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

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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.

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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

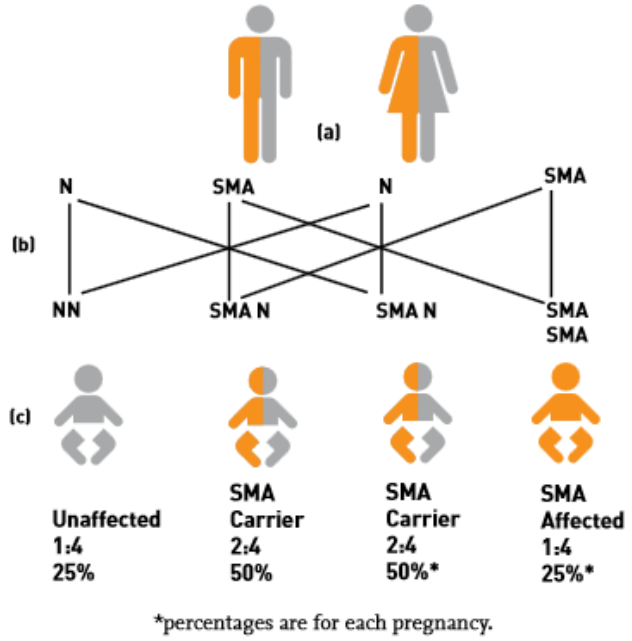
Encompasses:

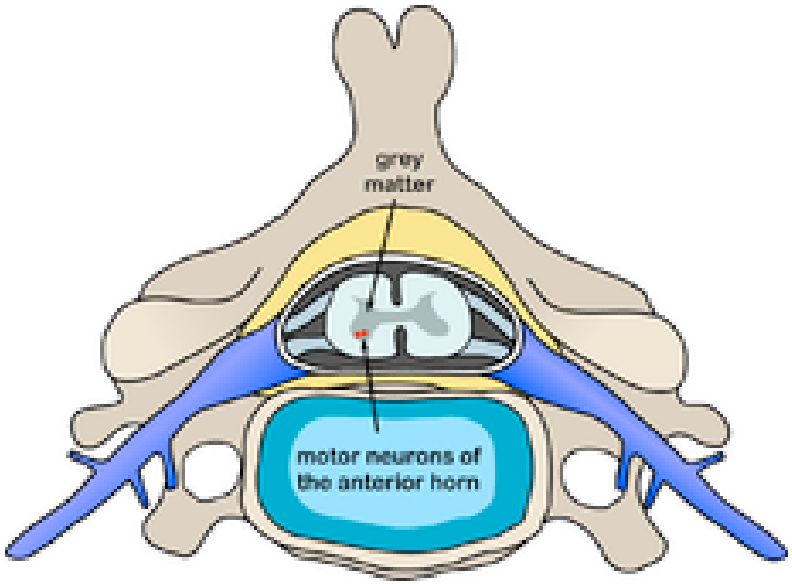
- Diagnosis
- Respiratory Care
- GI and Nutrition
- Orthopedic Concerns
- Palliative Care

Wang C et al, J. Child Neurol 2007; 22:1027.

Spinal Muscular Atrophy

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





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

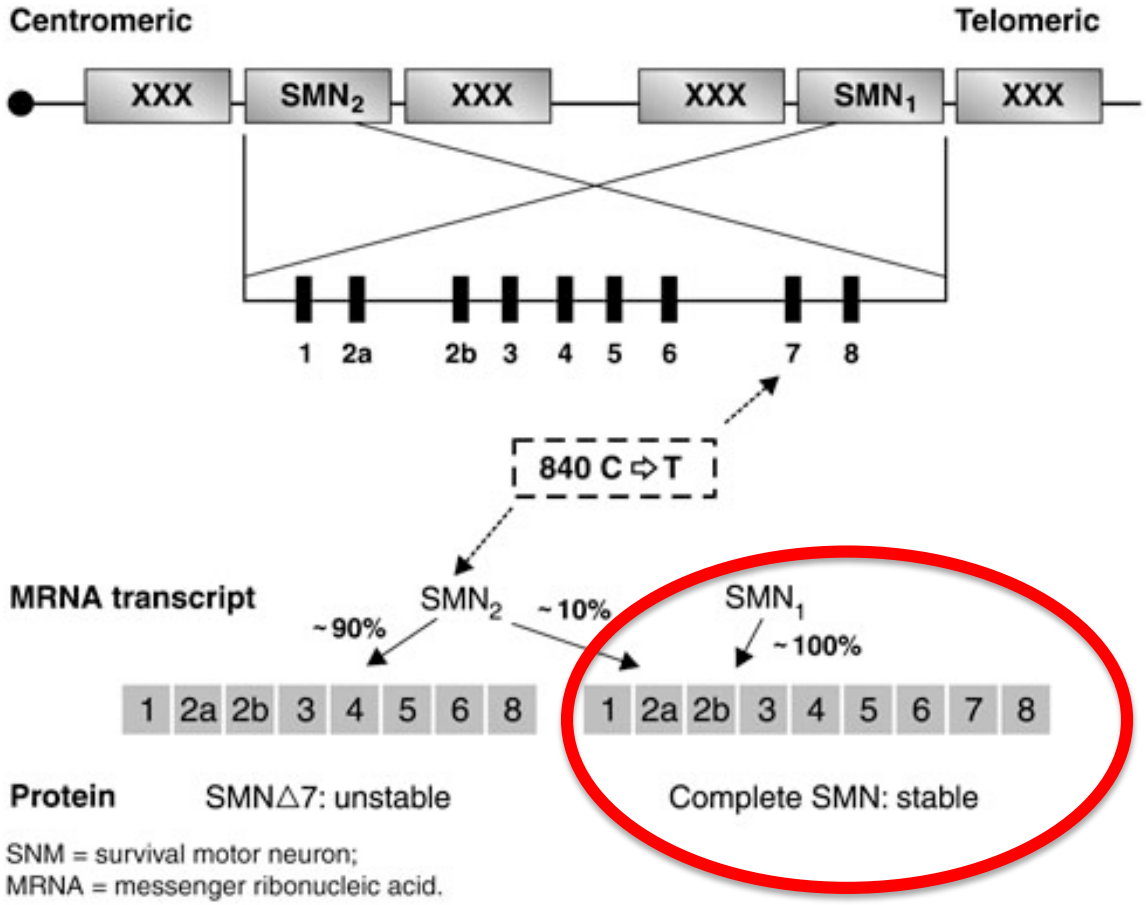


Figure 1 - Structure of the SMN gene in chromosome 5

Baioni MTC, et al, J Pediatr (Rio J). 2010;86(4):261-270

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

SMA TYPE	Age of Onset	Motor Milestones	Ave Age of Death (limited interventions)
I	< 6 mths	Unable to sit w/o support	< 2years
II	< 18 mths	Sit independently, cannot stand	2nd - 3rd decade
III	> 18 mths	Stand and walk independently	Normal life expectancy

