

Understanding ALS

Introduction

Amyotrophic Lateral Sclerosis (more commonly referred to as Lou Gehrig's disease) is a neuromuscular disease that causes damage to the nerve cells controlling voluntary muscle movement, also known as motor neurons. It belongs to a group of diseases known as motor neuron diseases that affect the motor system. To understand ALS and the spectrum of motor neuron diseases, we will review the motor system, what the signs and symptoms of motor system damage are, and the different motor system diseases (Table 1). This will set the stage for an in depth discussion of ALS including the clinical picture, possible causes, and treatment of the disease.

What is ALS?

ALS is a disease that affects the motor system, which is a tag team of motor nerve cells (motor neurons) that carries messages from the area that controls movement in the brain to the muscle (Figure 1 below). The first part of the motor system carries the signal from the brain to the lower part of the brain (brainstem) and the spinal cord. It is referred to as the upper motor neuron (UMN) or corticospinal tract. The upper motor neuron contacts a second motor neuron referred to as the lower motor neuron (LMN) or anterior horn cell. The LMN then carries the signal to the muscle. The LMNs in the brainstem contact the muscles of the speech and swallowing. Involvement of this area is called bulbar involvement. Motor neurons in the highest part of the spinal cord, known as the cervical cord, send messages to the arm muscles and diaphragm (one of the muscles that are important for breathing). The middle part of the spinal cord is called the thoracic cord and neurons here control the muscles of the trunk and the muscles of the chest. The lowest part of the spinal cord is the lumbar spinal cord and the motor nerves at this level innervate the leg muscles.

How can we tell that there is motor neuron damage?

It is possible to determine that there is motor neuron damage by the symptoms that a person has and by examination of the motor system (Figure 1 below). When a physician considers motor neuron disease (MND), he/she must evaluate whether there is damage to the motor system, where the damage is-i.e. whether the damage involves the UMN, the LMN, or both pathways, and whether there is any indication of damage outside the motor system (which could indicate a diagnosis of something other than MND). Sometimes a special test called the EMG-NCV (Electromyogram and Nerve Conduction studies) is also needed to help to detect damage to the lower motor neurons and exclude more treatable diseases such as motor

neuropathy with multifocal conduction block (See the section on classification of motor neuron diseases and the section on differential diagnosis).

Symptoms of damage to the UMN include stiffness, cramps, slowness of movement, laughing or crying too easily (termed pseudobulbar affect), nasal, slow speech, and sometimes urgency of urination. The signs of upper motor neuron damage on exam include an increase in muscle tone or stiffness with resistance to movement called spasticity, increased reflexes (when the knee, ankle, inner elbow and arm are tapped with the reflex hammer), and abnormal reflexes (this includes an increase in chin movement with a tap called a jaw jerk, the presence of a Babinski sign where the big toe goes up instead of down when the sole of the foot is stimulated, and the presence of increased finger flexion on the appropriate stimulus).

Symptoms of LMN damage include weakness, thinning of the muscles or atrophy, twitching of the muscles or fasciculations, and cramps. The examination demonstrates weakness and atrophy with fasciculations and a decrease in tone with absent or diminished reflexes. The EMG will demonstrate damage due to LMN loss in the weakened muscles and may also show changes in muscles that are still strong. NCV studies should be normal, however, these studies are important because they help to detect motor neuropathy with or without conduction block in people with mainly LMN damage. In this case, these individuals may have a form of motor neuropathy that is treatable.

It is very important to understand that the presence of motor neuron damage does not mean that someone has ALS or any other motor neuron disease. A physician will rule out other causes of motor neuron damage before diagnosing ALS.

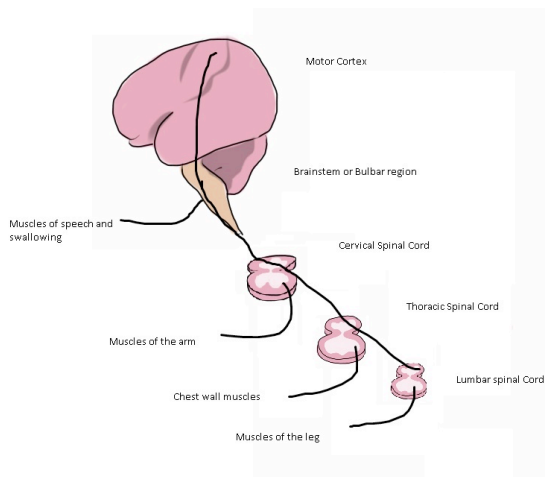


Figure 1: The motor system is comprised of the upper motor neuron (corticospinal tract) and the lower motor neuron (anterior horn cell).

