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[Invasiv ventilatorbehandling hos patienter med Amyotrofisk Lateral Skleros och respiratorisk insufficiens]

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Published June 2014

2014:72

Suggested citation: Mitre B, Davidson M, Daxberg E-L, Jivegård L, Rosén H, Svanberg T, Strandell A.

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Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum; 2014. Regional activity-based HTA 2014:72

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Abbreviations

ALS	Amyotrophic lateral sclerosis
EFNS	European Federation of Neurological Societies
IV	Invasive ventilation
MND	Motor neuron disease
NIV	Non-invasive ventilation
NICE	National Institute for Health and Clinical Excellence
QoL	Quality of life
QALY	Quality- adjusted life-year
SEK	Swedish kronor

Summary of the Health Technology Assessment (1 & 2) from The Regional Health Technology Assessment Centre (HTA-centrum)

The Regional Health Technology Assessment Centre (HTA-centrum) of Region Västra Götaland, Sweden (VGR) has the task to make statements on HTA reports carried out in VGR. The English summary is a concise summary of similar outline as the summaries in the Cochrane systematic reviews. The Swedish summary summarises the question at issue, results and quality of evidence regarding efficacy and risks, and economical and ethical aspects of the particular health technology that has been assessed in the report, and is ended with a final statement/concluding remark from HTA-centrum.

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1. Summary of the Health Technology Assessment

Background

Amyotrophic lateral sclerosis (ALS) is an incurable neuromuscular disease with progressive muscular weakness due to degeneration of both the upper and lower motor neurons in the brain, brain stem and spinal cord. Cognition can be affected and dementia may develop. Respiratory failure and respiratory complications are the main causes of death in patients with ALS. Non-invasive ventilation (NIV) with a nasal, oral or facial mask to manage respiratory impairment in the late course of the disease has increased in use and is today a routine procedure. Invasive ventilation (IV) through a tracheostomy is now being introduced to some patients. The method implies ethically difficult concerns.

Objective

To assess whether tracheostomy and invasive ventilation prolong survival and improve quality of life in patients with ALS and respiratory failure in comparison to non-invasive ventilation and supportive care.

Search methods and study selection criteria

Systematic searches were performed in PubMed, EMBASE, the Cochrane Library, AMED, PROQUEST (PsycINFO, British Nursing Index, Nursing & Allied Health Source) and a number of HTA-databases. Reference lists of relevant articles were scrutinised for additional references. For outcome analysis, controlled studies with at least ten patients in the intervention group were included. The quality of evidence was rated using the GRADE system.

Results

Ten comparative studies and four case series/reports met the inclusion criteria. In general, the comparative studies were heterogeneous regarding the severity and stage of the disease and had a moderate to high risk of bias.

Seven studies (comprising 2 276 patients) reported survival. All but one study (inappropriate intervention group) demonstrated prolonged survival with the use of IV, although not statistically significant in some studies. The prolonged survival with IV varied from median 9 to 16 months. The only study with a low risk of bias evaluated IV vs. continued NIV or no assisted ventilation in patients with end-stage ventilatory insufficiency and demonstrated a prolonged survival with IV (mean 10.4 vs. 0.8 months, $p < 0.0001$). One-year survival in a Danish study was reported to increase from 65% with no ventilation, to 73% with NIV, and to 80% with IV.

Only one study reported quality of life at follow-up comparing IV to NIV without showing any difference.

Ethical aspects

It is important that the patient is adequately informed about IV and its consequences for daily life before the intervention, to ensure a proper informed consent. The use of IV requires preserved cognition. Invasive ventilation impairs communication and the patient's ability to exert his own autonomy. Use of the method implies increasing dependence on caring personnel and/or the next of kin. The equipment and the care are expensive and an increasing number of patients treated with IV would require a reallocation of resources.

Concluding remarks

Invasive ventilation with tracheostomy probably prolongs survival considerably compared with non-invasive ventilation or no ventilation in ALS-patients with respiratory failure. The effect size is highly dependent on the severity of the respiratory failure when the treatment is initiated.

Moderate quality of evidence (⊕⊕⊕○).

It is uncertain whether there is any influence on quality of life with tracheostomy and invasive ventilation as compared to non-invasive ventilation.

Very low quality of evidence (⊕○○○).

2. Svensk sammanfattning

Bakgrund

Amyotrofisk lateral skleros (ALS) är en obotlig sjukdom med progredierande muskelförlamning, orsakad av degeneration av motorneuron i hjärna, hjärnstam och ryggmärg. Kognitiv funktion kan påverkas och demens utvecklas. Vanligaste dödsorsakerna är respiratorisk insufficiens och andra lungkomplikationer. När ALS-patienter börjar få andningspåverkan är det numera rutin att stödja andningen med icke-invasiv ventilation (NIV) via mask. Invasiv ventilation (IV) via tracheostomi har börjat erbjudas vissa patienter. Det kan ske elektivt, i samförstånd med patienten, men ibland i en akut situation där patienten inte hinner tillfrågas och där tracheostomi och efterföljande respiratorbehandling är omedelbart livräddande. Denna metod har många etiska implikationer.

Syfte

Att utvärdera om invasiv ventilation via tracheostomi förlänger överlevnad och förbättrar livskvalitet hos ALS-patienter med påverkad andningsfunktion, jämfört med icke-invasiv ventilation och allmänt stödjande behandling.

Resultat

Tio jämförande studier och fyra fallserier/rapport uppfyllde kriterierna (=PICO) för inklusion. De jämförande studierna uppvisade patienter i olika stadier av sjukdomsförloppet och de flesta hade måttliga eller allvarliga brister i studiekvaliteten.

Sju studier (2276 patienter) rapporterade överlevnad efter invasiv, icke-invasiv och utan assisterad ventilation. Alla utom en studie (som hade en inadekvat interventionsgrupp), visade förlängd överlevnad med IV, dock utan statistisk signifikans i flera av studierna. Förlängd överlevnad varierade mellan median 9 och 16 månader. Den enda studien utan selektionsbias jämförde IV mot NIV eller ingen assisterad ventilation, i en patientgrupp där NIV började bli otillräcklig för adekvat ventilation. Medelöverlevnaden var då 10.4 respektive 0.8 månader, $p < 0.0001$.

Ett-års överlevnaden i en dansk studie i ett tidigare stadium av sjukdomen var 65% utan ventilation, 73% med NIV och 80% med IV.

Tre observationsstudier rapporterade livskvalitet, mätt med validerade skalor. Två redovisade endast resultat från studiestart (ingen skillnad mellan grupper). Den tredje påvisade ingen skillnad (IV mot NIV) i livskvalitet vid uppföljning.

Etiska aspekter

Det är angeläget att ALS-patienter är välinformerade om IV och dess konsekvenser, så att patienten själv kan uttrycka sina önskemål och medverka vid beslut om behandling.

Metoden försämrar kommunikationsförmågan och möjligheten att utöva sin autonomi. Beroendet av vårdpersonal och anhöriga ökar. Kostnaden för IV är hög och skulle orsaka undanträngningseffekter om IV skulle införas som rutinbehandling.

Slutsatser

Invasiv ventilation med tracheostomi ökar troligen överlevnaden avsevärt jämfört med icke-invasiv eller ingen ventilation hos ALS-patienter med andningsinsufficiens. Effektens storlek är helt beroende av vid vilken tidpunkt under sjukdomsprogressen, som behandlingen sätts in.

Måttligt starkt vetenskapligt underlag (⊕⊕⊕○).

Livskvalitet under de vunna levnadsåren är dåligt studerat.

Otillräckligt vetenskapligt underlag (⊕○○○).

3. Participants in the project

Who posed the question?

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Are there any conflicts of interest for the proposer or any of the participants?

No

Project time

HTA was accomplished during the period 2013-11-21 – 2014-04-23.
Last search updated in November 2013

4. Amyotrophic lateral sclerosis and present treatment of respiratory failure

Amyotrophic lateral sclerosis (ALS) is an incurable and progressive neuromuscular disease with muscular weakness due to degeneration of both the upper and lower motor neurons in the brain, brain stem and spinal cord. Cognition can be affected and approximately 10% of the patients develop dementia. Respiratory muscle weakness is often a late symptom. Respiratory failure and respiratory complications are the main causes of death.

