to which patients complied with these orders. Making more referrals to pulmonary rehabilitation and smoking cessation programs, and recommending new inhaler regimens, have the potential to improve outcomes, but only if patients adhere to these recommendations. Third, a curious finding was that similar clinical benefits were observed regardless of whether patients were considered to have COPD, raising questions about the mechanism of action of the intervention.

Beyond the results presented in this manuscript, the study raises as many questions as it answers, begging further investigation. For example, qualitative methods could be used to assess the perspective of PCP and health system administrators to better understand acceptability, feasibility, and sustainability to strengthen the intervention for future applications. Second, the application of implementation frameworks might generate additional insights regarding how and why the program succeeded and failed (11). Theoretical frameworks can "enable knowledge to emerge out of seeming chaos and for translation of that knowledge to be widely and reliably implemented" (12).

Ultimately, the most significant aspect of this trial was that it yielded clinical benefits without burdening busy PCPs with a cascade of "best practice alerts" and other forms of workflow interruption. Surveillance, hovering, and proactive e-consultation like those tested here are population health management techniques that have shown promise in other settings and may represent a path toward better outcomes for patients with COPD and other chronic conditions (13). We look forward to future research aimed at evaluating the costs and benefits of such approaches. ■

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Less Haste, More Speed, More Science: Lessons to be Learned from COVID-19 Studies

Coronavirus disease (COVID-19) emerged in Wuhan, China, in late 2019; hit Italy in February 2020; rampaged across Europe and North America from March 2020; and subsequently struck other continents. A pandemic was declared on March 11, 2020. The biomedical research community sprang into action in a quest to save humanity. Anything sitting on the shelf with an immunomodulatory profile could be considered. A search of www.clinicaltrials.gov on July 3, 2020, identified 1,366 registered studies, of which 279 were randomized controlled trials assessing immunomodulatory therapies (1) Thirty-nine immune pathways were targeted with 90 separate interventions. By April 2021, 2,981 interventional trials had been

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registered, but only 415 had been completed; of 629 phase III trials, one-eighth had been completed (2). As of April 2022, only 200 of 866 phase III trials had been completed.

Worryingly, the biological rationale underpinning many of these interventions remains questionable. The oft-trumpeted cytokine storm was, in most patients with COVID-19, a breeze if not a puff (3). This fact was clearly identified as early as January 24, 2020, when one of the major Wuhan publications appeared online in *The Lancet* (4). Notably, two contradictory interventional strategies, inhibition and administration, were targeted at granulocyte-macrophage colony-stimulating factor (GM-CSF). Lang and colleagues attempted to reconcile these conflicting approaches (5), speculating that administration could benefit during early COVID-19 disease by stabilizing alveolar macrophage and epithelial cell function, increasing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) clearance, protecting against secondary infection, and aiding lung repair. Inhibition could be useful later, in moderate to severe disease, counteracting the proinflammatory effects of GM-CSF and myeloid cell overactivation, thereby quenching the cytokine storm. Identifying when the crossover should optimally or safely occur was not elaborated upon.

In this issue of the *Journal*, Criner and colleagues (pp. 1290–1299) report a double-blind study (BREATHE [A Study to Assess the Efficacy and Safety of Gimsilumab in Subjects With Lung Injury or Acute Respiratory Distress Syndrome Secondary to COVID-19]) assessing the impact of gimsilumab, an anti–GM-CSF monoclonal antibody, on hospitalized patients with COVID-19 pneumonia (6). The trial was impressively quick off the mark. Enrollment commenced on April 15, 2020, a mere 5 weeks after the pandemic was declared. This achievement was all the more notable, considering that they had to develop a protocol and statistical plan, undergo regulatory and ethical review, identify study sites, obtain local approvals, generate case record forms, and distribute blinded drugs. Although this pace would be unsustainable under normal circumstances, it highlights what can be accomplished when bureaucratic hurdles are removed without compromising trial integrity, quality, and safety. This represents an important lesson to be taken from the COVID-19 response, but one I fear will be lost as we regress to the status quo.

At study entry, the patients ranged from requiring low-dose supplemental oxygen to needing mechanical ventilation. Study inclusion required raised inflammatory markers with a C-reactive protein threshold ⩾50 mg/L or ferritin ⩾1,000 ng/ml in the belief that this reflected hyperimmune activation that would respond positively to blocking the proinflammatory effects of GM-CSF. At least one dose of the study drug was administered to 225 patients, after which the trial was discontinued prematurely because of futility. No significant impact was seen in any predetermined outcome parameter, including the primary outcome (Day 43 mortality) or others such as time on a ventilator.

The investigators subsequently found nonelevated plasma concentrations of GM-CSF in most of their patients, a finding also noted in *The Lancet* Wuhan study (4). If the general absence of the biological target had been recognized in advance, would they have progressed with the study in the first place, been more circumspect in terms of initial ambition, or tried to first identify readily measurable surrogates that correlate with raised GM-CSF concentrations to enrich their study population? Nonetheless, it is to their huge credit that they actually collected and analyzed blood samples. Failure to do so in the large majority of interventional COVID-19 studies means many questions remain unanswered, particularly with regard to understanding the biological response to the interventions and in identifying subsets of patients who could potentially benefit or be harmed. Counter to the prevailing philosophy of pragmatic trials, should sample biobanking not be a prerequisite, particularly when uncertainty surrounds pathophysiological mechanisms and response to treatment?

