PRACTICE PARAMETER: THE CARE OF THE PATIENT WITH AMYOTROPHIC LATERAL SCLEROSIS (AN EVIDENCE-BASED REVIEW)

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MISSION STATEMENT

The Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN) is charged with developing practice parameters for physicians. This evidence-based review addresses some of the major management issues in patients with ALS, and highlights the many areas in which more research is needed.

JUSTIFICATION

ALS is a progressive, degenerative motor neuron disease of unknown cause. Muscle atrophy and spasticity in limb and bulbar muscles result in weakness and loss of ambulation, oropharyngeal dysfunction, weight loss, and ultimately respiratory failure. Although advances in understanding the pathophysiology of ALS have stimulated the development of new drug therapies,[1] the mainstay of treatment for ALS patients remains symptomatic management.

The practice parameters presented here comprise the first recommendations for the management of ALS based on a prescribed review and analysis of the peer-reviewed literature. These practice parameters were developed to improve the care and the quality of life of people with ALS by providing a rational basis for managing the disease.

DESCRIPTION OF THE PROCESS

A multidisciplinary task force, all with extensive ALS experience, included 19 physicians, 3 patients with ALS, 1 gastroenterologist, 1 pulmonologist, 1 occupational therapist whose mother has ALS, and 1 nurse. In addition, consultants with expertise on eth-

ics, practice parameter development, and medical library research participated in the process. The task force agreed to investigate five areas: 1) informing the patient and the family about the diagnosis and prognosis (also called "breaking the news") of ALS; 2) symptomatic treatment; 3) nutrition, and decisions about precutaneous endoscopic gastroscopy (PEG); 4) respiratory insufficiency and mechanical ventilation; and 5) advance directives and palliative care. To help achieve this goal, they developed several guiding principles or attributes of care:

Principles of ALS Management

1. High priority should be placed on patient self-determination or autonomy as an underlying assumption in the therapeutic relationship. Delivery of both information and care must take into consideration the cultural and psychosocial context of the patient and the family.

2. Patients and families need information that is timed appropriately for decision making, and delivered well in advance of major management crossroads, especially for respiratory care. Moreover, decision making is a dynamic process that may be subject to change as the disease becomes more severe.

3. The physician, in conjunction with other health care professionals, should address the full continuum of care for the patient with ALS, and nurture the therapeutic relationship from diagnosis through palliative care for the terminal phase of the disease.

4. Discussions regarding advance directives should be introduced by the physician and re-evaluated at intervals of no more than 6 months. Similarly, helping patients understand the issues to be faced in the terminal phase of the disease must be accomplished in a timely and empathic fashion.

Within each of the areas of study, the task force developed a list of clinical questions faced by physicians caring for the ALS patient (table 1).

We searched OVID MEDLINE (1966 to date), OVID Excerpta Medica (EMBASE; 1974 to date), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to date), OVID Current Contents (weeks 27 to 46, 1997), OVID BIOETHICSLINE (1973 to date), and OVID International Pharmaceutical Abstracts (IPAB; 1970 to date). The search included studies on humans only and all languages. In the first search, ALS, Lou Gehrig's disease, and motor neuron disease were searched for relevant subtopics. The second search on respiratory issues included neuromuscular diseases such as Duchenne muscular dystrophy, postpoliomyelitis, and spinal muscular atrophy. A third search regarding relating the diagnosis, palliative care, and advance directives included all neurologic diseases as well as AIDS and cancer.

The search yielded approximately 5,350 references with abstracts. After reviewing these abstracts, 750 articles containing the highest level of evidence were obtained (symptomatic management subcommittee reviewed 150 papers; palliative care, 190; nutrition, 230; and respiratory, 180). The strength of evidence in each paper was ranked using the definitions in table 2. Based on the strength of evidence, management recommendations were developed as guidelines or options using the definitions shown in table 3. Evidence tables containing the extracted data are placed in a registry (National Auxiliary Publications Service [NAPS]: see Note at end of article) and are available on request. Position statements or guidelines from national societies on issues such as communicating the diagnosis, advance directives, and respecting patient autonomy were included as broad expert opinion, which in some cases was elevated to guideline status. However, evidence of therapeutic intervention from diseases other than ALS was downgraded to class III. Invasive therapy for symptom management (e.g., surgery or irradiation for sialorrhea) was not recommended unless there was evidence from ALS.

BREAKING THE NEWS

The diagnosis should be established according to well-accepted criteria.[2] Telling the patient and the family that the diagnosis is ALS is a daunting task for the physician. If not performed appropriately, the

Table 1. Clinical questions addressed in ALS treatment recommendations.

Subcommittee	Clinical question
Breaking the news	How should a physician tell patients that they have ALS?
Symptom management	What pharmacologic interventions reduce sialorrhea?
	What nonpharmacologic treatment options reduce sialorrhea?
	What pharmacologic measures reduce pseudobulbar affect?
Nutrition management	When is PEG indicated in ALS?
	What is the best way to detect dysphagia in ALS?
	What is the risk of PEG placement in patients with ALS?
	What is the effect of PEG in preventing aspiration and aspiration pneumonia?
	What is the efficacy of PEG in prolonging survival?
Respiratory management	What are the early indications of respiratory insufficiency?
	Does noninvasive ventilation improve respiratory function or increase survival?
	Does experience with noninvasive ventilation aid decision making regarding invasive ventilation?
	How do invasive and noninvasive ventilation impact quality of life?
	What is the optimal method of withdrawing both noninvasive and invasive ventilation from patients with ALS?
Palliative care	Is pain common in the terminal phase of ALS?
	Can terminal dyspnea be relieved by therapeutic intervention?
	Does hospice care improve quality of life in the terminal phase?
	Do advance directives improve quality of life in the terminal phase of ALS?

