Clinical care of patients with amyotrophic lateral sclerosis

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Although amyotrophic lateral sclerosis and its variants are readily recognised by neurologists, about 10% of patients are misdiagnosed, and delays in diagnosis are common. Prompt diagnosis, sensitive communication of the diagnosis, the involvement of the patient and their family, and a positive care plan are prerequisites for good clinical management. A multidisciplinary, palliative approach can prolong survival and maintain quality of life. Treatment with riluzole improves survival but has a marginal effect on the rate of functional deterioration, whereas non-invasive ventilation prolongs survival and improves or maintains quality of life. In this Review, we discuss the diagnosis, management, and how to cope with impaired function and end of life on the basis of our experience, the opinions of experts, existing guidelines, and clinical trials. We highlight the need for research on the effectiveness of gastrostomy, access to non-invasive ventilation and palliative care, communication between the care team, the patient and his or her family, and recognition of the clinical and social effects of cognitive impairment. We recommend that the plethora of evidence-based guidelines should be compiled into an internationally agreed guideline of best practice.

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Introduction

Amyotrophic lateral sclerosis (ALS or motor neuron disease) is a progressive neurodegenerative disease associated with loss of upper and lower motor neurons. Charcot, the 19th century pioneer of neurology, first defined the syndromes that could be gathered under the umbrella of ALS before laying the groundwork for current approaches to clinical diagnosis.[1,2] Despite developments in histopathological techniques, the introduction of clinical neurophysiology, and the use of neuroimaging techniques, the diagnosis of ALS is still made at the clinic or bedside by an experienced neurologist with techniques that were available at the turn of the nineteenth century. Although in most patients ALS presents as a motor disorder, it is now recognised as a multisystem disease with extramotor involvement.[3–12] Cognitive impairment of the frontal lobe type and even frontotemporal dementia are not uncommon in patients with ALS.[13–16] No population-based studies of the prevalence of cognitive changes have been published; therefore, estimates of the prevalence of the neuropsychological abnormalities in ALS range from 20–50% and depend on the patient sample. In some ALS clinic samples, the criteria for frontotemporal dementia are met in about 40% of people.[13,15,16]

The management of patients with ALS has changed rapidly over the past 20 years. Although ALS is incurable, it is treatable. Recommendations and guidelines for the care of patients with ALS have been compiled on both sides of the Atlantic (table 1).[17–22] The recommendations of the American Academy of Neurology (AAN) ALS Practice Parameter were compared with the baseline features of the management of patients with ALS in the 3 years before the AAN ALS Practice Parameter was published.[23] Many patients with ALS received the care set up by the AAN ALS Practice Parameter, but only 30% of patients with significant dysphagia had a gastrostomy tube, and less than 10% of patients with a forced vital capacity of less than 40% of the predicted value, and only 28% of those with severe dyspnoea, received non-invasive ventilation. The standards of management for 2001–2002 showed an improvement, although many patients still did not have a gastrostomy tube or receive non-invasive ventilation;[24] however, these findings are biased because they are from a self-selected patient group, rather than from a population-based group of patients.

The European Federation of Neurological Societies task force on the management of ALS has recently done an objective appraisal of the evidence on the clinical management of patients with ALS and has established evidence-based and patient and carer-centred guidelines.[19] Recommendations for the management of nutrition,[20] respiration,[21] and the end-of-life care of patients with ALS have also been defined.[22]

In this Review, we discuss post-diagnosis management interventions, coping with impaired function, and end-of-life and post-death care. It should be bourne in mind that there are now several published guidelines (some with little user involvement) that present some significantly different conclusions (eg, thresholds for starting assisted ventilation). The aim of this Review is to place these guidelines in a pragmatic, clinical context on the basis of the experience of two major ALS clinical care and research centres. Where the evidence base in areas covered by this Review is weak, we have tried to indicate what is expert opinion, derived from published consensus guidelines, by providing relevant references and what is our own opinion.

	Evidence-based	Scope	User involvement	Audited
AAN, 1999[17]	Yes	All aspects of care	Yes	Yes
ABN, 1999[18]	No	All aspects of care	No	No
EALSC, 2005[19]	Yes	All aspects of care	No	No
MNDA Nutrition, 2004[23]	Yes	Focused on nutrition	Yes	No
MNDA Respiration, 2006[24]	Yes	Focused on respiration	Yes	No
ALSA End-of-life, 2005[22]	Yes	Focused on end of life	Yes	No

AAN=American Academy of Neurology Practice Parameter. ABN=Association of British Neurologists Exerpta Medica MND Advisory Group. EALSC=European ALS Consortium. MNDA=Motor Neurone Disease Association. ALSA=Amyotrophic Lateral Sclerosis Association Peer Working Group on End-of-Life Care.

Table 1: **Published guidelines for the care of patients with amyotrophic lateral sclerosis**

Diagnosis and clinical progression

No specific test for ALS is available, and diagnosis is usually made by clinical evaluation supported by electrophysiological confirmation. The diagnosis of ALS should be made as early as possible, and patients suspected of having ALS should be fast-tracked through the health system to avoid delays. The delay from onset of the disease to confirmation of the diagnosis can vary from between 13 and 18 months.[25, 26]

Up to 10% of patients who are initially diagnosed with ALS might have other disorders,[27,28] and this figure is greater for specific types of ALS. Progressive spinal muscular atrophy, cervical radiculomyelopathy, thoracolumbar-sacral disc disease, multifocal motor neuropathy, chronic inflammatory demyelinating neuropathy, adult-onset spinal muscular atrophy, myasthenia gravis, spinobulbar muscular atrophy (Kennedy's disease), multiple sclerosis, cerebrovascular disease, and multiple system atrophy have been misdiagnosed as ALS.[27–29] The factors that guide clinicians to the correct diagnosis include the lack of progression, the development of atypical symptoms, and the results of additional investigations.[27,28] Therefore, it is advisable for patients with a suspected diagnosis of ALS to have brain and spine imaging, chest X-ray, routine laboratory tests, and electrophysiological studies, although, in our view, MRI of the brain or spinal cord might not be needed in patients with widespread upper and lower motor neuron signs (definite ALS, as defined by the El Escorial criteria). Difficulties in the diagnosis arise when patients present with only upper or lower motor neuron signs. Although the prognosis might be better in patients with only upper or lower motor neuron signs, a physician must weigh the balance of probability and decide whether or not the patient has ALS. In these circumstances, an honest explanation of the basis for doubt and periodic review are required and, in our view, a second opinion is desirable.

