Causal inference methods to study gastric tube use in amyotrophic lateral sclerosis

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ABSTRACT

Objective: To estimate effects of gastric tube (G-tube) on survival and quality of life (QOL) in people with amyotrophic lateral sclerosis (ALS) correcting for confounding by indication inherent in nonrandomized observational data.

Methods: To complement a recent causal inference analysis, which concluded that G-tube placement increases the hazard of death, permanent assisted ventilation, or tracheostomy by 28%, we fit causal inference models on a different sample of 481 patients with ALS enrolled in a recent clinical trial of ceftriaxone. Forward selection identified predictors of G-tube placement. Effects of G-tube on survival and QOL were estimated using structural nested models and marginal structural models, accounting for predictors of G-tube treatment.

Results: Forced vital capacity and the total score and bulbar subscale of the revised ALS Functional Rating Scale best predicted G-tube placement. Correcting for these confounders, G-tube placement decreased survival time by 46% ($p < 0.001$) and had no effect on QOL ($p = 0.078$). Sensitivity survival analyses varied in significance, but none revealed a survival benefit.

Conclusions: In the absence of randomization, causal inference methods are necessary to correct for time-varying confounding. G-tube placement may have a negative effect on survival with no QOL-related benefit for people with ALS. A randomized controlled trial is warranted to further evaluate the efficacy of this widely used intervention.

Clinicaltrials.gov identifier: NCT00349622.

Classification of evidence: This study provides Class III evidence that for patients with ALS, G-tube placement decreases survival time and does not affect QOL. *Neurology*® 2017;89:1483-1489

GLOSSARY

AAN = American Academy of Neurology; **ALS** = amyotrophic lateral sclerosis; **ALSFRS-R** = ALS Functional Rating Scale-Revised; **ALSSQOL** = ALS-Specific Quality of Life; **BMI** = body mass index; **FVC** = forced vital capacity; **G-tube** = gastric tube; **HRQOL** = health-related quality of life; **IPW** = inverse probability weights; **LOCF** = last observation carried forward; **LTFU** = loss to follow-up; **PAV** = permanent assisted ventilation; **QOL** = quality of life; **RCT** = randomized controlled trial.

Studies of gastric tubes (G-tubes) in people with amyotrophic lateral sclerosis (ALS) report inconsistent conclusions regarding efficacy, perhaps attributable to a lack of randomized controlled trials (RCTs).¹⁻⁸ Most published findings come from nonrandomized observational studies in which controls are patients who refused G-tubes. Such results contain bias when receipt of the intervention is influenced by some characteristic related to the outcome, i.e., confounding by indication. Simply adjusting for confounders in a regression model fails in longitudinal settings when treatment also affects future values of that same confounder.⁹ In such cases, simple adjustment removes the part of the treatment effect that is mediated through the confounder.

Causal inference methods are better suited to analyze nonrandomized data.¹⁰ One such technique, the marginal structural model, was previously applied to a sample of 300 patients with ALS, concluding that G-tube placement was associated with a 28% increase in the hazard of death, permanent assisted ventilation (PAV), or tracheostomy after accounting for

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Supplemental data
at Neurology.org

From the Biostatistics Center (E.M., D.S.) and Neurological Clinical Research Institute (S.P., N.A.), Massachusetts General Hospital; and Harvard Medical School (D.S., S.P., N.A.), Boston, MA.

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confounding from vital capacity and functional capability.¹ This finding contradicts the current standard of care, which recommends G-tube placement for prolonging survival.¹¹

The primary objective of this study is to apply a second class of causal inference models, structural nested models,^{12,13} to estimate the effect of G-tubes on survival in another, larger sample of people with ALS. As a secondary objective, we also estimate the effect of G-tubes on quality of life (QOL).

METHODS Classification of evidence. This secondary analysis was designed to determine with Class III evidence whether G-tube placement has a causal relationship with survival or QOL in people with ALS.

