

pervasive consequences of institutional racism and the wide-ranging systems and structures that have led to asthma disparities in the United States. Future work will need to build upon these findings and, in particular, develop novel measures of structural racism influencing environmental asthma risk among vulnerable populations. ■

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Sonali Bose, M.D., M.P.H.
Division of Pulmonary, Critical Care, and Sleep Medicine
Icahn School of Medicine at Mount Sinai
New York, New York

and
Division of Pulmonary and Critical Care Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Jaime Madrigano, Sc.D., M.P.H.
Department of Environmental Health and Engineering
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland

Nadia N. Hansel, M.D., M.P.H.
Division of Pulmonary and Critical Care Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

and
Department of Environmental Health and Engineering
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland

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Use of Computed Tomography Lung Densitometry as an Outcome Measure for Emphysema Progression: The Case of Losartan

The current treatments available for chronic obstructive pulmonary disease (COPD) have shown to improve lung function, relieve symptoms, and reduce the risk of exacerbations, but there is an urgent need for therapies that can change the natural history of the disease (1). In the current issue of the *Journal*, Wise and colleagues (pp. 838–845) provide the results of a randomized, placebo-controlled trial aimed at demonstrating the efficacy of the angiotensin receptor

blocker losartan in reducing emphysema progression (2). Credit must be given to the authors for conducting this trial without support from industry and overcoming the hurdles of the coronavirus disease (COVID-19) pandemic, but above all, for investigating a possible new mechanism to treat lung emphysema and prevent disease progression.

Investigating a new treatment is always associated with a high risk of negative results. In this trial, losartan administered to patients with COPD and emphysema did not demonstrate any radiological reduction in the rate of emphysema progression; in fact, subgroup analysis showed that former smokers treated with losartan had significantly more emphysema progression than current smokers on placebo, which is difficult to understand (2). On the other hand, some possible positive effects of losartan were a reduction in the risk of hospitalizations and improvement in the score of the PROMIS-20a

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(Physical Function–Short Form 20a) questionnaire. However, the study was not powered for hospitalizations, the number of hospitalizations was very low, the differences observed were not statistically significant (7 patients in the losartan and 21 in the placebo group; $P = 0.487$) and, there was no effect on the number of moderate exacerbations. Regarding the PROMIS-20a, the differences in scores between the two treatment groups (1.04 units), although statistically significant, did not even reach half of what is considered the minimal important difference (2.5 units) (2). All these findings question any possible clinical benefit of losartan in patients with COPD and emphysema.

Because most of the patients included were former smokers and received appropriate treatment for their respiratory disease, the rate of emphysema progression may have been very slow, and demonstration of a significant further reduction in the rate of its progression may be extremely difficult. Interestingly, the rate of progression found in the placebo arm of the trial (0.66%) was almost the same as the mean progression in lung emphysema observed in a group of 1,928 patients with COPD followed for 3 years in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study (0.63%) (3), which highlights the robustness of the methodology of the trial and the difficulties in furthermore reducing this rate of decline. This slow progression suggests that large groups of patients should be studied over extended time periods to detect a significant effect of an intervention on the rate of decline of lung density. Interestingly, the sample size of this trial was estimated on the basis of a pilot study that showed an unusually large decline in the placebo arm of 2.18% (2). Nevertheless, as pointed out by the authors, the results of the trial did not suggest that a larger or longer study would have provided positive results.

Despite the negative results, this trial provides important information that needs to be considered when designing interventional studies to reduce emphysema progression in patients with COPD. The investigators used the change in lung density on full inspiratory high-resolution computed tomography (HRCT) as the primary outcome measure. In contrast, previous studies investigating the impact of pharmacological treatments on the natural history of COPD have mainly used spirometric measurements as their primary outcome (1, 4), mainly because these treatments are usually bronchodilators, which directly influence lung function (1, 4). In contrast, the possible effect of systemic treatments that may influence the pathogenetic mechanisms of the disease, such as angiotensin receptor blockers, must be measured by the correct variable, in this case, the change in lung density measured by HRCT (5). As a comparison, a drug for osteoporosis is not evaluated by the frequency of falls or changes in health-related quality of life; instead, it is directly evaluated by changes in bone density (6). Similarly, a drug that is expected to interfere in the progression of emphysema should be evaluated by changes in lung density and not by its possible effect on spirometry, exacerbations, or SGRQ (St. George Respiratory Questionnaire) scores. The best example is the treatment for emphysema associated with alpha-1 antitrypsin deficiency (7), in which some therapeutic trials have used the HRCT densitometry measure as a primary outcome measure (8, 9). The largest trial, including 180 patients, demonstrated a significant 34% reduction in the rate of decline of lung density measured at total lung capacity (an absolute difference of 0.74 g/L/yr) (9). Interestingly (but not unexpectedly), there were no differences in changes in FEV₁ decline, SGRQ, or exacerbation rates. Choosing the right primary outcome

may have a strong impact on the future of treatments for emphysema in patients with COPD. Expecting an unrealistic direct effect of drugs, such as losartan or intravenous alpha-1 antitrypsin, on lung function, exacerbations, or quality of life may prevent the regulatory authorities from considering their possible effect on the progression of emphysema, which translates into increased survival (10, 11).

