study area, and in particular these findings may not be applicable to areas with much lower air pollution exposures. It is important to note that although the median air pollution levels in this study are high compared with levels in the United States and Western Europe, almost half of the world's population is exposed to comparable or higher levels of ambient air pollution (11).

Although asthma mortality has decreased over time, rates have been relatively stable since the 1980s and remain significant despite advances in the management and care of patients with this disease (12). Worldwide, over 250,000 people still die of asthma annually (13). Asthma deaths have been attributed to several risk factors, with majority considered to be preventable and mostly dealing with the management of asthma (14). Liu and colleagues' article is important because it is the first report of an association between asthma mortality and short-term air pollution exposure in a large population. Thus, it is possible that reducing air pollution could have a significant effect on reducing asthma mortality worldwide. ■

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Corporate Memory and Rediscovering the Wheel

Although there is a generally accepted concept that inflammation plays a role in the pathophysiology of chronic obstructive lung diseases, the complexity and compartmentalization of the inflammation present many challenges to clinicians, scientists, and the pharmaceutical industry. Bronchiectasis is a condition in which the damage caused is largely bronchial and the relevant inflammation is readily accessible through studies of expectorated sputum, which is often colonized by bacteria that drive the local inflammatory response.

With the advent of computed tomography and its widespread use, recognition of permanently dilated airways (the pathological hallmark of bronchiectasis) show not only a wide variation in pathological types and distributions but also a marked prevalence in patients with an underlying diagnosis of smoking-related chronic obstructive pulmonary disease (COPD) (1). So does this represent a paraphenomenon or a specific trait for treatment? In some cases the bronchiectasis is limited to minor tubular changes and thus is clinically quiescent, whereas in others it is widespread and varicose in nature, leading to clinically important features that are more consistent with a classical primary diagnosis of bronchiectasis. Indeed, in the past, such a diagnosis was considered more likely in nonsmokers (and therefore believed to exclude

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possible COPD) with persistent cough and expectoration, especially if an acute previous respiratory illness could be implicated, although most patients with non-cystic fibrosis bronchiectasis have no currently definable underlying cause.

Bronchiectatic damage to the airways compromises the airway epithelial barrier and is usually associated with excess mucus production. This in its own right impedes mucociliary clearance, which is an important mechanism (together with other primary and secondary host defenses) for bacterial clearance. Indeed, animal models show clearly that bacteria in the airway can be cleared via local innate immune systems until the initiating "load" is high enough ($>10^6$ cfu/ml) to overcome the local primary and even secondary host defenses. Thereafter, the bacteria continue to proliferate, perpetuating the secondary neutrophil response (2).

This secondary neutrophilic response in patients is associated with purulent sputum (due to neutrophil myeloperoxidase) and also occurs when the prevailing bacterial load exceeds 10^6 cfu/ml, as shown in Figure 1. This change is associated with other features of airway inflammation, including increased neutrophil chemoattractants and damaging proteinases (3). The inflammatory state can become persistent in some patients with bronchiectasis. Indeed, early computed tomography scan data indicated that chronic purulent sputum production was often a clinical biomarker of radiological bronchiectasis (4).

In the 1980s, this relationship between bacterial numbers and neutrophilic inflammation leading to potential proteolytic damage of tissues became a topic of research interest and led to interventional strategies that included nebulized antibiotics to maximize deposition in the airways (the bacterial load compartment), which were more effective than oral treatment (5, 6). Although no placebo-controlled studies were undertaken, this logical step improved patients' health (6) and reduced inflammation (7), albeit only when the sputum was initially purulent and subsequently cleared.

In recent years, clinical trials of inhaled antibiotics in subjects with cystic fibrosis and subjects with non–cystic fibrosis bronchiectasis have been undertaken largely to prevent recurrent exacerbations. These trials have resulted in mixed responses, especially in the latter group.

As reported in this issue of the *Journal*, Sibila and colleagues (pp. 33–41) have undertaken a *post hoc* analysis of two negative trials in patients with non–cystic fibrosis bronchiectasis (8) and generated important messages for clinicians, scientists, and the pharmaceutical industry. The data confirm a relationship between routine quantitative microbiology with a bacterial load of 10^7 cfu and neutrophilic inflammation as reflected by the green color of myeloperoxidase. In addition, and importantly, antibiotic treatment only influenced this "stable" inflammatory state when the bacterial load and inflammation were high, resulting in a beneficial improvement in quality of life. These changes were not a feature of patients with a low colonizing microbial load. The analysis clearly identifies a microbial load threshold that affects a subset of patients and links it to a clear clinical response even in the apparently "stable" clinical state. This is also important because patients with bronchiectasis become used to being "unwell" and only recognize this state when interventions change it and their health improves.

