the age of a worldwide increase in antibiotic resistance, it is questionable whether the broad use of antibiotics as maintenance treatment for chronic diseases is a wise decision, as antibiotic resistance is closely correlated to infectious disease–related mortality. King Arthur and the Knights of the Round Table died, and the Holy Grail was lost forever. Even though this is only a Welsh tale, it should be a lesson. ■

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Is More Better? Promising Biological Effects of Double-Dose Alpha 1-Antitrypsin Therapy

The pilot study reported in this issue of the *Journal* by Campos and colleagues (pp. 318–326) tests the hypothesis that a higher concentration of circulating alpha-1 antitrypsin (AAT) than that achieved with the current standard AAT therapy will more effectively decrease the protease and inflammatory burden in AAT-deficient (AATD) patients (1). Enrolling 10 patients with AATD who were treated with a standard weekly intravenous dose of AAT (60 mg/kg/wk), they administered AAT at twice the dose (120 mg/kg/wk) for 4 weeks, followed by return to standard dose for another 5 weeks. This approach follows this group's previous analysis of the safety profile and pharmacokinetics of double-dose AAT over the course of 8 weeks in a crossover design with standard dose administration (2). In the current study, the investigators perform study bronchoscopies to more thoroughly explore the effect of double-dose AAT on airway and airspace parameters of proteolysis and immune responses.

Similar to their previous report, the double-dose administration had few adverse effects, most of which were mild and related to bronchoscopy, prompting the withdrawal of two subjects. Compared with the standard dose, the double-dose AAT administration in the remaining eight subjects led to significant reductions in biochemical markers of protease activation and elastolysis and of immune system activation. The latter effect included diminished levels of IL-17 and TNFα (tumor necrosis

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factor α) and decreased T-cell receptor signaling, macrophage migration, eosinophil recruitment, and neutrophil activation. These biochemical and immune effects were most prominent in the BAL fluid. In contrast, patients receiving standard dose therapy exhibited ongoing protease activity and elastin degradation.

These results suggest that a trough circulating level of AAT that is approximately 50% of normal (~11 μM), typically achieved with current standard therapy, is insufficient to ameliorate the biochemical consequences of AATD. The authors have shown in their previous report that circulating levels of AAT in AATD are dose-proportionally increased by AAT intravenous therapy, reaching ~25 μM with double dosing (2). Other studies evaluated higher doses of AAT augmentation, with the hope that it may lessen the weekly frequency of its administration, which is considered cumbersome by many patients. For example, infusion of 250 mg/kg, administered at less frequent intervals (every 28 d), recorded promising sustained increases in serum AAT levels (3). However, frequencies of administration of longer than 21 days would often require individualized monitoring of circulating AAT levels (4). Even at an interval of administration of every 2 weeks, the double-dose therapy (120 mg/kg) lacked the ability to maintain serum AAT levels of 11 μM (~80 mg/dl) throughout the dosing interval of 14 days (5). These studies suggest that double dosing would still require weekly infusion in order to achieve sustained levels of 25 μM (~130 mg/dl) of AAT in the circulation. Interestingly, the current study suggested that weekly double dosing may have a biological carryover effect, although the absence of a controlled study design limits this conclusion.

The current report stimulates further studies to determine what is the optimal regional bioavailability of AAT necessary to protect the lung in general, and in AATD in particular. The bulk of circulating AAT is secreted by the liver, yet small concentrations of AAT are being released in various tissue compartments by other cells, in particular epithelial and immune cells. We have shown that endothelial cells do not produce AAT (6); rather, they actively endocytose it (7), and may facilitate its transport from the vascular intraluminal to the interstitial lung compartment (8). In experiments in which endothelial cells were cocultured with polarized epithelial cells at the air–liquid interface, the transport of AAT across the bicellular monolayers was preferentially conducted from the apical endothelial surface toward the apical surface of the epithelium (8). Further, the uptake and transport of AAT across the endothelium was dependent on the endothelial fitness for endocytosis and was vulnerable to stresses such as cigarette smoking (9). Taken in the context of the current report, it is possible that a higher serum concentration of AAT is needed to ensure adequate transport and availability of AAT to the airways and lung interstitium. Future studies will have to determine whether there is insufficient uptake of AAT across endothelia in AATD and/or insufficient local (from lung epithelial and resident immune cells) production of functional AAT, which would require higher doses of AAT than would be provided by current standard therapy. Whereas inhaled AAT therapy is a viable alternative to intravenous supplementation (10), and may deliver higher serpin concentrations to the airways and airspaces, it is still unclear whether it will be able to achieve effective levels of AAT in the lung interstitium. Further, the association of AATD with systemic comorbidities that share endothelial dysfunction and immune dysregulation in their pathogenesis such as diabetes mellitus, panniculitis, and vasculitides may hamper the use of airway-focused, inhaled AAT (11) as a single therapeutic approach for AATD.