What are Motor Neuron Diseases?

Motor neuron diseases (MND) damage the motor system. They can affect either the upper motor neuron (UMN), the lower motor neuron (LMN), or both. These diseases are named for the part of the motor system they affect. In ALS, both the UMN and the LMN are damaged. Table 1 presents the classification of the more common diseases, listed by which portion of the motor system they involve. The classical MNDs include:

Progressive Muscular Atrophy (PMA):

Constitutes roughly 8-10% of patients with sporadic ALS. PMA is sometimes called Aran-Duchenne type of motor neuron disease (MND). The initial symptoms are manifestations of LMN involvement of the spinal cord and, in a later stage, of the lower brainstem. If UMN disease does not develop within two years, the disease is likely to remain PMA.

Primary Lateral Sclerosis (PLS):

PLS was first described by Erb in 1875. The clinical signs of PLS consist only of UMN signs. It is the rarest of all the forms of ALS.

Amyotrophic Lateral Sclerosis:

The ALS originally described by Jean-Martin Charcot in the mid-1800s that is often called Charcot's disease in Europe. Classical ALS is a distinct syndrome characterized by a combination of UMN and LMN signs and symptoms without other neurologic problems and no other explanation but a motor system disorder. In approximately two thirds of patients with ALS, the disease takes this classical form.

What are some basic facts about ALS?

ALS generally affects people between 55 and 75 years of age although it can occur in individuals of all ages. The prevalence rate (how many people have the disease at one time) of ALS is about 4 per 100,000 people and its incidence rate (how many new cases occur in a time period) is about 1 per 100,000 new cases each year. There is also a male-to-female ratio of about 2:1.

The symptoms of ALS vary from one person to the next. Symptoms reflect weakness and thinning of muscles due to the involvement of the LMN as well as stiffness from the UMN involvement. Onset can begin in the muscles that are innervated by the bulbar neurons (speaking, swallowing) or in muscles innervated by nerve cells in the spinal cord causing weakness in one

arm or one leg. In 20% of ALS cases, the ability to speak and swallow begin to decline first. 40% of cases have symptoms that initialize in the arm, while the remaining 60% experience problems due to leg involvement. A person newly diagnosed with ALS may trip, drop things, slur his/her speech, twitch, and laugh or cry uncontrollably. The person may also experience abnormal fatigue of the arms or legs and muscle cramps. Walking and activities requiring the hands may prove more difficult for a person with the disease. Over time, the disease spreads from one area to another and gradually, people living with ALS will lose movement in the muscles throughout their body, including the muscles that allow them to breathe. While the average lifespan for someone with ALS is about 36 months, it is important to recognize that 20% of people with ALS live for five years and 10% of patients live for 10 years.

Recently, the medical community has begun to understand that in a small group of people with ALS, there may be frank dementia. This happens in only 5% of people with ALS. However, up to 40% of people with ALS do have mild cognitive involvement that may be evident on testing in the clinic

What are the variations of ALS?

There are both sporadic (no family history) and Familial (family history) forms of ALS. 10% of people with ALS have a family history of the disease that has been identified as a genetic abnormality in more than two thirds of these people. Ninety percent of people with ALS do not have any family history of the disease, though it is now known that 10% of these sporadic cases do carry one of the genetic abnormalities described in Familial cases.

Sporadic ALS

Classical ALS – Classical ALS is a distinct syndrome characterized by a combination of UMN and LMN problems and occurs in about two thirds of people with ALS.

Progressive Bulbar Palsy (PBP) – was originally described by Duchenne in 1860. In approximately 25 percent of people with ALS, the initial symptoms begin in muscles innervated by the lower brainstem that control articulation, chewing, and swallowing. Sometimes the disease remains in this form for years, but usually it progresses to generalized muscle weakness, that is, to ALS. When the disease is strictly limited to the bulbar muscles it is called PBP, not classical ALS.

