Consensus Statement for Standard of Care in Spinal Muscular Atrophy

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

J Child Neurol 2007 22: 1027
DOI: 10.1177/0883073807305788

Special Issue Article

Journal of Child Neurology
Volume 22 Number 8
August 2007 1027-1049
© 2007 Sage Publications
10.1177/0883073807305788
http://jcn.sagepub.com
hosted at
http://online.sagepub.com

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

Spinal muscular atrophy is a neurodegenerative disease that requires multidisciplinary medical care. Recent progress in the understanding of molecular pathogenesis of spinal muscular atrophy and advances in medical technology have not been matched by similar developments in the care for spinal muscular atrophy patients. Variations in medical practice coupled with differences in family resources and values have resulted in variable clinical outcomes that are likely to compromise valid measure of treatment effects during clinical trials. The International Standard of Care Committee for Spinal Muscular Atrophy was formed in 2005, with a goal of establishing practice guidelines for clinical care of these patients. The 12 core committee members worked with more than 60 spinal muscular atrophy experts in the field through conference calls, e-mail communications, a Delphi survey, and 2 in-person meetings to achieve consensus on 5 care areas: diagnostic/new interventions, pulmonary, gastrointestinal/nutrition, orthopedics/rehabilitation, and palliative care. Consensus was achieved on several topics related to common medical problems in spinal muscular atrophy, diagnostic strategies, recommendations for assessment and monitoring, and therapeutic interventions in each care area. A consensus statement was drafted to address the 5 care areas according to 3 functional levels of the patients: nonsitter, sitter, and walker. The committee also identified several medical practices lacking consensus and warranting further investigation. It is the authors' intention that this document be used as a guideline, not as a practice standard for their care. A practice standard for spinal muscular atrophy is urgently needed to help with the multidisciplinary care of these patients.

Keywords: spinal muscular atrophy; standard of care; consensus statement

Current Problems in the Medical Care of Patients With Spinal Muscular Atrophy

Spinal muscular atrophy is a recessively inherited neuromuscular disease characterized by degeneration of spinal cord motor neurons, resulting in progressive muscular atrophy and weakness. The clinical spectrum of spinal muscular atrophy ranges from early infant death to normal adult life with only mild weakness. These patients often require comprehensive medical care involving multiple disciplines. There is, however, no published practice standard for the care of these patients. Disparity in family resources, medical practitioners' knowledge, and regional and cultural standards produces wide variation in care and clinical outcome. Spinal muscular atrophy, as a field, has recently seen major advances in molecular diagnosis and clinical therapeutics that have not been matched by wide understanding and application. Parents of children newly diagnosed with spinal muscular atrophy often seek care over the Internet or outside of their geographic area to obtain expert care needed for their children, albeit in a costly and inefficient manner. This also undermines trust in local practitioners and their potential to render good clinical care during acute illness. Another consequence of these variations in practice is loss of trust in traditional medicine and increase in the attractiveness of untested and potentially harmful unconventional therapies. The large variation of clinical care in spinal muscular atrophy also

From Stanford University Medical Center, Stanford, California (CHW, AT); The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (RSF); Bambino Gesu' Children's Research Hospital, Rome, Italy (ESB); University of Wisconsin Children's Hospital, Madison (MS); Sleep & Ventilation Unit, Royal Brompton & Harefield NHS Trust, London, England (AS); Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (BW); Hammersmith Hospital, London, England (AA, MM); University of New Mexico Health Sciences Center, Albuquerque (LM); and The Johns Hopkins Hospital, Baltimore, Maryland (TOC).

Address correspondence to: Ching H. Wang, MD, PhD, Department of Neurology and Neurological Sciences, Stanford University Medical Center, 300 Pasteur Drive, Room A373, Stanford, CA 94305-5235; e-mail: wangch@stanford.edu.

Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, Aloysius A, Morrison L, Main M, Crawford TO, Trela A, and Participants of the International Conference on SMA Standard of Care. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol*. 2007;22:1027-1049.

results in challenges for future therapeutic trials. For all these reasons, we have identified an urgent need to establish a practice guideline, both to improve patient care and to provide a baseline standard for future clinical trials in spinal muscular atrophy.

The International Standard of Care Committee for Spinal Muscular Atrophy

Committee Formation

In September 2004, the National Institute of Neurological Diseases and Stroke sponsored an International Spinal Muscular Atrophy Conference in Bethesda, Maryland, with the goal of formulating strategies to coordinate future clinical trials in spinal muscular atrophy.[1] During the conference, it became clear that the wide variation of medical care received by spinal muscular atrophy patients likely increases the variability of outcomes in clinical trials. Thus, this Spinal Muscular Atrophy Standard of Care Committee was formed in January 2005, as a standing committee of the International Coordinating Committee for Spinal Muscular Atrophy clinical trials, to investigate the current state of science in clinical practice in spinal muscular atrophy and to attempt to achieve consensus on the standard of care for these patients.

Committee Structure

The Standard of Care Committee for Spinal Muscular Atrophy is cochaired by a US and a European neurologist. There are 12 core members and 3 consultants on the committee. Eleven of the core members are currently practicing pediatric neurologists, and 1 is a pediatric pulmonologist. The 3 consultants consist of 1 National Institute of Neurological Diseases and Stroke liaison and 2 representatives from patient advocacy groups. The committee is subdivided into 4 working groups: diagnostics/new interventions, pulmonary, gastrointestinal/nutrition, and orthopedics/rehabilitation. Each group is headed by a leader from the United States and a coleader from Europe. All committee members participated voluntarily, without pay. They were either nominated by their peers or have volunteered themselves for this task force. Each working group is composed of 6 to 11 experts in the field for that particular care issue (please see the Web site http://smascc.stanford.edu for a current roster of committee members).

Committee Missions

The committee has identified the following goals for all 4 working groups: (1) to identify current care issues in spinal muscular atrophy clinical practice, (2) to search for existing practices in spinal muscular atrophy clinical care and the rationale or data supporting such practices, (3) to achieve consensus of the most appropriate medical practice in caring for patients with spinal muscular atrophy, (4) to use this standard of care consensus to establish clinical care guidelines for future spinal muscular atrophy clinical trials, (5) to identify future research directions in the care of patients with spinal muscular atrophy, and (6) to publish the consensus as guidelines for clinical care of patients with spinal muscular atrophy.

Methods of Achieving Consensus on Standard of Care for Spinal Muscular Atrophy

Standards of medical practice are ideally established upon evidence-based clinical trial data. Unfortunately, committee core members found little data from well-designed clinical studies upon which evidence-based practice parameters in spinal muscular atrophy could be drafted (please see literature reviews in each care topic in the following sections). The absence of well-designed clinical trial data requires substitution of widely held opinion drawn from a survey of experts in the field. It is hoped that this consensus statement will serve both as an initial practice guideline for the care of spinal muscular atrophy and an outline of areas where needed clinical investigation may be best focused. We describe here the process leading to the drafting of this consensus statement.

Periodic Conference Calls and Literature Review

Since the inception of the committee in early 2005, the members have held periodic conference calls to discuss the ways to establish practice guidelines for spinal muscular atrophy. Group leaders were tasked with conducting literature reviews in their particular care areas. A password-protected Web site was established during this time. References of literature reviews were uploaded to the Web site. Having concluded that there were not enough published data to allow drafting of an evidence-based practice parameter, the group explored the possibility of using a Delphi survey to achieve consensus among experts in the field.

The Delphi Survey

The Delphi technique[2] was initially used to explore consensus expert opinion in government and education. More recently, it has been used in medicine, notably in rheumatology and neurology.[3-5] The goal of the Delphi technique is to identify if in aggregation there is a rank-ordered cluster of answers from respondents that reflects group consensus on that particular question. It also serves to identify if no consensus is present and where topics need further study. It presents group opinions anonymously, avoids domination by a few strong voices in the group, and can be completed by

electronic communications within a few weeks. Exploratory use of the Delphi technique was performed during an initial committee meeting in Philadelphia in June 2005. This served to familiarize the attending committee members with the mechanics of the Delphi technique and of its strengths and limitations. Having completed 2 rounds of pilot surveys among the committee members, the group concluded that the Delphi technique was suitable for establishing a consensus opinion among experts in spinal muscular atrophy. Group leaders then met by conference calls and e-mail communications to construct a formal Delphi survey questionnaire. During the first round of the Delphi survey, a set of open-ended questions was constructed for each of the 5 spinal muscular atrophy care topics (diagnostic/new interventions, pulmonary, gastrointestinal/nutrition, orthopedics/ rehabilitation, and palliative care). Each topic is divided into 3 parts: presenting signs and symptoms, diagnostic testing, and intervention options. The intervention part is then divided into acute management and health maintenance. These open-ended questions are named Question #1 (Q#1, available on the Web site http://smascc.stanford.edu). The Q#1 was distributed by ane-mail attachment to survey participants. A total of 86 spinal muscular atrophy experts were invited to participate in the survey. They were invited from 4 medical disciplines: 18 from the gastrointestinal/nutrition group, 21 from the pulmonary group, 25 neurologists from the diagnostic/new interventions group, and 22 from the orthopedics/rehabilitation group. Thirty-four of them were from Europe, and 52 were from the United States and Canada. All invited participants were recommended by committee members. The participants were allowed 3 weeks to respond to the questionnaire. Neurologists were encouraged to answer all 5 care topics. Respondents in the other 3 working groups generally limited their responses to respective areas of expertise. Fifty-six of the original 86 invited participants (65%) completed this Q#1. Twenty-two of them were from Europe, and 34 were from the United States and Canada. To ensure the anonymity of the process, a numeric code was assigned to each respondent by the survey coordinator upon receipt of answers to Q#1. Analysis and presentation of the data were performed by the survey coordinator using these numeric codes. The answers from Q#1 were collected and analyzed. The most frequent occurring answers to these Q#1 questions were chosen to construct the Question #2 (Q#2, available on the Web site http://smascc.stanford .edu) during the second round of the Delphi survey. In this second round, the questions were the same as those in Q#1 except that respondents were asked to rank order from the highest to the lowest importance among a list of choices. Forty-four (79%) respondents who answered the Q#1 also completed Q#2. These responses were summarized and presented to committee participants at the Standard of Care Conference described in the following section.

The International Conference on the Standard of Care for Spinal Muscular Atrophy

This conference was held May 5-6, 2006, at Stanford University Medical Center, Palo Alto, California. Thirty-five members of the committee and Delphi survey participants gathered to work on a consensus statement for spinal muscular atrophy standard of care. First, leaders and designated members of each working group presented a critical review of the literature. The individual working group then reviewed the results of the Delphi survey in their care areas during breakout sessions. The final consensus within each working group was achieved by using the Delphi data as a guideline, incorporating the available data in the literature and the opinions of group members. These results were presented by group leaders to all conference participants for comments. The group leaders and coleaders then worked with each working group to draft the consensus statement on each care area. The summaries of these statements are listed in the following sections.

Diagnostic Testing and Care of New Spinal Muscular Atrophy Patients

Clinical Diagnosis and Classification of Spinal Muscular Atrophy

Physicians encountering children with hypotonia and weakness should maintain a high index of suspicion for the diagnosis of spinal muscular atrophy. Certain physical characteristics are readily identifiable. The weakness is usually symmetrical and more proximal than distal. Sensation is preserved. Tendon reflexes are absent or diminished. Weakness in the legs is greater than in the arms. The severity of weakness generally correlates with the age of onset. The most severe type presents in infancy. The infant may appear normal at birth. Weakness evolves within the first few months of life. Occasionally, decreased intrauterine movements suggest prenatal onset of the disease and present with severe weakness and joint contractures at birth.[6] Milder types of spinal muscular atrophy present with later onset, and the course is more insidious. Some children sit but never walk, whereas others show delayed walking but may be able to maintain walking until adult years. For the purpose of clinical care and discussion, individuals manifesting different levels of weakness due to spinal muscular atrophy have been divided into 4 groups defined by functional ability. We list typical clinical features of spinal muscular atrophy in Table 1. The first 3 types are classified according to criteria established by the International Spinal Muscular Atrophy Consortium.[7,8] Type 4 spinal muscular atrophy is a mild form that presents in adulthood. It can be expected that some patients will manifest features that are at the margins between groups.

Table 1. Clinical Classification of Spinal Muscular Atrophy

SMA Type	Age of Onset	Highest Function	Natural Age of Death
Type 1 (severe)	0-6 mo	Never sits	<2 y
Type 2 (intermediate)	7-18 mo	Never stands	>2 y
Type 3 (mild)	>18 mo	Stands and walks	Adult
Type 4 (adult)	Second or third decade	Walks during adult years	Adult

NOTE: SMA = spinal muscular atrophy.

In addition to these defining criteria, unique clinical features of each spinal muscular atrophy type include the following: (1) Type 1 spinal muscular atrophy. This type is also called Werdnig-Hoffmann disease. Children with this disease have impaired head control, with a weak cry and cough. Swallowing, feeding, and handling of oral secretion are affected before 1 year of age. The tongue may show atrophy and fasciculation. Weakness and hypotonia in the limbs and trunks are eventually accompanied by intercostal muscle weakness. Combining intercostal weakness with initial sparing of the diaphragm, the infants exhibit characteristic paradoxical breathing and a bell-shaped trunk with chest wall collapse and abdominal protrusion. Early morbidity and mortality are most commonly associated with bulbar dysfunction and pulmonary complications. (2) Type 2 spinal muscular atrophy. These children have delayed motor milestones. Some learned to achieve independent sitting, whereas others need help to sit up. The defining characteristic is an ability to maintain a sitting position unsupported. At the strongest end of this category are those who can stand with a standing frame or long leg braces but are not able to walk independently. Bulbar weakness with swallowing difficulties may lead to poor weight gain in some children. Intercostal muscles are weak, and some are also diaphragmatic breathers. They have difficulty coughing and clearing tracheal secretion. They have fine tremors with extended fingers or when attempting hand grips. Kyphoscoliosis eventually develops, and bracing or spinal surgery is needed. Joint contractures commonly evolve over years. (3) Type 3 spinal muscular atrophy. This type is also called Kugelberg-Welander disease or juvenile spinal muscular atrophy. These patients have later but variable age of onset. All achieve independent walking. Some patients lose the ability to walk in childhood, yet others maintain walking until adolescence or adulthood. Scoliosis can develop in these patients. Swallowing, cough, and nocturnal hypoventilation are less common than in type 2 spinal muscular atrophy but may occur. Muscle aching and joint overuse symptoms are common. (4) Type 4 spinal muscular atrophy. The onset of weakness is usually in the second or third decade of life. Motor impairment is mild without respiratory or gastrointestinal problems.

