Pulmonary care in SMA: what the spine surgeon should know

Mary Schroth MD
Professor, Pediatric Pulmonology

University of Wisconsin School of Medicine and Public Health, Madison
UW Health American Family Children’s Hospital
Director, Pediatric Pulmonary Center Training Grant
mschroth@wisc.edu

Cure SMA Medical Director
Chair, Cure SMA Medical Advisory Council
mary@curesma.org
Disclosures

- Cure SMA – Paid Medical Director
- AveXis - Advisory Committee Member
- Biogen Idec – Advisory Committee Member
- IONIS Pharmaceuticals – Advisory Committee Member
- HHS/HRSA/Maternal Child Health Bureau – Pediatric Pulmonary Center Training Grant
Learning Objectives

Participants will:

1. Identify the effects of neuromuscular weakness on respiratory pathophysiology and the resulting respiratory complications.

2. Describe management strategies that optimize respiratory function.

3. Consider the impact of gene modifying therapy on SMA.
Standard of Care Guidelines SMA

Consensus Statement for Standard of Care in Spinal Muscular Atrophy

Ching H. Wang, MD, PhD, Richard S. Finkel, MD, Enrico S. Bertini, MD, Mary Schroth, MD, Anita Simonds, MD, Brenda Wong, MD, Annie Aloysius, MRCSLT, HPC, Leslie Morrison, MD, Marion Main, MCSP, MA, Thomas O. Crawford, MD, Anthony Trela, BS, and Participants of the International Conference on SMA Standard of Care

Encompasses:

• Diagnosis
• Respiratory Care
• GI and Nutrition
• Musculoskeletal
• Palliative Care

Spinal Muscular Atrophy

- Multi-organ involvement
  - Musculoskeletal
  - Respiratory
  - GI and nutrition
  - Bone health
  - Autonomic
  - Mental health
  - Cardiac

- It takes a village…
Neuromuscular Disorders

• Cause of death is usually respiratory failure.
Normal breathing

Respiratory and bulbar muscle weakness

REM related sleep disordered breathing

Ineffective cough reduced peak cough flows

NREM and REM sleep disordered breathing

Swallow dysfunction

Chest infections

Daytime ventilatory failure

Death

Physical examination

Pulmonary function, peak cough flow, respiratory muscle strength

Chest xray, Sleep study

Swallow function evaluation

Airway clearance with cough assistance

Nocturnal non-invasive ventilation

Nocturnal or continuous non-invasive ventilation

Spinal Muscular Atrophy

- **Progressive autosomal recessive** genetic disorder
  - affects the motor neurons of the anterior horn cells.

![Diagram showing genetic inheritance and phenotypes of Spinal Muscular Atrophy](image)

- Unaffected 1/4 25%
- SMA Carrier 2/4 50%
- SMA Carrier 2/4 50%
- SMA Affected 1/4 25%

*percentages are for each pregnancy.*
SMA Genetics

- Carrier rate: 1 in 50
- Incidence estimate: 1/6,000-1/10,000 live births
- Diagnose by gene mutation testing
  - Chromosome 5q (>95%)
    - Homozygous deletion of SMN1 exon 7 and/or exon 8 OR
    - Gene conversion of SMN1 to SMN2-like
  - Remaining 5% have point mutation

- Most common lethal genetic disease of children under 2 yo
SMA Clinical Manifestations

- Symmetric muscle weakness
- Wasting of voluntary muscles
  - Proximal muscles weaker than distal muscles
  - Legs weaker than arms
  - Tongue fasciculations
  - Absent deep tendon reflexes
  - Weak intercostal muscles in SMA type I and II

- Normal intellect and sensation
- “Bright-eyed hypotonic baby”
# Clinical Classification of SMA

