Can Identifying Pulmonary Exacerbation Phenotypes Guide New Treatment Approaches for Cystic Fibrosis?

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Cystic fibrosis (CF) pulmonary exacerbations (PEx) are clinical events characterized broadly by signs and symptoms of worsening pulmonary health. Common signs and symptoms of PEx include increased cough and sputum production and decreased lung function, but PEx are known to be heterogeneous in both presentation and treatment response (1, 2). The fundamental components of treatment are relatively uniform across PEx and include increased mucus clearance therapies, nutritional support, and antibiotics directed at recent respiratory culture results (though there are significant variations across PEx in antibiotic selection and duration) (3, 4). PEx are associated with significant morbidity, including worsening lung function and decreased quality of life and are thus clinically important events for people with CF (1, 5, 6). Additional morbidity can result from PEx treatments, such as antibiotic toxicities, healthcare costs, and antimicrobial resistance (7, 8). As such, efforts to improve treatment approaches for PEx and to improve PEx outcomes are high priorities.

In this issue of *AnnalsATS*, Carter and colleagues (pp. 1818–1826) analyzed phenotypes of CF PEx, focusing on inflammatory markers and viral infections (9). They first performed an observational cohort study of a discovery cohort of 59 adults with CF admitted for intravenous antibiotic treatment for PEx in Dublin, Ireland. PEx were categorized on the basis of predefined plasma C-reactive protein (CRP) concentrations and viral infection status. Subjects with a normal CRP at onset of PEx were categorized as "pauci-inflammatory," and those with elevated CRP were further categorized based on viral PCR results as either "nonviral with systemic inflammation" or "viral with systemic inflammation," and clinical outcomes were compared across these groups. Viruses were identified in 33% of the PEx, including some in the pauci-inflammatory group, and overall subject demographics were similar across the groups. Subjects with viral infections and systemic inflammation had the greatest decrease in forced expiratory volume in 1 second percentage predicted (FEV_1pp) at onset of PEx, but FEV_1pp recovery after treatment was similar across the groups.

A strength of the study was the use of three independent cohorts from two CF centers. After the discovery cohort analyses, the authors performed a retrospective study to evaluate CRP as a marker of phenotypes of PEx in two independent validation cohorts: one internal cohort at the same Irish center (188 PEx from 80 people with CF) and one external cohort from a CF center in Vancouver, Canada (83 PEx from 43 people with CF). Using the same CRP cutoffs as in the discovery cohort, PEx were categorized as either pauci-inflammatory or "inflammatory" (viral infection data were not available for the validation cohorts). In contrast to the discovery cohort, subject demographics differed across the categories in both validation cohorts, with lower baseline FEV_1pp values in those with inflammatory PEx compared with the pauci-inflammatory group. Of subjects with multiple PEx in these cohorts, ~30% had PEx classified in each category across different time points. There was a greater drop in FEV_1pp at PEx in the inflammatory compared with the pauci-inflammatory group only among those with higher baseline FEV_1pp. After adjusting for baseline FEV_1pp, the odds of lung function recovery to within 10% (relative) of baseline FEV_1pp were about threefold higher with pauci-inflammatory compared with inflammatory PEx.

The identification of a pauci-inflammatory phenotype associated with less FEV_1pp loss at onset of PEx and better response to treatment of PEx are strengths of this study. The pauci-inflammatory group accounted for a minority of CF PEx (elevated CRP concentrations were present in 63–80% of the cohorts). Other studies have also evaluated the utility of CRP as a biomarker of CF PEx (10). Recently, in a secondary analysis of data from the STOP2 (Standardized Treatment of Pulmonary Exacerbations II) study, CRP values from 951 subjects across courses of intravenous antibiotic treatment of CF PEx were analyzed as biomarkers of clinical response (11). In the STOP2 study, CRP concentrations were positively associated with respiratory symptom severity and negatively associated with lung function (11). Although the overall conclusion of the STOP2 analyses was that CRP changes have limited utility as a marker of response to treatment for PEx, these data together with those presented by Carter and colleagues (9) suggest a potential role for CRP values in identifying PEx phenotypes, with potentially differing pathophysiology, that may warrant prospective testing of different treatment approaches.

Consideration should be given to the study's interpretation of intravenous antibiotic duration as a clinical outcome. Although pauci-inflammatory PEx were

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treated with significantly fewer antibiotic days than inflammatory PEx in the external validation cohort, with similar trends in the discovery and internal validation cohorts, it is worth noting that the treating physicians were not blinded to CRP concentrations, which may have influenced treatment decisions. Treatment duration may also have been confounded by the lower baseline lung function in the subjects with inflammatory PEx: in the STOP (Standardized Treatment of Pulmonary Exacerbations) observational study, physicians tended to use longer durations of antibiotics for patients with lower lung function (3).

The study took place before the approval of elexacaftor–tezacaftor–ivacaftor, so it is not clear how the described phenotypes will translate to the larger population of people with CF on highly effective CF transmembrane conductance regulator modulators or how these phenotypes will translate to children and younger adults with milder lung disease or to milder PEx treated with oral antibiotics in the outpatient setting. Limitations of the study also include the lack of viral data from the validation cohorts, as well as limited data on viral infection and outcomes in the pauci-inflammatory group of the discovery cohort. The role of viral infection in CF PEx, and optimal treatment approaches for virally induced PEx, remain knowledge gaps.