Within each spinal muscular atrophy type, subclassifications have been proposed and can add to prognostic significance. For example, only 22% of patients with type 3a, with onset of symptoms before age 3 years, were still ambulatory at age 40 years, whereas 58.7% of the patients with type 3b, with onset after age 3 years, were still walking by age 40 years.[9] Type 1 patients have also been subclassified into types 1a (neonatal or antenatal onset), 1b (typical Werdnig-Hoffmann disease with onset after neonatal period), and 1c (later onset, better head control in supported sitting, mild feeding or respiratory difficulties during the first 6 months of life).[10,11] However, these subclassifications have not been widely used among clinicians.

During the preparation of the Delphi survey, the committee decided that the most appropriate care for patients with spinal muscular atrophy should be tailored according to their current functional status rather than the original classification of disease types because these represent the best level of function rather than the present status. Therefore, the committee decided to use the classification of current functional level in the form of nonsitters, sitters, and walkers. The nonsitters include the group of children who currently are not able to sit independently. The sitters include those who can sit independently but cannot walk independently. The walkers can walk independently.

Other Forms of Spinal Muscular Atrophy

There are other inherited motor neuron disorders, not caused by mutation of the *SMN* gene (non-5q spinal muscular atrophy), that present with early denervation weakness but different clinical symptoms than those stated above.[12] These atypical symptoms include joint contractures, distal rather than proximal weakness, diaphragmatic paralysis with early respiratory failure, and pontocerebellar degeneration. DNA testing has become available for some but not all of these disorders. If a child with clinical features of spinal muscular atrophy is found not to have an *SMN* deletion on either chromosome 5, the child should be reexamined and receive additional diagnostic testing. (Please see the next section for the diagnostic strategies for these patients.) Table 2 lists some spinal muscular atrophy variants that exhibit early symptoms overlapping with 5q spinal muscular atrophy. Several later-onset motor neuron diseases overlap with milder 5q spinal muscular atrophy. These are beyond the scope of this document and are not listed here.

Table 2. Other Forms of Severe Spinal Muscular Atrophy Not Linked to *SMN* Gene

SMA Variants	Inheritance/Linkage/Gene	Clinical Presentation	Reference
Scapuloperoneal spinal muscular atrophy	Autosomal dominant 12q24.1-q24.31	Congenital absence of muscles, progressive weakness of scapuloperoneal and laryngeal muscles	(13, 14)
Pontocerebellar hypoplasia with spinal muscular atrophy	Autosomal recessive	Onset 0-6 mo, cerebellar and brainstem hypoplasia, absent dentate nucleus, neuronal loss in basal ganglia, cortical atrophy	(15-19)
X-linked infantile spinal muscular atrophy with arthrogryposis	X-linked Xp11.3-q11.2	Onset at birth or infancy, contractures, death less than 2 y	(20, 21)
Spinal muscular atrophy with respiratory distress type 1	Autosomal recessive 11q13.2-q13.4 IGHMBP2	Onset within the first 3 mo of life, eventration of the right or both hemidiaphragms, finger contractures, pes equines foot deformities	(22, 23)

NOTE: SMA = spinal muscular atrophy.

Diagnostic Procedures

The stepwise algorithm of the diagnostic procedure is summarized in Figure 1. Briefly, the first diagnostic test for a patient suspected to have spinal muscular atrophy should be the *SMN* gene deletion test. This test is currently performed by several diagnostic laboratories, and the result can be obtained within 2 to 4 weeks. The test achieves up to 95% sensitivity and nearly 100% specificity.[24,25] A homozygous deletion of *SMN1* exon 7 (with or without deletion of exon 8) confirms the diagnosis of *SMN*-associated spinal muscular atrophy (5q spinal muscular atrophy). The next group of tests following a negative *SMN* test result includes repeat clinical examination of the patient for atypical clinical features as listed in Table 2. Laboratory tests should include muscle enzyme creatine kinase, electrophysiological testing such as electromyography (EMG), and nerve conduction study with repetitive stimulation. This will help to identify muscle diseases, motor neuropathies, and disorders of neuromuscular junctions. If EMG suggests a motor neuron disease, then further testing for *SMN* mutations should be pursued. Some laboratories are currently offering *SMN1* gene copy number testing. If the patient possesses only a single copy of *SMN1* (missing 1 copy), then it is possible that the remaining copy contains subtle mutations, including point mutations, insertions, and deletions, rendering homozygous dysfunction of the gene. Sequencing of the coding region of the remaining *SMN1* copy may identify the mutation on the remaining copy and confirm the diagnosis of 5q spinal muscular atrophy. Unfortunately, sequencing the coding region of *SMN* is currently not widely available and is usually performed only in a few diagnostic or research laboratories. If the patient possesses 2 copies of *SMN1*, then other motor neuron disorders such as spinal muscular atrophy with respiratory distress, X-linked spinal muscular atrophy, distal spinal muscular atrophy, and juvenile amyotrophic lateral sclerosis should be considered. If EMG, nerve conduction study, and repetitive stimulation reveal characteristic patterns associated with diseases in muscle, nerve, or neuromuscular junction, then further diagnostic tests, including muscle or nerve biopsy and edrophonium test, may be performed. When disease of the neuromuscular system is ruled out, then one should pursue diagnostic tests to identify spinal cord or brain anomalies by imaging studies such as magnetic resonance imaging or computed tomography scans. Other diagnostic tests should then be performed to identify systemic diseases, such as metabolic disorders or other genetic disorders.

Clinical Management of Newly Diagnosed Spinal Muscular Atrophy Patients

Many care issues arise when a patient is newly diagnosed with spinal muscular atrophy. Clinicians need to address the various aspects of care issues as soon as possible.

Family Education and Counseling

Because of the complexity of medical problems associated with the diagnosis of spinal muscular atrophy, the committee suggests that medical providers designate a person to meet with the family. This person is usually a pediatric neurologist or a geneticist. The primary care physician (pediatrician or family physician) should be well informed of the multidisciplinary needs of these patients and play a central role in coordinating follow-up care. During the first meeting with parents, it is important to explain the disease process, pathogenesis, phenotype classification, and the patient's prognosis. The physician should also formulate a plan of multidisciplinary intervention with the family. This usually includes referral to a pediatric neuromuscular clinic and/or pediatric subspecialties such as genetics, pulmonary, gastroenterology/nutrition, and orthopedic/rehabilitation. The families will appreciate online resources for further information regarding spinal muscular atrophy. Providing information on spinal muscular atrophy patient advocacy groups has proved to be the most useful to help families cope with the diagnosis (please see the acknowledgments section for links to some patient support group Web sites). Several clinical trials are currently in progress both in the

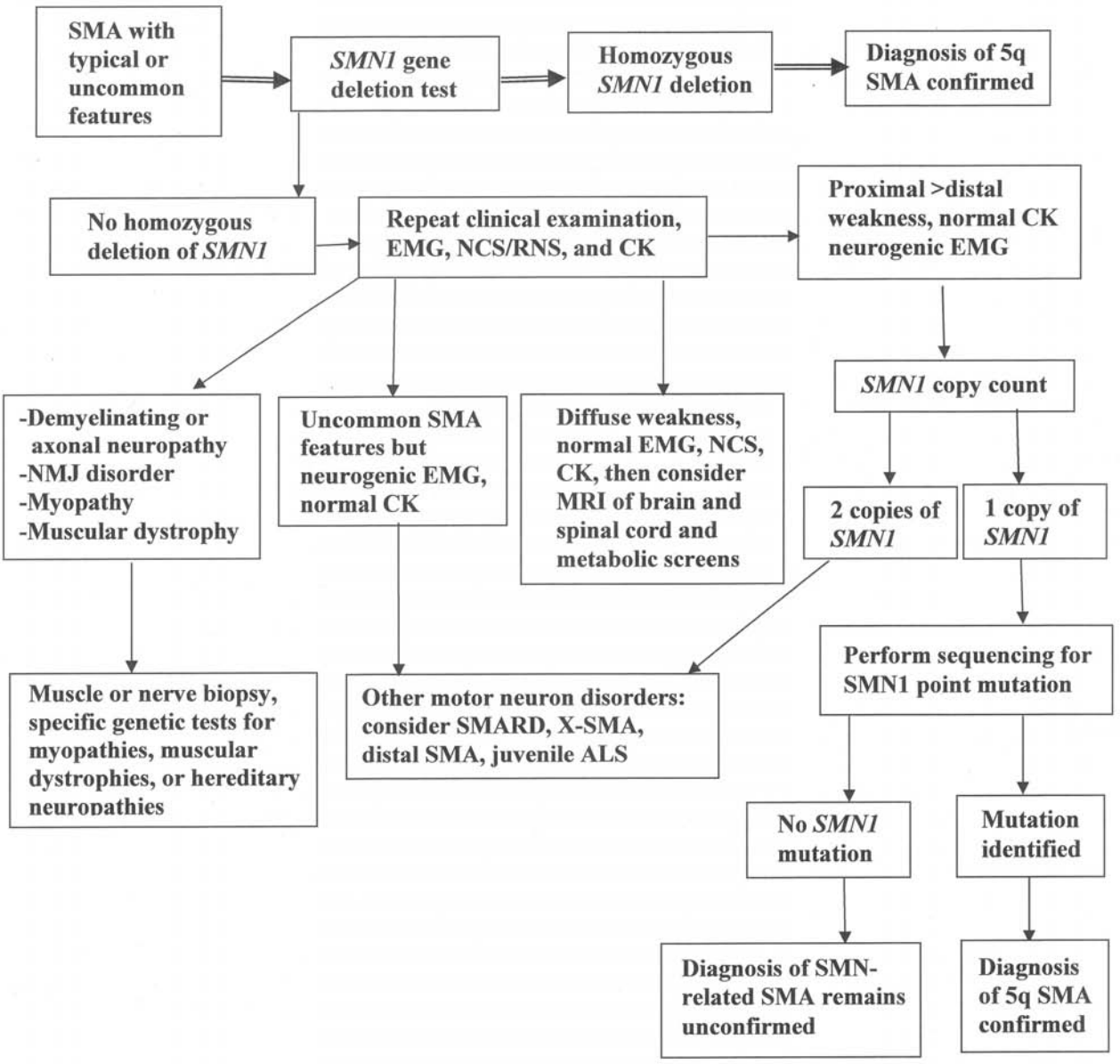

Figure 1. Diagnostic evaluation for spinal muscular atrophy. A diagnostic algorithm for spinal muscular atrophy and other neuromuscular disorders. The Standard of Care Committee recommends the stepwise diagnostic procedure outlined in this flow chart when encountering patients with clinical symptoms of spinal muscular atrophy (SMA). Please see text for detailed explanation of this diagram. EMG = electromyography; NCS = nerve conduction study; RNS = repetitive nerve stimulation; CK = creatine kinase; NMJ = neuromuscular junction; MRI = magnetic resonance imaging; SMARD = spinal muscular atrophy with respiratory distress; X-SMA = X-link SMA; ALS = amyotrophic lateral sclerosis.

United States and in Europe. Physicians should provide information regarding these trials or refer families to clinical trial Web sites (www.clinicaltrials.gov provides a current listing of open clinical trials). Many factors can influence the families' choice to participate in a clinical trial. The families should be encouraged to contact as many study sites as possible before they decide to participate in any trial.

Genetic Topics

Several genetic topics should be addressed with the diagnosis of spinal muscular atrophy. This is often done by a neurologist or geneticist. Topics related to the genetics of spinal muscular atrophy, such as autosomal recessive inheritance and genomic structure of *SMN—SMN1* and *SMN2*

copies—should be explained to the family. The current literature suggests *SMN2* copy numbers correlate with spinal muscular atrophy clinical phenotypes.[24-27] However, although a higher copy number of *SMN2* is correlated with milder phenotype, phenotypes can vary substantially given *SMN2* copy number. Therefore, predicting clinical phenotype using *SMN2* copy number can be risky and is not currently recommended. Other important genetic topics include sibling recurrence risk, carrier testing, and information that may help with reproductive planning (prenatal diagnosis or preimplantational diagnosis). Presymptomatic diagnosis of unaffected siblings is controversial. According to American Society of Human Genetics guidelines, presymptomatic diagnosis in children should be considered only if early intervention can delay the onset or slow the progression of the disease.[28] The committee agrees that presymptomatic diagnosis of at-risk siblings of spinal muscular atrophy patients may lead to early intervention and improve clinical outcome. Therefore, parental request of testing unaffected siblings of the spinal muscular atrophy patient should be granted. The current *SMN1* deletion test will detect the *SMN1* copy number and provide the information of whether the sibling is affected (0 copy) or is a carrier (1 copy). The topic of neonatal screening is also controversial. Although there is currently no proven therapy in spinal muscular atrophy, the committee recognizes the utility of neonatal screening as a tool for identifying effective treatments. Furthermore, in view of recent therapeutic advances, it is possible that in the future, spinal muscular atrophy may be treated more effectively if presymptomatic patients are detected through neonatal screening and treatment is started prior to weakness becoming apparent.

