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Indicators of pulmonary exacerbation in cystic fibrosis: A Delphi survey of patients and health professionals

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Abstract

Background: There is uncertainty about the most important indicators of pulmonary exacerbations in CF.
Methods: Two parallel Delphi surveys in 13 CF centres (UK and Ireland). Delphi 1: 31 adults with CF, ≥ one exacerbation over 12 months. Delphi 2: 38 CF health professionals. Rounds 1 and 2 participants rated their level of agreement with statements relating to indicators of exacerbation; Round 3 participants rated the importance of statements which were subsequently placed in rank order.
Results: Objective measurements were of higher importance to health professionals. Feelings of increased debility were rated most important by adults with CF.
Conclusions: There were clear differences in perspectives between the two groups as to the most important indicators of an exacerbation. This highlights that CF health professionals should take more cognisance of specific signs and symptoms reported by adults with CF, especially since these may be a precursor to an exacerbation.

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Keywords: Pulmonary exacerbation; Delphi technique; Cystic fibrosis

1. Introduction

Pulmonary exacerbations (PEXs) in cystic fibrosis (CF) are associated with disease progression, increased morbidity, mortality, and substantial healthcare costs [1–4]. PEXs are experienced by a large proportion of patients with CF. The most recent annual information from the CF Registry of Ireland reported 451 paediatric admissions and 680 adult admissions for a PEX treated with intravenous antibiotics, using data that was available for 881 registered patients [5]. The CF Registry of the UK reported 3732 paediatric lung infections and 5062 adult lung infections using data that was available for 8794 registered patients [6]. Minimising PEXs is critical for the long term health of adults with CF since patients who have more than two PEXs per year have a significantly reduced three year survival compared to those who have one or none [4]. PEXs are associated with a more rapid decline in FEV1, which results in a further decline in overall wellbeing [7,8]. Health related quality of life (HRQoL) worsens during PEX and more severe exacerbations have a greater negative impact on HRQoL [1,8]. Most people with CF die of respiratory failure which has typically been induced by a PEX [9–11].
PExs are also frequently used as an end point in clinical trials and recommended by European Medicines Agency (EMA) and Food and Drug Administration (FDA) as primary efficacy end points [2,12–14]. However, neither agency mandates any definition of a PEx. Consequently definitions used in clinical trials are multiple and are inconsistent with each other [15]. In addition, they often show inconsistencies with criteria routinely used by CF health professionals [16–18].

Previously it was suggested that the Delphi technique is an appropriate methodology to identify which criteria should be included in a definition of a PEx in CF [17]. This technique uses a series of repeated surveys to gain consensus on a given issue [19–22].

This method reduces peer pressure and encourages unbiased responses, as participants remain anonymous to the core members of the research team and to other participants [19,21–23]. The Delphi technique is a practical, efficient, inexpensive and widely used consensus research method in health care research [24,25].

The aim of this study was to identify the important indicators of an exacerbation determined by a group of adults with CF and a group of CF health professionals.

2. Methods

2.1. Design and recruitment

Two parallel Delphi surveys were used to investigate agreement among a group of adults with CF and CF health professionals regarding the important indicators of an exacerbation.

This was a multicentre study across the UK and Ireland. Twenty-seven CF centres were approached to take part aiming to recruit two to three adults with CF and two to three CF health professionals per centre. Participants were identified by a designated key health professional at each CF centre who was responsible for ensuring that all participants met the inclusion criteria for their participant group. The inclusion criteria for adults with CF were: confirmed diagnosis of CF, over 18 years, FEV₁ less than or equal to 80% predicted, experienced at least one exacerbation requiring IV antibiotics in the previous 12 months and computer literate with internet access available for the duration of the study. The inclusion criteria for CF health professionals were: CF health professionals working in adult CF centres in the UK/Ireland, currently involved in assessing if CF patients are having an exacerbation and deciding a treatment plan and computer literate with internet access available for the duration of the study.

The stages of this Delphi survey are summarised in Fig. 1. Ethical approval was obtained from the Office for Research Ethics Committees Northern Ireland. Research governance was sought at participating sites. Data collection took place over a seven month period (Sept 2010–April 2011). In each round non responders were followed up and sent weekly reminders to complete the survey.

2.2. Delphi Round 0: statement generation

The aim of Round 0 was to generate a list of statements for Round 1 of the Delphi survey. The first step in developing the Delphi survey for this study was to conduct a systematic literature search and extract criteria used to identify an exacerbation. This search identified 218 criteria from 86 articles. However, there were many similarities in the terminology used, consequently criteria that were similar in meaning were grouped together to

Fig. 1. Summary of the stages of the Delphi surveys. Key. Health professionals: HPs, cystic fibrosis: CF.
form one category. The list of 218 criteria was condensed to form 31 themes, which were then agreed by the research team.

