Spinal Muscular Atrophy: What’s new in the management of pediatric neuromuscular disease

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Disclosures

• Cure SMA – Consultant and Chair, Medical Advisory Council
• American College of Chest Physicians – Speaker
• Avexis - Advisory Committee Member
• Biogen Idec – Advisory Committee Member
• IONIS Pharmaceuticals – Advisory Committee Member
• HHS/HRSA/Maternal Child Health Bureau – Pediatric Pulmonary Center Grant
• This presentation is sponsored in part by Smith's Medical

Thank you!
Learning Objectives

Participants will:

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

2. Identify the areas of improved clinical care that has altered the survival of children with Spinal Muscular Atrophy.

3. Describe management strategies that optimize respiratory function.
Encompasses:

- Diagnosis
- Respiratory Care
- GI and Nutrition
- Orthopedic Concerns
- Palliative Care
Spinal Muscular Atrophy

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

![Diagram of Spinal Muscular Atrophy genetics]

- **Diagram (a)** shows the inheritance pattern:
  - **NN** (Normal Normal) - unaffected
  - **SMA** (SMA) - affected
  - **N** (Normal) - unaffected

- **Diagram (b)** illustrates the genetic makeup:
  - **Unaffected**
    - 1:4
    - 25%
  - **SMA Carrier**
    - 2:4
    - 50%
  - **SMA Carrier**
    - 2:4
    - 50%
  - **SMA Affected**
    - 1:4
    - 25%

*percentages are for each pregnancy.*
Spinal Muscular Atrophy

- Carrier rate: 1 in 50.
- Incidence estimate: 1/6000-1/10,000 live births
- Diagnose by gene mutation testing (>95%)
  - Chromosome 5q, homozygous deletion of SMN1 exon 7 and/or 8 OR gene conversion of SMN1 to SMN2-like
  - Remaining 5% have point mutation

- Most common lethal disease of children under 2 yo.
SMA Gene

Figure 1 - Structure of the SMN gene in chromosome 5

- **Protein**: SMNΔ7: unstable
- **Complete SMN**: stable

SNM = survival motor neuron;
MRNA = messenger ribonucleic acid.
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 weak baby”
## Clinical Classification of SMA

<table>
<thead>
<tr>
<th>SMA TYPE</th>
<th>Age of Onset</th>
<th>Motor Milestones</th>
<th>Ave Age of Death (limited interventions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt; 6 mths</td>
<td>Unable to sit w/o support</td>
<td>&lt; 2years</td>
</tr>
<tr>
<td>II</td>
<td>&lt; 18 mths</td>
<td>Sit independently, cannot stand</td>
<td>2nd - 3rd decade</td>
</tr>
<tr>
<td>III</td>
<td>&gt; 18 mths</td>
<td>Stand and walk independently</td>
<td>Normal life expectancy</td>
</tr>
</tbody>
</table>
Cure SMA Newly Diagnosed Database

• Each year, ~350 newly diagnosed patients/families contact Cure SMA
• Incidence based on 5 years of data:
  • 48% Type I
  • 26% Type II
  • 13% Type III
  • 5% Type IV
  • 7% unknown
Cure SMA Newly Diagnosed Database

- Average Age Diagnosis (2009-2014):
  - Type I - 4.9 months
  - Type II – 22.9 months

- Average time from diagnosis until Type I family contacts Cure SMA is 3 weeks
Patient case

- 7# 14 oz product of uncomplicated pregnancy
  - 1 month
    - Decreased head movement and extremities
  - 2 months
    - SMA diagnosed by Gene mutation testing
Patient case

• 2.5 months
  – First cold with rhinorrhea and difficulty breathing
    • Respiratory arrest on way to hospital
    • Resuscitated and placed on NIV
    • G-tube placed
    • Treated with albuterol, Pulmozyme, Tobi for Pseudomonas in secretions, and Zantac
11 days later
Patient case

• 3.5 months
  – Discharged to home with oxygen while waiting for sleep study to be done in one month.
Patient case

• 4 months
  – Oxygen desaturations at night
    • Supplemental oxygen 0.25 LPM started during sleep
  – Seen in ED for low heart rate to 80
    • Discharged and advised to continue airway clearance
  – Oxygen desaturations progress to day and night
    • Supplemental oxygen increased to 1 LPM per NC
    • Frequent emesis
Patient case

