BMJ Best Practice

Amyotrophic lateral sclerosis

Straight to the point of care

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Summary

Amyotrophic lateral sclerosis (ALS) is a progressive disease characterized by degeneration of motor neurons with cortical, brainstem, and ventral cord locations.

ALS usually presents as a combination of upper motor neuron and lower motor neuron symptoms and signs, involving initially one segment of the neuroaxis (i.e., cranial, cervical, thoracic, or lumbosacral), and then progressively spreading, typically to contiguous areas.

Typical presentations include limb-onset and bulbar-onset ALS or, less frequently, respiratory-onset ALS. Generalization of the symptoms follows in time, without intervals of remission, exacerbation, or stabilization, resulting in progressive disability and death.

There is no cure for ALS. The focus of medical care is to provide supportive and palliative interventions, aiming to optimize the patient's quality of life. Riluzole prolongs survival and should be offered to patients at the time of diagnosis.

Continued discussions with the patient and their family regarding advance directives, as well as methods of respiratory and nutritional support, are critical. Palliative care options should be presented and discussed before they are needed.

Definition

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive muscle weakness that can start in limb, axial, bulbar, or respiratory muscles and then generalizes relentlessly, causing progressive disability and ultimately death, usually from respiratory failure. ALS is the most common form of motor neuron disease (MND), and the term ALS is often used synonymously with the term MND.

Epidemiology

The Global Burden of Disease Study 2016 estimated the worldwide all-age prevalence of all motor neuron diseases to be 4.5 per 100,000 people, with an increase in age-standardized prevalence of 4.5% over the period 1990 to 2016. The estimated all-age incidence was 0.78 per 100,000 person-years.[8] [9] An earlier analysis of ALS incidence per 100,000 population reported values of 2.1 for Europe, 1.8 in the US, and 0.6 in Asia.[10]

The mean age of onset of ALS is about 62 years, with a peak incidence between 60 and 75 years.[10] Limb-onset ALS occurs in about 70% of patients, and bulbar-onset disease in around 25% of patients.[11]

The prevalence of ALS is consistently reported to be higher in men than in women, with a ratio of 1.25:1.[9] [12] Some studies have reported that this difference disappears with age.[13]

There are no definite data regarding the distribution of ALS among people of different ethnicities, but a higher incidence in white people than in Asian, African, and Hispanic groups has been suggested.[10] [14]

Etiology

ALS is mostly a sporadic disease without a clear cause. However, there is an autosomal dominant genetic cause in 10% of people with ALS. In the 90% of patients without a monogenic cause, a single factor cannot be identified. A gene-time-environment hypothesis has been put forward, suggesting that genetic susceptibility, age-related cellular damage, and a burden of environmental exposures may combine to trigger ALS.[1]

Pathophysiology

ALS is a neurodegenerative disorder characterized by progressive loss of cortical (frontotemporal), bulbar (pons, medulla), and ventral cord motor neurons. After motor cell death, retrograde axonal degeneration follows, with subsequent denervation and reinnervation in corresponding muscles.

Although the mechanism of disease is unknown, several theories regarding pathophysiology have been proposed.

- Glutamate toxicity. Excessive extracellular levels of glutamate (excitatory neurotransmitter) result in increased calcium entry in neuronal cells, causing cell dysfunction - mitochondrial dysfunction and oxidative stress, and ultimately cell death. This may occur due to defective activity of glial glutamate transport proteins, with posttranslational defects in mRNA for these proteins being reported. The antiglutaminergic drug riluzole improves survival in patients with ALS, thus supporting a role for glutamate neurotoxicity.[15] [16]
- Protein misfolding. Aggregation of both wild-type and mutant proteins is a universal pathologic feature in sporadic and familial ALS.[17] Aggregated proteins can result in either gain-of-function pathology due to direct toxicity, or loss-of-function pathology via aggregates sequestering normal proteins and preventing normal function. For example, aggregation of the DNA- and RNA-binding proteins TDP-43 and FUS into inclusions impairs their normal function, causing changes to transcription and processing of RNA.[17]

- Oxidative stress. Superoxide radicals, oxygen, and hydrogen peroxide might induce neuronal damage and ultimately death through activation of the apoptotic pathway or by damaging neuronal mitochondria. Damaged mitochondria will also worsen oxidative stress.[18]
- Inflammation. There are inflammatory components to the pathophysiologic mechanism of ALS. However, the story around inflammation is complicated, as some components of inflammation are toxic in ALS and other components are protective.[17]
- Mitochondrial dysfunction. Mitochondrial impairment might cause neuronal degeneration and ultimately death through various mechanisms, including oxidative stress, calcium-mediated excitotoxicity, and activation of programmed cell death/apoptosis. Mitochondrial abnormalities are well documented in patients with sporadic as well as familial ALS.[19]
- Disrupted axonal transport. This might result from accumulation of neurofilament inclusions with subsequent slowing of the neurofilament transport and deficient dynein-dynactin complex, with dysfunction of retrograde axonal transport. Deficient axonal transport appears to relate to initiation and progression of the disease.[20]
- DNA and RNA metabolism. One of the core pathologic features of the majority of ALS cases is the presence of TDP-43 (TAR-DNA binding protein 43) aggregates. TDP-43 is known to have various functions in transcription, pre-mRNA splicing, and translation control. The finding that other ALS genes are also involved in RNA regulation (e.g., C9orf72 and FUS) emphasizes the importance of RNA biology to understanding ALS pathophysiology.[21] In normal cells, TDP-43 shuttles back and forth between the nucleus and the cytoplasm. The loss of nuclear TDP-43 induces accumulation of double-stranded DNA breaks, which could impair genome stability. In addition, aggregates of TDP-43, mutant FUS, and C9orf72 repeat expansions impair shuttling of cargo between the nucleus and the cytoplasm, which can negatively affect cell function.[17]

Classification

Motor neuron disease (MND) may be primary (neurodegenerative) or secondary (related to a non-neurodegenerative cause). Primary motor neuron diseases can be classified by phenotype, site of onset, and genetics. Patients should be assessed to determine if they have:

- Only upper motor neuron (UMN) signs, only lower motor neuron (LMN) signs, or both
- Only motor signs, or also nonmotor signs such as behavioral or cognitive changes
- Bulbar onset, limb onset, or respiratory onset (defined by the location of the first symptom)
- Hereditary MND or sporadic MND.

Primary motor neuron diseases

Amyotrophic lateral sclerosis (ALS)[1]

- The most common form of motor neuron disease (MND); the name is often used synonymously with the term MND.
- Represents a combination of UMN and LMN findings. Typical UMN findings include loss of coordinated movement, spasticity, muscle spasms, and hyperreflexia. LMN symptoms and signs are weakness with atrophy and fasciculations.
- ALS has a progressive, unrelenting course with median survival of 3-5 years.

Primary lateral sclerosis (PLS)[1] [2] [3]

- An isolated UMN disorder characterized by progressive weakness with generalized spasticity affecting speech, upper extremities, and lower extremities.

- Patients may go on to develop LMN features assessed either clinically or neurophysiologically, so that the disease evolves to "UMN-dominant ALS," but this is rare after 4 years from diagnosis.
- Survival is usually often greater than 10 years if there is no conversion to ALS.

Progressive muscular atrophy[2]

- An isolated LMN disorder characterized by progressive weakness, atrophy, and fasciculations.
- Some patients develop UMN symptoms and signs later during the disease course, converting into "LMN-dominant ALS."

Progressive bulbar palsy

- MND that remains isolated to the bulbar segment.
- Most patients with just bulbar involvement initially will progress to have limb involvement, converting to "bulbar-onset ALS."
- A minority of patients will remain as having progressive bulbar palsy.

Amyotrophic lateral sclerosis with frontotemporal dementia

- Presents as a combination of symptoms and signs suggestive of ALS and frontotemporal dementia.
- Cognitive deficits might include language, executive function, personality, and behavior. These features can precede or follow ALS symptoms.

Case history

Case history #1

A 60-year-old man presents with right foot drop, which has developed gradually over the last year and progressed to involve more proximal areas in the last 2 months. The patient reports associated muscle twitching and painful muscle cramps involving the same areas. The neurologic examination reveals bilateral lower-extremity weakness, more severe on the right, with associated spasticity, atrophy of the right foot intrinsic muscles, diffuse fasciculations, and hyperreflexia, with deep tendon reflexes being brisker on the right lower extremity, and a positive right Babinski sign. Sensation is preserved throughout. Several other family members have been diagnosed with ALS (some have died) with a pattern suggesting autosomal dominant disease.

Case history #2

A 65-year-old woman presents with progressive slurred speech with nasal quality, and episodes of choking on liquids, for the last 4-5 months. Neurologic examination reveals facial and tongue weakness, tongue muscle wasting and fasciculations, dysarthria, hypophonic speech, and brisk reflexes throughout (including jaw jerk).

Other presentations

ALS may present as upper motor neuron (UMN)-dominant ALS, lower motor neuron (LMN)-dominant ALS, or bulbar-onset ALS. Patients may present with associated cognitive and behavioral impairment that may precede the onset of motor neuron disease symptoms or may become evident late in the disease course. Some of these patients have sufficient frontotemporal impairments to meet the criteria for dementia.[4] [5] Patients may occasionally have associated extrapyramidal-type (parkinsonian)

symptoms, such as rigidity, resting tremor, postural instability, bradykinesia, or bradyphrenia. They may also present with a combination of UMN and/or LMN symptoms and signs, extrapyramidal signs, and frontotemporal-type cognition deficit. Patients with typical ALS may develop associated autonomic symptoms, such as urinary urgency, constipation, and perspiration, later in the course of the disease.[6] [7]

Approach

Any patient with symptoms suggestive of ALS should be referred to a neurologist without delay, and investigations performed with high priority.[35] [36] [37] Diagnosis is based on the presence of upper motor neuron (UMN) and lower motor neuron (LMN) signs, disease progression, and absence of any other explanation for the presentation. Diagnosis of ALS is primarily based on clinical criteria. A thorough history and physical examination are central to the diagnostic process, followed by electrodiagnostic testing when required for additional evidence of occult LMN involvement.