Degree of severity:

- Risk of premature death
- Risk of permanent illness or damage, or reduced quality of life
- Risk of disability and health-related quality of life

Prevalence and incidence of ALS

There are at least 600-700 ALS patients in Sweden. The annual incidence is 200 patients (Socialstyrelsen, 2010). The ALS-MND Clinical Centre at Sahlgrenska University Hospital takes care of approximately 65 patients with ALS/Motor neuron disease (MND) from the Göteborg area. Other hospitals in Region Västra Götaland have responsibility for patients in their vicinity. The total number of patients with ALS within VGR is estimated to be approximately 130 of which 32 receive non-invasive and six invasive ventilation.

Non-invasive ventilation

Non-invasive ventilation (NIV) supports the patient's own breathing. Through a facial, nasal or oral mask a ventilator delivers a positive airway pressure that supports and facilitates breathing. NIV requires spontaneous breathing.

Number of patients per year who undergo treatment with non-invasive ventilation

Thirteen (20%) of the 65 patients at the ALS-MND Clinical Centre at Sahlgrenska University Hospital currently have NIV. Most of them use the ventilator during night, and only when needed during daytime. The use of NIV has increased during the last years. During 2013, 13 patients started treatment with NIV. A follow-up in February 2014 revealed that eight of those patients have died.

The normal pathway of patients with respiratory failure through the health care system

The patient will regularly meet a neurologist in the ALS-team every second or third month to discuss problems that arise during the course of the disease. When the breathing capacity is impaired, medication that reduces the production of saliva will be prescribed and a coughing machine will be added. With further decline of the respiratory function, the patient will be offered a non-invasive ventilator. The patients are then referred to the Neurological department at the Sahlgrenska University Hospital in Göteborg. The patient is taught breathing techniques by a physiotherapist during one or two days. When comfortable with the ventilator, the patient can be discharged. The patient is followed by a neurologist every second or third month with regard to the function of the non-invasive ventilator. Patients with severe symptoms late in the course of the disease will receive assistance from home care facilities, and advanced ambulatory medical treatment at home. Some patients spend their final days at hospice or homes designed for elderly.

Actual wait time in days for medical assessment /treatment

ALS patients with respiratory failure are highly prioritised. The maximum waiting time for assessment and start of non-invasive ventilation is two weeks.

5. Invasive ventilation with tracheostomy

Description of invasive ventilation with tracheostomy

Invasive ventilation (IV) secures the airway by insertion of a tube into the trachea. For long-term ventilation a tracheotomy is performed, and a tracheostomy tube is inserted. The ventilator independently overrides the patient's own breathing. Thus, IV is a life sustaining treatment when respiratory function fails and NIV no longer is an alternative. Invasive ventilation with portable ventilators is an established long-term treatment at home for patients with severe respiratory failure, e. g. patients with spinal cord injuries. Some patients have a limited remaining breathing capacity and they use an invasive ventilator as supportive treatment.

The work group's understanding of the potential value of invasive ventilation

The use of NIV to manage respiratory impairment in ALS has increased (O'Neill et al., 2012). The treatment is included in clinical guidelines (NICE, 2010 and EFNS, 2012). At the ALS-MND Clinical Centre at Sahlgrenska University Hospital, NIV is offered to all patients with symptoms of respiratory failure in the absence of contraindications. A Cochrane systematic review has concluded based on one single randomized trial that NIV significantly prolongs survival and improves or maintains quality of life, compared with no assisted ventilation in patients with ALS (Radunovic et al., 2013). Several retrospective and some prospective studies have reported that NIV may be associated with a gain in survival. Patients with ALS who have significant bulbar involvement may have lower tolerance to non-invasive ventilation compared with patients with little or no bulbar muscle (oral and pharyngeal) weakness (Radunovic et al., 2013).

In contrast to NIV, IV is not considered to be a standard treatment to manage respiratory impairment in ALS at our ALS-MND Clinical Centre. At present three (5%) and 13 patients (20%) of a total of 65 patients are on IV and NIV respectively. In Sweden there are no national guidelines on the management of respiratory failure in ALS. The use of IV in different parts of Sweden is unknown. We believe that other Swedish ALS-MND Clinical Centres also have a restrictive approach to initiate IV. The use of IV varies greatly in different countries (Chiò et al., 2010). The variation can be related to cultural and religious factors, differences in legislation on life sustaining treatment, and different organization of the healthcare systems. Despite the similarities between countries, a recent study from Denmark shows a higher proportion of patients on both NIV and IV compared to our ALS-MND Clinical Centre (Dreyer et al., 2013).

Non-invasive ventilation can prolong survival and improve quality of life in patients with ALS (Radunovic et al., 2013). To assume that IV would further prolong survival is logical. IV is a life sustaining treatment overcoming the respiratory muscles weakness. In cases with a significant bulbar muscle weakness it also overcomes the upper airway closure and difficulties with clearing airway secretions. Prolonged survival allows the paralyses of all voluntary muscles to progress, resulting in a deterioration of physical function and an increased need for care. Even the treatment with IV itself increases the need for care with maintenance and attention of the equipment. It is important to consider the effects of prolonged survival on the patient's quality of life.

Amyotrophic lateral sclerosis affects the ability to communicate and ultimately, disease progression can lead to a locked-in state with no ability to communicate. The patient autonomy should be considered during the entire course of the disease and the patient's wish to accept, decline or discontinue any treatment should be respected. Invasive ventilation could increase the number of patients in a locked-in state where the patient's desire is difficult to interpret.

Invasive ventilation is a treatment with a potential to prolong survival in ALS patients. Whether IV should be considered an alternative to NIV in patients with ALS and respiratory failure, is dependent on its effectiveness to prolong survival with maintained or improved quality of life without increased risk of serious complications. Invasive ventilation might be an alternative to NIV only in a limited number of patients, e. g. patients with significant bulbar muscle weakness.

The central question for the current HTA project in one sentence

Does invasive ventilation with tracheostomy prolong survival and improve quality of life in patients with amyotrophic lateral sclerosis and respiratory failure in comparison to non-invasive ventilation and supportive care?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P	Patients with ALS and respiratory failure
I	Tracheostomy and assisted ventilation
C	No tracheostomy C1: non-invasive assisted ventilation C2: supportive care without assisted ventilation
O	<u>Critical for decision making</u> Survival Quality of life and satisfaction with life quality Complications Communicative capability of the patient to influence the subsequent treatment <u>Important but not critical for decision making</u> Quality of life for relatives

6. Review of Quality of Evidence

Search strategy, study selection and references (Appendix 1)

During November 2013 two librarians (TS, ELD) performed systematic searches in PubMed, Embase, the Cochrane Library, AMED, PROQUEST (PsycINFO, British Nursing Index, Nursing & Allied Health Source) and a number of HTA databases. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in Appendix 1. The librarians conducted the literature searches, selected studies and independently assessed the obtained abstracts, and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to the participants, who read the articles independently and then decided in a consensus meeting the articles that should be included.

The literature search identified a total of 1168 articles (after removal of duplicates). The librarians then excluded 1107 articles after reading the abstracts. Another 26 articles were excluded by the librarians after reading the articles in full text.

The remaining 35 articles were sent to the participants, and 14 of them were finally included in the assessment. The included studies are presented in Appendix 2. Ten of these articles have been critically appraised; the remaining four were case series or case reports. The appraisal of articles was based on checklists from SBU (Swedish Council on Health Technology Assessment) designed for cohort studies. Excluded studies and reasons for exclusions are presented in Appendix 3.

Ongoing research

A search in Clinicaltrials.gov (2014-03-18 using the search terms ((amyotrophic lateral sclerosis OR ALS OR MND OR (Motor Neuron* OR Motoneuron* OR Motoneuron* OR Moto Neuron* OR Gehrig* OR Charcot) AND Disease*) AND (ventilator* OR ventilation* OR Artificial respiration OR Tracheotom* OR tracheostom* OR Tracheal intubation OR intratracheal intubation OR Endotracheal intubation)) identified 68 trials.