The results of this study are important because they open the door to larger controlled clinical trials to determine whether doubling the dose of AAT replacement/augmentation therapy will improve clinical outcomes in individuals with AATD. This pilot study was, of course, underpowered and of too brief duration to provide information on clinical outcomes pertinent to AATD. Taken together with the earlier crossover study, which suggested that during the 8 weeks of double-dose therapy subjects tended to report fewer exacerbations of chronic obstructive pulmonary disease (2), this pilot study showing improvement in biochemical parameters of lung elastolysis and inflammation provides a source of optimism. Although AAT standard therapy has been adopted as a management strategy for select AATD individuals in the United States, its widespread use has been hampered by skepticism of clinical effectiveness. Most of this is the result of the failure of prospective randomized controlled trials of standard AAT therapy to show a significant effect on major clinical outcomes such as survival, rate of COPD exacerbations, and improvement in lung function, with effectiveness being limited to decreasing the progression of radiographic emphysema (12). However, it is important to caution against applying the results of this pilot study directly to clinical practice in the absence of data from larger appropriately designed studies that test clinical efficacy. Furthermore, clinical applications will require a careful cost analysis of this already expensive therapy. Also, even in this pilot study of only a few subjects, it became apparent that individuals exhibit distinct responses to double-dose therapy, and as the authors pointed out, a personalized approach may be required and should be considered even in the design of a larger clinical trial.

This report and the recent advances in experimental gene therapy (13–15) and in the discovery of novel therapeutic targets in AATD (16), highlight the concerted effort of the medical and research community to provide much needed relief for individuals affected with AATD. ■

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Identifying Sepsis Subtypes from Routine Clinical Data

The heterogeneity of sepsis is often cited as a key factor impeding the identification of new treatments (1). By lumping diverse patients with sepsis together in clinical trials, it is reasoned, we may fail to identify the benefit of therapies that help only a subset of patients (1). As a result, there is growing interest in identifying subgroups of patients with sepsis who may respond differently to treatments.

Recent studies have identified subtypes of patients with sepsis, defined by leukocyte genome-wide expression profiles, some of which are associated with differential response to hydrocortisone treatment (2). However, the optimal method to subtype patients with sepsis remains unclear, and different approaches may be necessary to identify responders to corticosteroids versus other therapies.

In this issue of the *Journal*, Bhavani and colleagues (pp. 327–335) sought to identify meaningful subtypes of infected patients on the basis of a readily available clinical parameter: temperature trajectory in the first 72 hours after hospital presentation (3). Hypothermia is known to be associated with sepsis mortality, whereas fever is protective (4). However, temperature is recorded repeatedly in nearly all hospitalized patients, and dynamic assessment may provide additional prognostic and theranostic information.

The study examined a cohort of 12,413 patients hospitalized for infection at the University of Chicago. Patients had a median of 20 temperature measurements during the 3-day study period, and abnormal temperatures were common. A total of 38% of patients were febrile, and 81% were hypothermic on at least one occasion.

To identify subgroups with different temperature trajectories, the authors used group-based trajectory modeling. This method is an extension of cluster analysis and identifies subgroups (or classes) based on changes in a characteristic over time. In contrast to hierarchical or growth curve models that estimate a mean trajectory and then measure variation around this mean, group-based trajectory models identify subpopulations, each with a different trajectory (5). These are not necessarily biologically distinct subgroups but, rather, a convenient way to describe the variation of trajectories seen in a population (5). Group-based trajectory models also assume that all variation is explained by the subgroups, and that there is no variation in trajectories among individuals within the same subgroup (5). However, this assumption is routinely violated in practice.

Group-based trajectory modeling was first developed to study developmental trajectories (6) (e.g., trajectories of antisocial behavior during adolescence and early adulthood), but has recently been applied to critical care research. The technique has been used to study functional trajectories before and after critical illness (7), quick Sepsis-related Organ Failure Assessment trajectory

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