History

ALS presents as a combination of UMN and LMN symptoms and signs, involving initially any segment of the neuroaxis (i.e., cranial, cervical, thoracic, or lumbosacral) and then progressively spreading typically to contiguous areas, without intervals of remission, exacerbation, or stabilization. Patients will report insidious onset of focal weakness in the absence of pain or sensory symptoms, with symptoms worsening over time. Initial symptoms may include isolated dysarthria, hand weakness, foot drop, gait changes, or shortness of breath. On direct questioning, they may have noticed fasciculations, atrophy, muscle cramping, and sometimes weight loss.[37]

- Clinical presentation and disease course can be quite variable between patients.
- Asymmetric limb involvement is the most common presentation (70% of cases). Typically, weakness then progresses from the first limb affected to involve the ipsilateral limb or the same limb on the contralateral side. It is uncommon for weakness to progress noncontiguously from one limb to the limb diagonally across from it.[17] [21]
- If the disease initially involves the bulbar muscles (occurring in around 25% of patients), the next affected segment will typically be neck muscles with head drop, or cervical with involvement of one arm; and then the contralateral arm or ipsilateral leg. Uncommonly, progression of weakness in patients with bulbar onset can initially skip the cervical segment and involve the lumbar segment.
- Some patients may present with initial involvement of respiratory muscles (1% to 3%).[38]
- The time interval between the onset of symptoms affecting one segment of neuroaxis and progression to the next is variable. For example, patients with severe bulbar symptoms (e.g., dysarthria, dysphagia) might have preserved limb function for months.
- Up to 50% of patients will have concomitant cognitive or behavioral impairments, which can manifest as disinhibition, obsessive behaviors, impaired decision-making, and occasionally memory impairment.[5]

After elucidating symptom progression, it is important to obtain data regarding relevant family history of ALS, as well as other neurodegenerative conditions such as dementia and parkinsonism. Familial ALS represents about 10% of all ALS cases, the rest being sporadic.[22]

Dementia typically associated with familial ALS is frontotemporal dementia (FTD), which may have been labeled as Pick disease. However, patients with FTD sometimes are misclassified as having Alzheimer dementia, so a family history of Alzheimer dementia may be relevant. Similarly, patients with motor neuron disease can sometimes be misclassified as having parkinsonism.

Physical examination

ALS presents with a combination of UMN and LMN symptoms and signs in a given segment of neuroaxis. These clinical features may involve the limb, axial, bulbar, and/or respiratory muscles.

UMN signs consist of:

- Weakness in a pyramidal distribution
- Spasticity
- Hyperreflexia and other pathologic reflexes (usually found on examination): Babinski sign, Hoffmann or Trömner reflexes, crossed adductors (elicited by tapping the finger placed on the medial condyle of the femur or malleolus internus triggering contraction of the adductors of the thigh), exaggerated jaw jerk (elicited by percussion of the finger placed on the chin, with the patient's jaw relaxed and slightly opened), and re-emergence of primitive reflexes such as the palmomental reflex or the snout reflex.

LMN signs include:

- Weakness
- Atrophy
- Fasciculations.

The patient might present with limb and/or axial weakness, with associated hyperreflexia in the affected segments of the neuroaxis. Alternatively, the patient's presentation might be with respiratory dysfunction (i.e., dyspnea or orthopnea) and bulbar signs such as dysphagia, dysarthria, sialorrhea, and pseudobulbar affect (inability to control emotions, with uncontrolled crying and/or laughing). The dysarthria associated with ALS typically has mixed spastic and flaccid components. Symptoms of frontotemporal dementia may precede a diagnosis of ALS, or may occur during the disease course.

Testing to exclude alternate diagnoses that mimic ALS

Given that ALS is a clinical diagnosis, there are two reasons to perform laboratory and/or radiology evaluations. The first reason is to exclude alternate diagnoses that may resemble ALS, including neuropathies that affect only motor nerves or diseases that cause a combination of LMN and UMN signs due to anatomic compression of spinal cord and nerve roots.

- Neuroimaging is performed primarily to rule out alternative causes for the signs and symptoms. Imaging the most affected portion of the neuroaxis is indicated in all cases.[35]
- Nerve conduction studies are performed to evaluate the possibility of peripheral nerve disease mimicking ALS, such as multifocal motor neuropathy. The presence of severe slowing of motor conduction velocity or the finding of conduction block in motor nerves indicates the presence of an alternative etiology and eliminates ALS as the diagnosis.[39]
- If the nerve conduction studies suggest possible peripheral nerve disease, blood tests to assess vitamin B_{12} level and the presence of specific antibodies (anti-GM1, acetylcholine receptor, muscle-specific tyrosine kinase, and voltage-gated calcium-channel antibodies) may be indicated.
- In patients without clear bulbar signs, a combination of spinal cord and multiple spinal root compression may resemble ALS; magnetic resonance imaging is performed to rule out this possibility.
- Very rarely, infectious diseases may resemble ALS; lumbar puncture is occasionally performed to rule out such diseases. Cerebrospinal fluid analysis, if considered, should include routine studies with cytology.
- HIV testing may be considered if there is a history of exposure, and paraneoplastic antibody panels can be added if there is a history of malignancy.
- Creatine kinase may be elevated to a maximum of 1000 units/L as a consequence of denervated muscles in ALS. Higher levels suggest an alternate diagnosis.

Testing to assess LMN involvement in asymptomatic limbs

The second role of laboratory evaluation in patients with suspected ALS is to detect the presence of LMN disease in limbs that are clinically unaffected.[21] [40] [41]

- Electromyography (EMG) is performed for this purpose. Testing may be limited to the study of limbs in which clear symptoms or signs of LMN disease cannot be obtained. EMG of clinically unaffected limbs or muscles may demonstrate LMN disease and be diagnostic in patients whose clinical presentation is limited to one or two limbs.
- Abnormalities sought include the presence of fibrillation or fasciculation potentials, as well as enlarged, prolonged, and polyphasic motor units that indicate chronic axon loss with subsequent compensatory reinnervation.
- If initial results are equivocal, additional electrodiagnostic studies may include repetitive nerve stimulation and single-fiber EMG.
- The sensory nerve conduction studies should be normal.

Genetic testing

Guidelines recommend that all patients with ALS are offered genetic testing with an ALS gene panel that includes the C9orf72, SOD1, FUS, and TARDBP genes. Additional genetic testing is recommended for genes strongly and definitively associated with ALS as determined by ClinGen, and any gene for which there is an approved gene-targeted therapy.[24]

Genetic counseling and education should be provided for all patients with ALS, and this should precede the offer of testing. Pretest counseling should cover the range of possible testing outcomes, and prepare patients for possible personal, psychological, and economic impacts of testing on themselves and family members. Post-test counseling should also be provided, giving the patients the opportunity to discuss their result and understand the implications for them and their family.[24]

DIAGNOSIS

History and exam

Key diagnostic factors

upper extremity weakness (common)

- Results in difficulties performing activities of daily living, such as brushing teeth, dressing, and brushing hair. Can be the result of upper motor neuron (UMN) or lower motor neuron (LMN) weakness.

stiffness, with poor coordination and balance (common)

- Weakness as an UMN symptom is usually moderate, with progressive disability resulting from associated stiffness, poor coordination, and balance problems.

spastic, unsteady gait (common)

- May indicate UMN weakness affecting lower limbs.

painful muscle spasms (common)

- LMN symptom.

difficulties arising from chairs and climbing stairs (common)

- Caused by LMN weakness affecting proximal lower limbs.

foot drop (common)

- Caused by LMN weakness affecting distal lower limbs; associated with tendency to trip and fall.

stiffness and decreased balance with impact on gait (common)

- Caused by UMN-type truncal weakness.

head drop (common)

- Caused by neck extensor weakness; result of LMN-type axial weakness.

progressive difficulties maintaining erect posture, with stooping (common)

- Caused by paraspinal weakness; result of LMN-type axial weakness.

muscle atrophy (common)

- LMN symptom.

increased lumbar lordosis and tendency for abdominal protuberance (common)

- Caused by abdominal and paraspinal weakness; result of LMN-type axial weakness.

hyperreflexia (common)

- UMN sign.
- Hyperreflexia in an otherwise weak, atrophic limb is suggestive of motor neuron disease pathology. In a plegic, severely atrophic limb, the presence of even a trace of reflex is considered pathologic.
- Pathologic reflexes, such as Babinski sign, positive Hoffmann or Trömner reflexes, crossed adductors, or exaggerated jaw jerk can be found. Re-emergence of primitive reflexes such as the snout and palmomental reflexes may also be observed.
- An equivocal/mute Babinski sign is considered positive if the contralateral side is clearly negative.

dyspnea (common)

- Dyspnea and orthopnea result from progressive diaphragmatic weakness.
- Orthopnea causes frequent awakenings through the night, with subsequent lost sleep.

coughing and choking on liquids (including secretions) and eventually on food (common)

- Dysphagia of UMN type results from lack of coordination of the tongue and pharyngeal constrictor muscles.
- Dysphagia of LMN type results from actual weakness of the tongue and pharyngeal muscles.
- In both types, the consequence is dysfunction of the oral and pharyngeal phases of swallowing, with increased risk for aspiration.
- Although severe coughing triggered by aspiration of liquid or food is acutely distressing for patient and caregiver, it is very unusual for a patient with ALS to choke to death.
- With symptom progression, nutrition deficit and weight loss occurs.

strained, slow speech (common)

- Dysarthria of UMN type (i.e., spastic dysarthria) results from incoordination of the tongue, lips, and pharyngeal muscles.

slurred, nasal, and, at times, dysphonic speech (common)

- Dysarthria of LMN type results from actual weakness of the tongue, lips, palate, pharyngeal muscles, and, sometimes, vocal cords.
- Resulting speech is poorly articulated (slurred), hypophonic (nasal quality), and, at times, dysphonic (hoarse).

hypophonic speech (common)

- Poor respiratory support due to respiratory muscle weakness can cause a hypophonic speech pattern, whereby the voice is quiet and cannot be projected, and frequent breaks for breaths interrupt sentences.

