

QUESTION

Should non-invasive ventilation vs. no intervention be used for restrictive lung disease in Friedreich ataxia?

POPULATION:	restrictive lung disease in Friedreich ataxia
INTERVENTION:	non-invasive ventilation
COMPARISON:	no intervention
MAIN OUTCOMES:	Blood gas parameters; Daytime sleepiness and fatigue; Mortality;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Preliminary data collected by one of the authors indicates decline in respiratory volumes in severe FA and also impaired cough mechanisms. Also, in a web-based survey of FA patients presented at IARC (Patterson et al, 2018), 16.5% FA patients reported sleep apnoea, correlated with higher age, longer duration and higher functional stage.</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of pulmonary function.</p> <p>6/7 indicated that the problem was serious, 1/7 indicated they didn't know if serious.</p> <p>6/7 indicated that the problem was urgent, 1/7 indicated they didn't know if urgent.</p> <p>6/7 indicated that the problem was a priority, 1/7 indicated they didn't know if a priority. (Aug 2020)</p>

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input checked="" type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 28 October 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p> <p>A 2014 Cochrane review on nocturnal mechanical ventilation in neuromuscular disorders looked at randomized or quasi-randomized studies for chronic hypoventilation treated with any modality of long term ventilation (Annane et al, 2014). Outcome measures were: primary - 1 year mortality; secondary - unplanned admissions, reversal of hypoventilation related symptoms, daytime hypercarbia, improved lung function and improved sleep disordered breathing. There were 10 eligible studies with 173 participants. 50% of studies were deemed to have significant bias. The pooled risk ratio for mortality was 0.62 in favor of nocturnal ventilation (4 trials). Two trials reported hospitalization data and pooled risk was 0.25 in favor of ventilation. One trial with 16 participants did not report any difference between</p>	

	<p>volume and pressure cycled ventilation. Two additional trials with cross-over designs reported that volume cycled ventilation was associated with less time with desaturation below 90% and lower apnea hypopnea index (AHI). It was concluded that evidence was of very low quality but consistent and suggested alleviation of symptoms, prolongation of survival and fewer hospitalizations.</p>	
--	--	--

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know 	<p>A search of four databases (CENTRAL, MEDLINE, EMBASE, CINAHL) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 28 October 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	<p>No published evidence.</p>	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
-----------	-------------------	---------------------------

- Important uncertainty or variability
- Possibly important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty or variability

Outcomes	Importance	Certainty of the evidence (GRADE)
Blood gas parameters - not measured	IMPORTANT ^a	-
Daytime sleepiness and fatigue - not measured	IMPORTANT ^b	-
Mortality - not measured	CRITICAL ^c	-

- a. Identified as critical (1/6), important (4/6) and low importance (1/6) by people with FA and critical by expert authors on this topic
- b. Identified as important (4/6) and low importance (2/6) by people with FA and critical by expert authors on this topic
- c. Identified as critical (5/5) by people with FA and critical by expert authors on this topic.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know 	<p>No published evidence.</p> <p>Among 26 FA experts polled, 16 had no opinion. All other respondents felt that this intervention was beneficial. A similar number reported benefit on daytime sleepiness and benefit on mortality.</p>	<p>A survey designed to systematically collect expert-based opinions from clinicians involved in the development of these guidelines and providing clinical care for individuals with Friedreich ataxia, was conducted. Clinical experts from Australia, Europe, UK, South America, Canada and the USA were asked to consider the harms/benefits of using peak expiratory cough flow or similar cough assessments as a management strategy for people with impaired airway clearance.</p> <p>Reflecting on the impact of peak expiratory cough flow or similar cough assessments on <u>prevalence of chest infections</u>, 28% (7/25) clinical experts reported a benefit (large, moderate or small), 4% (1/25) reported no effect and, 0% (0/25) reported observing a harm (large, moderate or small). 17 clinicians could not provide any information on this outcome. Reflecting on the impact on <u>airway clearance</u>, 28% (7/25) clinical experts reported a benefit, 4% (1/25) reported no effect. 17 expert clinicians could not provide any information on this outcome.</p> <p>Clinical experts were asked to consider the harms/benefits of an</p>

		<p>assisted coughing method as a management strategy for people with impaired airway clearance.</p> <p>Reflecting on the impact of assisted coughing method on <u>prevalence of chest infections</u>, 34.61% (9/26) clinical experts reported a benefit (large, moderate or small), and 0% (0/26) reported observing a harm (large, moderate or small). 17 clinicians could not provide any information on this outcome. Reflecting on the impact on <u>airway clearance</u>, 34.61% (9/26) clinical experts reported a benefit. 17 expert clinicians could not provide any information on this outcome.</p>
--	--	---

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know 	No published evidence.	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if using assisted coughing in people with impaired airway clearance was acceptable (weighing up the balance between benefits, harms and costs).</p> <p>1/3 indicated the intervention was acceptable, 1/3 indicated probably acceptable, 1/3 indicated they didn't know if acceptable. (Aug 2020).</p>

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
---	--	---	---	---

CONCLUSIONS

Recommendation

We conditionally recommend non-invasive assisted ventilation for patients with Friedreich ataxia and documented restrictive lung disease meeting the following thresholds: FVC <50% predicted; maximum inspiratory pressure <60 cm H₂O; nocturnal hypercarbia (pCO₂ >50 mm Hg for ≥2% of sleep time or a 10 mm Hg increase in pCO₂ compared to awake baseline pCO₂ for ≥2% of sleep time); nocturnal hypoxia (SpO₂ ≤88% for ≥2% of sleep time or 5 minutes continuously); or apnea-hypopnea index ≥5. Daytime hypoventilation indicated by hypercarbia of >45 mm Hg or baseline PO₂ <95% on room air is also an indication for nocturnal assisted ventilation.

Justification

Restrictive lung disease can lead to abnormal blood gases with deleterious effects on cardiopulmonary health and also lead to symptoms that impair quality of life, both during the daytime and during sleep. There is no data on the use of non-invasive assisted ventilation in patients with FRDA. This recommendation is based on limited data from similar disorders and expert guidelines in such disorders.

Subgroup considerations

This recommendation is for individuals with advanced Friedreich ataxia and abnormal pulmonary function.

Research priorities

More research is needed as to the prevalence of restrictive lung disease in patients with FRDA and benefits and adverse effects from non-invasive assisted ventilation in this population.

Reference

Annane D, Orlikowski D, Chevret S. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. *Cochrane Database Syst Rev.* 2014(12):CD001941.

Patterson A, Almeida L, Monari E, et al. Sleep and fatigue in Friedreich ataxia. IARC Meeting; Pisa, Italy 2018.