Consensus on Pulmonary Care

Overview of Pulmonary Problems in Spinal Muscular Atrophy

The key respiratory problems in spinal muscular atrophy are as follows:

1. impaired cough resulting in poor clearance of lower airway secretions;
2. hypoventilation during sleep;
3. chest wall and lung underdevelopment; and
4. recurrent infections that exacerbate muscle weakness.

Pulmonary disease is the major cause of morbidity and mortality in spinal muscular atrophy types 1 and 2 and may occur in a small proportion of patients with spinal muscular atrophy type 3. Without respiratory support, infants who are unable to sit usually die before the age of 2 years.[8] Pulmonary compromise is caused by a combination of inspiratory and expiratory muscle weakness, with greater involvement of expiratory and intercostal muscles. The diaphragm is relatively spared. In nonsitters, the result is a bell-shaped chest with sternal depression. In older sitters and walkers, respiratory function may be compromised further by scoliosis. Swallowing dysfunction and reflux are important contributors to pulmonary morbidity. Individuals tend to progress to daytime respiratory failure via a sequence of recurrent chest infections, nocturnal oxygen desaturation, nocturnal hypoventilation, and then daytime hypercarbia.[29-31] In contrast to Duchenne muscular dystrophy, there is no strong correlation between pulmonary functional score and need for mechanical ventilation in spinal muscular atrophy.[32] However, baseline assessment and longitudinal monitoring can identify those at risk for sleep-disordered breathing and ineffective clearance of secretions. There are several case series of the natural history of severe to mildly affected spinal muscular atrophy patients but no large prospective study of treatment intervention.[9,33] The evidence base is limited by heterogeneous groups of patients with a mixture of neuromuscular disorders in natural history and intervention studies, variable classification of spinal muscular atrophy subtypes, and different respiratory support protocols employing a range of ventilators and cough assistance techniques.[30,33-36] Case series[29,30,36,37] and consensus conference[38,39] evidence demonstrate that ventilatory support should be added at night if sleep-disordered breathing is present and cough assistance provided if cough efficiency is reduced. Figure 2 shows a flow chart for pulmonary natural history, assessment, and intervention in spinal muscular atrophy.

Assessment and Monitoring

There is no formal study evaluating any protocol for routine pulmonary assessment of patients with spinal muscular atrophy. However, consensus was achieved within the pulmonary working group on current standard of care for spinal muscular atrophy. The following assessments should be used during baseline and subsequent evaluations of respiratory status and are listed by order of importance as identified by the Delphi survey. Assessment frequency depends on the clinical status and rate of progression of disease for each individual. Suggested frequency of evaluation is every 3 to 6 months, less often in stable walkers, and more frequently in clinically unstable nonsitters.

Nonsitters

Recommendations for respiratory assessment include evaluation of cough effectiveness, observation of breathing, and monitoring gas exchange. Respiratory muscle function tests are indirect measures of cough effectiveness and include peak cough flow, maximal inspiratory pressure, and maximal expiratory pressure. The majority of nonsitters with spinal muscular atrophy may be too weak or too young to perform

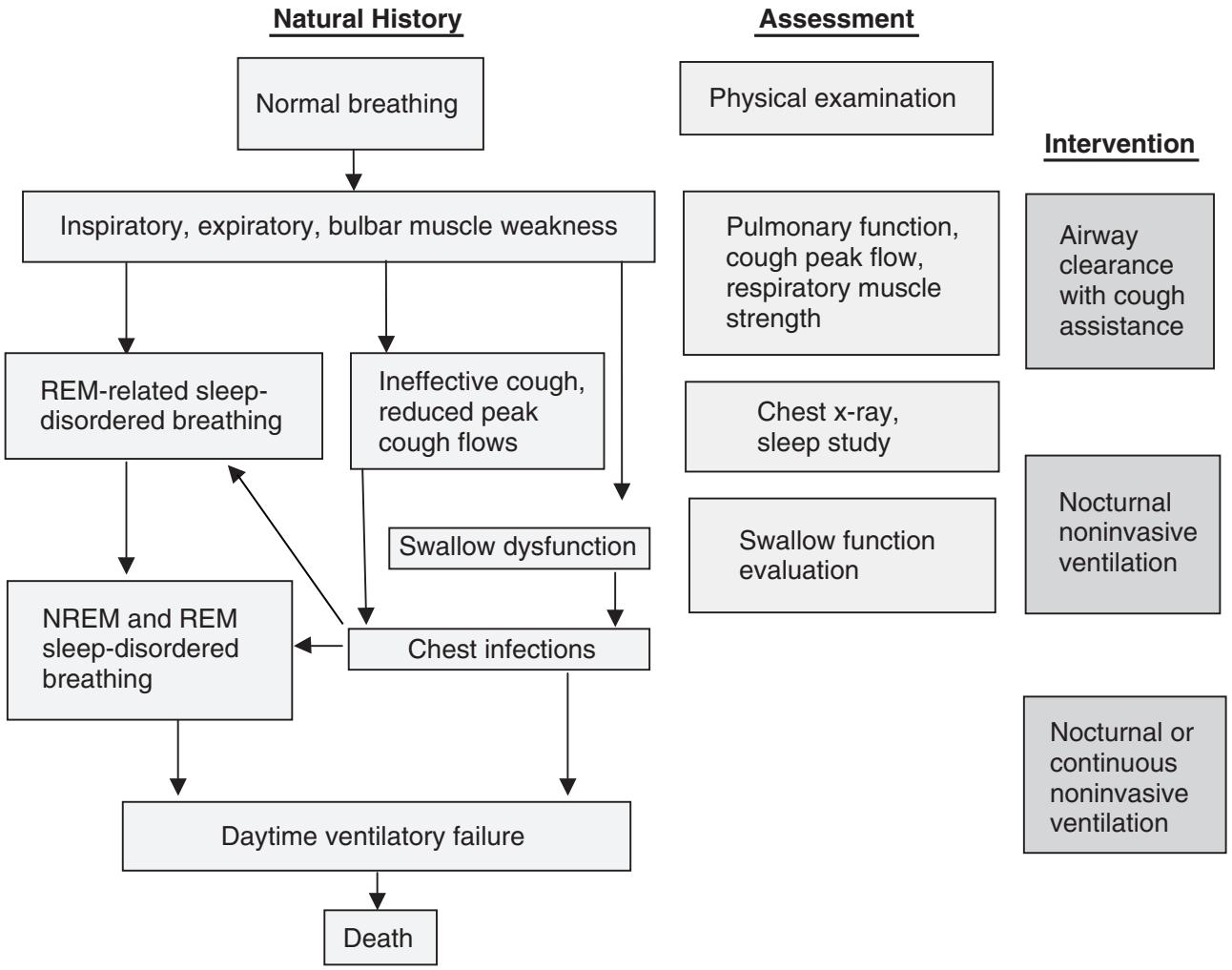

Figure 2. Summary of the natural history of pulmonary problems, assessment, and intervention in spinal muscular atrophy. The progression of pulmonary problems is accompanied by appropriate assessment and intervention strategies. REM = rapid eye movement; NREM = non–rapid eye movement.

pulmonary function testing. Therefore, the most useful evaluation of respiratory muscle function may be observation of cough ability. The physical examination also provides an important assessment of respiratory status including respiratory rate, work of breathing, presence of paradoxical breathing, chest wall shape, and skin color (cyanosis or pallor). Gas exchange monitoring, including pulse oximetry, can be used as a spot check during the day for hypoxemia and as a guide to direct airway clearance. For example, if oxygen saturation is less than 94%, airway clearance techniques should be used. Overnight pulse oximetry with chart recording can be used to screen for nocturnal hypoxemia. Routine overnight monitoring using pulse oximetry may help identify unsuspected hypoxic events but is usually very disruptive to the family due to frequent false alarms. Currently there are no data to support routine continuous oximetry monitoring. Further research is needed before recommending this as part of routine clinical care.

End-tidal carbon dioxide, transcutaneous CO_2, and serum bicarbonate measurement were also identified as important assessment tools. However, serum bicarbonate may give a false sense of reassurance, as normal values may exist despite significant respiratory compromise during sleep. End-tidal carbon dioxide and transcutaneous CO_2 are frequently difficult to obtain and not available routinely. If available, these measurements can be used to assess for sleep-related hypoventilation. The onset of hypoventilation is insidious, and patients may be clinically asymptomatic. Initially hypoventilation will occur in sleep (particularly rapid eye movement sleep), but as deterioration progresses, daytime respiratory function will be impacted.[29,31] Polysomnography is a diagnostic tool during which respiration and sleep state are continuously monitored,[40] and thus it identifies the presence and severity of sleep-disordered breathing.[41] Polysomnography is useful in nonsitters, even in children without obvious symptoms, and can be used to initiate and

titrate respiratory support. When polysomnography is not available, an alternative is to use a 4-channel sleep study that records end-tidal carbon dioxide or transcutaneous CO_2, oxygen saturation, heart rate, nasal airflow, and chest wall movement during sleep. In cases where neither polysomnography nor 4-channel study is available, overnight pulse oximetry with continuous CO_2 monitoring may provide useful information about nighttime gas exchange. However, this will not detect sleep-disordered breathing not associated with oxygen desaturation or CO_2 retention. Further study to better identify the optimal methods for evaluation and monitoring is recommended. Additional screening tests include a baseline chest x-ray to provide an initial reference point and for comparison during respiratory deterioration or unexplained hypoxemia due to unsuspected atelectasis. Although formal radiologic evaluation of swallowing was not ranked very highly for routine evaluation during this Delphi survey, the risk for dysphagia and aspiration is high in nonsitters. Therefore, formal evaluation of swallowing is indicated in cases of acute unexplained respiratory deterioration and recurring pneumonia. Arterial blood gases for routine monitoring of respiratory function are not recommended because the discomfort could result in apnea or spurious hyperventilation.

Sitters

Recommendations of respiratory assessment for sitters are similar to nonsitters and include physical examination and evaluation of cough effectiveness with respiratory muscle function tests (maximal inspiratory pressure, maximal expiratory pressure, and peak cough flow) as described above. In addition, sitters should be evaluated for presence and severity of scoliosis and consider further evaluation with radiographs. Additional recommended assessments include forced vital capacity and lung volume measurements during pulmonary function tests, assessment of sleep-disordered breathing, and pulse oximetry monitoring. Less important assessments identified for sitters include blood gas, CO_2 monitoring, and chest x-ray. Routine swallow study was not recommended for sitters unless clinically indicated.

Walkers

In general, spinal muscular atrophy walkers have relatively preserved pulmonary function until late into their disease course. Recommendations for routine assessment include complete pulmonary function tests, including spirometry, lung volumes, and respiratory muscle function tests. In addition, cough effectiveness and the physical examination are important routine assessments. Further evaluation should be directed by clinical symptoms and indications.

Anticipatory Respiratory Care

Providing families with information about options for care and anticipating future needs are crucial to respiratory management of spinal muscular atrophy. Nonsitters are the most fragile group, and early discussions should include the option of noninvasive ventilation and secretion management because of the rapid progression of the disease. Ongoing discussion of the family's desires for support should occur, and the result should be a negotiated care plan with maximums and minimums outlined.[42]

In addition, anticipatory guidance and education for chronic care, illness management, and perioperative care should be provided. Day-to-day management should include understanding the child's baseline and deviations from his or her baseline, routine cough and secretion management techniques, understanding hypoventilation, and intervention. Illness management includes rapid access to specialty medical care providers, airway clearance and secretion management techniques, respiratory support (including noninvasive ventilation), nutrition and hydration management, and a low threshold to start antibiotics. Routine immunizations, including influenza vaccine, pneumococcus vaccine, and respiratory syncytial virus prophylaxis (palivizumab), are recommended.

Chronic Management

Essential to chronic management is discussion of the family's goals, which includes balancing caring for the child at home for as long as possible, long-term survival, quality of life and comfort, and the availability of resources. Goals of chronic management are to normalize gas exchange, improve sleep quality, facilitate home care, reduce hospitalizations and intensive care unit care, and reduce the burden of illness on the family. There is insufficient evidence, but based on experience and consensus, early aggressive and proactive intervention may prolong life without compromising quality of life.

Airway Clearance

Airway clearance is very important in both acute and chronic management of all patients with spinal muscular atrophy. Caregivers of these patients should learn to assist coughing in all patients with ineffective cough. These techniques include manually and mechanically assisted cough.[43-46] Availability of mechanically assisted cough devices (mechanical insufflation-exsufflation) varies by country but is now widely accepted in management of neuromuscular disease in the United States.[47] Daily assisted cough is recommended in more severely affected patients. Secretion mobilization techniques are also helpful and include chest physiotherapy and postural drainage. Oximetry should be used to provide feedback to guide therapy. Oral suctioning can assist in secretion management after assisted coughing. There is no evidence to support specific secretion mobilization devices such as high-frequency chest wall oscillation and intrapulmonary percussive ventilation in the spinal muscular atrophy population for chronic management.

Respiratory Support

In patients with daytime hypercapnia, respiratory support is clearly indicated. In children with sleep-disordered breathing, nocturnal noninvasive ventilation reduces symptoms of sleep disturbance, nocturnal sweating, and morning headaches and improves appetite and concentration.[29] Objectively, noninvasive ventilation reduces respiratory disturbance index, improves sleep stage distribution,[30] and enhances quality of life. In a randomized controlled trial using mixed groups of patients with neuromuscular disease who showed nocturnal hypoventilation and daytime normocapnia, noninvasive ventilation significantly improved nocturnal blood gas tensions.[48] Noninvasive ventilation with bilevel positive pressure support has been studied most frequently, although there is no evidence to suggest any 1 type of ventilator interface is superior. In addition, the optimal settings for noninvasive ventilation have not been established. In general, noninvasive ventilation settings are individualized to achieve adequate inspiratory chest wall expansion and air entry and normalization of oxygen saturation and end-tidal carbon dioxide or transcutaneous CO_2 measurements. Noninvasive ventilation should be combined with airway clearance techniques.