Other diagnostic factors

propensity for falls (common)

- Can result from UMN or LMN weakness.

sialorrhea and drooling (common)

- Usually result from a combination of facial diplegia with poor lip seal and dysphagia.

inappropriate bursts of crying or laughing (common)

- Pseudobulbar affect, otherwise called emotional incontinence.
- Inappropriate bursts of crying or laughing are triggered by stimuli that would not be expected to cause such reaction, and are difficult to stop.

cognitive impairment (uncommon)

- Various domains of cognitive functions might be affected in a patient with ALS, including psychomotor speed, language, executive function, and memory.[42]
- Most prominent presentation is that of frontotemporal degeneration.

features of frontotemporal dementia (uncommon)

- May precede a diagnosis of ALS or may occur during disease course. Has a gradual onset and progression.
- May present with behavioral dysfunction (including emotional blunting, lack of insight, abnormal social conduct, irritability) and/or cognitive impairment (especially executive dysfunction, decreased word generation) with relative sparing of the memory.
- Presence in ALS may correlate with more rapid disease progression.[43] [44]

Risk factors

Strong

genetic predisposition or family history

- Familial ALS represents about 10% of all ALS cases, the rest being sporadic.[22] Most cases of hereditary ALS are indistinguishable from sporadic ALS.
- Patterns of inheritance involve predominantly autosomal dominant genetics, although less common autosomal recessive forms also occur.
- The most common cause of familial ALS (30% to 40% of cases) is hexanucleotide expansion in the C9orf72 gene. Normal numbers of the C9orf72 gene hexanucleotide repeat are less than 30, whereas patients with autosomal dominant ALS can have repeat lengths of 700 to 1600.[23] Patients with an expansion in C9orf72 can present with ALS, ALS with frontotemporal dementia (FTD), or FTD. Even within the same family, patients may have different phenotypic presentations.
- Other genes include SOD1 (15% to 20% of familial ALS cases), TARDBP, and FUS.[21] [24] More recently discovered genes associated with ALS include VCP, SQSTM1, TBK1, KIF5A, TIA1, CHCHD10, and OPTN.[22] Commercial panels can test for 30 associated ALS genes.

age >40 years

- ALS is rare in people under 40 years of age.[13] Mean age of onset of ALS is about 62 years, with a peak incidence between 60 and 75 years.[10] Age of onset is associated with rate of disease progression, with disease in younger patients tending to progress more slowly than in older patients.

Weak

military service

- An increased incidence of ALS has been reported among military veterans, although the quality of evidence is limited. Exposures to intense exercise, trauma/electric shock, or toxic agents are thought to be possible risk factors in this group.[25] [26][27]

professional athletic activity

- The risk of developing ALS may be higher in professional athletes, such as soccer and American football players, and seems to correlate with the number of years of exposure.[28] High amounts of lifetime physical activity can slightly increase the risk of developing ALS, particularly in people with a genetic predisposition.[29] [30]

cigarette smoking

- The risk of developing ALS increases with exposure to tobacco. There is a positive correlation with cumulative pack-years, duration of exposure, and (possibly) sex (i.e., female smokers might have an increased risk for developing ALS).[31] [32]

agricultural chemical exposure

- A positive association between ALS and occupational exposure to pesticides, herbicides, insecticides, fungicides, and fertilizers has been described.[33]

lead exposure

- Occupational exposure to lead (total lifetime exposure of 200 hours) was found to correlate with increased risk of ALS.[34]

Tests

1st test to order

Test	Result
clinical diagnosis • A thorough history and physical exam are central to the diagnostic process, followed by electrodiagnostic testing when required for additional evidence of occult lower motor neuron involvement.	**presence of upper and lower motor neuron signs, disease progression, and absence of any other explanation for the presentation**

Other tests to consider

Test	Result
electromyography (EMG) and nerve conduction studies • Evidence of diffuse, ongoing (fibrillation potentials and positive waves) and chronic (motor unit potentials with large amplitude and long duration) denervation involving muscles innervated by different nerves or roots in upper limbs, lower limbs (cervical, lumbosacral segments), and thoracic paraspinal muscles or tongue muscle (bulbar). • Can be normal or might show decreased compound motor action potential (CMAP) amplitude, with severe axonal loss. • The presence of severe slowing of motor conduction velocity or the finding of conduction block in motor nerves indicates the presence of an alternative etiology and eliminates ALS as the diagnosis.[39] • The sensory nerve conduction studies should be normal.[40] [41] • EMG of clinically unaffected limbs or muscles may demonstrate lower motor neuron disease and be diagnostic in patients whose clinical presentation is limited to one or two limbs.	**evidence of diffuse, ongoing, chronic denervation**
repetitive nerve stimulation • Rarely indicated, as myasthenia gravis should not be confused with ALS in most situations. • Abnormal in >50% of patients with ALS, but milder abnormalities than typical in myasthenia.	**only modest decreases in compound motor action amplitude after repetitive stimuli**
MRI brain and spine • In patients without clear bulbar signs, a combination of spinal cord and multiple spinal root compression may resemble ALS; imaging is performed to rule out this possibility.	**normal in ALS**
anti-GM1 antibodies • GM1 ganglioside antibody titer should be obtained in patients with suspected multifocal mononeuropathy; anti-GM1 antibodies are positive in up to 80% of patients with this condition, although this test does not have a high specificity.[45]	**usually negative in ALS**
voltage-gated calcium-channel antibodies • To rule out Lambert-Eaton syndrome.	**negative in ALS**
acetylcholine receptor (AChR) and muscle-specific tyrosine kinase (MuSK) antibodies • To evaluate for myasthenia gravis.	**negative in ALS**
vitamin B_{12} • Should be checked when the clinical picture consists of a combination of neuropathy and myelopathy.	**normal in ALS**
creatine kinase • Consequence of denervated muscles in ALS. Higher levels suggest alternate diagnosis.	**might be elevated to maximum of 1000 units/L**
lumbar puncture • Rarely necessary. CBC, glucose, protein, cytology.	**normal in ALS**
HIV test • To consider: HIV testing with a history of exposure.	**may be negative or positive**

Test	Result
genetic testing • Guidelines recommend that all patients with ALS are offered genetic testing with an ALS gene panel that includes the C9orf72, SOD1, FUS, and TARDBP genes. Additional genetic testing is recommended for genes strongly and definitively associated with ALS as determined by ClinGen, and any gene for which there is an approved gene-targeted therapy.[24] • Genetic counseling and education should be provided for all patients with ALS, and this should precede the offer of testing. Pretest counseling should cover the range of possible testing outcomes, and prepare patients for possible personal, psychological, and economic impacts of testing on themselves and family members, Post-test counseling should also be provided, giving the patients the opportunity to discuss their result and understand the implications for them and their family.[24]	**may be positive**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Cervical spondylosis with myelopathy and radiculopathy	• Presents with lower motor neuron (LMN) signs at lesion level and upper motor neuron (UMN) signs below the lesion level. • Usually has associated sensory symptoms and bladder and bowel disturbances.	• MRI cervical spine shows cord compression and multiple spinal root compressions.
Multifocal motor neuropathy	• Presents with LMN-only signs, involving one or both upper extremities. • Might begin with severe weakness in a limb without significant atrophy, with atrophy occurring later in the disease course.[46]	• Electrodiagnostic studies: multifocal nerve conduction block (with other locations than the usual entrapment sites). High GM1 ganglioside antibody titer (up to 80% of patients).[45]
Inclusion body myositis	• Slowly progressive. • Weakness affecting mainly the finger flexors and knee extensors. • There are no UMN signs.	• Electromyography: evidence for myopathy. • Clinical examination should not show UMN signs.
Monomelic amyotrophy	• Focal, predominantly LMN signs and symptoms, with usual occurrence in young people. • Commonly involves an upper extremity. • Severity of symptoms may progress over a few years while remaining limited to the initially involved limb.[47] • More frequent in Indian and Japanese populations.	• Clinical evaluation distinguishes this entity from ALS.
Myasthenia gravis	• Symptoms fluctuate. • Ocular symptoms (ptosis, diplopia, extraocular muscle dysfunction) are common. • UMN/LMN signs are absent. • Can mimic bulbar-onset ALS, if presents with dysphagia, dysarthria, or facial diplegia. • Weak but otherwise normal tongue in electromyography (EMG).	• Acetylcholine receptor or muscle-specific tyrosine kinase antibodies usually present. • Repetitive nerve stimulation may be abnormal in both conditions, but in ALS, the EMG of tongue and facial muscles shows ongoing and chronic denervation.
Benign fasciculations	• Focal or diffuse fasciculations, without other	• Electromyography shows only simple fasciculations,

Condition	Differentiating signs / symptoms	Differentiating tests
	neurologic symptoms or signs such as UMN signs, atrophy, or weakness.[48]	without any motor unit potential abnormalities.
Post-polio syndrome	• Only LMN symptoms. • Slow progressive course. • Occurs in the segments initially involved by polio a long time after the initial viral disease.[49]	• Clinical evaluation distinguishes this entity from ALS.
Primary lateral sclerosis	• An isolated UMN disorder. Slowly progressive weakness with associated spasticity. • May convert into UMN-dominant ALS if LMN features develop over time. • Progresses at a slower pace than ALS.[2] [3]	• Serial clinical evaluation provides data for diagnosis. Electromyography excludes the LMN signs.
Progressive muscular atrophy	• Isolated LMN disorder. • Progressive weakness, atrophy, and fasciculation. • Some patients develop UMN symptoms and signs later during the disease course, converting into LMN-dominant ALS.[2]	• Serial clinical evaluations used for diagnosis.
Progressive supranuclear palsy	• Characteristic abnormal eye movements: slowness of vertical saccades, progressing to vertical supranuclear gaze palsy, typically causing difficulty with tasks that involve looking downwards (e.g., reading, eating, walking downstairs). • Axial-predominant (trunk and neck) symmetric parkinsonism and/or freezing of gait - with a poor response to levodopa.[50]	• Brain MRI typically shows significant midbrain atrophy, resulting in various diagnostic radiographic signs in the midsagittal and axial planes.[51]

Criteria

Revised El Escorial criteria for ALS[52][53]

These criteria require the presence of upper motor neuron (UMN) signs (by clinical evaluation) and lower motor neuron (LMN) signs (by clinical, electrodiagnostic, or neuropathologic evaluation) involving the cranial, cervical, thoracic, and lumbosacral segments of neuroaxis, with progressive quality over time. These criteria

are mainly used to ensure a homogeneous population in clinical trials and are not particularly helpful in routine clinical practice.

