# Understanding ALS
# for Planning Best Outcomes

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## Background

ALS (amyotrophic lateral sclerosis) is a degenerative disease of the motor neurons in adults. ALS is nicknamed "Lou Gehrig's Disease" after the New York Yankee baseball star whose career ended in 1939. Motor neurons are the nerve cells in the brain, brain stem and spinal cord that contract the skeletal (voluntary) muscles for moving the body, including the respiratory muscles for moving air in and out of the lungs.

Motor neuron degeneration causes progressive weakness and atrophy (wasting) of the affected skeletal muscles. This may include muscles which control walking, arm movements, speech, and swallowing. Not all people with ALS, however, lose the ability to walk, talk or swallow. Invariably, respiratory muscles become affected. This may occur at the disease onset or any time after the onset. Nevertheless, respiratory failure will eventually occur, unless prevented and treated by using noninvasive or invasive breathing support.

Because ALS selectively destroys motor neurons, ALS is a motor neuron disease. ALS is the most common degenerative disease of the motor neuron system. ALS and MND are abbreviations for amyotrophic lateral sclerosis and motor neuron disease, respectively. Internationally, the disease is referred to as ALS/MND. Since motor nerve loss affects the muscles, ALS is classified as a neuromuscular disease.

ALS can strike any adult of any age. The average ages of onset are 40's to 70's, although ALS most often occurs in people over their fifties. ALS affects men slightly more often than women. However, with increasing age, it is believed that ALS affects both men and women nearly the same.

The incidence of ALS in the USA is only an estimation. Tracking the accurate incidence of the disease has been challenging due to the widely scattered ALS population and multiple clinical settings where people with ALS are diagnosed. Other reasons are unawareness of the National ALS Registry or unwillingness of ALS patients to enroll in the registry. For many years, it has been believed that the incidence of ALS is similar to multiple sclerosis (MS). The prevalence of MS, however, is significantly higher than ALS because persons with MS can survive a lifetime. Factors which significantly lower survival and the prevalence of ALS are the underutilization of noninvasive breathing support and ineffective management of care.

The Ice Bucket Challenge of 2014 demonstrated that ALS is not such a rare disease. According to epidemiologists, the risk of getting ALS is 1 in 300 persons. Moreover, it is predicted that 600,000 people alive today in the USA will eventually get ALS during this generation. Thus, it is important for every person who is diagnosed with ALS in the USA to register with the National ALS Registry to assure being counted in the ALS census.

ALS does not typically affect a person's intellect, vision, sensation, or bladder and sexual function. Atypically, a small number of ALS persons develop frontotemporal dementia (FTD). Associated signs of FTD include alterations in behavior, personality, and language skills. FTD does not cause memory loss and must not be confused with Alzheimer's Disease.

ALS results in the progression of respiratory muscle weakness, causing hypoventilation (under-ventilation) of the lungs. Invariably, breathing failure will occur, unless hypoventilation is treated. People with ALS can choose short-term (noninvasive) or long-term (invasive) breathing support and survive well beyond respiratory failure. In fact, ALS itself is not fatal when breathing support is used and adequate ventilation is maintained.

People with ALS do not die directly from motor neuron degeneration, but from respiratory pump failure, if they so choose. ALS families need to know the options for breathing and living for achieving desired outcomes.

Currently, there is no treatment to stop ALS. Potential risk factors that may cause ALS are being investigated. Although ALS is incurable, ALS symptoms are manageable.

## Discovery of ALS

In 1869, Dr. Jean-Martin Charcot of the Salpêtrière Hospital in Paris, France, first identified and described ALS. Later, in 1874, he coined the name, Amyotrophic Lateral Sclerosis, based on his clinical and pathological findings of the disease outcomes. "Amyotrophic" refers to atrophy of the muscles; "lateral" refers to the motor nerve tracks that run down both outer sides of the spinal cord; and "sclerosis" refers to the hardening which is the result of the scarring that remains after the nerves disintegrate. Dr. Charcot is known as the Father of Modern Neurology for his years of study of patients with neurologic diseases, his publications, and his famous *Tuesday Lessons*. In the 19th century, the Salpêtrière became the birthplace of the field of neurology. Today, the historic center of neurology continues to have one of the largest ALS clinics in the world.

## How Motor Nerves Control Skeletal Muscles

**There are two sets of motor neurons: the upper and lower motor neurons.** The upper motor neurons extend their fibers called axons from the brain to the spinal cord, and the lower motor neurons extend their axons directly from the brain stem and spinal cord to the skeletal (voluntary) muscles for moving the body. Voluntary muscles are those that can be contracted consciously.