Assessment of disease progression is difficult. Several different functional scales, new neurophysiological tests, and imaging techniques have been developed but none of these has sufficient diagnostic or prognostic certainty.[30,31] The most useful clinical measures are vital capacity[32] and the revised ALS functional rating scale.[33–35]

About 50% of patients survive for about 30 months from the onset of symptoms,[26,36] although some survive beyond 10 years, which is an important source of hope for people with ALS.[37] In the King's ALS Centre population, 4% of patients survived for more than 10 years:[37] the patients who survived the longest were younger and had mostly upper motor signs at presentation. Furthermore, their survival was not obviously influenced by treatment: only 8 out of 30 of the longest-suviving patients received riluzole, one had percutaneous gastrostomy, and none received assisted ventilation. Bulbar onset of ALS or definite ALS at presentation, as defined by the El Escorial criteria, were associated with survival of more than 10 years.[38] Poor prognosis with bulbar onset disease depends on confounding variables, such as being older at onset or being assigned a higher El Escorial category at presentation.[39]

Long survival times are also seen in primary lateral sclerosis or in predominantly lower motor neuron syndromes, such as the flail arm syndromes (man in a barrel syndrome or Vulpian–Bernhardt syndrome) or flail leg syndrome (table 2).[40–44] Degeneration of the motor cortex and corticospinal tracts is seen in patients with flail arm syndrome,[40] and 50–70% of patients with flail limb syndrome develop upper motor neuron signs later in the disease. A mutation in *SOD1,* the gene encoding superoxide dismutase 1, has also been found in a patient with flail arm syndrome.[45] Flail limb syndrome might have a better prognosis than ALS, which is important because about 10% of all patients diagnosed with ALS have flail limb syndrome.[41,46] In other distinct lower motor neuron disorders, such as monomelic juvenile onset amyotrophy (Hirayama's syndrome), progressive weakness in the initial phase is followed by stabilisation and a lack of spread to other areas.[47,48] A monomelic form of ALS has been reported in two people with the D90A mutation in *SOD1.*[49]

Although some researchers have argued that primary lateral sclerosis is separate from ALS—patients with primary lateral sclerosis lack lower motor neuron signs and thus do not meet the El Escorial criteria for ALS—other investigators have shown electrophysiological evidence for lower motor neuron involvement, albeit less pronounced than it is in ALS.[44] The primary lateral sclerosis phenotype can also be a part of the clinical spectrum of familial ALS, which indicates common underlying pathogenic mechanisms.[50] Clinically, primary lateral sclerosis can be defined by isolated upper motor neuron signs that occur 3 years after the onset of symptoms and is a slowly progressing syndrome.[51,52] Upper motor neuron-dominant ALS, which has only minor lower motor neuron signs, has disability similar to ALS but has a slower progression.[53]

	Number of patients	M:F	Onset (years)	Mean duration of symptoms (months)
Flail arm[40]	8	3:1	60·0	55·5
Flail arm[41]	39	9:1	58·0	57·0
Flail arm[42]	9	8:1	60·3	76·3
BAD[43]	10	1.5:1	53·3	66·0
PLS[44]	20	3:1	53·4	102·0

BAD=brachial amyotrophic diplegia. M:F=male:female. PLS=primary lateral sclerosis.

Table 2: **Mild forms of amyotrophic lateral sclerosis**

Strategy for care

The autonomy of the patient should be respected when care is planned. The care plan should be made on the basis of accepted guidelines that are interpreted with common sense—an inherent flaw of evidence-based guidelines is publication bias. There are several phases