Clinically definite ALS:

- Clinical evidence for UMN and LMN signs in 3 segments of neuroaxis.

Clinically probable ALS:

- Clinical evidence of UMN and LMN signs in at least 2 segments of neuroaxis
- Some of the UMN signs located rostral to the LMN signs.

Clinically probable-laboratory supported ALS:

- Clinical signs of UMN and LMN are present in 1 segment
- Or UMN signs are present in 1 region and LMN signs defined by electromyography criteria (acute denervation with reinnervation) are present in at least 2 regions, and other diagnoses were excluded.

Clinically possible ALS - criteria needed for clinically probable-laboratory supported ALS could not be met, and:

- Clinical signs of UMN and LMN are present in 1 segment
- Or only UMN signs are found in 2 or more regions
- Or LMN signs are found rostral to UMN signs, and other diagnoses were excluded.

Clinically suspected ALS:

- Only clinical signs of LMN or of UMN in 1 or more regions.

Awaji criteria[54]

The revised El Escorial criteria were felt to be too restrictive and limited early diagnosis of ALS, thus precluding many patients from involvement in clinical trials. Therefore, the World Federation of Neurology ALS group proposed a revision to the revised El Escorial criteria, called the Awaji criteria. The main change was that the Awaji criteria accept electromyography (EMG) fasciculations as evidence of acute denervation on EMG, whereas previously EMG had to demonstrate fibrillation potentials and/or positive sharp waves. Also, the Awaji criteria state that EMG evidence of denervation is equivalent to clinical bedside evidence, making the "clinical probable-laboratory supported ALS" category from the revised El Escorial criteria obsolete.

Gold Coast criteria[55]

The El Escorial criteria were felt to be overly complicated and prone to error. In addition, ALS clinicians were concerned that patients would perceive doubt in their diagnosis if they were told that they had "probable" ALS rather than definite ALS, when there was really no doubt. Therefore, in 2020 the World Federation of Neurology ALS group proposed new criteria for diagnosis of ALS, called the Gold Coast criteria:

1. Progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function, and
2. Presence of upper and lower motor neuron dysfunction in at least 1 body region (with upper and lower motor neuron dysfunction noted in the same body region if only 1 body region is involved) or lower motor neuron dysfunction in at least 2 body regions, and
3. Investigations excluding other disease processes.

Approach

Currently there is no cure for ALS, so the focus of medical care is to provide symptomatic management for all patients. Disease-modifying pharmacologic therapies to treat ALS include riluzole, edaravone, and sodium phenylbutyrate/taurursodiol.[11] [56] There is no evidence for a differential response to treatment between patients with familial versus sporadic ALS.[57]

Care of patients with ALS is best provided in a multidisciplinary ALS clinic, with a team comprising a respiratory therapist, physical and occupational therapists, a dietitian, a speech and swallowing specialist, a social worker, and other specialists as needed. This approach allows for optimization of care, and has been shown to be associated with improved survival, fewer hospital admissions, increased use of adaptive equipment, and better quality of life.[11] [58] [59] [60][61]

Immunizations, including pneumococcal vaccination, COVID-19 vaccination, and annual seasonal influenza vaccination, are recommended in patients with ALS, given the underlying chronic pulmonary dysfunction.

Informing patients and their families about the diagnosis, and ongoing counseling regarding prognosis, treatments, and end-of-life issues, with special emphasis on advance directives, are extremely important aspects of the patient-physician relationship.[11] [35][62] [63]

Pharmacologic therapy

Riluzole

All patients are started on riluzole at the time of diagnosis.[35] [64] [65] Riluzole prolongs survival in patients with ALS, with potential advantage in patients with bulbar onset.[11] [64][66] Annual survival benefit with riluzole is approximately 9%.[11]

Significant hepatic toxicity and neutropenia are associated with riluzole use, but are rare.[67] Liver function tests and complete blood count should be monitored monthly for the first 3 months, then every 3 months thereafter.[64] Nausea and lethargy are possible adverse effects of riluzole.[59]

Edaravone

Edaravone is a free radical scavenger that exerts neuroprotective effects by reducing oxidative stress in motor neurons. It is approved in the US and some other countries (but not in Europe) for treating ALS. Although one phase 3 randomized controlled trial did not show an overall benefit of intravenous edaravone in slowing ALS progression, a benefit has been demonstrated in a subgroup of patients.[68] [69] The effect of edaravone on survival was not evaluated in the study; one real-world analysis reported that intravenous edaravone was associated with prolonged overall survival in a large predominantly riluzole-treated US cohort.[70] However, one cohort study reported that although intravenous edaravone therapy for approximately 1 year was feasible and mainly well tolerated, no disease-modifying benefit was observed compared with standard therapy alone (riluzole).[71]

The treatment regimen for edaravone is very intensive, with treatment needed for 14 days initially, followed by treatment for a further 10 consecutive days a month as maintenance therapy. Edaravone is available in intravenous and oral formulations.

Sodium phenylbutyrate/taurursodiol

Sodium phenylbutyrate/taurursodiol is a combination of the salt of an aromatic fatty acid and a bile acid. The mechanism of action in patients with ALS is unclear. This combination therapy was demonstrated in one clinical trial to modestly slow progression of ALS over a 6-month period in patients with definite ALS (as defined by the revised El Escorial criteria) who had onset of symptoms within the previous 18 months. The magnitude of effect was similar to the effect size of edaravone over a 6-month period.[56] A larger confirmatory trial with expanded inclusion criteria is ongoing, with results expected in 2024. The combination drug received Food and Drug Administration (FDA) approval in 2022 and has conditional approval in Canada, but is not yet approved in Europe.

Symptomatic management

ALS is a progressive disease of the motor system and, as such, produces symptoms primarily relating to the location and degree of weakness. The exact treatment needs vary between patients, and will change with time for individual patients.[11] [35] [36] [59] [65] [72]

- Respiratory and nutritional support is critical, with the actual intervention required dependent on the status of the patient.
- Patients with significant weakness of bulbar musculature may require interventions for dysphagia, sialorrhea, and communication difficulties.
- Patients with weakness in the extremities may require support aimed at maintaining mobility, therapy for spasticity, or devices aimed at maintaining upper extremity function.
- Mental status changes that may require treatment include depression, anxiety, and pseudobulbar affect. Cognitive and behavioral changes associated with frontotemporal impairment may also require interventions.

General principles of respiratory dysfunction management

Patients with mild or moderate respiratory dysfunction may be entirely asymptomatic, or may have symptoms that are either nocturnal or exercise-related. Monitoring of respiratory function every 3 months is recommended by screening for subjective symptoms of respiratory insufficiency and objective signs of respiratory insufficiency.

Symptoms of respiratory insufficiency may be shortness of breath on exertion or at rest, orthopnea, frequent awakenings at night, early morning headaches or confusion (due to nocturnal hypercapnia), poor vocal projection, and poor cough efficacy.

Options for objectively monitoring respiratory function include forced vital capacity (FVC), slow vital capacity (SVC), and sniff nasal inspiratory pressure (SNIP).[11] [72] As supine FVC correlates well with symptoms of nocturnal hypoventilation, monitoring may be considered, along with erect FVC.[65] SNIP may be particularly useful in patients with bulbar weakness who might not be able to form a complete seal around the mouthpiece for obtaining FVC.[73] SNIP <40 cm H_2O has been found to be related to nocturnal hypoxia and has demonstrated a higher sensitivity for predicting 6-month mortality when compared with FVC <50%. In addition, nocturnal oximetry and/or sleep study can provide data regarding nocturnal hypoxia.[65] [72]

Symptomatic patients or asymptomatic patients with at least one of: FVC values of less than 50% to 65% of predicted value, or SNIP <40 cm H_2O, or abnormal nocturnal oximetry

Noninvasive ventilation (NIV) is indicated for these patients.[35][36] [58] [72] Historic guidelines have used a threshold for asymptomatic patients of FVC <50% of predicted value for initiation of NIV. More recent

expert-based best practice recommendations have suggested earlier initiation of NIV in asymptomatic patients, with a threshold of FVC <65% of predicted, because of evidence suggesting that NIV initiation at FVC around 50% is better than at FVC below 50%.[11] [72][74] All guidelines suggest NIV initiation for symptomatic patients, even if they have FVC >65%.

When NIV is prescribed, modification in pressure settings to ensure maximum comfort is often required, as is individual determination of the most appropriate interface (contact between ventilator and patient). Anxiolytic medication, such as lorazepam, might help with the process of adjustment to this type of treatment.

NIV is usually used initially at night, but with symptom progression can be used up to 24 hours per day. Patients usually need uptitration of NIV pressures as their respiratory function declines. Also, patients often require different interfaces for day use and night use as they increase their NIV usage, to avoid constant pressure points with a single mask and to allow for better integration with activities.[72] For example, some patients with ALS will still be able to speak if supported by a nasal-only interface for NIV during the day. Successful NIV use has been shown to have a positive impact on quality of life and survival.[65] [75]

Diaphragm pacing should not be used for patients with ALS because it is ineffective and may be harmful.[11] [76] [77]

Severe respiratory insufficiency not sufficiently treated with NIV

For patients who would consider long-term invasive ventilation, tracheostomy and permanent positive pressure ventilation can be life-prolonging.[65] [72][78]

Consideration of treatment should be preceded by revisiting advance directives and a thorough discussion regarding the type of care that is needed for patients with invasive ventilation. This discussion should take place well in advance of respiratory failure.[11] [62] [72] As caring for a patient on permanent mechanical ventilation requires a high level of skill and 24-hour support for management of the ventilator and deep suctioning, most often patients cannot be supported in a home environment and placement in a chronic hospital environment is required. Less than 10% of patients with ALS consider invasive ventilation.