Familial ALS (FALS)

In some instances, ALS runs in the family, i.e. it is genetic. This happens in 10% or less of all people with ALS, although it is likely that genetic makeup may play a role in an individual's susceptibility to disease.

Familial ALS (FALS) cases comprise between 5-10% of all cases and is generally a dominantly inherited disease, meaning that one of the individual's parents passed on the abnormal gene. Almost 20 % of people with FALS have damage (called a mutation) in the gene that codes for the protein Cu/Zn superoxide dismutase located on chromosome 21. This was the first gene to be identified. Recently there has been an explosion of information and at the time this chapter was written, scientists have identified more than 30 different genes that are either causal or increase the risk of developing ALS. In fact, the most common genetic cause of ALS is the abnormal extra chromosomal material in the C9ORF72 gene, called a hexanucleotide repeat. This abnormality has been found not only in 23% of families with ALS but also in 5-7% of people with ALS and no family history. Some of the genetic abnormalities can be present with either dementia, ALS, or both, underscoring the possible shared mechanisms in these diseases and the findings of cognitive involvement in people with ALS. It is expected that more genes will be found to be responsible for the disease through research and genetic studies in families and siblings of people with both sporadic and familial ALS. These genetic changes will give us information about the pathways that are important for disease and lead to therapeutic strategies not only directed at FALS, but also for SALS.

What are the potential causes of ALS?

The cause of ALS is not known, however, there are many pathologic mechanisms that may play a role in disease (see Table 2 below). It is likely that ALS is a complex multisystem disease with several mechanisms that cause the death of motor neurons. Any one of these mechanisms or a combination of several may be responsible for the disease and many of these mechanisms also play a role in other neurodegenerative diseases. Furthermore, as pointed out above, there are likely to be genetic and hereditary factors that will modify the disease and susceptibility. The most important mechanisms are outlined below:

Defective glutamate metabolism:

To date, one of the most robust theories of the pathogenesis of ALS is the excito-toxicity of glutamate. Glutamate is a common chemical in the nervous system used for the signaling between neurons. While it is important for normal nerve cell function, it is toxic in excess. There is evidence of increased glutamate in ALS patients and in ALS mice, and this may be responsible for nerve cell death. The increased glutamate may result from either the abnormal transport of glutamate out of the nerve cell environment or the increased release of glutamate from nerve cells. To date, there is some evidence indicating that the transporter responsible for removing glutamate from the nervous system may be altered and/or the process for making the transport protein is damaged in those individuals with ALS.

Free radical injury and oxidative stress:

Free radicals are molecules with unpaired electrons. These molecules are unstable and liable to damage cellular structures including proteins and lipids (fats) within nerve cells. Free radicals are a normal part of cellular life and cells are usually able to neutralize them and keep their numbers in check. However, in ALS, free radicals build to toxic levels and damage cells, through an attack process called oxidative stress. It is worth noting that 20% of Familial ALS patients have mutations in SOD1, an enzyme that detoxifies oxygen free radicals. There is evidence that there are higher levels of protein carbonyl groups (caused by oxidative stress to proteins) and oxidized nucleic acids in brain tissue from patients with sporadic ALS.

Mitochondrial dysfunction:

Free radicals are also produced in the powerhouse of the cell called the mitochondria. Mitochondria and its genetic material are especially sensitive to the oxidative damage from free radicals and may be one of the earliest sites of damage in ALS, and in familial ALS. This results in lower energy production by the nerve cell and less ability to do its' job.

Gene defects and RNA processing:

Ten percent of all instances of ALS is inherited and there are several mechanisms implicated by the genetic abnormalities found in FALS. First 20% of patients carry a mutation in the Superoxide Dismutase Gene (SOD1) and this abnormality leads to increased free radical production as well as multiple other pathologic changes including clumping or aggregation of proteins and inflammation. Additionally, several of the genetic abnormalities identified cause problems in the way RNA is processed to produce proteins while other implicated genes are important to protein metabolism and turnover. This field is exploding and new genes are identified every few months now.