PEG = percutaneous endoscopic gastroscopy.

Table 2. Definitions of classification of evidence.

Class	Definition
I	Evidence provided by one or more well-designed, randomized, controlled clinical trials
II	Evidence provided by one or more well-designed, observational clinical studies with concurrent controls (e.g., case control and cohort studies)
III	Evidence provided by expert opinion, case series, case reports, and studies with historical controls

Table 3. Classification of management recommendations.

Classification	Definition
Standard	A principle for patient management that reflects a high degree of certainty based on class I evidence, or very strong evidence from class II studies when circumstances preclude randomized trials
Guideline	Recommendations for patient management reflecting moderate clinical certainty (usually class II evidence or strong consensus of class III evidence)
Option	A strategy for patient management for which the evidence (class III) is inconclusive or when there is some conflicting evidence or opinion

Table 4. How should a physician tell patients that they have ALS (adapted from Ptacek and Eberhardt[11])?

Task	Recommendations
Location	Quiet, comfortable, and private
Structure	In person, face-to-face[7–10]
	Convenient time
	Enough time to ensure no rushing or interruptions
	Make eye contact and sit close to patient
Participants	Have patient's support network present
What is said	Find out what the patient already knows about the condition[12]
	Ascertain how much the patient wants to know about ALS
	Give a warning comment that bad news is coming
	There is no cure, symptoms tend to steadily worsen, and prognosis is highly variable
	Acknowledge and explore the patient's reaction and allow for emotional expression
	Summarize the discussion verbally, in writing, and/or on audiotape[3,4]
	Allow for questions
Reassurance	Explain that the complications of ALS are treatable
	Reassurance that every attempt will be made to maintain the patient's function and that the patient's treatment decisions will be respected
	Reassurance that the patient will continue to be cared for and will not be abandoned[7,8]
	Discuss opportunities to participate in research treatment protocols
	Acknowledge willingness to get a second opinion if the patient wishes
How it is said	Emotional manner: warmth, caring, empathy, respect
	Give news at person's pace; allow the patient to dictate what he or she is told
Language	Simple and careful word choice, yet direct; no euphemisms or medical jargon

effect can be devastating, leaving the patient with a sense of abandonment and destroying the patient-physician relationship.[3] Studies of other fatal illnesses[4–12] clearly demonstrated the advantages of utilizing specific techniques (table 4).

Recommendations. The following recommendations for communicating the diagnosis are based on the literature review and broad expert consensus (position statements, etc.):

1. The physician should give the diagnosis to the patient and discuss its implications. Respect the cultural and social background of the patient in the communication process by asking whether the patient wishes to receive information or prefers that the information be communicated to a family member. (Guideline)
2. The diagnosis should always be given in person and never by telephone. (Guideline)
3. Provide printed materials about the disease and about support and advocacy organizations (Guideline), and a letter or audiotape summarizing what the physician has discussed. (Option)
4. Avoid the following: withholding the diagnosis, providing insufficient information, delivering information callously, or taking away or not providing hope. (Guideline)

Research Recommendations. Surveys or controlled studies are needed in ALS to 1) assess patient and caregiver perceptions of each step in breaking the news to help improve the process, 2) determine whether current recommendations about breaking the news have an effect on outcomes (with focus on adequacy of patient coping strategies), 3) study the impact of culture and social environment on disclo-

sure methods, and 4) include disclosure techniques in medical curricula and to evaluate their implementation.

SYMPTOM MANAGEMENT (SIALORRHEA AND PSEUDOBULBAR AFFECT)

The goal of symptom management is to improve the quality of life of the patient, family, and healthcare provider. Prominent symptoms include sialorrhea, pseudobulbar affect, speech impairment, sleep disorders and fatigue, depression, difficulties with activities of daily living, and ambulation. This section focuses on two particularly bothersome but treatable problems—sialorrhea and pseudobulbar affect—

whereas other symptoms will be addressed in future documents.

Sialorrhea. Sialorrhea is important to the patient because it causes significant social stress. The physician must distinguish between sialorrhea and thick mucus production because treatment of these symptoms differs. Saliva production is actually decreased in patients with ALS.[13,14] Thus, poor handling of saliva appears to be the major cause of sialorrhea in ALS and in other disorders such as cerebral palsy, mental retardation, developmental disability, Down syndrome, and oropharyngeal carcinoma. In these patients sialorrhea has been managed by attempting to decrease saliva production, improve handling of secretions, or divert and remove saliva. Because there is scant evidence in ALS, treatment of sialorrhea in other neurologic conditions was included in the analysis.