The study discussed here is another example that the use of HRCT lung density measurement as a primary outcome in multicenter pharmacological trials of patients with COPD is feasible and provides reliable information (5, 9, 12). Lung density measurements in multicenter trials should be carefully standardized, but there is enough experience in lung densitometry for it to be used as a primary outcome in clinical trials (13). In addition, there is also enough evidence about the relationship between lung density and other outcomes in COPD, particularly mortality (10, 14, 15).

Unfortunately, losartan is not the answer, but patients with COPD need new treatment options that can change the course of their disease; thus, measurement of lung density by HRCT scan must become the gold standard for the trials designed to evaluate emphysema progression. ■

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Marc Miravittles, M.D.
Pneumology Department, Hospital Universitari Vall d'Hebron and Vall d'Hebron Institut de Recerca (VHIR)
Barcelona, Spain

Antonio Anzueto, M.D.
Pulmonary Disease/Critical Care
University of Texas Health and South Texas Veterans Health Care System
San Antonio, Texas

ORCID ID: 0000-0002-9850-9520 (M.M.).

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⊕ Untangling Lower Airway Dysbiosis in Critically Ill Patients with COVID-19

For patients with coronavirus disease (COVID-19) that require management in an ICU, mortality varies between 30–70% and keystone treatment still relies on supportive measures such as invasive mechanical ventilation, vasopressor administration, and renal replacement therapy (1–6). Among these critically ill patients, there is significant heterogeneity in the natural history of the disease process varying from patients requiring transient ventilatory support, others developing thrombosis, cardiovascular complications and, frequently, prolonged mechanical ventilation, and death. Despite a growing understanding of the pathophysiological derangements that occur during a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the reasons for the heterogeneous evolution among the most severe cases are not well understood. Multiple investigations have utilized a case-control design comparing patients infected with SARS-CoV-2 with differing degrees of severity (e.g., hospitalized patients versus not hospitalized or those admitted to an ICU versus those in the general wards) or with noninfected individuals. Although significant knowledge has been gained from these investigations, they do not help in our understanding of the heterogeneous evolution among critically ill patients with COVID-19. Although there is increased interest in molecular profiling, or endotyping, to uncover biomarkers that may help us understand

patients' heterogeneity, few studies have focused on applying this to a cohort with similar disease severity (e.g., exclusively critically ill patients) and with longitudinal follow-up. Furthermore, most investigations have focused on noninvasive assessments, such as blood, to develop biomarkers that may predict disease outcome. Although that for sure would be quite convenient, the samples we really need to study are those collected from the primary site of the disease: the lung (7).

In this issue of the *Journal*, Kullberg and colleagues (pp. 846–856) studied how the lower airway microbiome on 114 critically ill, mechanically ventilated patients infected with SARS-CoV-2 can be associated with poor clinical outcome (8). In these patients, BAL samples were obtained after days or weeks from initial intubation (median time from intubation to sample collection was 9 d) and in 32 patients they were able to analyze follow-up samples. The authors evaluated for microbial signatures associated with successful liberation from mechanical ventilation by day 60 after intubation (versus deceased or intubated >60 d). To do that, the lower airway microbiota was characterized by 16S rRNA gene sequencing and bacterial and fungal load were measured by qPCR targeting the 16S and 18S rRNA genes, respectively. In line with a prior study of >140 critically ill patients with COVID-19 (9), poor clinical outcome was associated with higher bacterial load. Importantly, the authors showed that increased fungal load was also associated with poor clinical outcome. The authors also found that some inflammatory markers measured in these samples correlated with bacteria/fungal load, such as tumor necrosis factor α . Moreover, the study aimed to evaluate if secondary bacterial pneumonia, defined here as BAL culture positivity (which occurred in 22% of cases), was associated with changes in the microbiota. They found that BAL culture positivity was indeed associated with increased bacterial load and there was some concordance between the isolated bacterial strain

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