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

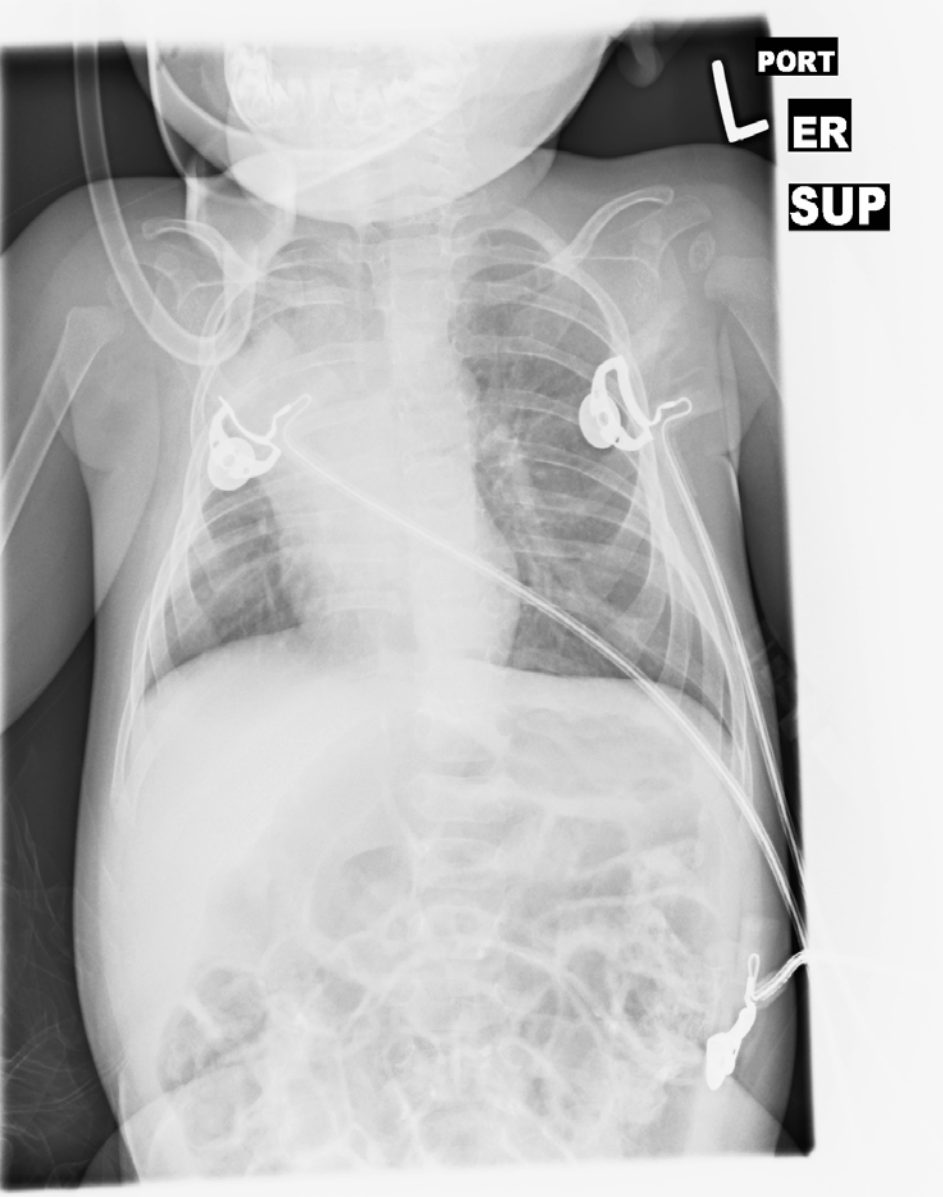
- Average time from diagnosis until Type I family contacts Cure SMA is 3 weeks

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



Admission

11 days later

Patient case

- 3.5 months
  - Discharged to home with oxygen while waiting for sleep study to be done in one month.