The cell bodies or nuclei of the motor neurons are headquartered in three specific regions: [1] the brain (cerebral motor cortex) [2] the brain stem and [3] the spinal cord (anterior horn cells in the gray matter).

**The upper motor neurons lie in the cerebral motor cortex**, which is a narrow arched strip along the frontal lobe of the brain from side to side. Upper motor neuron fibers called axons pass down through the corticospinal tracts of the spinal cord to make connections or synapses with the lower motor neurons which control muscle movements. Each small segment of the arch controls a specific muscle group for moving the toes, ankle, knee, hop, trunk, shoulder elbow, wrist, hand, fingers, thumb, neck, brow, eye, face, lips, jaw, tongue, and for swallowing.

**Signs of upper motor neuron involvement include:** muscle spasticity, loss of dexterity, impaired fine muscle movement, loss of muscle strength, slow movements, and limb stiffness.

**The lower motor neurons originate from two locations: the brain stem and the anterior horn cells in the gray matter of the spinal cord.**

**The brain stem is the stem-like part of the brain** that joins together the brain and spinal cord. In the brain stem lays the nerve cell group (nuclei) for most of the 12 pairs of cranial nerves. **The "bulbar region" of the brain stem consists of bulb-shaped structures**, called the medulla and pons.

The motor cranial nerves in the medulla (bulbar region) control muscles for speaking and swallowing. These include muscles in the throat (pharynx), tongue, larynx (voice box) and for controlling the gag/cough reflexes. The pons (bulbar region) governs facial and jaw movement and muscles for chewing.

**Signs of bulbar impairment include:** trouble forming words or impaired speech, impaired ability to swallow resulting in excessive oral secretions and saliva drooling, and impaired ability to chew food. Approximately 25% or more of people with ALS have bulbar involvement at the onset of the disease. Nevertheless, many people with ALS probably more than 25% never develop bulbar symptoms.

***People with ALS who have trouble talking and swallowing and have excessive oral secretions are referred to as being "bulbar." People with ALS who do not have trouble talking and swallowing and have no excessive oral secretions are referred to as being "nonbulbar."***

**The anterior horn cells are the lower motor neurons of the spinal cord.** Inside the entire length of the spinal cord is a cone of gray matter in the shape of the letter H. The anterior horn cells are located at the two anterior ends of the H. They send impulses through all the spinal root nerves branching from the anterior horn cells to the muscles, as these lower motor neuron axons branch throughout the body, extending to all the

skeletal muscle fibers. The anterior horn cells govern movement of all the extremities and trunk of the body. **In the spinal cord, anterior horn cells selectively disintegrate in ALS.**

The opposite two ends of the H on the posterior horns are the cell bodies of the sensory neurons which are unaffected in ALS. From each of the two posterior horns and anterior horns emerge nerve fibers into a root. One posterior and one anterior root from each side of the horn join together, forming a spinal nerve. Therefore, each spinal nerve arises from the anterior and posterior roots. **However, in ALS, only the anterior motor roots are affected, not the posterior sensory roots.**

**Thirty-one pairs of spinal nerves emerge from the spinal cord** through holes in the vertebral bones of the spinal column and extend to outlying body areas. Each pair of spinal nerves is named and numbered according to the name and level of the spinal cord segment from which it originates. There are 8 cervical (neck); 12 thoracic (between neck and lower back); 5 lumbar (lower back); 5 sacral (bottom of spine); and 1 coccygeal (final end of spine). The motor spinal nerves control muscles, according to their levels in the body, beginning at the neck and back of the head, down to the soles of the feet.

Death of the anterior horn cell bodies, leads to the degeneration of the associated motor axons, which are the peripheral nerve fibers that branch throughout the body to innervate the skeletal muscles and induce muscle contraction. Thus, failure to transmit power from the motor nerve cell bodies results in paralyzed muscle from dead axons. Affected muscles gradually atrophy or waste away.

**Signs of lower motor neuron involvement include:** muscle weakness and atrophy, flaccid (soft, flabby), muscles fasciculations which are fine, rapid, flickering muscle twitchings, while muscles are at rest, and muscle cramps.

**In Classic ALS** which involves both upper and lower neurons **the hallmark sign is the combination of both muscle weakness and spasticity.**

**The cardinal sign of ALS is muscle weakness. Signs of muscle weakness include:** difficulty walking, trouble climbing steps, foot drop, stumbling, trouble raising the arms, dropping things, difficulty turning door knobs and keys and performing tasks, inability to stand or sit upright due to trunk weakness, trouble with balance, and trouble with holding head upright if there is neck weakness. Not all people with ALS lose the ability to walk or lose use of their hands and arms.

All people with ALS, however, experience fatigue and some weight loss due to muscle shrinkage. Excessive weight loss due to impaired swallowing, inadequate nutrition, or loss of appetite is a preventable complication and may compound muscle weakness.

