All of these factors, combined with cluster randomization and associated rapid recruitment, have implications for future research. Collectively, they may make research that informs clinical practice feasible in hospitals in which it otherwise would not be. Particularly in situations in which idiosyncratic practice variation is exposing patients to a range of treatments in usual practice, trials like this have tremendous potential to improve the quality of care through standardization and to advance knowledge. ■

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Two Steps Forward: Improving the Management of Cystic Fibrosis Pulmonary Exacerbations

In this issue of the *Journal*, Goss and colleagues (pp. 1295–1305) report the findings of the STOP2 (Standardized Treatment of Pulmonary Exacerbations) study, a randomized trial of antimicrobial duration for cystic fibrosis (CF) pulmonary exacerbation (PEx) treatment (1). Adults with CF experiencing PExs treated with intravenous antibiotics were enrolled at presentation and assessed at an interim time point (7–10 days into antibiotic therapy) for clinical response based on lung function and symptom improvement. Early responders were randomized to either 10 or 14 days of total antibiotic treatment duration, whereas non–early responders were randomized to 14 or 21 days' duration. The primary outcome was the change in FEV_1 from the start of antibiotics to 2 weeks after antibiotic cessation. Almost 1,000 patients with CF were randomized in the study; among the approximate one-third of early responders, 10 days was not inferior to 14 days of antibiotics, and among the remaining non–early responders, 21 days was not shown to be superior to 14 days of antimicrobial therapy.

The STOP2 trial represents a landmark study in the treatment of CF pulmonary exacerbations as it is the first to be adequately powered to compare varying lengths of antibiotic courses. The choice of antibiotic duration in the treatment of infectious diseases is frequently guided by clinical experience or observational studies

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rather than by evidence from comparative randomized controlled trials (2). Recent randomized controlled trials have examined shorter antimicrobial regimens for the treatment of ventilator associated or community acquired pneumonia, intraabdominal sepsis, and gram-negative bacteremia and found that shorter courses were not inferior to longer courses (3, 4). Prolonged antimicrobials are associated with an increased number of days in hospital, central line–associated thrombotic complications, toxicity such as ototoxicity secondary to aminoglycoside use, and drug hypersensitivity reactions, to name a few. Although the study by Goss and colleagues did not identify a statistically significant difference in adverse events between treatment arms, it is important to remember that antimicrobial side effects are cumulative over the lifespan of a patient with CF who will require repeated antibiotic courses to treat pulmonary infections. In addition, although not assessed in this study, increased antimicrobial exposure invariably leads to antimicrobial resistance, which ultimately limits the long-term effectiveness of antibiotic therapy in patients with CF (5). By demonstrating that shorter courses are not inferior to longer courses (and in the case of non–early responders, longer ones are not superior), the authors have provided valuable data in the guidance of antimicrobial stewardship (6). The main strength of this study is thus its clinical relevance, as the results have the potential to directly impact the care of individuals with CF.

Another strength of the study was its feasibility and pragmatic design. The management of CF PExs is often complex and variable with no universally accepted definition or complete understanding of the etiology of the condition (7). The investigators are to be commended on the institution of a management protocol that resulted in only 6–16% deviations, proving that standardized approaches are clinically feasible. The advantage of such protocols is the resulting ability to study other interventions aimed at improving the outcomes of PExs without having to control for an endless number of variables. Standardized approaches to the management of CF PExs will become increasingly important as the decreased incidence of exacerbations associated with highly effective modulator therapy limits the sample size available for study (8). Although there will always be certain patients requiring unique, individualized treatment plans, the guidance provided by Goss and colleagues on antibiotic treatment duration will aid in the design of future CF PEx trials.

The choice of primary outcome in this study, change in FEV_1 from start of antibiotics to 2 weeks after ending antibiotics, has certain limitations. Although the absolute change in FEV_1 from start to end of therapy may be the most direct measure of an intervention, the primary driver of this change is the initial drop in FEV_1 from baseline, with greater drops associated with greater increases from Day 0 to end of treatment (9, 10). Within the early responders and non–early responders, the FEV_1 drop from baseline was similar between treatment arms. However, between the groups, the drop was very different, on average 9% in the early responder group and 2% in the non–early responder group. These data highlight the differences between the two study populations and, as the authors correctly point out, does not mean that one can infer that 10 days would be equivalent to 21 days of antibiotic treatment. These differences also beg the question as to why intravenous antibiotics were initially started in the non–early responder group with only a 2% drop in FEV_1 from baseline and whether an increase in FEV_1 was the appropriate measure of clinical response. The non–early responders would seem to represent a different exacerbation phenotype, perhaps not driven by an infective process, given the minimal change in lung function with prolonged antibiotic therapy. Clinical assessment of lung function and symptom scores should thus occur at the interim time point 7–10 days into antibiotic treatment to distinguish these patient populations and apply the findings of the current study.