Of course, such an effect should be predictable from our knowledge of lung host responses and previous clinical studies, but the current *post hoc* analysis demonstrates this clearly from multicenter clinical trial data, and at the same time indicates how the trial design could have been more focused in relation to the proposed hypothesis and study outcomes. After all, why would an antibiotic improve inflammation if the bacterial load was not sufficient to drive inflammation? The logic relates to the concept of "enrichment" of clinical studies for the outcome of interest used in exacerbation studies in patients with COPD. Treatment aimed at reducing exacerbations is easier to demonstrate and clinically more relevant for those prone to such events.

So, what are the important lessons derived from the current *post hoc* analysis?

1. In bronchiectasis (with or without COPD), bacterial colonization is common and detectable in sputum. Routine

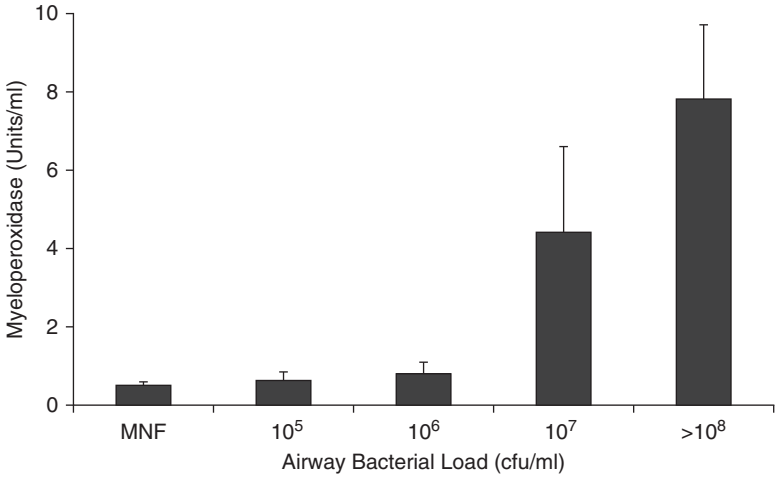

Figure 1. Sputum myeloperoxidase concentration is shown with mean and SE bars related to whether the sample culture identified mixed normal flora (MNF) or a potential pathogen (usually nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Pseudomonas aeruginosa*). Culture quantification is shown as colony-forming units. Data are derived from Reference 3, indicating the inflammatory threshold between 10^6 and 10^7 cfu/ml.

microbiology identifies organisms that are viable using the appropriate media and culture conditions, and the load can be easily quantified.
2. The greater the viable load, the more likely it is that secondary defense systems, including neutrophilic recruitment, will be activated. This turns the sputum green and is associated with airway inflammation and destructive neutrophil products that may also impede host defenses (9).
3. The presence of inflammation and the response to it can be monitored even by simple observation of sputum purulence, and a change to mucoid sputum with a reduction in microbial load or clearance reflects a successful intervention.
4. If that is the aim, those are the patients!
5. The persistent production of purulent sputum should be investigated and, when possible, treated to decrease airway neutrophilia and the accompanying damaging neutrophil products, as this also improves the patient's well-being. This can be achieved with long-term inhaled therapy. The wheel is rediscovered: it is still a wheel, but certainly a more robust one.
6. Such a strategy points the way not only to a more personalized approach to patient management but also to a more focused clinical trial design.
7. Sometimes simple methodologies and clinical understanding outrank modern technological approaches. The authors conclude that "molecular techniques may be better" at identifying all airway bacteria (alive or dead). However, it remains to be seen whether such information will lead to better focused management strategies, as the load of the dominant species will likely remain the critical clinical factor in driving inflammation, as was confirmed in a previous study that used such a methodology in COPD (10). ■

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Peeking under the Hood of Acute Respiratory Distress Syndrome Phenotypes: Deeper Insights into Biological Heterogeneity

Given the biological heterogeneity inherent to acute respiratory distress syndrome (ARDS), it is unsurprising, or perhaps even inevitable, that a pharmacotherapy "magic bullet" targeting a specific mechanistic pathway has failed to emerge. A silver lining in the plethora of failed clinical trials is the foresight of the original trial investigators to judiciously collect and store biospecimens, which, coupled with the richness of the trial data, has permitted informative secondary analyses. Investigators have used these data to perform unsupervised subgrouping analyses and have consistently identified two biologically and clinically distinct phenotypes in ARDS, referred to as the "hypoinflammatory" and "hyperinflammatory" phenotypes (1–4). The hyperinflammatory phenotype is associated with elevated plasma levels of proinflammatory biomarkers and an increased incidence of shock and organ dysfunction. More recently, researchers identified two phenotypes using only plasma biomarkers in an observational cohort of patients with ARDS (5). These phenotypes, termed "uninflamed" and "reactive," share similarities with the hypoinflammatory and hyperinflammatory

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