THE PALLIATION OF AMYOTROPHIC LATERAL SCLEROSIS

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Objectives

1. Review the clinical features, epidemiology, pathophysiology, and prognostic factors associated with ALS.
2. Discuss the management of ALS throughout disease progression.
3. Consider the end-of-life care for the ALS patient.

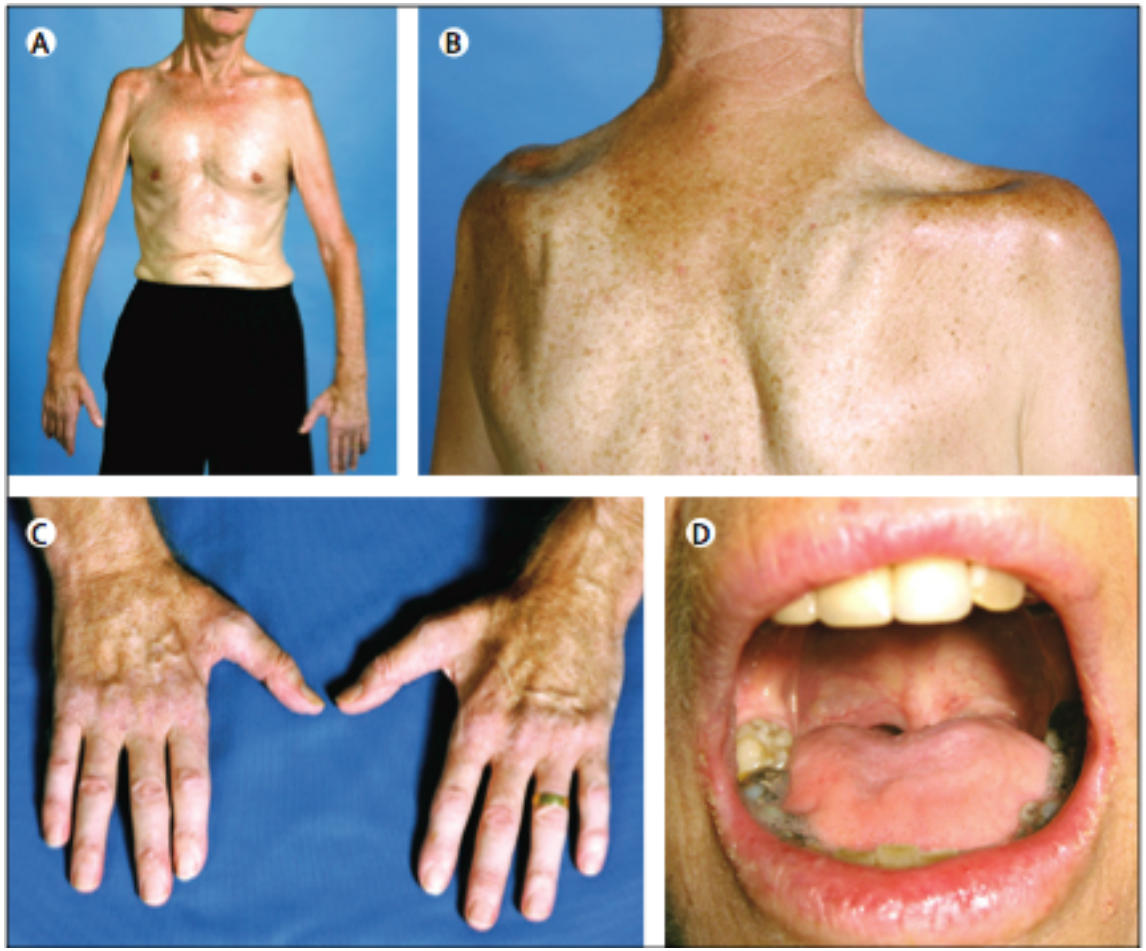
Amyotrophic Lateral Sclerosis (ALS)

