clinical characteristics and outcomes, particularly for nonbacterial pathogens. The finding of benefit with early antibiotic administration requires more nuanced understanding of patient subgroups most likely to benefit and appropriate antibiotic choices to mitigate risks of antimicrobial overuse and resistance. Improving sepsis outcomes will require national investments in performance improvement for early recognition and treatment and in improving access to primary, secondary, and tertiary health care. In addition, sepsis incidence and outcomes act as a barometer of a country's overall state of public health. Any improvements based on clinical care alone are likely to be small unless parallel actions improve sanitation and hygiene, access to clean drinking water, vaccination, and the burden of poverty. ■

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Heatwaves and Air Pollution: a Deadly Combination

Climate change is one of the most pressing health challenges of our time, and the rapid pace of change means we will face growing health risks in the coming decades. Although gradual trends are important for some factors, such as a rise in sea level, human impacts are especially driven by extremes of weather, including heat waves, intense rain events, coastal storms, flooding, draft, and others (1). These, in turn, can influence a series of downstream impacts, including increases in wildfire frequency and extent, which have adverse health impacts. Indeed, trends of warmer, drier conditions in California have led to a fivefold increase in the area burned by wildfires in California between 1972 and 2018 (2).

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In addition to their immediate impacts on loss of life and property, wildfires release vast quantities of particulate pollution that travel long distances, potentially creating prolonged periods of exposure and adverse health outcomes for populations over wide areas. With the success of clean air programs addressing anthropogenic pollution sources, wildfire is becoming the dominant source of high concentrations of fine particulate matter ($PM_{2.5}$) pollution in California. This is because of the increasing frequency and severity of wildfires that now extend far beyond the summer season in California. Because wildfire emissions cannot be controlled easily via regulations, and fires often coincide with periods of warm temperatures, an issue of special concern is whether the combination of exposure to high $PM_{2.5}$ and temperature would create adverse health impacts that are additive or even synergistic.

Individually, both $PM_{2.5}$ and temperature have been associated with a wide range of adverse impacts, including respiratory and cardiac conditions, as well as premature mortality (3–8). Wildfire smoke contains a complex mix of combustion particles, including those related to the burning of homes, cars, and other products, and may present unique health challenges (9). In this issue of the *Journal* (pp. 1117–1127), the results of a new study by Rahman and colleagues provide substantial evidence that combined extremes of $PM_{2.5}$ and temperature in California over recent years have had superadditive effects on premature deaths (10).

The study included data on daily all-cause, cardiovascular, and respiratory deaths for all of California from 2014 to 2019. These were analyzed using a case-crossover design in relation to four strata of exposure to daily temperature and $PM_{2.5}$ concentrations: days with only extreme $PM_{2.5}$, days with only extreme temperature, days with extremes for both $PM_{2.5}$ and temperature, and days with no extremes. Four cutoffs for extreme days were analyzed on the basis of the 90th, 95th, 97th, and 99th percentiles of the respective exposure distributions. Results showed substantially higher mortality effects of the combined exposure than for the individual exposures, higher than the sum of the individual exposures. Results were more pronounced, though noisier, for respiratory and cardiovascular mortality than for total mortality and minimum versus maximum daily temperature.

What might be responsible for the observed synergistic mortality impacts of extremes of temperature and $PM_{2.5}$? Combined extreme events may involve a different compositional mix of $PM_{2.5}$ than other days, perhaps driven by wildfire smoke and chemical transformations facilitated by high temperatures. Another possibility is that population exposure to smoke and/or temperature change because of alterations in time activity patterns during fire events. Joint exposures to other pollutants such as ozone during combined events could also play a role. It has been noted that high temperatures are associated with an elevation in ozone, thus potentially triggering greater interactions of biological pathways to adversely affect the cardiorespiratory system. Because of the growing severity of wildfires that include the loss of buildings and homes and their contents, multiple chemical markers have been found in wildfire PM, including multiple phthalates, thus potentially enhancing the toxicity of wildfire smoke over large areas where smoke is transported (9).

With accelerating climate change and the emergence of wildfires as a significant source of high air pollution episodes, it will be increasingly important to understand and mitigate the human health effects of exposure to degrees of air pollution and temperature. Future research should explore further whether, how, and to what extent wildfire $PM_{2.5}$ has a distinct toxicity profile as compared with nonwildfire $PM_{2.5}$ and how those factors are influenced by temperature. Relatedly, we need to understand the mechanisms by which wildfire smoke interacts with and affects the respiratory and cardiovascular systems at higher temperatures. Toxicologic and epidemiologic studies will be needed to both understand mechanistic pathways and potential therapeutic interventions, as well as to quantify population impacts and extend findings to intermediate morbidity outcomes on the pathway to mortality. Because the extreme events studied here were relatively rare events, there is also potential for developing forecast systems that could provide advance warning to patients and care providers of anticipated extreme events. More information will also be needed on effective measures to protect individuals from exposure to extreme climate events, including building air cleaning and conditioning systems. The urgency for further research on these topics will continue to intensify together with further changes in our climate. ■