<table>
<thead>
<tr>
<th>SMA TYPE</th>
<th>Incidence</th>
<th>Age of Onset</th>
<th>Motor Milestones</th>
<th>Ave Age of Death (limited interventions)</th>
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<tbody>
<tr>
<td>I</td>
<td>50-60%</td>
<td>&lt; 6 months</td>
<td>Non sitter</td>
<td>&lt; 2 years</td>
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<tr>
<td>II</td>
<td>25%</td>
<td>&lt; 18 months</td>
<td>Sitter</td>
<td>2nd - 3rd decade</td>
</tr>
<tr>
<td>III</td>
<td>10%</td>
<td>&gt; 18 months</td>
<td>Stander/walker</td>
<td>Normal life expectancy</td>
</tr>
<tr>
<td>IV</td>
<td>5%</td>
<td>Adolescent or Adult onset</td>
<td>Retain walking, muscle pain</td>
<td>Normal life expectancy</td>
</tr>
</tbody>
</table>
Changing Natural History of SMA Type I

- Comparison of children with SMA type I born between:
  - 1980-1994 (n=65)
  - 1995-2006 (n=78)
- Subjects identified using the Indiana University International SMA Patient Registry
- Surveyed by mail with follow up questions.

Kaplan–Meier survival plots of Spinal Muscular Atrophy type 1

Event death

- Birth 1995-2006
- Birth 1980-1994

Events death or ventilation >16 hours

- Birth 1995-2006
- Birth 1980-1994

SMA Gene

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### Phenotype/Genotype (cont.)

<table>
<thead>
<tr>
<th>$SMN\ 2\ copy\ #$</th>
<th>SMA 1</th>
<th>SMA 2</th>
<th>SMA 3</th>
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<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>0</td>
<td>0</td>
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<tr>
<td>2</td>
<td>73</td>
<td>11</td>
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<td>3</td>
<td>20</td>
<td>82</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>7</td>
<td>45</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

SMN2 gene copy number varies in the population and modifies disease severity.

Courtesy of Thomas Crawford MD, Presentation at Cure SMA Annual Conf 2015
### 2017 SMA Drug Discovery Pipeline

<table>
<thead>
<tr>
<th>ORGANIZATION/RESEARCH NAME OR APPROACH</th>
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<tbody>
<tr>
<td>- Spinraza</td>
</tr>
<tr>
<td>- AVXS-101 (systemic)</td>
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<tr>
<td>- Otsuka</td>
</tr>
<tr>
<td>- CK-2177107</td>
</tr>
<tr>
<td>- LM970</td>
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<tr>
<td>- Ro7916</td>
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<tr>
<td>- AVXS-101 (CNS-delivered)</td>
</tr>
<tr>
<td>- SRM-015 (muscle drug)</td>
</tr>
<tr>
<td>- Small Molecule (muscle drug)</td>
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<tr>
<td>- ACE-249 (muscle drug)</td>
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<tr>
<td>- CNS Gene Therapy</td>
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<tr>
<td>- Gene Therapy</td>
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<tr>
<td>- Small Molecule (CNS)</td>
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<td>- Morphine ASQ</td>
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<tr>
<td>- Small Molecule (CNS)</td>
</tr>
<tr>
<td>- Small Molecule (muscle)</td>
</tr>
<tr>
<td>- p38a/HAPK Inhibitor</td>
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<tr>
<td>- JNK Inhibitor</td>
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#### Basic Research Seed Ideas
- **Identification**
- **Optimization**
- **Safety & Manufacturing**

#### Preclinical: Discovery
- **Phase 1**
- **Phase 2**
- **Phase 3**

#### Clinical Development
- **FDA Approval**
- **To Patients**

**IND = Investigational New Drug**
**NDA = New Drug Application**

Last updated: May 2017
Gene Modified SMA
Respiratory Management
Complications of Respiratory Muscle Weakness in SMA

1. Impaired cough
   - Poor clearance of lower airway secretions

2. Hypoventilation during sleep
   - hypercarbia
   - hypoxemia

3. Recurrent infections that contribute to muscle weakness.

4. Chest wall and lung underdevelopment in SMA type I and II

Chest Wall Changes

Normal  SMA  DMD

NMD Lung Function Loss

- **VIRAL RESPIRATORY INFECTIONS**
  - Rhinovirus RSV Parainfluenza Influenza Etc…
  - Transient muscle function weakness

- **IMPACT:**
  - Increased muscle weakness
  - Copious airway secretions
  - More difficulty breathing
  - Risk for respi
Perioperative Care