The themes were built further through the results of patient interviews with 47 adults with CF to identify their perception of the indicators of an exacerbation and a review of CF specific quality of life instruments [16,26,27]. While these questionnaires are assessing quality of life, they contain signs, symptoms and feelings that are related to people with CF and are used in clinical trials and in clinical practice to help identify the health status of patients which were not already covered by the themes identified.

The agreed themes were used to formulate statements for “Round 1” of the Delphi survey. Finally, health professionals at the Belfast CF centre independently reviewed the statements. A few minor changes were made. One issue related to haemoptysis can have a range of severity levels. It was agreed that it should be represented as two separate statements: ‘Sputum streaked with blood’ and ‘Frank haemoptysis’ (referred to as ‘Coughing up blood’ in the adults with CF survey). Although it was recognised that haemoptysis is not a particularly common feature of exacerbations in CF, clearly frank bleeding is of concern. The research team therefore agreed that inclusion of two statements was sufficient when considering this potential sign.

The statements were then piloted with several adults with CF to ensure clarity of the wording. The research team recognised that there is some overlap between some of the statements used in the Delphi survey, however, this was partly a result of the feedback from the adults with CF. For example, they considered that there was a distinction between the statements, “Feeling more short of breath than usual” and “Trouble breathing” and advised that they should remain as distinct statements. The adults with CF also provided their views on different response formats recommended for use in Delphi methodology in order to inform the preferred response format for this survey and to finalise the survey [22]. Two surveys with statements (n = 48) focussing on indicators of PEX were compiled, one for adults with CF and one for CF health professionals. The only difference was in the use of lay terminology in the patient survey e.g. instead of haemoptysis “Sputum streaked with blood” was used.

2.4. Delphi Round 2

In Round 2 statements from Round 1 that did not reach consensus (defined as 75% agreement), along with five additional statements identified from the open question were presented to both groups. In Round 2, the adults with CF survey contained 32 statements and the CF health professional survey contained 30 statements. Participants were also provided with a summary of the results from Round 1 for their participant group; this included their individual original response, the group response, and a summary chart showing the responses to that particular statement. Participants were asked to reconsider the statement again, taking into account the feedback of results from Round 1, and to re-rate their level of agreement with each statement. They were advised that they did not have to change their response if they did not wish to. There were five additional statements developed from the open question in Round 1 which were also presented as new statements using the original format from Round 1.

2.5. Delphi Round 3

In Round 3 participants were presented with statements that had reached 75% agreement in Round 1 or 2. Both surveys contained 35 statements (adults with CF survey: 31 statements along with four additional statements to rate that had only reached consensus in the health professional survey; CF health professional survey: 30 statements along with five additional statements to rate that had only reached consensus in the adults with CF survey). Participants were asked to rate the level of importance on a scale of one to 10, where one represented the lowest level of importance and ten represented the highest level of importance.

2.6. Data analysis

The data generated from each round was analysed with SPSS 17.0 using descriptive statistics. The data from each participant group was analysed separately. The researcher summarising the data from all rounds was blinded to the study participant’s identity. In order to identify which statements had reached consensus in Round 1 or Round 2 the percentage agreement and median response were calculated. In Delphi surveys the level of consensus is determined prior to initiating data collection, and this can vary depending on the topic being investigated. A consensus level of 75% was selected following guidance from the literature; this meant including responses where a person had indicated that they ‘strongly agree’ or ‘agree’ [21]. For Round 3 results were analysed by applying a rating average and then placing criteria in a ranked order of importance, in order to identify factors of importance within each group and to facilitate comparison between the groups.

Further analysis was conducted in Round 3 to identify if the differences for individual statements between the groups were statistically significant, using the independent t-test for statements with normally distributed data and the Mann–Whitney U test was used for data which was not normally distributed.
3. Results

The CF centres that participated in this study were identified through the CF Trust website (www.cftrust.org.uk) and the CF Association of Ireland website (www.cfireland.ie). The centres were all specialist CF centres providing care for adults with CF. All 27 centres identified were invited to participate in the study and data was obtained from 13 (48%) centres. Of the 14 centres that did not participate, seven declined due to a variety of reasons including commitments to other studies or staffing restraints, five did not respond, and two agreed initially but due to difficulties with their local research governance approval they were unable to take part.