What Pharmacologic Interventions Reduce Sialorrhea? Two reports supported the use of glycopyrrolate (Robinul) for control of sialorrhea in patients with cerebral palsy or developmental disabilities.[15,16] Amitriptyline (Elavil) has been used widely in ALS but not studied in controlled trials. Decreased drooling in patients with cerebral palsy was also reported with benztropine (Cogentin),[17] trihexyphenidyl hydrochloride (Artane),[18] and transdermal hyoscine (Scopolamine).[19,20] Transdermal hyoscine decreased drooling in developmentally delayed children, patients with mental retardation, and patients with oropharyngeal carcinoma.[19,21] Atropine reduced sialorrhea in a crossover study of a patient with closed head injury.[22] For thick mucus production associated with sialorrhea, the addition of a beta blocker, such as propranolol (Inderal) or metoprolol (Toprol), appeared to confer clinical benefit for patients with ALS in an uncontrolled trial.[23]

What Nonpharmacologic Treatments Reduce Sialorrhea? Suction machines are widely used for symptom control, although we found no evidence supporting their value in ALS. Both manually assisted coughing techniques and mechanical insufflation—exsufflation (In-Exsufflator cough machine) were effective in extracting excess mucus from the airway.[24] This device works by providing deep insufflation followed by an immediate decrease in pressure that creates a forced exsufflation. The In-Exsufflator was clinically effective in acutely ill ventilator-dependent, postpolio patients.[25]

Two additional approaches may be considered when medical treatments fail. External beam irradiation (3 to 30 Gy, 3 to 10 fractions) to a single parotid gland may be effective in reducing sialorrhea,[26] but it has not been evaluated in ALS. Surgical intervention has been tried in patients with ALS.[14,27] However, no consistent evidence demonstrated efficacy, and there were reports of increased adverse events including death.[27]

Pseudobulbar Affect. Pseudobulbar affect, or pathologic crying or laughing, is a troubling symptom for patients with ALS. The emotional lability is not a mood disorder,[28] but an abnormal affective display[29] that occurs in as many as 50% of patients.[30,31] The physician must be alert for pseudobulbar affect because patients and families often do not volunteer symptoms.

What Pharmacologic Measures Reduce Pseudobulbar Affect? A randomized controlled trial in patients with MS supported the use of amitriptyline for pseudobulbar affect.[32] A single study in a mixed population of patients including ALS reported satisfactory results with fluvoxamine (Luvox).[33]

Recommendations.

For Sialorrhea:

1. Treat sialorrhea with glycopyrrolate (figure 1), benztropine, transdermal hyoscine, atropine, trihexyphenidyl hydrochloride, or amitriptyline. (Option)
2. Treat thick mucus production associated with sialorrhea with propranolol or metoprolol. (Option)
3. Consider manually assisted coughing and mechanical insufflation—exsufflation for clearing secretions, especially during acute infection. (Option)

For Pseudobulbar Affect (Emotional Lability):

1. Treat pseudobulbar affect with amitriptyline. (Option)
2. Consider fluvoxamine as an alternate choice. (Option)

Research Recommendations.

1. Conduct randomized controlled trials to study anticholinergic medications for sialorrhea in ALS.
2. Develop more efficient mechanical devices for handling saliva and thick mucus.
3. Examine the safety and efficacy of parotid irradiation and surgical procedures for sialorrhea in ALS.
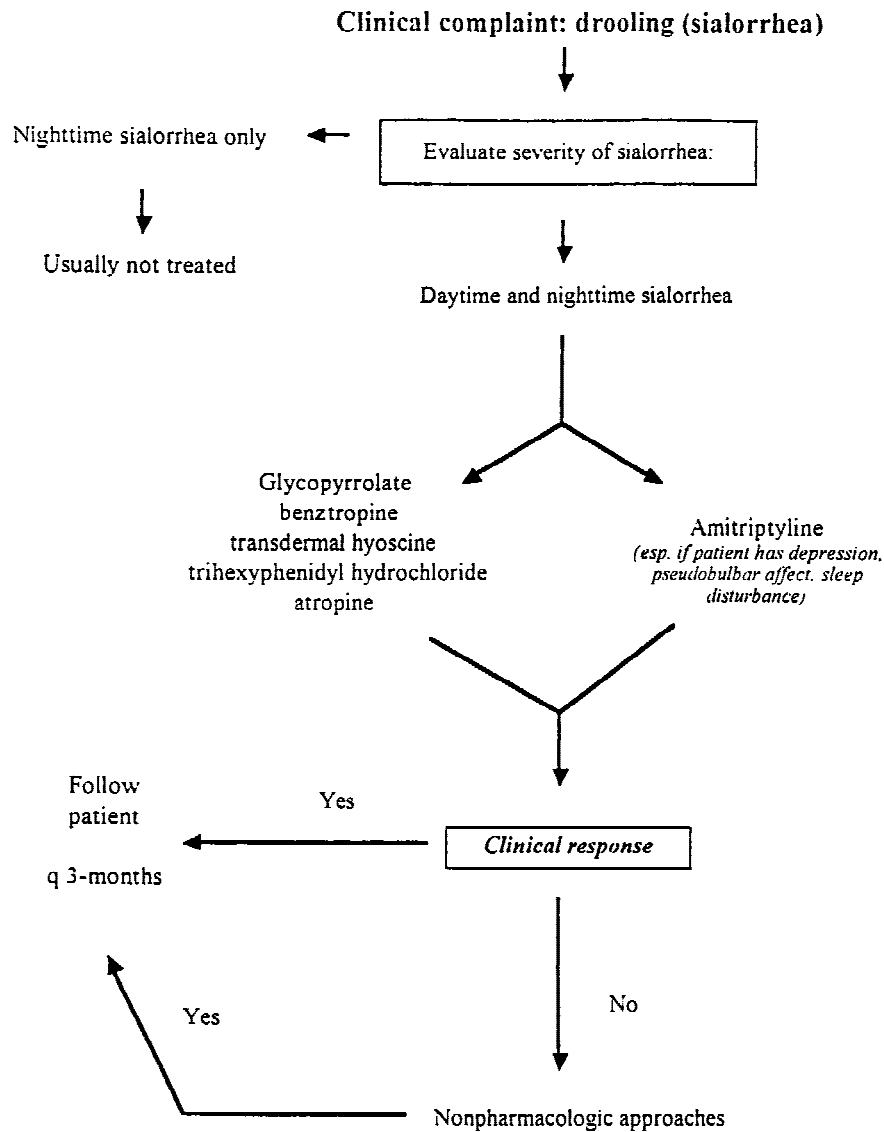
Clinical complaint: drooling (sialorrhea)