With permanent ventilation in place, patients may survive a variable number of years. Invasive ventilation can be withdrawn any time at the patient's request, although it is recognized that this may become a difficult decision, particularly if the patient has developed cognitive impairment or has progressed to a locked-in state, with no means left to express their wishes.[11] [79]

For patients who would not consider long-term invasive ventilation and who have progressed to this degree of severity of respiratory dysfunction, care becomes palliative.[11] [62] Palliative care focuses on comfort, with special emphasis on symptomatic treatment of shortness of breath with opioids and/or benzodiazepines and consideration of concurrent support via NIV. Increased airflow in the room via an open window or fan can also be considered.[59] [80] [81]

Mild to moderate symptomatic dysphagia with mild weight loss (<10%)

For weight loss, the first step is diet modification. A dietitian should be involved to suggest nutritionally adequate substitutions. Diet modification with high-calorie supplements is usually effective in maintaining weight for a variable period of time, after which other options must be discussed.[82]

For management of dysphagia, texture modification of food can be suggested by a speech-language pathologist or occupational therapist trained in dysphagia assessment. Early intervention may include avoiding dry and particulate food. As dysphagia worsens, the swallowing assessor may suggest progression to pureed food and thickening of liquids.

Moderate symptomatic dysphagia with significant weight loss (>10%)

For patients who are unable to maintain a stable weight, percutaneous endoscopic gastrostomy (PEG) or radiologically inserted gastrostomy (RIG) tube placement should be suggested. Feeding tube placement should be discussed as part of the decision-making related to long-term care. Nutrition by feeding tube allows for weight stabilization and overall might have a beneficial impact on survival.[11] [35] [65][83] It has an uncertain impact on patient quality of life.[65] [83] [84]

Gastrostomy surgery should be considered before FVC decreases below 50% of its predicted value, to reduce the risks of perioperative morbidity associated with respiratory dysfunction, even if the patient does not have significant dysphagia at that time.[65] [85] If a feeding tube is placed presymptomatically, patients are encouraged to maintain the oral intake as tolerated, while the tube is only flushed with normal saline daily to maintain patency. Even with tube feeding, aspiration precautions should be maintained.

There is insufficient evidence on whether PEG or RIG tube feeding is better in terms of safety and clinical outcomes.[11] [86] RIG allows placement in patients with more advanced respiratory failure, but RIG tubes have been found to have a high rate of blocking, leaking, and needing to be replaced in the months after insertion.[86]

Dysarthria

Most (but not all) patients with ALS experience significant dysarthria progressing to anarthria. Speech therapy is usually not effective, so the most effective intervention consists of finding appropriate communication strategies to substitute for normal speech. This may include writing, as well as use of a variety of augmentative and alternative communication systems that can be activated with hand movements, facial movements, eye gaze, or whatever movement a given patient is able to perform.[11] [59][87][88] As the patient's mobility is progressively changing, close monitoring and regular reassessment is necessary to enable them to maintain effective communication ability.

Sialorrhea

Patients with dysphagia often experience drooling because of inability to swallow saliva. Symptomatic treatments usually consist of anticholinergic drugs such as hyoscyamine hydrobromide, amitriptyline, atropine, or glycopyrrolate.[11] [72]

For patients with refractory sialorrhea, rimabotulinumtoxinB (formerly known as botulinum toxin type B) may be considered.[11] [59] [72][89] If injected into each parotid and submandibular gland, it can interrupt saliva release; however, localization for injections is variable and the response is also variable. When effective, repeat injections are usually required at approximately 3-month intervals. Maximum benefit is usually experienced at 4 weeks.[90]

Low-dose radiation therapy to the salivary glands is also possibly effective in patients with medically refractory sialorrhea, although evidence is uncertain.[11] [59] [72][89] It may decrease saliva secretion for up to 6 months.[59] [90] [91]

Difficulty with mucus secretions

Reduced cough volume and strength may result in inability to expel pulmonary secretions. Mechanical cough assist devices may be very helpful, particularly if peak cough flow is reduced.[11] [65] [72] Carbocysteine is a mucolytic that can break down mucus, making it easier to clear, but it is not available in the US.[92] Other mucolytics such as nebulized acetylcysteine or oral guaifenesin can be tried.[11] Ensuring sufficient hydration and reduction in anticholinergics can potentially help with management of thick secretions. Occasionally, patients may elect to undergo tracheostomy to allow for more complete suctioning of airways, but this is uncommon.

Pseudobulbar affect

Occasionally patients with significant bulbar upper motor neuron signs will also display pseudobulbar affect, manifested by excessive or inappropriate laughing or crying. Most often, explanation of the etiology of these symptoms and reassurance are sufficient to allow patients to deal with this symptom.

If treatment is needed, the combination of dextromethorphan and quinidine has been found to be efficacious in controlling the pseudobulbar affect and is well tolerated.[11] [59] [93] Alternatively, amitriptyline may be considered for treating sleep problems and pseudobulbar affect, or a selective serotonin-reuptake inhibitor (SSRI) may be used to treat depression and pseudobulbar affect.[11]

Physical therapy for muscle weakness

Physical therapy is for maintenance of muscle elasticity and joint range of motion, to prevent contractures, and to determine the level of appropriate bracing and the need for ambulation devices. Such devices include ankle foot orthoses, cervical collars (neck weakness), canes, walkers, and wheelchairs. In each case, a range of devices is available, and the choice must be made by an experienced professional, taking into account the patient's needs and preferences.[61] Functional decline is an inevitable feature of ALS, so serial evaluations by physical therapists will be necessary throughout the course of the illness.

Individualized exercise programs of moderate intensity are considered safe and beneficial for patients with early disease.[11] [94] [95] These should be home-based and monitored by physical therapists, using telemedicine approaches if necessary.[61]

Occupational therapy for muscle weakness

The goal is to assess the needs of a patient in order to support their independence in performing activities of daily living and to assist with the care for patients with advanced disease. Examples include devices to assist with transfer from and to a wheelchair (e.g., bed rails, Hoyer-lift) and adapting the environment (e.g., ramps, shower chair, commode, powered hospital-type bed, modifying keyboards, adaptive utensils, accessible clothing).

Serial evaluations by occupational therapists will be required as the disease progresses, in order to define the patient's needs at different points in time.[11] [36]

Therapy for fully paralyzed patients

Treatment goals relate to maintaining skin integrity and comfort. Motorized beds and water and air mattresses can reduce pressure and vary sites of skin contact, preventing pressure ulcers and aiding in providing adequate pain control.[96]

Muscle spasms and spasticity

Muscle spasms are usually a reflection of spasticity, and are treated with exercises and antispasticity medication. Medications that may be considered include baclofen, tizanidine, botulinum toxin, benzodiazepines, and cannabinoids.[11] [59][97] [98] Antispasticity medications can sometimes worsen ambulation or transfer ability due to the emergence of underlying muscle weakness when limb tone is reduced, and benzodiazepines bring a risk of respiratory suppression.

Physical therapy for spasticity aims to reduce muscle tone, maintain range of motion and mobility, and improve comfort. Modalities include strengthening, stretching, and positioning exercises. Individualized exercise programs of moderate intensity are considered safe and beneficial for patients with early disease.[94] [95] Therapy to actively or passively perform range-of-motion movements will reduce tone as effectively as pharmacologic therapy, but is time-consuming and often requires family members or therapists to provide passive movements.

Depression and anxiety

Symptoms of depression and anxiety should be sought at every patient visit. The incidence of depression in patients with ALS is not well studied, but may be higher than in the general population, especially in those with advanced disease.[99] Depression is often well treated pharmacologically with an SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI).[11] [59] Because most patients with ALS eventually develop dysphagia, it is appropriate to consider initiating treatment with an antidepressant that can be safely crushed (by avoiding capsules or coated medications).

Evidence for psychological interventions for patients with ALS is limited, but there is some evidence of effectiveness for mindfulness and cognitive behavioral therapy for treating depression and anxiety.[100] [101]

Insomnia

If insomnia is a problem, it is important to determine the cause so that appropriate treatment can be started. If insomnia is related to respiratory insufficiency, nocturnal NIV may be an effective treatment. Other possible causes of insomnia include mood disorders and pain.[11]

Treatment of insomnia with benzodiazepines should generally be avoided in patients with ALS due to the risk of respiratory suppression. Non-benzodiazepine sleep medication such as melatonin or zopiclone can be considered.

Cognitive and behavioral impairment

Up to 45% of patients with ALS have associated cognitive and behavioral impairment, and in approximately 14% of patients these deficits are severe enough to meet criteria for frontotemporal dementia.[102] Symptoms may precede the onset of motor neuron disease symptoms, or may become evident late in the disease course.[4] [103] Screening for behavioral, cognitive, and language dysfunction should be carried out for patients with ALS.[11] [59] Interventions are generally supportive, as there is no evidence for effectiveness of pharmacologic therapies.

Palliative care

ALS does not have a cure, and weakness and functional deficits will progress throughout the disease course. Patients living with ALS should be supported using the principles of palliative care and, in particular, the use of a holistic approach to support patients and their families throughout the course of

their illness. Key components of palliative care in ALS are goals-of-care discussions, advance directive planning, symptom management, and end-of-life support.[11] [62] There are several models of palliative care that can be followed, including integration of palliative care into the multidisciplinary ALS clinic, separate involvement of a palliative care specialty team, home-based palliative care, telemedicine-supported care, and hospice care.