Programmed cell death (apoptosis):

ALS may be due to an early death of motor neurons or a premature initiation of programmed cell death or suicide (called apoptosis).

Cytoskeletal protein defects:

Neurofilaments provide a scaffold structure to maintain the long process (called the axon) that extends from the cell body of nerve cells out to the muscle or down the spinal cord. These filaments also provide the ability to transport important molecules up and down the axon. It has been shown that neurofilaments accumulate in the nerve cell body and processes (called axons) in ALS, as well as animal models. Furthermore, mutations in proteins integral to the structure of the scaffold and neurofilament function have led to genetic forms of motor neuron disease.

Autoimmune dysfunction:

There is a higher incidence of immune disorders and abnormal immune system made proteins in people with ALS. There is evidence that the *immune system*, particularly immunologic cells in the nervous system known as *microglia*, can be both beneficial and harmful in ALS. Microglia may be protective up to a certain point but they then become damaging to the immune system. There are now several therapies in trial directed at correcting the immune system abnormalities.

Protein Clumping and Aggregation:

In both genetic and sporadic forms of ALS, abnormal clumping called aggregation of proteins occurs in the motor neurons. This aggregation indicates abnormal protein turnover and clearance may play a role in the disease. In fact, there have been familial cases linked to mutations in Ubiquitin, which tags proteins for degradation.

Toxic exposures:

Epidemiologists have studied the possible relationship of environmental toxins, occupational hazards, places of work or residence, exposure to chemicals, heavy metals, trauma, etc. to the risk of developing ALS but results have been conflicting. However the association between developing ALS and having served in the military is one of the strongest proposed risk factors. It is not clear if the exposure during military service is due to environmental toxins, cyanobacterial exposure, or other causes but there is ongoing research.

What kind of treatments are there for ALS?

While there is no cure for ALS as of this writing, there are treatments including medicines and interventions directed at the symptoms as well as the disease. First, there is medicine, Rilutek, which slows the disease progression by decreasing glutamate levels. In addition there are many ongoing clinical trials that use agents that target possible causes of the disease. Furthermore, advances in the aggressive treatment of respiratory complications of ALS with noninvasive ventilation and respiratory management as well as aggressive nutritional intervention have provided significant improvements in morbidity and mortality. Finally, there are symptom-specific treatments and interventions that are best implemented in a multidisciplinary approach that has led to improved quality of life and maximization of function in people living with ALS.

In the multidisciplinary setting, physicians works in tandem with a team of health care professionals skilled in the care of people with ALS. This is how the MDA /ALS Center of Hope

is structured at Temple University Lewis Katz School of Medicine. The team typically includes nurses, nutritionists, occupational therapists, physical therapists, speech and language pathologists, mental health specialists, and case management professional. These professionals will help to identify problems as well as provide solutions while working together to maintain the individual's function and mobility along with his/her overall quality of life. The role of each clinic team member is outlined in Table 3.

A review of disease specific treatment, clinical trials, and symptom management follows. We will also address two major areas in detail within this chapter: swallowing and breathing difficulties.

Several drugs are identified in providing a modest effect in the diseases progression: Riluzole, an oral glutamate blocker and Tigtutik its oral suspension form; Radicava an infusion treatment, and now oral treatment, that reduces oxidative stress, and Relyvrio (AMX0035) whose mechanism of action is directed at blocking cell death pathways originating in the mitochondria and endoplasmic reticulum.

The key to selecting possible therapeutic agents lies in the understanding of the disease. To date, the cause of ALS is not known but several theories have been proposed and there is experimental evidence to support each theory. There may be an interplay of one or more of these mechanisms that lead to nerve cell death in ALS. Furthermore there may be genetic factors that are important to the predisposition to develop disease with the right provocation. The mechanisms of neuronal death in ALS that have been theorized include defective glutamate metabolism, free radical injury, protein aggregation, mitochondrial dysfunction, gene defects, programmed cell death (apoptosis), cytoskeletal protein defects (including neurofilament abnormalities), and immune system dysfunction. These proposed causes of ALS have provided targets for drug and stem cell therapies. Several resources for finding updated information regarding enrolling trials are available including: ALS Hope Foundation, NEALS, MDA.org, <http://www.als.net/ALS-Research/ALS-Clinical-Trials/>, ALSA.org, and clinicaltrials.gov.

