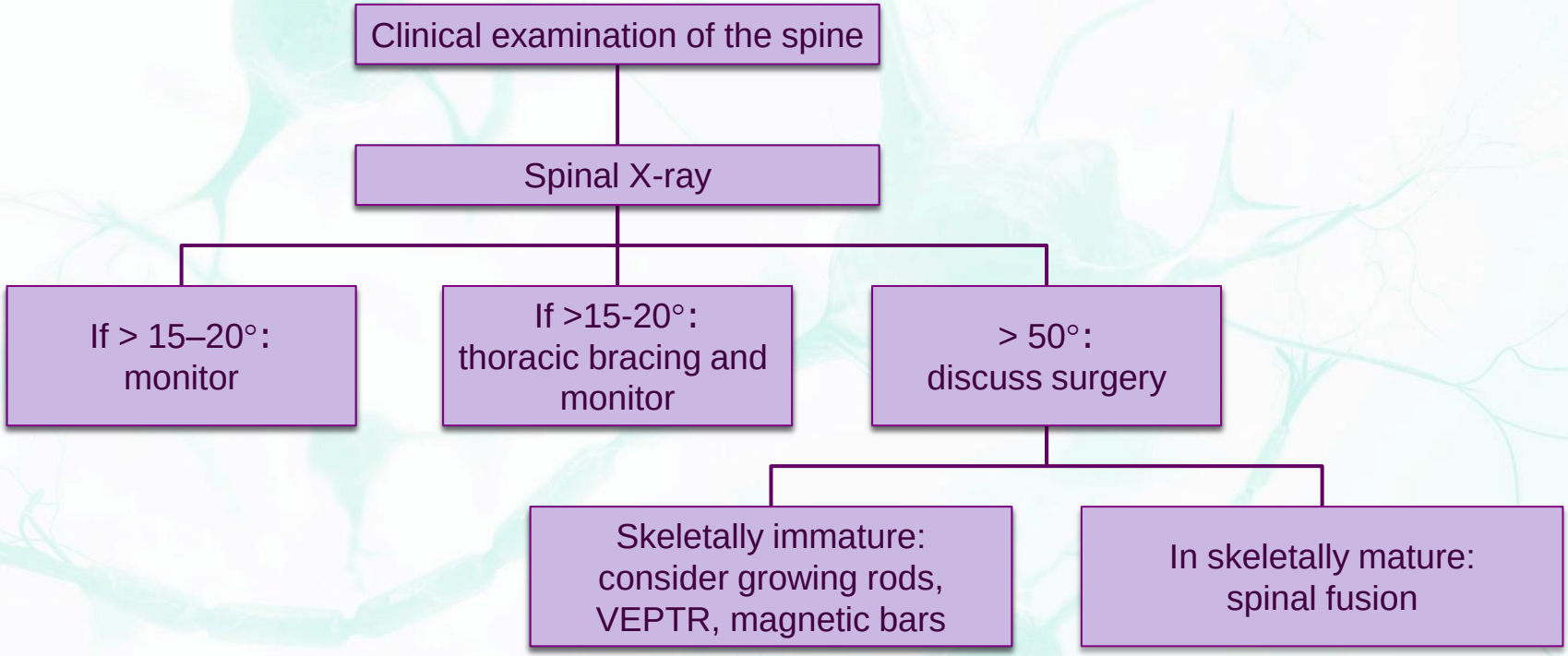
Orthopedic Care Algorithm



VEPTR, vertical expandable prosthetic titanium rib.

Mercuri E, et al. Neuromuscul Disord. 2018;28:103-15.
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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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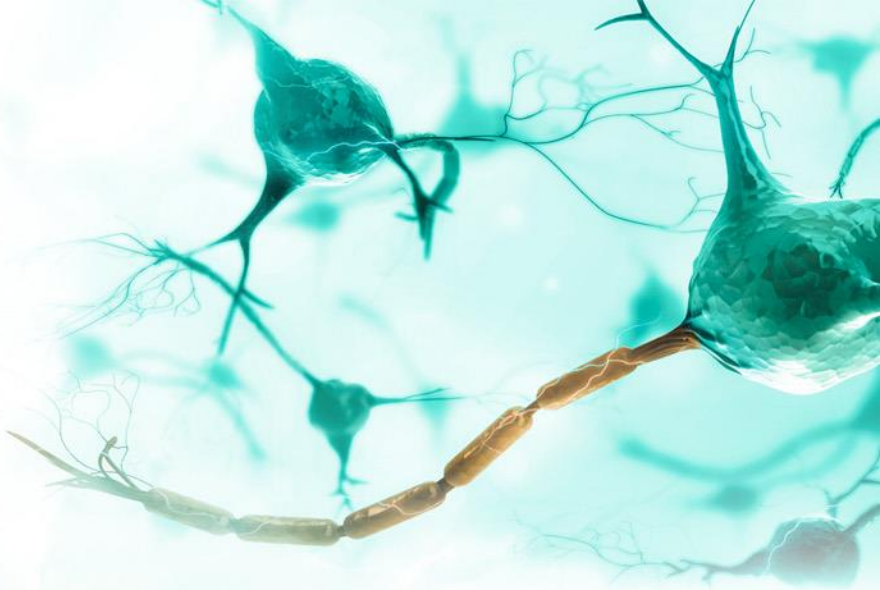