- First described by Charcot in 1874:
  - Clinical observations: atrophic muscular weakness (amyotrophy), spasticity
  - Pathological findings: hardening of the lateral columns of the spinal cord (lateral sclerosis), lesions of the anterior horn
- Neurological deterioration involving the corticospinal tract, brainstem, and anterior horn cells
  - Leads to limb paralysis, dysarthria, dysphagia, and respiratory failure
- Median survival of 3 years
  - Up to 10% of patients survive for more than 8 years
  - With mechanical ventilation, survival can be 15 years or greater

ALS: Clinical Features

- Disease phenotype often is classified by site of onset:
  - Limb symptoms: 65%
  - Bulbar dysfunction: 30%
  - Respiratory: 5%
- Extraocular and sphincter muscles spared
- Sensory neurons intact

ALS: Clinical Features



Kiernan, M.C. *et al.* 2011Lancet 377: 942-955

ALS: Associated Cognitive Dysfunction

- Frequent feature of ALS ➔ executive and behavioural impairment in up to 60% of patients
- Frontotemporal dementia (FTD) occurs in up to 15%
  - Personality change
  - Irritability
  - Poor insight
  - Pervasive deficits on frontal executive tests
- Mild form of executive impairment in approximately 20%
  - Impaired judgement, impulsivity
- Cognitive or behavioural changes may precede or follow motor symptoms
- No definitive screening test
- Concern of decision-making capacity as disease progresses

ALS: Epidemiology

- Incidence: 2-3 people per 100 000 → most common degenerative disorder of the motoneuronal system in adults
- Caucasians more frequently affected than other ethnic groups
- Men more than women (1.2-1.5:1)
- Risk peaks between ages of 50-75 years, then declines
- Not increasing
- Both sporadic and inherited forms of the disease
  - 10% due to inherited gene mutations

ALS: Etiology

- Currently unknown → geographic and occupational clusters, ? environmental factors
- Possible mechanisms:
  - Mitochondrial dysfunction
  - Protein aggregation
  - Free radical generation
  - Excitotoxicity
  - Inflammation and apoptosis
- Multifactorial → contributions from multiple genes and environmental exposures

ALS: Diagnosis

- Up to 14 months from onset of symptoms until diagnosis → initial broad differential diagnosis
- Based primarily on clinical exam
- No definitive diagnostic test → may involve:
  - Laboratory testing
  - Electromyography (fasciculation, denervation discharges, polyphasic units)
  - Genetic testing
  - Neuroimaging (MRI)
- El Escorial criteria in 1994 (World Federation of Neurology) → multiple revisions
- Definite diagnosis requires:
  - LMN degeneration on clinical, electrophysiological, or neuropathological exam
  - UMN degeneration on clinical exam
  - Progression of motor syndrome within a region or to other regions
  - Absence of evidence of other disease processes that may explain the symptoms

ALS Treatment: Riluzole

- Only drug approved by the FDA
- First developed as an antiepileptic drug
- Inhibit the synaptic release of glutamate, but mechanism in ALS is unknown
- Common side effects: fatigue, somnolence, nausea, diarrhea, dizziness
- Miller, R.G., *et al*. 2012 Cochrane Database of Systematic Review, Issue 3:
  - 4 RCTs involving 1477 ALS patients
  - 100 mg daily: median survival benefit of 2-3 months
  - Reasonably safe, very modest effect, expensive
- Consensus: all affected patients should be offered riluzole

ALS: Prognostic Factors

POSITIVE	NEGATIVE
Diagnostic delay	Older age
Limb-onset	Respiratory- or bulbar-onset
Psychological well-being	Presence of FTD
Marital status	Low BMI and weight loss
Interdisciplinary care	** lower predicted forced vital capacity (FVC)