While there is no cure for ALS at present, there is treatment. Clinical management of ALS is focused primarily on symptom relief. Treatment of symptoms increases the quality of life for people living with ALS by reducing complications and increasing comfort. Furthermore, aggressive respiratory and nutritional intervention can improve both the morbidity and mortality that result from ALS.

The most common symptoms in ALS include muscle cramps and stiffness, increased salivation, and drooling, increased secretions with thickened phlegm, constipation, depression, and anxiety, increased laughing and crying called pseudobulbar affect, fatigue, and insomnia. Less frequently, people with ALS may have urinary urgency and throat spasms. There are many strategies including physical interventions and medicines available to treat the symptoms that are associated with ALS. Table 3 lists some of the commonly used physical interventions and medicines.

Remember that each person is different and the choice of medicine to be used is best determined by the treating physician. Careful attention to swallowing and feeding is also important and aggressive management should be initiated to avoid aspiration (food entering the windpipe) and weight loss. If swallowing problems (dysphagia) are present, the speech and swallow therapist should educate the person living with ALS about the appropriate food consistency and proper swallow technique using a chin tuck. Additionally, the patient should sleep with his/her head elevated and should never lay flat following meals. A physician, along with a speech and language pathologist, may recommend a video swallow evaluation to assess the risk of aspiration. As swallowing difficulties worsen or its vital capacity drops below 50%, a percutaneous gastrostomy (PEG) tube should be recommended to maintain nutrition. This is a small tube inserted into the stomach during endoscopy and requires only sedation without general anesthesia. While the PEG tube will improve nutrition and reduce risk of aspiration it does not fully prevent aspiration. Early intervention with PEG tube can prolong life.

How are symptoms of breathing problems treated?

Breathing trouble is another symptom that must be managed by those with ALS. Normally, the lungs function to allow a person to breathe in air (oxygen) and exchange it for carbon dioxide, a waste product of metabolism in the body. This exchange takes place in the air sacs called alveoli. During inspiration, which is an active process, air is drawn into the mouth, down the large airway called the trachea, and then into the bronchi, and finally into the smaller airways (bronchioles) to the air sacs (alveoli). The exchange of oxygen and carbon dioxide takes place in the air sacs or alveoli and carbon dioxide is then expired out of the lungs through the passive process of expiration. The diaphragm and chest muscles (called intercostals) are responsible for inspiration and the abdominal muscles and other chest muscles (the internal intercostals) help with expiration

In individuals with ALS, several problems cause difficulties in breathing. First, as the respiratory muscles weaken, oxygen cannot be adequately exchanged with carbon dioxide which then builds up in the blood stream. This leads to sleepiness and fatigue. Furthermore, since the respiratory muscles are weak, there is a decrease in the strength of the individual's cough. A weakened cough and a decrease in gag reflex leads to problems clearing the airway and mouth full of secretions. As swallowing difficulties progress, oral secretions increase as a result. These secretions can get into the airways and alveoli blocking adequate exchange of oxygen. The

decrease in effective coughing further compromises the ability to clear these secretions. Finally, if the muscles in the back of the throat are weakened, the airway is unprotected when the individual swallows. This leads to aspiration, wherein the contents of the oral cavity can enter the individual's airways. Aspiration can lead to infection (aspiration pneumonia) as well as the further compromise of carbon dioxide exchange. Additionally, with increased swallowing difficulties, oral food intake is reduced and malnutrition occurs. Malnutrition leads to further compromise by increasing overall muscle weakness including the respiratory muscles.

