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Optimizing treatment of CF pulmonary exacerbation: A tough nut to crack

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Pulmonary exacerbations are a common occurrence in cystic fibrosis (CF) and their impact real, detrimentally affecting quality of life (1, 2), morbidity (3, 4), and mortality (5). Treatment often includes a prolonged course of intravenous aminoglycosides, beta-lactams, and increased airway clearance but there is neither consensus nor standard protocol for therapeutic options in the setting of CF pulmonary exacerbation (PEX). The United States CF Foundation conducted a systematic review and published guidelines (6, 7) for the treatment of a CF PEX; the data presented in the systematic review highlighted the paucity of evidence that guides current clinical management. Recent advances in CF chronic therapies such as inhaled antibiotics, CFTR modulators, mucolytics and macrolides have proven to reduce the occurrence of PEX or delay the time to next exacerbation; however, very limited research (8) has occurred in the area of acute management of PEX including the development of novel therapeutics. This is due, in part, to the challenges in conducting such studies. Randomized, controlled trials of acute PEX management are mired by challenges, including variability in treatment location (home versus inpatient versus both), duration and selection of antibiotics, and use of mucolytics or corticosteroids – many of which are driven by differences in physician goals or patient preferences. Conducting a trial in an environment with this constellation of variable treatment factors can be a daunting task, but without such trials, we can never improve the care of acute PEX for our CF patients.

Dentice et. al.* report findings of a randomized, blinded, placebo controlled trial of hypertonic saline (HS) administered during a hospital admission for PEX in CF adults. HS is

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an osmotic agent responsible for hydrating airway surface liquid and improving mucus clearance in the CF lung and is commonly used as a chronic therapy (65.7% of US patients over 6 years old in 2014) (9). The primary objective of the study was to show that hypertonic saline was harmful or beneficial when used as an adjunctive therapy during a PEx based on tolerability, length of hospital stay, rate of resolution of signs and symptoms of acute PEx and time to next exacerbation. While the primary endpoint was not met (HS group hospital stay was 1 day shorter than placebo with 95% CI: 0–2 days), the authors were able to show astoundingly high adherence and tolerability to HS (albeit in an inpatient setting) in addition to significant improvements in congestion symptoms and recovery of pre-exacerbation lung function by discharge (75% versus 57%). The authors should be commended for conducting this relatively large study of CF exacerbation (n=132). While they were unable to show a significant reduction in hospital days, they did see indications of improved outcomes with HS *in spite* of the reduced duration of treatment (only 1 day shorter).

While the paper demonstrates strong data that symptoms as measured by a Leikert scale and lung function as measured by forced expiratory volume in one second (FEV₁) were improved, length of hospital stay as an outcome measure for CF PEx studies raises some interesting challenges. Length of hospital stay is a highly meaningful measure of clinical efficacy in that it reduces patient burden and health system costs and *should* be a direct reflection of clinical improvement such as FEV₁ recovery and symptom resolution. However, the authors do not describe what constituted criteria for discharge and instead state that discharge timing remained at the discretion of the treating physician. How much improvement in FEV₁ or symptoms was enough to warrant discharge? While the study was blinded with a masked placebo using 0.19% saline (a clear strength of the study), having clear criteria is essential to understanding the meaning of their primary endpoint. The best chance for moving the needle on an outcome such as length of stay is to provide specific criteria directing IV discontinuation or patient discharge based on specific lung function thresholds and/or symptom resolution. Doing so would ensure treatment duration be a direct measure of patient improvement, less subject to physician and patient interpretation, decision, and variability. In a recent study of PEx, 46% of physicians reported intent to treat for a fixed duration (commonly 14 days) (9, 10) and only *add* hospital or IV days if a patient is not responding to therapy. Physicians and patients may be reluctant to shorten an IV course of antibiotics unless they note a marked improvement in patient signs and symptoms.

The advantage to using PEx treatment duration to measure efficacy in a controlled trial is to remove it as a confounding factor for any other clinical measures otherwise chosen to demonstrate effectiveness. Standardizing treatment discontinuation criteria would objectify the endpoint; however implementing a protocol to dictate treatment length is not without challenges. What would be universally acceptable criteria for patient discharge or extending the treatment duration? A 10% improvement in forced expiratory volume in 1 second (FEV₁) plus significant reductions in chest congestion might be a meaningful benchmark for one patient, whereas another, with more advanced disease, may never be expected to meet that threshold. Would it be acceptable to let the former patient discontinue PEx therapy after placing a peripherally inserted central catheter and only four days of therapy (if that is when they met the a priori definition) while the latter languishes on in the hospital for weeks with an 8% FEV₁ improvement? The unique patient profiles, therapeutic needs, and achievable

outcomes make research in the area of CF pulmonary exacerbation extremely difficult. An alternative to using duration as an outcome would be to first optimize exacerbation treatment, and then fix the antibiotic period in subsequent studies of adjunct therapies to eliminate its confounding effect on clinically relevant measures such as lung function or symptom resolution.

What other key endpoints should one consider in PEx studies? Time to next acute pulmonary exacerbation was reported in this study by Dentice et. al^{*}. and others (11, 12); a number of studies have suggested that this is not a relevant endpoint (13, 14). When one evaluates the time to next pulmonary exacerbation for an acute treatment, there is a clear disconnect between the primary event and the next event. Exacerbations are likely stochastic events that relate more to the timing of viral upper respiratory tract infections and adherence to routine treatments. Treatment failure is also a possible endpoint, but patient response to antibiotics for exacerbation is fairly consistent thus rates of true treatment failure (like retreatment in 30 days) are likely rare (15). The key endpoints will need to resonate with patients and providers. These endpoints will need to include lung function and symptoms preferably assessed using a measure like the CF Respiratory Symptom Diary (CFRSD) to clearly track treatment response (16).

The study by Dentice et. al. is not unlike other interventional trials (17–21) in CF PEx – unable to conclusively demonstrate a clinically meaningful treatment effect despite promising trends in a study population that was too small to show efficacy. Hypertonic saline appears to be tolerated and while it didn't significantly reduce length of hospital stay, it is probably safe to say it doesn't lengthen it, while showing some evidence that recovery of pre-PEx FEV₁ is improved with HS. Is this enough evidence to advocate for its adoption in overall management of PEx? Maybe the more important question: are we putting forth our best effort to advance the care for CF patients during their most vulnerable periods of acute illness? Yes, it is expensive to conduct very large trials for conclusive results. Yes, it is hard to impress upon physicians the need for equipoise when standardizing aspects of care long thought to be the 'art of medicine'. Yes, it is difficult to educate patients and families on the importance of participating in research even when they are very sick. But when it comes to CF pulmonary exacerbation we are not currently practicing evidence based medicine, and decades with dozens of inconclusive studies aren't getting us much closer. We are in an exciting era where CFTR modulators are available for almost half the CF population, it's about time we start devoting resources to appropriately address pulmonary exacerbation.

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