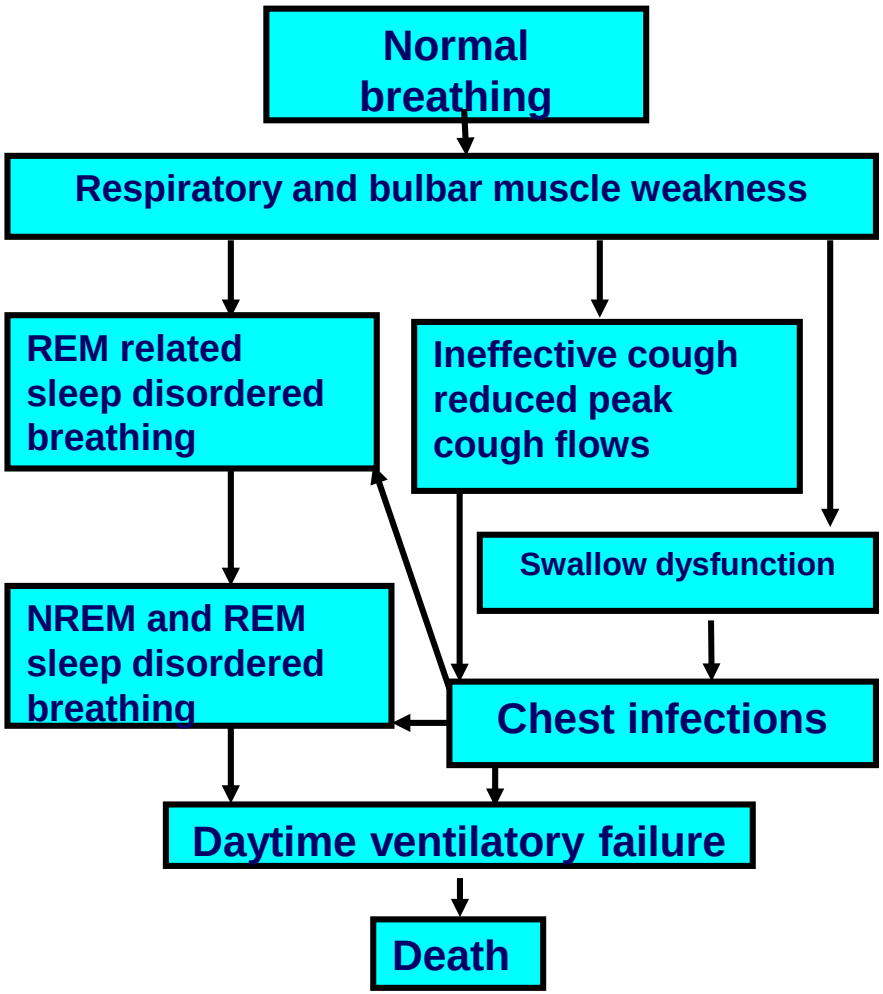
Patient case

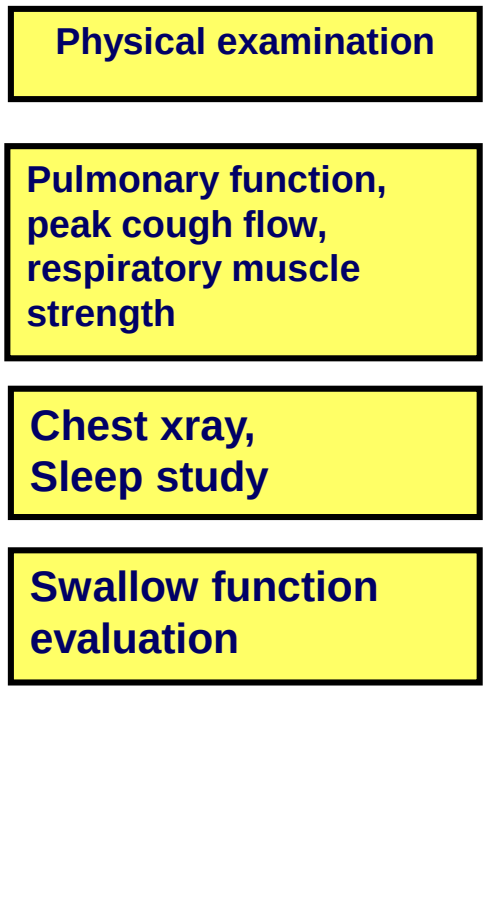
- 4 months
  - Oxygen desaturations at night
    - Supplemental oxygen 0.25 LPM started during sleep
  - Seen in ED for low heart rate to 80
    - Discharged and advised to continue airway clearance
  - Oxygen desaturations progress to day and night
    - Supplemental oxygen increased to 1 LPM per NC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





Wang C et al, J. Child Neurol 2007; 22:1027.

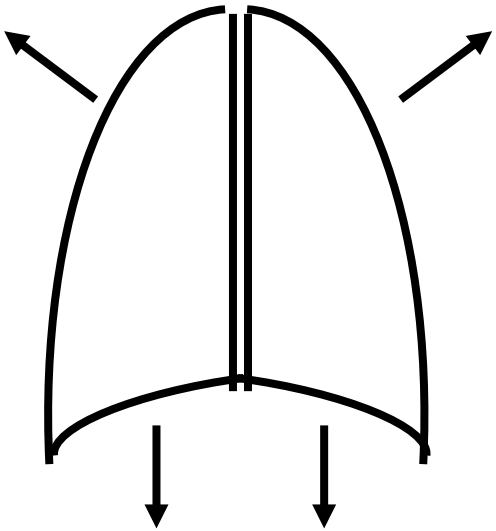
Complications of Respiratory Muscle Weakness in SMA

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

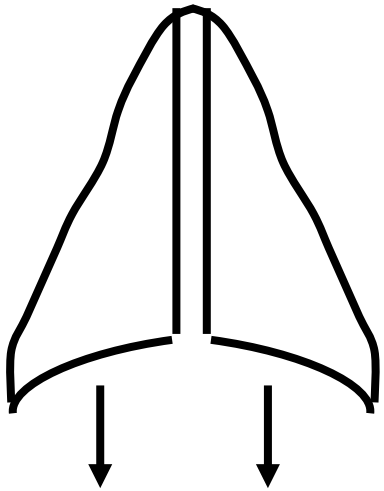
Wang C et al, J Child Neurol 2007; 22:1027.