The symptoms of respiratory failure, which can be a serious issue for an individual with ALS, include shortness of breath during exertion or at rest, fatigue, inability to sleep flat, troubled sleep, daytime sleepiness, yawning, and morning headaches. Examination may show rapid breathing, the use of extra muscles to help breathe, problems with speaking including low volume and frequent breaths along with an ineffective cough. If aspiration is also a problem there may be coughing with eating, watery eyes, sneezing, alterations in breathing, changes in the lung sounds, gagging, frequent throat clearing, swallowing more than once for each bite or sip, and even a gurgly sound to the voice. As respiratory failure worsens, there can be a build up of carbon dioxide which results in sleepiness and confusion,

In order to combat these symptoms, in addition to asking about symptoms that indicate respiratory muscle weakness, a doctor can measure the muscle strength and function in the clinic using a machine called a spirometer. The amount of air that the lungs can hold is called its VC or vital capacity. Similarly, the strength of inspiration (breathing in) and expiration (breathing out) can be measured with a small pressure gauge. Most centers measure the vital capacity at a baseline and with each visit. As the vital capacity decreases or symptoms occur, measurement of the oxygen and carbon dioxide levels in arterial blood can be performed. Furthermore, as the level of the vital capacity drops to half that of a normal set of lungs (50%), consideration to the initiation of NIPPV should be given.

Given this backdrop, the specifics for the treatment of breathing problems due to weakness of respiratory muscles in ALS consists of an assessment of respiratory muscle involvement, prevention of infection, secretion mobilization, and the use of noninvasive and invasive ventilation. This is reviewed in detail below.

General assessment

Physicians will generally perform a baseline examination and pulmonary function testing as well as assess any other medical conditions that might contribute to respiratory problems, including asthma, COPD, and congestive heart failure. Risk factors, such as cigarette smoking, secondhand smoke, dusts and fumes, and exposure to people with acute viral respiratory illness should be identified and avoided. Pneumovax immunization and yearly influenza immunizations are advised. Respiratory symptoms along with pulmonary function testing should be performed at every visit to allow early intervention and treatment of respiratory problems. As part of the

routine care of people with ALS, physicians should aggressively treat acute respiratory infections, manage secretions, and institute noninvasive ventilation at the appropriate time.

Since acute respiratory infections can precipitate respiratory failure leading to invasive ventilation with intubation in an already compromised ALS patient, infections must be treated aggressively. The additional secretions combined with an ineffective cough and reduced strength of the breathing muscles leads to increased secretions obstructing the airways. This further reduces the exchange of carbon dioxide and oxygen and resultant elevated carbon dioxide. For this reason, individuals with ALS may need to be in the hospital even with a mild upper respiratory infection to allow for intravenous hydration, antibiotics, and aggressive secretion management,

As mentioned earlier, increased secretions, whether from an acute respiratory infection or the inability to swallow properly, combined with reduced protection of the airways from a weakness of the protective muscles oropharynx or poor cough, leads to a plugging of the airways, collapse of the air sacs, and infections secondary to aspiration. These all result in increased carbon dioxide as well as reduced oxygenation of the blood. Treatments are directed both at decreasing and thinning the secretions as well as increasing clearance. Medicines that *decrease* secretions include: Anticholinergic medications (Glycopyrrolate, amitriptyline, transderm scopolamine, levsin or hyoscyamine), and a botulinum toxin injection into the salivary gland. If these modalities fail, irradiation of the parotid gland can be helpful. If the secretions are thickened, especially with use of anticholinergic agents, hydration, guaifenesin, propranolol, and acetylcysteine, nebulizing treatments can also be considered.

As the cough weakens, it may not be able to clear the individual's airways. At this point, a doctor should recommend a program to promote the clearance of secretions. Some of the interventions that can help include the use of an assisted cough or coughalator machine. If secretions are thick, a nebulizer may help along with chest percussion either manually by cupping the hands and tapping the back in different positions (postural drainage and pulmonary toilet) or through a mechanical vest that can help to mobilize the secretions. If the cough is weak, an assisted cough or coughalator can help to bring secretions up and, if necessary, a suction machine can be used to clear the mouth when the secretions are brought up.

Use of noninvasive ventilation in ALS

As the deterioration of muscle strength and respiratory function caused by ALS progresses, the need for ventilatory assistance should be considered. In recent years, nocturnal noninvasive positive-pressure ventilation (NIPPV) has become the treatment of choice for patients with chronic respiratory insufficiency due to ALS. The noninvasive ventilator is triggered by the patient's own breathing and reduces the work of breathing, improves the exchange of carbon dioxide and oxygen, and improves sleep quality. Furthermore, it has been shown to prolong survival as well as improve the quality of life in people with ALS who are able to use it regularly. Other beneficial effects of NIPPV in patients with ALS include improvements

in their overall quality of life and their cognitive functions. This includes measures of fatigue. Presently the accepted recommendation for starting NIPPV is an FVC (forced vital capacity test) of 50% expected or symptoms of respiratory failure (shortness of breath, daytime sleepiness, etc.).