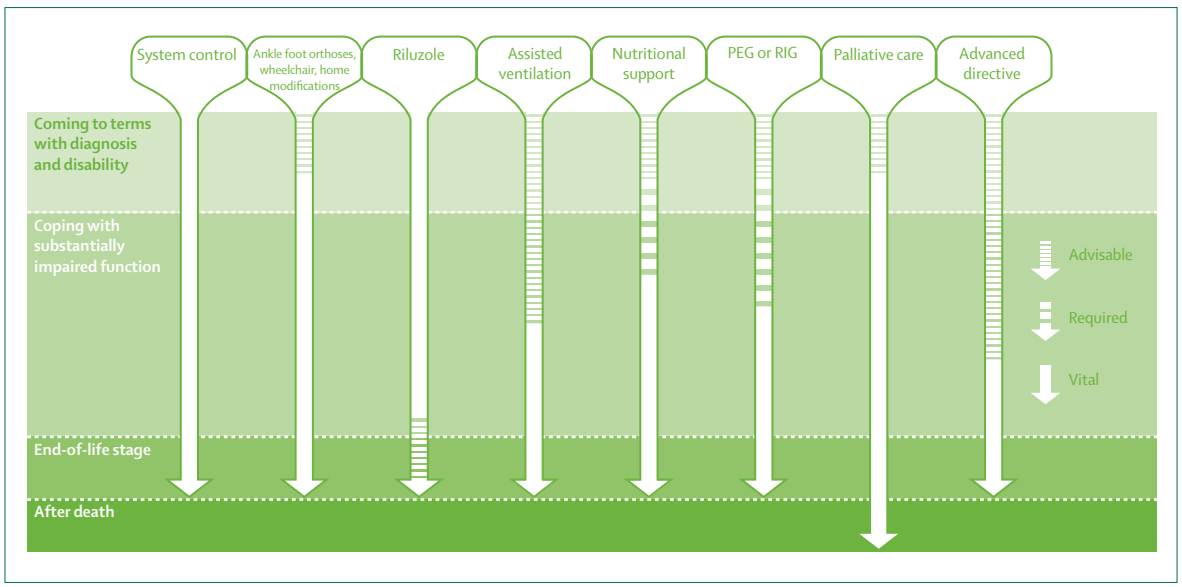

Figure 1: **Recommended strategy for the care of patients with amyotrophic lateral sclerosis**
PEG=percutaneous endoscopic gastrostomy. RIG=radiologically inserted gastrostomy.

that a patient with ALS goes through (figure 1), from adapting to the diagnosis to coping with significantly impaired function and increasing disability, to dealing with end-of-life issues. The phase after death is also important for the needs of the family and carers.

Multidisciplinary approach

The treatment of people with ALS is complex for both patients and health professionals because it requires the management of medical problems, severe disability, and psychosocial issues.[54] Consequently, expert opinion[17–22] and some evidence[55–57] implies that a multidisciplinary approach is preferable, and patients with ALS should be referred to such a team. Attendance at specialist multidisciplinary ALS clinics might prolong survival and improve the quality of life of patients with ALS;[55–57] patients who attend specialist ALS clinics have fewer and shorter hospital admissions.[56] The percentage of patients with adequate aids and appliances is higher in those receiving multidisciplinary care, particularly if the patients have problems communicating and swallowing.[57]

In the UK, close liaison with a primary care team is important because the general practitioner has an important role in coordinating day-to-day care, prescribing drugs, doing blood tests (eg, monitoring liver function while taking riluzole), and referring patients to community services and palliative teams. The policy of the ALS care team at King's College London is that care should be provided in or close to the patient's home. This approach might not be feasible where local multidisciplinary support and primary care are weak or do not exist. It is our experience that even when local care is excellent, many patients wish to visit a specialist ALS centre occasionally.

The challenge for care providers is to adapt the multidisciplinary approach to ensure that patients maintain quality of life, despite deterioration in their strength and function, an aspiration exemplified in the recently established UK National Service Framework for Long-term Disorders. The framework aims to ensure that a coordinated team approach and access to palliative care becomes the standard of care for complex progressive disorders such as ALS.

For more information on **NSF for long-term disorders** see http://www.dh.gov.uk/en/Policyandguidance/Healthandsocialcaretopics/Longtermconditions/Long-termNeurologicalConditionsNSF/index.htm

Coming to terms with diagnosis and increasing disability

Once a diagnosis is made, patients, their carers, and their families will need to adapt. Guidelines for communicating the diagnosis have been proposed.[17,19] Patients prefer to have a family member present when they are told and expect to be able to ask questions.[58] There is no justification for withholding the diagnosis or relevant information, but it is wise and humane to avoid crushing all hope in relation to the prognosis. Long-term survival is possible, although difficult to predict, and some phenotypes have a better prognosis than others.[40–44] Although recovery from true ALS is unlikely, disorders that closely mimic ALS can be misdiagnosed. Information should not be forced on patients or their carers. In our experience, the manner in which the diagnosis is imparted can have a major effect on subsequent relationships with health professionals, and insensitivity is a common source of anger and resentment. Patients and their carers should not feel abandoned, and contact details for the team and local patient support groups must be provided. Action points and care plans are helpful if explained in lay terms, and this clarity is useful for patients when they deal with the many agencies and healthcare professionals that are involved in their care.

For more information about ALS for children and young adults see http://www.mndassociation.org and http://www.marches-of-faces.org

In the weeks and months after diagnosis, concerns might be raised about the course the disease will take, including options for respiratory support, the possibility of gastrostomy, how to control the symptoms and maintain quality of life, how to resolve spiritual and emotional difficulties, and what palliative care is available. For younger families, advice on how to tell children about a parent's condition is important, although there are no recommendations to help children deal with a parent having ALS, such as those available for the children of people with cancer.[59] However, information about ALS for children and young adults is available from the Motor Neurone Disease Association and at ALS March of Faces website.

	Drugs	Other treatments
Cramps	Carbamazepine[17,19] Phenytoin[17,19] Quinine (removed from US market)	Physiotherapy[17,19] Physical exercise[17,19] Massage[17,19] Hydrotherapy[17,19]
Spasticity	Baclofen Tizanidine Dantrolene Botulinum toxin type A[77,78]	Physiotherapy[76] Hydrotherapy Cryotherapy
Excessive watery saliva	Atropine[17,19] Hyoscine hydrobromide[17,19] Hyoscine butylbromide[17,19] Hyoscine scopoderm[79] Glycopyrronium[17,19] Amitriptyline[23]	Home suction device[19] Dark grape juice Sugar-free citrus lozenges Nebulisation[17,19] Steam inhalation[17,19] Injections of botulinum toxin into parotid glands[80–84] Irradiation of the salivary glands[85,86]
Persistent saliva and bronchial secretions	Carbocisteine Propranolol[87] Metoprolol[87]	Home suction device[17,19] Assisted cough insufflator–exsufflator[88] Rehydration (jelly or ice) Pineapple or papaya juice Reduced intake of diary products, alcohol, and caffeine Butter
Excessive or violent yawning	Baclofen	
Laryngospasm	Lorazepam	Reassurance
Pain	Simple analgesics Non-steroidal anti-inflammatory drugs Opioids	Comfort (seating, sleeping, day and night care)
Emotional lability	Tricyclic antidepressant[89] Selective serotonin-reuptake inhibitors[89] Levodopa Dextrometorphan and quinidine[90]	
Communication difficulties		Speaking techniques[91] Low-tech augmentative and alternative communication tools[91] Voice amplifiers Light writers Scanning systems operated by switches Brain–computer interfaces[92]
Constipation	Lactulose Senna	Hydration Increased fibre intake
Depression	Amitriptyline Citalopram	Psychological support, counselling
Insomnia	Amitriptyline Zolpidem	Comfort, analgesia
Anxiety	Lorazepam Midazolam	Psychological support, counselling
Fatigue		Modafinil[93]