Chest Wall Changes

Normal



SMA



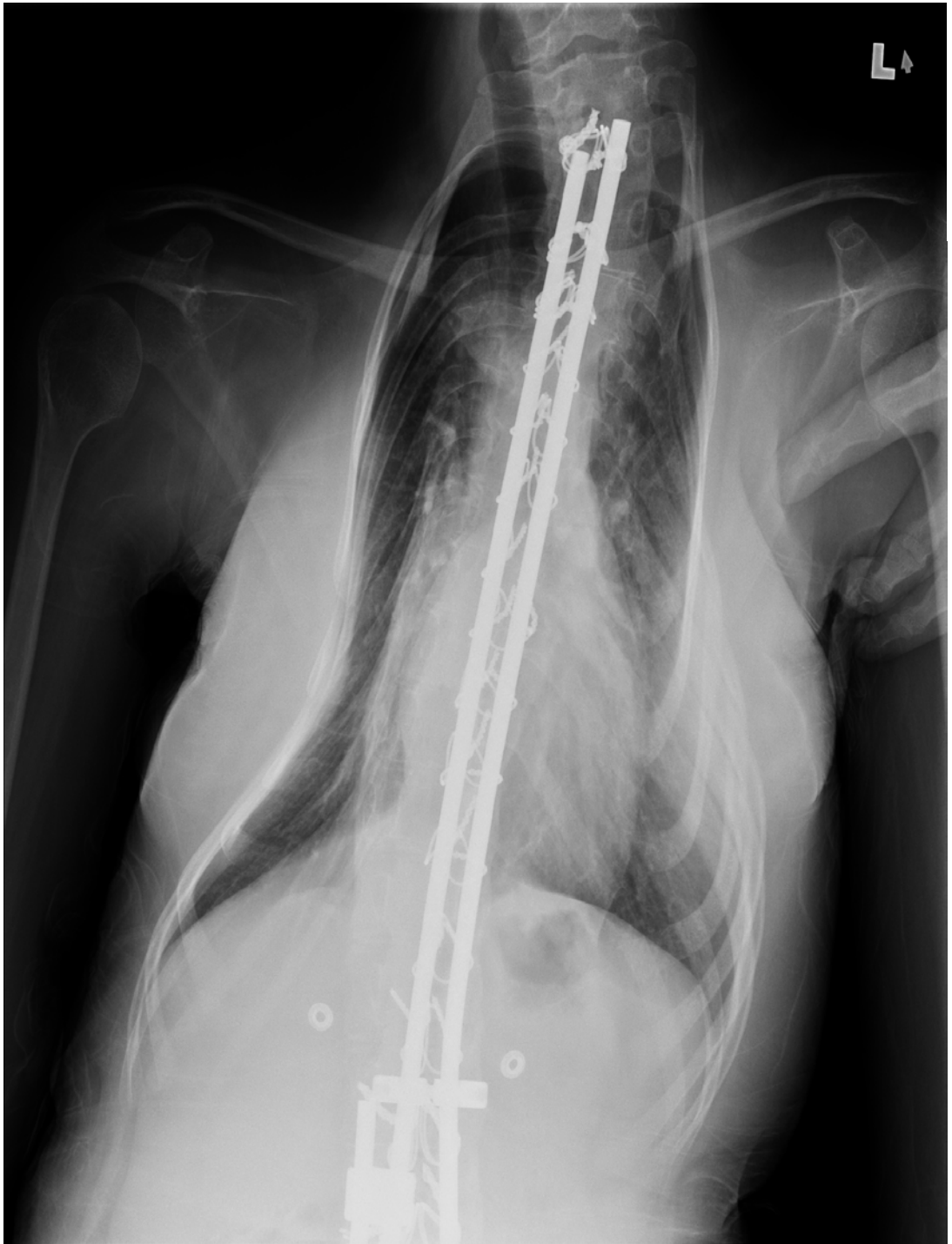
Schroth, Pediatrics, 2009; 123 Suppl 4, S245-9.

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: fatiquable 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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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.

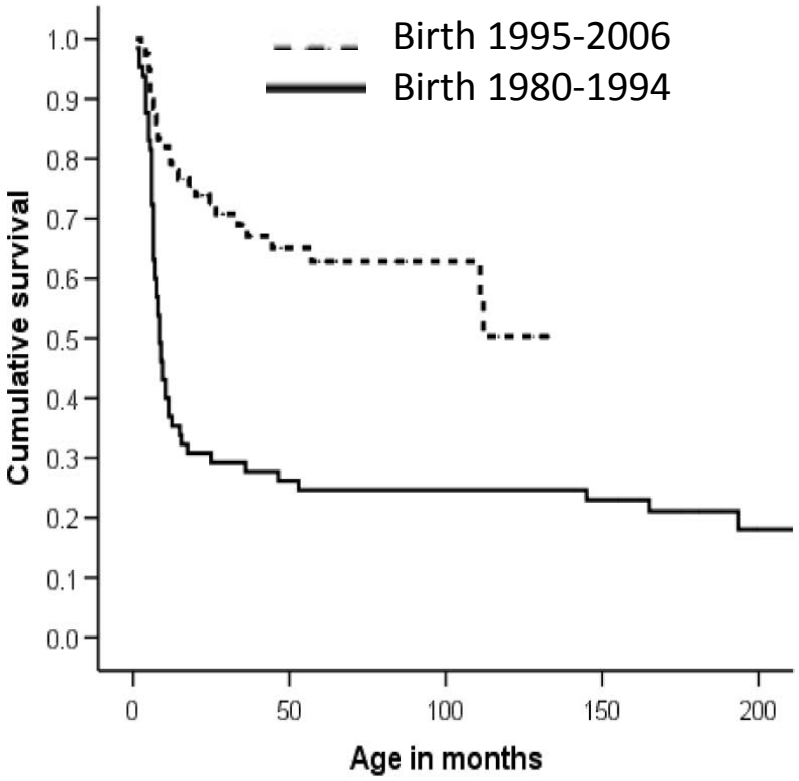
Changing Natural History of SMA Type I

- 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.

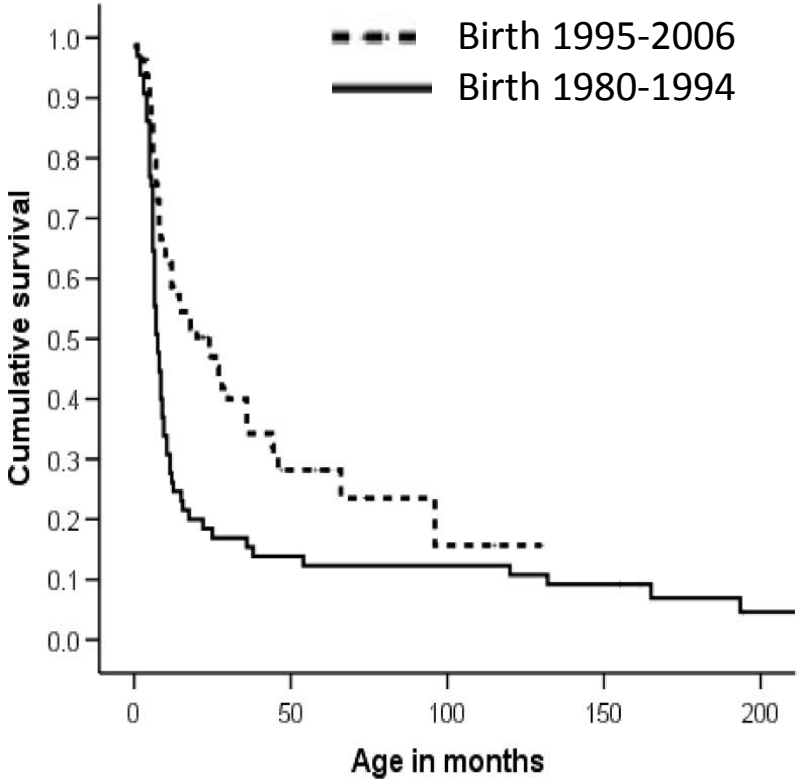
Oskoui M et al, Neurol 2007; 69:1931.