- Respiratory Support
- Nutrition
Breathing Basics

- Secretion mobilization
- Cough Augmentation
- Respiratory support
Secretion Mobilization

• Manual Chest Physiotherapy or Mechanical Percussion

• Postural Drainage
Other Techniques

High Frequency Chest Wall Oscillation

Intrapulmonary Percussive Ventilation
Cough Mechanism

3 Phases of a cough

1. Inspiratory phase
2. Closure of vocal cords/contraction of expiratory muscles
3. Opening of the vocal cords
Mechanical Insufflation-Exsufflation: Cough Machines

- Respironics Cough Assist™ CA-3000
- Respironics Cough Assist™ T70
- Hill-Rom Vital Cough™
Cough Machine

- SETTINGS to use by mask, mouth piece, tracheostomy tube or endotracheal tube.
  - INSPIRATORY
    - Start at +25-30, increase to +40 cm H₂O for 1-2 sec.
  - EXPIRATORY
    - Start at –25-30, increase to -40 cm H₂O for 1-2 sec.
  - PAUSE TIME
    - 1-2 sec.
  - Perform 4 sets of 5 breaths
Pulse Oximetry

- Use to guide airway clearance therapy
- Acutely decreased oximetry (< 95% while AWAKE)
  - suggests increased secretions, mucus plugging, or atelectasis.
  - may be the first sign of respiratory compromise.
- < 95% while ASLEEP
  - suggests hypoventilation or mucus plugging.

OXYGEN IS A LAST RESORT AFTER ALL OTHER INTERVENTIONS ARE OPTIMIZED!
FRC Relative to Position

From Nunn’s Applied Respiratory Physiology, 2000
Respiratory Support Options

- Used during sleep or at least 6 hours per day
- Non-invasive ventilation
  - Bilevel positive airway pressure
  - Mechanical ventilation
- Invasive ventilation
  - Tracheotomy with Mechanical ventilation
Chronic Respiratory Failure: Bilevel Positive Airway Pressure Effects

- Sustained reduction of daytime PaCO2
  - 3 Theories for NIV effect:
    - Rests chronically fatigued respiratory muscles
    - Reverses micro-atelectasis
    - Alters the CO2 “set point”

Mehta and Hill, Am J Respir Crit Care Med 2001; 163:540
Positive Pressure Ventilation Devices

1. Bilevel positive airway pressure devices
   Non-invasive only

CPAP is NOT INDICATED for Neuromuscular hypoventilation
Non Invasive Bilevel Positive Airway Pressure

• Goals:
  • Ventilation
  • Decrease work of breathing – rest respiratory muscles
    » Decrease belly breathing
    » Normalize heart rate during sleep
  • Improve chest wall expansion
Indications for Positive Pressure Ventilation

• **Sleep study:**
  – Hypoventilation (↓ SpO2, ↑ pCO2)
  – Obstructive sleep apnea

• **Specific to NMD**
  – Respiratory failure during a viral illness
  – Recurrent pneumonia or atelectasis
  – Post-operative care
Chest Wall Development After NIV

6 mths

18 mths

Courtesy of A. Simonds, Royal Brompton Hospital, UK
Nasal Masks

Respironics Wisp Pediatrics

Infant to 2 yo:
- Respironics Wisp Pediatrics
- AG Industries Nonny

Over 2 years old:
- ResMed Pixi
- Sleepnet MiniMe 2
- Respironics Wisp
- Fisher & Paykel Eson
- Fisher & Paykel Zest

AG Industries Nonny, Size Small Child, AG-PEDKIT-S
Invasive Ventilation

- Tracheostomy placement
  - Not an acute intervention
  - Involve primary medical team in decision making
- Indications
  - 24 hour per day NIV dependent
  - Frequent cyanotic episodes or respiratory instability on NIV
  - NIV intolerance
  - Failure to extubate
  - Patient preference

Positive Pressure Ventilation

• Goals during sleep:
  – Respiratory muscle rest
  – Synchronization
  – Chest wall expansion

• Recommended modes:
  – **PC (Pressure control)** guaranteed inspiratory time with back up rate
  – ST (spontaneous timed) with back up rate
  – PC-AVAPS (average volume assured pressure support) targeted tidal volume within IPAP range
    • IPAPmin must be high enough to support ventilation

• Backup respiratory rate required
Non Invasive Bilevel Positive Airway Pressure

- IPAP: 14-20 cm of H₂O
- EPAP: 4-6 cm of H₂O
- Respiratory Rate: high enough to capture breathing efforts and rest during sleep.
- Inspiratory Time: Longer time preferred to maximize inflation 1.2 seconds
- Rise time: time between exhalation and rise to peak inspiratory pressure (IPAP)
GI and Nutrition Complications

- Dysphagia
  - Aspiration
  - Weight loss
- Gastroesophageal reflux
- Gastroparesis
- Constipation
  - Decreased appetite
  - NIV intolerance
- Poor weight gain
- Obesity
GI and Nutrition Complications (cont.)

- Large insensible fluid losses
  - Perspiration
  - Suctioning oral/nasal secretions
  - Hospital I&Os are never balanced
  - 1.2x maintenance
GI and Nutrition Complications
SMA Specifically

• Abnormal fatty acid oxidation
  – Abnormal dicarboxylic aciduria in response to fasting
  – Avoid high fat diet (Max: 20% of calories)
  – Ketosis and ketonuria with fasting/dehydration
  – Avoid fasting in weakest group: anyone with tube feeds

Respiratory Therapy NMD Protocol

• Scoring system to guide frequency of airway clearance and time off ventilation if not 24 hour dependent

• Aggressive airway clearance:
  – Cough assist machine while intubated
  – Secretion mobilization techniques
  – Postural drainage if not ETT intubated
Extubation

Extubate when the patient is:
1. Afebrile
2. Not requiring supplemental O2
3. CXR is without atelectasis or infiltrates
4. Minimal respiratory depressants
5. Airway suctioning is 1 time/hour or less
6. Motor strength and alertness approaching baseline
Extubation (cont.)

• Extubate from reasonable settings:
  – respiratory rate similar to the optimal baseline positive pressure device respiratory rate
  – pressures that approximate BiPAP IPAP (15-20) and EPAP (3-6)
  – room air
  – Wean to use during sleep

• Avoid low ventilator rates through ET tube especially during sleep
  \[\Rightarrow\] atelectasis/fatigue.

• Continue aggressive airway clearance post extubation.
  – Increased airway secretions for 24 hours post extubation
Other Complications of NMD

• Osteopenia – poor bone health
• Scoliosis
• Joint contractures
• Rapid fatigue
• Pain
• Depression
UW Pediatric Neuromuscular Disorder Program

• Respiratory Care
  – Physician/Nurse practitioner
  – Respiratory care practitioners
• Neurology
  – Physician/Nurse practitioner
• Care coordination
  – Clinic coordinator
  – Case Manager
• Palliative Care
  – Physician/Nurse practitioner
• Genetic Counselor
• Nutritionist
• Social Worker

• Orthopedic and Rehabilitation Medicine Services
  – Physician/Nurse practitioner
  – Physical Therapist
  – Occupational Therapist
  – Speech Therapist
  – Orthotist
  – Vocational Rehabilitation Coordinator
• Cardiology
  – Physicians
  – Nurse Practitioner
Summary

• The respiratory complications of neuromuscular disease include:
  – Hypoventilation during sleep and with disease progression while awake
  – Compromised airway secretion clearance
• Supplemental oxygen is not the answer
• Use positive pressure ventilation at settings to ventilate and rest the patient during sleep.
Summary

• Perioperative care includes optimization of pulmonary status and nutrition status.
  – Pulmonary consultation
  – Nutrition consultation
Summary

• The natural history of many neuromuscular diseases are evolving with longer survival and improved care options.
• Gene modifying therapy is creating another form of SMA.
• Interdisciplinary management is essential.
Additional Information

• Cure SMA website: www.curesma.org
• SMA Foundation website: www.smafoundation.org
• Muscular Dystrophy Association website: www.mdausa.org
Questions/ Comments/ Discussion