in dramatic bacterial clearance in the *Pseudomonas* case (9), but intravenous-only administration did not result in eradication of MRSA in the experimental model (8). A higher lung necrosis score was associated with nonsurvival (see Figure E3 in Reference 8), raising concerns about intravenous delivery of both phage and antibiotic to the lumen of cavity pneumonia. Phage therapy is not neutral for the host: phages may transcytose host cells and stimulate Toll-like receptor 9 and other pattern recognition molecules (13). Generally, phage infusions or mucosal applications are well tolerated without an inflammatory signal, as was seen in the mouse model (8). More importantly, neutralizing antibodies are common in individuals exposed to naturally occurring phages, and may blunt the benefit of intravenous therapeutic phage therapy. Because aerosolization is less likely to induce neutralizing antiphage antibodies and less likely to be blunted by preformed antibodies, this route may be preferred for pneumonia treatment in the critically ill.

Validation of the benefit of routine phage treatment of AMR pneumonia requires much more work. Only further data will demonstrate whether phage therapy is truly a new chapter in pneumonia treatment or just another interesting footnote.

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concentrations of nicotine. Previous studies have focused on the toxic effects of these ingredients either as a whole or as separate components of e-cigarettes. Using airway epithelial cell lines, Sassano and colleagues showed that PG/VG itself adversely affected cell viability, and that certain e-liquids, including the most common ones on the market, are more toxic than PG/VG alone (2). White blood cells in the airways, such as neutrophils and macrophages, are crucial for the innate defense of the airways. However, when they are exposed to constant stimulation, such as from cigarette smoke, they can contribute to the initiation and progression of chronic lung diseases such as chronic obstructive pulmonary disease. It has been shown that e-cigarettes can also trigger neutrophils and macrophages to release their enzymes such as elastase and MMP9 (matrix metalloproteinase 9) (3, 4), which are known to cause tissue damage in the long run. Furthermore, e-liquids, even without nicotine, can trigger an inflammatory and oxidative response and cytotoxicity on the human monocyes (5). Moreover, in vivo human unbiased proteomics studies using human induced sputum and epithelial cells derived from human airways from smokers and e-cigarette users revealed that vaping causes marked adverse changes in the airways, including altered epithelial and sputum proteomes and mucus/mucin composition (3, 6) in both a similar and a unique way relative to cigarette smokers.

Nicotine is a highly addictive substance, and the high level of nicotine delivered by the current generation of e-cigarette devices can cause addiction in never-smokers (7) and could subsequently provide a foundation to start traditional cigarette smoking (8). The nicotine content of e-cigarettes typically varies between 3 and 36 mg/ml. Most recent generations of e-cigarettes contain much more nicotine (up to 60 mg/ml), typically in a salt form, to speed up and increase the delivery of nicotine to the brain at rates comparable to those found with cigarette smoking. The adverse effect of nicotine on the airways and its consequences, however, is an understudied area. As reported in this issue of the Journal, Chung and colleagues (pp. 1134–1145) addressed this critical issue by performing a comprehensive mechanistic study using in vivo (sheep) and in vitro (human primary bronchial epithelial cell cultures) to observe lung hemostasis and pathobiology in response to nicotine (9). The authors previously showed that chronic e-cigarette exposure caused chronic obstructive lung disease in mice in a nicotine-dependent manner (10). In this work, they used primary airway epithelial cells derived from nonsmoking healthy individuals for in vitro exposure experiments. They then assessed the effects of e-cigarette vapor on airway cells via sophisticated mucociliary transport (MCT), mRNA and protein expression, calcium imaging, mucus concentration, and complex viscosity assays. For in vivo animal (sheep) studies, tracheal mucus velocity (TMV), a surrogate marker for mucociliary clearance, was measured after nebulized e-cigarette exposure.

The relative viscosity analysis of cell secretions showed that compared with an air-only control and e-cigarette vapor with no nicotine, e-cigarette vapor with nicotine increased mucus viscosity and decreased the airway surface liquid height in a dose-dependent fashion. Also, human primary bronchial epithelial cell mucus concentrations, measured by percent solids, increased approximately 1.5- to 2-fold. Given the fact that increased mucus concentration and viscosity are inversely related to mucociliary clearance rates, they measured the MCT in cell cultures. As predicted, MCT was significantly reduced, by approximately sixfold on average, in the cultures exposed to nicotine. To understand the mechanism of the adverse effect of nicotine on the cells, the authors focused on a Ca\(^{2+}\)-selective ion channel, TRPA1 (transient receptor potential ankyrin 1), as a possible nicotine receptor. In fact, using known inhibitors of TRPA1, the authors averted the adverse effects of the nicotine on airway surface liquid, mucus concentration, and viscosity, which strongly suggests that the effects of nicotine were transmitted through TRPA1 and not the nicotinic acetylcholine receptor.