Invasive ventilation

As ALS progresses, the person living with the disease may become increasingly dependent on ventilation and, ultimately, will require invasive ventilation with a tracheostomy (tube placement into the main breathing pathway, the trachea, through the neck.) This will provide more efficient ventilation and better control of the upper airway and secretions. The decision to proceed with tracheostomy and invasive ventilation is often difficult and is highly individual. During the decision making process there must be an ongoing educational program that includes the person living with ALS and their family and caregivers, along with healthcare professionals, as the decision can certainly change. As the person living with ALS considers whether to choose a ventilator program they should understand their insurance coverage, family support, level of independence, and financial resources. The choice of a home ventilation program requires supportive families and 24 hour supervision with family members and nurses. The cost of invasive ventilation has been estimated at \$153,252 - \$336,852 per year, most of which is the cost of home nursing. While few people living with ALS chose invasive ventilation and a home program, 90% of those people who are cared for at home were glad they chose to be ventilated and would choose to be ventilated again while 72% of those patients who were in nursing homes would make the same choice.

Withdrawal of care

If a person who is on a ventilator program decides that he/she would like to terminate ventilator support, a careful and thoughtful approach is necessary. There needs to be a complete discussion of the decision to terminate care and the ramifications of such action. Counseling to assure that the person understands the decision and treatment of depression is important. Once the decision is finalized, palliative care and sedation should be initiated as the ventilator is titrated off. Comfort care should be attended to by the physician throughout the process.

Table 1: Classification of Motor Neuron Diseases

- UMN:
 - Primary Lateral Sclerosis (PLS)
 - Familial Spastic Paraparesis
- LMN:
 - Spinal Muscular Atrophy (SMA)
 - Progressive Muscular Atrophy
 - Monomelic amyotrophy (one extremity with slow progression)
 - Brachial amyotrophic diplegia (progressive weakness of both arms with no bulbar or respiratory involvement)
 - Motor Neuropathy with or without conduction block *
 - Kennedy's Disease (an hereditary disease of the androgen receptor)
- UMN and LMN:
 - Amyotrophic Lateral Sclerosis (ALS)
 - Variants include Bulbar Palsy

* Motor neuropathy with conduction block is an important disease as it is treatable. It is an autoimmune disorder characterized by “conduction block” on Nerve Conduction studies, predominantly lower motor neuron clinical picture, the presence of anti GM1 antibodies (a blood test), and elevated spinal fluid protein. It responds to intravenous gamma globulin.

Table 2: Possible Contributing Mechanisms to Motor Neuron Death in ALS

- Defective glutamate metabolism
- Free radical injury
- Mitochondrial dysfunction
- Gene defects and RNA processing abnormalities
- Programmed cell death (apoptosis)
- Cytoskeletal protein defects
- Protein aggregation (clumping)
- Autoimmune dysfunction