**Most importantly, it is necessary to know that ALS affects the nerves that govern the respiratory muscles for breathing in and out. The diaphragm is the principal muscle of inspiration or breathing in.** Breathing failure in ALS, is caused primarily by

inspiratory failure of the diaphragm. Exhalation requires much less work and is ordinarily a passive (inactive) process.

**Other muscles of respiration include the external and internal intercostals** which are muscles between the ribs **and the accessory muscles**, certain muscles of the neck, shoulders, chest and abdomen. The intercostals and accessory muscles assist the diaphragm for breathing. For a time, they can help compensate for diaphragm weakness. However, the intercostals and accessory muscles are unable to maintain respiration alone without a functional diaphragm. Eventually, respiratory failure occurs, unless mechanical ventilation (breathing support) is used and airway clearance is maintained. **The abdominal muscles play a key role for exhaling forcefully and coughing** to clear the upper and lower airways, as needed.

**Early "hallmark" signs of respiratory impairment that are often overlooked include:** inability to fully inhale and exhale, a weak cough and a reduced voice volume. These signs signal the need for pulmonary evaluation. Signs of early respiratory impairment may also include feelings of overall fatigue. **As respiratory muscle weakness advances, common symptoms include:** slow or rapid shallow breathing, inability to breathe when lying down, the need to sit upright to breathe (orthopnea), disrupted sleep, disrupted speech, frequent yawning, anxiety, restlessness, headaches, marked fatigue, daytime drowsiness, and visible signs of accessory muscle use. **Late symptoms if go untreated include:** shortness of breath/respiratory distress while sitting upright, paradoxical breathing - when the chest moves inward during inhalation instead of moving outward, excessive sleepiness, hallucinations and panic attacks.

## Pattern of Progression

No two people with ALS progress exactly the same. The onset of the disease begins in one of the three motor neuron levels: the brain, brain stem or spinal cord and gradually spreads to the other motor nerve cells. Which muscles lose function depend on which motor neurons are affected. Thus, muscle weakness initially begins in one group of muscles, gradually spreads to other muscles nearby in a sequence, and then to another region of the body. The rate of progression is different for everyone.

People diagnosed with ALS have either a limb, bulbar or respiratory onset of the disease. Approximately 25% or more have an onset in an arm or hand, 25% or more have an onset in a foot or leg; 25% or more have an onset in the bulbar muscles, and 10% or less have an onset in the respiratory muscles. A diagnosis of ALS may be overlooked or delayed in respiratory onset patients. Consequently, this may result in unexpected respiratory failure and unplanned outcomes. Also, people with a respiratory onset are always ambulatory and a high risk for respiratory failure and delayed treatment.

## Diagnosing ALS

In diagnosing ALS, a physical and neurologic exam is performed by a neurologist. The electromyogram (EMG) is a diagnostic test to determine abnormal nerve and muscle

activity. A definite diagnosis may not be possible in early ALS, since it may require a period of time to observe the progression of symptoms and to rule out other conditions that might mimic motor neuron disease. The diagnosis of ALS is based on the upper and lower motor neuron signs, according to the El Escorial Criteria that was established by the World Federation of Neurology.

**The diagnostic categories for ALS are:** [1] Definite ALS [2] Probable ALS and [3] Possible ALS.

## Three Subtypes or Forms of ALS

Some persons are diagnosed to have a form of ALS that usually evolves later to become Classic ALS (within months or years):

1. **Progressive bulbar palsy (PBP):** the "bulbar form" of ALS due to motor neuron involvement restricted to the brain stem, causing speech and swallow impairment.

2. **Progressive muscular atrophy (PMA):** the "lower motor neuron form" of ALS due to motor neuron involvement restricted to the spinal cord, resulting in limb and trunk weakness.

3. **Primary lateral sclerosis (PLS):** the "upper motor neuron form" of ALS due to motor neuron involvement restricted to the motor cortex of the brain, resulting in limb and bulbar dysfunction. The progression of PLS is usually very slow. People with PLS may survive many years, even decades. Living with long term disability is very challenging for people with PLS and their family caregivers.

## Sporadic Vs. Familial ALS

ALS can strike any adult of any age, anywhere in the world. About 90 percent of ALS cases are generally sporadic with no known family history of the disease.

Approximately 10% of people with ALS have familial ALS (FALS) in which at least one other family member has been affected with ALS. Inherited ALS is caused by a mistake in the genetic code that is passed down from one generation to the next. The most common genes known to cause FALS are C9ORF72, SOD1, TARDBP (TDP-43), and FUS.