Study design and population. This analysis was performed using data from a multicenter, placebo-controlled RCT (NCT00349622) designed to assess ceftriaxone's effects on survival and functional decline in patients with ALS.^{14,15} The trial ran from 2006 to 2012, enrolling 513 participants with laboratory-supported probable, probable, or definite ALS according to the El Escorial criteria¹⁶ and a vital capacity of at least 60% at the time of screening. Initial ALS symptoms occurred less than 3 years before screening and if taking riluzole the dose was stable. Per protocol, participants completed assessments at baseline; weeks 1, 2, and 4; and every 4 weeks thereafter. Dates of G-tube placement were recorded.

Standard protocol approvals, registrations, and patient consents. The ceftriaxone trial was institutional review board–approved and all participants gave informed consent to participate.

Statistical analysis. Survival was defined as time in weeks from screening until death, PAV, or tracheostomy. QOL was measured using the average total score of the ALS-Specific Quality of Life (ALSSQOL) inventory, a 59-item patient-reported assessment that evaluates perceived QOL with respect to such domains as negative emotion, interaction with people and the environment, intimacy, religiosity, physical symptoms, and bulbar function.¹⁷

Characteristics considered for confounding included sex, age, disease duration, site of symptom onset, respiratory comorbidities (history and prevalence at screening), cardiovascular comorbidities (history and prevalence at screening), use of riluzole, use of ceftriaxone, the ALS Functional Rating Scale (ALSFERS-R) total score and 4 subscales (bulbar, breathing, fine motor, and gross motor),¹⁸ percent change in body mass index (BMI) from screening, forced vital capacity (FVC), grip strength using handheld dynamometry, and the ALSSQOL. The ALSFERS-R was collected every 8 weeks while all other repeated assessments were collected every 16 weeks. Missing values throughout follow-up were imputed using last observation carried forward (LOCF) and values were assumed to remain constant between assessments. Student *t* tests and Fisher exact tests were used to compare continuous and categorical characteristics, respectively, by eventual receipt of G-tube. We used forward selection to identify the most significant predictors of the probability of G-tube placement over time, representing each longitudinal predictor by its values at both baseline and a given visit. Predictors of loss to follow-up

(LTFU), defined as censoring prior to August 1, 2012, were identified in the same manner. The resulting sets of significant confounders were then accounted for in the analyses of QOL and survival.

We estimated the effect of G-tube on survival using a structural nested accelerated failure time model.^{12,13} Conceptually, this technique first assumes that treatment expands survival time by a certain factor. Patients' counterfactual or hypothetical survival times had they never been treated can be derived by inflating or deflating all periods of received treatment by the inverse of this factor throughout their observed survival times. Second, this technique assumes that patients with the same treatment and confounder histories have identically distributed counterfactual survival times under any given treatment plan. In other words, the decision for one patient to receive treatment over another is random—not due to differences in how well he or she would do under a given treatment plan—after adjusting for past treatment and confounders. Third, this technique assumes that within levels of treatment and confounder history, variability exists in treatment decisions. Combining these assumptions, if the effect of treatment on survival is known and is used to calculate patients' hypothetical survival times had they never been treated, then this set of counterfactual survival times should not predict the probability of treatment after adjusting for treatment and confounder histories. In a process called g-estimation, a search is conducted for the treatment effect, with each candidate testing whether the effect of the calculated counterfactual survival times on the probability of treatment is exactly 0 in a logistic regression model adjusting for past levels of treatment and confounders. Statistical inference was made using a bootstrap method. LTFU was corrected for using inverse probability weights (IPW). Administrative censoring was accounted for by only allowing participants to contribute information from a given time forward if their counterfactual survival times would have been observed under all possible subsequent treatment decisions.

Several sensitivity analyses were performed. First, we refit the structural nested model considering all censored cases as LTFU, using IPW to correct for their exclusion from the model. Second, we handled all censored cases as administratively censored, omitting the IPW. Third, we restricted missing data imputation by artificially censoring patients after more than a 17-week gap between 2 ALSFERS-R assessments or more than a 33-week gap between 2 BMI, FVC, grip strength, or ALSSQOL measurements. Censoring prior to August 1, 2012, was again used to distinguish LTFU from administrative censoring.