We still do not know whether these observations apply to patients with frequent, recurrent exacerbations, those with end-stage lung disease, or children with CF, our most vulnerable populations. Nor do we know how to improve the outcomes of those who do not respond to traditional PEx antimicrobial therapy. However, by defining a standardized antibiotic duration for CF PExs, the results of the STOP2 trial by Dr. Goss and colleagues have the potential to improve quality of life for individuals with CF by minimizing antimicrobial exposure as well as providing the infrastructure on which to investigate new treatment modalities. Two steps forward. ■

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Integrated Biomarkers for Pulmonary Nodules: Proving What Is Possible

Determining the nature of pulmonary nodules is a common problem in need of better tools. Rapid identification of those with cancer and avoiding unnecessary invasive biopsies in those with benign nodules are equally desirable outcomes that are often at odds with one another. A reliable biomarker able to classify the probability of cancer (P_{ca}) of indeterminate nodules is a significant and unmet clinical need that would facilitate these outcomes (1). A dizzying array of possibilities have been studied as potential diagnostic biomarkers for indeterminate pulmonary nodules: protein-based biomarkers, autoantibodies, models of clinical and demographic variables, multidimensional radiographic features ("radiomics"), and signatures employing proteomics, genomics, transcriptomics, metabolomics, et cetera (2). Determining how these might be integrated, individually or in combination, into the already complex evaluation of patients with solitary pulmonary nodules is a daunting prospect. It can frankly seem impossible.

In this issue of the *Journal* (3), Kammer and colleagues (pp. 1306–1316) evaluated a combined set of biomarkers incorporating clinical data (Mayo; incorporating variables easily available in the medical record and radiology report) (4), a blood-based biomarker (a high-sensitivity measurement of the cytokeratin fragment 21-1 [hs-CYFRA 21-1]) (5), and radiomic features extracted from computed tomographic images of the nodule (6). Each biomarker's "score" was determined independently by investigators blinded to the outcomes (cancer vs. benign) as well as to the measurement of each other marker. The combined biomarker model (CBM) integrated the Mayo risk score, hs-CYFRA 21-1, and radiomic score through a logistic regression model derived on a cohort of patients enrolled at one center and validated on three independently archived cohorts. After validation the model was fitted to a pooled sample of all four cohorts. The primary endpoint was a simulated diagnostic evaluation based on P_{ca} determined by the CBM that compared the Mayo models as well as each individual marker or combinations of two. To show this, the authors randomly sampled subjects from their pooled cohort of patients with intermediate risk nodules (P_{ca} between 10% and 70% as determined by the Mayo predictor) and simulated a clinical evaluation based upon CBM reclassification of the nodule. Those recharacterized from intermediate to low risk by the CBM would undergo follow-up chest computed tomography, and those recharacterized from intermediate to high P_{ca} would go directly to definitive surgery or biopsy. As the Mayo score was part of the CBM, it is not a surprise that the added information from radiomic and blood-based markers resulted in improved performance, but the CBM clearly outperformed each individual marker in accurately reclassifying nodules into high or low probability. From a practical perspective, the authors showed that the CBM could avoid unnecessary biopsies in those with benign nodules. Roughly speaking, in their simulated analysis, for every eight patients with intermediate probability pulmonary nodules, one biopsy could be avoided. In addition, clinical evaluation based upon the P_{ca} determined by the combined biomarker significantly hastened the diagnosis in patients with malignant nodules.

Combining biomarkers to guide lung nodule management is a difficult task, and the investigators should be recognized for taking it on. When pondering how to put this work into context, I was reminded of the saying "How do you eat an elephant? One bite at a time." Wanting to properly credit the source, I tried to find the origin, but even the Internet could not provide an answer; however, it did provide a suitable and more eloquent alternative by Francis of Assisi: "Start by doing what's necessary; then do what's possible; and suddenly you are doing the impossible."

Kammer and colleagues started with the "necessary" by repurposing previously identified, individually useful biomarkers, hs-CYFRA-21-1 assay with a high sensitivity (5), and a radiomic signature with high specificity (6). They also recognized and demonstrated what is possible by integrating these complementary biomarkers with a widely used clinical model (4) into a combined tool. Using prospectively collected specimens and data and applying the CBM in retrospective blinded evaluation (ProBE design), they studied subjects enrolled in numerous clinical trials or nodule registries. The authors identified the population in which this combined biomarker might be most useful (those with intermediate P_{ca}). This study lays the groundwork for a tool that can simultaneously help avoid unnecessary biopsies *and* delays in cancer diagnosis.

The authors did not systematically incorporate the use of positron emission tomography (PET) scans in all subjects, so this study cannot fully compare the utility of PET scans with the CBM. This will prove important in future iterations of this work. Where PET scans were available in two of their cohorts, the impact of information

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