ALS: Practice Guidelines

- Published by the American Academy of Neurology (AAN) and European ALS Consortium (EALSC)
- Evidence-based guidelines ➔ mostly level B and C evidence (small numbers, lack of RCTs)
  - Expert consensus
- Recommendations:
  - Delivery of diagnosis
  - Use of multidisciplinary care team
  - Use of riluzole
  - Specific symptom management
  - End-of-life care

SYMPTOM MANAGEMENT

ALS: Multidisciplinary Care Team

- Neurologist
- Specialized nurse
- Physical therapist
- Occupational therapist
- Respirologist
- Respiratory therapist
- Speech pathologist
- Gastroenterologist
- Dietician
- Social worker
- Psychologist
- Spiritual Care
- Family physician
- Palliative Medicine physician

ALS: Symptom Management

- Sialorrhea: socially disabling, impaired handling of secretions
  - Medications: antimuscarinic agents, TCA
  - Home suction device
  - Botulinum toxin, radiotherapy
- Bronchial secretions:
  - Mucolytics
  - Manual assisted cough
  - Suction, insufflator-exsufflator
- Pseudobulbar affect: pathological weeping/laughing/yawning, occurs in 20-50%, not a mood disorder (brain lesion)
  - Antidepressants, dextromethorphan/quinidine

ALS: Symptom Management

- Impaired communication:
  - Alphabet board, computerized systems, infrared eye movements, voice amplification systems
- Cramps:
  - Massage, PT, exercise, hydrotherapy
  - Medications: quinine, anticonvulsants, benzodiazepenes → efficacy in ALS?
- Spasticity:
  - PT, hydrotherapy, ultrasound, TENS
  - Medications: baclofen, benzodiapenes, dantrolene, tizanidine, anticonvulsants → Efficacy in ALS?
- Depression/anxiety/insomnia: occur frequently at all stages of disease
  - Medications: SSRIs, TCAs, benzodiazepines, zopiclone, Benadryl

ALS: Symptom Management

- DVT prophylaxis: increased risk in paralysis, but incidence in ALS is unknown
  - Insufficient evidence to recommend prophylaxis
- Pain: occurs frequently (up to 80%), may involve neuropathic component, typically increases with disease progression → atrophy affecting bones/joints, muscle contractures, immobility
  - Medications: according to WHO analgesic ladder
  - Brettschneider, J. *et al*. 2010 Cochrane Database of Systematic Reviews Issue 11:
    - No RCTs on drug therapy for pain in ALS

ALS: Management of Nutrition

- Functional consequences of bulbar symptoms: choking, aspiration, weight loss, dehydration
- Hypermetabolic state in 50-60% of patients ➔ independent of increased WOB, ? Mitochondrial dysfunction
- Social impact
- Interventions:
  - Texture modification
  - Nutritional supplements
  - Modified feeding aids
  - Percutaneous endoscopic gastrostomy tube (PEG) or radiologically-inserted gastrostomy (RIG)

ALS: Feeding via PEG Tube

- Recommended in patients with difficulty maintaining good nutrition
- Increased mortality if placed once the FVC is less than 50% predicted
  - Procedure: 1.8%
  - 24 hour: 3.6%
  - 30-day: 11.5%
- Associated complications:
  - Laryngospasm
  - Localized infection
  - Gastric hemorrhage
  - Failure to place PEG due to technical difficulties
  - Death due to respiratory arrest

* RIG may be an alternative if placed in advanced stage of disease

ALS: Feeding via PEG TUBE

- Probably effective in stabilizing body weight
- Currently, no evidence of survival benefit
- Lou, J. *et al*. 2010 Amyotroph Lateral Scler 11: 116-121
  - 412 ALS patients enrolled in clinical trial (minocycline)
  - Analyzed how PEG affects QoL ➔ used McGill Quality of Life Scale to assess 52 patients with PEGs placed during the study period
  - Rate of decline on QoL scale slowed after initiation of PEG
  - Reasons for suspected improvement in QoL unknown
- Impact on quality of life:
  - Reduces risk of rapid weight loss
  - Avoids dehydration
  - May reduce anxiety and social isolation associated with prolonged meal times