In nonsitters, care without ventilation support is an option if the burden of treatment outweighs benefit. Noninvasive ventilation can be used palliatively to facilitate discharge to home from a hospital and reduce work of breathing. Continuous positive airway pressure may be an option in a very young nonsitter infant who is not synchronous with bilevel positive airway pressure and can be used with the goal of transitioning to bilevel positive airway pressure. Use of noninvasive ventilation with high-span bilevel positive airway pressure, even for short daytime periods, may improve chest wall and lung development and reduce ribcage and sternal deformity in nonsitters and sitters,[49] resulting in potential beneficial effects on pulmonary function. Uncommonly, adult walkers may develop sleep-disordered breathing or acute ventilatory failure at the time of a chest infection or intercurrent event (eg, surgery). Noninvasive ventilation is an appropriate intervention and may be required during sleep chronically.

Tracheotomy for chronic ventilation is a decision that needs to be carefully discussed if requested by parents. In nonsitters, this is controversial and an ethical dilemma. There is a large spectrum of options that can be provided, ranging from no respiratory support to noninvasive ventilation to tracheotomy and mechanical ventilation. Our recommendation is to explore options with the family regarding the child's potential, quality-of-life issues, and family's desires.[50] Palliative care is an option for nonsitters. It should be noted that noninvasive ventilation can be used as a routine therapy or as a palliative tool. A key goal is to prevent pediatric intensive care unit stays and avoid tracheotomy if possible. If supportive ventilation is chosen by the family, noninvasive ventilation is recommended.

Additional Management

Recommended additional therapies are routine vaccinations, appropriate nutritional support orally or via a feeding tube, hydration management, and medical or surgical gastroesophageal reflux disease management. In addition, medical management for saliva control may be considered. Inhaled bronchodilators should be considered in children with asthma or bronchial hyperresponsiveness. Use of these agents in other situations requires further evaluation. There is no evidence to support the use of mucolytics on a chronic basis.

Perioperative Care

Patients with spinal muscular atrophy are at high risk for postanesthesia complications, which may lead to prolonged intubation, nosocomial infections, tracheotomy, and death. Perioperative complications include upper airway obstruction, hypoventilation, and atelectasis from impaired cough and impaired mucociliary clearance due to anesthetic agents. Postoperative pain may exacerbate respiratory compromise. Noninvasive ventilation associated with aggressive airway clearance techniques can successfully treat hypoventilation and airway secretion retention.

It is crucial that the patient's respiratory status be optimized before surgery. Preoperative evaluation, including pulmonary consultation, is strongly recommended. The assessment of respiratory function should include a physical examination, measurements of respiratory function and cough effectiveness, chest x-ray, and, if at risk, an evaluation for sleep-disordered breathing. In addition, complicating factors should be considered, including oropharyngeal aspiration, gastroesophageal reflux, and asthma. If measurements of respiratory function and/or sleep study are abnormal, nocturnal noninvasive ventilation and assisted coughing techniques may be indicated before surgery. The patient should become familiar with these techniques prior to surgery. The anesthesiology preoperative evaluation should include assessment for possible difficult intubation due to jaw ankylosis. If present, intubation should be performed by fiberoptic bronchoscopy.

Postoperative management should be determined by preoperative respiratory function and the type of surgery performed. Patients with normal cough clearance and relatively preserved muscle function are not at an increased risk for postoperative complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive respiratory management. Any patient who requires respiratory support during sleep will require similar respiratory support in the immediate postoperative course. Extubation in the recovery room to noninvasive ventilation should be planned as a bridge to weaning to the patient's baseline respiratory support. Careful planning and coordination with the hospital respiratory therapists are crucial for success in this setting. Patients with continuous ventilator

support requirements (either via noninvasive interface or via tracheotomy tube) or patients who receive muscular blocking agents during surgery are best transferred directly from the operating room to the intensive care unit. Patients are encouraged to bring their personal devices, such as noninvasive ventilation and mechanical insufflation-exsufflation-E machines, to use in the postoperative period because the availability of these devices in hospitals may be limited. Although oxygen is used frequently in the postoperative setting, it must be applied with caution in the patient with spinal muscular atrophy. Hypoxemia secondary to hypoventilation may be mistaken with hypoxemia due to other causes, such as mucus plugging and atelectasis. End-tidal carbon dioxide or transcutaneous CO_2 monitoring or arterial blood gas analysis will facilitate appropriate oxygen use. Adequate pain control will aid in preventing hypoventilation secondary to splinting. Postoperative pain management should be titrated to promote airway clearance and minimize respiratory suppression. Transient increased respiratory support may be needed while controlling postoperative pain.

Acute Care Management

The goal of acute management is to normalize gas exchange by reducing atelectasis and enhancing airway clearance where possible by noninvasive respiratory support. Blood gas monitoring may be of benefit.

Airway Clearance

For nonsitters, sitters, and walkers experiencing acute illness, airway clearance with manual cough assist or mechanical insufflation-exsufflation, together with oral or airway suctioning, chest physiotherapy, oximetry feedback to guide airway clearance, and postural drainage, are important and recommended. Assisted cough techniques are preferred over deep suctioning and bronchoscopy.

Respiratory Support

Nonsitters. In acute illness, a vicious cycle of added ventilatory load, increased respiratory muscle weakness, and ineffective secretion clearance leads to ventilatory decompensation. Acute use of noninvasive ventilation reverses these features. Continuous positive airway pressure is not indicated in this situation because it does not reduce the ventilatory load. In nonsitters and sitters already using nocturnal noninvasive ventilation, daytime use may be required during acute illness, and airway clearance techniques can be carried out during noninvasive ventilation. Noninvasive ventilation in combination with airway clearance techniques may reduce the need for intubation. Oxygen therapy entrained into the noninvasive ventilation circuit should be used to correct oxygen desaturation, after inspiratory and expiratory positive pressure settings are optimized and airway clearance techniques are optimally utilized. If a noninvasive approach fails, nonsitters can be intubated and mechanically ventilated as a short-term measure. After recovery from the acute illness and arterial oxygen saturation on room air has normalized, they should be extubated back to noninvasive ventilation. Decision making about escalation to intubation should be carried out in advance as part of anticipatory care planning. In nonsitters with increasingly frequent acute pulmonary infections, tracheotomy and ventilation can be considered but may not improve quality of life or reduce hospitalizations. A tracheotomy is not an acute intervention. A noninvasive approach is preferred where feasible. In some nonsitters, with deteriorating function, it may be appropriate to redirect care to a palliative approach.

Sitters. For those already using nocturnal noninvasive ventilation, daytime noninvasive ventilation may be needed during acute illness. Noninvasive ventilation in combination with airway clearance techniques may reduce the need for intubation. Oxygen therapy and need for transient intubation should be carried out as outlined above for nonsitters. Continuous positive airway pressure and/or a tracheotomy are not appropriate interventions in sitters.

Walkers. Walkers may need noninvasive ventilation during an acute illness. Noninvasive ventilation in combination with airway clearance techniques may reduce the need for intubation. Oxygen therapy and need for transient intubation should be carried out as outlined above for nonsitters. If noninvasive ventilation was needed during an acute illness, noninvasive ventilation should be considered for home use. Continuous positive airway pressure and/or a tracheotomy are not appropriate interventions in walkers.

Additional Management

For nonsitters, sitters, and walkers, recommended additional therapies are antibiotics, adequate nutritional support via nasogastric or nasojejunal or gastrostomy tube, hydration, and gastroesophageal reflux management (see more details in the next section). In patients with bronchial hyperresponsiveness or asthma, bronchodilator therapy and inhaled steroids may be indicated. Uses of inhaled mucolytics, bronchodilators, and corticosteroids are areas in need of further research.

Conclusion

Pulmonary disease is the major cause of morbidity and mortality in spinal muscular atrophy types 1 and 2. Respiratory muscle weakness results in impaired cough and ability to clear lower airway secretions, lung and chest wall underdevelopment, and hypoventilation. Respiratory care of patients with spinal muscular atrophy is essential to their survival and quality of life. The pulmonary working group has achieved the following consensus recommendations:

1. Referral for respiratory care evaluation and discussion of options should occur shortly after diagnosis. Key components of the respiratory assessment include evaluation

of cough effectiveness, observation of breathing, and monitoring gas exchange.
2. Chronic respiratory management includes providing methods for airway clearance, including mechanical insufflation-exsufflation or manual cough assist and noninvasive ventilatory support. Routine immunizations are also recommended.
3. Discussion with families about the options for respiratory care and identifying the goals for chronic and acute respiratory care should occur early in the disease course and continue in an ongoing dialogue.
4. Acute respiratory illness management requires increased airway clearance and secretion management techniques using mechanical insufflation-exsufflation or manual cough assist, increased respiratory support (including noninvasive ventilation), nutrition and hydration management, and a low threshold to start antibiotics.
5. Perioperative care includes a thorough preoperative evaluation of respiratory status, ideally by a pulmonologist, and anticipatory guidance of the surgical team and postoperative management team regarding optimal care.

Future Research Directions

The following topics were identified as areas in which no consensus could be achieved because research data are lacking. These areas are in need of further study:

1. Optimal methods for evaluation and monitoring of hypoventilation.
2. Use of pulse oximetry in the home.
3. Optimal secretion mobilization techniques (eg, chest physiotherapy, postural drainage, high-frequency chest wall oscillation, and intrapulmonary percussive ventilation).
4. Optimal ventilatory support settings.
5. Effectiveness of inhaled and nebulized medications, including bronchodilators, mucolytics, and corticosteroids.

Consensus on Gastrointestinal and Nutritional Care

Overview of Gastrointestinal and Nutritional Complications in Spinal Muscular Atrophy

The key clinical problems associated with gastrointestinal and nutritional complications in spinal muscular atrophy are as follows:

1. *Feeding and swallowing problems*. Bulbar dysfunction is universal in spinal muscular atrophy patients with severe weakness and can result in feeding and swallowing difficulties and aspiration pneumonia, which often results in death. The severity of bulbar dysfunction is variable in patients with spinal muscular atrophy of intermediate severity and rare in those who are mildly affected.
2. *Gastrointestinal dysfunction*. Gastroesophageal dysmotility problems include constipation, delayed gastric emptying, and potentially life-threatening gastroesophageal reflux.
3. *Growth and undernutrition/overnutrition problems*. Without optimal management, growth failure is universal in nonsitters, whereas excessive weight gain is more common in sitters and walkers.
4. *Respiratory problems*. The presence of respiratory complications (weak cough, increased work of breathing, dyspnea, pneumonias, and cyanosis or desaturation with feeds) raises concern for gastrointestinal problems of aspiration and gastroesophageal reflux, which can be serious and life-threatening. Increased work of breathing may also result in increased energy expenditure.

In the following sections, we will take a problem-oriented approach to discussing the evaluation and management of these problems during chronic care and acute illness.

Feeding and Swallowing Problems

Feeding and swallowing difficulties are common in nonsitters and sitters but are rarely a concern in walkers. Key symptoms of feeding difficulties include prolonged mealtime, fatigue with oral feeding, and evident choking or coughing during or after swallowing. The presence of recurrent pneumonias is a potential indicator of aspiration, which may be silent (ie, without evident choking or coughing). Articles in the literature addressing the role of oral motor structures and specific chewing and swallowing impairments that impact oral feeding performance in spinal muscular atrophy are limited to class III and IV evidence. One review found a 36% prevalence of at least 1 feeding-related issue in children with spinal muscular atrophy.[51] Several other population studies and case series report swallowing problems in patients with spinal muscular atrophy.[51-53] Difficulties in the preoral phase included limited mouth opening and difficulties in getting food to the mouth for self-feeding.[51] In the oral phase, difficulties included weak bite force, reduced range of mandibular motion limiting mouth opening, and increased fatigue of masticatory muscles.[54] This affects biting and chewing abilities and can lead to prolonged mealtimes and fatigue, precluding sufficient intake. Masticatory and facial muscle weakness affects oral bolus control, chewing, and bolus propulsion, all of which contribute to reduced feeding efficiency. Difficulties with strength and efficiency are reported in the oral and pharyngeal phase of the swallow. Poor coordination of the swallow with airway closure can lead to penetration and aspiration of the airway. Poor head control may also be a factor in the development of feeding difficulties, precluding neck tuck or other compensatory postures to enhance the safety of swallowing.[55] The psychosocial impact of feeding difficulties on these children and their family should not be underestimated. Prolonged mealtimes can put time pressure on other activities. In addition, their inability to feed themselves can make these children seem more dependent

than their peers and lead to a sense of loss of control. In the weakest children, tube feeding can limit the nurturing role parents perceive from being able to orally feed their child.[53]

Evaluation of Feeding and Swallowing Problems

Assessment of feeding problems should be performed by a feeding specialist, most commonly a speech or occupational therapist. Routine clinical evaluation of feeding and swallowing difficulties should include a feeding assessment. Videofluoroscopic swallow studies should be performed when indicated. A feeding case history with mealtime observation is desirable. Examination of oral structures that influence feeding efficiency and consideration of the effect of positioning and head control on feeding and swallowing are essential. Videofluoroscopic swallow studies should be carried out after initial assessment if there are concerns about swallow safety.[51,53,56,57] Laryngeal aspiration requires specific assessment, as it is sometimes silent (ie, no clearing cough is triggered).[56] In severely affected children, vocal fold paralysis and consequent inability to protect the airway may be a diagnostic sign.[57,58] A videofluoroscopic swallow study is not simply a diagnostic test of aspiration but is an opportunity to evaluate therapeutic strategies, such as adapted food texture and positioning, to assess impact on swallow function. As position and consistency can affect swallow physiology, it is important that the videofluoroscopic swallow studies procedure is as representative of the child's usual meal and feeding position as possible.