In Round 1, 31 adults with CF with moderate to severe disease completed the survey. The participants ranged from age 23 to 52 years. All participants confirmed that they had experienced at least 1 exacerbation in the previous year (defined by their centre) and were treated with IV antibiotics. The number of exacerbations reported by the adults with CF were 1–3 n = 17; 4–6 n = 11; and >6 n = 3. A lung function (FEV1,%predicted) of less than 40% was reported by 11 participants and 8 participants reported a lung function of 40–60%. In Rounds 2 and 3 the surveys were completed by 28 and 27 participants respectively.

All 38 CF health professionals who registered completed all survey rounds. Their professions are as follows: nurse n = 13, physiotherapist n = 6, dietician n = 1, and doctor n = 18. By the end of Round 2, 31 statements from adults with CF, and 30 statements from CF health professionals, had reached consensus (Fig. 1). In Round 3 there were clear differences between adults with CF and CF health professionals as to the important indicators of an exacerbation. Tables 1 and 2 show the mean scores, standard deviation and ranking order for all the statements (adults with CF and health professionals) from Round 3. Indicators from the adults with CF that were rated of higher importance were commonly rated lower by CF health professionals; for example, “An increase in symptoms at night” was rated higher by adults with CF (rank order 5) and lower by

<table>
<thead>
<tr>
<th>Statement</th>
<th>Mean score</th>
<th>Std. deviation</th>
<th>Rank order</th>
</tr>
</thead>
<tbody>
<tr>
<td>A large decrease in lung function (greater than 10% FEV1)</td>
<td>9.33</td>
<td>0.784</td>
<td>1*</td>
</tr>
<tr>
<td>Feeling more short of breath than usual</td>
<td>8.52</td>
<td>1.087</td>
<td>2*</td>
</tr>
<tr>
<td>Trouble breathing</td>
<td>8.52</td>
<td>1.805</td>
<td>2</td>
</tr>
<tr>
<td>Feeling the need to do more airway clearance than usual</td>
<td>8.37</td>
<td>1.115</td>
<td>4</td>
</tr>
<tr>
<td>An increase in symptoms at night</td>
<td>8.22</td>
<td>1.450</td>
<td>5</td>
</tr>
<tr>
<td>Producing more sputum</td>
<td>8.19</td>
<td>1.388</td>
<td>6*</td>
</tr>
<tr>
<td>Finding it harder than normal to do your usual exercise</td>
<td>7.96</td>
<td>1.581</td>
<td>7</td>
</tr>
<tr>
<td>Finding it harder than normal to do your usual activities</td>
<td>7.93</td>
<td>1.838</td>
<td>8</td>
</tr>
<tr>
<td>Feeling more exhausted than usual</td>
<td>7.85</td>
<td>1.703</td>
<td>9</td>
</tr>
<tr>
<td>More coughing than usual</td>
<td>7.85</td>
<td>1.610</td>
<td>9*</td>
</tr>
<tr>
<td>A change in the colour of your sputum</td>
<td>7.78</td>
<td>1.601</td>
<td>11</td>
</tr>
<tr>
<td>More wheezing or chest tightness</td>
<td>7.7</td>
<td>1.815</td>
<td>12</td>
</tr>
<tr>
<td>Feeling more fatigue than usual</td>
<td>7.59</td>
<td>1.760</td>
<td>13</td>
</tr>
<tr>
<td>Generally feeling unwell</td>
<td>7.59</td>
<td>1.716</td>
<td>13</td>
</tr>
<tr>
<td>Breathing at a faster rate than usual</td>
<td>7.48</td>
<td>1.805</td>
<td>15</td>
</tr>
<tr>
<td>Thicker sputum than usual</td>
<td>7.44</td>
<td>2.082</td>
<td>16</td>
</tr>
<tr>
<td>Less energy than usual</td>
<td>7.41</td>
<td>1.600</td>
<td>17</td>
</tr>
<tr>
<td>Feeling more tired than usual</td>
<td>7.37</td>
<td>1.779</td>
<td>18</td>
</tr>
<tr>
<td>Having to use more inhaled medications (i.e. inhalers, mucolytics) than usual</td>
<td>7.33</td>
<td>2.287</td>
<td>19</td>
</tr>
<tr>
<td>Knowing you have an increase in the infection markers in your blood (for example CRP, white cell count)</td>
<td>7.33</td>
<td>2.201</td>
<td>19</td>
</tr>
<tr>
<td>Knowing that your oxygen levels are low</td>
<td>7.33</td>
<td>2.130</td>
<td>19</td>
</tr>
<tr>
<td>More chest pain than usual</td>
<td>7.33</td>
<td>2.434</td>
<td>19</td>
</tr>
<tr>
<td>Coughing up blood</td>
<td>7.15</td>
<td>2.231</td>
<td>23</td>
</tr>
<tr>
<td>Knowing that you have a decrease in your oxygen saturation (measured with a finger probe)</td>
<td>7.15</td>
<td>2.013</td>
<td>23</td>
</tr>
<tr>
<td>Increased time spent resting</td>
<td>7.11</td>
<td>1.672</td>
<td>25</td>
</tr>
<tr>
<td>Sputum that is harder to cough up</td>
<td>7.11</td>
<td>1.888</td>
<td>25</td>
</tr>
<tr>
<td>Fever or increased temperature</td>
<td>7.07</td>
<td>2.183</td>
<td>27</td>
</tr>
<tr>
<td>A change in the taste of your sputum</td>
<td>7.04</td>
<td>2.047</td>
<td>28</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>6.93</td>
<td>1.859</td>
<td>29</td>
</tr>
<tr>
<td>Knowing that you have new bacteria in your sputum</td>
<td>6.81</td>
<td>2.095</td>
<td>30</td>
</tr>
<tr>
<td>Generally looking unwell</td>
<td>6.81</td>
<td>2.113</td>
<td>30</td>
</tr>
<tr>
<td>Knowing that you have new additional breath sounds when your chest is examined</td>
<td>6.78</td>
<td>1.888</td>
<td>32</td>
</tr>
<tr>
<td>Sputum streaked with blood</td>
<td>6.7</td>
<td>1.728</td>
<td>33</td>
</tr>
<tr>
<td>Weight loss</td>
<td>6.59</td>
<td>1.947</td>
<td>34</td>
</tr>
<tr>
<td>Knowing that you have new changes on chest x-ray</td>
<td>6.56</td>
<td>1.888</td>
<td>35</td>
</tr>
</tbody>
</table>