Kaplan–Meier survival plots of Spinal Muscular Atrophy type 1

Event death



Events death or ventilation >16 hours



Oskoui M et al, Neurol 2007; 69:1931.

Changing Natural History of SMA Type I

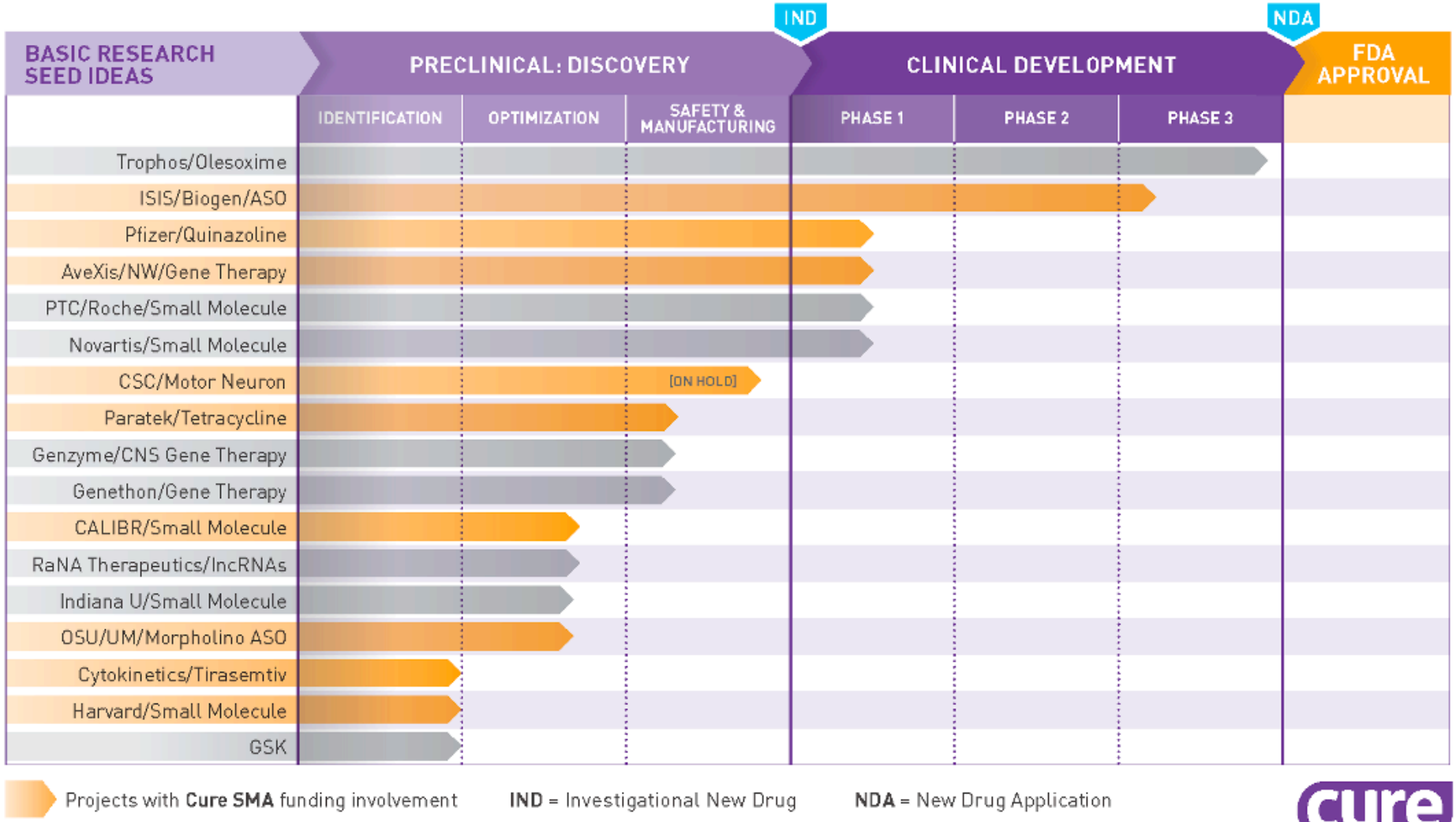
- Variables that reduced the risk of death:
  - Ventilation for more than 16 hours/day
  - use of a mechanical insufflation–exsufflation device
  - gastrostomy tube feeding

Oskoui M et al, Neurol 2007; 69:1931.