Management of Feeding and Swallowing Difficulties

Treatment should aim at reducing the risk of aspiration during swallow and optimizing efficiency of feeding and promote enjoyable mealtimes. A Cochrane review[59] of treatment of swallowing difficulties in chronic muscle disease concluded it was not possible to determine the benefit or otherwise of dietary and feeding advice, surgical intervention (cricopharyngeal myotomy or upper esophageal dilatation), and enteral feeding. Changing food consistency and optimizing oral intake are appropriate treatment strategies. The literature suggests there is currently widespread use of consistency modification in helping to optimize oral intake.[51,53] A semisolid diet can be used to compensate for poor chewing and reduce length of mealtimes. Thickened liquids may protect against aspiration of thin fluids. Preferably, this intervention would be evaluated objectively on videofluoroscopic swallow studies. In 1 study, complete restriction orally to eliminate risk of aspiration during swallowing was not found to significantly affect the clinical course in severe spinal muscular atrophy.[60] This study failed to consider the risk of aspiration due to concomitant gastroesophageal reflux. Positioning and seating alterations and orthotic devices (eg, Neater Eater, elbow support, valved straw) to enhance self-feeding ability may improve swallow safety and efficiency.[51] Such interventions should be planned in liaison with an occupational therapist and/or physiotherapist as required. There is currently no supporting evidence that oral motor treatment programs impact safety or efficiency of oral feeding.

The gastrointestinal/nutrition working group did not reach consensus regarding when to refer a patient with spinal muscular atrophy for consideration for gastrostomy tube placement and whether one should supplement or replace oral feeding with tube feeding in a nonsymptomatic patient. Some practitioners prefer a proactive approach, particularly in the nonsitters, whereas others believe that exposing such patients to the risk of surgery is inappropriate prior to the onset of symptoms. However, 1 clear consensus is that optimal management requires proactive nutritional supplementation as soon as inadequate oral intake is recognized. Whether a gastrostomy tube is placed in a particular child often requires extensive discussion with multiple caregivers. It usually takes time to schedule a surgical procedure like gastrostomy tube placement. In the interim, nutritional supplementation via nasogastric or nasojejunal feeding is desirable. Nasojejunal feeding may be preferable in circumstances when gastroesophageal reflux with aspiration is a concern, especially when the patient is on ventilatory support. However, technical difficulty may prevent its feasibility. Gastrostomy tube feeding is the optimal method of feeding when insufficient caloric intake or unsafe oral feeding is of concern. It prevents the potential morbidity associated with prolonged use of either nasogastric or nasojejunal tubes. The presence of a nasojejunal or nasogastric tube may also result in a less-than-ideal mask fit when there is a need for the use of noninvasive ventilation such as bilevel positive airway pressure.

There are several options for gastrostomy tube placement, including insertion via percutaneous methods with endoscopic guidance, or placement via open or laparoscopic surgical techniques[61] together with an antireflux procedure such as Nissen fundoplication. The open surgical technique is associated with a relatively large upper abdominal incision, increased postsurgical pain, and risk for respiratory complications due to diaphragmatic splinting. A laparoscopic surgical technique provides the best possible setting for immediate or early postoperative extubation.[62] Such procedures are typically performed with general anesthesia, although placement using percutaneous methods with endoscopic guidance is performed in some centers with conscious sedation and local anesthesia. Care should be taken to minimize the amount of fasting preoperatively and to resume full nutritional support as quickly as possible following the procedure. Possible pulmonary complications of sedation should be anticipated and may require treatment with noninvasive ventilation (see "Pulmonary Care").

Gastrointestinal Dysfunction

Children with spinal muscular atrophy suffer from the following gastrointestinal problems: gastroesophageal

reflux, constipation, and abdominal distension and bloating. Gastroesophageal reflux is an important determinant of mortality and morbidity in patients with spinal muscular atrophy. It can be associated with silent aspiration and results in pneumonias and, at times, life-threatening events.[60] Frequent "spitting up" or vomiting after meals, complaints of chest or abdominal discomfort, bad breath, or obvious regurgitation of feeds may indicate gastroesophageal reflux. Some children may refuse feeds when they develop discomfort with swallowing, placing them at risk for undernutrition. High-fat foods delay gastric emptying and increase the risk of gastroesophageal reflux. Constipation is a frequently reported problem and is likely multifactorial in origin (ie, abnormal gastrointestinal motility, reduced intake of dietary fiber, inadequate fluid intake, low muscle tone of the abdominal wall). Infrequent bowel movements can lead to abdominal distention and bloating. In children dependent on their abdominal muscles to assist with respiration, desaturation or respiratory distress in association with attempted bowel movements may occur.

Evaluation of Gastrointestinal Dysfunction

The symptoms of gastroesophageal reflux (emesis, regurgitation, gurgling after feeds) should be sought early. A routine upper gastrointestinal series is recommended for presurgical evaluation for gastrostomy tube placement to primarily rule out anatomic anomalies and secondarily to document reflux. In rare cases, esophageal stricture, foreign body, or other abnormality may contribute to swallowing difficulties or gastrointestinal dysmotility. Motility studies, including scintigraphy, can be helpful in documenting delayed gastric emptying, which may contribute to gastroesophageal reflux and early satiety. There are no data to support the routine diagnostic use of pH probe studies in documenting reflux.

Management of Gastroesophageal Reflux

Medical management of gastroesophageal reflux typically involves the use of acid neutralizers (eg, magnesium or calcium carbonate) and/or inhibitors of acid secretion. This latter category includes both histamine blockers and proton pump inhibitors (eg, famotidine, ranitidine, omeprazole). Short-term use of these agents is reasonable for symptomatic management. However, increasing evidence suggests that prolonged use of these agents may be associated with a greater risk for gastroenteritis and pneumonia.[63,64] When delayed gastric emptying or diminished motility is present, prokinetic agents may be useful (eg, metaclopramide, erythromycin). Use of probiotics such as acidophilus or lactobacillus to help maintain a healthy gastrointestinal flora, particularly after antibiotic treatment or in the setting of prolonged use of acid inhibitors, is an area deserving further study.

Gastrostomy tube feeding does not ameliorate gastroesophageal reflux. This is of particular concern in nonsitters who are the least able to protect their airway via a triggered cough. Determining whether aspiration has occurred during swallow or as a result of gastroesophageal reflux is often difficult, and sometimes both may contribute. A laparoscopic antireflux procedure (eg, Nissen fundoplication) is commonly performed as a combined procedure during the same general anesthesia for gastrostomy tube insertion. Although some physicians support a proactive combined laparoscopic Nissen and gastrostomy tube procedure in those children with spinal muscular atrophy who are deemed at greatest risk for aspiration, there is as yet no published data nor consensus to support this strategy. However, in the spinal muscular atrophy patient with medically refractory gastroesophageal reflux, and in whom the benefit is deemed to outweigh the associated surgical and anesthetic risks, laparoscopic Nissen fundoplication during gastrostomy tube placement is supported as an appropriate intervention.

Growth and Undernutrition/Overnutrition Problems

Children with spinal muscular atrophy are at risk for growth failure or excessive weight gain. Growth failure is commonly seen in nonsitters and some sitters, whereas obesity is a problem of the stronger sitters and walkers. There are no articles in the literature that specifically address body composition and growth expectations or typical anthropometric measures in children with spinal muscular atrophy. However, data can be extrapolated from literature on patients with spinal cord injury. Individuals with spinal cord injury have been shown to have lower lean tissue and higher percentage body fat than controls. Body mass index significantly underestimates body fat in these patients.[65,66] Children with spinal muscular atrophy may have acceptable fat mass but may plot as underweight based on weight/height criteria due to the decrease in lean body mass.[53] Hence, normal body mass indexes may not represent the ideal weights for children with spinal muscular atrophy. Decreased activity and lean body mass will lead to reduced resting energy expenditure and increased risk of obesity.

Management of Growth and Undernutrition or Overnutrition Problems

Routine history, physical examination, and monitoring of growth velocity measures (growth charts) form the evaluation process to detect signs and symptoms of growth failure or excess. This will influence decisions regarding when and how to intervene. The goal is to maintain each child on his or her own growth velocity. Growth velocity curves (weight, height/length, weight/height) followed over a period of time are, for the most part, the most accurate indicator of nutritional status. Difficulty in obtaining accurate standing height measurements due to contractures or inability to

stand may complicate growth monitoring in these children. Recumbent length, segmental measurements, or arm span may be useful surrogate markers for linear growth in these children. Other methods for monitoring body composition include skinfold measurements, muscle circumference, or bioelectric impedance analysis.[67] Assessment of nutritional intake by a dietitian or other health care provider proficient in nutrition is recommended at each visit. A 3-day dietary record is a simple and accurate tool that can help assess whether nutritional intake is adequate.[53] A 24-hour food recall is a practical method to highlight major nutritional concerns and to obtain information regarding use of any special supplements. Analysis should target adequacy of macronutrient (including fiber intake) as well as micronutrient intake. Currently, there is no indication for increasing or decreasing specific nutrients (ie, protein, fat, or selected vitamins or minerals). Until more specific data are available, nutrient intake should meet the daily recommended intakes for age. Supplements to provide more than the dietary recommended intake for vitamin, mineral, protein, or fat should be discouraged. Although anecdotal benefit with the use of elemental or semi-elemental formulas has been reported by some families and care providers (satisfactory growth and decreased secretions), there is currently insufficient data to make specific recommendations regarding their use. If an elemental formula is used, a dietitian should be involved to help ensure the child does not receive insufficient or excessive amounts of nutrients, to perform laboratory assessments as needed, and to monitor adequate growth.[68] As previously mentioned, with a reduction in lean body mass, calculated body mass index will significantly underestimate body fat.[66] Children with spinal muscular atrophy may have acceptable fat mass but may be perceived as underweight based on weight/height criteria because of their decreased lean body mass. This will result in inappropriate dietary recommendations that could lead to relative obesity.[53] The spinal muscular atrophy patients at risk for obesity should have growth parameters in the lower percentiles for weight/height and body mass index. In any case, each child should be evaluated individually on a routine basis, with the goal of following their established growth curves and avoiding inadequate or excessive intake. There is some evidence that decreased bone mineral density may occur in nonsitters and sitters, resulting in recurrent fractures in a subset of patients.[69] There is preliminary evidence that dual energy x-ray absorptiometry could be a useful technique for estimating lean versus fat mass in spinal muscular atrophy patients.[70-73] However, insufficient data are available at this time to recommend the routine use of dual energy x-ray absorptiometry scans for monitoring bone mineral density or body composition. Instead, the importance of documenting appropriate intake of calcium and vitamin D was emphasized. There is no consensus regarding performing biochemical tests to monitor nutritional status for patients with spinal muscular atrophy. However, consideration should be given to checking prealbumin levels to help assess adequate protein status.[53]

Management of Nutrition in the Acutely Sick Spinal Muscular Atrophy Patient

Spinal muscular atrophy patients are particularly vulnerable to catabolic and fasting states. Patients with severe muscle wasting from any disorder, including spinal muscular atrophy, are more likely to develop hypoglycemia in the setting of fasting.[74,75] A number of case series and individual case reports have documented secondary mitochondrial dysfunction and abnormalities of mitochondrial fatty acid oxidation in spinal muscular atrophy patients.[76-83] Significant abnormalities are most likely in nonsitters and sitters, increasing their vulnerability for metabolic decompensation in the setting of a catabolic state. Thus, it is necessary to avoid prolonged fasting, particularly in the setting of acute illness, in all spinal muscular atrophy patients. Nutritional intake should be optimized to meet full caloric needs within 4 to 6 hours after an admission for acute illness, via enteral feeding, parenteral feeding, or a combined approach as necessary. Prompt postoperative caloric supplementation is recommended to avoid muscle catabolism, particularly in a child with reduced fat store. If enteral intake is not imminent, then intravenous caloric feeding should be considered.

Conclusion and Future Directions

Because nutritional problems associated with spinal muscular atrophy influence the patient's pulmonary status and general well-being, optimal management of these problems by a multidisciplinary or interdisciplinary team of physicians, speech therapists or occupational therapists, dietitians, and pediatric surgeons should greatly improve survival and quality of life.[62]

The following topics were identified as areas in need of further study:

1. Use of elemental formulas to support/refute perceived benefits of optimal growth and decreased oral and airway secretions.
2. Need for a reduced fat intake, in view of the concern for mitochondrial fatty acid oxidation abnormalities.
3. Need for protein supplementation beyond dietary recommended intake, in view of the problem of muscle wasting/atrophy.
4. Need for checking biochemical tests for metabolic/mitochondrial fatty acid abnormalities, in view of the concern for mitochondrial fatty acid oxidation abnormalities.
5. Need to determine body composition and establish growth charts for the population of patients with spinal muscular atrophy to enable optimal growth monitoring in these patients.

Consensus on Orthopedic Care and Rehabilitation

Overview of Orthopedic Care and Rehabilitation Strategies in Spinal Muscular Atrophy

Key Problems

Muscle weakness of varying severity limits motor function of trunk and upper and lower extremities, resulting in contracture formation, spinal deformity, limited mobility and activities of daily living, and increased risk of pain, osteopenia, and fractures.

Key Evaluation Procedures

These include evaluating range of motion, strength, function, seating and mobility, orthotics, radiographs (spine and other joints), and dual energy x-ray absorptiometry. The value of these procedures varies by degree of functional impairment.

Key Interventions

In nonsitters, nutritional support, posture management, seating, contracture and pain management, therapy for activities of daily living and assistive equipment, wheelchairs for mobility, limb orthotics, and developmental therapies are important. In sitters, wheelchair mobility, contracture management, physical therapy, and occupational therapy are of highest value, with strong considerations for spine and limb orthotics and spine surgery. In walkers, the highest emphasis is on provision of physical therapy, occupational therapy, and wheelchair/mobility, although orthotics, scoliosis surgery, and pain management figured prominently. In the United Kingdom and some other European countries, chest physiotherapy is often done by physical therapists.