- 4.5 months
  - Admitted
    - Serum bicarbonate 31
  - Treatment:
    - BiPAP per nasal mask, 18/4, RR 30
    - Aggressive airway clearance.
    - Nebulized medications stopped.
  - Supplemental oxygen bled into BiPAP.
    - Weaned off by 48 hours.
  - 72 hours
    - Tolerating time off BiPAP in room air
  - Discharged on hospital day 6
SMA Pulmonary Natural History

Natural History

- Normal breathing
  - Respiratory and bulbar muscle weakness
    - REM related sleep disordered breathing
    - Ineffective cough reduced peak cough flows
    - NREM and REM sleep disordered breathing
      - Chest infections
        - Daytime ventilatory failure
          - Death

Assessment

- Physical examination
  - Pulmonary function, peak cough flow, respiratory muscle strength
  - Chest x-ray, Sleep study
  - Swallow dysfunction
    - Swallow function evaluation

Intervention

- Airway clearance with cough assistance
- Nocturnal non-invasive ventilation
- Nocturnal or continuous non-invasive ventilation

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

SMA type I/Nonsitters

- Weak intercostal muscles
- Chest wall: very soft and flexible during the first year of life
- Diaphragm: easily fatigued, the primary muscle for breathing
- Other complications:
  - Dysautonomia
  - Dysphagia with aspiration
  - Scoliosis, joint contractures
  - Fatty acid oxidation metabolic disorder
  - Poor bone quality – increased fracture risk
  - Intermittent gastroparesis
SMA type II/Sitters

• Range of respiratory muscle weakness
  • Weak intercostal muscles
  • Chest wall: rib collapse over time (parasol deformity)
  • Diaphragm: fatiguable and the primary muscle for breathing

• Other complications:
  • Some develop dysphagia – can occur in teens
  • Scoliosis, joint contractures
  • Fatty acid oxidation metabolic disorder
  • Poor bone quality – increased fracture risk
  • Chronic pain
SMA type III/Walkers

• Generally normal pulmonary function tests
• At risk for:
  • Obstructive sleep apnea
  • Respiratory muscle weakness in adolescence and adulthood
  • Respiratory compromise with anesthesia, narcotic use, illness
• Other complications:
  • Obesity
  • Scoliosis, joint contractures
  • Mild fatty acid oxidation metabolic disorder
  • Chronic pain
Neuromuscular Disorders

• Cause of death is usually respiratory failure.
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

Changing Natural History of SMA Type I

• Variables that reduced the risk of death:
  – Ventilation for more than 16 hours/day
  – use of a mechanical insufflation–exsufflation device
  – gastrostomy tube feeding

The Last Straw for NMD Lung Function

- Viral respiratory infections impact:
  - Increased muscle weakness
  - Copious airway secretions
  - More difficulty breathing
## 2015 Cure SMA Drug Discovery Pipeline

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<th>BASIC RESEARCH SEED IDEAS</th>
<th>PRECLINICAL: DISCOVERY</th>
<th>CLINICAL DEVELOPMENT</th>
<th>FDA APPROVAL</th>
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<td>Trophos/Dlesoxime</td>
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<td>AveXis/NW/Gene Therapy</td>
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<td>Paratek/Tetracycline</td>
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<td>Genzyme/CNS Gene Therapy</td>
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<td>Indiana U/Small Molecule</td>
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<td>Harvard/Small Molecule</td>
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- Projects with **Cure SMA** funding involvement
- **IND** = Investigational New Drug
- **NDA** = New Drug Application
Therapeutic Strategies: Molecular Biology of SMN2

Therapeutic Strategies
1. Gene Therapy

- Replace SMN1 Gene with normal gene.
  - Vectors $\rightarrow$ WT Gene
  - Stem Cells $\rightarrow$ WT Gene
- **INCREASES SMN1 levels**
- SMN2 is unchanged.
- Examples:
  - AveXis/Nationwide Children’s Hosp
  - Genzyme/CNS Gene Therapy

Therapeutic Strategies

2. Gene Activation

- ↑ Transcription of SMN2
  - ↑ Unstable SMN2
  - ↑ Stable SMN1
- Increases SMN2 and SMN1 protein levels.
- HDAC inhibitors
  - Valproic Acid
  - Hydroxyurea
  - Sodium butyrate
  - Quinazolines

Therapeutic Strategies

3. Splicing Modulation

• Block the splicing site of SMN2 so that exon 7 is included in more transcripts.
  – Produces more full length SMN mRNA and protein

• New therapies
  – IONIS/Biogen: Antisense Oligonucleotide
  – PTC /Roche/Genentech: Small Molecule