**Bold** = the top 10 statements ranked.
Note: Scores with the same average rating were given the same joint ranked position.

* Also ranked in the top 10 by CF HPs.
CF health professionals (rank order 29). Indicators from CF health professionals that were rated high were commonly rated lower by patients with CF; for example “haemoptysis (blood streaked sputum)” was rated higher by CF health professionals (rank order 13) and lower by adults with CF (rank order 33).

It is difficult to select a cut off point however; few statements were rated high by both groups. For example the top ten indicators from the adults with CF, six of these were not ranked in the top 10 by CF health professionals. In the top 10 indicators from the CF health professionals, six of these were not ranked in the top 10 by adults with CF. The four statements in the top 10 where there was agreement were “A large decrease in lung function (Greater than 10% FEV1)”, “Feeling more short of breath than usual”, “Producing more sputum than usual” and “More coughing than usual”. Although FEV1 is an objective indicator it is perhaps not surprising that it appeared as the top item on the adults with CF list, since there is a big emphasis on this measurement in the clinic. Examination of the standard deviations for each of the indicators showed that there was reasonably good agreement for individual criteria, although there was a trend to a reduced level of consensus in the less highly rated criteria. Following analysis via the independent t-Test or Mann–Whitney U, there were 15 statements in Tables 1 & 2 which showed a statistically significantly different rating with a p-value <0.05. While it is interesting to note results which were significantly different this was, of necessity, a semi-quantitative study. While a certain degree of importance can be placed on the statistical significance, the research team felt that more importance should be placed on the clinical relevance which is detailed through the hierarchy of average rating scores for each group.

4. Discussion

This study has used a series of surveys, including an initial systematic analysis of the literature, to clarify what are the key criteria for identifying a PEX in CF. It has demonstrated that
adults with CF and CF health professionals generally identify a
different hierarchy of important indicators of PEX. In general,
the important indicators identified by the adults with CF were
more subjective than those identified by the health profes-
sionals, who preferred more objective clinical measurements
(Tables 1 and 2). The importance of physiological measure-
ments, such as oxygen saturation, to CF clinicians has recently
been reported in a study using clinical vignettes to identify
evacuation criteria [18]. However, often the relationship between
changes in physiological measurements and changes in symptoms
and function in people with respiratory conditions is weak, and this
may help to explain why patients have different criteria than health
professionals.

It is not surprising that the two groups identified different
hierarchies of importance for the signs and symptoms since they
have access to different information; the patients experience
symptoms, whereas the health professionals observe or measure
them, or rely on patient reporting whichever symptoms they think
are relevant, possibly in response to specific questioning by the
clinician. A more defined series of questions and/or tests might
help to improve information gathering. The timing of when
indicators of an exacerbation occur could also be relevant, as
symptoms may be apparent to patients which later trigger the
health professionals to evaluate with objective investigations.
This highlights that CF health professionals should consider the
signs and symptoms described by an adult with CF; this is
especially pertinent when the patient indicates that a specific
symptom is often a likely precursor to an exacerbation in their
condition.