Advance directives and wishes for end-of-life care should be discussed with the patient and family/caregivers as early as possible, long before hospice care is needed, and should be an ongoing conversation.[62] [104]

Revisiting advance directives should precede discussions about starting hospice care and end-of-life management.[11] [59] [80] End-of-life management should focus on the patient's comfort and dignity.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing (summary)		
all patients		
	1st	**riluzole + supportive care**
	adjunct	**edaravone**
	adjunct	**sodium phenylbutyrate/taurursodiol**
with respiratory symptoms	**plus**	**noninvasive ventilation (NIV) or chronic invasive ventilation or palliative care**
with difficulty expelling mucus secretions	**plus**	**supportive respiratory management**
with dysphagia and weight loss	**plus**	**diet modification or feeding tube**
with dysarthria	**plus**	**alternative communication methods**
with drooling (sialorrhea)	**plus**	**pharmacotherapy or radiation therapy**
with muscle weakness	**plus**	**physical therapy and occupational therapy or palliative treatment**
with spasticity	**plus**	**pharmacotherapy + physical therapy**
with depression and/or anxiety	**plus**	**pharmacotherapy and/or psychological therapy**
with insomnia	**plus**	**treatment of underlying cause and/or pharmacotherapy**
with pseudobulbar affect	**plus**	**reassurance ± pharmacotherapy**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

all patients

1st **riluzole + supportive care**

Primary options

» riluzole: 50 mg orally twice daily
May be available as an oral tablet, oral dissolving film, or oral suspension, depending on the location. The oral dissolving film and oral suspension provide options for patients who have difficulty swallowing.

» All patients are started on riluzole at the time of diagnosis.[35] [64][65] Riluzole prolongs survival in patients with ALS, with potential advantage in patients with bulbar onset.[11] [64] [66] Annual survival benefit with riluzole is approximately 9%.[11]

» Liver function tests and complete blood counts should be monitored monthly for the first 3 months, then every 3 months thereafter; neutropenia can also occur but is rare.[64] [67] Nausea and lethargy are possible adverse effects.[59]

» Care of patients with ALS is best provided in a multidisciplinary ALS clinic, with a team comprising a respiratory therapist, physical and occupational therapists, a dietitian, a speech and swallowing specialist, a social worker, and other specialists as needed. This approach allows for optimization of care, and has been shown to be associated with improved survival, fewer hospital admissions, increased use of adaptive equipment, and better quality of life.[11] [58] [59] [60][61]

» Patients living with ALS should be supported using the principles of palliative care and, in particular, the use of a holistic approach to support patients and their families throughout the course of their illness. Key components of palliative care in ALS are goals-of-care discussions, advance directive planning, symptom management, and end-of-life support.[11] [35][62] [63] There are several models of palliative care that can be followed, including integration of palliative care into the multidisciplinary ALS clinic, separate

Ongoing

involvement of a palliative care specialty team, home-based palliative care, telemedicine-supported care, and hospice care.

» Advance directives and wishes for end-of-life care should be discussed with the patient and family/caregivers as early as possible, long before hospice care is needed, and should be an ongoing conversation.[62] [104]

» Revisiting advance directives should precede discussions about starting hospice care and end-of-life management.[11] [59] [80] End-of-life management should focus on the patient's comfort and dignity.

adjunct **edaravone**

Treatment recommended for SOME patients in selected patient group

Primary options

» edaravone: 60 mg intravenously once daily for 14 days followed by 14 days off for the initial treatment cycle, then 60 mg once daily for 10 days within a 14-day period followed by 14 days off for subsequent treatment cycles; 105 mg orally once daily for 14 days followed by 14 days off for the initial treatment cycle, then 105 mg once daily for 10 days within a 14-day period followed by 14 days off for subsequent treatment cycles
The oral suspension may be given orally or via a feeding tube. It is only available under a restricted distribution scheme in the US (this may vary between countries).

» Edaravone is approved in the US and some other countries (but not in Europe) for treating ALS. Although one phase 3 randomized controlled trial did not show an overall benefit of intravenous edaravone in slowing ALS progression, a benefit has been demonstrated in a subgroup of patients.[68] [69] The effect of edaravone on survival was not evaluated in the study; one real-world analysis reported that intravenous edaravone was associated with prolonged overall survival in a large predominantly riluzole-treated US cohort.[70] However, one cohort study reported that although intravenous edaravone therapy for approximately 1 year was feasible and mainly well tolerated, no disease-modifying benefit was observed compared with standard therapy alone (riluzole).[71] It may be used in addition to riluzole and sodium phenylbutyrate/taurursodiol.

Ongoing

adjunct **sodium phenylbutyrate/taurursodiol**

Treatment recommended for SOME patients in selected patient group

Primary options

» sodium phenylbutyrate/taurursodiol: 3 g (sodium phenylbutyrate)/1 g (taurursodiol) orally once daily for 3 weeks initially, followed by 3 g (sodium phenylbutyrate)/1 g (taurursodiol) twice daily

One packet contains 3 g of sodium phenylbutyrate plus 1 g of taurursodiol.

» Sodium phenylbutyrate/taurursodiol is a combination of the salt of an aromatic fatty acid and a bile acid. The mechanism of action in patients with ALS is unclear. The combination was demonstrated in one clinical trial to modestly slow progression of ALS over a 6-month period in patients with definite ALS (as defined by the revised El Escorial criteria) who had onset of symptoms within the previous 18 months. The magnitude of effect was similar to the effect size of edaravone over a 6-month period.[56] A larger confirmatory trial with expanded inclusion criteria is ongoing, with results expected in 2024. The combination drug received Food and Drug Administration (FDA) approval in 2022 and has conditional approval in Canada, but is not yet approved in Europe. It may be used in addition to riluzole and edaravone.

with respiratory symptoms **plus** **noninvasive ventilation (NIV) or chronic invasive ventilation or palliative care**

Treatment recommended for ALL patients in selected patient group

» Patients with mild or moderate respiratory dysfunction may be entirely asymptomatic, or may have symptoms that are either nocturnal or exercise-related. Monitoring of respiratory function every 3 months is recommended by screening for subjective symptoms of respiratory insufficiency and objective signs of respiratory insufficiency.

» Symptoms of respiratory insufficiency may be shortness of breath on exertion or at rest, orthopnea, frequent awakenings at night, early morning headaches or confusion (due to nocturnal hypercapnia), poor vocal projection, and poor cough efficacy.

» Options for objectively monitoring respiratory function include forced vital capacity (FVC), slow vital capacity (SVC), and sniff nasal

Ongoing

inspiratory pressure (SNIP).[11] [72] As supine FVC correlates well with symptoms of nocturnal hypoventilation, monitoring may be considered, along with erect FVC.[65] SNIP may be particularly useful in patients with bulbar weakness who might not be able to form a complete seal around the mouthpiece for obtaining FVC.[73] SNIP <40 cm H_2O has been found to be related to nocturnal hypoxia and has demonstrated a higher sensitivity for predicting 6-month mortality when compared with FVC <50%. In addition, nocturnal oximetry and/or sleep study can provide data regarding nocturnal hypoxia.[65] [72]

» NIV is recommended for patients with FVC of less than 50% to 65% of predicted value, or maximal SNIP <40 cm H_2O, or abnormal nocturnal oximetry.[35] [36] [58][72] Historic guidelines have used a threshold for asymptomatic patients of FVC <50% of predicted for initiation of NIV. More recent expert-based best practice recommendations have suggested earlier initiation of NIV in asymptomatic patients, with a threshold of FVC <65% of predicted, because of evidence suggesting that NIV initiation at FVC around 50% is better than at FVC below 50%.[11] [72][74] All guidelines suggest NIV initiation for symptomatic patients, even if they have FVC >65%.

» When NIV is prescribed, modification in pressure settings to ensure maximum comfort is often required, as is individual determination of the most appropriate interface (contact between ventilator and patient). Anxiolytic medication, such as lorazepam, may help with the process of adjustment to this type of treatment.

» NIV is usually used initially at night, but with symptom progression it can be used up to 24 hours per day. Patients usually need uptitration of NIV pressures as their respiratory function declines. Also, patients often require different interfaces for day use and night use as they increase their NIV usage to avoid constant pressure points with a single mask and to allow for better integration with activities.[72] For example, some patients with ALS will still be able to speak if supported by a nasal-only interface for NIV during the day. Successful NIV has been shown to have a positive impact on quality of life and survival.[65] [75]

» Chronic invasive ventilation is an option for patients with severe respiratory insufficiency not sufficiently treated with NIV. For those who would consider long-term invasive ventilation,

Ongoing

tracheostomy and permanent positive pressure ventilation can be life-prolonging.[65][72] [78]

» Consideration of treatment should be preceded by revisiting advance directives and a thorough discussion regarding the type of care that is needed for patients with invasive ventilation. This discussion should take place well in advance of respiratory failure.[11] [62] [72] As caring for a patient on permanent mechanical ventilation requires a high level of skill and 24-hour support for management of the ventilator and deep suctioning, most often patients cannot be supported in a home environment and placement in a chronic hospital environment is required. Less than 10% of patients with ALS consider invasive ventilation.

» With permanent ventilation in place, patients may survive a variable number of years. Invasive ventilation can be withdrawn any time at the patient's request, although it is recognized that this may become a difficult decision, particularly if the patient has developed cognitive impairment or has progressed to a locked-in state, with no means left to express their wishes.[11] [79]

» For patients with severe respiratory insufficiency who would not consider long-term invasive ventilation, care becomes palliative.[11] [62] Palliative care focuses on comfort, with special emphasis on symptomatic treatment of shortness of breath with opioids and/or benzodiazepines and consideration of concurrent support via NIV. Increased airflow in the room via an open window or fan can also be considered.[59] [80] [81]

with difficulty expelling mucus secretions **plus** **supportive respiratory management**

Treatment recommended for ALL patients in selected patient group

» Mechanical cough assist devices may be very helpful, particularly if peak cough flow is reduced.[11] [65] [72] Carbocysteine is a mucolytic that can break down mucus, making it easier to clear, but it is not available in the US.[92] Other mucolytics such as nebulized acetylcysteine or oral guaifenesin can be tried. Ensuring sufficient hydration and reduction in anticholinergics can potentially help with management of thick secretions. Occasionally, patients may elect to undergo tracheostomy to allow for more complete suctioning of airways, but this is uncommon.

with dysphagia and weight loss **plus** **diet modification or feeding tube**

Ongoing

Treatment recommended for ALL patients in selected patient group

» Frequently reported symptoms include choking, prolongation of meal times, and changes in diet due to decreased ability to swallow.