One trial (ClinicalTrials.gov Identifier: NCT00839033), a multicenter RCT from France was relevant for our question. The primary objective of the trial is to evaluate the number of patients who required invasive ventilatory support (endotracheal intubation or tracheotomy) in a group treated with cough assist machine compared to standard respiratory physiotherapy. Only 14 of 110 planned patients are recruited since 2009. It seems unlikely that the study will be completed.

Medical societies or health authorities that recommend invasive ventilation in amyotrophic lateral sclerosis

There are no national or regional guidelines regarding the use of IV. European guidelines recommend NIV to be considered in preference to IV, and IV is recommended to be initiated only after informed discussion with patient and caregivers. These recommendations were based on clear consensus of the task force (EFNS, 2012), despite the lack of high quality evidence.

The present knowledge of invasive ventilation in amyotrophic lateral sclerosis

The systematic literature search identified 14 articles; eight cohort studies (three prospective, five retrospective), two cross sectional studies, three case series and one case report (Appendix 2). A total number of 3915 patients were included, 957 of them receiving IV.

Survival (Appendix 4.1 and 5)

Seven studies (two prospective n=1921, five retrospective n= 355) reported survival. All but one study was limited by a moderate or a high risk of bias, mainly selection bias.

The only study with a low risk of bias, evaluating IV vs. continued NIV or no assisted ventilation in a group of patients with end stage ventilatory insufficiency, clearly demonstrated a prolonged mean survival with IV (10.4 vs. 0.8 months, p<0.0001) (Sancho et al., 2011).

Four studies compared IV to NIV. All but one study, which had an inappropriate intervention group, demonstrated a prolonged survival with the use of IV, although not statistically significant in all studies. Two studies compared IV to no assisted ventilation, and three studies did not report results separately for NIV and no assisted ventilation. The five studies demonstrated a prolonged survival with the use of IV. Results across studies are not meaningful to pool together, since treatment is initiated at different time points across studies. Prolonged median survival with IV varied from nine to 16 months.

Conclusion

Invasive ventilation with tracheostomy prolongs survival considerably compared with non-invasive or no assisted ventilation in ALS-patients with end stage ventilatory insufficiency.

Moderate quality of evidence (⊕⊕⊕○)

There are no valid data comparing the initiation of NIV with IV in earlier stages of ALS.

Quality of Life (QoL) and Satisfaction with quality of life (Appendix 4.2 and 5)

Three studies have reported data on QoL (two cross sectional, n=129, one prospective cohort, n=80) and used validated scales. Two of those reported QoL only at baseline. The third study was limited by a large number of drop outs. There was no difference in QoL at follow-up between IV and NIV patients.

Two studies had the aim to analyze satisfaction with quality of life (one retrospective cohort, n=89 and one partly prospective cohort, n=164). The studies reported no comparison between the intervention and control groups.

Conclusion

It is uncertain whether there is little or no difference in QoL if tracheostomy and invasive ventilation is applied as compared to non-invasive ventilation. No reports have explicitly studied the change in quality of life during the gained survival months.

Very low quality of evidence (⊕○○○)

Complications (Appendix 4.3)

Eight studies considered complications in IV (three retrospective cohort n=616, two prospective cohort n=1336, two case series n=130, one case report n=1).

Among reported causes of death, the most common were cardiopulmonary, cardiac failure and sudden death, respiratory tract infections and pneumonia. Other causes were acute complications of the tracheostomy itself and ventilator related accident. The development of a locked-in-state was reported in 8/70 cases (11%) in one study.

Conclusion

Tracheostomy may lead to specific complications not found for non-invasive ventilation. Infections related to a foreign body, bleedings related to the procedure of exchanging the tracheostomy tube and management of the equipment may cause lethal events. Weak respiratory muscles and secret stagnation contribute to acute worsening of the respiratory function. A locked-in state is not a direct consequence of IV but the intervention means that the patients survive longer and in some cases can have the ventilation secured without mobility in the extremities but only in the eyes. The incidence of ALS increases with advanced age, and thus with cardiac comorbidity, explaining some of the increased mortality in this patient group.

Communicative capability of the patient (Appendix 4.4)

Only one study evaluated the capacity to communicate (n=89). This study was from the early 1990s, it could not demonstrate any relation of communicative capability to survival. No study analysed whether there were any differences in communicative capability in IV and NIV patients, and changes during the course of the treatment.

Quality of life for relatives (Comments in Appendix 4.2)

Two studies addressed the experience of the caregivers (one prospective cohort, n=80, one cross sectional, n=102). According to one study, the next of kin were less prone to advise patients and recommend the intervention with IV, and were less apt to have this choice for themselves if they would be put in the same situation. The other study found a tendency for caregivers at baseline to be more distressed and burdened by a future with IV with tracheostomy. However, satisfaction with caregiving was high. At the last assessment before death the caregivers reported both more satisfaction as well as greater burden.

7. Ethical consequences

Ethical consequences (Appendix 6)

Invasive ventilation impacts the patient's ability to maintain independence and autonomy and affects quality of life. It is important that the patient is well informed about IV and its consequences for daily life before the intervention to ensure that the patient is able to make a well-founded decision. The use of the method requires preserved cognition. Patients with dementia would not be eligible. Invasive ventilation impairs communication and the patient's ability to exert his own autonomy. The method implies increasing dependence on caring personnel and/or the next of kin. The equipment and the care are expensive and increasing number of patients treated with IV would require additional resources.

8. Organisation

When invasive ventilation with tracheostomy can be put into practice

The infrastructure for IV is available and the treatment could be put into practice immediately.

Is invasive ventilation with tracheostomy used in other hospitals in Region Västra Götaland of Sweden?

Yes

Will there be any consequences of invasive ventilation with tracheostomy for personnel?

Hospital personnel at the specialised units are trained and familiar to IV. However, there may be a need to train personnel at other units if the number of patients with IV increases. Personnel in home health care need to be trained during the hospitalisation period to be able to take care of the patient and the equipment in their home.

Consequences for other clinics or supporting functions at the hospital or in the whole Region Västra Götaland of Sweden

The number of patients is expected to be limited. Thus, the consequences for the Departments of Ear, Nose and Throat, Pulmonary Medicine and Anesthesiology will be minor. The need of home health care will increase but ALS patients already need extensive care and attention.

More patients will request this treatment in the Region Västra Götaland if IV is introduced as a treatment alternative for ALS patients with respiratory failure.

9. Economy aspects

Present costs of non-invasive ventilation

The cost of initiating NIV varies from 26 000 to 62 000 SEK per patient. The cost is dependent on the ventilator model and the number of ventilators per patient. Most patients will use their ventilator both during night and day. This means a need of two ventilators and a backup battery. The cost to initiate NIV with one ventilator without backup battery and one day of hospitalisation is 26 000 SEK. Two ventilators with backup battery result in a cost of 62 000 SEK. If the time at hospital is prolonged the cost will increase with 11 000 SEK per day.

Total cost for check-ups at a ventilation unit and for accessories is 5 000 SEK yearly.

The use of a cough assist machine is increasing. Patients who benefit from a cough assist machine are most likely to benefit also from NIV. An additional cost of 55 000 SEK for a cough assist machine and an additional cost of 5 000 SEK per year for accessories can be expected.

Expected costs of invasive ventilation with tracheostomy?

The cost of initiating IV varies from 450 000 to 540 000 SEK. The cost is dependent on the duration of hospitalisation with a range between approximately three to four weeks. All patients on IV use a cough assist machine and a suction pump and the related costs are included. Total cost for follow-up and accessories is 75 000 SEK per year.

Additional costs for possible complications related to tracheotomy and a possible increased need of hospitalisations in intensive care units are not included. Increased costs for advanced medical care and home care services are not included.

Total change of cost

The initial cost increase for one patient with ALS and respiratory failure who starts IV instead of NIV is approximately 433 000 SEK (range 388 000- 478 000 SEK depending on ventilator model and hospitalisation time). If a cough assist machine is used in both IV and NIV the initial cost increase is approximately 378 000 SEK (range 333 000-423 000 SEK).