Currently available criteria-based definitions only capture
some of the indicators that were rated important in our study [15].
For example, indicators such as “Feeling the need to do more
airway clearance than usual” which was considered important by
adults with CF in our study are not in current criteria. Also
indicators in our study such as “Increased inflammatory markers”
considered important by health professionals are not in the current
criteria [15]. Other indicators of PEX such as the four that adults
with CF and CF health professionals agreed were important
(Tables 1 and 2) are captured in current definitions. These
variations represent the complexity involved in developing an
agreed definition and resulting clinical tool(s) or research tool.
However, attempting to define an exacerbation in CF continues to
be relevant because the presence/absence of an exacerbation is
recognised by EMA as an important end point [14].

A single set of criteria may not be the most useful in defining
an exacerbation in CF. It may be more accurate to identify an
individual set of signs and symptoms of a PEX for each patient;
the extent of the deviation from their “usual signs and symptoms”
could then be used to identify an exacerbation. This could be
valuable to enable patients to share their management with their
health professional, and perhaps incorporate an action plan
relating to monitoring usual symptoms and recognising the onset
of an exacerbation. It could help clinical teams to standardise the
criteria used for admission to hospital with an exacerbation and
with decisions around commencing oral or IV antibiotics, or
more intensive therapy. If the criteria were useful in establishing
the severity of the exacerbation this could help with decisions
around treatment delivered at home versus hospital. It could also
have a research utility in assessing the response of specific
therapies in limiting the severity of exacerbations by bench
marking efficacy against clearly identified personalised criteria
for each individual patient. This is generally what CF clinicians
do informally as part of clinical reasoning, and it would be helpful
if this was formalised into a tool that could be used by patients at
home and in clinical trials.

Further research is required to build on the findings of this
study. It is notable that the signs and symptoms that prompt adults
with CF to seek medical attention are often different from those
considered most important by the health professionals. Therefore,
a dialogue between clinicians and patients should be encouraged
to help individuals identify which signs and symptoms are critical
for them in identifying the onset of a PEX. The aim would be to
promote earlier engagement with their CF centre which could
result in earlier intervention and triage of treatment options. The
results of this study could also be used to explore if the criteria
selected by CF health professionals provide scope for helping to
determine treatment plans. A clinical tool may be an appropriate
way forward. For example, the Chronic Respiratory Disease
Questionnaire (CRDQ) enables patients to identify up to 5
activities which induce breathlessness; in the same way a clinical
tool for defining PEX could consider 5 (or more) criteria
which individual patients select as important in defining their
exacerbation [29]. A new tool could also incorporate objective
indicators that health professionals consider important. For
example, the Asthma Control Questionnaire incorporates
patient’s views on whether their asthma is under control as well
an objective measurement of peak respiratory flow rate [30]. Any
new tool should consider that different indicators of a PEX may
be associated with different degrees of disease severity and also
different severities of exacerbation [16].

Despite the high response rate with 94% of participants
completing all three rounds of the Delphi, a limitation of
this study is the small sample size. However, this study
included a large spread of centres across the British Isles
giving confidence that we obtained a representative range of
experience from CF centres of different sizes and localities.
In Delphi studies it is proposed that the consensus level be
defined in advance of acquiring the data so that the researchers
cannot influence the outcome of the survey [22]. The 75%
consensus level was chosen through reference to previously
published Delphi studies but the choice of a specific consensus
level is an aspect of Delphi methodology that remains contentious
[22]. The validity of this study was optimised by providing
explicit participant inclusion criteria, pilot testing, setting a
predetermined consensus level, and monitoring the number
of rounds [20–23].

5. Conclusions

This study used a Delphi consensus method to ascertain
important indicators of PEX from the perspectives of adults with
CF and CF health professionals. There were clear differences in
perspectives between the two groups in relation to the important
indicators of an exacerbation in CF.
Contributor statement page

All authors attest to the following roles in the preparation of this manuscript:

1) Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data — McCourt, O’Neill, Logan, Abbott, Plant, McCrum-Gardner, McKeown, Elborn, Bradley.

2) Drafting the article or revising it critically for important intellectual content — McCourt, O’Neill, Logan, Abbott, Plant, McCrum-Gardner, McKeown, Elborn, Bradley.

3) Final approval of the version to be published — McCourt, O’Neill, Logan, Abbott, Plant, McCrum-Gardner, McKeown, Elborn, Bradley.

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