Management of Respiratory Symptoms

- Respiratory muscle weakness: inability of respiratory muscles to generate normal levels of pressure and airflow during inspiration and expiration
- Respiratory insufficiency: inadequate pulmonary ventilation to the point where gas exchange is impaired, resulting in carbon dioxide retention, hypoxemia, and frank respiratory failure
- Respiratory failure (with or without pneumonia) is the most common cause of death in ALS patients

Symptoms: Respiratory Muscle Weakness

- Dyspnea on exertion
- Orthopnea
- Nightmares and fragmented sleep
- Morning headaches
- Daytime somnolence
- Cough impairment
- Lower respiratory tract infection

Noninvasive Positive Pressure Ventilation (NIPPV)

- Provided via BiPAP → enough support to offload work of breathing
- Recommended by the AAN, EALSC, and the American College of Chest Physicians
  - Not widely used in USA and Europe
  - Poor compliance in patients with bulbar symptoms and FTD
- No guidelines in literature for initiation of NIPPV → respiratory symptoms and/or evidence of respiratory muscle weakness (FVC < 50% pred.)
  - Polysomnography plays no significant role in determining when to start
  - No RCTs that address whether initiating before the onset of symptoms or hypercapnia prolongs time to respiratory failure or death
- Debate about which test optimally detects impending respiratory muscle insufficiency:
  - Forced vital capacity (FVC)
  - Maximum inspiratory and expiratory pressure (MIP/MEP)
  - Maximum sniff nasal pressure (SNIP)

ALS: RCTs for NIPPV

- Radunovic, A. *et al*. 2009 Cochrane Database of Systematic Reviews Issue 4:
  - Examine the efficacy of mechanical ventilation in improving survival, on disease progression, and quality of life in ALS
  - Only one study judged to be of adequate methodological quality → no meta-analysis

ALS: RCT for NIPPV

- Bourke, S.C. *et al*. 2006 Lancet Neurol 5: 140-147:
  - Effect of NIPPV on quality of life and survival
  - 92 patients at a single centre were assessed every 2 months → randomised to NIPPV (n=22) or standard care (n=19) when they developed either orthopnea with MIP less than 60% predicted or symptomatic hypercapnia
  - QoL measured with Mental Component Summary and Sleep Apnea Quality-of-life Index → time maintained above 75% of baseline and mean improvement