Nutrition

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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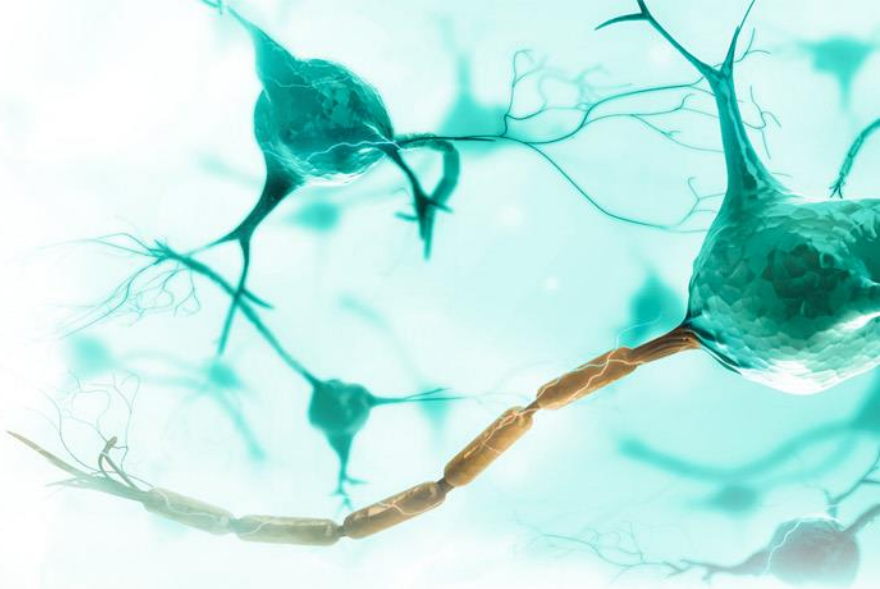

Pulmonary Care

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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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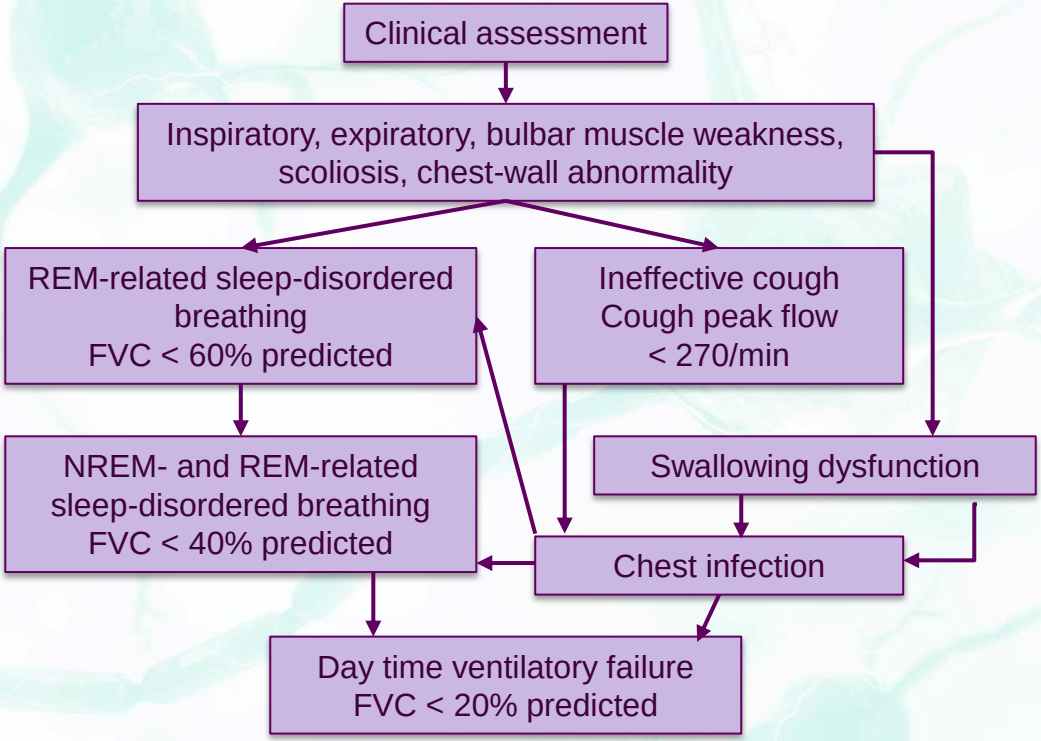
Pulmonary Care Algorithm



