There is no 'one size fits all' approach to treat severe asthma, study shows

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Wheezing, coughing that doesn't stop, a pale and sweaty face: clinically, severe asthma attacks look very similar from patient to patient. But biologically, not all severe asthma is the same—and a team of scientists has, for the first time, identified the key difference in people, a finding that has important implications for treatment.

In a paper published today in *Cell Reports*, a group of scientists led by immunologists and pulmonologists at the University of Pittsburgh, in collaboration with Stanford University, used advanced tools of immunology, molecular biology and unbiased computational and bioinformatic approaches to characterize immune profiles of patients with severe asthma. These findings invite a new appreciation for the complexity of disease mechanisms and can lead to improved treatments.

"We started this study to better understand immune mediators of inflammation in asthma," said lead author Matthew Camiolo, M.D., Ph.D., clinical instructor of medicine at Pitt. "We found that despite being grouped broadly as 'clinically severe," these asthma patients actually had very different and distinct immune profiles."

Asthma is a debilitating condition that affects millions of people each year. According to the Centers for Disease Control and Prevention, 25 million Americans, or 1 in 13 people suffer from asthma. And while current standards of treatment—inhaled immunosuppressive corticosteroids, such as beclomethasone and budesonide—are effective in most patients, clinical markers that can help identify those who are likely to be resistant to treatment are lacking.

For patients who do not respond to standard corticosteroid treatment or respond to it poorly, there is no "one size fits all" approach to treat severe disease. Because of that, while severe asthma accounts for 5 to 10 percent of all asthma cases, it consumes 50 percent of associated health care costs, amounting to $28 billion annually.

"Although breakthroughs in asthma therapy have greatly improved our ability to treat patients, many people still continue with disease that greatly diminishes their quality of life," said co-senior author Sally Wenzel, M.D., director of Pitt's Asthma and Environmental Lung Health Institute, and chair of Pitt Public Health's Department of Environmental and Occupational Health.

To characterize immune cells within the airways of severe asthma patients, the researchers, in collaboration with Kari Nadeau, M.D., Ph.D., director of the Sean N Parker Center for Allergy & Asthma Research at Stanford University School of Medicine, used mass cytometry, RNA-sequencing and machine learning, and established a novel algorithm that links immune cells to cellular pathways potentially related to disease pathogenesis.

The research team found that lung aspirates from one group of patients were enriched with T cells polarized to fight infections, while the other group

had a much lower level of T cells. At the same time, the second group had an increased number of innate immune cells expressing an inflammatory molecule IL-4—a cytokine known to be elevated in asthma.

"We have identified two clusters of severe asthma patients with very similar biomarkers but with strikingly distinct immune profiles and associated biological pathways," said senior author Anuradha Ray, Ph.D., professor of medicine and immunology at Pitt. "These findings identify new targets for therapy, which are distinct in the two subgroups of severe asthma patients who otherwise would be indistinguishable based on biomarker profiles."

"We believe that the cell types expressing IL-4 in the airways of one of the groups have not been previously identified in humans in any setting," Ray added.

Researchers are optimistic that these findings will enhance precision medicine approaches to treating severe asthma patients.

"These important findings are the result of a successful team effort among physician-scientists and basic scientists across institutions that has established a new frontier in asthma research," said Ray. "We hope the new knowledge gained will be used to develop new therapeutics to treat severe asthma patients and also allow improved stratification of patients for better efficacy of existing therapies."

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