» For mild weight loss, dietary modification with high-calorie supplements under the care of a dietitian or nutritionist can stabilize the patient's weight for a variable period of time.[82]

» For management of dysphagia, texture modification of food can be suggested by a speech-language pathologist or occupational therapist trained in dysphagia assessment. Early intervention may include avoiding dry and particulate food. As dysphagia worsens, the swallowing assessor may suggest progression to pureed food and thickening of liquids.

» For patients who are unable to maintain a stable weight, percutaneous endoscopic gastrostomy (PEG) or radiologically inserted gastrostomy (RIG) tube placement should be suggested. Feeding tube placement should be discussed as part of the decision-making related to long-term care. Nutrition by feeding tube allows for weight stabilization, and overall might have a beneficial impact on survival.[11] [35] [65] [83] It has an uncertain impact on patient quality of life.[65][83] [84]

» Gastrostomy surgery should be considered before forced vital capacity (FVC) decreases below 50% of its predicted value, to reduce the risks of perioperative morbidity associated with respiratory dysfunction, even if the patient does not have significant dysphagia at that time.[65] [85] If a feeding tube is placed presymptomatically, patients are encouraged to maintain the oral intake as tolerated, while the tube is only flushed with normal saline daily to maintain patency. Even with tube feeding, the aspiration precautions should be maintained.

» There is insufficient evidence on whether PEG or RIG tube feeding is better in terms of safety and clinical outcomes.[11] [86] RIG allows placement in patients with more advanced respiratory failure, but RIG tubes have been found to have a high rate of blocking, leaking, and needing to be replaced in the months after insertion.[86]

with dysarthria **plus** **alternative communication methods**

MANAGEMENT

Ongoing

Treatment recommended for ALL patients in selected patient group

» Speech therapy is usually not effective, so the most effective intervention consists of finding appropriate communication strategies to substitute for normal speech. This may include writing, as well as use of a variety of augmentative and alternative communication systems that can be activated with hand movements, facial movements, eye gaze, or whatever movement a given patient is able to perform.[11] [59] [87] [88] As the patient's mobility is progressively changing, close monitoring and regular reassessment is necessary to enable them to maintain effective communication ability.

with drooling (sialorrhea) **plus** **pharmacotherapy or radiation therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» hyoscyamine: (0.125 mg/5 mL) 0.125 to 0.25 mg orally every 4-6 hours when required, maximum 1.5 mg/day

OR

» amitriptyline: 10 mg orally once daily at bedtime initially, increase gradually according to response, maximum 75 mg/day

OR

» atropine: 0.4 mg orally every 4-6 hours when required

OR

» glycopyrrolate: 1-2 mg orally twice or three times daily

Secondary options

» rimabotulinumtoxinB: consult specialist for guidance on dose

» Pharmacologic options include anticholinergics or rimabotulinumtoxinB (formerly known as botulinum toxin type B).[72]

» Anticholinergics decrease pharyngeal secretions and should be titrated to provide comfort.

Ongoing

» For patients with refractory sialorrhea, rimabotulinumtoxinB may be considered.[11] [59] [72][89] If injected into each parotid and submandibular gland, it can interrupt saliva release; however, localization for injections is variable and the response is also variable. Uncommonly, adverse effects may include worsening dysphagia, neck pain, and speech disturbance. More severe adverse effects include dyspnea with respiratory compromise.[105] When effective, repeat injections are usually required at approximately 3-month intervals. Maximum benefit is usually experienced at 4 weeks.[90]

» Low-dose radiation therapy to the salivary glands (e.g., a single dose of 7 Gy to 12.5 Gy) is possibly effective in patients with medically refractory sialorrhea, although evidence is uncertain.[11] [59] [72][89] It may decrease saliva secretion for up to 6 months.[59] [90] [91] Adverse effects may include sore throat, nausea, erythema, and persistent xerostomia.[59] [90]

with muscle weakness **plus** **physical therapy and occupational therapy or palliative treatment**

Treatment recommended for ALL patients in selected patient group

» Physical therapy is for maintenance of muscle elasticity and joint range of motion to prevent contractures, and to determine the level of appropriate bracing and the need for ambulation devices. Such devices include ankle foot orthoses, cervical collars (neck weakness), canes, walkers, and wheelchairs. In each case, a range of devices is available, and the choice must be made by an experienced professional, taking into account the patient's needs and preferences.[61]

» Individualized exercise programs of moderate intensity are considered safe and beneficial for patients with early disease.[11] [94] [95] These should be home-based and monitored by physical therapists, using telemedicine approaches if necessary.[61]

» The goal of occupational therapy is to assess the needs of a patient in order to support their independence in performing activities of daily living and to assist with the care for patients with advanced disease. Examples include devices to assist with transfer from and to a wheelchair (e.g., bed rails, Hoyer-lift) and adapting the environment (e.g., ramps, shower chair, commode, powered hospital-type

Ongoing

bed, modifying keyboards, adaptive utensils, accessible clothing).

» Serial evaluations by both physical and occupational therapists will be necessary as the disease progresses, in order to define the patient's needs at different points in time.[11] [36]

» In patients with severe generalized weakness, treatment goals relate to maintaining skin integrity and comfort. Motorized beds and water and air mattresses can reduce pressure and vary sites of skin contact, preventing pressure ulcers and aiding in providing adequate pain control.[36] [96]

with spasticity **plus** **pharmacotherapy + physical therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» baclofen: 5 mg orally three times daily initially, increase by 5 mg/dose increments every 3 days according to response, maximum 80 mg/day

OR

» tizanidine: 4 mg orally initially, increase by 2-4 mg/dose increments every 6-8 hours according to response, maximum 24 mg/day

OR

» onabotulinumtoxinA: consult specialist for guidance on dose

» Muscle spasms are usually a reflection of spasticity, and are treated with exercises and antispasticity medication (e.g., baclofen, tizanidine, botulinum toxin, benzodiazepines, and cannabinoids).[11] [59][97] [98] [106] Baclofen, tizanidine, and botulinum toxin (e.g., onabotulinumtoxinA) are approved in the US for the treatment of spasticity. Antispasticity medications can sometimes worsen ambulation or transfer ability due to the emergence of underlying muscle weakness when limb tone is reduced, and benzodiazepines bring a risk of respiratory suppression.

» Physical therapy for spasticity aims to reduce muscle tone, maintain range of motion and mobility, and improve comfort. Modalities include strengthening, stretching, and positioning

Ongoing

exercises. Individualized exercise programs of moderate intensity are considered safe for patients with early disease.[94] [95] Therapy to actively or passively perform range-of-motion movements will reduce tone as effectively as pharmacologic therapy, but is time-consuming and often requires family members or therapists to provide passive movements.

- **with depression and/or anxiety** — **plus** — **pharmacotherapy and/or psychological therapy**

  Treatment recommended for ALL patients in selected patient group

  » Symptoms of depression and anxiety should be sought for at every patient visit. The incidence of depression in patients with ALS is not well studied, but may be higher than in the general population, especially in those with advanced disease.[99]

  » Depression is often well treated pharmacologically with a selective serotonin-reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI).[11] [59] Because most patients with ALS eventually develop dysphagia, it is appropriate to consider initiating treatment with an antidepressant that can be safely crushed (by avoiding capsules or coated medications).

  » Evidence for psychological interventions for patients with ALS is limited, but there is some evidence of effectiveness for mindfulness and cognitive behavioral therapy for treating depression and anxiety.[100] [101]

- **with insomnia** — **plus** — **treatment of underlying cause and/or pharmacotherapy**

  Treatment recommended for ALL patients in selected patient group

  » If insomnia is a problem, it is important to determine the cause so that appropriate treatment can be started. If insomnia is related to respiratory insufficiency, nocturnal noninvasive ventilation (NIV) may be an effective treatment. Other possible causes of insomnia include mood disorders and pain.[11]

  » Treatment of insomnia with benzodiazepines should generally be avoided in patients with ALS due to the risk of respiratory suppression. Non-benzodiazepine sleep medication such as melatonin or zopiclone can be considered.

- **with pseudobulbar affect** — **plus** — **reassurance ± pharmacotherapy**

Ongoing

Treatment recommended for ALL patients in selected patient group

Primary options

» dextromethorphan/quinidine: 20 mg/10 mg orally once daily for 7 days, followed by 20 mg/10 mg twice daily thereafter

OR

» amitriptyline: 10 mg orally once daily at bedtime initially, titrate dose until symptomatic relief, maximum 75 mg/day

» Occasionally patients with significant bulbar upper motor neuron signs will also display pseudobulbar affect, manifested by excessive or inappropriate laughing or crying. Most often, explanation of the etiology of these symptoms and reassurance are sufficient to allow patients to deal with this symptom.

» If treatment is needed, the combination of dextromethorphan/quinidine has been found to be efficacious in controlling the pseudobulbar affect and is well tolerated.[11] [59] [93] Amitriptyline may be considered for treating sleep problems and pseudobulbar affect.

