Evaluating the Evidence for Airway-Clearance Therapy in Cystic Fibrosis

Cystic fibrosis (CF) is caused by an abnormality of the gene that encodes for CF transmembrane conductance regulator, which leads to dysregulation of the salt and water content of the airway surface liquid. Abnormal airway surface liquid compromises mucociliary clearance and airway defenses against infection, resulting in an ongoing spiral of chronic infection, inflammation, mucus plugging, and worsening airway obstruction that leads to irreversible and diffuse bronchiectasis.1

Physical airway-clearance therapy has for decades been considered one of the cornerstones of therapy for the prevention and treatment of CF lung disease.2 However, clinical trials of the efficacy and effectiveness of airway-clearance therapy in CF are challenging to perform and difficult to evaluate. Some of these challenges are specific to CF, no matter what therapies are tested. CF is a rare disease, and studies performed at a single CF care center are almost always underpowered,3 so there are logistical barriers to enrolling an adequate number of subjects into the many clinical trials that should be done. CF is a chronic disease, so studies that evaluate short-term efficacy measures may not provide clinically relevant information on long-term outcomes.4

Aside from the problem of evaluating CF disease outcomes, other challenges to performing valid clinical trials are specific to airway-clearance therapy. Blinding is virtually impossible: one cannot plausibly deliver sham airway-clearance therapy or disguise the treatment assignment, so the subject and investigator know what form of airway-clearance therapy is being used. This can bias both the outcome and also the subject’s decision on whether to continue in the study, because of preconceptions regarding a favored therapy. For example, a multicenter trial in the 1990s that compared several airway-clearance therapies was irremediably biased because many patients enrolled in the study to get access to high-frequency chest wall compression and then dropped out of the trial if they were not randomized to that therapy. Further, there are large variations in the teaching and practice of various airway-clearance therapies, so the methods used in one trial might not be identical to those used in another. Finally, as adherence to airway-clearance therapy among patients with CF is estimated5 to be well below 50%, and probably worse if technique is considered, and adherence during a clinical trial is typically better that what can be expected in practice,6 the design and interpretation of clinical trials of airway-clearance therapy should recognize the distinction between efficacy (the ability of an intervention to work under ideal conditions) and effectiveness (the success of an intervention in actual clinical practice). In “real life,” patient preference is not a trivial matter, as adherence seems to correlate best with patient satisfaction with the technique.7

The end result of the problems itemized above is that the literature on airway-clearance therapy in CF contains research articles with contradictory conclusions and many narrative review articles that present authors’ anecdotal experience and preconceived viewpoints. This is confusing to clinicians who need to decide on what treatments to prescribe to patients, and also to researchers, who would benefit from consensus on what topics would be fruitful for further investigation. The field has advanced in the last 10 years from the work of several groups that have performed methodologically rigorous systematic reviews of the airway-clearance-therapy literature. In contrast to a traditional narrative review, a systematic review uses an explicitly stated, objective, and transparent approach to find and critically appraise studies and create a valid synthesis in a way that minimizes bias.8 This synthesis may be qualitative, or, if the data are sufficiently homogeneous, a systematic review may include a quantitative meta-analysis that mathematically combines the results of individual studies. The latter approach is particularly helpful when primary studies are underpowered; the meta-analysis may allow new statistically valid conclusions to be drawn where they were not possible before.

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This issue of Respiratory Care features new clinical practice guidelines on airway-clearance therapies for patients with CF,9 as recommended by the Cystic Fibrosis Foundation. These guidelines represent the latest in a series of efforts by the Cystic Fibrosis Foundation’s Pulmonary Therapies Committee to shed light on the treatment of CF lung disease by developing clinical practice guidelines guided by systematic review of the literature. The committee exhaustively searched multiple databases for

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published studies and previous systematic review, and used the United States Preventive Services Task Force evidence-grading system to evaluate the quality of the evidence on the efficacy of airway-clearance therapies in determining recommendations. Regrettably, the committee chose not to perform or update previous quantitative syntheses of the data by performing meta-analyses, which would have provided an even stronger weight of evidence to support the committee’s recommendations. Nonetheless, these guidelines are an important reference point for all CF clinicians.