As an additional sensitivity analysis and to complement prior work,¹ we fit a marginal structural model, which in a simplified form models the effect of an intervention on an outcome after weighting each observation by both (1) the inverse probability of a patient's observed treatment status at the given visit adjusting for past treatment and select confounders and (2) the inverse probability of not yet being censored for any reason at the given visit adjusting for select confounders. These weights conceptually create a pseudopopulation in which the effect of the intervention on the outcome is no longer confounded.^{19–21} We used the same predictors of G-tube and censoring as those from our primary analysis. We present results using stabilized versions of the weights, adding baseline values of the predictors of G-tube and censoring as covariates in the final weighted survival model.

For the secondary QOL objective, marginal structural models were also fit to estimate the causal effect of G-tube use on the ALSSQOL average total score, using the same predictors of G-tube and censoring.

Table 1 Select baseline characteristics by eventual gastric tube (G-tube) placement

Characteristic	Overall (n = 481)	Eventual G-tube placement		p Value
		No (n = 257)	Yes (n = 224)	
Age, y, mean $\pm$ SD	55.2 $\pm$ 10.4	55.2 $\pm$ 11.0	55.1 $\pm$ 9.8	0.853
Male, % (n)	61.1 (294)	63.8 (164)	58.0 (130)	0.223
Caucasian, % (n)	95.0 (454)	95.7 (243)	94.2 (211)	0.532
Ceftriaxone, % (n)	66.5 (320)	67.7 (174)	65.2 (146)	0.563
Any bulbar onset, % (n)	21.2 (102)	13.2 (34)	30.4 (68)	<0.001
Time from symptom onset to diagnosis, mo, mean $\pm$ SD	11.1 $\pm$ 6.8	11.8 $\pm$ 7.1	10.2 $\pm$ 6.3	0.009
ALSFRS-R, total, mean $\pm$ SD	37.0 $\pm$ 5.6	38.1 $\pm$ 5.2	35.7 $\pm$ 5.7	<0.001
ALSFRS-R, bulbar subscale, mean $\pm$ SD	10.0 $\pm$ 2.2	10.7 $\pm$ 1.7	9.2 $\pm$ 2.3	<0.001
ALSFRS-R, fine motor subscale, mean $\pm$ SD	8.1 $\pm$ 2.7	8.4 $\pm$ 2.5	7.8 $\pm$ 3.0	0.017
ALSFRS-R, gross motor subscale, mean $\pm$ SD	7.7 $\pm$ 2.7	7.7 $\pm$ 2.5	7.7 $\pm$ 3.0	0.949
ALSFRS-R, breathing subscale, mean $\pm$ SD	11.2 $\pm$ 1.3	11.3 $\pm$ 1.3	11.1 $\pm$ 1.4	0.096
Forced vital capacity %, mean $\pm$ SD	89.3 $\pm$ 16.7	91.8 $\pm$ 17.0	86.5 $\pm$ 15.9	<0.001
Grip strength, kg, mean $\pm$ SD	36.6 $\pm$ 26.8	39.4 $\pm$ 27.4	33.4 $\pm$ 25.8	0.014

Abbreviation: ALSFRS-R = ALS Functional Rating Scale-Revised.

Continuous and categorical characteristics were compared using Student t tests and Fisher exact tests, respectively. Characteristics were selected to be displayed in this table based on either clinical relevance or statistical significance. A complete set of baseline characteristics is available in table e-1.

All analyses were performed at the 0.05 significance level in SAS version 9.4 (Cary, NC). Structural nested models and marginal structural models were fit using publicly available example codes.^{13,21}

RESULTS Among the 513 participants in the ceftriaxone trial, 481 with complete baseline data who were not already using a G-tube at the time of screening were included in this analysis. Mean age was 55.2 $\pm$ 10.4 years and 61.1% of patients were male. A total of 268 patients (55.7%) eventually experienced a survival event during follow-up, specifically death (39.5%), PAV (10%), tracheostomy (1%), or

both PAV and tracheostomy (5.2%). Among the other 213, median follow-up duration was 99 weeks (range 31–306) or approximately 23 months (range 7.2–71.2 months) and 17 patients were LTFU. Grip strength and FVC were used to construct weights that corrected for this LTFU. By the end of follow-up, 224 (46.6%) eventually received a G-tube. Among them, at the time of G-tube placement, mean ALSFRS-R total score was 25.1 $\pm$ 7.7; mean FVC was 63.0 $\pm$ 21.5 percent predicted. Per American Academy of Neurology (AAN) guidelines,¹¹ 158 (70.5%) patients had low exposure to risk from