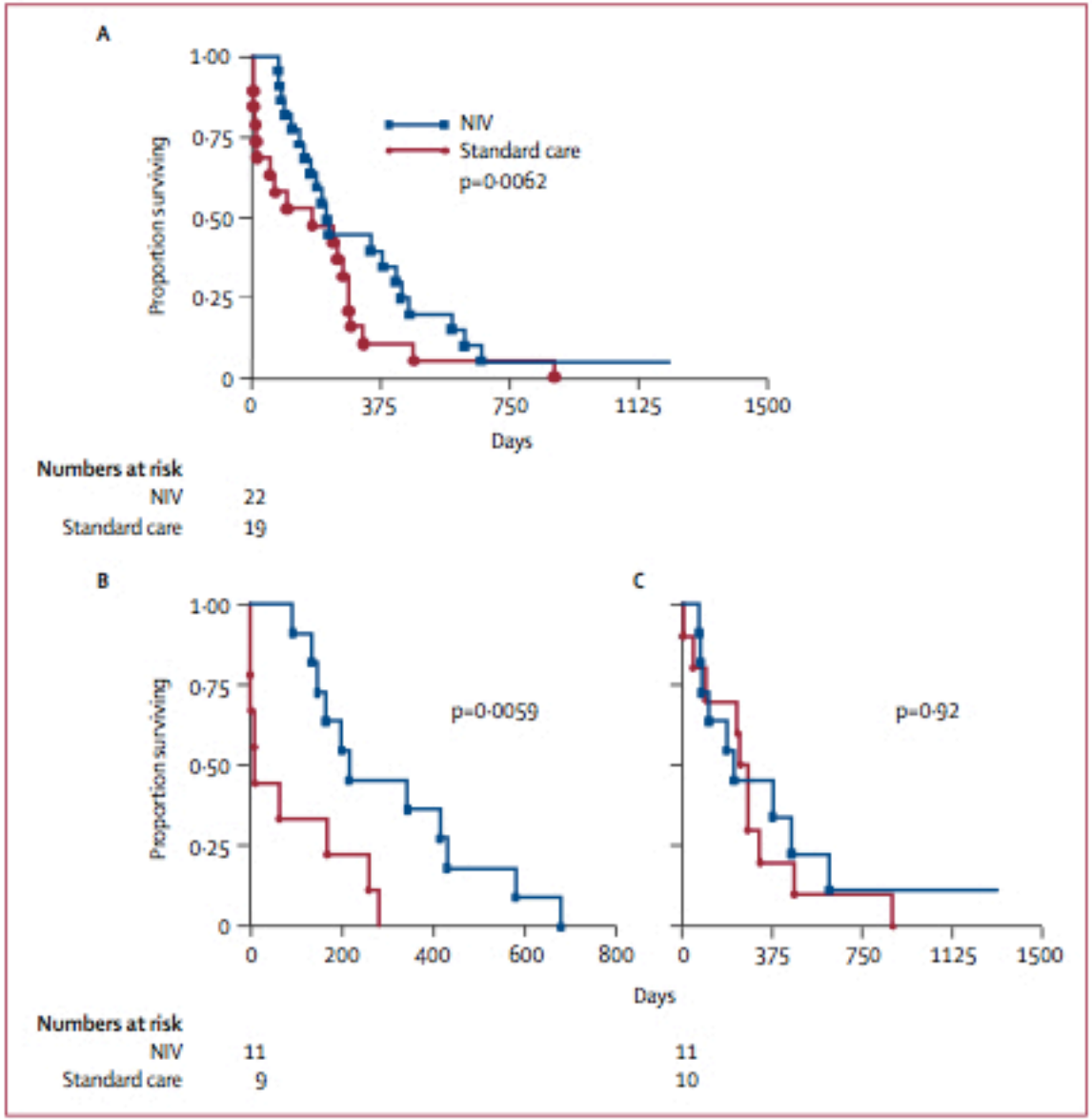


Figure 2: **Survival from randomisation**
A: all patients; B: patients with normal or moderately impaired bulbar function; C: patients with severe bulbar impairment.