Genetic testing can determine if a person has one of the discovered mutated genes. People with a history of the disease in their family members may wish to undergo genetic testing to see if they also have the gene. If they do, it does not mean that they will necessarily develop ALS. In fact, it is possible that risk factors may trigger the onset of FALS. Genetic counseling is an option for people with family members who have or had FALS.

## What Causes Sporadic ALS?

People with ALS want to know how they acquired the disease. The causes of sporadic ALS have yet to be proven. Potential risk factors that may trigger the onset of ALS are being investigated. These include: genetic, environmental, infectious (i.e., viral, prion), autoimmune, physical activity, trauma, and lifestyle factors. The discovery of ALS genes has revealed that mutation of genes predisposes to ALS, both in familial and sporadic cases. According to one of the most comprehensive genetic studies of ALS, genetics may play a larger role in causing ALS than previously believed, perhaps accounting for more than one-third of all cases of sporadic ALS. This reveals that genetic factors may be associated with an increased risk in developing ALS.

Studies have shown that changes in the nucleic acid of motor neurons trigger the onset of ALS. Evidence also suggests that "misfolded proteins" or toxic proteins are associated with damage and death of the motor neurons. Hereditary or acquired nucleic acid changes may increase the genetic risk of misfolded proteins.

A high level of physical activity has shown to be consistently associated with an increased risk for getting ALS. Also, some studies have shown that viral infections are risk factors for various neurodegenerative diseases and that viral pathogens may be linked to misfolded proteins and neurodegeneration. Service in the US military has also shown to be a risk factor for ALS. By understanding the mechanisms that can trigger motor neurons to degenerate, this will hopefully shed light on how to stop ALS and the progression of cell death.

## Treatment

To date, there is no known treatment to stop or slow the progression of motor neuron degeneration. Nevertheless, two drugs have shown possible therapeutic benefits for people with ALS. For more than 20 years, riluzole has been the only treatment available for ALS. Although the drug has no effect on muscle function, breathing function or the quality of life, the drug has shown that it may improve survival of ALS by approximately two to three months. Riluzole is not a cure and does not prevent, stop or reverse ALS. Riluzole inhibits the action of glutamate, an excitatory neurotransmitter that may contribute to motor neuron degeneration. Because of the high cost and limited benefits, many physicians do not prescribe the drug, unless the patients have adequate healthcare reimbursement to cover the expense. It is important to be aware that riluzole may cause loss of appetite. Thus, the drug should be used with caution in patients who have or had excessive weight loss.

In 2017, Radicava (edaravone) was approved by the U.S. Food and Drug Administration (FDA) for treating ALS, after a study in Japan showed that the drug reduced the decline in physical ability by 33%, compared to the placebo. The American developer of the drug is Mitsubishi Tanabe Pharma America (MT Pharma). Despite the possible benefits, Radicava may cause side effects. For further information about the current treatment, ALS patients need to contact their neurologists.

## Planning Best Outcomes

Although ALS is incurable, ALS is a manageable disease. Many methods are available to manage the progression of disability; enhance mobility, comfort and safety; maintain effective communication; achieve and maintain adequate nutrition; manage excessive saliva and oral secretions, cope with ongoing changes and losses, maintain adequate ventilation and achieve desired outcomes. As respiratory muscle weakness progresses, people with ALS have choices for breathing and living.

## LIFE CHOICES

1. **Noninvasive (nasal/oral) ventilation (NIV):** positive pressure air is delivered from a ventilator (small, portable machine) through the nose and/or mouth and into the lungs to support breathing. **NIV can be tolerated unless oral secretions become severe.**

2. **Tracheostomy invasive ventilation (TIV):** positive pressure air is delivered from a ventilator (small, portable machine) through a tracheostomy (surgical opening in the neck) and into the lungs to support breathing. TIV supports breathing beyond respiratory failure, despite severe oral secretions. Use of TIV can be long term. ALS patients have the right to stop TIV, if desired. Also, if TIV users are nonbulbar, they should have the right to transition to NIV, if they so desire.

***Nonbulbar ALS patients who can talk and swallow, and who do not have excessive oral secretions, they can tolerate noninvasive ventilation and do not need a tracheostomy to maintain adequate ventilation.**

3. **Comfort (hospice) care:** indicated if NIV is no longer tolerated due to severe oral secretions and tracheostomy invasive ventilation is not desired.

****** Education on life choices is necessary for making informed choices and fulfilling patient wishes. ******

***All people with ALS have the right to accurate, necessary and understandable information about ALS and options for breathing and living. People should know that ALS ultimately results in progressive respiratory muscle weakness and that breathing failure may be prevented or treated, if desired. All people with ALS should be given the choice to live, or if they so choose, to refuse or stop life-sustaining treatment and be given the right to comfort care.***

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