The annual change of cost for one patient with ALS and respiratory failure on treatment with IV instead of NIV is 70 000 SEK per year. If a cough assist machine is used in both IV and NIV the cost increase is 65 000 SEK per year. Increased costs for advanced medical care and home care services are not included but reach considerable proportions. A house-bound patient with tracheostomy and an invasive ventilator is in need of constant surveillance and assistance.

It is estimated that one or two patients at Sahlgrenska University Hospital every year would start IV, if the method is introduced. The incremental cost is distributed among the departments of Neurology (hospital stay, purchase of equipment, initiating IV), Ear, Nose and Throat (tracheotomy), Pulmonary Medicine (purchase and follow-up of ventilators) and Primary home care (purchase of accessories). Increasing costs for home care services are paid by local social services and national social insurances. There are no savings with IV in comparison to NIV.

Can the invasive ventilation be adopted and used within the present budget (clinic budget/hospital budget)?

No.

Available analyses of health economy

There are no available Swedish or European analyses of health economy on invasive ventilation with tracheostomy in ALS with respiratory failure. An Israeli review article on cost effectiveness of treatments for ALS estimated a cost of around 386 000 USD per QALY for ventilation, not clear if referred to NIV or IV (Ginsberg & Lowe, 2002).

10. Unanswered questions

Important gaps in scientific knowledge

There is a lack of data on quality of life during ventilation treatment.

It is unknown whether other treatments, like diaphragm stimulation, are effective for ALS-patients with respiratory failure.

Cough assist machine is frequently used in clinical practice although it is not established whether it could delay initiation of IV.

It is unknown whether tracheostomy without assisted ventilation would be sufficient for ALS-patients in respiratory failure and preserve patient's physical autonomy.

The optimal time to start treatment with IV is unknown.

Interest in your own clinic/research group/organisation to start studies/trials within the research field at issue

It is difficult to initiate a study on this issue due to the very small number of patients who benefit from this treatment through time. Our main aim is to discuss this procedure with colleagues from other regions in the country in the first Swedish multidisciplinary ALS team meeting this autumn 2014.

Appendix 1. Search strategy, study selection and references

Question(s) at issue:

Does invasive ventilation with tracheostomy prolong survival and improve quality of life in patients with amyotrophic lateral sclerosis and respiratory failure in comparison to non-invasive ventilation and supportive care?

P	Patients with ALS and respiratory failure
I	Tracheostomy and assisted ventilation
C	No tracheostomy C1: non-invasive assisted ventilation C2: supportive care without assisted ventilation
O	<u>Critical for decision making</u> Survival Quality of life and satisfaction with life quality Complications Communicative capability of the patient to influence the subsequent treatment <u>Important but not critical for decision making</u> Quality of life for relatives

Eligibility criteria

Study design:

Systematic reviews
Randomized controlled trials
Non-randomized controlled studies if ≥ 10 patients in experimental group
Case series etc. if ≥ 50 patients for complications
Case reports if death reported as a complication
Qualitative studies

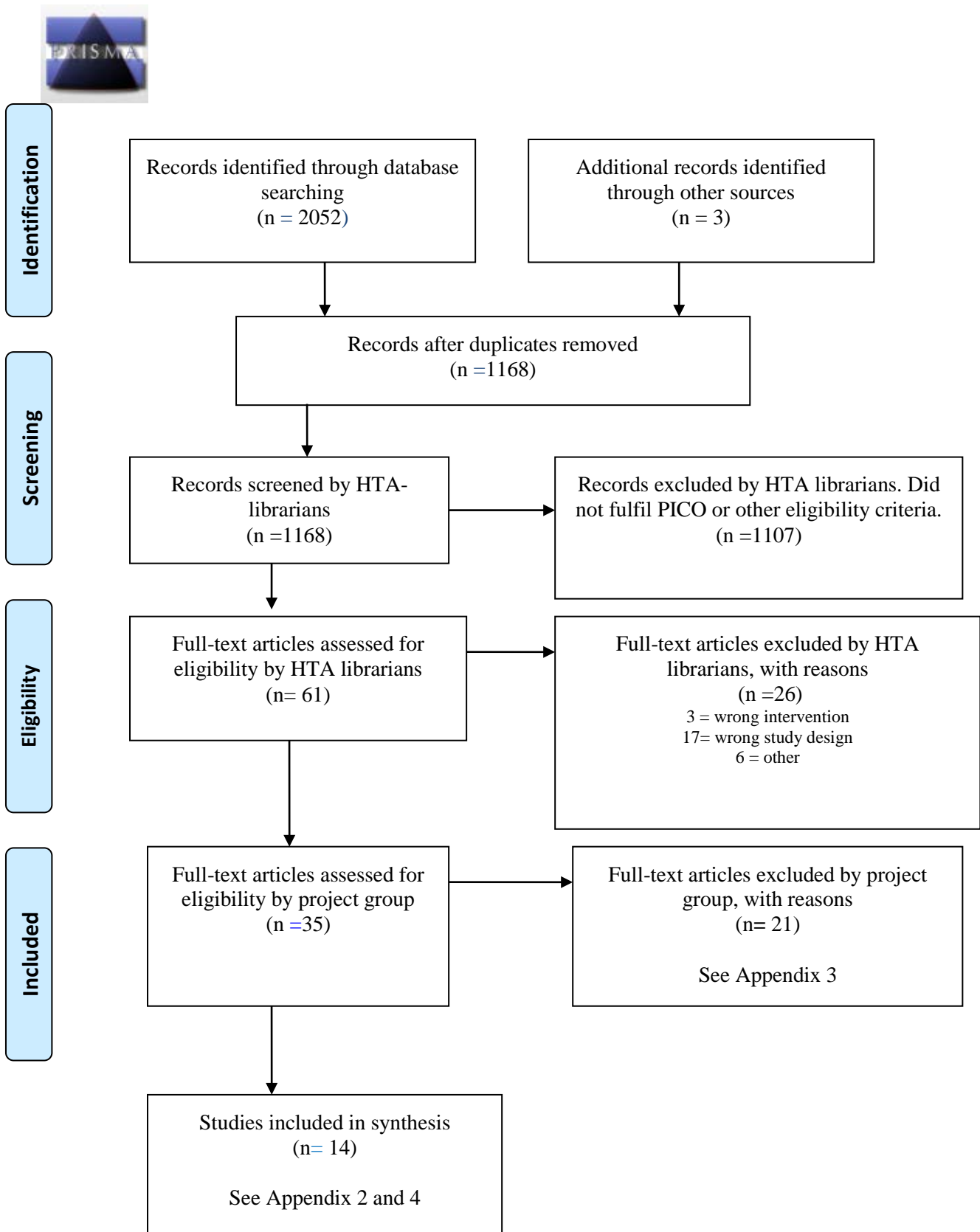
Language:

English, Swedish, Norwegian, Danish

Publication date:

No limit

Selection process – flow diagram



Project:

Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

3 (9)

Search strategies

Database: PubMed

Date: 2013-11-29

No of results: 817

Search	Query	Items found
#13	Search #7 NOT #8 Filters: Danish; English; Norwegian; Swedish	817
#9	Search #7 NOT #8	1043
#8	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	3834653
#7	Search #5 NOT #6	1060
#6	Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1279193
#5	Search #3 AND #4	1139
#4	Search Respiration, artificial[mh] OR Ventilators, mechanical[mh] OR ventilator*[tiab] OR ventilation*[tiab] OR Artificial respiration[tiab] OR Tracheostomy[mh] OR Tracheotomy[mh] OR Tracheotom*[tiab] OR tracheostom*[tiab] OR Tracheal intubation[tiab] OR Intratracheal intubation[tiab] OR Endotracheal intubation[tiab] OR Intubation, intratracheal[mh]	174000
#3	Search #1 OR #2	31601
#2	Search (Motor Neuron*[tiab] OR Motorneuron*[tiab] OR Motoneuron*[tiab] OR Moto neuron*[tiab] OR Gehrig*[tiab] OR Charcot[tiab]) AND Disease*[tiab]	11859
#1	Search ALS[tiab] OR Amyotrophic lateral sclerosis[tiab] OR Amyotrophic lateral sclerosis[mh] OR MND[tiab] OR Motor Neuron Disease[mh]	25921