Evaluate severity of sialorrhea:

Nighttime sialorrhea only

Usually not treated

Daytime and nighttime sialorrhea

Glycopyrrolate
benztropine
transdermal hyoscine
trihexyphenidyl hydrochloride
atropine

Amitriptyline
*(esp. if patient has depression,
pseudobulbar affect, sleep
disturbance)*

Follow
patient

q 3-months

Yes

Clinical response

Yes

No

Nonpharmacologic approaches

FIGURE 1. Algorithm for sialorrhea management.

4. Study selective serotonin reuptake inhibitors for pseudobulbar affect in ALS.

NUTRITION

Patients with dysphagia are at risk for suboptimal caloric and fluid intake,[34,35] and a worsening of muscle atrophy, weakness, and fatigue. Common symptoms include jaw weakness and fatigue, drooling, choking on fluid and food, and slow eating. Barium swallow may assist in developing strategies to maintain oral intake. The presence of laryngeal penetration on video fluoroscopy in the setting of dysphagia indicates a high risk for subsequent pneumonia.[36,37] However, the variance among experienced speech pathologists in interpreting video fluoroscopy is large.[38]

As dysphagia progresses, PEG should be considered as an alternative or supplemental route for oral nutrition (figure 2). The immediate benefits are adequate nutritional intake, weight stabilization, and an alternate route for medication.[39,40] People with PEG can often continue to swallow some liquids and solids. Patients and families are generally positive regarding PEG,[41–43] although the impact of PEG on quality of life in ALS has not been studied in detail.

When Is a PEG Indicated in ALS? Initial management of dysphagia in patients with ALS includes modification of food and fluid consistency, and coaching by a speech pathologist. If this fails, evaluation for PEG tube placement is then warranted.[43]
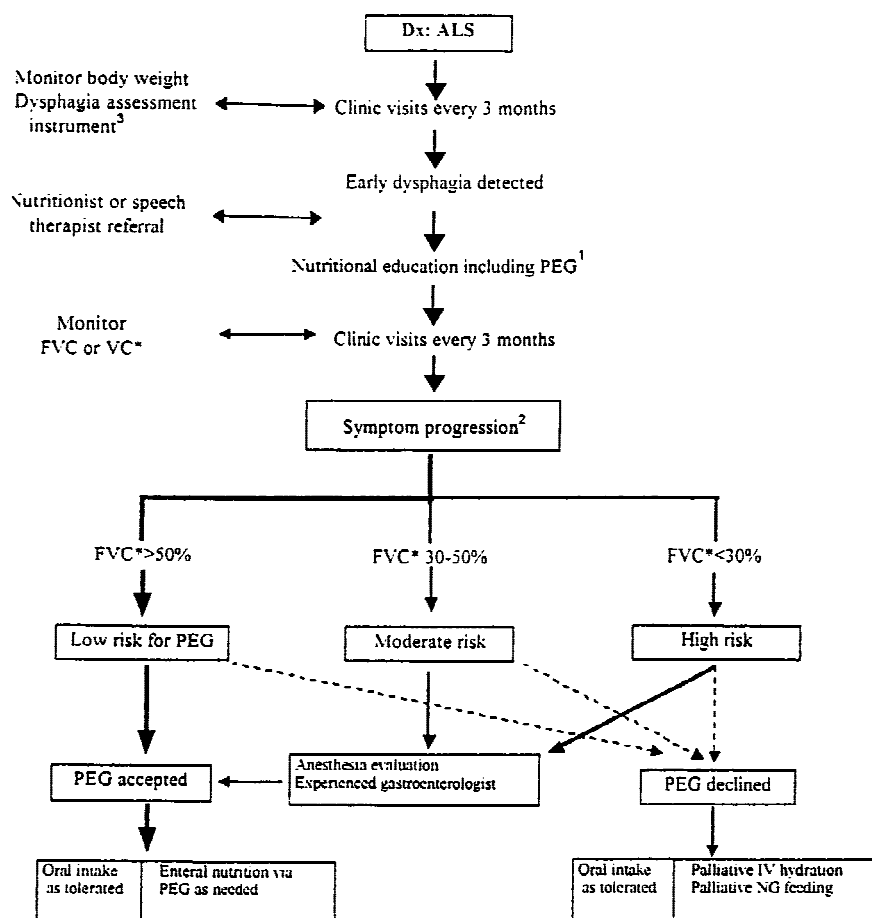
FIGURE 2. Algorithm for nutrition management. [1]Rule out contraindications. [2]Prolonged mealtime, ending meal prematurely because of fatigue, accelerated weight loss due to poor caloric intake, family concern about feeding difficulties. *Forced vital capacity (FVC) or vital capacity (VC) can be used. VC may be more accurate in patients with bulbar dysfunction. [3]For example, Colorado Dysphagia Disability Inventory, bulbar questions in the ALS Functional Rating Scale, or other instrument. Dx = diagnosis; PEG = percutaneous endoscopic gastrostomy.