Table 2 Primary and sensitivity analyses of the effect of gastric tube on survival

Analysis	Confounders	Predictors of loss to follow-up (structural nested models) or any censoring (marginal structural models)	Survival time ratio (95% CI)	Causal rate ratio equivalent (95% CI)	p Value
Primary structural nested model	ALSFRS-R total; ALSFRS-R bulbar; FVC	Grip strength; FVC	0.54 (0.38–0.76)	2.1 (1.41–3.40)	<0.001
Sensitivity analysis 1: treating all censored observations as lost to follow-up	ALSFRS-R total; ALSFRS-R bulbar; FVC	Grip strength; FVC	0.77 (0.52–1.14)	1.2 (0.91–1.55)	0.199
Sensitivity analysis 2: treating all censored observations as administratively censored	ALSFRS-R total; ALSFRS-R bulbar; FVC	Grip strength; FVC	0.17 (0.13–0.23)	6.7 (4.76–9.13)	<0.001
Sensitivity analysis 3: censoring patients with >17 weeks between 2 ALSFRS-R assessments or >33 weeks between 2 FVC, grip strength, BMI, or ALSSQOL assessments	ALSFRS-R total; ALSFRS-R bulbar; FVC	ALSFRS-R; grip strength; ceftriaxone; ALSFRS-R fine motor; ALSSQOL	0.34 (0.11–1.07)	4.8 (0.91–28.82)	0.065
Sensitivity analysis 4: marginal structural model	ALSFRS-R total; ALSFRS-R bulbar; FVC	Grip strength; FVC	—	1.01 (0.45–2.26)	0.978

Abbreviations: ALSFRS-R = ALS Functional Rating Scale-Revised; ALSSQOL = ALS-Specific Quality of Life; BMI = body mass index; CI = confidence interval; FVC = forced vital capacity.

Figure 1 Counterfactual survival times among gastric tube (G-tube) recipients

Kaplan-Meier curves compare observed survival times in G-tube recipients vs their estimated survival times had they never received a G-tube. Receipt of a G-tube results in 46% shorter survival times ($p < 0.001$).

G-tube (FVC $>50\%$), 54 (24.1%) had moderate risk (FVC 30%–50%), and 12 (5.4%) had high risk (FVC $<30\%$). For a given longitudinal assessment (ALSFRS-R, FVC, BMI, and ALSSQOL), the total number of completed assessments ranged from 84% to 98% of expected over total patient follow-up time.

As described in table 1 and table e-1 at Neurology.org, those who eventually received a G-tube were more likely to have bulbar onset and had a shorter mean duration between symptom onset and diagnosis than those who did not receive a G-tube. At baseline, they had lower ALSFRS-R total, bulbar, and fine motor scores, lower FVC, and lower grip strength. Longitudinally, using forward selection, FVC and the ALSFRS-R total score and bulbar subscale were selected as the top predictors of G-tube placement over time (table e-2).

Survival. Primary and sensitivity survival analyses are presented in table 2. Using g-estimation, we performed a grid search for the effect of G-tube on survival, testing over 600 potential estimates. With each proposed effect estimate, we constructed patients' counterfactual survival times had they never received G-tube by inflating/deflating observed times of G-tube use by the inverse of the effect. Choosing the effect estimate for which patients' counterfactual survival times did not influence G-tube placement after correcting for censoring and adjusting for time-varying FVC and the ALSFRS-R total score and bulbar subscale, G-tube placement decreased

patients' survival time by 46% ($p < 0.001$), which is equivalent to a hazard ratio of 2.1.