Literature Review

Rehabilitation and Orthopedic Problems in Spinal Muscular Atrophy

Literature review pertinent to these rehabilitation and orthopedic concerns reflects similar musculoskeletal and functional problems to those presented in "Key Problems".[1,84-86] Hip subluxation is a common comorbidity in patients with spinal muscular atrophy.[87,88] As patients with spinal muscular atrophy age, there is a significantly higher prevalence of kyphoscoliosis, difficulty coughing, joint contractures, and voice/speech problems in types 1 and 2. In type 3, there is also a significantly higher prevalence of fatigue and hypermobility of the hand.[89] Scoliosis develops in more than 50% of children with spinal muscular atrophy, most commonly in nonambulatory children or in those who lose the ability to walk.[90]

Evaluation

Traditional measurements of strength are not possible in severely affected infants and children; thus, emphasis is on observation of function. Evaluation procedures that address rehabilitation/orthopedic concerns include the CHOP-INTEND,[91] the Hammersmith Functional Motor Scale for Spinal Muscular Atrophy,[92,93] the Modified Hammersmith Functional Motor Scale for Spinal Muscular Atrophy,[94] the Gross Motor Function Measure,[95] and the Motor Function Measurement scale for neuromuscular disease.[86,93] Most children with spinal muscular atrophy require help or supervision with bathing and dressing and assistance with mobility. Stairs present a major obstacle.[96] Early and generalized joint contractures and scoliosis correlate with level of motor function and walking with support, rolling by 5 years of age correlates with eventual walking, and inability to roll correlates with severe disease (greater weakness).[97] Muscle strength can be quantified using myometers, videotaped movements,[98] handheld dynamometers,[99] and quantitative muscle testing in children with the type 2 or 3 forms of the disease.[100-102] Flexion contractures, which affect almost half of spinal muscular atrophy patients, are often noted during periods of inactivity and are considered intractable if greater than 45° Activities of daily living are hampered, and contractures are perceived to be associated with disability in about half. Pain increases in frequency and severity over time and correlates with decreased scores on quality-of-life indicators.[103] In all studies of scoliosis, spine radiographs were routinely used for diagnosis. A retrospective review of spinal full-length radiographs revealed a predominance of right-sided thoracic and thoracolumbar curves and left-sided lumbar curves.[104]

Interventions

No studies directly address physical therapy and occupational therapy as general therapies, although a case report documented the ability of a 20-month-old girl with spinal muscular atrophy to learn to operate a power wheelchair independently in 6 weeks and demonstrated developmental gains in all domains of the Batelle Developmental Inventory over the ensuing 6 months.[65] Regarding other interventions, 3 case series discussed the use of knee-ankle-foot orthoses in patients with spinal muscular atrophy. Evans[105] presented 5 cases (3 who had lost the ability to walk) who were treated with serial casting and bracing and were still ambulatory 2 to 5 years later. Granata presented 7 cases and later 12 cases of patients with type 2 spinal muscular atrophy. All were able to stand independently with knee-ankle-foot orthoses, and 7 achieved assisted ambulation. When compared with a historical control group, the treatment group had less scoliosis. There may have been a trend toward greater hip subluxation in the treatment group.[106]

Consensus Recommendations on Evaluation and Treatment by Functional Levels

The natural history of the disorder should be considered along with the results of the examination and the goals of the patient and family in planning treatment. Intervention should address the problems that were identified through a thorough history and examination. On the basis of the literature review, the results of the Delphi survey, and our group conferences, we list recommendations in this care area by the functional levels of these patients.

Nonsitters

These patients present in early infancy to rehabilitation providers with impairments in respiratory function and profound weakness. Limited range of motion, head control, postural control and alignment, and progressive scoliosis are found. There is significant fatigue during and after medical care and with therapies. Weakness leads to varying functional deficits that interfere with caretakers' abilities to perform activities of daily living and that also limit participation in developmental activities and later in school. A multidisciplinary approach to evaluation and management includes a strong partnership between therapists, patients and families, and physicians. Assessments include physical and occupational therapy and speech therapy if swallowing is impaired or if speech production is affected by jaw contractures and inadequate ventilatory support of voice. Play and occupational support should include lightweight toys and assistive technology with variable controls and a myriad of activation systems. Consideration of the patient's primary posture should direct choice of equipment and devices that support function. Upper extremity orthotics to aid in function include the use of mobile arm supports or slings that augment active range of motion and functional abilities. Use of linear elastic elements to balance out the effects of gravity in multiple dimensions can aid those with proximal weakness and improve control of distal function. Upper extremity or hand orthoses should be considered with caution because attempts to correct postural deviations and compensations with an orthosis may result in reduced function. Compensations due to hypermobility and lack of power should not always be discouraged. Splinting to preserve range of motion and prevent pain may be indicated.

Sitters

Weakness, contractures, respiratory dysfunction, and scoliosis characterize the main problems of this group. These impairments contribute to limitations in mobility, endurance, and activities of daily living. Evaluations by physical therapists, occupational therapists, and orthopedic surgeons include measurement of contractures and strength by goniometry, manual muscle testing, or myometry, with judicious use of spine and hip radiographs. Equipment evaluation includes seating and mobility, positioning, and equipment for self-care. The need for assistive technology and adaptive aids should be determined in the context of improved function. Pulmonary evaluation should be conducted, as it pertains to exercise tolerance and endurance. Evaluations for manual and power mobility may be conducted as early as 18 to 24 months of age. Contracture management and exercise are a major focus of treatment, with implementation of a regular stretching and bracing program to preserve flexibility. Serial casting for contractures may improve participation in a standing program and improve tolerance of bracing. Regular exercise should be encouraged to maintain fitness and endurance and might include swimming and adaptive sports. Lightweight ischial weight-bearing knee-ankle-foot orthoses or reciprocal gait orthoses should be considered for standing or assisted ambulation with a walker for patients with sufficient strength. Where this is not possible, a standing frame or mobile stander with ankle-foot orthoses should be considered. Upper extremity orthotics with mobile arm supports or slings augment active range of motion and functional abilities. Assistive technology and other adaptive equipment to enhance independent work and play should be considered.

Walkers

The combination of proximal weakness and impaired balance results in frequent falls. Limitations are found in transitions between the floor, sitting and standing, distance ambulation, changes in terrain, and stair climbing. There are consistent complaints of fatigue with activity. Musculoskeletal deformities and pain are most commonly reported in late childhood and early adolescence, and with their onset, functional limitations become more pronounced. Patients may present acutely for management of fractures or other musculoskeletal injury. Balance and ambulation evaluations include a specific survey of environmental adaptability and access. Evaluation of joint range of motion and spinal alignment as they affect function, comfort, and balance guides more specific orthotic and spinal assessment and x-rays. Physical and occupational therapy assessments to determine appropriate mobility aids, adaptive equipment, assistive technology, and environmental access will allow patients to maintain independence and mobility and to conserve energy. Activities of daily living assessment for equipment and adaptation may improve independence and access to home and community environment. Nonspine x-rays and dual energy x-ray absorptiometry are considered in the event of acute musculoskeletal injuries as a result of overuse, an accident, or a fall. Treatment and interventions should consider goals of the family and/or caretakers and should be problem-driven. Physical therapy consultation helps to maximize safety, endurance, and independence or to prolong ambulation. Orthotics also support functional walking. Wheelchair

mobility for longer distance transportation adds mobility and independence. Walkers appear less likely to develop scoliosis; thus, continued walking should be encouraged. Contracture management and education to maximize joint protection should be a part of any treatment program. Maximum functional activity includes access to leisure, adaptive sport, and play activities. Regular exercise to maintain fitness and stamina should be encouraged and may include swimming, aquatic therapy, horseback riding, and adaptive sports. Weight management with attention to fitness and education about nutrition are necessary. Equipment needs related to activities of daily living and assistive technology and other adaptive equipment may be useful to enhance abilities for independent work and play. Environmental controls and home modifications to allow for safe accessibility and optimal independence should be explored. Driver's education alternatives and consideration of customized driving controls should be part of the overall rehabilitation management of the adult with spinal muscular atrophy.

Orthotics

In selecting and fabricating an orthosis for patients with spinal muscular atrophy, it is important that the orthotist, therapist, and family work together to ensure that the appropriate orthosis is fabricated and allows wearers to meet their functional goal. For patients with spinal muscular atrophy, it is particularly important that the orthotist has a good background and experience in working with patients with neuromuscular disorders. Familiarity with patterns of weakness and compensations allows the orthotist to choose proper materials and to make adaptations that allow for "best" fit and function.

Spinal orthoses may be used for postural support, but there is insufficient evidence to support delayed curve progression. When used, spinal orthoses should be fabricated with an abdominal cutout to allow appropriate diaphragmatic excursion and access to gastrostomy tubes where present.

Orthopedic Surgery

Surgical correction of scoliosis should be considered based on the patient's curve progression, pulmonary function, and bony maturity. Scoliosis surgery in children with prolonged survival provides benefits in sitting balance, endurance, and cosmesis.[105,107-111] Evidence suggests that earlier surgery results in better outcome. Beneficial effects on pulmonary function remain controversial, but the rate of pulmonary decline may be slowed.[112] Intraoperatively, excessive bleeding may occur. Postoperatively, complications include loss of correction, pseudarthrosis, a requirement for prolonged ventilatory support, and chest and wound infections. Careful consideration is warranted for the spinal muscular atrophy patient who is still ambulatory because altered function, balance, and respiration may result in loss of independent walking. Pelvic obliquity may require surgical fixation.[113] Intraoperative neurophysiologic monitoring may detect temporary abnormalities during scoliosis surgery.[114]A survey of patient/parent satisfaction and clinical/functional outcome was sent to 21 patients with spinal muscular atrophy who underwent operations for scoliosis. Of those who returned the surveys, all found benefit from scoliosis surgery regarding cosmesis, quality of life, and overall satisfaction.[115] Although there is a higher rate of hip subluxation in spinal muscular atrophy, few are painful. Surgical reduction and osteotomy are frequently followed by redislocation.[116,117] In most circumstances, this surgery is avoidable. Ankle and foot deformities make conventional shoes difficult to wear, and orthopedic surgeons may consider soft tissue releases at the child and family's request. In walkers, if soft tissue releases are performed, rapid and aggressive physical therapy may improve outcome.

Perioperative Management in Spinal Muscular Atrophy

Perioperative management and the role of rehabilitation should be customized according to the specifications and needs of the patient and family, therapist, and surgeon. In general, preoperative management includes appropriate modification of the individual's environment, a plan for orthotic intervention, and confirmation of timing and modification of orthoses. New wheelchairs or wheelchair modifications of the seat, back, arm, leg, or headrests are likely to be required. One may anticipate increased sitting height after scoliosis surgery, resulting in the need for van modifications. Families need instruction in transfers, including arrangements for a mechanical lift, if necessary. Arrangements for bathing, toileting, and dressing equipment and potential modifications to clothes for ease in donning and doffing over, under, and/or around casts or orthoses are necessary. Two small studies found that noninvasive positive pressure ventilation, 1 with mechanical-assisted cough training prior to surgery, resulted in successful extubation.[118,119] Incentive spirometry practice may be initiated and coordinated with preoperative noninvasive pulmonary supports, such as bilevel positive airway pressure and exsufflator (cough-assist) devices.

Postoperatively, one must confirm timing of appropriate casting and fitting of orthoses, allowed range of motion, and activity and that appropriate adaptive equipment is available. Therapists can ensure appropriate use of incentive spirometry and instruction of nursing staff and family on bed mobility, transfers, dressing, bathing, and toileting. The individual should be mobilized as soon as possible, as allowed by the procedure and surgeon.

Conclusion

Infants and children with spinal muscular atrophy should have appropriate evaluation for their presenting musculoskeletal and functional deficits. Goals of therapy and surgery depend on functional level and the family's wishes. Even young children should be offered independent mobility and activities of daily living, which includes play. Whenever possible, walking should be encouraged with appropriate assistive devices and orthotics. Hip subluxation is rarely painful, and there is a high risk of recurrence despite surgical correction. Spinal orthoses may provide postural support but do not prevent curve progression and may impair respiratory effort. Scoliosis surgery appears to benefit patients who survive beyond 2 years of age when curves are severe and progressive and should be performed while pulmonary function is adequate. Preliminary studies show the benefit of preoperative training with noninvasive ventilation and cough-assist devices. Intraoperative neurophysiologic monitoring detects early neurologic compromise in some and may improve outcome.

Recommendations for Future Direction

The optimal evaluation procedure to assess motor function in very weak infants is evolving, with ongoing research efforts under way. Many questions remain regarding best practices in therapeutic interventions. There is a need for the development of creative technology to improve independent function. Further research is suggested to evaluate the effects of spinal bracing and surgery on function, balance, and respiratory function. The role of bone density evaluation and treatment of osteopenia must be further examined.

Palliative Care Issues

In most circumstances in the course of medical practice, the goal of therapy—to further quality and extent of life—is straightforward. In the case of patients with spinal muscular atrophy, however, the appropriate goal of therapy may not be clear. Some therapies may be perceived as placing quality of life in conflict with duration of life, prolonging suffering rather than relieving the burden of disease. Thus, there is little national or international consensus about the appropriate level of care, and local experience, training, habit, and resource availability appear to have a large effect upon recommendations and ultimately family decisions about interventional support.[120-122] Although not surveyed formally, the committee is aware of a similar broad range of practice regarding appropriate pulmonary, nutritional, orthopedic, and other forms of therapy.

Optimal clinical care for these patients should be mindful of potential conflict of therapeutic goals. This conflict is made more difficult by the need for surrogate decision makers for a dependent infant and the fact that many—including parents, siblings, other relatives, caregivers, payers, and the wider community—will be affected by and thus have some valid interest in care decisions. The committee reached consensus that these conflicts are real and that there is no moral imperative to any therapy. There is, however, a deep responsibility to present care options in an open, fair, and balanced manner.