In ALS, the recommendation for PEG should be made before the forced vital capacity (VC) falls to 50% of predicted (discussed later) and not in the preterminal phase.[39,40] The decision is based on progression of dysphagia and family concern about feeding difficulties. Specifically, PEG is indicated when patients with ALS have symptomatic dysphagia with accelerated weight loss due to insufficient caloric intake, dehydration, or ending meals prematurely because of dysphagia or choking on food.[39,40] The timing of PEG should be considered in the context of pulmonary status (discussed later).

What Is the Best Way to Detect Dysphagia in ALS? A careful history should be obtained at each visit to identify symptomatic dysphagia. There is no single test to detect dysphagia in patients with ALS. Questions regarding the physical manipulation of food and fluid (e.g., frequency of choking, texture of foods that cause problems, drooling, duration of meals, fatigue while eating) are revealing. Although a barium swallow study may provide supportive evidence for dysphagia, the indication for PEG in ALS depends on the presence of inadequate oral intake and diminished quality of life due to choking rather than the result of a swallowing study.[43–46]

What Is the Risk of PEG Placement in Patients with ALS? The onset of dysphagia may coincide with the insidious development of respiratory insufficiency, which is the major determinant of survival.[47,48] Because PEG tube insertion typically employs procedural sedation, knowledge of a patient's respiratory capacity and monitoring of oxygen saturation are essential.[49] To minimize risks, evidence indicates that PEG should be placed before VC falls below 50% of predicted.[39,40]

Complications of PEG placement include transient laryngeal spasm (7.2%), localized infection (6.6%), gastric hemorrhage (1 to 4%), failure to place PEG due to technical difficulties (1 to 9%), and death due to respiratory arrest (1.9%).[39,40]

What Is the Effect of PEG on Preventing Aspiration and Aspiration Pneumonia?
PEG or percutaneous endoscopic jejunostomy does not prevent aspiration pneumonia.[41,43,50–54] Therefore, prevention of aspiration pneumonia is not an indication for PEG.[46] The major risk factors for post-PEG pneumonia include a pre-PEG history of aspiration pneumonia, presence of reflux esophagitis during endoscopy, and concurrent infection.[51,52–56]

Although not studied in ALS, a prokinetic agent (such as cisapride) to enhance gastric emptying may reduce the incidence of post-PEG aspiration.[57] There is some evidence that recurrent aspiration pneumonia in aphonic patients with ALS may be treated with conservative laryngectomy or laryngeal diversion.[58,59] The role of cricopharyngeal myotomy in the management of dysphagia in ALS is uncertain.[45,60]

What Is the Efficacy of PEG in Prolonging Survival?
Two studies suggest that insertion of PEG may prolong survival.[39,40] Patients with PEG lived an average of 1 to 4 months longer than patients who refused or who were deemed ineligible for PEG.[39,40] The survival advantage was greatest in patients with a VC > 50% at time of PEG insertion.[40] However, control subjects were not randomized and other factors that might influence survival (such as depression) were not evaluated systematically.

Recommendations.

1. PEG is indicated for patients with ALS who have symptomatic dysphagia and should be considered soon after symptom onset. (Guideline)
2. For optimal safety and efficacy, PEG should be offered and placed when the patient's VC is more than 50% of predicted. (Guideline)

Research Recommendations.

1. Establish the fluid and caloric requirements of patients with ALS at different stages of the illness.
2. Evaluate the incidence of utilizing PEG in ALS and of aspiration pneumonia after PEG.

3. Measure the effect of PEG intervention on survival and quality of life in ALS.
4. Study the decision-making process to understand which factors are important to patients.
5. Promote understanding of nutritional issues and standardize nutritional care to facilitate planning future clinical trials and meta-analyses of new drugs for ALS.
6. Evaluate the efficacy of conservative laryngectomy for recurrent aspiration pneumonia in aphonic patients.
7. Study the impact of advance directives on future PEG placement.

RESPIRATORY MANAGEMENT
Respiratory care presents the greatest challenge for the ALS patient and the clinician. Deciding when to initiate noninvasive mechanical ventilation is critical because of the risk of either sudden death or ventilator dependence without proper advance planning.[61–64] An early understanding of the patient's preferences will help ensure careful and timely planning (figure 3).

What Are the Early Indications of Respiratory Insufficiency?
Early signs and symptoms of weakness of the respiratory muscles are subtle and easily overlooked if not sought specifically.[65] Symptoms include dyspnea on exertion, supine dyspnea, marked fatigue, disturbed sleep (frequent nocturnal awakenings, excessive daytime sleepiness), and morning headaches.[66,67] No evidence indicated the best test of detecting early signs of impending respiratory failure. Probably the most sensitive pulmonary measurement to detect early respiratory muscle weakness (respiratory insufficiency) is maximal inspiratory pressure,[65] but no studies test its efficacy in detecting impending respiratory failure in ALS. Erect sitting VC, and possibly supine VC (to detect early diaphragmatic weakness),[66] are useful in monitoring declining respiratory function. Thus, VC should be monitored in patients with ALS (although no published data indicated how frequently this should be performed).[48,68] Nocturnal oximetry is useful in evaluating nocturnal hypoventilation. A full polysomnogram is an alternative test, but is not needed in most patients.[66,69,70]