Database: EMBASE (OVID SP) 1980 to Present

Date: 2013-11-29

No of results: 852

#	Searches	Results
1	exp amyotrophic lateral sclerosis/	21687
2	exp motor neuron disease/	26802
3	(ALS or Amyotrophic lateral sclerosis or MND).af.	65577
4	((Motor Neuron\$1 or Motorneuron\$1 or Motoneuron\$1 or Moto neuron\$1 or Gehrig\$2 or Charcot) adj2 disease\$1).ti,ab.	6206
5	1 or 2 or 3 or 4	70647
6	exp artificial ventilation/	116700
7	exp mechanical ventilator/	274
8	exp ventilator/	14941
9	exp assisted ventilation/	102277
10	exp respiratory tract intubation/	38303
11	exp endotracheal intubation/	34963
12	exp tracheostomy/	12658
13	exp tracheotomy/	9494
14	(Ventilator\$ or ventilation\$ or Artificial respiration or Tracheotom\$3 or tracheostom\$3).ti,ab.	149563

Project:

Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

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15	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	254498
16	5 and 15	2091
17	limit 16 to (embase and (danish or english or norwegian or swedish) and (article or conference paper or note or "review"))	852
18	(animal not (animal and human)).sh.	1402864
19	17 not 18	852

Database: The Cochrane Library

Date: 2013-11-29

No of results: 61

Cochrane reviews 7

Other reviews 3

Trials 48

Technology assessments 2

Economic evaluations 1

ID	Search	Hits
#1	amyotrophic lateral sclerosis or ALS or MND:ti,ab,kw (Word variations have been searched)	592
#2	(Motor Neuron* or Motoneuron* or Motoneuron* or Moto neuron* or Gehrig* or Charcot) and Disease*:ti,ab,kw (Word variations have been searched)	317
#3	#1 or #2	829
#4	ventilator* or ventilation* or Artificial respiration or Tracheotom* or tracheostom* or Tracheal intubation or Intratracheal intubation or Endotracheal intubation:ti,ab,kw (Word variations have been searched)	15505
#5	#3 and #4	61

Database: CRD

Date: 2013-11-29

No of results: 23

Line	Search	Hits
1	amyotrophic lateral sclerosis or ALS or MND	82
2	(Motor Neuron* or Motoneuron* or Motoneuron* or Moto Neuron* or Gehrig* or Charcot) and Disease*	61
3	#1 OR #2	111
4	ventilator* or ventilation* or Artificial respiration or Tracheotom* or tracheostom* or Tracheal intubation or intratracheal intubation or Endotracheal intubation	1088
5	#3 AND #4	23

Database: AMED
Date: 2013-11-29
No of results: 24

#	Query	Results
S5	S3 AND S4	24
S4	Ventilator? or ventilation? or Artificial respiration or Tracheotom? or tracheostomy? or Tracheal intubation or Intratracheal intubation or Endotracheal intubation	1,066
S3	S1 OR S2	735
S2	(Motor Neuron? or Motorneuron? or Motoneuron? or Moto neuron? or Gehrig? or Charcot) and Disease?	20
S1	amyotrophic lateral sclerosis or ALS or MND	718

Databases: PROQUEST (PsycINFO, British Nursing Index, Nursing & Allied Health Source)
Date: 2013-11-29
No of results: 275

Set	Search	Results
S6	S5 Limits applied Limited by: Source type: Reports, Scholarly Journals, Trade Journals Language: 4 languages searched Danish, English, Norwegian, Swedish	(298) 275 Duplicates deleted
S5	S3 AND S4	315
S4	S1 OR S2	17135
S3	all(ventilator* or ventilation* or Artificial respiration or Tracheotom* or tracheostom* or Tracheal intubation or Intratracheal intubation or Endotracheal intubation)	32454
S2	all(Motor Neuron* or Motorneuron* or Motoneuron* or Moto neuron* or Gehrig* or Charcot) AND all(disease*)	7774
S1	all(amyotrophic lateral sclerosis or ALS or MND)	11706

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited
Nothing relevant to the question at issue was found.

Reference lists

A comprehensive review of reference lists brought 3 new records

Included studies:

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Sancho J, Servera E, Diaz JL, Banuls P, Marin J. Home tracheostomy mechanical ventilation in patients with amyotrophic lateral sclerosis: causes, complications and 1-year survival. *Thorax.* 2011; 66(11): 948-52.

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Excluded studies:

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Cedarbaum JM, Stambler N. Disease status and use of ventilatory support by ALS patients. *BDNF Study Group. Amyotroph Lateral Scler Other Motor Neuron Disord.* 2001; 2(1): 19-22.

Dreyer PS, Felding M, Klitnaes CS, Lorenzen CK. Withdrawal of invasive home mechanical ventilation in patients with advanced amyotrophic lateral sclerosis: ten years of Danish experience. *J Palliat Med.* 2012; 15(2): 205-9.

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Appendix 2. Included studies: Design and patient characteristics.

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

Author, Year, Country	Study Design	Study Duration (years)	Study Groups; Intervention vs control	Patients (n)	Mean Age (years (SD))	Men (%)	Outcome variables
Bach JR, 1993 USA	Retrospective cohort from a case series	1977-1993 16 years	Tracheostomy vs Non-invasive ventilation	64 25	56.9 (13.8) 54.3 (11.5) at onset of ventilation	55 (total cohort)	Survival Communicative capability Satisfaction with QoL Complications
Berlowitz DJ, 2006 Australia	Retrospective cohort from a case series	1996-2003 7 years	Tracheostomy vs. Non-invasive ventilation vs. No assisted ventilation	23 52 43	54 (14.9) 61 (9.7) 60 (15.6) at onset of symptoms	78 82 65	Survival Complications
Cazzolli PA, 1996 USA	Partly prospective cohort from 2 case series	1988-1995 15 years 1990-1995 5 years	Tracheostomy Nasal non-invasive ventilation	50 25	60 (range 31-89) 64 (range35-86)	66 64	Satisfaction with quality of life for patients and family caregivers
Chadwick 2011 UK	Retrospective cohort	1992-2007 15 years	Tracheostomy vs. Non-invasive ventilation	30 126	67.1 (8.0) 63.8 (9.9) at admission to study center	83 70	Survival
Chio A, 2010 Italy	Case series	1995-2004 9 years	Tracheostomy Non-invasive ventilation and No assisted ventilation	134 1126	60.9 (10.7) 65.2 (10.4) at onset of symptoms	64 53	Complications
di Paolo M, 2013 Italy	Case report	-	-	1	69	One female	Complications
Dreyer P, 2013 Denmark	Retrospective cohort	1998-2012 14 years	Tracheostomy vs Non-invasive followed by tracheostomy vs Non-invasive ventilation vs No assisted ventilation	21 69 173 146	60.3 (10.3) 52.5 (9.1) 61.9 (9.5) 66.8 (10.6) at onset of symptoms	67 67 63 52	Survival Complications

Appendix 2. Included studies: Design and patient characteristics.

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

Author, Year, Country	Study Design	Study Duration (years)	Study Groups; Intervention vs control	Patients (n)	Mean Age (years (SD))	Men (%)	Outcome variables
Hayashi H, 2003 Japan	Case series	1980-1999 19 years	Tracheostomy	70	Not reported	Not reported	Complications
Kaub-Wittemer D, 2003 Germany	Cross-sectional	Not reported	Tracheostomy vs Non-invasive ventilation	21 32	61.6 (range 47-82) 60.0 (range 46-74)	91 72	Quality of life for patients and family caregivers
Lee CT, 2013 Taiwan	Population based retrospective cohort	1999-2008 10 years	Tracheostomy vs Non-invasive ventilation and No assisted ventilation	241 908	56.3 (14.2) at diagnosis (total cohort)	62 (total cohort)	Survival
Rabkin JG, 2006 USA	Prospective cohort	2000-2005 5 years	Tracheostomy vs. Non-invasive ventilation and No assisted ventilation	14 58	51.4 (12.39) 65.3 (13.0) at baseline in study	50 53	Quality of life Caregiver experience
Sancho J, 2011 Spain	Prospective cohort	2001-2010 9 years	Tracheostomy vs. Non-invasive ventilation	38 38	65.0 (9.2) 67.0 (9.2) at admission to study center	42 37	Survival Complications
Spataro R, 2012 Italy	Prospective cohort	2001-2010 9 years	Tracheostomy vs. Non-invasive ventilation and No assisted ventilation	87 192	61 (range 47-66) 63 (range 55-71) at onset of symptoms	63 54	Survival
Vianello A, 2011 Italy	Retrospective case series	1995-2008 13 years	Tracheostomy	60	62.3 (10) at tracheostomy	60	Complications
	Cross-sectional study	2008	Tracheostomy vs. Non-invasive ventilation and No assisted ventilation	13 14	61.8 (10.5) 62.6 (9.4)	46 57	Quality of life