Table 3: **Treatment of symptoms in amyotrophic lateral sclerosis**

Riluzole

Riluzole, a glutamate-release antagonist, is the only disease-modifying drug approved for ALS. Treatment with riluzole should be discussed and, if appropriate, started at diagnosis. The patient and their carers should be told that in two clinical trials and meta-analyses, including a Cochrane collaboration review, riluzole prolonged survival by about 3 months after 18 months' treatment.[60–62] Retrospective studies have reported that the survival benefit of riluzole might be even greater (4–19 months).[63–66] Further prospective studies are unlikely, and the existing results should be interpreted with caution because all retrospective and clinic-based studies are prone to bias from equal balance of known (and unknown) prognostic factors in favour of patients who are prescribed the drug tested. Riluzole might have little effect in the advanced stages of the disease,[67] and it is not clear if and when the treatment should be stopped. Riluzole is usually well tolerated but treatment should be stopped if liver function tests exceed five times the upper limit of normal values or if the patient develops neutropaenia. In rare circumstances riluzole has been linked to hypersensitivity pneumonitis.[68] Several other therapeutic trials have reported no benefit, although the results of some phase II/III trials are still outstanding.[69,70]

Palliative care

Patients can be referred to a specialist palliative care team before reaching the advanced stages of ALS, although this will depend on the resources available and the framework of the local or national healthcare system. The goal of palliative care is to achieve the best possible quality of life for patients whose disease is not responsive to curative treatment, and the best quality of life for their families,[71] although palliative care is still perceived as the last resort (terminal care). Too often, end-of-life discussions are started only when patients are ill, in severe distress, and have little time to discuss with their family and health professionals their preferences and decisions about interventions (eg, assisted ventilation and advance directives for life support or resuscitation). Although early referral to a palliative care team for assessment and home care (in the first instance) is commonly limited by availability and funding, our experience is that this approach is valuable. The aim of palliative care is to ensure a whole-person approach to care that is local and supplements primary care with expertise in symptom control and (later on) end-of-life care. Ideally, palliative care continues after death, through bereavement support. This approach can obviate the need to travel to a specialist centre without prejudicing the quality of care. As yet, there is no formal evidence to

support this approach, and trials of such complex interventions are needed.

Advance directives have been advocated as a means for patients to communicate their wishes about end-of-life care to healthcare professionals, their family, and friends. Advance directives are common in the USA, where 90% of patients who died from ALS had an advanced directive, and only a minority (3%) were not followed.[23] In Europe, the use of advance directives varies, probably because of cross-cultural differences.[72] Physicians are expected to initiate discussions about advance directives with all patients, and these discussions should be honest, forthright, and detailed.[58] ALS-specific advance directives that deal with respiratory failure and the use of mechanical ventilation have been proposed.[73]

Substantially impaired function

Patients with ALS develop deficits that impair their ability to speak, swallow, breathe, use their arms, and walk. The principles of care listed in the previous section apply to this phase, although the approach, either locally or at a multidisciplinary clinic, should be more active and concentrated. Furthermore, because the deficits are more severe, adjustments to the management plan must be made frequently. There is no evidence to support a particular interval for review, but in our practice patients are reviewed every 2–3 months and more frequently if problems arise. The capacity to make decisions is often maintained until death, and advance directives should be reviewed regularly: patients with ALS have been known to change their preferences for cardiopulmonary resuscitation and ventilator care for respiratory failure.[74] The dual role of spouse carers is of particular importance at this stage, because the burden of care increases as the disease progresses.[75]

Symptomatic care

Patients with ALS have symptoms that are directly related to the disease process, such as weakness, wasting, fasciculations and cramps, spasticity, difficulty in communicating, dyspnoea, chronic hypoventilation, excessive watery saliva, persistent secretions, dysphagia, emotional lability, and symptoms that are indirectly related, such as depression, anxiety, insomnia, fatigue, constipation, pain, and discomfort. Symptoms should be treated if they impair the quality of life, and the patient can use drugs or take the non-pharmacological approach, or a combination of both (table 3, figures 2 and 3).[17,19,23,76–97]

Here, we discuss the management of respiratory impairment and nutrition in more detail, in light of recent developments; management of other symptoms, including genetic counselling, has previously been described.[17,19]

Dyspnoea and respiratory impairment

Respiratory weakness in patients with ALS causes dyspnoea, either at exertion or rest, and orthopnoea, but can also present with symptoms of nocturnal hypoventilation. However, some patients who have severe respiratory insufficiency are not breathless, and other symptoms should be carefully looked for (panel).[19,98]