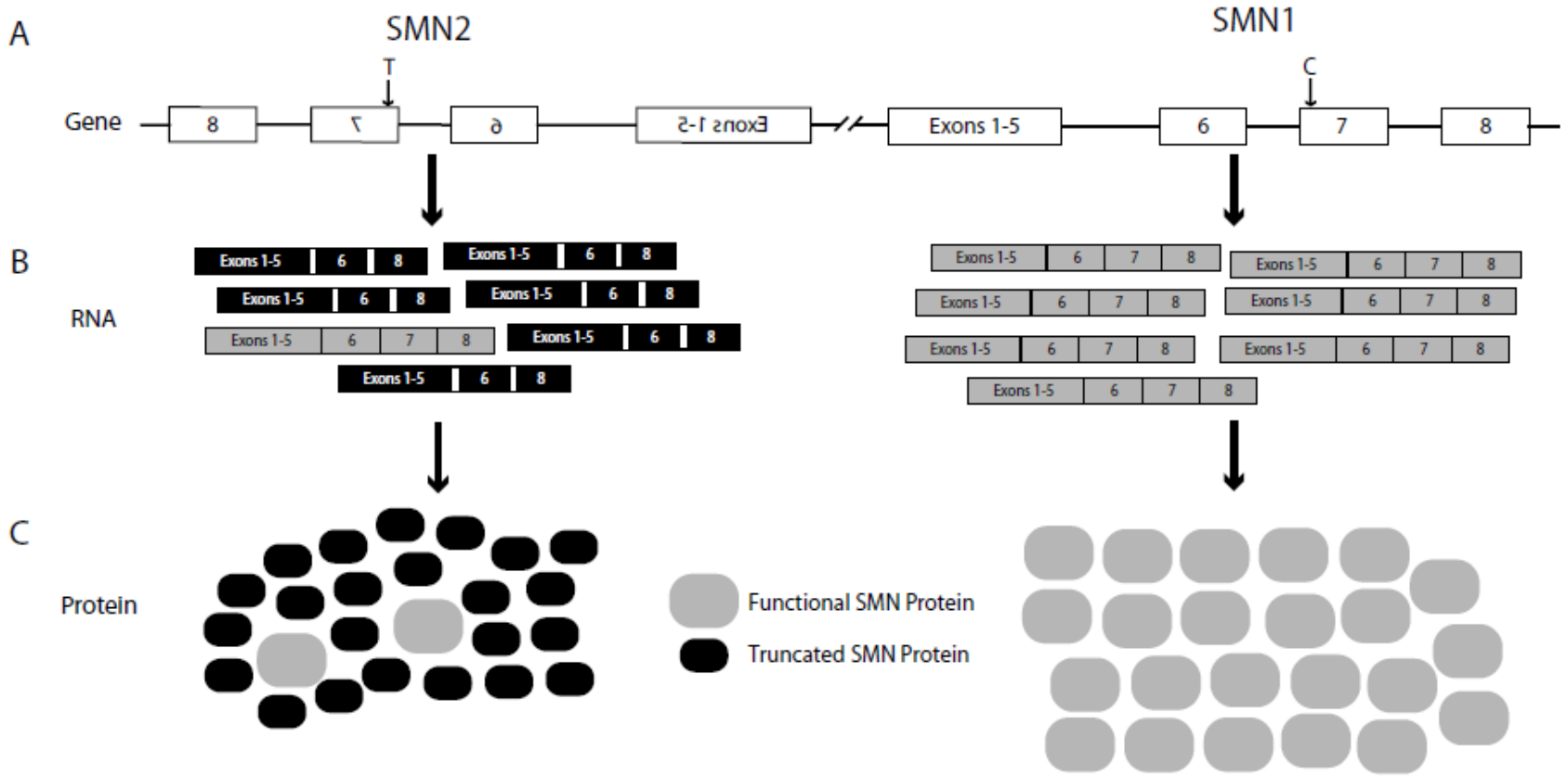
The Last Straw for NMD Lung Function

- Viral respiratory infections impact:
  - Increased muscle weakness
  - Copious airway secretions
  - More difficulty breathing

2015 Cure SMA Drug Discovery Pipeline



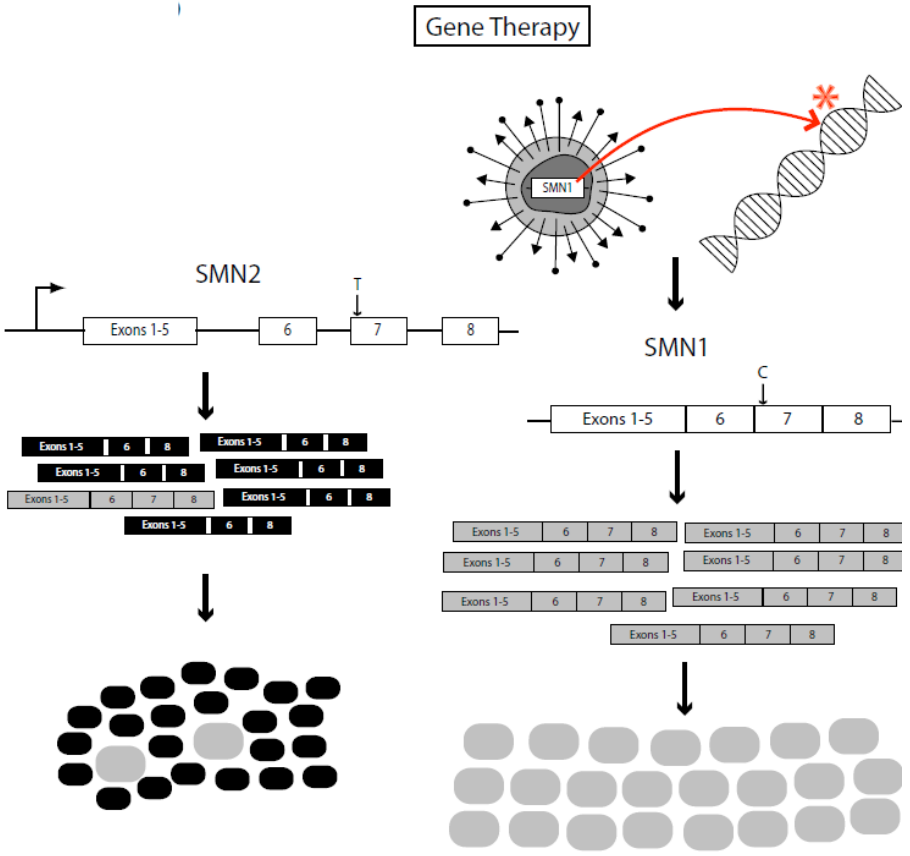
Therapeutic Strategies: Molecular Biology of SMN2



Van Meerbeke JP, Sumner CJ., Discov Med. 2011. (65):291-305.