Bourke, S.C. *et al*. 2006 Lancet Neurol 5: 140-147

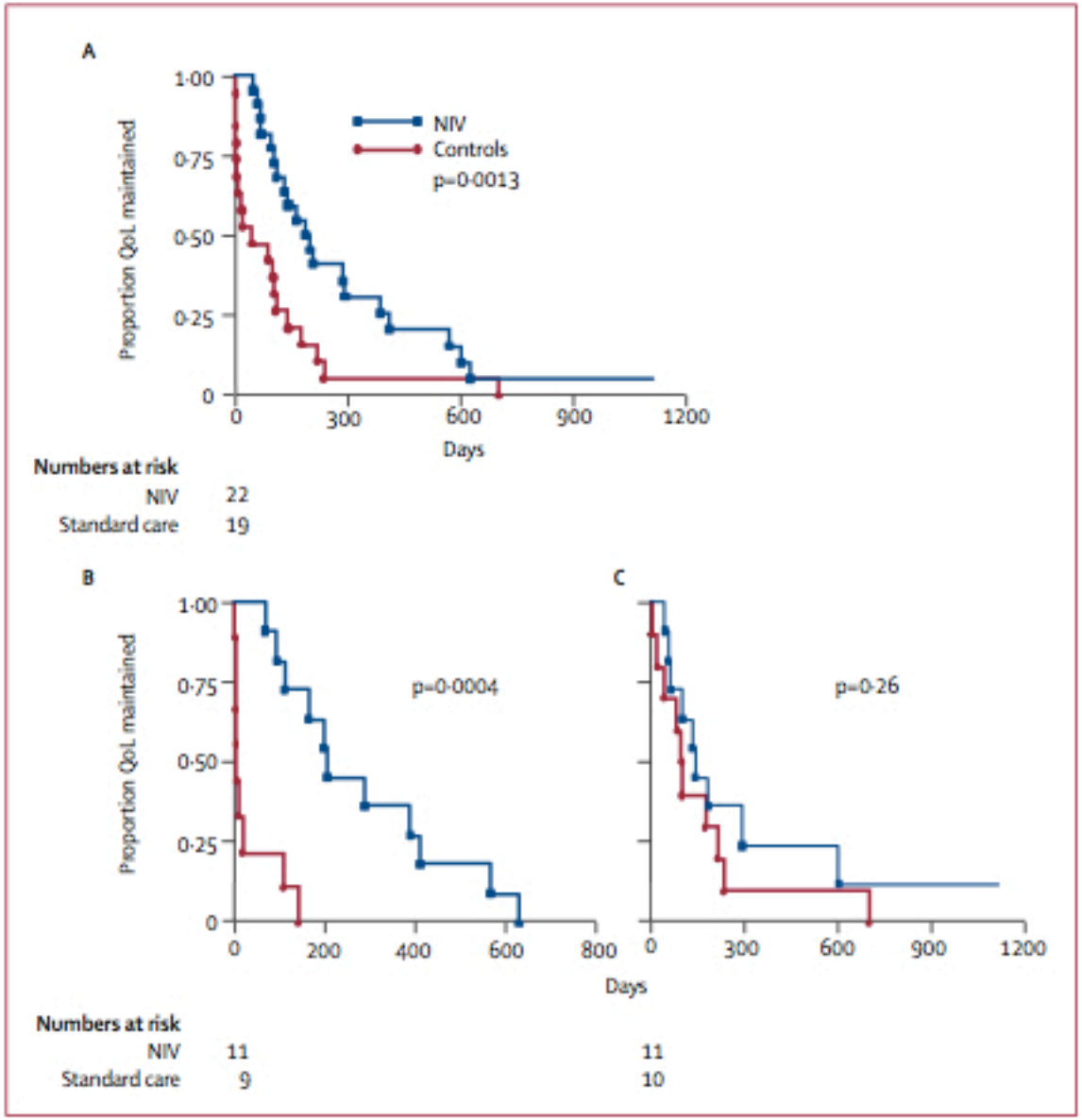


Figure 3: **Time SAQLI symptoms domain maintained above 75% of prerandomisation assessment**
A: all patients; B: patients with normal or moderately impaired bulbar function; C: patients with severe bulbar impairment. QoL=quality of life.

Bourke, S.C. *et al*. 2006 Lancet Neurol 5: 140-147

ALS: RCT for NIPPV

- Bourke, S.C. *et al*. 2006 Lancet Neurol 5: 140-147:
  - NIPPV improved QoL and survival (median of 205 days) in ALS patients without severe bulbar dysfunction
  - Survival benefit greater than available drug treatment
  - Reason for lack of survival benefit in patients with severe bulbar function unclear → NIPPV may not be effective in this subgroup or may be related to intolerance
    - Cannot comment on use of NIPPV in this subgroup

Long Term Mechanical Ventilation (LTMV)

- Generally considered for symptoms of respiratory failure: intolerance of NIPPV or failure of NIPPV ➔ Often initiated in emergent situation
  - Secures airway
  - Prevents/reduces aspiration pneumonia
  - Prolongs life
- Patient factors associated with tracheostomy:
  - Male gender
  - Younger
  - Higher income
  - Young children
  - Belief in future cure
- Varying tracheostomy rate between countries:
  - USA: 3%
  - Germany: 3%
  - United Kingdom: 0%
  - Japan: 27-45%