» A selective serotonin-reuptake inhibitor (SSRI) may also be used to treat depression and pseudobulbar affect; because most patients with ALS eventually develop dysphagia, it is appropriate to consider initiating treatment with an SSRI that can be safely crushed (by avoiding capsules or coated medications).[11]

Emerging

Stem cells

There has been substantial interest in the potential of stem cells to treat ALS. Trials have used different types and methods of delivery of stem cells. One phase 1/2 trial of implantation of human spinal cord-derived neural stem cells in the ventral horn of both cervical and lumbar spine of patients with ALS showed that injections can be performed safely.[107] Studies have been carried out on both peripheral and intrathecal injections of treated adult bone marrow-derived mesenchymal stromal cells (MSCs) designed to produce a variety of neurotrophic factors. One phase 3 study using intrathecally administered neurotrophic factor-secreting stem cells failed to reach its primary end point, but there was some improvement noted in biochemical markers.[108] Expert opinion is mixed as to whether this method and mechanism of stem cell delivery should continue to be developed or abandoned. One systematic review concluded there is a lack of high-quality evidence to recommend stem-based therapies and that further trials are needed.[109]

Masitinib

Masitinib is an anti-inflammatory agent that targets mast cells and microglia. One randomized controlled phase 2/3 trial reported slowing of decline of function in patients receiving masitinib in combination with riluzole, compared with placebo plus riluzole. Adverse events included maculopapular rash and peripheral edema.[110] [111] A phase 3 trial is under way.[112]

Ibudilast

Ibudilast is an oral, small-molecule phosphodiesterase and a macrophage migration inhibitory factor inhibitor, which suppresses pro-inflammatory cytokines and promotes neurotrophic factors. The pharmacokinetics, safety, tolerability, and efficacy of ibudilast on function, muscle strength, quality of life, and survival in ALS patients are being investigated in a randomized, double-blind, placebo-controlled, multicenter phase 2b/3 study.[113]

Tofersen

Tofersen (also known as BIIB067) is an investigational antisense oligonucleotide that reduces the levels of the abnormal protein superoxide dismutase 1 (SOD1) by binding to SOD1 mRNA. In one phase 1/2 trial, SOD1 concentrations were reduced in cerebrospinal fluid following intrathecal administration of tofersen over 12 weeks in adults with ALS due to SOD1 gene mutations.[114] Although a placebo-controlled phase 3 trial of intrathecal tofersen did not improve clinical end points, data from the open-label extension phase suggest that patients randomized to the treatment arm had improved outcomes during the open-label phase compared with patients receiving placebo initially.[115] The potential effects of earlier compared with later initiation of tofersen are being evaluated in an ongoing extension study.[116] The ATLAS study evaluating early treatment with tofersen in presymptomatic patients carrying a SOD1 mutation is under way.[117]

Reldesemtiv

Reldesemtiv is an activator of fast skeletal muscle troponin, which may improve the efficiency of muscle contraction in weak muscles. An international phase 3 study is evaluating whether reldesemtiv may slow the reduction in vital capacity or hand grip in patients with ALS.[118]

AP-101

AP-101 is a human monoclonal antibody designed to selectively target and reduce levels of misfolded SOD1, which can be seen in the pathology of both sporadic ALS and SOD1 hereditary ALS. This intravenous therapy is currently undergoing a phase 2 trial.[119]

SAR443820

SAR443820 (also known as DNL788) is an oral central nervous system-penetrant inhibitor of receptor-interacting protein kinase 1 (RIPK1), a signaling protein in the tumor necrosis factor pathway, which may reduce neuroinflammation and slow neuronal death. A phase 2 trial is under way.[120]

Trehalose

Trehalose is a low molecular weight disaccharide that crosses the blood-brain barrier and may reduce aggregation of misfolded proteins and activate autophagy to clear aggregated proteins. An intravenous formulation of trehalose is being evaluated as part of the Healey ALS platform trial.[121]

Secondary prevention

Immunizations, including pneumococcal vaccination, COVID-19 vaccination, and annual seasonal influenza vaccination, are recommended in patients with ALS, given their underlying chronic pulmonary dysfunction.

Patient discussions

Communication of the diagnosis and information relating to ALS should be tailored to the needs of the patient and their family. Not all patients will want detailed information about prognosis straight away. Patients should be asked about their preferences for involving their family members and/or other caregivers. Both verbal and written information about symptoms, management (especially nutritional and respiratory support), and specific treatments should be provided.[11] [36] [63] [72]

All patients with ALS should be offered genetic testing, and both pretest and post-test counseling. Pretest counseling should cover personalized risk assessments and the range of possible outcomes, and prepare the patient for possible personal, psychological, and economic impacts of testing on themselves and family members. Post-test counseling allows the patient to discuss their result and the implications for them and their family.[24]

Advance directives and wishes for end-of-life care should be discussed with the patient and family/caregivers as early as possible (but only when they are ready to do so), and long before hospice care is needed. Ongoing discussion of advanced care planning should be part of regular follow-up.[11] [36] [62]

Patients who have feeding tubes and their caregivers should be instructed in their use: for example, how to prevent clogging.[129]

The patient, and their family members and other caregivers, should be advised to seek immediate medical evaluation if the patient shows symptoms of severe respiratory dysfunction, especially when associated with fever.

Online information from recommended sources may be helpful for patients and families. [MDA (Muscular Dystrophy Association): ALS division] (https://www.mda.org/disease/amyotrophic-lateral-sclerosis)

FOLLOW UP

Monitoring

Monitoring

- Monitoring for respiratory decline (forced vital capacity) is recommended every 3 months, or as clinically indicated.[11] [36]
- Monitoring for nutrition deficit (weight and body mass index) is also recommended every 3 months, or as clinically indicated.[11]
- In patients taking riluzole, monitoring for hepatotoxicity (liver function tests) and neutropenia (complete blood count) should be done every month in the first 3 months and every 3 months afterwards.[11] [64] [128]
- Patients should be asked regularly about pain, mood disorders, and insomnia.[11]

Complications

Complications	Timeframe	Likelihood
respiratory failure	**variable**	**high**
Respiratory failure is an inevitable consequence of ALS. Early symptoms can be effectively treated with noninvasive ventilation, while severe end-stage respiratory failure requires either tracheostomy, with permanent assisted ventilation, or palliative care.		
nutritional deficit	**variable**	**medium**
Every effort should be made to ensure that ALS patients receive adequate nutrition throughout the course of their disease.		
aspiration pneumonia	**variable**	**medium**
In patients with dysphagia and difficulty with airway maintenance, choking and aspiration pneumonia may develop at any time. The risk for aspiration pneumonia persists in patients on tube feeds; thus, precautions against aspiration should be maintained after feeding tube placement.		
riluzole-related hepatotoxicity	**variable**	**low**
There is a risk of hepatotoxicity associated with the use of riluzole; however, with careful monitoring of liver function tests (LFTs), this adverse effect may be prevented. Drug should be discontinued if there is a persistent increase in LFTs, or with alanine aminotransferase exceeding 5 times the upper limits of normal.[128]		
riluzole-related neutropenia	**variable**	**low**
There is a rare risk of neutropenia associated with the use of riluzole. Close monitoring of CBC every month for the first 3 months and every 3 months thereafter is necessary during treatment. Drug must be discontinued if neutropenia is identified.[67]		

Prognosis

ALS follows a progressive course without intervals of remissions, relapses, or stabilization, causing progressive disability and ultimately death. The disease is highly variable between affected individuals in terms of clinical presentation and time course. Median survival is 3-5 years, but survival for up to 10 years and even beyond (in approximately 10% to 20% of patients) has been reported.[21] [122] [123]

Prognostic factors

Prognostic factors associated with more prolonged survival include:

- Treatment with noninvasive ventilation (NIV)[123]
- Enteral nutrition[84]
- Younger age at diagnosis[124] [125]
- Limb onset[124] [126]
- Baseline forced vital capacity (FVC) of >75% (median survival 5 years)[126]
- Longer time from symptom onset to diagnosis.[125]

Prognostic factors associated with worse outcome include:

- Older age at diagnosis
- Bulbar onset
- Comorbidity with frontotemporal dementia
- Baseline FVC of <75%
- Substantial weight loss.[127]

The rate of symptom progression is considered to be an independent prognostic factor.[123]

Diagnostic guidelines

International

Evidence-based consensus guidelines for ALS genetic testing and counseling#(https://onlinelibrary.wiley.com/doi/10.1002/acn3.51895) [24]

Published by: ALS Genetic Testing and Counseling Guidelines Expert Panel **Last published:** 2023

A proposal for new diagnostic criteria for ALS (https://www.sciencedirect.com/science/article/pii/S1388245720301383) [55]

Published by: World Federation of Neurology ALS group **Last published:** 2020

El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis (https://pubmed.ncbi.nlm.nih.gov/11464847) [53]

Published by: World Federation of Neurology Research Group on Motor Neuron Diseases **Last published:** 2000

Clinical management of amyotrophic lateral sclerosis (MALS) – revised report of an EFNS task force (https://www.ean.org/research/ean-guidelines/guideline-reference-center) [35]

Published by: European Academy of Neurology (European Federation of Neurological Societies) **Last published:** 2012

Treatment guidelines

International

Respiratory management of patients with neuromuscular weakness (https://www.chestnet.org/Guidelines) [72]

Published by: American College of Chest Physicians **Last published:** 2023

Clinical guidance in neuropalliative care: an AAN position statement (https://n.neurology.org/content/98/10/409) [62]

Published by: American Academy of Neurology **Last published:** 2022

Canadian best practice recommendations for the management of amyotrophic lateral sclerosis (https://als.ca/research/als-canada-research-program/canadian-best-practice-recommendations-for-the-management-of-als) [11]

Published by: ALS Canada **Last published:** 2020

Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (https://www.aan.com/Guidelines/Home/Search?topic=Neuromuscular) [59]

Published by: American Academy of Neurology **Last published:** 2009 (reaffirmed 2023)

Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (https://www.aan.com/Guidelines/Home/Search?topic=Neuromuscular) [65]

Published by: American Academy of Neurology **Last published:** 2009 (reaffirmed 2023)

EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) - revised report of an EFNS task force (https://www.ean.org/research/ean-guidelines/guideline-reference-center) [35]

Published by: European Academy of Neurology (European Federation of Neurological Societies) **Last published:** 2012

Motor neurone disease: assessment and management (https://www.nice.org.uk/guidance/ng42) [36]

Published by: National Institute for Health and Care Excellence **Last published:** 2019

Online resources

1. MDA (Muscular Dystrophy Association): ALS division (https://www.mda.org/disease/amyotrophic-lateral-sclerosis) *(external link)*

Key articles

- Shoesmith C, Abrahao A, Benstead T, et al. Canadian best practice recommendations for the management of amyotrophic lateral sclerosis. CMAJ. 2020 Nov 16;192(46):E1453-68. Full text (https://www.cmaj.ca/content/192/46/E1453) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33199452?tool=bestpractice.bmj.com)

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

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numerals < 1: 0.25

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