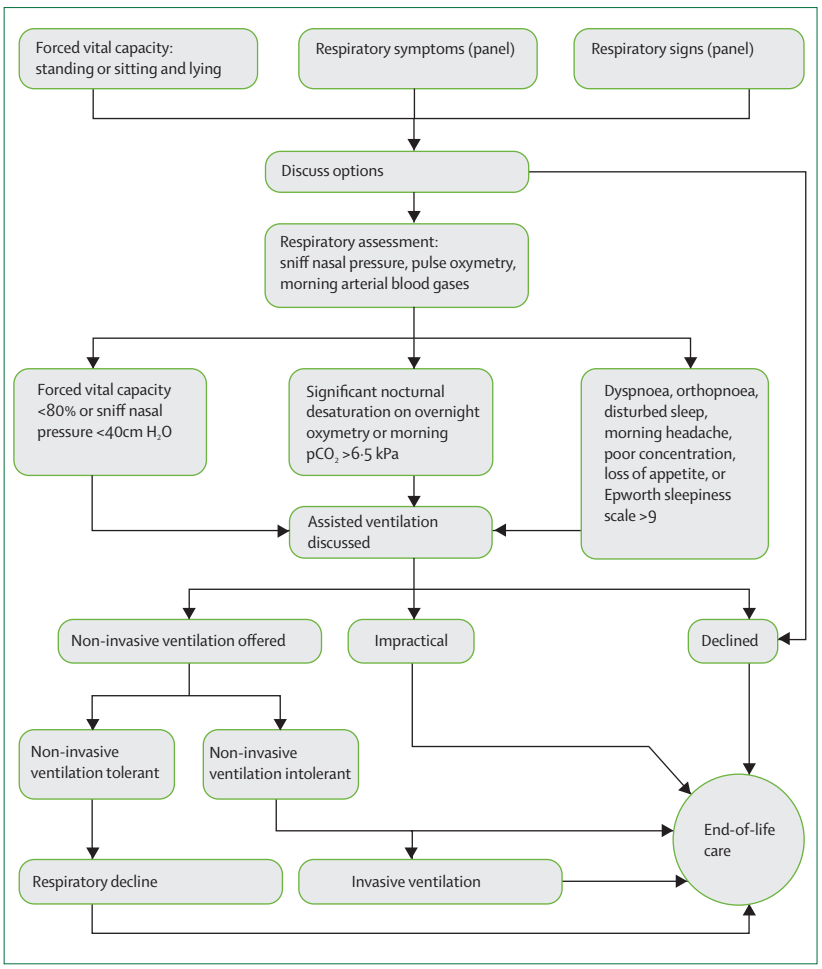

Figure 2: **Recommended respiratory management of patients with amyotrophic lateral sclerosis**

The management of respiratory impairment in patients with ALS comprises ventilatory support, which can be invasive or non-invasive, and pharmacological approaches (figure 2). Assisted ventilation is usually provided by a bilevel positive pressure device (BiPAP), whereas continuous positive pressure (CPAP) ventilation is not usually helpful. Any infection or airway obstruction should be treated with antibiotics and physiotherapy, and patients with ALS should receive annual influenza immunisations.

Patients with ALS who start and can tolerate non-invasive ventilation at the onset of respiratory insufficiency have a significant survival advantage compared with those who cannot.[99] This observation was confirmed in a randomised controlled trial of patients with ALS with no or moderate bulbar dysfunction;[94] in these patients, the survival benefit of non-invasive ventilation was much greater than that of riluzole, and quality-of-life domains improved in patients with severe bulbar impairment.[94] Non-invasive ventilation improves

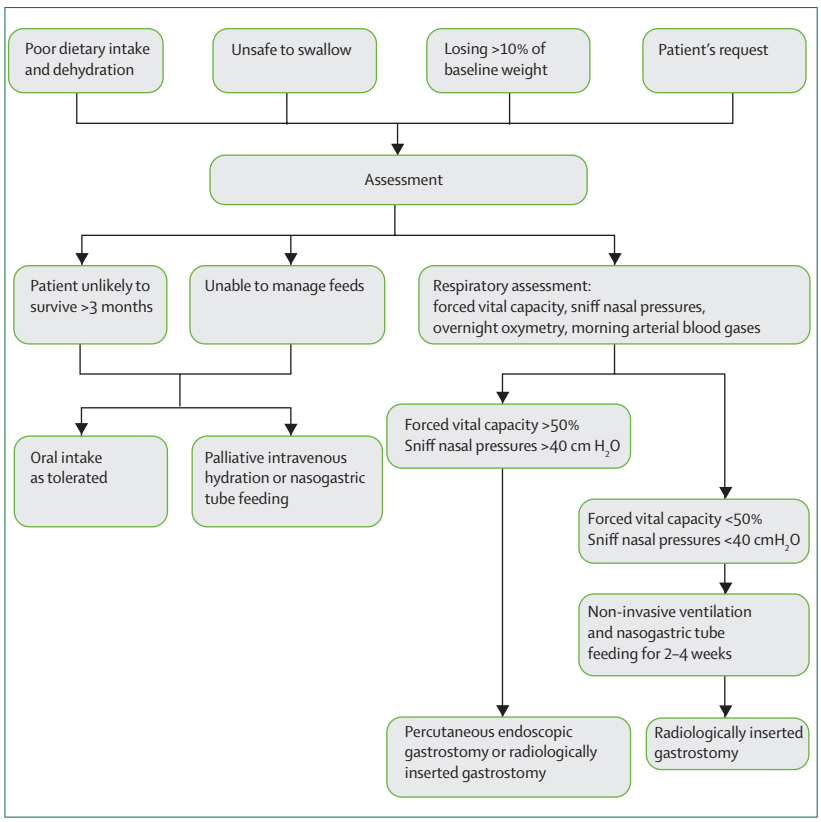

Figure 3: **An algorithm for starting enteral feeding in patients with amyotrophic lateral sclerosis with nutritional deficit**

***Panel:* Symptoms and signs of respiratory insufficiency**[19,98]

Symptoms
Shortness of breath on exertion
Orthopnoea
Difficulty in clearing secretions
Restless and unrefreshing sleep
Excessive daytime sleepiness
Morning headache
Poor concentration and memory
Depression
Lethargy
Fatigue
Nocturia
Poor appetite