Appendix 3 Excluded articles

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

Study (author, publication year)	Reason for exclusion
Bach 1995	Wrong outcome (measures alveolar ventilation)
Bradley 2002	Case series with too few cases according to predefined limitations- see Appendix 1
Cedarbaum 2001	Non-randomized controlled study with too few cases according to predefined limitations- see Appendix 1
Dreyer 2012	Case series with too few cases according to predefined limitations- see Appendix 1
Eisen 2013	PICO not applicable
Escarrabill 1998	Case series with too few cases according to predefined limitations- see Appendix 1
Gray 1998	PICO not applicable
Hayashi 1991	Case series with too few cases according to predefined limitations- see Appendix 1
Hèritier Barras 2013	Systematic review of studies included in the HTA literature search
Hirano 2006	Case series with too few cases according to predefined limitations- see Appendix 1
Hirano 2010	Case series. Wrong outcome (measures factors influencing decision-making in invasive ventilation)
Kitamura 2011	PICO not applicable
Lo Coco 2007	Case series with too few cases according to predefined limitations- see Appendix 1
Marchese 2008	Case series with too few cases according to predefined limitations- see Appendix 1
McDonald 1996	Not stated if invasive or no- invasive mechanical ventilation in intervention group
Moss 1996	PICO not applicable

Appendix 3 Excluded articles

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

Study (author, publication year)	Reason for exclusion
Rousseau 2011	Case series with too few cases according to predefined limitations- see Appendix 1
Sancho 2010	Duplicate publication with Sancho 2011
Sherman 1994	Wrong intervention (non-invasive mechanical ventilation)
Shimizu 1994	Case series with too few cases according to predefined limitations- see Appendix 1
Vianello 2000	Wrong intervention (non-invasive mechanical ventilation combined with cricothyroid “minitracheostomy”) compared with historical controls with mechanical ventilation via endotracheal intubation.

Appendix 4.1

Outcome variable: Survival

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients n=	With draws - dropouts	Result			Comments	Directness*	Study limitations*	Precision*
					Intervention	Control C1 Non-invasive Ventilation	Control C2 No assisted ventilation				
Bach 1993	US	Retrospective cohort study from a case series 1977-1993	89	1 with-drew from tracheostomy and assisted ventilation	n= 64 Mean survival (± SD): Deceased n=36, 4.2 ± 2.9 yr Alive n=28, 5.0 ± 3.5 yr	n=13 Mean survival: Deceased n=7, 2.0 ± 1.2 yr, Alive n=6, 2.9 ± 2.0 yr		Mean survival from tracheostomy and onset of assisted ventilation. Both acute and elective initiation of assisted ventilation. Details not reported Treatment with riluzole unclear.	+	-	-
					Switched from non-invasive to tracheostomy n=12, Mean survival (± SD): Deceased n=9, 3.7 ± 3.3 yr, Alive n=3, 10.9 ± 13.5 yr						
					Ultimately received tracheostomy n=76, Mean survival (± SD): 4.5 ± 4.0 yr (range: 1 mo-26.3 yr) Deceased n=45, 4.1 ± 2.9 yr (range: 1 mo-14.5 yr)						
Berlowitz 2006	Australia	Retrospective cohort study from a case series 1996-2003	118	Only intervention group reported: 13 with-drew from assisted ventilation	n=23 Median survival: 41 mo	n= 52 Median survival: 32 mo	n=43 Median survival: 25 mo	Median survival from symptom onset. Both acute and elective initiation of assisted ventilation. Details not reported No patients received riluzole.	+	-?	?+
					Survival significantly different only at time=4 yr after symptom onset. p=0.0497 If 3 patients who initially received non-invasive ventilation >1 month and then switched to tracheostomy are excluded median survival in intervention group falls to 37 mo. No significant difference in survival is then observed at any time.						

Appendix 4.1

Outcome variable: Survival

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients n=	With drawsals - dropouts	Result			Comments	Directness*	Study limitations *	Precision *
					Intervention	Control C1 Non-invasive Ventilation	Control C2 No assisted ventilation				
Chadwick 2011	UK	Retrospective cohort study 1992-2007	156	Not reported in detail for both intervention and control groups	n=30 1-year Survival: 43.3% Median survival: 7.8 mo (95% CI 2.6-12.9 mo) NS (p>0.05) n=3 died in hospital. n=14 were weaned from tracheostomy to non-invasive. Mean survival: 14.3 mo (95% CI 5.5-23.1) n=13 failed to wean. Mean survival: 14.0 mo (95% CI 5.9-22.1) NS difference between 14.3 and 14.0 mo	n=126	Median survival: 9.4 mo (95% CI 6.9-12.0)	Survival from tracheostomy and onset of assisted ventilation. Patients with acute initiation of tracheostomy and assisted ventilation admitted for ventilatory weaning compared to patients with elective initiation of non-invasive assisted ventilation. Treatment with riluzole unclear.	?+	?	-

Appendix 4.1

Outcome variable: Survival

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients n=	With draws - dropouts	Result			Comments	Directness*	Study limitations*	Precision*
					Intervention	Control C1 Non-invasive Ventilation	Control C2 No assisted ventilation				
Dreyer 2013	Denmark	Retrospective cohort study 1998-2012	409	Not reported in detail	n=21 1-year survival: 80% (SE 0.10) 3- year survival: 40% (SE 0.13) 5-year survival: 13% (SE 0.09) Survival HR (95% CI): 0.67 (0.38-1.19) p=0.177	n=173 1-yr survival: 73% (SE 0.04) 3- yr survival: 21% (SE 0.04) 5-yr survival: 6% (SE 0.02) Survival HR (95% CI): 0.90 (0.67-1.21) p=0.484	n=146 1-yr survival: 65% (SE 0.05) Survival 3 yr: 17% (SE 0.4) 5-yr survival: 5% (SE 0.2) Survival HR (95% CI): 1.50 (1.16-1.96) p=0.002	Survival from tracheostomy and onset of assisted ventilation or initiation of no treatment. Acute or elective initiation of treatment not reported. Age and treatment with non-invasive followed by tracheostomy were significantly related to survival. Unclear statistical methods Treatment with riluzole unclear.	+	-	?
					Switched from non-invasive to tracheostomy n=69 1-year survival: 83% (SE 0.06) 3- year survival: 53% (SE 0.08) 5-year survival: 25% (SE 0.07) Survival HR (95% CI): 0.41 (0.26-0.63) p<0.001						
					Survival in the four different groups: Intervention: 1031 days, C1: 788 days, Switch from C1 to Intervention: 1735 days, C2: 699 days, p=0.0001						
Lee 2013	Taiwan	Population based retrospective cohort study 1999-2008	1149	No with-drawals or dropouts reported	n=241 Mortality HR: 0.52 (95% CI 0.36-0.77) p=0.001	C1 and C2 not separately reported, n=908, which of n=193 non-invasive ventilation Mortality HR: 1.00		Mortality rate during follow-up after ALS diagnosis. Acute or elective initiation of treatment not reported. Age, sex, residence, economic status, tracheostomy and riluzole treatment were independently related to mortality. Treatment with riluzole n=698.	+	?	+