ALS: LTMV

- Median survival: 12-37 months
- Most common cause of death: respiratory tract infection
- Controversial:
  - 50-70% of patients with tracheostomy will have minimal ability to communicate or locked-in
  - Expensive
  - Increased caregiver burden
  - Very limited data, re: survival, QoL

ALS: Respiratory Symptoms

- Dyspnea: opioids, benzodiazepines
- Diaphragmatic pacing stimulators: intramuscular implantation of electrodes, with goal of postponing need for invasive mechanical ventilation
  - Remains controversial → no evidence for ALS patients
- Supplemental oxygen therapy may suppress respiratory drive, worsen hypoventilation, cause carbon dioxide retention, and lead to respiratory arrest
  - Can be used for concomitant cardiac or respiratory disease
  - Can be used as comfort measure in terminal stage of disease

END-OF-LIFE CARE

ALS: End-of-Life Care

- Currently unclear from international guidelines when Palliative Care should become involved in patient care ➔ suggestion of early on in disease
  - To develop rapport
  - To introduce end-of-life planning prior to onset significant cognitive or communication issues
- Suggested triggers for end-of-life discussions:
  - Patient initiated
  - Presence of severe psychological, social, or spiritual distress or suffering
  - Presence of pain requiring high-dose analgesic medications
  - Dysphagia requiring feeding tube
  - Presence of dyspnea, symptoms of hypoventilation, or FVC <50%
  - Loss of body function in two regions (bulbar, arms, or legs)
- UK studies:
  - 30-75 % of PC/hospice units provide ALS care
  - Only 8% involved from time of diagnosis

ALS: End-of-Life Management

- Palliative Medicine consultant generally involved only during terminal phase of disease
  - Hospice/PC unit admission
  - Withdrawal of LTMV
- Majority of patients die at home → may have difficulty accessing community PC programs
- Common barriers to palliative care intervention:
  - Unpredictable non-cancer disease trajectory
  - Lack of defined referral criteria for non-malignant conditions
  - Lack of non-cancer disease specific expertise
  - Limited resources

ALS: End-of-Life Management

- Anxiety surrounding final stages of disease ➔ dyspnea, choking, and pain
- Mandler, R.N. *et al*. 2001 Amytroph Lateral Scler Other Motor Neuron Disord 2: 203-208:
  - Observational registry of 1014 American and Canadian ALS patients who died during 4 year period
  - Questionnaire filled out by caregiver or family member
  - Mean age at death: 62 years
  - 64.1% of patients died at home, 20.7% in hospital, 7.7% in skilled nursing facility, 6.9% in hospice
  - >90% of patients were followed at a tertiary care centre with ALS expertise and multidisciplinary approach

ALS: End-of-Life Management

- Mandler, R.N. *et al.* 2001 Amytroph Lateral Scler Other Motor Neuron Disord 2: 203-208:
  - 88.9% had advance care directives in place
  - 90.7% of patients died peacefully
  - 9.3% with distress during dying process:
    - Breathing difficulties: 82.1%
    - Fear/anxiety: 55.2%
    - Pain: 23.9%
    - Insomnia: 14.9%
    - Choking: 14.9%
  - Palliative care relatively well-managed and interventions effective

Conclusions

- Complex, progressive disease with very limited treatment options
  - No evidence of change in median survival
- Despite attempts to establish evidence-based guidelines, very few well-designed trials to guide symptom management ➔ reliant on expert consensus and clinical experience
- Ongoing loss of function, including cognition and communication ➔ early Palliative Care and end-of-life planning is essential
  - Significant burden of disease
  - Difficult decisions to be made
- Likely to be controversy in the near future as Canada contemplates euthanasia and physician-assisted suicide