Therapeutic Strategies
1. Gene Therapy

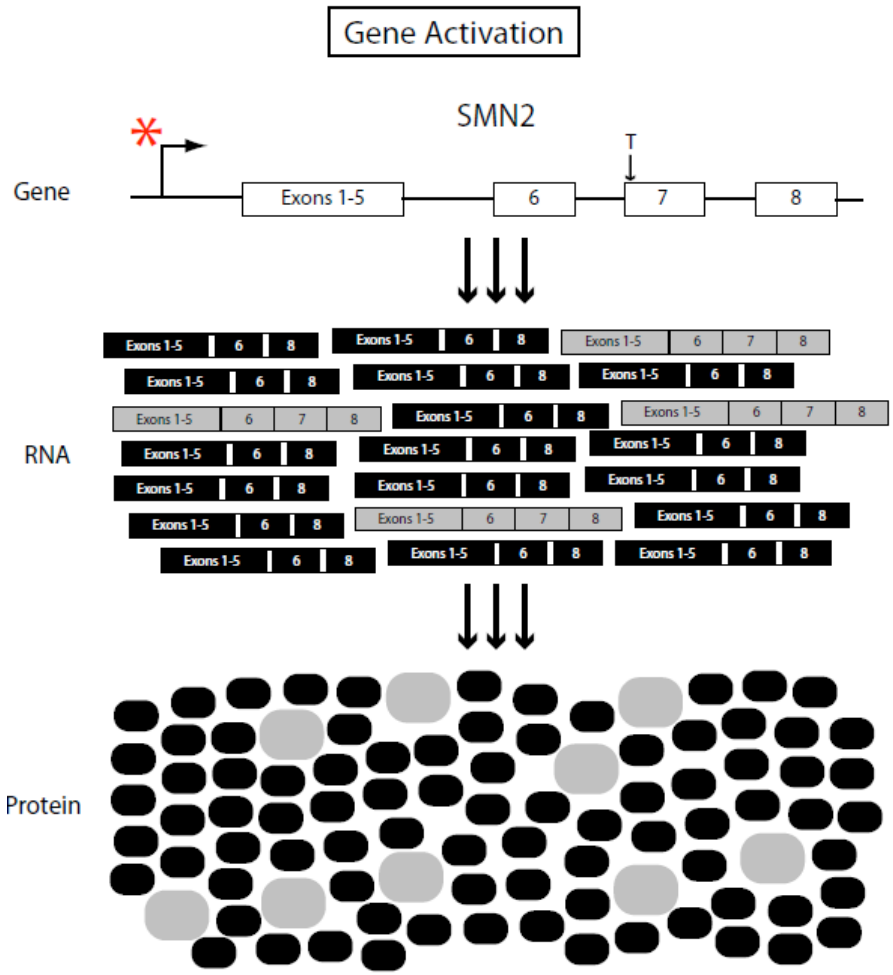
- Replace SMN1 Gene with normal gene.
  - Vectors→ WT Gene
  - Stem Cells→ WT Gene
- **INCREASES SMN1 levels**
- SMN2 is unchanged.
- Examples:
  AveXis/Nationwide Children's Hosp
  Genzyme/CNS Gene Therapy



Van Meerbeke JP, Sumner CJ., Discov Med. 2011. (65):291-305.

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



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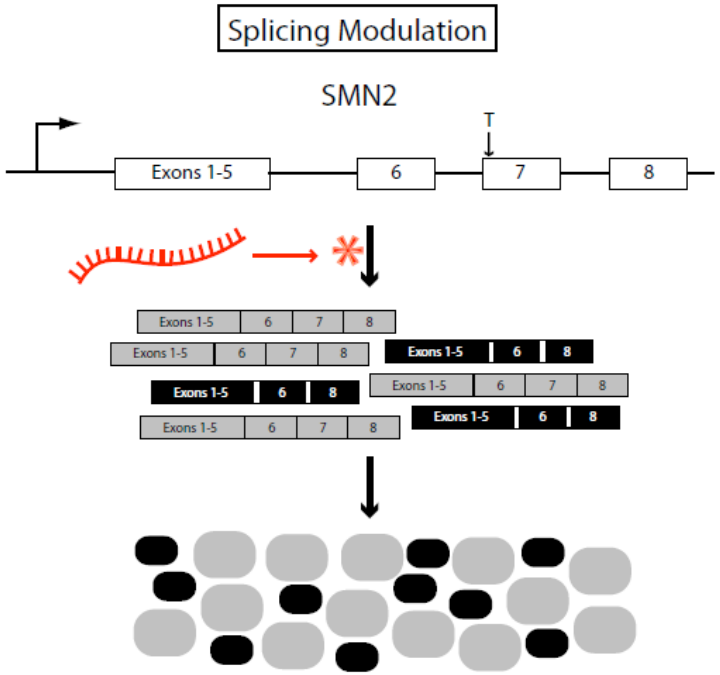
Therapeutic Strategies
3. Splicing Modulation

- **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



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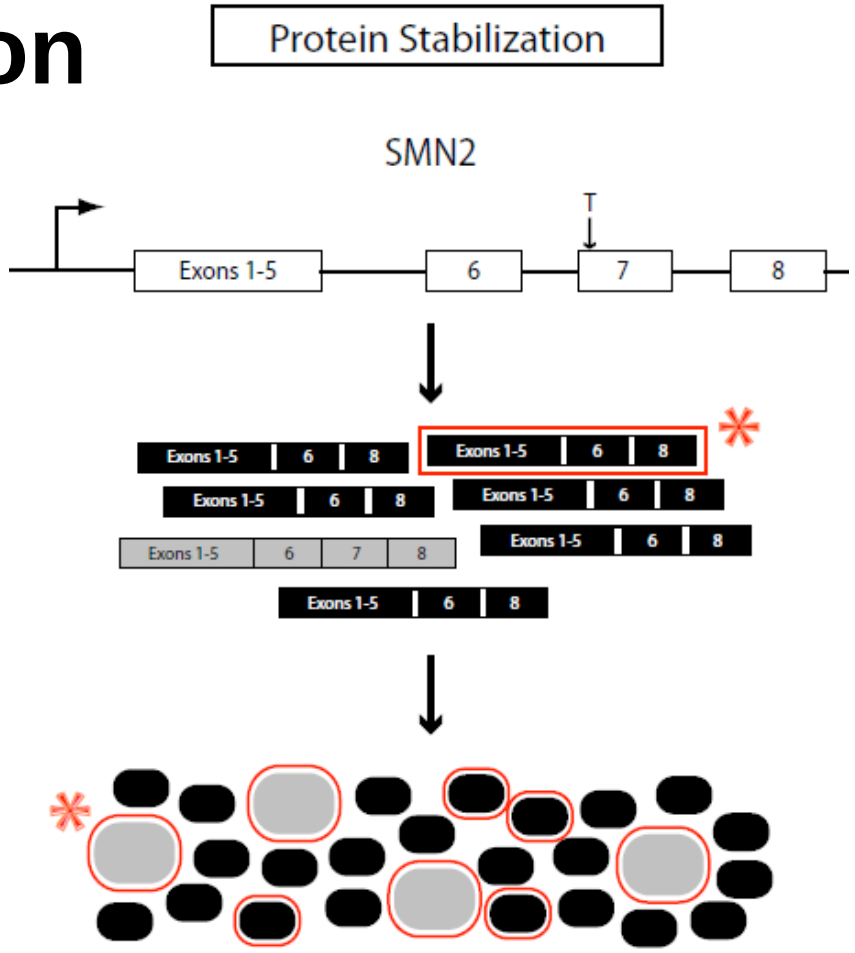
Therapeutic Strategies
4. Protein Stabilization

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



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Neuroprotection

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

Van Meerbeke JP, Sumner CJ., Discov Med. 2011. (65):291-305.