In sensitivity analyses (table 2), the decrease in survival time due to G-tube weakened to insignificance when treating all censoring as LTFU and strengthened in both magnitude and significance when treating all censoring as administrative. In the sensitivity analysis that truncated follow-up to restrict missing data imputation, 246 patients were deemed LTFU. Predictors of this premature censoring included ceftriaxone study group assignment, grip strength, QOL, and the ALSFRS-R total and fine motor scores. In this sensitivity analysis, 181 patients (37.6%) eventually received G-tube and 129 (26.8%) eventually experienced death, PAV, or tracheostomy. Adjusting for FVC and the ALSFRS-R total score and bulbar subscale, G-tube decreased patients' survival time by a marginally significant 66%. Finally, fitting a marginal structural model, G-tube increased the hazard of death, PAV, or tracheostomy by a nonsignificant 1%.

Quality of life. Again using FVC and the ALSFRS-R total and bulbar scores to construct IPW for treatment, and using grip strength and FVC to construct IPW for censoring, a marginal structural model estimated that G-tube worsened the ALSSQOL average total score by 0.23 points, though not significantly (95% confidence interval -0.50 to 0.03 , $p = 0.078$).

G-tube comorbidity. We further explored the subset of 224 patients who received a G-tube. Figure 1 depicts this subset's observed and counterfactual survival times had they never received a G-tube, assuming the estimated survival time ratio of 0.54. Thirteen patients either died or began PAV or tracheostomy within 1 month of G-tube placement, resulting in a 1-month failure rate of 5.8%.

Regarding safety, 21 patients (9.4%) reported abdominal pain related to the G-tube, all grade 2 or below. Five patients (2.2%) experienced serious adverse events related to the G-tube, including displacement, obstruction, infection, and leak at the G-tube site.

Finally, we evaluated potential predictors of survival among those who received a G-tube, from the time of G-tube placement forward. Using a log-rank test from a standard Kaplan-Meier estimator, the 3 risk categories of G-tube recipients per AAN guidelines had vastly different trajectories ($p < 0.001$) (figure 2). Ten out of 12 patients who had high exposure to risk (FVC $<30\%$) at the time of G-tube placement eventually died or initiated PAV or tracheostomy, with a median post-G-tube survival time of 1.9 months compared to 10.7 months in the lowest risk patients. Those with BMI loss of at least 15% at the time of G-tube placement had

Figure 2 Survival after gastric tube (G-tube) placement by American Academy of Neurology guidelines

Kaplan-Meier curves compare survival times among G-tube recipients with forced vital capacity (FVC) <30%, FVC 30%–50%, and FVC >50% at the time of G-tube placement. Lower FVC is associated with poorer survival free of permanent assisted ventilation or tracheostomy after G-tube placement ($p < 0.001$).

a shorter median survival than the rest; however, this difference was not significant (6.1 vs 9.5 months; $p = 0.464$) (figure 3).

DISCUSSION This study replicates the harmful effects of G-tube placement on survival using a different

causal inference method in an independent, larger cohort of patients with ALS.¹ Our primary analysis showed that G-tube reduced survival by 46%, with sensitivity analyses showing at best no advantage and at worst a 6-fold increase in hazard. We also demonstrated that G-tube placement neither improved nor worsened QOL.

Our findings contradict other claims that G-tubes stabilize weight, which may be a mediator for improving survival time.^{22–24} The AAN currently advises G-tube use in patients with ALS but recognizes that the benefit cannot be quantified from the current literature, nor has optimal timing been determined.¹¹

It is possible that G-tubes only benefit a subgroup of patients who, for example, have maintained strong vital capacity or weight.^{24–26} Our analysis of the G-tube subgroup suggests that survival postprocedure depends on FVC, but not the percent change in BMI, at the time of the procedure. A total of 29.5% of patients who received a G-tube in these data had $FVC \leq 50\%$, despite AAN guidelines classifying such patients as having moderate to high risk of poor outcome. A similar proportion was reported in another observational study.²⁷ Ideally, one might consider restricting this analysis to patients with $FVC > 50\%$ at the time of G-tube placement. However, to do so would require analogously restricting the control group to those who would have had $FVC > 50\%$ at the time they would have received a G-tube in a counterfactual world. Without an RCT there is no defined time point at which to evaluate control patients' FVC

Figure 3 Survival after gastric tube (G-tube) placement by body mass index (BMI) loss from baseline to G-tube placement

Kaplan-Meier curves compare survival times among G-tube recipients with $\geq 15\%$ loss in BMI from baseline vs stable BMI at the time of G-tube placement. Survival free of permanent assisted ventilation or tracheostomy after G-tube placement is not associated with BMI loss ($p = 0.464$).

for inclusion in such an analysis; therefore it cannot be done in this observational study.

