Assessing the Burden and Prognostic Value of Cough in Idiopathic Pulmonary Fibrosis

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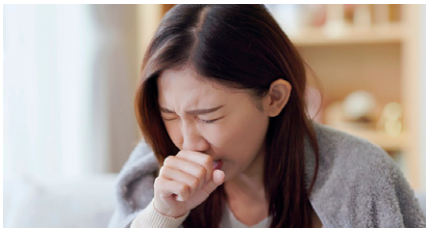

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease that mainly affects older adults and males (1). Approximately 6,000 new cases of IPF are diagnosed per year in the United Kingdom, and over 32,000 patients are currently living with the disease (1). Improving symptoms and quality of life (QoL) for patients with IPF remains a challenge, with antifibrotic medications such as pirfenidone and nintedanib currently used to slow disease progression. A U.K. IPF registry found that 66% of patients reported symptoms of exertional breathlessness and/or cough for ⩾12 months at diagnosis (1). Ryerson and colleagues conducted a study of 242 patients with IPF and found that 84% of them had cough. They also identified cough as an independent predictor of disease progression (2). Similarly, the Australian IPF Registry showed an association between cough and mortality after adjusting for baseline demographics, including age, sex, body mass index, smoking status, and percent predicted forced vital capacity (FVC) (3).

In this issue of *AnnalsATS*, Saunders and colleagues (pp. 1267–1273) present one of the first prospective, longitudinal cohorts (PROFILE [Prospective Study of Fibrosis in the Lung Endpoints] study) characterizing cough burden and its impact on QoL in patients with IPF. The study recruited 632 patients and assessed them at multiple time points over 3 years (4). The results showed a weak association between cough burden and pulmonary function test results. In contrast to previous large studies, cough was not a significant predictor of disease progression or survival in patients with IPF. This study by Saunders and colleagues differs from the one by Ryerson and coworkers in terms of cough assessment, using the Leicester Cough Questionnaire (LCQ) as a measure of cough-related QoL instead of cough as a dichotomous variable. Moreover, progression data were available for only two-thirds of the cohort in the study by Ryerson and coworkers, and data were assessed at 6 months, whereas Saunders and colleagues assessed progression at 12 months. A small study of 19 patients with IPF highlighted a strong correlation between objective cough measurements and subjective cough scoring (visual analog scale [VAS] and LCQ), suggesting through these tools that the cough perception of patients with IPF can be accurate (5). The study by Saunders and colleagues, therefore, bridges a gap in knowledge, given its large, multicenter longitudinal cohort design and the comprehensive assessment of cough using the LCQ.

The study by Saunders and colleagues has limitations, including lack of full examination of the potential impact of comorbidities on cough-related QoL, particularly in relation to gastroesophageal reflux (GER), a comorbidity with a complex relationship with IPF characterized by a "chicken or egg" dilemma, further complicated by confounding factors such as smoking (6). Recent research by Reynolds and colleagues on this complex relationship, using genetic variants to eliminate confounding factors, found that GER increased the risk of IPF (odds ratio, 1.6), but there was no evidence that IPF increased the risk of GER (6). An earlier study suggested this correlation when it found that 87% of patients with IPF had abnormal acid GER on 24-hour pH monitoring, with 71% of these patients not receiving any treatment with a proton pump inhibitor (PPI) at the time (7). Interestingly, only 47% of those with abnormal acid GER exhibited symptoms of GER, and there was no correlation between acid GER severity and IPF severity as measured by pulmonary function tests (7). Although no large randomized controlled trials have evaluated the efficacy of PPI treatment in patients with IPF, PPI treatment has become a common practice. A small pilot randomized controlled trial evaluating the impact of omeprazole on cough frequency found a reduction in the omeprazole group, but the trial was not sufficiently powered to establish statistical significance (8). A pooled analysis of two observational studies found that antacid medication had no statistically significant effect on disease progression when defined as a 10% or more decline in FVC or 6-minute-walk distance or death (9). The Saunders and colleagues cohort had almost half of the patients diagnosed with GER, but only 27.8% received PPI treatment, raising concerns about potential impacts on LCQ scores. Because the role of GER in IPF remains unclear, further research is needed in this regard. A current U.K.-based study, TIPAL (Treating People with Idiopathic Pulmonary Fibrosis with the Addition of Lansoprazole; ClinicalTrials.gov identifier NCT04965298), aims to address some of these questions through a randomized, placebo-controlled multicenter clinical trial.

Effective treatments for IPF-related cough are currently not available as part of the standard of care, and this cough appears to be resistant to conventional therapies. In the Saunders and colleagues study, only a small minority (8.8%) of patients started antifibrotic treatment (53 with pirfenidone, 3 with nintedanib) during the follow-up

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period. The study was not designed to assess the impact of antifibrotic therapy on cough burden and QoL, and the small number of patients who received this treatment limits its statistical power for such an analysis. Neither of the landmark antifibrotic trials, ASCEND (Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis) or INPULSIS (Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis), specifically assessed the impact of antifibrotics on cough (10, 11). ASCEND, however, did note that cough occurred more frequently in the placebo group (10). An international observational study recruited treatment-naive patients with IPF with IPF-related cough (VAS, ⩾40 mm) who were about to start pirfenidone therapy (12). Cough was assessed at baseline using a cough monitor, VAS, and LCQ and after 4 and 12 weeks of treatment. Of the 31 patients who completed follow-up at 12 weeks, objective 24-hour cough decreased by 34%, with 20 (74%) of 27 patients showing improvement. Subjective cough measures also consistently improved, but no significant changes in disease-specific QoL were observed. Although showing some promising results, a key limitation of the study was its lack of a control group. As Saunders and colleagues state, significant work is still needed to develop treatments that effectively address the debilitating symptom of cough in some individuals with IPF.