To validate their in vitro observations, the authors used an in vivo (sheep) exposure model. They found that TMV diminished by approximately half after exposure to e-cigarette liquid with 15–20 mg/ml nicotine as compared with e-cigarette liquid with 10 mg nicotine or e-cigarette vapor with no nicotine. This effect was prevented when a TRPA1 inhibitor was added to the mixture, which is consistent with the cell culture results and confirms that the nicotine effect occurs via the TRPA1 receptor. However, this important in vivo observation (i.e., impaired mucociliary clearance via nicotine and its consequences) needs to be tested and replicated in the future in vivo human studies involving e-cigarette users with no history of smoking cigarettes. Although this study focused on certain e-cigarette liquids with nicotine up to 36 mg/ml, some new e-cigarette devices and some e-liquids contain a much higher nicotine content and can potentially deliver more nicotine to the airways (10). Given the nicotine concentration–dependent nature of the impaired TMV shown here, it can therefore be speculated that these new devices could be more harmful to the airways.

Mucus abnormalities, such as increased viscoelasticity, elevated mucus/mucin concentrations, and impaired MCT, are commonly seen in cigarette smokers with and without chronic bronchitis, and are closely related to chronic inflammatory muco-obstructive lung diseases such as chronic obstructive pulmonary disease (11). Altogether, this important report published by Chung and colleagues provides novel and unique data showing the harmful effect of e-cigarettes on mucociliary clearance, a crucial part of the lungs’ first line of defense. Along with previously reported adverse effects of e-cigarettes, such as increased oxidative stress, neutrophil and macrophage activation, impaired and altered innate defense, and inflammatory response and cytotoxicity, the current findings provide further convincing evidence that e-cigarette smoking is harmful to the airways.

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Idiopathic pulmonary fibrosis (IPF) is a progressive, chronic, fibrosing lung disease with high mortality (1). The diagnosis rests upon a compatible clinical picture of insidious dyspnea, dry cough, and the exclusion of exposure to mineral or organic dusts, connective tissue disease, fibrogenic drugs, or radiation. High-resolution computed tomography (CT) is an essential part of a clinical diagnosis, with typical features of bibasilar reticular interstitial markings and a lack of atypical features such as nodularity, upper-lobe distribution, and considerable amounts of ground-glass infiltrates or emphysematous changes. The presence of honeycombing in the bases strongly adds to the confidence of a radiographic diagnosis of usual interstitial pneumonia (UIP). When necessary, a surgical lung biopsy (SLB) can be performed to identify histologic features of UIP. A confident diagnosis of IPF is believed to be critical, as it helps direct considerations for antifibrotic medications, rehabilitation, referral to lung transplantation, enrollment in clinical trials, and, in cases of advanced disease, palliative care.

Since 2014, two antifibrotic medications, nintedanib and pirfenidone, have received U.S. Food and Drug Administration approval following the publication of two parallel phase III randomized controlled trials (INPULSIS 1 and 2, and ASCEND [Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis]) that demonstrated a slowing of the rate of decline in lung function in IPF (2, 3). However, there were no significant beneficial effects in terms of mortality, respiratory symptoms, or quality of life for either medication. The 2015 American Thoracic Society (ATS) IPF clinical practice guideline statement supported a “conditional recommendation” for the use of these medications in patients with IPF (4). In a recent study, Dempsey and colleagues used data from a large U.S. insurance database to compare patients with IPF who had been treated with antifibrotics with propensity-matched control subjects who had not received such therapy, and the authors found that the use of antifibrotic medications was associated with a decreased risk of all-cause mortality over the first 2 years of treatment, as well as decreased acute hospitalization (5). No differences were noted between patients taking pirfenidone and those receiving nintedanib. However, given the high costs of these antifibrotic agents, insurers are increasingly requiring rigorous diagnostic confidence, based on either typical CT findings or lung biopsy, to approve coverage of these agents.

In a study presented in this issue of the Journal, Walsh and colleagues (pp. 1146–1153) examined the level of diagnostic likelihood at which physicians prescribe antifibrotic therapy without requesting an SLB in patients suspected of having IPF (6). The study consisted of an international cohort of respiratory physicians who evaluated 60 cases of interstitial lung disease and reported differential diagnoses along with diagnostic likelihood, whether an SLB would be requested, and recommendations for initial management. IPF was included in the differential diagnosis in 41% of all physician–patient evaluations. SLB was requested in 8%, 29%, and 48% of definite, provisional high-confidence, and provisional low-confidence diagnoses of IPF. Antifibrotic therapy was prescribed without requesting an SLB in over 60% of provisional high-confidence IPF diagnoses (6). The team concluded that most respiratory physicians prescribe antifibrotic therapy without requesting an SLB if a “working diagnosis” of IPF can be rendered with high confidence. Using...