A decrease in VC to 50% of predicted is often associated with respiratory symptoms.[71,72] Even in the absence of symptoms, when the VC falls to this level, a number of planning steps must be taken (see figure 3). A VC less than 1 L (or less than 25 to 30% of predicted) indicates significant risk of impending respiratory failure or death.[65] Bulbar impairment in-
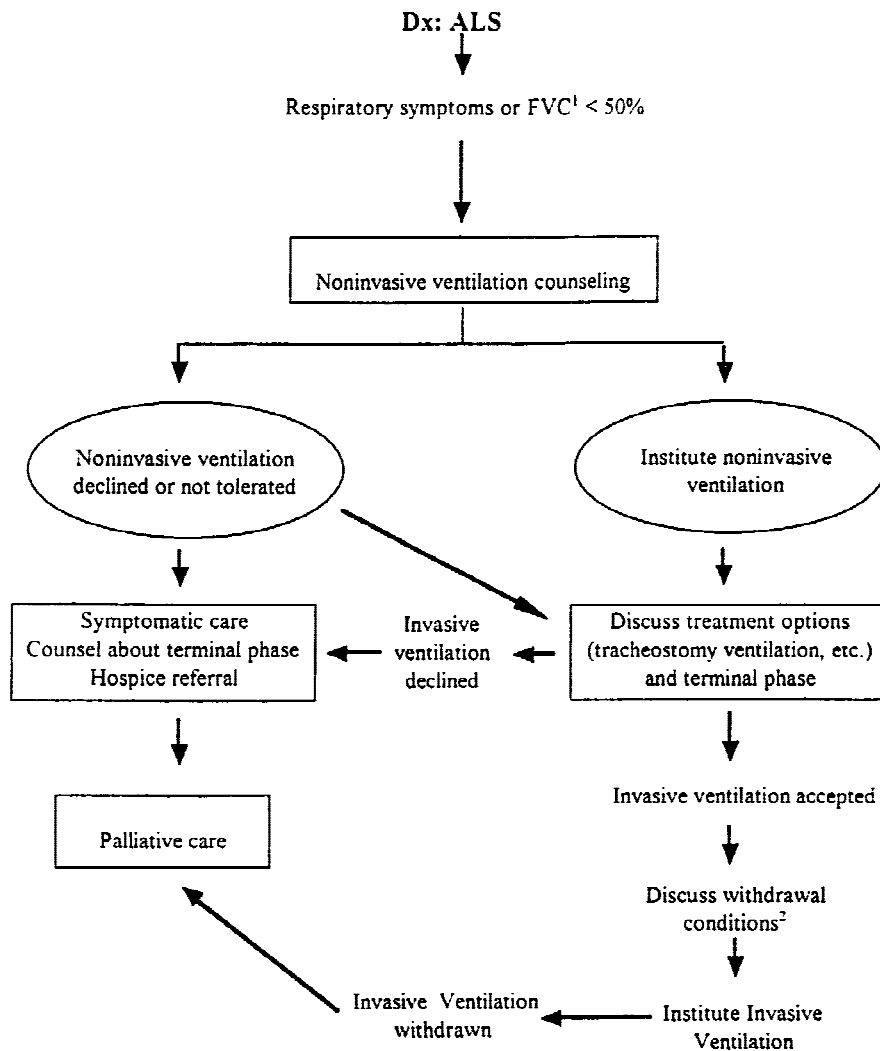
Dx: ALS

Respiratory symptoms or FVC[1] < 50%

Noninvasive ventilation counseling

Noninvasive ventilation declined or not tolerated

Institute noninvasive ventilation

Symptomatic care
Counsel about terminal phase
Hospice referral

Invasive ventilation declined

Discuss treatment options (tracheostomy ventilation, etc.) and terminal phase

Palliative care

Invasive ventilation accepted

Discuss withdrawal conditions[2]

Invasive Ventilation withdrawn

Institute Invasive Ventilation

FIGURE 3. Algorithm for respiratory management. [1]Forced vital capacity (FVC) or vital capacity (VC) can be used. VC may be more accurate in patients with bulbar dysfunction. [2]Agreement needed for conditions of withdrawal prior to or concurrent with instituting invasive ventilation (e.g., locked in state, coma, etc.). DX = diagnosis.

creases the risk of aspiration,[64] and acute respiratory infection can precipitate sudden respiratory failure.[64]

Does Noninvasive Ventilation Improve Respiratory Function or Increase Survival? Impaired ventilatory function, which is expected late in the course of ALS, occasionally occurs shortly after onset of symptoms. Patients, families, and physicians must then consider chronic ventilatory support. Patients and physicians often consider noninvasive ventilation more desirable than invasive ventilatory support with tracheostomy. Moreover, noninvasive ventilation offers direct clinical benefit to the patient. Several studies indicate that noninvasive ventilation improved the symptoms of hypoventilation, thereby improving quality of life[63,73,74] and increasing survival

of patients with ALS by several months.[47,61,71,75] Invasive ventilation may increase survival more effectively but with a greater financial and care burden.[71]

Loss of bulbar muscle tone and difficulty clearing secretions reduce tolerance of noninvasive ventilation and may define the limit of noninvasive ventilation.[61] Thus, patients with bulbar ALS may not tolerate noninvasive ventilation, and invasive ventilation should be considered.[72]

Does Experience with Noninvasive Ventilation Aid Decisions about Invasive Ventilation? When a patient can no longer tolerate noninvasive positive-pressure ventilation or it fails to be effective, he or she has to choose between invasive ventilation with tracheostomy or palliative care (see figure 3). Limited evidence in patients with ALS suggests that some

patients who experienced noninvasive ventilation decided against invasive ventilation when the noninvasive ventilation became ineffective.[47,61,76,77] Moreover, some patients were on long-term invasive ventilation following emergency hospitalization in the absence of prior planning.[71]