Saunders and colleagues aimed to investigate the burden of cough and its association with the mucin 5B (MUC5B) polymorphism, but they found no significant difference in cough between the various MUC5B genotypes. This contrasts with a previous study by Scholand and colleagues, who found a significant relationship between cough severity and the IPF risk allele (T) of MUC5B (13). However, Saunders and colleagues provide a stronger body of evidence because they genotyped and evaluated cough with LCQ in a larger sample size of 561 patients than the sample in the Scholand and colleagues study, which only had 68 responders out of the initial cohort of 136 (13). Peljto and colleagues explored the correlation between MUC5B polymorphism and survival in two independent cohorts of patients with IPF. Their results showed that patients with at least one T allele had a lower 2-year cumulative incidence of death, regardless of age, sex, FVC, or diffusing capacity of the lung for carbon monoxide. The study concluded that the MUC5B polymorphism is linked to better survival in patients with IPF (14). The association of the MUC5B promoter polymorphism with pulmonary fibrosis varies greatly on the basis of racial or ethnic background. It is the strongest genetic risk factor for pulmonary fibrosis among non-Hispanic White patients and Mexican patients with IPF, whereas it is rare among Korean patients with IPF (15). In studying health disparities, the relationship between race, genetics, and disease has become a focus in recent years. Adegunsoye and colleagues recently published a study in *JAMA Network Open* revealing significant disparities in outcomes for racial and ethnic minority individuals with interstitial lung disease, including earlier diagnoses, hospitalizations, lung transplants, and deaths for Black patients compared with Hispanic and White patients (16). Although Saunders and colleagues did not collect race or ethnicity data, it would be interesting to investigate the effects of these factors on IPF cough burden and MUC5B polymorphism in their U.K. cohort.

Despite the advances in understanding IPF-related cough, several knowledge gaps remain, including its possible prognostic value. We hope that addressing them will bring us closer to the goal of finding better management and treatment options for patients with IPF affected by this debilitating symptom. ■

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

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Antimicrobials in Sepsis: Time to Pay Attention to *When* Delays Happen

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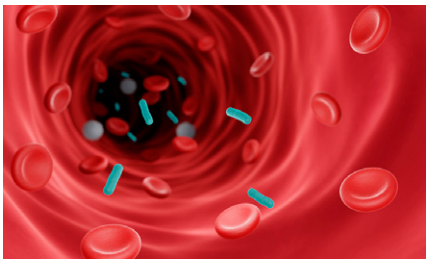

Antimicrobial timeliness ("time to antibiotics") has become a commonly measured sepsis process outcome. Because prompt antimicrobials are associated with reduced sepsis mortality (1), clinical guidelines and performance incentive programs encourage minimizing the interval between sepsis onset and the first dose of antibiotics (2, 3). Variation in antimicrobial timeliness and sepsis outcomes—at the hospital, departmental, and provider levels—suggests that although sepsis recognition and responses are risk based, they are also influenced by important externalities (4–6).

Time of day may be one such factor. In the outpatient setting, later time in the workday is associated with worse rates of vaccination and more inappropriate antimicrobial prescribing, presumably because of decision fatigue and inefficient workflows (7, 8). Analogously, time might influence sepsis care in the hospital through physical and decision fatigue, temporal clinical workflows (e.g., rounding and cross-cover), or competing priorities (e.g., educational conferences) (9).

In this issue of *AnnalsATS*, Ginestra and colleagues (pp. 1299–1308) evaluated the relationship between time of day and antimicrobial initiation in a retrospective cohort of patients with hospital-onset sepsis on the wards (10). After adjusting for patient characteristics, hospital factors, and potential secular and seasonal trends, the authors found substantial variation in the times when antimicrobials were started, with profoundly lower rates at shift change and certain portions of the night. Juxtaposing these findings against the realities of hospital workflows, the authors hypothesized that shift handoffs, nighttime staffing, and the timing of prerounding and rounding activities might compound decision fatigue in terms of delaying antimicrobials.

The authors' methodology is thoughtful and well described, including several particularly noteworthy choices. First, the clinical problem of interest is hospital-onset, rather than community-onset, sepsis. This focus has several implications, including prognostic enrichment (hospital-onset sepsis has worse outcomes) and different mechanisms underlying the relationship between time of day and antimicrobial initiation (e.g., ward rounds are predominantly diurnal, whereas many emergency department workflows exist independent of time of day).

Second, the authors used discrete-time methods for their analysis, dividing continuous time into equal-length intervals and modeling outcomes in each time window (11). Several features of discrete-time analyses are particularly relevant to this research question. For instance, electronic health record (EHR) data are interval censored: Observations are recorded only at specific time points, which do not necessarily correspond to an event's occurrence in continuous time. As a relevant example, vital signs and labs are measured periodically on the wards, but sepsis generally begins between these observed time points. Discrete-time survival analysis mirrors these realities, estimating probabilities that an event occurs *within a time window* rather than at a specific instances. Discrete-time analyses also accommodate nonproportional hazards (i.e., situations in which an event's hazard rate changes over time), a necessary feature when the time–exposure–outcome relationship is anticipated to be nonuniform. Finally, discrete-time survival analysis easily incorporates time-varying exposures and covariates; in fact, the time-varying exposure here might be conceptualized as time itself.

Third, Ginestra and colleagues performed their analyses against the two most commonly used sepsis definitions: the Centers for Disease Control and Prevention's Adult Sepsis Event (ASE) and Sepsis-3. These criteria-based sepsis definitions identify distinct cohorts with different baseline characteristics and outcomes (Sepsis-3 generally identifies individuals who are not as sick as those identified by the ASE) (12). Similar associations between time of day and antibiotic initiation regardless of sepsis

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