Appendix 4.1

Outcome variable: Survival

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients n=	With drawsals - dropouts	Result			Comments	Directness*	Study limitations *	Precision *
					Intervention	Control C1 Non-invasive Ventilation	Control C2 No assisted ventilation				
Sancho 2011	Spain	Prospective cohort study 2001-2010	76	1 with-drawals and no dropouts reported	n=38 Mean survival: 10.4 mo (95% CI 9.36-11.43), p<0.0001 1-year survival: 78.9%	C1 and C2 not separately reported, n=38 Mean survival: 0.8 mo (95% CI 0.60-1.06)	Survival from tracheostomy or refusing tracheostomy. Both acute (n=21, 55%) and elective (n=17, 45%) initiation of tracheostomy. No significant difference in survival between acute and elective. No variable independently related to survival. Uncuffed, cuffed and fenestrated tracheostomy tubes were used. Treatment with riluzole unclear.	+	+	+	
Spataro 2012	Italy	Prospective cohort study 2001-2010	279	Not reported in detail	n=87 Deceased n= 52 Median survival (n=52): 47 mo (interquartile range 33-61) p=0.0008	C1 and C2 not separately reported. n=192 Median survival (n=192): 31 mo (IQR 20-47)	Survival from symptom onset. Both acute (60%) and elective (40%) initiation of tracheostomy. Age independently related to survival after tracheostomy. 92% of total cohort on treatment with riluzole.	+	?	+	

* + No problem
 ? Some problems
 - Major problems

Appendix 4:2

Outcome variable: Quality of Life and Satisfaction with life quality

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

Author, year	Country	Study design	Number of patients n=	With draws - dropouts	Result			Comments	Directness*	Study limitations *	Precision *
					Intervention	Control C1 Non-invasive Ventilation	Control C2 No assisted ventilation				
Bach 1993	USA	Retrospective cohort study from a case series 1972-1992	89	1 withdrew from tracheostomy and assisted ventilation	2 out of 89 patients (2%) claimed to regret the use of ventilator.				+	-	-
Cazzolli 1996	USA	Partly prospective cohort from 2 case series 1988-1995 vs. 1990-1995	75	2 withdrew from tracheostomy. 11 withdrew from non-invasive assisted ventilation	41 of 50 patients (82%) with tracheostomy were satisfied with their quality of life.	100% of patients with nasal non-invasive ventilation indicated they were glad they chose the treatment.			+	-	-
Kaub-Wittemer 2003	Germany	Cross sectional study	102	49 dropouts	n=21 (n=20 caregivers) No significant difference between the groups when assessing QOL. 81% of patients in intervention and 94% of control C1 group would choose ventilation again. 75% of caregivers in intervention group would advise their patient to choose ventilation again, compared to 97% of control C1 caregivers. p=0.008 50% of caregivers in intervention group would opt for ventilation if faced with decision for themselves compared to 94% of C1 caregivers. p<0.001	n=32 (n=32 caregivers)		QOL instruments: Profile of Mood States and Munich Quality of Life Dimensions List	+	-	-

* + No problem
 ? Some problems
 - Major problems

Appendix 4:2

Outcome variable: Quality of Life and Satisfaction with life quality

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

Author, year	Country	Study design	Number of patients n=	With draws - dropouts	Result			Comments	Directness*	Study limitations *	Precision *
					Intervention	Control C1 Non-invasive Ventilation	Control C2 No assisted ventilation				
Rabkin 2006	USA	Prospective cohort study 2000-2005	80	3 did not reached endpoint 5 dropouts	n=14 Scores at baseline: Overall sense of well-being: 4.1 ± 0.4 (mean ± SD) p<0.05 Overall life satisfaction: 4.0 ± 0.1 p<0.05 Ability to function in daily life: 2.8 ± 1.2 p<0.001 Satisfaction with physical health: 2.6 ± 1.2 p<0.05 Satisfaction with household activities: 2.9 ± 1.4 p<0.05 No presentation of follow-up	C1 and C2 not separately reported. n=58. Scores at baseline: Overall sense of well-being: 3.5 ± 1.3 (mean ± SD) Overall life satisfaction: 3.6 ± 1.1 Ability to function in daily life: 4.0 ± 0.8 Satisfaction with physical health: 2.6 ± 1.2 Satisfaction with household activities: 3.7 ± 0.5 No presentation of follow-up		QOL instruments: Endicott Quality of Life Enjoyment and Satisfaction Questionnaire Patients with FVC<50% were followed until death or tracheostomy. Patients who opted for tracheostomy were followed up after tracheostomy. QOL only reported at baseline. When assessing caregiver experience a trend suggested at baseline that caregivers to future tracheostomy patients were more distressed and burdened although satisfaction with caregiving was similar. At last assessment before death or tracheostomy same group of caregivers reported both more caregiver satisfaction and greater burden.	+	-?	-
Vianello 2011	Italy	Cross sectional study 2008	27	No with-drawals or dropouts reported	n=13 Scores at baseline: Mean Life Satisfaction Life score (± SD): 9.3 ± 3.6 p>0.05 No presentation of follow-up	C1 and C2 not separately reported, n=14, which of n=2 non-invasive ventilation Mean Life Satisfaction Life score (± SD): 9.3 ± 4.3 No presentation of follow-up		QOL instruments: 11-item short-form Life Satisfaction Index QOL only reported at baseline. 11 of 13 patients in intervention group said they would want to undergo tracheostomy if they could make the decision again.	+	?	-

Appendix 4.3

Outcome variable: Complications

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

Author, year	Country	Study design	Number of patients n=	With draws - dropouts	Result and Comments
Bach 1993	USA	Retrospective cohort study from a case series 1977-1993	89	1 with-drew from tracheostomy and assisted ventilation	49 of 52 deceased patients (9%) died from sudden death or ALS-associated cardiopulmonary complications. 3 patients died from renal failure, intestinal hemorrhage and sepsis respectively.
Berlowitz 2006	Australia	Retrospective cohort study from a case series 1996-2003	118	Only intervention group reported: 13 with-drew from assisted ventilation	3 of 23 patients (13%) with tracheostomy developed pneumonia and declined life-sustaining treatment and died. 3 of 23 patients (13%) with tracheostomy developed locked-in state (TLS) before death.
Chiò 2010	Italy	Cohort from a prospective regional register 1995-2004	1260	No with-drawals or dropouts reported in intervention group	Acute complications of tracheostomy were reported as cause of death in 15 of 114 deceased patients (11%). Respiratory tract infections as cause of death in 48 patients (42%). Cardiopulmonary complications as cause of death in 9 patients (8%). Sudden death as cause of death in 6 patients (5%).
di Paulo 2013	Italy	Case report	1	-	Ventilator-dependent patient with tracheostomy was found dead with the ventilator in “stand-by” mode. Forensic autopsy strongly suggested death due to acute asphyxia.

Appendix 4.3

Outcome variable: Complications

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

Author, year	Country	Study design	Number of patients n=	With draws - dropouts	Result and Comments
Dreyer 2013	Denmark	Retrospective cohort study 1998-2012	409	Not reported in detail	269 patients (66%) died during study period. Causes of death were sudden death, heart failure, respiratory failure, cancer and locked in syndrome where the ventilation was switched off.
Hayashi 2003	Japan	Case series 1980-1999	70	No with-drawals or dropouts reported	8 of 70 patients (11%) developed totally locked-in state (TLS). 6 of 33 (18%) on mechanical ventilation for more than 5 yr developed TLS. 47 of 70 patients (67%) died during study period: 2 (4%) of ventilator accident 27 (57%) of bronchopneumonia
Sancho 2011	Spain	Prospective cohort study 2001-2010	76	1 with-drawals and no dropouts reported	19 patients (50 %) in intervention group required hospitalization during first year after tracheostomy. The third most common cause, 2 patients (5%), was tracheotomy management problems (stomal hemorrhage and tracheal granuloma) 8 patients (21 %) died in intervention group during first year after tracheostomy: 4 (50%) of sudden death 1 (13%) of ventilation withdrawal 1 (13%) of respiratory tract infection
Vianello 2011	Italy	Case series 1995-2008	60	No with-drawals or dropouts reported	Cause of death was reported in 43 patients: 20 (46%) pneumonia 11 (26%) sudden death of unknown origin 4 (9%) cardiac failure

* + No problem
 ? Some problems
 - Major problems

Appendix 4.4

Outcome variable: Communication capacity

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result			Comments	Directness*	Study limitations *	Precision *
					Intervention	Control C1 Non-invasive Ventilation	Control C2 No assisted ventilation				
Bach 1993	USA	Retrospective cohort study from a case series 1972-1992	89		-	-	-	Intervention and control groups not separately reported. Communication capacity not significant related to survival.	+	-	-

Appendix 5. Summary of Findings.