Therapeutic Strategies

4. Protein Stabilization

• Modulate the proteins (SMN1 or SMN2) to increase their t_{1/2}.
• INCREASED STABILIZED PROTEIN LEVELS
• Example:
  • Repurposed aminoglycosides

Neuroprotection

- Riluzole - Developed for ALS treatment
- Olesoxime (TRO19622) – new agent developed by Trophos/Roche

Newborn Screening for SMA

- Dr. Kathryn Swoboda – Univ of Massachusetts: multi-state, multi-region newborn screening pilot study in SMA
- Greatest challenge: Consent process
- NICHD Resource Newborn Screening Translational Research Network (NBSTRN) [www.NBSTRN.org](http://www.NBSTRN.org)
The Last Straw for NMD Lung Function

• Viral respiratory infections impact:
  – Increased muscle weakness
  – Copious airway secretions
  – More difficulty breathing
Breathing Basics

• Secretion mobilization
• Cough Augmentation
• Respiratory support
Secretion Mobilization

- Manual Chest Physiotherapy or Mechanical Percussion

- Postural Drainage
Other Techniques

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

Respiratorics Cough Assist™ T70

Hill-Rom Vital Cough™
Mechanical In-Exsufflation

- In-exsufflator cough machine improved cough expiratory flow rates
  - Mean peak expiratory flow rates of 21 patients with NMD
    - Unassisted $1.81 \pm 1.03$ L/sec
    - Assisted cough $4.27 \pm 1.29$ L/sec
    - Exsufflator $7.47 \pm 1.02$ L/sec
    - Normal PCF 6-12 L/sec
    - Critical PCF is 2.7 L/sec

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.
Cough Machine

- Perform 4 sets of 5 breaths and rest 1-2 minutes between sets.
- Ideally use manual cough assist with cough machine.
- Suction upper airway or tracheostomy tube or ET tube after use.
- Use as often as needed.
Mechanical Insufflation-Exsufflation Device Indications for Home

- SMA type I and II
- Consider for anyone with neuromuscular disease and impaired cough
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

- 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
Indications for NIPPV

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

• Specific to SMA (NMD)
  – Respiratory failure during a viral illness
  – Recurrent pneumonia or atelectasis
  – Chest wall collapse/pectus excavatum
  – Post-operative care
  – SMA type I
Chest Wall Development After NIV

6 mths

18 mths

Courtesy of A. Simonds, Royal Brompton Hospital, UK
Non-Invasive Positive Pressure Ventilation Devices

1. Bilevel positive airway pressure device

2. Home mechanical ventilator

CPAP is not indicated for Neuromuscular hypoventilation
Respironics
Profile Lite
Nasal Mask and
Head Gear, Size Small
Child

AG Industries
Nonny Mask and
Head Gear, Size Small
Child
AG-PEDKIT-S
ResMed
Pixi
Nasal Mask and Head Gear, one size

Respironics
Wisp with fabric frame and Reduced Size Head Gear, sizes Petite, S/M, L
Non Invasive Bilevel Positive Airway Pressure

• Goals:
  • Ventilation
  • Decrease work of breathing
    » Decrease belly breathing
    » Normalize heart rate during sleep
  • Improve chest wall expansion
Non Invasive Bilevel Positive Airway Pressure

- Recommended modes:
  - ST (spontaneous timed) with back up rate
  - PC (Pressure control) guaranteed inspiratory time with back up rate
  - AVAPS (average volume assured pressure support) targeted tidal volume within IPAP range

- Provides backup respiratory rate
- True respiratory muscle rest
- Synchronizes with efforts
Non Invasive Bilevel Positive Airway Pressure

- IPAP: 14-20 cm of H₂O
- EPAP: 3-6 cm of H₂O
- Respiratory Rate: high enough to capture breathing efforts and rest child.
- Inspiratory Time: depends on age and set respiratory rate
- Rise time: time between exhalation and rise to IPAP
Acute Respiratory Failure: Bilevel Positive Airway Pressure Pressure Effects

• Decrease respiratory muscle work
  • Increase TV
  • Decrease RR
• Greater respiratory muscle rest
  • BiPAP >> CPAP
• Improved gas exchange
• Improved minute ventilation

Mehta and Hill, AJRCCM 2001; 163:540
Home Mechanical Ventilator

• Modes:
  – Assist control (Every breath is the same)
    • With pressure or volume ventilation
  – Synchronized intermittent mechanical ventilation (SIMV)
    • With pressure or volume ventilation
Invasive Ventilation

- Tracheostomy placement
  - Not an acute intervention
- Indications
  - 24 hour per day NIV dependent
  - Frequent cyanotic episodes or respiratory instability
  - NIV intolerance
  - Failure to extubate
  - Family preference

Palliative Care

• Goals:
  • Family-directed quality of life optimization
  • Avoid PICU stays and tracheotomy.
  • Provide symptom relieve
    - pain, dyspnea, agitation, nausea, anxiety
  • Provide psychological, social and spiritual support for patient and family

• NIV can be used as palliative therapy.