Signs
Tachypnoea
Use of accessory muscles
Paradoxical abdominal movement
Decreased chest movement
Weak cough
Dry mouth
Sweating
Tachycardia
Dizziness
Syncope
Confusion
Weight loss
Papilloedema (rare)

and maintains quality of life in patients with ALS without substantially lowering the quality of life of the carers.[95,96,100,101]

Only 28% of patients with dyspnoea and 9% of those with a forced vital capacity of less than 40% of the predicted value received non-invasive ventilation before the publication of the AAN ALS Practice Parameter.[23] Only 5·5% of 2280 patients with ALS under review in the UK in 2000 received non-invasive ventilation, with substantial variation between treatment centres.[102] Non-invasive ventilation was used in a similar number of patients with ALS in other European countries.[72] The reasons for such low uptake of non-invasive ventilation are multifactorial but are influenced by differences in the experience of physicians, uncertainty of the benefits and timing for starting non-invasive ventilation, and concerns that ventilatory support might prolong suffering, render home care less feasible, and lead to dependency or ventilator entrapment.[102] The availability and cost of non-invasive ventilation is also a contributing factor. Nowadays, at some centres in the USA more than 50% of patients with respiratory impairment are estimated to receive non-invasive ventilation.[103] 70% of patients with ALS use non-invasive ventilation for more than 4 hours per night, and the procedure is well tolerated.[103] Tolerance is reduced in patients with bulbar onset[103] but, in our experience, bulbar features do not prevent successful ventilation. We would offer non-invasive ventilation to patients with poor bulbar function, particularly because of a recent randomised controlled trial that showed improvement in quality of life.[94] However, the increased risk of aspiration in patients with bulbar onset and problems because of difficulties in clearing secretions or obstructions, such as those related to abnormal function of the vocal cords, should be considered.

The AAN ALS Practice Parameter recommends starting non-invasive ventilation when forced vital capacity declines to 50% of the predicted value.[17] However, forced vital capacity is insensitive to substantial change in the strength of expiratory muscles, is poorly associated with respiratory failure, and is inaccurate in patients with bulbar weakness and patients with pseudobulbar palsy who have an apraxia of facial movements.[99] Patients can develop respiratory failure with a forced vital capacity above 70% of the predicted value;[104–106] therefore, a forced vital capacity of 75% or less is probably more appropriate as a threshold for closer monitoring of respiratory symptoms than a forced vital capacity of 50%. However, in our experience, patients will not consider non-invasive ventilation on the basis of a forced vital capacity

measurement alone, nor is there evidence that early non-invasive ventilation improves survival, functional status, or quality of life. Researchers in France who tried to recruit patients for early, non-invasive ventilation (sniff nasal pressure <60% of the predicted value and forced vital capacity >70% of the predicted value) did not recruit sufficient people for the study to proceed (Perez T, Centre Hospitalier Regional, Université de Lille, personal communication).

Measurement of sniff nasal pressure is a more sensitive test for predicting respiratory failure than forced vital capacity, although despite being easy to assess in the clinic, it has not yet found a place in routine assessment.[97,107,108] A sniff nasal pressure of 32% (~25 cms H_2O) or less is predictive of respiratory failure, whereas a forced vital capacity of 50% is an insensitive indicator of respiratory failure.[107] In another study, sniff nasal pressures of less than 40 cms H_2O were a strong predictor of survival.[108] Nocturnal pulse oximetry might provide evidence of hypoventilation, and measurements of morning arterial blood gases can provide evidence for hypercapnia.[109] Other tests, such as inspiratory and expiratory mouth pressures, polysomnography, sniff trans-diaphragmatic pressure, and diaphragmatic electromyography might provide useful additional information.[110]

Expert opinion is in accord with starting non-intensive ventilation when patients with ALS have symptoms related to nocturnal hypoventilation, frequently with dyspnoea and orthopnoea. Evidence of respiratory weakness is required: forced vital capacity of less than 80%; supine vital capacity of less than 25% of sitting or standing vital capacity; sniff nasal pressure of less than 40 cm H_2O; and evidence of either morning hypercapnia (PCO_2 >6·5 kPa) or significant nocturnal desaturation (<90% for >5% of the time asleep).[96]

The disorder will eventually progress to the stage where non-invasive ventilation will not be able to compensate for respiratory impairment. The guidelines and our practice emphasise that the next step should have already been discussed with the patient, and an advance directive should be in place. The choice is between invasive ventilation by tracheotomy or a pharmacological approach to end-of-life palliative care.

Invasive ventilation by tracheotomy prolongs survival in patients with ALS;[111,112] however, the cost of invasive ventilation by tracheotomy (eg, the ventilator and 24-hour nursing care) are beyond the means of most patients. Unplanned and unwanted tracheotomy could be avoided by discussions early in the course of the disease of the options for respiratory support and through advanced directives.[17,19] Unplanned tracheotomy is done in patients without an established diagnosis of ALS or when doctors are not informed of the diagnosis or the wishes of the individual. Once intubated, patients are rarely free from the ventilator.[113] Patients with tracheotomy seem less satisfied with their quality of life than patients who use non-invasive ventilation;[111] however, invasive ventilation by tracheotomy is acceptable to some patients and their carers and should be discussed as an option with all patients. If patients decide to have tracheotomy ventilation, they and their carers must agree on the circumstances under which ventilator support will be withdrawn.