Ideally, a clinical practice guideline should derive all of its conclusions from a systematic literature review, but existing evidence is often inconclusive or incomplete, so many clinical practice guidelines represent an amalgam of clinical experience, expert opinion, and research evidence. The committee’s recommendations are of interest both for what can and what cannot be concluded with confidence; the identification of knowledge gaps helps set important research agenda items. The 4 primary recommendations of these guidelines are that:

1. Airway-clearance therapy is recommended for all patients with CF for clearance of sputum, maintenance of lung function, and improved quality of life.
2. In general, no airway-clearance therapy has been demonstrated to be superior to any other.
3. For the individual, one form of airway-clearance therapy may be superior to the others. The prescription of airway-clearance therapy should be individualized, based on factors such as age, patient preference, and adverse events, among others.
4. Aerobic exercise is recommended for patients with CF as an adjunctive therapy for airway clearance and its additional benefits to overall health.

These recommendations are made based upon what the committee describes as a “fair” level of evidence, meaning that the data are solid enough to make the connections plausible without having rigorously proven that they exist. Recommendations 1 and 4 (ie, which suggest airway-clearance therapy and exercise for all patients) clearly follow the published literature and conventional standards of care. Recommendation 2 needs to be understood in context. The committee’s discussion explains more clearly that “the studies reviewed were inadequately powered to demonstrate superiority or equivalence. Rather than stating that these methods are equivalent, we choose to state that none have been demonstrated to be superior to the others.” It is important to recognize the nuance: the committee did not conclude that all forms of airway-clearance therapy are equal; it concluded that there isn’t enough evidence to determine if any one airway-clearance therapy is superior to any other. It might be a bit misleading, therefore, to label that statement as having “fair” evidence, because in truth there is inadequate evidence to say anything more definitive. The evidence behind recommendation 3, which follows logically from recommendation 2, is somewhat problematic as well; no studies actually demonstrate that “for the individual, one form of airway-clearance therapy may be superior to the others,” or that “the prescription of airway-clearance therapy should be individualized based on factors such as age, patient preference, and adverse events, among others.” This, again, is really a logical principle to operate under, given the lack of evidence; it is not a recommendation based upon “fair” evidence.

An elaboration of the recommendations is more clearly stated at the end of the document to be based upon expert opinion rather than evidence. The suggestion to begin airway-clearance therapy in asymptomatic infants is a reflection of the growing appreciation that CF centers with the best disease outcomes take an aggressive and proactive approach to CF care. Thus, since “the presence of lung disease early in life is well-established...the committee believes there is potential benefit and little harm in teaching airway-clearance therapy to parents early and encouraging airway clearance to be part of the child’s daily routine.” The committee’s recommendation to individualize airway-clearance therapy based upon patient circumstances and preferences is an example of another established approach to improving outcomes, the promotion of disease self-management and patient participation in determining aspects of care. It is probably best to provide CF patients and families with the complete menu of techniques and let them choose which they find most satisfactory, given lifestyle considerations and subjective impression of benefit, as well as the scant available objective evidence.

In summary, these new clinical practice guidelines on airway-clearance therapy, while not completely evidence-based, represent the current best synthesis of existing clinical evidence and expert opinion. The committee recommends that all CF patients perform airway-clearance therapy starting in early infancy, and that exercise should be encouraged as an adjunctive therapy. In the absence of evidence of clear superiority of any specific airway-clearance therapy, the committee recommends that therapy be individualized for each patient. As we cannot actually state with certainty that all forms of airway-clearance therapy are equal, these guidelines are a clear call for further research to identify the most effective airway-clearance therapies in CF. Given the challenges that constrain our ability to classically research treatment applications for CF, the Cystic Fibrosis Foundation has supported benchmarking as an alternative method. Benchmarking involves the identification of specific practices that are used at centers that have achieved superior disease outcomes.
eral CF centers and clinicians have reported improved disease outcomes by promulgating certain standardized airway-clearance therapy methods, and that experience might be an excellent starting point for developing further formal research investigations.

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REFERENCES

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