BAL neutrophils, allergic sensitization, and different bacterial detection may lay the foundation for therapeutic decisions for this difficult-to-manage population. Unbiased phenotype clustering has helped redefine the framework of severe asthma (12), although even "unbiased" approaches are constrained by the selection of variables (13). Acknowledging the difficulty in procuring airway samples in preschool children, validation of these findings in similar cohorts is needed. Although these clusters have face validity, baseline and predictive validity (i.e., association with important health outcomes), long-term prognosis, or differential treatment response in the clinical setting is needed. Longer-term follow-up of this unique cohort will be critical to answer many of these questions.

Fully understanding the mechanisms and optimal treatment approaches for preschool children with recurrent wheeze remains a significant research challenge. Robinson and colleagues begin to chart a different course highlighting the discordance between current clinical labels and airway pathology and identifying clusters of clinical–pathologic features that may lay the foundation for future prognostic studies and therapeutic trials in this heterogenous condition. ■

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Jonathan M. Gaffin, M.D., M.M.Sc.
Boston Children's Hospital
Boston, Massachusetts

and

Harvard Medical School
Boston, Massachusetts

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Place Matters: Residential Racial Segregation and Chronic Obstructive Pulmonary Disease

The combination of the striking racial disparities in coronavirus disease (COVID-19) outcomes and the tragic series of the deaths of Black people caused by police violence during the pandemic has brought unprecedented attention to the structural racism that persists in the United States (1). Segregation by race and ethnicity is a prominent feature of American cities that has not diminished over time despite civil rights laws (2). Black-segregated neighborhoods have been disproportionately burdened by many adverse social, economic, and environmental factors. Historical "redlining" was a federally promoted program during the 1930s and 1940s that inflicted severe and permanent economic harm to communities of color by systematically denying residents home mortgage loans (3). This overtly racist policy deprived Black families of legacy wealth as home property has been the primary vehicle for accumulating such wealth and is one of the major reasons for the Black–White income gap in the United States (4). Despite enactment of legislation to prevent segregation-promoting real estate practices, many formerly redlined neighborhoods remain very segregated. These neighborhoods are more likely to be characterized by poverty, greater exposures to air pollution, less green space, less access to

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healthy foods, more liquor stores, more violent crime, and poorer housing—all factors that contribute to heath disparities. For example, residents of the formerly redlined community of West Oakland have almost 7 years lower average life expectancy than the more affluent and White residents of the Oakland hills (5).

In the context of persistent segregation in the United States, the article by Woo and colleagues (pp. 536–545) in this issue of the *Journal* is timely and impactful (6). The authors use a subset of the well-characterized SPIROMICS cohort to study the question of whether Black individuals either with or at risk for chronic obstructive pulmonary disease (COPD) who live in a segregated neighborhood have worse respiratory health. Although racial segregation has been shown to increase risk of other respiratory outcomes such as lung cancer and asthma, the study by Woo and colleagues is the first to show this risk for COPD. Racial residential segregation was measured with the isolation index, a validated metric that has been used in studies of the impacts of segregation on other health outcomes, including breast cancer, tuberculosis, and hypertension (7–9). The SPIROMICS outcome data are rich, including assessment of symptoms and exacerbations, spirometry, 6-minute-walk test, and quantitative computed tomographic (CT) measurement of emphysema and gas trapping. For Black participants, most of the outcome measures were associated with living in a predominantly Black-segregated neighborhood (isolation index >0.6) and whether they had COPD or were at risk of the disease. As expected, the segregated neighborhoods had higher rates of poverty and unemployment as well as lower median household income than nonsegregated neighborhoods. The results of the authors' multivariable regression analysis were robust to adjustment for age, sex, smoking status, pack-years, obesity, marital status, occupational exposure, and total population size of the residential neighborhood. The results for participants with COPD were largely consistent with those among the combined population, including at-risk participants. Interestingly, White people living in Black-segregated neighborhoods similarly had worse COPD morbidity for several outcomes.

Because residential segregation is associated with lower socioeconomic status (SES), higher prevalence of conditions other than COPD, mental health outcomes, and increased exposure to air pollution, the authors conducted mediation analyses for these factors. After controlling for individual and neighborhood SES, comorbidities, and depression or anxiety, the associations between segregation and COPD outcomes were somewhat attenuated but generally remained significant. When additional adjustment for outdoor concentrations of air pollution (1-year average ozone and fine particulate matter) at the residential address was done, there was further attenuation of the segregation effect on symptom and exacerbation outcomes. Although levels of air pollution and other potential mediators accounted for variable proportions of the segregation differences, there continued to be a segregation effect not captured by these mediators, indicating that racial residential segregation leads to more severe respiratory outcomes by mechanisms not measured in this study.