The results of these studies suggest that previous experience with noninvasive ventilation may assist the patient and the family in deciding whether to use invasive ventilation, but this point is still not clear.[47,71,76,77]

How Do Invasive and Noninvasive Ventilation Impact Quality of Life?
Patients with ALS who depend on long-term invasive or noninvasive ventilation, either full- or part-time, can lead meaningful lives, and few regret being on a ventilator.[78–81] Collectively, these studies provide evidence that ventilatory support should be discussed with each patient with ALS well before the development of respiratory insufficiency symptoms.[78,79] Ventilator-dependent patients with ALS are not more depressed than patients with ALS who are not ventilator dependent.[79] Additionally, because patient satisfaction is higher with noninvasive than invasive ventilation, noninvasive ventilation should be considered before tracheostomy.[71] Patients on chronic invasive ventilation, and their familes, bear a great financial, social, and emotional burden.[80] The cost and possible benefit should be discussed openly and honestly with the patient and the family.

Caveat: Outside observers cannot assess accurately a patient's quality of life. In one study, medical personnel overestimated patient dissatisfaction significantly in every aspect measured, and they judged incorrectly that patients would be dissatisfied with life on a ventilator.[82]

What Is the Optimal Method of Withdrawing the Patient from Noninvasive and Invasive Ventilation?
Legal and ethical precedents support the right of a mentally competent, informed patient to refuse or to discontinue any treatment, including life support and mechanical ventilation. Healthcare providers are required to respect such a request.[26,76,77–88]

As ALS progresses, most patients who select a ventilator become completely dependent on it.[75] Unfortunately the patient may ultimately become unable to communicate; therefore, it is critical to agree, prior to this point, which circumstances will trigger withdrawal of the ventilator. Although no rigorous comparative studies have investigated the optimal method for withdrawing mechanical ventilation, some retrospective studies, although not in

patients with ALS, provided information on how to carry out this important procedure in a humane manner.[88] The evidence in these studies was based on acute critical care experience with intubated patients in which the patient or family agreed to withdraw mechanical ventilation because there was no reasonable hope of recovery, and death was anticipated without ventilator support. From this experience, a stepwise approach is suggested.[88] As defined by the principle of "double effect," the intention is to relieve suffering, not to hasten death, although death may be hastened as a consequence.[89]

When initiating ventilatory withdrawal, the primary goal is to maintain patient comfort. If utilizing supplemental oxygen, the first step is to discontinue supplemental oxygen and end positive expiratory pressure, followed by conversion to a T-piece and spontaneous breathing.[88] Several reports provide timing and dosing details when withdrawing ventilatory support.[85,90,91] At each step in the withdrawal process, patients may require pretreatment with a sedative—hypnotic (equivalent to 15 mg per hour of IV diazepam [Valium]) and/or opioid (equivalent to 15 mg per hour of IV morphine), raising the dose as necessary to relieve dyspnea and anxiety, even to the point of unconsciousness if necessary and requested.[85,86] The use of a muscle-paralyzing agent during ventilator withdrawal was not supported in the literature.[89]

Recommendations.

1. Be vigilant for symptoms indicating hypoventilation. Serial measures of pulmonary function (especially VC) are recommended to guide management and to determine prognosis with the understanding that no single test can detect hypoventilation reliably. (Guideline)
2. Offer noninvasive ventilatory support as an effective initial therapy for symptomatic chronic hypoventilation and to prolong survival in patients with ALS. (Guideline)
3. When long-term survival is the goal, offer invasive ventilation and fully inform patient and family of burdens and benefits. (Guideline)
4. In accordance with the principle of patient autonomy, physicians should respect the right of the patient with ALS to refuse or withdraw any treatment, including mechanical ventilation. (Guideline)
5. When withdrawing ventilation, use adequate

opiates and anxiolytics to relieve dyspnea and anxiety. (Guideline)

Bioethics Statement: It is a strong consensus of both the ALS Task Force and the Quality Standards Subcommittee of the AAN that during withdrawal of ventilation, paralyzing drugs should not be used.

Research Recommendations.

1. Study whether noninvasive ventilation improves quality of life and prolongs survival for patients with ALS.
2. Identify (a) whether early ventilatory support alters prognosis, (b) the optimal timing of ventilatory intervention, and (c) better noninvasive methods of ventilatory support.
3. Study methods of withdrawing both invasive and noninvasive respiratory support in ALS.

PALLIATIVE CARE

Ethical Considerations. *Shared Decision Making.* The physician and the patient should share in decision making, understanding that cultural and religious values will have an impact on decisions.[12] The physician should explain the risks and benefits of treatments at each visit in an unbiased way, and understand that the patient's choices could change as the disease progresses.

Goals of Palliative Care. As ALS progresses, the goal of patient care changes from maximizing function to providing effective and compassionate palliative care.[82–87] One approach to provide adequate relief from two of the most prevalent and unpleasant symptoms in the terminal phase—dyspnea and anxiety—is as follows[112]:

1. Treatment of reversible causes of dyspnea if present (e.g., bronchospasm, pneumonia)
2. Treatment of intermittent dyspnea
   a. Relief of anxiety (0.5 to 2 mg lorazepam sublingually)
   b. Inhaled opiates (e.g., 5 mg morphine)
   c. A total of 5 to 10 mg IV midazolam (slowly) for severe dyspnea
3. Treatment of constant dyspnea
   a. Opiates (e.g., morphine, start with 2.5 mg IV/subcutaneously/transdermally, or oral equivalent every 4 hours)
   b. For severe dyspnea, continuous IV morphine infusion
   c. Add 2.5 to 5 mg diazepam or midazolam for nocturnal symptom control
   d. For terminal restlessness, chlorpromazine

(25 mg every 4 to 12 hours rectally or 12.5 mg every 4 to 12 hours IV)
4. Treatment of hypoxia with oxygen only

Continued communication with the paralyzed patient is often difficult and must be given high priority. Psychological and spiritual guidance should also be offered.