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

Finkel RS, et al. Neuromuscul Disord. 2018;28:197-207.
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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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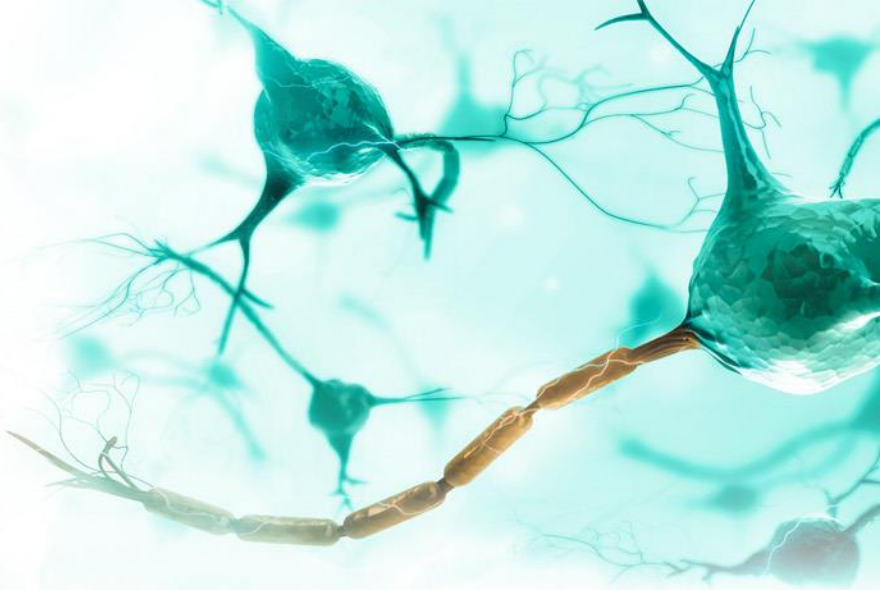

Acute Care

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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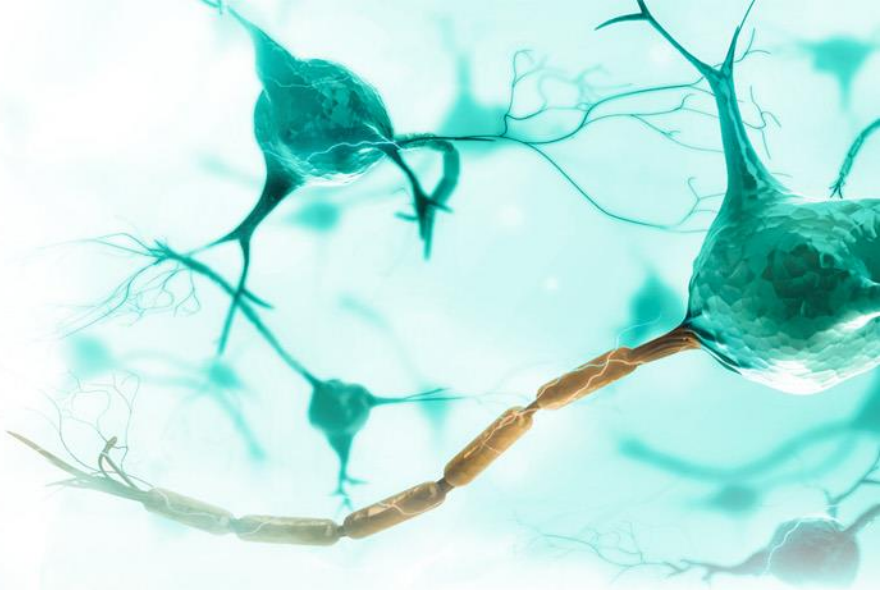

Medication

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

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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

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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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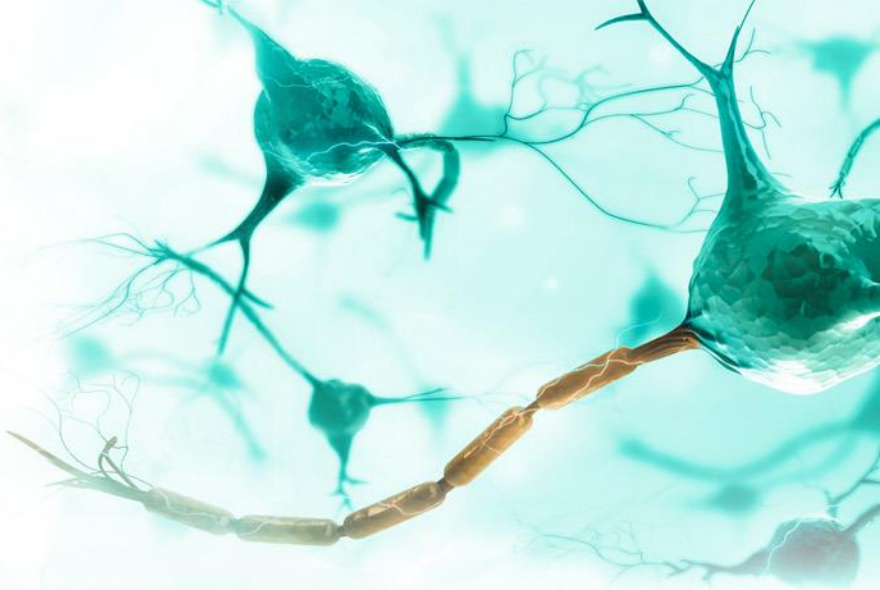

Current and Future Prospects in SMA Management

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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

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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

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