This is an important finding that supports the position of those who argue that structural racism and racial discrimination should be considered risk factors for poor health outcomes independent of SES. Although the results of the epidemiological study by Woo and colleagues cannot shed light on the mechanistic pathway between residential racial segregation and COPD beyond the potential mediators analyzed, it is likely that chronic psychosocial or "toxic" stress not measured by the authors plays a role. Accumulating evidence supports activation of neuroendocrine pathways by exposure to psychosocial stressors such as racial discrimination (10), and individuals reporting racial and/or ethnic discrimination have been shown to have elevated levels of cytokines, including TNF-α, compared with those not reporting racial and/or ethnic discrimination (11). In asthma, there is evidence that perceived discrimination is associated with poor asthma control (12), and psychosocial stress secondary to experiences of racial and/or ethnic discrimination may enhance airway inflammation by modulating immune cell function through hormonal pathways (13). In addition, several studies support an interaction between exposures to air pollution and psychosocial stress on development of asthma (14). Although not directly studied in COPD, it is likely that chronic psychosocial stress due to racial discrimination contributes to severity of disease.

Gustafsson and colleagues have studied the relationship between neighborhood features and allostatic load from adolescence into middle age (15). Cumulative neighborhood adversity was assessed with indicators, including the percentage of residents considered low-income, unemployed, living in single-parent households, and with low occupational status or low educational attainment. Neighborhood adversity was associated with increased allostatic load in adulthood as measured by multiple biomarkers. Although these investigators did not measure the effect of residential segregation, their indicators are all features of segregated, historically redlined neighborhoods.

In brief, racial segregation has been independently shown to be a fundamental cause of health disparities in general and in asthma in specific. Thus, it is not surprising that this consequence of structural racism has now been associated with COPD outcomes. The opportunity and challenge of this newly demonstrated association is for pulmonary healthcare providers to identify those at highest risk and intervene as early as possible to mitigate the health consequences of racial segregation (1). We have the responsibility to our patients and society at large to advocate for policies to reduce disproportionate exposure to indoor and outdoor air pollution, improve substandard housing, increase access to healthy foods and green space, and reduce exposure to community and police violence. ■

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John R. Balmes, M.D.*
Department of Medicine
University of California, San Francisco
San Francisco, California
and
Division of Environmental Health Sciences School of Public Health
University of California, Berkeley
Berkeley, California

ORCID ID: 0000-0002-2246-7002 (J.R.B.).

*J.R.B. is Associate Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

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Bacterial Coinfection in COVID-19 and Influenza Pneumonia

The crucial question at the time a patient is hospitalized for pneumonia is whether the infection is bacterial and, therefore, whether an antibiotic should be administered. Availability of highly sensitive PCR technology to identify a respiratory virus tells us whether a viral infection (most of which are as yet untreatable) is present but does not answer the question of whether a patient has bacterial coinfection (1).

In this issue of the *Journal*, the European Multicenter Comparative Clinical Trial by Rouzé and colleagues (pp. 546–556) retrospectively compares the frequency of bacterial coinfection in patients requiring ICU care for infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or influenza virus (2). The subject is of great interest as well as of practical importance. Pfeiffer discovered *Haemophilus influenzae* during an influenza outbreak in 1892, and by 1918, *Haemophilus*, *Streptococcus pneumoniae*, and *S. pyogenes* were well recognized as prominent bacterial coinfecting organisms in influenza. Morens and colleagues (3) restudied all available evidence in persons who died of influenza in the 1918–1919 pandemic, reporting evidence of secondary bacterial infection in "virtually all" patients. *Staphylococcus aureus* was added as an important coinfecting organism in the influenza epidemic of 1958 (3).

These findings have led physicians to use empiric antibiotics in patients admitted to the hospital for influenza. They have led me to redouble my efforts to determine the presence or absence of a bacterial coinfection, an approach I greatly prefer to empiricism. Influenza has widespread effects on bacterial clearance, adherence, and invasion (4, 5) and may or may not be unique among respiratory viruses in its association with bacterial coinfection—the question addressed in the study by Rouze and colleagues. One cannot be certain whether influenza is more highly associated or just more intensively studied than, for example, respiratory syncytial virus pneumonia.

When the SARS-CoV-2 pandemic began, the role of bacterial coinfection was undetermined. Patients were dreadfully ill, and physicians and ICU staff were dreadfully stressed. Antibiotics were used liberally, perhaps excessively (6), based in part on recommendations of the surviving sepsis campaign, which, it should be noted, was not endorsed by the Infectious Diseases Society of America (7).

Studies of bacterial coinfection in coronavirus disease (COVID-19) have reported a broad range of results (8–10). Their methods need to be examined carefully to understand the discrepancies, and the results need to be contextualized. For example, in one multicenter cohort study of 48,902 patients hospitalized for COVID-19 (8), microbiologic studies were done in 8,649 (17%), of which 1,107 (13% of those with microbiologic studies, 2% of the total number of patients) yielded positive cultures for a recognized pathogen. Only 318 (0.7% of the total) were obtained within 2 days of admission. No wonder the authors concluded that, "microbiologically confirmed bacterial infections are rare."

In contrast, a meta-analysis of 7,107 patients hospitalized with COVID-19 identified bacterial coinfection in 4.9% on admission and 16.0% on admission to an ICU (10). Although much higher than the former study (and still subject to all the same problems of numerator and denominator), these seemingly low proportions need to be considered in the context of the documentation of bacterial infection in community-acquired pneumonia (CAP), most of which we regard as (and treat for) bacterial infection. The CDC's prospective study of community-acquired pneumonia in adults identified a bacterial cause in only 17% of CAP (11). My identically designed but smaller and more

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