It requires a more detailed discussion for another time and place, but I still harbor doubts about the efficacy of specific immunomodulating agents in COVID-19 disease, such as when positive results in open-label studies have not been replicated by methodologically more rigorous double-blind studies (7). Why should IL-6 receptor blockade work when plasma IL-6 concentrations are rarely elevated to any significant degree (3)? Even corticosteroid therapy gets a lukewarm approval rating from a Cochrane systematic review (8). An appropriately targeted treatment could benefit specific patient subsets, avoiding futility or even harm in others. In a retrospective analysis of corticosteroid response, survival benefit was seen only in the minority of patients with COVID-19 with a baseline hyperinflammatory state (9).

Lessons either have been ignored or have not been learned from the repeated trial failures during three decades of one-size-fits-all immunomodulatory strategies for sepsis. With so many studies performed on a single disease, some positive results would be predicted by chance. To my knowledge, positive findings have not been consistently reproduced for any single therapeutic intervention in COVID-19 disease. With respect to other large anti–GM-CSF trials, lenzilumab (a GM-CSF–neutralizing monoclonal antibody) was associated with improved Day 28 survival without invasive mechanical ventilation, though the perhaps more pertinent outcome of overall mortality failed to reach significance (10% vs. 14% placebo; $P = 0.24$) (10). The OSCAR (Otilimab in Severe COVID-19 Related Disease) trial, published as a preprint in April 2021 (11) but still to appear in a peer-reviewed publication, randomized 806 patients to otilimab, another anti–GM-CSF monoclonal antibody, or to placebo. Again, no overall survival benefit was shown, but there was a significant reduction in predefined model-adjusted 60-day all-cause mortality in patients aged ⩾70 years. The argument made here was that older patients could be predisposed to inappropriate, myeloid cell–driven hyperinflammation because of normal aging of the immune system. This prompted continuation of the study in this subset only, but a recent posting (clinicaltrials.gov/ct2/show/results/NCT04376684) also revealed no survival benefit (all-cause mortality 42.3% vs. 43.4% placebo). A randomized, double-blind trial (NCT04447469) of the anti–GM-CSF receptor-α monoclonal antibody, mavrilimumab, enrolled 815 patients but has not yet been published. As for GM-CSF administration, several trials have been performed in patients with COVID-19 using sargramostim or molgramostim, but none have yet been reported in peer-reviewed journals.

In summary, high-quality trials can be developed, regulated, and conducted at pace. My plea, however, is for less of the hare and more of the tortoise. We certainly do not want a ponderous tempo, especially in a novel pandemic. However, a more circumspect, stepwise, directed approach would have likely yielded greater dividends, enabling more focus on testing biologically appropriate therapies in the right patient subsets. ■

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High Positive End-Expiratory Pressure and Lung Recruitment in Moderate to Severe Acute Respiratory Distress Syndrome

Does One Size Really Fit All?

Since David Ashbaugh turned the positive end-expiratory pressure (PEEP) knob for the first time to stabilize a 12-year-old patient with acute respiratory distress syndrome (ARDS) in 1964, ARDS as well as PEEP have transitioned to behemothian entities in respiratory critical care (1).

Although PEEP was initially considered primarily an oxygenation-improving intervention, its major role in preventing ventilator-induced lung injury through alveolar recruitment, reduction of stress between heterogeneously ventilated airspaces, and minimization of cyclic distal airway closing was soon recognized. Recruitment maneuvers, consisting of a transient and pronounced elevation of transpulmonary pressure over a few seconds to multiple minutes, were proposed shortly thereafter to achieve even larger aeration of the lung. However, despite their strong theoretical foundation, neither high PEEP nor recruitment maneuvers have succeeded in improving clinical outcomes. Much to the contrary, their potential to harm has become readily apparent (2, 3).

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In this issue of the *Journal*, Dianti and colleagues (pp. 1300–1310) report a Bayesian network meta-analysis of 18 randomized trials in which they attempt to unravel the effects of lower and higher PEEP, as well as brief and prolonged lung recruitment maneuvers, on 28-day mortality in patients with moderate to severe ARDS ($Pa_{O_2}/F_{I_{O_2}} \leq 200$ mm Hg) (4). Network meta-analyses allow comparison of multiple therapy combinations by merging direct and indirect evidence. Direct evidence emanates from pooling of effectively performed head-to-head treatment trials. Indirect evidence, on the other hand, is estimated by modeling "loops" of evidence. In this way, trials comparing treatments A and B are combined with trials comparing treatments B and C to estimate the effect of treatment A against that of treatment C, thus enabling exploration of previously untested hypotheses. In addition, through the Bayesian approach prior knowledge is included into Bayesian network meta-analyses, which permits estimation of the intuitive posterior probability of treatment efficacy.

In their well-performed Bayesian network meta-analysis, Dianti and colleagues show that, in the included 4,646 patients with moderate to severe ARDS, the use of higher PEEP was superior to that of lower PEEP regarding 28-day mortality, with a posterior probability of treatment efficacy of 99% and a high certainty of benefit. Similarly, the use of a brief recruitment maneuver (<60 s) coupled to higher PEEP and the titration of PEEP by means of an esophageal pressure probe were both associated with moderate