A choice for or against interventional supportive care is not a single binary choice, nor must it be unchanging with circumstance. There are, however, some interventions that are better done early so as not to constrain later potential assistance. For example, placement of a gastrostomy tube is better done relatively early, when associated risks are lower, to provide more stable and comfortable nutritional support later when feeding is more tenuous. Similarly, it is important to discuss and determine the appropriate response to potential life-threatening respiratory insufficiency, as emergency resuscitation and endotracheal intubation during times of crisis without prior respiratory support are associated with many more problems in care than when decisions are made in advance. If appropriate, other forms of noninvasive respiratory device that might reduce the potential for emergent respiratory support should be introduced according to increasing need. Whenever possible, caregivers should ideally permit sufficient time after diagnosis prior to discussing these difficult issues; in all cases, sufficient time, honest appraisal of the choices, openness to revisiting decisions made, and personal rapport are essential to these discussions. If appropriate, other family members or trusted friends or spiritual advisors should be invited. End-of-life care decisions need to be defined and neither delayed nor aggressively foisted upon unsuspecting, grieving, and stunned parents.

Care for patients with spinal muscular atrophy is often best accomplished with a multispecialty team approach, when possible. Successful teams have a point person who is mindful of the many needs and can obtain appropriate medical, social, and spiritual assistance as appropriate. In addition, hospice referral or other provision for the specific issues regarding terminal care, grief, and bereavement support is important. In the circumstance of a choice against mechanical ventilatory support, appropriate provision for management of terminal dyspnea can be of comfort to the patient and family alike. Use of nebulized narcotics can avoid much of the concern that overdosing contributes to death and provide comfort to the patient.

Acknowledgments

We thank Dr Edward Giannini for his critical suggestions on the construction of the Delphi questions and surveys. We also thank all SMA experts who participated in the Delphi survey.

Participants of the International Conference on Spinal Muscular Atrophy Standard of Care: Craig T. Albanese, MD, Stanford, Calif; Annie Aloysius nee Bagnall, London, UK; Nancy Baugh, RD, Stanford, Calif; Enrico Bertini, MD, Rome, Italy; David J. Birnkrant, MD, Cleveland, Ohio; Anne M. Connolly, MD, St Louis, Mo; Thomas O. Crawford, Md, Baltimore, MD; Jonathan D. Finder, MD, Pittsburgh, Pa; Richard S. Finkel, MD, Philadelphia, Pa; Julaine M. Florence, PT, St Louis, Mo; Richard Gee, MPT, Palo Alto, Calif; Allan M. Glanzman, PT, DPT, PCS, ATP, Philadelphia, Pa; Jill Jarecki, PhD, Libertyville, Ill; Cynthia Joyce, New York, NY; Kristin J. Krosschell, PT, MA, PCS, Chicago, Ill; Nancy L. Kuntz, MD, Rochester, Minn; Ian MacLusky, MD, Toronto, Canada; Jo Anne Maczulski, MA, OTR/L, Chicago, Ill; Marion Main, MCSP, MA, London, UK; Leslie A. Morrison, MD, Albuquerque, NM; Fabrizio Racca, MD, Torino, Italy; Kirana Rao, MS, RD, LD, Cincinnati, Ohio; Barry Russman, MD, Portland, Ore; Mary K. Schroth, MD, Madison, Wis; Anita K. Simonds, MD, FRCP, London, UK; Kathryn J. Swoboda, MD, Salt Lake City, Utah; Jiri Vajsar, MD, MSc, FRCPC, Toronto, Canada; Ching H. Wang, MD, PhD, Stanford, Calif; Daniel J. Weiner, MD, Philadelphia, Pa; Gail Wiebke, MS, RD, Salt Lake City, Utah; Brenda Wong, MBBS, MRCP, Cincinnati, Ohio; Nanci Yuan, MD, Stanford, Calif.

Presented at the Neurobiology of Disease in Children: Symposium on Spinal Muscular Atrophy, in conjunction with the 35th annual meeting of the Child Neurology Society, Pittsburgh, Pa, October 18-21, 2006. This project is supported by grants from the Patient Advocacy Groups of the International Coordinating Committee for Spinal Muscular Atrophy clinical trials. The patient advocacy groups include the Muscular Dystrophy Association, USA (www.mdausa.org); the Spinal Muscular Atrophy Foundation (www.smafoundation.org); FightSMA (www.fightsma.org); Families of Spinal Muscular Atrophy (www.fsma.org); and The Jennifer Trust (www.jtsma.org).

References

1. Hirtz D, Iannaccone S, Heemskerk J, et al. Challenges and opportunities in clinical trials for spinal muscular atrophy. *Neurology*. 2005;65:1352-1357.
2. Delbecq A, Van de Ven A, Gustafson D. The Delphi technique. In: Delbecq A, Van de Ven A, Gustafson D, et al, eds. *Group Techniques for Program Planning: A Guide to Nominal Group and Delphi Processes*. Madison, Wis: Scott Foresman; 1975:83-107.
3. Ruperto N, Ravelli A, Murray KJ, et al. Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis. *Rheumatology*. 2003;42:1452-1459.
4. Wallace CA, Ruperto N, Giannini E; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology International Trials Organization; Pediatric Rheumatology Collaborative Study Group. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol*. 2004;31:2290-2294.
5. Lux AL, Osborne JP. A proposal for case definitions and outcome measures in studies of infantile spasms and West syndrome: consensus statement of the West Delphi group. *Epilepsia*. 2004; 45:1416-1428.
6. Munsat TL. The spinal muscular atrophies. *Current Neurology*. St Louis, Mo: Mosby; 1994:55-71.
7. Munsat TL, Davies KE. International SMA consortium meeting (26-28 June 1992, Bonn, Germany). *Neuromuscul Disord*. 1992;2:423-428.
8. Dubowitz V. Disorders of the lower motor neurone: the spinal muscular atrophies. In: Dubowitz V, ed. *Muscle Disorders in Childhood*. London: W B Saunders; 1995:325-367.
9. Zerres K, Rudnik-Schoneborn S, Forrest E, et al. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. *J Neurol Sci*. 1997;146:67-72.
10. Dubowitz V. Very severe spinal muscular atrophy (SMA type 0): an expanding clinical phenotype. *Eur J Paediatr Neurol*. 1999; 3:49-51.
11. Bertini E, Burghes A, Bushby K, et al. 134th ENMC International Workshop: Outcome Measures and Treatment of Spinal Muscular Atrophy, 11-13 February 2005, Naarden, the Netherlands. *Neuromuscul Disord*. 2005;15:802-816.
12. Zerres K, Rudnik-Schoneborn S. 93rd ENMC international workshop: Non-5q-spinal Muscular Atrophies (SMA)—Clinical Picture (6-8 April 2001, Naarden, the Netherlands). *Neuromuscul Disord*. 2003;13:179-183.
13. Isozumi K, DeLong R, Kaplan J, et al. Linkage of scapuloperoneal spinal muscular atrophy to chromosome 12q24.1-q24.31. *Hum Mol Genet*. 1996;5:1377-1382.
14. DeLong R, Siddique T. A large New England kindred with autosomal dominant neurogenic scapuloperoneal amyotrophy with unique features. *Arch Neurol*. 1992;49:905-908.
15. Barth PG. Pontocerebellar hypoplasias. An overview of a group of inherited neurodegenerative disorders with fetal onset. *Brain Dev*. 1993;15:411-422.
16. Chou SM. Controversy over Werdnig-Hoffmann disease and multiple system atrophy. *Curr Opin Neurol*. 1993;6:861-864.
17. Chou SM, Gilbert EF, Chun RW, et al. Infantile olivopontocerebellar atrophy with spinal muscular atrophy (infantile OPCA + SMA). *Clin Neuropathol*. 1990;9:21-32.
18. Gorgen-Pauly U, Sperner J, Reiss I, et al. Familial pontocerebellar hypoplasia type I with anterior horn cell disease. *Eur J Paediatr Neurol*. 1999;3:33-38.
19. Ryan MM, Cooke-Yarborough CM, Procopis PG, Ouvrier RA. Anterior horn cell disease and olivopontocerebellar hypoplasia. *Pediatr Neurol*. 2000;23:180-184.
20. Greenberg F, Fenolio KR, Hejtmancik JF, et al. X-linked infantile spinal muscular atrophy. *Am J Dis Child*. 1988;142: 217-219.
21. Kobayashi H, Baumbach L, Matise TC, et al. A gene for a severe lethal form of X-linked arthrogryposis (X-linked infantile spinal muscular atrophy) maps to human chromosome Xp11.3-q11.2. *Hum Mol Genet*. 1995;4:1213-1216.
22. Grohmann K, Varon R, Stolz P, et al. Infantile spinal muscular atrophy with respiratory distress type 1 (SMARD1). *Ann Neurol*. 2003;54:719-724.
23. Grohmann K, Schuelke M, Diers A, et al. Mutations in the gene encoding immunoglobulin mu-binding protein 2 cause spinal muscular atrophy with respiratory distress type 1. *Nat Genet*. 2001;29:75-77.

24. Rodrigues NR, Owen N, Talbot K, et al. Deletions in the survival motor neuron gene on 5q13 in autosomal recessive spinal muscular atrophy. *Hum Mol Genet*. 1995;4:631-634.
25. Lefebvre S, Burglen L, Frezal J, et al. The role of the SMN gene in proximal spinal muscular atrophy. *Hum Mol Genet*. 1998;7: 1531-1536.
26. Swoboda KJ, Prior TW, Scott CB, et al. Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. *Ann Neurol*. 2005;57:704-712.
27. Zerres K, Wirth B, Rudnik-Schoneborn S. Spinal muscular atrophy—clinical and genetic correlations. *Neuromuscul Disord*. 1997;7:202-207.
28. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors. *Am J Hum Genet*. 1995;57: 1233-1241.
29. Mellies U, Dohna-Schwake C, Stehling F, Voit T. Sleep disordered breathing in spinal muscular atrophy. *Neuromuscul Disord*. 2004; 14:797-803.
30. Mellies U, Ragette R, Dohna Schwake C, et al. Long-term noninvasive ventilation in children and adolescents with neuromuscular disorders. *Eur Respir J*. 2003;22:631-636.
31. Ragette R, Mellies U, Schwake C, et al. Patterns and predictors of sleep disordered breathing in primary myopathies. *Thorax*. 2002;57:724-728.
32. Lyager S, Steffensen B, Juhl B. Indicators of need for mechanical ventilation in Duchenne muscular dystrophy and spinal muscular atrophy. *Chest*. 1995;108:779-785.
33. Ioos C, Leclair-Richard D, Mrad S, et al. Respiratory capacity course in patients with infantile spinal muscular atrophy. *Chest*. 2004;126:831-837.
34. Barois A, Estournet-Mathiaud B. Ventilatory support at home in children with spinal muscular atrophies (SMA). *Eur Respir Rev*. 1992;10:319-322.
35. Barois A, Estournet-Mathiaud B. Nasal ventilation in congenital myopathies and spinal muscular atrophies. *Eur Respir Rev*. 1993;3:275-278.
36. Simonds AK, Ward S, Heather S, et al. Outcome of paediatric domiciliary mask ventilation in neuromuscular and skeletal disease. *Eur Respir J*. 2000;16:476-481.
37. Mellins RB, Hays AP, Gold AP, et al. Respiratory distress as the initial manifestation of Werdnig-Hoffmann disease. *Pediatrics*. 1974;53:33-40.
38. Manzur AY, Muntoni F, Simonds A. Muscular dystrophy campaign sponsored workshop: recommendation for respiratory care of children with spinal muscular atrophy type II and III. 13th February 2002, London, UK. *Neuromuscul Disord*. 2003; 13:184-189.
39. Wallgren-Pettersson C, Bushby K, Mellies U, Simonds A. 117th ENMC workshop: ventilatory support in congenital neuromuscular disorders—congenital myopathies, congenital muscular dystrophies, congenital myotonic dystrophy and SMA (II) 4-6 April 2003, Naarden, the Netherlands. *Neuromuscul Disord*. 2004;14:56-69.
40. Standards and indications for cardiopulmonary sleep studies in children. *Am J Respir Crit Care Med*. 1996;153:866-878.
41. Marcus CL. Sleep-disordered breathing in children. *Am J Respir Crit Care Med*. 2001;164:16-30.
42. Bush A, Fraser J, Jardine E, et al. Respiratory management of the infant with type 1 spinal muscular atrophy. *Arch Dis Child*. 2005;90:709-711.
43. Bach JR. Mechanical insufflation-exsufflation. Comparison of peak expiratory flows with manually assisted and unassisted coughing techniques. *Chest*. 1993;104:1553-1562.
44. Bach JR, Niranjan V, Weaver B. Spinal muscular atrophy type 1: a noninvasive respiratory management approach. *Chest*. 2000; 117:1100-1105.
45. Bach JR, Baird JS, Plosky D, et al. Spinal muscular atrophy type 1: management and outcomes. *Pediatr Pulmonol*. 2002; 34:16-22.
46. Chatwin M, Ross E, Hart N, et al. Cough augmentation with mechanical insufflation/exsufflation in patients with neuromuscular weakness. *Eur Respir J*. 2003;21:502-508.
47. Finder JD, Birnkrant D, Carl J, et al. Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. *Am J Respir Crit Care Med*. 2004;170:456-465.
48. Ward S, Chatwin M, Heather S, Simonds AK. Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. *Thorax*. 2005;60:1019-1024.
49. Bach JR, Bianchi C. Prevention of pectus excavatum for children with spinal muscular atrophy type 1. *Am J Phys Med Rehabil*. 2003;82:815-819.
50. Simonds AK. Ethical aspects of home long term ventilation in children with neuromuscular disease. *Paediatr Respir Rev*. 2005;6:209-214.
51. Willig TN, Paulus J, Lacau-Saint-Guily J, et al. Swallowing problems in neuromuscular disorders. *Arch Phys Med Rehab*. 1994;75:1175-1181.
52. Nutman J, Nitzan M, Grunebaum M. Swallowing disturbances in Werdning-Hoffmann disease. *Harefuah*. 1981;101:301-303, 336.
53. Tilton AH MM, Khoshoo V. Nutrition and swallowing in pediatric neuromuscular patients. *Semin Pediatr Neurol*. 1998;5:106-115.
54. Granger MW, Buschang PH, Throckmorton GS, Iannaccone ST. Masticatory muscle function in patients with spinal muscular atrophy. *Am J Orthod Dentofacial Orthop*. 1999;115:697-702.
55. Houston KD, Buschang PH, Iannaccone ST, Seale NS. Craniofacial morphology of spinal muscular atrophy. *Pediatr Res*. 1994;36:265-269.
56. Grunebaum M, Nutman J, Nitzan M. The pharyngo-laryngeal deficit in the acute form of infantile spinal muscular atrophy (Werdnig-Hoffmann disease). *Pediatr Radiol*. 1981;11:67-70.
57. Roulet E, Deonna T. Vocal cord paralysis as a presenting sign of acute spinal muscular atrophy, SMA type I. *Arch Dis Child*. 1992;67(3):352.
58. Lapena JF Jr, Berkowitz RG. Neuromuscular disorders presenting as congenital bilateral vocal cord paralysis. *Ann Otol Rhinol Laryngol*. 2001;110:952-955.
59. Hill M, Hughes T, Milford C. Treatment for swallowing difficulties (dysphagia) in chronic muscle disease. *Cochrane Database Syst Rev*. 2004;2:CD004303.
60. Birnkrant DJ, Pope JF, Martin JE, et al. Treatment of type I spinal muscular atrophy with noninvasive ventilation and gastrostomy feeding. *Pediatr Neurol*. 1998;18:407-410.
61. Diaz DM, Gibbons TE, Heiss K, et al. Antireflux surgery outcomes in pediatric gastroesophageal reflux disease. *Am J Gastroenterol*. 2005;100(8):1844-1852.
62. Yuan N, Wang CH, Trela A, Albanese CT. Combined laparoscopic Nissen fundoplication during gastrostomy tube placement and noninvasive ventilation improve survival in children with type 1 and severe type II SMA. *J Child Neurol*. In press.