Is Pain Common in the Terminal Phase of ALS? Although pain in ALS is not usual in the initial stages,[92] between 40 and 73% of patients experience pain in later stages.[93–96] It may be caused by stiff joints, muscle cramps, or pressure on the skin or joints from immobility. In one series, 55% of patients responded to combinations of anti-inflammatory, anti-spasticity, and non-narcotic analgesic drugs. Among hospice patients with ALS, approximately 80% reported a good response to opioids.[94] The World Health Organization (WHO) pain management recommendations for patients with cancer[97] should be useful for pain management in patients with ALS. Strong evidence has documented the effectiveness of opioids for cancer pain, and two position papers from the AAN advocate opioids for treatment of pain in palliative care settings.[83,86]

Can Dyspnea in Terminal Stages by Relieved by Therapeutic Intervention? Dyspnea from respiratory muscle weakness occurs in approximately 50% of patients with ALS.[94–96] Relief of dyspnea using opioids was rated as good by 81% of hospice patients with ALS.[94] Opioids are advocated for treating dyspnea in two AAN position papers regarding care of terminal neurologic patients.[83,86] Although not studied in patients with ALS, oxygen was an effective treatment for dyspnea in hypoxemic cancer patients with restrictive lung disease.[98] Extreme caution is indicated when administering oxygen to nonterminal patients to avoid inducing hypoventilatory respiratory failure in hypercapnic patients.[99]

Patients who have attacks of dyspnea may benefit from calming techniques to reduce anxiety. Anxiety attacks due to dyspnea may be treated with short-acting anxiolytics, such as 0.5 to 2.0 mg lorazepam sublingually. A prospective, uncontrolled study of cancer patients indicated that chlorpromazine (Thorazine) helped relieve symptoms of dyspnea.[100] In an uncontrolled study of patients with cancer, acupuncture appeared to be helpful in treating dyspnea.[101]

Does Hospice Care Improve Quality of Life in the Terminal Phase? Uncontrolled studies reported some benefit from hospice care in improving the quality of

life of patients with ALS.[94–96] In a randomized, controlled clinical trial in cancer patients, "satisfaction with interpersonal care," "involvement of care," and pain management were significantly better with hospice care than with conventional care.[102] Using a measure of quality of death in cancer patients, hospice patients had better quality-of-death scores than conventional care patients.[103] Uncontrolled studies suggest similar results from hospice care for patients with ALS. A retrospective analysis of hospice chart data showed that 94% of patients with motor neuron disease were judged to be "peaceful and settled" at death in hospice.[94]

Do Advance Directives Improve Quality of Life for the Patient in the Terminal Phase of ALS? We found no evidence that advance directives improve quality of life in any disease. In two studies, advance directives did not enhance physician–patient communication or decision making substantially for seriously ill cancer patients.[104,105] Enhancing opportunities for more patient–physician communication and advance care planning also seemed inadequate to change established practices.[106] However, physician education about advance directives can increase the frequency of their use significantly.[107] Physicians are more likely to follow therapy-specific advance directives that are supported by a discussion with the patient than advance directives that are stated in generalities.[108] Several studies reported that physicians and patients want to utilize advance directives. Patients want to initiate discussion about advance directives earlier than their physicians, but both patients and physicians believe that it should be the physician who initiates discussion.[109,110] However, physicians often do not initiate discussion of advance directives.[79] Importantly, patients with ALS have been shown to change their preference for life-sustaining measures (e.g., ventilators) over a 6-month period.[111]

Recommendations.

For Pain Management:
1. Utilize non-narcotic analgesics, anti-inflammatory drugs, and antispasticity agents for initial treatment of pain in patients with ALS. (Option)
2. Administer opioids liberally, following the WHO guidelines, when non-narcotic analgesics fail. (Guideline)

For Treating Dyspnea in Terminal Stages of ALS:
1. Use opioids, alone or with supplemental oxygen, to treat dyspnea at rest in patients with ALS, despite the risk of respiratory depression with higher doses. (Guideline)
2. Consider chlorpromazine (Thorazine) and acupuncture as possible adjuncts. (Option)

For Hospice Care:
1. Consider referral to hospice in the terminal phase of ALS. (Option)

For Advance Directives:
1. Initiate a discussion of advance directives well in advance of the terminal phase and reevaluate at least every 6 months. (Option)

Research Recommendations.

1. Study symptom prevalence and quality of life in the terminal phase of ALS.
2. Test the effectiveness of current treatments for palliative care.
3. Develop new therapeutic approaches for terminal ALS symptoms.
4. Study the effect of hospice care on quality of life for patients with ALS and families.
5. Compare hospice home care with hospice in-patient care.
6. Study the role and impact of advance directives on the dying process.
7. Include palliative care of the dying patient in medical education.
8. Examine the psychological impact of ALS on caregivers and health care providers.

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This document has been endorsed by the American College of Chest Physicians.

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physican caring for the patient, based on all of the circumstances involved.

APPENDIX

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