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Goldilocks and the Three Trials: Clinical Trials Targeting the $\alpha_v\beta_6$ Integrin in Idiopathic Pulmonary Fibrosis

In this issue of the *Journal*, we report the eagerly awaited phase 2a and 2b trials conducted by Raghu and colleagues (pp. 1128–1139 and 1166–1168) using a humanized monoclonal antibody targeting the $\alpha_v\beta_6$ integrin (1, 2). The $\alpha_v\beta_6$ integrin is a cell surface protein found specifically on epithelial cells and is upregulated after injury with a primary function to activate TGF-β (transforming growth factor β), a key profibrogenic cytokine in the lung and other organs (3). Preclinical studies demonstrated that gene deletion (4), antibody inhibition (5), and small molecular inhibition of the $\alpha_v\beta_6$ integrin (6) protected against the development of pulmonary fibrosis, and data from humans found that high concentrations of the $\alpha_v\beta_6$ integrin were present in the lungs of patients with idiopathic pulmonary fibrosis and were associated with worse outcomes (7). Together these studies suggest that uncontrolled $\alpha_v\beta_6$ integrin-mediated TGF-β activation promotes lung fibrosis and may be "too hot" for normal repair!

TGF-β is a potent profibrotic molecule, but several strategies to globally inhibit it have been limited by toxicity, which may reflect the role of TGF-β in homeostatic and physiological functions (8). The current studies were on the basis of the hope that epithelial cell-specific inhibition of TGF-β activation would limit local and systemic toxicity. Unfortunately, the results of these phase 2 studies suggest systemic administration of an anti-$\alpha_v\beta_6$ monoclonal antibody (BG0001) is associated with a lack of clinical benefit and increased adverse events, including acute exacerbations with fatalities leading the Data Safety Monitoring Board to advise premature termination of the 2b trial. There were no antidrug antibodies detected in any patients; it is therefore unlikely that the adverse effects were off-target effects related to antibody administration and probably reflect an on-target effect of inhibition of the $\alpha_v\beta_6$ integrin.

Given what is known about the $\alpha_v\beta_6$ integrin, can we offer a potential explanation? Several lines of investigation have indicated that $\alpha_v\beta_6$ integrin-mediated TGF-β activation plays an important homeostatic function. Genetic deletion studies demonstrated that completely switching off this pathway can lead to activation of alveolar macrophages (9), increased alveolar inflammation, increased MMP12 generation, and emphysema (10). Therefore, insufficient $\alpha_v\beta_6$ integrin-mediated TGF-β activation leaves the lungs "too cold" and unable to regulate macrophage behavior, which may promote inflammatory responses in the event of a lung injury or infection.

Thus, the precise regulation of $\alpha_v\beta_6$-mediated TGF-β activation is likely critical for its biological outcome. This raises the question of the ideal approach to targeting the integrin. Data from the phase 2a study showed a dose response with an increased risk of acute exacerbations at the highest concentration; the 3.0 mg/kg arm was terminated early in the phase 2a study because of excess acute exacerbations. High concentrations of TGF-β inhibition were observed in BAL macrophages at BG0001 doses over 1.0 mg/kg, and the half-life was 6 days. The phase 2b study was conducted with a dose of 56 mg (approx. 0.7 mg/kg) administered every 10 days on the basis of the data from the phase 2a study. However, it is clear from the exposure–response analysis that there is a narrow therapeutic window for BG0001, and with a long half-life, even a small increase in steady-state could lead to high concentrations of prolonged TGF-β suppression, and with it the risk of acute exacerbations.

Would small molecular inhibitors be more successful and provide inhibition that was "just right"? There is theoretical evidence to support this theory (11), as well as recent clinical data via a press release from Pliant Therapeutics. This release showed data from their phase 2 study in which patients were treated with an increasing concentration of PLN-74809, an oral small molecule, dual inhibitor of $\alpha_v\beta_6$ and alphavbeta1 (a total of 67 patients were treated with 40, 80, or 160 mg once daily for 12 wk). They reported no treatment-related serious adverse drug events and no treatment withdrawals even at the highest concentrations. This is in contrast with BG0001, in which four of six patients withdrew from the highest dose arm, which was ultimately terminated.

Why the difference between these studies? The two obvious differences reflect the chemistry of the drugs and the spectrum of inhibition. PLN-74809 is a small molecule, and BG0001 is a monoclonal antibody. In the absence of human receptor binding studies, it remains a concern that monoclonal antibodies may struggle to penetrate the dense fibrotic matrix associated with pulmonary fibrosis; thus, BG0001 may preferentially inhibit integrins in nonfibrotic regions of the lung and disproportionately affect homeostatic rather than pathological $\alpha_v\beta_6$ integrin function.

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