63. Canani RB, Cirillo P, Roggero P, et al. Working Group on Intestinal Infextions of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics*. 2006; 117:e817-e820.
64. Laheij RJ, Sturkenboom MC, Hassing RJ, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA*. 2004;292:1955-1960.
65. Ruben JA, Jones TD, Geist NR. Respiratory and reproductive paleophysiology of dinosaurs and early birds. *Physiol Biochem Zool*. 2003;76:141-164.
66. Liusuwan AWL, Abresch RT, McDonald CM. Altered body composition affects resting energy expenditure and interpretation of body mass index in children with spinal cord injury. *J Spinal Cord Med*. 2004;27(Suppl 11):S24-S28.
67. Lee RD, Nieman DC. Nutritional assessment. Madison, Wis: Brown & Benchmark; 1993:172-173, Appendix O.
68. Jones M, Campbell KA, Duggan C, et al. Multiple micronutrient deficiencies in a child fed an elemental formula. *J Pediatr Gastroenterol Nutr*. 2001;33:602-605.
69. Kinali M, Banks LK, Mercuri E, et al. Bone mineral density in a paediatric spinal muscular atrophy population. *Neuropediatrics*. 2004;35(6):325-328.
70. Chan GM. Performance of dual-energy x-ray absorptiometry in evaluating bone, lean body mass, and fat in pediatric subjects. *J Bone Miner Res*. 1992;7:369-374.
71. Crabtree NJ, Kibirige MS, Fordham JN, et al. The relationship between lean body mass and bone mineral content in pediatric health and disease. *Bone*. 2004;35:965-972.
72. Margulies L, Horlick M, Thornton JC, et al. Reproducibility of whole body bone and body composition measures by dual-energy X-ray absorptiometry using GE Lunar Prodigy. *J Clin Densitometry*. 2005;8:298-304.
73. Swoboda KJ, McNaught TP, Gill G, et al. Total body lean mass and bone mineral content in spinal muscular atrophy [abstract]. Presented at: the American Society for Pediatric Research; May, 2005; Warrington, Pa.
74. Bruce AK, Jacobsen E, Dossing H, Kondrup J. Hypoglycaemia in spinal muscular atrophy. *Lancet*. 1995;346(8975):609-610.
75. Orngreen MC, Sacho M, Hebert A, et al. Patients with severe muscle wasting are prone to develop hypoglycemia during fasting. *Neurology*. 2003;61:997-1000.
76. Berger A, Mayr JA, Meierhofer D, et al. Severe depletion of mitochondrial DNA in spinal muscular atrophy. *Acta Neuropathol*. 2003;105(3):245-251.
77. Bresolin N, Freddo L, Tegazzin V, et al. Carnitine and acyltransferase in experimental neurogenic atrophies: changes with treatment. *J Neurol*. 1984;231:170-175.
78. Crawford TO, Sladky JT, Hurko O, et al. Abnormal fatty acid metabolism in childhood spinal muscular atrophy. *Ann Neurol*. 1999:337-343.
79. Gobernado JM, Gosalvez M, Cortina C, et al. Mitochondrial functions in chronic spinal muscular atrophy. *J Neurol Neurosurg Psychiatry*. 1980;June:546-549.
80. Ohtake E. Secondarily reduced cytochrome c oxidase activity in various neuromuscular disorders. *Brain Dev*. 1990;12:326-333.
81. Sperl W, Skladal D, Gnaiger E, et al. High resolution respirometry of permeabilized skeletal muscle fibers in the diagnosis of neuromuscular disorders. *Mol Cell Biochem*. 1997:71-78.
82. Tein I, Sloane AE, Donner EJ. Fatty acid oxidation abnormalities in childhood-onset spinal muscular atrophy: primary or secondary defect(s)? *Pediatr Neurol*. 1995;12:21-30.
83. Tews DS, Goebel HH. DNA fragmentation and BCL-2 expression in infantile spinal muscular atrophy. *Neuromuscul Disord*. 1996;6(4):265-273.
84. Russman BS, Buncher CR, White M, et al. Function changes in spinal muscular atrophy II and III. The DCN/SMA Group. *Neurology*. 1996;47:973-976.
85. Eng GD, Binder H, Koch B. Spinal muscular atrophy: experience in diagnosis and rehabilitation management of 60 patients. *Arch Phys Med Rehabil*. 1984;65:549-553.
86. Barois A, Mayer M, Desguerre I, et al. Spinal muscular atrophy. A 4-year prospective, multicenter, longitudinal study (168 cases). *Bull Acad Natl Med*. 2005;189:1181-1198, discussion 1198-1199.
87. Sporer SM, Smith BG. Hip dislocation in patients with spinal muscular atrophy. *J Pediatr Orthop*. 2003;23:10-14.
88. Granata C, Magni E, Merlini L, Cervellati S. Hip dislocation in spinal muscular atrophy. *Chir Organi Mov*. 1990;75: 177-184.
89. de Groot IJ, de Witte LP. Physical complaints in ageing persons with spinal muscular atrophy. *J Rehabil Med*. 2005;37:258-262.
90. Rodillo E, Marini ML, Heckmatt JZ, Dubowitz V. Scoliosis in spinal muscular atrophy: review of 63 cases. *J Child Neurol*. 1989;4:118-123.
91. Finkel RS, Glanzman AM, Main M, Bertini E, Mercuri E. The CHOP INTEND: a reliable motor scale for infants with neuromuscular disease. *Neuromuscul Disord*. 2006;16:9-10. Abstract N.P.403.
92. Main M, Kairon H, Mercuri E, Muntoni F. The Hammersmith functional motor scale for children with spinal muscular atrophy: a scale to test ability and monitor progress in children with limited ambulation. *Eur J Paediatr Neurol*. 2003;7:155-159.
93. Mercuri E, Messina S, Battini R, et al. Reliability of the Hammersmith functional motor scale for spinal muscular atrophy in a multicentric study. *Neuromuscul Disord*. 2006;16:93-98.
94. Krosschell KJ, Maczulski JA, Crawford TO, et al. A modified Hammersmith functional motor scale for use in multi-center research on spinal muscular atrophy. *Neuromuscul Disord*. 2006;16:417-426. Epub 2006 Jun 5.
95. Nelson L, Owens H, Hynan LS, et al. The gross motor function measuretrade mark is a valid and sensitive outcome measure for spinal muscular atrophy. *Neuromuscul Disord*. 2006;16:374-380.
96. Chung BH, Wong VC, Ip P. Spinal muscular atrophy: survival pattern and functional status. *Pediatrics*. 2004;114:e548-e553.
97. Bono R, Inverno M, Botteon G, et al. Prospective study of gross motor development in children with SMA type II. *Ital J Neurol Sci*. 1995;16:223-230.
98. Kroksmark AK, Beckung E, Tulinius M. Muscle strength and motor function in children and adolescents with spinal muscular atrophy II and III. *Eur J Paediatr Neurol*. 2001;5:191-198.
99. Merlini L, Mazzone ES, Solari A, Morandi L. Reliability of hand-held dynamometry in spinal muscular atrophy. *Muscle Nerve*. 2002;26:64-70.
100. Iannaccone ST. Outcome measures for pediatric spinal muscular atrophy. *Arch Neurol*. 2002;59:1445-1450.
101. Iannaccone ST, Hynan LS. Reliability of 4 outcome measures in pediatric spinal muscular atrophy. *Arch Neurol*. 2003;60: 1130-1136.

102. Iannaccone ST, Smith SA, Simard LR. Spinal muscular atrophy. *Curr Neurol Neurosci Rep*. 2004;4:74-80.
103. Abresch RT, Carter GT, Jensen MP, Kilmer DD. Assessment of pain and health-related quality of life in slowly progressive neuromuscular disease. *Am J Hosp Palliat Care*. 2002;19:39-48.
104. Kouwenhoven JW, Van Ommeren PM, Pruijs HE, Castelein RM. Spinal decompensation in neuromuscular disease. *Spine*. 2006; 31:E188-E191.
105. Evans GA, Drennan JC, Russman BS. Functional classification and orthopaedic management of spinal muscular atrophy. *J Bone Joint Surg Br*. 1981;63B:516-522.
106. Tangsrud SE, Carlsen KC, Lund-Petersen I, Carlsen KH. Lung function measurements in young children with spinal muscle atrophy; a cross sectional survey on the effect of position and bracing. *Arch Dis Child*. 2001;84:521-524.
107. Phillips DP, Roye DP Jr, Farcy JP, et al. Surgical treatment of scoliosis in a spinal muscular atrophy population. *Spine*. 1990;15:942-945.
108. Bentley G, Haddad F, Bull TM, Seingry D. The treatment of scoliosis in muscular dystrophy using modified Luque and Harrington-Luque instrumentation. *J Bone Joint Surg Br*. 2001;83:22-28.
109. Granata C, Cervellati S, Ballestrazzi A, et al. Spine surgery in spinal muscular atrophy: long-term results. *Neuromuscul Disord*. 1993;3:207-215.
110. Merlini L, Granata C, Bonfiglioli S, et al. Scoliosis in spinal muscular atrophy: natural history and management. *Dev Med Child Neurol*. 1989;31:501-508.
111. Thacker M, Hui JH, Wong HK, et al. Spinal fusion and instrumentation for paediatric neuromuscular scoliosis: retrospective review. *J Orthop Surg (Hong Kong)*. 2002;10: 144-151.
112. Chng S, Wong Y, Hui J, et al. Pulmonary function and scoliosis in children with spinal muscular atrophy types II and III. *J Paediatr Child Health*. 2003;39:673-676.
113. Miladi LT, Ghanem IB, Draoui MM, et al. Iliosacral screw fixation for pelvic obliquity in neuromuscular scoliosis. A long-term follow-up study. *Spine*. 1997;22:1722-1729.
114. Noordeen MH, Lee J, Gibbons CE, Taylor BA, Bentley G. Spinal cord monitoring in operations for neuromuscular scoliosis. *J Bone Joint Surg Br*. 1997;79:53-57.
115. Bridwell KH, Baldus C, Iffrig TM, et al. Process measures and patient/parent evaluation of surgical management of spinal deformities in patients with progressive flaccid neuromuscular scoliosis (Duchenne's muscular dystrophy and spinal muscular atrophy). *Spine*. 1999;24:1300-1309.
116. Thompson CE, Larsen LJ. Recurrent hip dislocation in intermediate spinal atrophy. *J Pediatr Orthop*. 1990;10:638-641.
117. Zenios M, Sampath J, Cole C, et al. Operative treatment for hip subluxation in spinal muscular atrophy. *J Bone Joint Surg Br*. 2005;87:1541-1544.
118. Bach JR, Sabharwal S. High pulmonary risk scoliosis surgery: role of noninvasive ventilation and related techniques. *J Spinal Disord Tech*. 2005;18:527-530.
119. Vasconcelos M, Fineza I, Felix M, Estevao MH. Spinal muscular atrophy—noninvasive ventilatory support in pediatrics. *Rev Port Pneumol*. 2005;11:443-455.
120. Bach JR. Threats to "informed" advance directives for the severely physically challenged? *Arch Phys Med Rehabil*. 2003;84:S23-S28.
121. Hardart MK, Burns JP, Truog RD. Respiratory support in spinal muscular atrophy type I: a survey of physician practices and attitudes. *Pediatrics*. 2002;110:e24.
122. Sakakihara Y. Ethical attitudes of Japanese physicians regarding life-sustaining treatment for children with severe neurological disabilities. *Brain Dev*. 2000;22:113-117.