Project: Invasive ventilation in patients with amyotrophic lateral sclerosis and respiratory failure.

Outcome variable	Design Number of studies	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Effect IV vs NIV	Effect IV vs no assisted ventilation	Quality of evidence GRADE
Survival	7 observational studies: 2 IV vs NIV 2 IV vs NIV vs no assisted ventilation 3 IV vs (NIV+ no assisted ventilation)	Some limitations ⁱ (-0.5)	No inconsistency ⁱⁱ	No indirectness	No imprecision	Unlikely	Very large effect ⁱⁱⁱ (+2)	Median 41 vs 32 m 3-yr: 40 vs 21%	Median 41 vs 25 m 3-yr: 40 vs 17% HR (mortality) 0.52 95% CI (0.35; 0.77)	⊕⊕⊕○ Moderate
								Mean 10.4 vs 0.8 m P<0.0001 ⁱⁱⁱ		
Quality of life	1 observational study 2 additional showed results for baseline only	Serious limitations ^{iv} (-1)	No serious inconsistency	No indirectness	Serious imprecision ^v (-1)	Unlikely	Not relevant	No differences between groups in any of the scales.	No studies	⊕○○○ Very low

Abbreviations: IV = Invasive ventilation, NIV = Non-invasive ventilation

Footnotes:

- i. Selection bias in all but one study (Sancho 2011).
- ii. One study showed no effect (absolute numbers in opposite direction), but the intervention group comprised patients weaning from IV. The study was excluded from GRADE.
- iii. In Sancho 2011, the only study without selection bias (all patients in the same state of respiratory failure with NIV), demonstrated a very large effect of IV vs continued NIV or no assisted ventilation.
- iv. Low response rate (52/102).
- v. Small sample in only one study (n=52).

1. From the patient's perspective, how does invasive ventilation (IV) affect the patient's quality of life and life expectancy?

It is our experience that a majority of patients with ALS share the opinion that tracheostomy and IV is going to prolong their lives when respiratory function fails. Their expectations in this fact hopefully would have a positive effect in their experience of quality of life if treated with IV. It is important that the patient is well informed about IV and its consequences for daily life before the intervention to ensure that the patient is able to make a well-founded decision. Invasive ventilation limits the ability to communicate and this could negatively impact patient's quality of life. There is a very small, but still existing, risk of developing a locked-in state with no communication capacity at all. In this state the patient's experience of quality of life could be considered to be out of reach for relatives and medical caregivers to interpret. Continuous physical deterioration when life is prolonged could also signify a negative impact on quality of life. Some ALS patients develop cognitive insufficiency or frontal dementia. According to the literature up to 3-5 % of them suffer from dementia. These patients often deteriorate faster than those without dementia. Their capacity to understand the risks and negative effects of invasive ventilation is diminished. Their ability to give consent is also affected. In our opinion these patients should not be considered candidates to treatment with invasive ventilation.

2. How severe is the patient's need that the invasive ventilation must meet?

According to our experience the sensation of being short breathed is a very anxiety ridden state. Respiratory failure is a common cause of death among these patients. Without treatment the patient will die within the nearest future.

3. Does invasive ventilation influence the view on humanity or human dignity?

Tracheostomy and invasive ventilation prolong life and make the patient totally dependent on a mechanical device. This could be regarded a way of interfering with boundaries between life and death, but in our opinion the treatment does not influence the view on humanity and the definition of a human being. Human dignity is not influenced by disability or disease. Treatment with invasive ventilation does not put the view on human dignity in question.

4. Can invasive ventilation affect the patient's ability and possibility to be independent?

The treatment affects the patient's ability to communicate via spoken language but does not affect his ability to use light writer (non-verbal communication methods). Some patients, believed to be very few in numbers could be at risk of developing a condition with total inability to communicate with the environment. Invasive ventilation keeps the patient alive while physical deterioration continues and the patient becomes totally dependent on assistance in the activities of daily life.

5. If implemented, does invasive ventilation require any special steps to not compromise the patient's autonomy?

Invasive ventilation demands that the patient must be in full cognition in order to understand all the consequences of the treatment. If the method prolongs life this signifies that the patient would be able to exert his own autonomy during a longer period of time. However, the reduced ability to communicate and physical deterioration set limits to perform autonomy. Verbal communication is important to the human being. Technical advances make communication possible through other methods which lead to better opportunities to respect patient's autonomy.

6. How does invasive ventilation affect the patient's physical, moral and personal integrity?

Tracheostomy and invasive ventilation brings medical equipment and assistance from professional caregivers into the patient's own house. There is a continuous need of assistance and surveillance day and night. Physical integrity is affected as the patient becomes dependent on caregivers for personal care. Physical integrity is also affected by the need of adjustment of home facilities and medical equipment at home. The constant presence of professional caregivers could violate the patient's moral and personal integrity. It is of great importance that the professional caregiver is sensitive to the patient's needs and wishes. A patient centered care could diminish the impact on the patient's integrity.

7. Is invasive ventilation cost-effective?

No studies are available. Our point of view is that this treatment is expensive and most probably this means that the cost effectiveness is limited.

8. How does invasive ventilation affect resources?

The target group is not expected to be large. The treatment will cause increasing demands of resources for the actual patient with supervision at home both night and day. IV implies increasing demands of equipment, skilled staff and hospital beds. The hospitalization period is long before the patient could be discharged from hospital.

9. Is invasive ventilation in conflict with professional values?

The routines for this treatment have not been settled and a consensus has hopefully to be established in the nearest future. Doctors' approaches to IV in ALS patients are diverging, due to its complexity and its point of contact with life supporting care. Specialties involved are Anesthesiology, Ear, Nose and Throat, Neurology, Pulmonary medicine, and Palliative medicine.

10. Does invasive ventilation change the role of the professional in relation to the patient?

The launching of more frequent IV among ALS-patients should lead to increasing demands from the home care facilities and Advanced Medical Care in the home situation.

11. Does invasive ventilation affect, or does it put any new demands on, a third party?

The next of kin has to take more active role in the care of the patient, example given, react if the mechanical ventilator start to malfunction, and might have a role as home help. This active role implies a psychological load which would be worth considering.

The next of kin who is living with the patient is also affected by the presence of professional caregivers and medical equipment at home. This could be perceived as a violation of integrity and privacy.

12. Is there any legislation of relevance with regard to invasive ventilation?

Swedish legislation allows termination of ventilation treatment when a patient decides to end artificial ventilation support. However, the doctor responsible for the act of switching off the ventilator must be comfortable with the decision. The procedure itself requires not only psychological preparation by all persons involved, but also sedation and analgesia which must be managed by an anesthesiologist.

13. Is there any risk of conflict between invasive ventilation and values of the society, or values of different groups?

Not to the best of our knowledge.

14. Is there a risk that an introduction of invasive ventilation will cause a conflict with particular interests?

Our opinion is that IV does not imply economical profits.

15. Can an introduction of invasive ventilation influence the trust of the health care system?

This treatment has to be launched with preceding discussion on national level to reach consensus in order to prevent regional differences in availability of the treatment which could lead to a diminished trust of the health care system. A consensus or guidelines on regional or national level would facilitate and clarify the statement of the profession in communicating with patients and next of kin. It is important to have a discussion in an open ambiance to avoid a general opinion that the health care system withholds a possible life prolonging treatment for affected patients.

CONCLUSIONS

Invasive ventilation impacts the patient's ability to maintain independence and autonomy and affects quality of life. It is important that the patient is well informed about IV and its consequences for daily life before the intervention to ensure that the patient is able to make a well-founded decision. The use of the method requires preserved cognition. Patients with dementia would not be eligible. Invasive ventilation impairs communication and the patient's ability to exert his own autonomy. The method implies increasing dependence on caring personnel and/or the next of kin. The equipment and the care are expensive and increasing number of patients treated with IV would require additional resources.

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE ⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕○)
Low quality of evidence	= (GRADE ⊕⊕○○)
Very low quality of evidence	= (GRADE ⊕○○○)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum