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

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

Hill-Rom Vital Cough™

Respironics
Cough Assist™ T70

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 ± 1.03 L/sec
    - Assisted cough 4.27 ± 1.29 L/sec
    - Exsufflator 7.47 ± 1.02 L/sec
    - Normal PCF 6-12 L/sec
    - Critical PCF is 2.7 L/sec

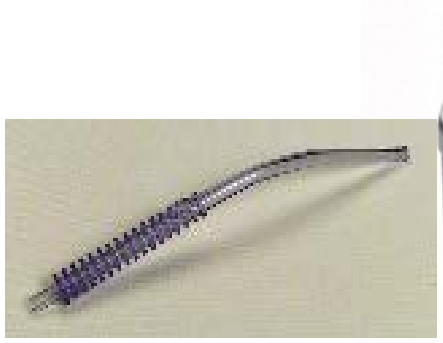
Bach J. Chest 1993; 104:1553.

Cough Machine

- SETTINGS to use by mask, mouth piece, tracheostomy tube or endotracheal tube.
  - INSPIRATORY
    - Start at +25-30, increase to +40 cm H_2O for 1-2 sec.
  - EXPIRATORY
    - Start at –25-30, increase to -40 cm H_2O for 1-2 sec.
  - PAUSE TIME
    - 1-2 sec.

Cough Machine

- Perform 4 sets of 5 breaths and rest 1-2 minute 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**

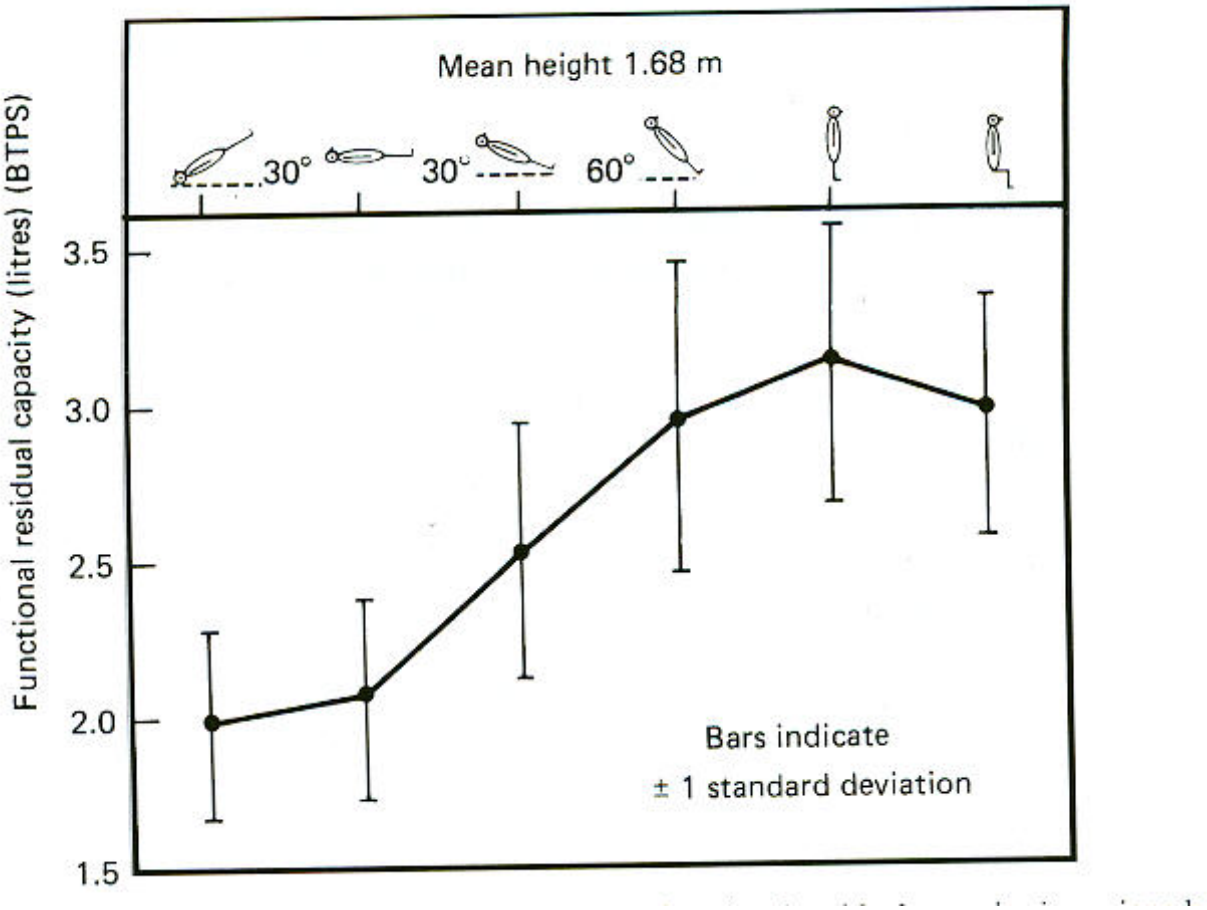
- SMA type I and II
- Consider for anyone with neuromuscular disease and impaired cough

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 ($\Downarrow$ SpO2, $\Uparrow$ 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 H_20
- EPAP: 3-6 cm of H_20
- 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 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

Wang C et al. J. Child Neurol 2007; 22:1027.

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.

Wang C et al. J. Child Neurol 2007; 22:1027.

Respiratory Illness Care Plan

- Perform every 4 hours:
  - Secretion mobilizaton
    - 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

Wang C et al, J. Child Neurol 2007; 22:1027.

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
  $\Rightarrow$ 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

Wang C et al, J. Child Neurol 2007; 22:1027.

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