Respiratory Illness Care Plan

• Perform every 4 hours:
  – Secretion mobilization
    • Chest physiotherapy
  – Cough Assist
    • 4 sets of 5 breaths
  – Postural drainage
  – Cough Assist
    • 4 sets of 5 breaths

• Use Cough Assist as often as needed to clear rattley breathing and lower airway secretions
Respiratory Illness Care Plan (cont.)

• In room air, use the pulse oximeter to guide airway clearance and support.
• SpO2 less than 94%: Use the cough machine.
• If no improvement:
  • Continue respiratory airway clearance treatment
    – Place on BiPAP - may need continuously.
    – If SpO2 < 90% on BIPAP room air, go to hospital or call 911.
Respiratory Illness Care Plan (cont.)

- Oxygen therapy
  - Use to correct hypoxemia when airway clearance techniques and respiratory support maximized.
- Intubation and mechanical ventilation may be needed during acute illness
Respiratory Illness Care Plan (cont.)

• Optimize fluid intake
  – Large insensible losses
    • Use solution with glucose for maintenance
    • Increase fluids by 10-20% of baseline total

• Avoid prolonged fasting
  – SMA type I: >4 to 6 hours
  – SMA type II: > 12 hours

• Continue to feed enterally or provide intravenous nutrition.

• Use antibiotics

Extubation

Extubate when the patient is:
1. afebrile
2. not requiring supplemental O2
3. CXR is without atelectasis or infiltrates
4. off respiratory depressants
5. airway suctioning is 1 time/hour or less
Extubation (cont.)

- Extubate from reasonable settings:
  - a rate similar to the optimal BiPAP rate
  - pressures that approximate BiPAP IPAP (15-20) and EPAP (3-6)
  - < 0.3 FIO2 (ideally room air)

- **Avoid** low ventilator rates through ET tube especially during sleep
  ⇒ atelectasis/fatigue.
Recommendations:
In-home respiratory equipment:

- CoughAssist machine
- Suction machine
- Spot check pulse oximeter
- Method for secretion mobilization, e.g., palm cups, electric percussor
- Nocturnal respiratory support as indicated.
- Supplemental oxygen for emergency use for SMA type I and weak type II
Primary Care Recommendations

• Routine immunizations
• Annual influenza vaccine
• RSV prophylaxis for SMA type I

UW Pediatric Interdisciplinary Neuromuscular Disorder Program

- **Respiratory Care**
  - Physicians
  - Respiratory care practitioners
- **Neurology**
- **Care coordination**
  - RNs
  - Case Manager
- **Palliative Care**
  - Physician
  - Nurse practitioner
- **Genetic Counselor**
- **Nutritionist**
- **Social Worker**

- **Orthopedic and Rehabilitation Medicine Services**
  - Physicians
  - Nurse Practitioner
  - Physical Therapist
  - Occupational Therapist
  - Speech Therapist
  - Orthotist
  - Vocational Rehabilitation Coordinator
- **Cardiology**
  - Physicians
  - Nurse Practitioner
Summary

• The respiratory complications of Spinal Muscular Atrophy include:
  – Hypoventilation during sleep and with disease progression while awake
  – Compromised airway secretion clearance

• Supplemental oxygen is not the answer
Summary

• Patients with neuromuscular disease can be managed non-invasively with aggressive airway clearance and nasal mask ventilation.

• Use non invasive ventilation at settings to ventilate and rest the patient during sleep.
Summary

- Individuals with neuromuscular weakness are at risk for interrelated multiorgan system complications in addition to musculoskeletal including:
  - Nutrition and GI
  - Bone Health
Summary

• The natural history of spinal muscular atrophy is evolving with longer survival and improved care options.

• Interdisciplinary management is essential.

• New therapeutics interventions offer the hope of longer and improved survival.
Additional Information

• Cure SMA website:  www.curesma.org
• Fight SMA website:  www.fightsma.org
• SMA Foundation website:  www.smafoundation.org
• Muscular Dystrophy Association website:  www.mdausa.org
• Mary Schroth email:  mschroth@pediatrics.wisc.edu