Table 3: Members of the Multidisciplinary Team

Team Member	Role
Neurologist	The neurologist will help to diagnose your disease and direct care throughout the course of your illness. The neurologist will see you at your clinic visits and identify changes in function and direct symptom management.
Nurse Coordinator	The Nurse Coordinator acts as your liaison or “go-to person” anytime you have questions or needs. While at the clinic, the nurse coordinator helps to ensure that all of your issues are addressed with each team member. After your appointment, your Nurse Coordinator will assist you with questions, medication renewals or any problems or concerns that arise between your visits.
Mental Health Specialist	The role of mental health specialist is to provide counseling to you and your family. She is also available to other healthcare providers as a consultant on the psycho-social dynamics of ALS and can recommend strategies for the identified concerns.
Physical Therapist	The physical therapist will address mobility issues including walking, transferring from one place to another, and getting in and out of bed. Recommendations to optimize the performance of these activities will then be made based on the findings. Assistive technology is also discussed to help optimize independence.
Occupational Therapist	The occupational therapist will concentrate on areas of self-care (such as dressing, feeding, bathing, grooming, etc.), work and leisure activities. Use of adaptive devices or techniques will be recommended as appropriate. The occupational therapist works along with the physical therapist to evaluate home accessibility; wheelchair specifications and provide caregiver education.
Speech and Language Pathologist	The speech language pathologist will monitor the status of your speech and swallowing ability. Suggestions will be provided to ensure maximum effectiveness in communication. Alternative or augmentative devices will be introduced and reviewed as you may need them. Safe swallowing techniques and possible diet modifications will also be discussed.
Nutritionist	The Nutritionist will assess your nutritional status by discussing your current diet, challenges with eating or digestion, and weight changes. It is critical that you maintain proper nutrition in order to feel your best. The Nutritionist may recommend diet modifications that will enhance longevity and quality of life, such as using thickened liquids, eating softer or chopped food, and alternative modes of nutrition such as a feeding tube.
Respiratory Therapist	The respiratory therapist will perform an assessment of your respiratory muscle function including PFTs and examination of your breath sounds. The therapist will also address some issues with noninvasive ventilation and clearance of secretions working closely with your physician to optimize your ventilator status.

Case Management	The case manager will advocate on your behalf and help you with your individual, medical, or insurance needs. The case manager is able to coordinate appropriate services ordered by the physician, such as home physical therapy, occupational therapy, nursing, respiratory therapy, and hospice care.
Research Coordinator	The Research Coordinator is available to disseminate information about current ALS studies and provide further information to interested individuals. They will screen prospective participants, conduct the study sessions with those individuals who meet the criteria, organize data and medical records, and attend communicate with other research staff throughout the country as indicated.

Table 4: Medicines for symptoms		
Symptom	Physical Interventions	Medicines
Cramps	Positioning, stretching, massage, pool therapy	Magnesium 400-600mg/day, Vitamin E 400iu 2-3/day, Clonazepam, baclofen, zanaflex, Dilantin, tegretol, gabapentin, pregabalin
Anxiety	Counseling, biofeedback	Lorazepam, Ativan, Paxil, Buspar
Constipation	Fluids, fiber, fruit	Dulcolax, milk of magnesium, colace; miralax, lactulose
Phlegm and thick secretions	Hydration, suction machine, coughalator, vest, cut back on dairy	Guaifenesin, nebulizer treatment
Depression	Counseling	Antidepressants including SSRIs (Sertraline, Paroxetine, Citalopram, Escitalopram, Fluoxetine), SNRIs (Venlafaxine), and others (Bupropion, Mirtazapine)
Increased Secretions and Drooling	Suction Machine	Atropine, glycopyrrolate, scopolamine transdermal patch, hyosciamine, amitriptyline, Botulinum toxin, radiotherapy ablation
Dry Mouth	drinking extra fluids, review medications	
Twitching or Fasciculations		Baclofen, neurontin
Fatigue	Rest	Amantadine, methylphenidate, amphetamine and dextroamphetamine combinations, pyridostigmine If breathing problems contributing with increased CO2 then NIPPV (noninvasive ventilator or bipap)
Emotional Lability (laughing or crying too easily)		Neudexta, sertraline, amitriptyline
Laryngospasm		Baclofen, diazepam, omeprazole
Sleep disturbance	Sleep hygiene	Amytriptyline, trazodone, chloral hydrate, diphenylhydramine, lorazepam, temazepam, ambien If respiratory problems contributing NIPPV
Stiffness (Spasticity)	Range of motion, stretching, massage, pool therapy	Tizanidine, baclofen; dantrium, diazepam, Botox injections
Urgency	Toileting schedule	Oxybutinin

Table 5: Considerations in the management of respiratory complications of ALS

- Pneumovac and Flu vaccine
- Gastrostomy placement to maintain adequate nutrition
- Control secretions
- Aspiration (Food or secretions down the windpipe)
- Treat any underlying medical conditions and acute infections
- Identify and treat respiratory failure with NIPPV
- Invasive ventilation
- Withdrawal of care