

## QUESTION

### Should assisted coughing (mechanical/manual) vs. no intervention be used for impaired airway clearance in Friedreich ataxia?

|                       |   |
|-----------------------|---|
| <b>POPULATION:</b>    | impaired airway clearance in Friedreich ataxia    |
| <b>INTERVENTION:</b>  | assisted coughing (mechanical/manual)             |
| <b>COMPARISON:</b>    | no intervention                                   |
| <b>MAIN OUTCOMES:</b> | Prevalence of chest infections; Airway clearance; |

## ASSESSMENT

### Problem

Is the problem a priority?

| JUDGEMENT   | RESEARCH EVIDENCE   | ADDITIONAL CONSIDERATIONS   |
|---|---|---|
| <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input checked="" type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul> | <p>There are no data on prevalence of impaired cough in FA. Unpublished data from one of the authors suggests that impaired cough mechanisms may occur in more advanced stages of the disease.</p> <p>A patient survey suggests that this is a problem that needs addressing.</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"> <li><input type="radio"/> Trivial</li> <li><input type="radio"/> Small</li> <li><input checked="" type="radio"/> Moderate</li> <li><input type="radio"/> Large</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul> | <p>There appear to be no large amount of data on this intervention and none in FA. However, the expert opinion from FA experts who did respond seems to indicate significant benefit for both monitoring PEF and cough assist intervention. An ENMC workshop on airway clearance techniques in neuromuscular disorders (Touissant et al, 2018) discussed many such methods and included guidance suggesting lung volume recruitment and manual assisted cough be considered with moderate impairment of cough flow (PECF 200 to 300) and addition of mechanical in-exsufflation with lower PECF. Adverse events reported included gastric distension and pneumothorax. Combined inspiratory and expiratory assistance was considered more effective.</p> <p>Limited patient input supports this.</p> |                           |

| Outcomes                        | No of participants (studies) Follow-up | Certainty of the evidence (GRADE)     | Relative effect (95% CI) | Anticipated absolute effects* (95% CI)   |  |
|---------------------------------|--|---------------------------------------|--------------------------|--|--|
|                                 |  |                                       |                          | Risk with no intervention  | Risk difference with assisted coughing (mechanical/manual) |
| Prevalence of chest infections  | 2 (1 observational study) <sup>1</sup> | ⊕○○○<br>Very low <sup>a,b,c,d,e</sup> | -                        | The impact of regular, home use of the cough assist machine (CAM) on the respiratory status of 6 children with neuromuscular disease was examined. Data two years prior to CAM admission was obtained and compared to data collected for two years following CAM initiation. All participants had fewer days hospitalised for respiratory infections per year following CAM initiation (78 days vs 181 days). (Phillips et al 2014). |  |
| Airway clearance - not measured | -                                      | -                                     | -                        | -  | -  |

1. Phillips R, Edwards E McNamara D Reed P. Does use of the Cough Assist Machine reduce respiratory morbidity for children with neuromuscular disease?. New Zealand Journal of Physiotherapy; 2014.
  - a. Diagnosis of either Spinal Muscular Atrophy or Congenital muscular dystrophy.
  - b. Small sample size.
  - c. No confidence intervals reported and small sample size.
  - d. Selection bias, unvalidated outcome measures, lack of control group
  - e. Predominantly female participants.

## Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

RESEARCH EVIDENCE

ADDITIONAL CONSIDERATIONS

- Large
- Moderate
- Small
- Trivial
- Varies
- Don't know

| Outcomes                        | № of participants (studies) Follow-up  | Certainty of the evidence (GRADE)     | Relative effect (95% CI) | Anticipated absolute effects* (95% CI)   |  |
|---------------------------------|--|---------------------------------------|--------------------------|--|--|
|                                 |  |                                       |                          | Risk with no intervention  | Risk difference with assisted coughing (mechanical/manual) |
| Prevalence of chest infections  | 2 (1 observational study) <sup>1</sup> | ⊕○○○<br>Very low <sup>a,b,c,d,e</sup> | -                        | The impact of regular, home use of the cough assist machine (CAM) on the respiratory status of 6 children with neuromuscular disease was examined. Data two years prior to CAM admission was obtained and compared to data collected for two years following CAM initiation. All participants had fewer days hospitalised for respiratory infections per year following CAM initiation (78 days vs 181 days). (Phillips et al 2014). |  |
| Airway clearance - not measured | -                                      | -                                     | -                        | -  | -  |

1. Phillips R, Edwards E McNamara D Reed P. Does use of the Cough Assist Machine reduce respiratory morbidity for children with neuromuscular disease?. New Zealand Journal of Physiotherapy; 2014.
  - a. Diagnosis of either Spinal Muscular Atrophy or Congenital muscular dystrophy.
  - b. Small sample size.
  - c. No confidence intervals reported and small sample size.
  - d. Selection bias, unvalidated outcome measures, lack of control group
  - e. Predominantly female participants.

## Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

RESEARCH EVIDENCE

ADDITIONAL CONSIDERATIONS

|  |   |  |
|--|---|--|
| <ul style="list-style-type: none"> <li>● Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul> | <p>Very certainty of the evidence of effects as per the evidence profile table.</p> |  |
|--|---|--|

## Values

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

| JUDGEMENT  | RESEARCH EVIDENCE   | ADDITIONAL CONSIDERATIONS             |            |                                   |                                |                       |                                       |                                 |                       |   |  |
|--|---|---------------------------------------|------------|-----------------------------------|--------------------------------|-----------------------|---------------------------------------|---------------------------------|-----------------------|---|--|
| <ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>○ Possibly important uncertainty or variability</li> <li>● Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul> | <table border="1" data-bbox="518 662 1423 922"> <thead> <tr> <th>Outcomes</th> <th>Importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Prevalence of chest infections</td> <td>CRITICAL<sup>a</sup></td> <td>⊕○○○<br/>VERY LOW<sup>b,c,d,e,f</sup></td> </tr> <tr> <td>Airway clearance - not measured</td> <td>CRITICAL<sup>a</sup></td> <td>-</td> </tr> </tbody> </table> <p data-bbox="562 964 1388 1170">           a. Identified as critical (3/6), important (1/6) and low importance (2/6) by people with FA and critical by expert authors on this topic<br/>           b. Diagnosis of either Spinal Muscular Atrophy or Congenital muscular dystrophy.<br/>           c. Small sample size.<br/>           d. No confidence intervals reported and small sample size.<br/>           e. Selection bias, unvalidated outcome measures, lack of control group<br/>           f. Predominantly female participants.         </p> | Outcomes                              | Importance | Certainty of the evidence (GRADE) | Prevalence of chest infections | CRITICAL <sup>a</sup> | ⊕○○○<br>VERY LOW <sup>b,c,d,e,f</sup> | Airway clearance - not measured | CRITICAL <sup>a</sup> | - |  |
| Outcomes   | Importance  | Certainty of the evidence (GRADE)     |            |                                   |                                |                       |                                       |                                 |                       |   |  |
| Prevalence of chest infections   | CRITICAL <sup>a</sup>   | ⊕○○○<br>VERY LOW <sup>b,c,d,e,f</sup> |            |                                   |                                |                       |                                       |                                 |                       |   |  |
| Airway clearance - not measured  | CRITICAL <sup>a</sup>   | -                                     |            |                                   |                                |                       |                                       |                                 |                       |   |  |

## 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"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul> | <p>Based on FA experts queried, 17/26 had no opinion. But among the responders, majority believed assessing PECF and recommending assisted coughing would lead to favourably affect chest infections, airway clearance.</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 <b>peak expiratory cough flow or similar cough assessments</b> 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 <b>an assisted coughing method</b> 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"> <li>○ No</li> <li>○ Probably no</li> <li>● Probably yes</li> <li>○ Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul> | <p>No published evidence.</p> | <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                                   | <b>Probably yes</b>                                      | Yes                                     |                         | Varies | Don't know          |
| DESIRABLE EFFECTS     | Trivial                              | Small   | <b>Moderate</b>  | Large                                   |                         | Varies | Don't know          |
| UNDESIRABLE EFFECTS   | Large                                | Moderate                                      | <b>Small</b>   | Trivial                                 |                         | Varies | Don't know          |
| CERTAINTY OF EVIDENCE | <b>Very low</b>                      | Low   | Moderate   | High                                    |                         |        | No included studies |
| VALUES                | Important uncertainty or variability | Possibly important uncertainty or variability | <b>Probably no important uncertainty or variability</b>  | No important uncertainty or variability |                         |        |                     |
| BALANCE OF EFFECTS    | Favors the comparison                | Probably favors the comparison                | Does not favor either the intervention or the comparison | <b>Probably favors the intervention</b> | Favors the intervention | Varies | Don't know          |
| ACCEPTABILITY         | No                                   | Probably no                                   | <b>Probably yes</b>                                      | Yes                                     |                         | Varies | Don't know          |

## TYPE OF RECOMMENDATION

|   |  |   |  |   |
|---|--|---|--|---|
| Strong recommendation against the intervention<br>○ | Conditional recommendation against the intervention<br>○ | Conditional recommendation for either the intervention or the comparison<br>○ | <b>Conditional recommendation for the intervention<br/>●</b> | Strong recommendation for the intervention<br>○ |
|---|--|---|--|---|

## CONCLUSIONS

### Recommendation

In individuals with Friedreich ataxia and impaired airway clearance (PECF <270 L/min or FVC <50% predicted), we suggest assisted coughing (mechanical/manual) be implemented to assist in airway clearance and reduce the prevalence of chest infections.

### Justification

Poor cough mechanisms likely occur in some individuals with advanced FRDA. There are no major studies that address assisted coughing interventions in FRDA. A patient survey suggests that this is an important problem and FRDA experts seem to agree. One of the authors has unpublished data indicating impaired cough flow occurs in advanced FRDA.

It may be conjectured that improved clearance of secretions will likely reduce probability of chest infections. Chest infection is second to cardiac disease as a cause of mortality in FRDA (Tsou et al, 2011).

## Subgroup considerations

This intervention should be considered for individuals with Friedreich ataxia who are non-ambulatory and have impaired cough flow and/or reduced forced vital capacity.

## Research priorities

Ideally studies would collect controlled data with some subjects using the device and others not (matched) and then assess infection rates prospectively. Some retrospective data could also be collected such as a survey of individuals with advanced FRDA to compare those using the assisted coughing interventions with those not using any intervention.

### References

Toussaint M, Chatwin M, Gonzales J, Berlowitz DJ, Consortium ERT. 228th ENMC International Workshop: Airway clearance techniques in neuromuscular disorders Naarden, The Netherlands, 3-5 March, 2017. *Neuromuscul Disord.* 2018;28(3):289-98.

Tsou AY, Paulsen EK, Lagedrost SJ, Perlman SL, Mathews KD, Wilmot GR, et al. Mortality in Friedreich ataxia. *J Neurol Sci.* 2011;307:46-9.