Pharmacological approaches to palliative sedation include giving opioids and benzodiazepines. Titrating sedation for the symptomatic treatment of dyspnoea or pain seldom, if ever, leads to respiratory depression.[114] When carefully managed, opioids do not shorten life and are probably underused in this context.[115] Intermittent, short dyspnoeic bouts can be relieved with sublingually given lorazepam, whereas longer attacks of dyspnoea can be relieved by inhaled morphine or intravenous midazolam.[17] Regular doses of morphine are used to relieve chronic dyspnoea.[19] Oxygen therapy alone should be avoided because it can exacerbate hypercapnia and mouth dryness and should be used only if symptomatic hypoxia is present and the patient is close to death.[19] The pharmacological approach is appropriate once the decision to withdraw ventilation has been made.[116] An algorithm for the respiratory management of ALS patients is shown in figure 2.

Dysphagia and nutrition

Most patients with ALS develop swallowing difficulties, which lead to malnutrition and weight loss. Nutritional status is a risk factor for survival;[117] however, dysphagia is not the only reason for malnutrition and weight loss in ALS. Upper limb weakness slows eating and also makes patients dependent on others for cutting their food and feeding them, which prolongs meal times, and patients frequently do not finish their meals. Anxiety and depression can also lead to anorexia, and immobility, reduced fluid and fibre intake and the use of opioids can lead to constipation and, consequently, loss of appetite.

A combination of body composition measures, such as dietary histories, body mass index, and anthropometry, is recommended for the accurate assessment of nutritional status.[18] Monitoring weight at each clinic visit is a simple and useful measure, and enteric feeding should be considered after loss of more than 10% of baseline weight.[19] Swallowing safety should be regularly assessed in collaboration with speech and language therapists: the frequency of choking, the texture of some food, drooling, meal duration, and fatigue during meals are useful measures in assessing swallowing impairment.[17] Videofluroscopy is a useful way to assess the progression of dysphagia in patients with ALS[118] and to identify patients at risk of aspiration.

To ease swallowing difficulties, the consistency of food should be modified by blending or adding thickeners to liquids, and patients should be taught lip-seal and tongue exercises and the chin-tuck manoeuvre (flexing the neck forward when swallowing to protect the airways). Patients should be encouraged to eat smaller, more frequent meals, and their diet should be sufficient in fluids and

calories. Vitamins and minerals should come from the diet rather than from supplements.[18]

These interventions will eventually stop working, and dysphagia, weight loss, and malnutrition will prevail; enteric feeding then becomes an important way to maintain nutritional status. Patients must be made aware of this option in good time. Enteric feeding can be done by nasogastric tube, percutaneous endoscopic gastrostomy, or radiologically inserted gastrostomy. Nasogastric tube insertion is a minor procedure but is useful, in our view, as a temporary measure to improve hydration and nutritional status before radiologically inserted gastrostomy or when neither percutaneous endoscopic gastrostomy nor radiologically inserted gastrostomy are suitable. A nasogastric tube will limit physical activity, lead to nasopharyngeal discomfort, pain, ulceration, and can increase oropharyngeal secretions and lead to aspiration. Percutaneous endoscopic gastrostomy is the standard procedure and is widely available. Mild sedation is needed, which might be hazardous in patients with a forced vital capacity of less than 50%.[119,120] Radiologically inserted gastrostomy does not need sedation or an endoscopic tube, has a high success rate on its own or after the failure of percutaneous endoscopic gastrostomy, and patients can stay upright rather than having to lie down;[121,122] however, an experienced interventional radiologist is needed. The frequency and type of complications in the period just after and during the first month after radiologically inserted gastrostomy and percutaneous endoscopic gastrostomy did not differ from each other, although there was more pain reported after radiologically inserted gastrostomy, and mechanical obstruction or tube migration were more common after percutaneous endoscopic gastrostomy.[123] Other complications include vomiting, diarrhoea, constipation, haemorrhage, peristomal infection, pneumoperitoneum, peritonitis, gastrocolic fistula formation, parietal necrosis, weight gain, and buried bumper syndrome.[124] Death can occur secondary to aspiration and respiratory arrest after percutaneous endoscopic gastrostomy placement or secondary to peritonitis after radiologically inserted gastrostomy placement; however, mortality rates in the first month were similar in both groups.[121,123]

Studies of enteric feeding have been reviewed.[18] Enteric feeding maintains good nutrition and hydration, stabilises weight, provides a way to give drugs, and might improve quality of life, although this has not yet been shown. There is no clear evidence for improved survival, which might be because of the timing of starting enteric feeding (figure 3).[125] Low forced vital capacity is not associated with the failure of percutaneous endoscopic gastrostomy[121] or survival if patients are protected with non-invasive ventilation.[126] Abnormal oximetry readings before radiologically inserted gastrostomy is a negative indicator of post-procedural survival.[127] Methods for radiologically inserted gastrostomy tube placement have been described in detail elsewhere.[121,128]

End-of-life issues

ALS is a progressive disease, and eventually all patients reach the phase of respiratory insufficiency, inadequate nutrition and hydration, increasing discomfort, and severe psychological distress. When a patient reaches this terminal phase, an appropriate symptom management regimen should be put in place to improve the quality of dying and death. There is no reason for a patient not to maintain autonomy in the terminal phase and in end-of-life decisions: almost 90% of patients in Oregon and Washington, USA, had advance directives and their decisions were honoured by healthcare professionals.[129]

End-of-life care is influenced by the type and quality of the care provided from the earliest stages.[52] Most patients with ALS in Europe and North America die peacefully.[130–132] Choking is rare and was reported in only 10 of 1014 American and Canadian patients with ALS.[132]

Hospice institutions provide care at home, support for carers, and have teams of experts in symptom management; therefore, they can greatly help patients and their families during the terminal stages of ALS.[133] However, hospice care differs among countries: most hospices in the UK will care for patients with ALS, whereas only 40% of German palliative care units accept neurological patients.[130] In one study, about half of the patients with ALS in the USA who died at home received home hospice services, and seemed to receive better than average access to hospice care.[23] The referral of patients with ALS to palliative care services on the basis of current criteria is, however, inflexible and should be improved.[134] Physicians should provide more information about palliative care services earlier in the course of the disease, enabling patients and their carers to make more informed and more timely decisions about hospice enrolment.[135]

After death

The death of a person has a lasting effect on their family, and only 22% of respondents in one study coped well in later life.[136] Nearly all carers incurred substantial financial hardship, and self-defined burn-out was reported in 82% of carers; however, more than two-thirds of carers expressed a need for ongoing information and involvement in ALS-related topics.[136] Grief and bereavement support should be an integral part of ALS care,[137] and measures such as a letter of condolence, the availability to talk to somebody, or the provision of appropriate referrals to physicians, psychologists, or psychiatrists, when required, are important. A letter of condolence can help a bereaved family and tie-up the relationship between the physician and the late patient's family.[138]

Patients with ALS are motivated to take part in research during the disease process, and a substantial number of them are also prepared to donate their brain and spinal cord. Our philosophy is that every person with ALS who visits a specialist clinic should have the opportunity to take part in research of some kind, if they wish.

Concluding remarks

The past two decades have seen important advances in the care of people affected by ALS; however, ALS is still a devastating, inexorably progressive, and ultimately fatal disease. We should not forget that long survival is possible, although the factors that determine longevity are not fully understood. A modicum of humility when counselling people on prognosis is fitting: all hope should not be destroyed. Despite evidence that multidisciplinary care improves quality of life, more evidence on the effectiveness of multidisciplinary care, combined with interventions such as non-invasive ventilation, gastrostomy, and palliative care, is required. These are complex interventions but there are models for randomised trials (eg, the Medical Research Council model).[139] The delivery of multidisciplinary care varies and is dependant on local and national resources and policy. In our experience, people affected by ALS think that coordination is an important factor.[140]

Any vision for future care must include general and equal access to responsive, coordinated, multidisciplinary, and palliative care that is delivered in or close to the home, in accordance with the individual needs and wishes of each patient and their family and friends. The UK National Service Framework on Long-term Conditions aspires to these goals but can only encourage their adoption. The challenges are even greater elsewhere in the world, and we surely have an ethical and moral responsibility to consider the needs of the people with ALS in low-income countries, who have no support outside their family. We must, somehow, balance the (legitimate) desire for high-cost technology and drugs with the responsibility to develop appropriate care and disease-modifying therapies that are both effective and accessible in low-income countries. Research into the epidemiology, natural history, and care of people with ALS in the most crowded and poorest parts of the world is much needed but almost absent.

Riluzole is the only drug that increases survival in ALS or any neurodegenerative disease but its mechanism of action in ALS is obscure and more work on this fundamental observation is needed. In our view, more effective, disease-modifying drugs are unlikely to be developed until we understand the basic mechanisms of the disease and can target therapies at specific molecular pathways.[141] Stem cell therapy remains entirely speculative at present.

Non-invasive ventilation prolongs life for longer (from months to several years, with gains in quality of life) than riluzole and is a major advance in the management of ALS. The use of riluzole is supported by evidence from a randomised controlled trial,[94] which will help to persuade funding agencies to support its wider availability. Specialists in ALS have overcome the reluctance of general neurologists to use non-invasive ventilation and gastrostomy—a pervasive scepticism that has now been largely dispelled. Physicians now understand that quality of life can be excellent, even when an individual is paralysed and ventilated, although patients with advanced ALS on ventilatory support commonly cannot communicate at all. This fearsome situation might be resolved, in part, by the development and dissemination of brain–computer interfaces.[92] Research into technical solutions and the potential of this approach must be matched by research and debate on the related ethical issues.[142]

Access to non-invasive ventilation is restricted in many parts of the world, including Europe and North America. We must understand the factors—personal and socioeconomic—that determine access to non-invasive ventilation. Likewise, although long-term assisted ventilation by tracheotomy is seldom done in Europe or North America, it is common in Japan. We need a deeper understanding of the attitudes of health professionals, people affected by ALS, health service planners, politicians, and society in general to the choices made and the problems posed by permanent assisted ventilation. At present, there is little information on the service costs of non-invasive ventilation, permanent assisted ventilation, or gastrostomy. Health economic and quality-of-life analyses will surely become part of future studies on these issues, and (ideally) will be integrated into clinical trials.

The current notion that the neuropsychological abnormalities in ALS cover a spectrum of cognitive involvement up to frontotemporal dementia is not proven; there might be subtypes of ALS in which cognitive change does not occur. This requires further investigation, as does the effect of cognitive abnormalities on day-to-day care, decision making, and autonomy.

Finally, we suggest that researchers, clinicians, people affected by ALS, and voluntary and statutory groups should develop a unified set of guidelines that more coherently combine an analysis of the (rather slender) evidence base with consensus expert opinion. The basic work is done; the challenge is to speak with a single, authoritative (but common sense) voice so that funding agencies will support what works best for people living with this terrible condition.

Search strategy and selection criteria

References for this Review were identified by searches of PubMed from 1985 to July, 2007, with the terms "amyotrophic lateral sclerosis", "diagnosis", "differential diagnosis", "survival", "nutrition", "assisted ventilation", "quality of life", "end-of-life", "palliative care", and "locked-in". Articles identified from that search and references cited in those articles were included. Only papers in English were reviewed.

Contributors

AR and PNL designed and developed the framework of the Review. AR wrote the Review and designed the tables and figures. PNL revised the Review at its different stages. HM made additions to the Review and edited it for the content. AR, PNL, and HM discussed the Review and prepared the final version together.

Conflicts of interest

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