The authors conclude that phenotypes of CF PEx with differing clinical presentations and outcomes are associated with markers of systemic inflammation (and to a lesser extent viral infection). The authors specifically hypothesize from these findings that the pauci-inflammatory phenotype of PEx may be less likely to be driven by bacterial infection and thus may not always require antibiotics. Identifying PEx that may not require antibiotics is an intriguing idea and worthy of future study, but the authors were not able to directly test the relative contribution of bacterial infection to the different phenotypes, other than through quantitative cultures of *Pseudomonas aeruginosa*, which did not significantly differ across the phenotypes. Prior studies have also not shown significant changes in *P. aeruginosa* density associated with PEx (12). Although bacterial infection is generally considered to be an key contributor to the pathophysiology of PEx, clear bacterial signatures of PEx have not been identified at the population level in large, cross-sectional studies (13). In addition, at the population level, many antibiotic-related variables (e.g., treatment duration beyond 14 days [STOP2 study], antibiotic susceptibility testing results) do not correlate with differential outcomes in CF PEx (14–17). Collectively, these and other studies raise hypotheses as to phenotypes of PEx that may have different primary drivers (e.g., bacterial infection, inflammation, viral infection, mucus plugging) relevant for future prospective studies to test novel treatment approaches.

Highly effective CF transmembrane conductance regulator modulators are now available for most people with CF, with anticipated continued improvements in life expectancy. As such, optimizing treatment of CF PEx is a high priority, to maximize the clinical benefits but minimize antibiotic side effects, antimicrobial resistance, and costs and burdens of treatment for PEx. Identifying phenotypes of PEx is a promising approach toward further personalizing treatment for CF PEx. The study by Carter and colleagues (9) in this issue is a contribution in this regard and is hypothesis generating for future evaluations of optimal treatment approaches and longer term outcomes for PEx stratified by markers of systemic inflammation. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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"The Cold Steel of a Surgeon or Some Fool of a Physician?": The Debate Continues

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Almost 20 years ago, the first British Thoracic Society (BTS) guideline on the management of pleural infection published in 2003 contained two important statements within its first paragraph. The first detailed that "there is great variation worldwide in the management of patients with pleural infection", and the second that "overall, 20% of patients with empyema die" (1). It is rather tragic and, to some degree, a failure on our part as a community caring for these patients that both these statements remain true today.

The importance of early sampling and chest tube drainage has long been a principle in treatment through the adage "the sun should never set on a parapneumonic effusion", coined by two pioneers of the field of pleural disease (Steven Sahn and Richard Light) (2). However, beyond this, the current treatment paradigm has changed relatively little. In most settings, clinicians start antibiotics, insert a chest tube, and "wait" for medical treatment failure to occur before promoting more aggressive intervention. Data published in the last 3–4 years have convincingly shown that time to intervention is one of the key contributors to adverse outcomes (3, 4). The question that follows, and to date remains unclear, is which intervention?

The role of surgery is well established in pleural infection, and some current guidelines advocate for it to be the primary treatment strategy (5). Indeed, modern Video Assisted Thoracoscopic Surgery (VATS) outcomes have shown considerable success with fewer complications (4). However, there remains a risk associated with the requirement for general anesthetic and a significant rate of conversion to open thoracotomy. In addition, the limitations in the evidence base for early surgery, including selection bias and lack of standardized criteria in the only two small randomized studies of surgery (6, 7) and the multiple case series, should not be overlooked.

The use of combination intrapleural enzyme therapy (IET) using tissue plasminogen activator (tPA) with deoxyribonuclease (DNase) as an alternative potential "rescue" treatment has been a much-needed and practice-changing addition to the landscape in the last decade, driven by the second Multicenter Intrapleural Sepsis (randomized placebo controlled) Trial (MIST-2) (8). Because of its publication, the MIST-2 regimen has been bolstered by a substantial amount of real-world series data demonstrating safety and efficacy in more than 2,000 and 700 patients, respectively (9–15). However, IET has not to date been directly compared head-to-head with surgery.

In current practice, the initial choice of intervention is often on the basis of clinician preference or local access, neither of which are particularly patient-centered. It is, therefore, timely that in this issue of *Annals ATS*, Wilshire and colleagues (pp. 1827–1833) report their data comparing outcomes of initial surgical versus initial IET (tPA and DNase) management (16). This was a large retrospective multicenter cohort study conducted in 18 hospitals over 5 states and comprising 566 patients with pleural infection (complicated parapneumonic effusion or frank empyema). Patients were managed with either initial surgery ($n = 311$ [55%]) or initial IET ($n = 255$ [45%]) with patients identified from retrospective billing data.

The primary study endpoints chosen are highly relevant to practice and included treatment failure and crossover. Treatment failure criteria were well defined and comprised evidence of ongoing infection, including fever or leucocytosis and a persistent pleural collection requiring intervention with additional treatment. Crossover was defined as receiving any dose of IET after surgery or receiving surgery after any dose of IET.

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