Despite a harmful estimated effect of G-tube on survival, the observed 5.8% 1-month mortality rate post-G-tube and 2.2% incidence of serious adverse events are lower than past reported 1-month mortality and complication rates as high as 25%⁶ and 45%,² respectively. It has been suggested that a cooling off period, or a scheduled week-long waiting policy before a G-tube insertion, would allow patients to change their minds or allow the sickest patients to die naturally without the added complications of a G-tube placement.²⁸ Perhaps among patients who survived past a certain point postprocedure with no complications, eliminating the sickest patients who may have opted out of the procedure had they been given a cooling off period, G-tubes may improve survival. Again, such analyses are infeasible in this observational study given the inability to subset the control group by postoperative survival time. However, the observed 5.8% mortality rate 1 month postprocedure renders it unlikely that these rapidly declining patients are the sole drivers of G-tubes' harmful effect on survival.

The question of efficacy of G-tubes in ALS is further raised by the lack of QOL benefit, which is supported by past work.²⁹ However, perhaps the lack of benefit is a result of the assessment tool. The ALSS-QOL measures overall QOL beyond the scope of disease, capturing factors such as interaction with people and the environment, religiosity, and intimacy.¹⁷ It may be that an underlying change in health-related QOL (HRQOL) post G-tube placement is masked by these non-health-related factors of the ALSSQOL. In one observational study, 17% of patients who received G-tubes reported improved psychological well-being, specifically regarding nutrition.⁷ More research is needed in this area, probably using HRQOL-specific assessments such as the 36-item Short Form Health Survey.³⁰

Two causal inference techniques have been employed to estimate effects of G-tube on survival in ALS: marginal structural models and structural nested models. While their results varied in significance in this analysis, confidence intervals overlapped, and neither method suggested a survival benefit. In practice, one method may be preferred over the other depending on the research question at hand. Marginal structural models are arguably more intuitive due to their structural similarity to standard regression models. However, although not implemented in this study for the sake of simplicity, structural nested models can accommodate effect modification with time-varying covariates.^{21,31}

Nonetheless, causal inference analyses cannot adequately substitute for an RCT of G-tubes in ALS. To

maintain equipoise, we suggest a RCT design that would guarantee G-tube for all patients, randomizing the timing of G-tube placement, as done previously with antiretroviral therapy in HIV.³² Not only could efficacy be estimated between G-tube recipients and nonrecipients before delayed treatment arms receive a G-tube, but optimal timing could also be identified.

As for limitations, although many potential confounders were considered in this analysis, smoking status and possibly other important characteristics were not systematically collected and therefore remained unaccounted for. This highlights the importance of thoughtful data collection in observational studies. Second, the LOCF technique for missing data imputation asserts that patients' characteristics remained constant during the time between visits. More complex multiple-imputation approaches were beyond the scope of this analysis, which intended to demonstrate causal inference methods and advocate for an RCT.

We have demonstrated the importance of applying causal inference methods in the presence of time-varying confounding in observational data. Although the body of research is inconclusive about the survival benefits of G-tube placement in patients with ALS, 2 advanced statistical analyses in 2 independent cohorts now suggest that G-tube placement may shorten survival time after properly accounting for bias inherent in longitudinal observational data. We also demonstrate a lack of improvement in QOL. Still, this study does not rule out the possibility that G-tube placement may increase survival in a subset of patients with ALS, perhaps those with relatively preserved FVC or overall function. RCTs are needed to verify the effect of G-tubes on survival in people with ALS, and to identify ALS subpopulations that may potentially benefit the most from G-tube placement.

AUTHOR CONTRIBUTIONS

Erin McDonnell: statistical analysis, interpretation of results, manuscript writing, and approval of the final draft. Sabrina Paganoni: interpretation of results, manuscript writing, and approval of the final draft. David Schoenfeld: statistical analysis, interpretation of results, manuscript writing, and approval of the final draft. Nazem Atassi: interpretation of results, manuscript writing, and approval of the final draft.

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