Stop the Asthma Treatment Elevator, We Need to Get Off!

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A man wanders into his doctor's office because he is taking medication for hypertension. He leaves satisfied but puzzled because, even though the doctor assures him his blood pressure control is excellent, only blood glucose was measured. On the way home, he passes a forest that has burned down, and all that remains are the cold ashes. Immediately, he picks up his mobile phone to call the fire brigade and helicopters to pour water on this long-extinguished fire. Sounds ridiculous? Yes, but those scenarios are being played out in asthma clinics the world over because we are not measuring what we are trying to treat and are reluctant to grasp what is crystal clear to rheumatologists, namely the difference between disease activity and irreversible damage. The consequences are that patients who are at high risk of an asthma attack, which may be fatal, or long-term deterioration to the point of severe asthma and/or fixed airflow limitation, are not identified early or treated energetically, and that those with symptomatic but long-burned-out inactive disease are pushed further and further up the stepwise treatment escalator (1).

All too often, asthma is assessed by asking about symptoms and measuring airflow obstruction even though the condition we are treating (or think we are treating) with inhaled corticosteroids is type 2 airway inflammation. We have known for years that inflammation without symptoms is a ticking time bomb with a high risk of asthma attacks (2). We now know that increases in two simple biomarkers, fractional exhaled nitric oxide (F_{ENO}) and peripheral blood eosinophil count (both practical point-of-care tests), represent a marker of risk, and conversely, if both are low, the risk of a subsequent attack is low across the entire age and disease severity spectrum (3–6).

Talking to patients and measuring spirometry are hallowed by tradition and, of course, have their place. Patient perception of symptoms is especially important in the era of maintenance and reliever therapy. Spirometry may show that a "well" patient has not appreciated severe airflow obstruction or that the shape of the flow–volume curve is suggestive of an alternative diagnosis such as tracheal obstruction.

However, the relationship among symptom burden, spirometry, and airway inflammation is complex (1). Symptoms may relate to inflammation or may be the results of bronchospasm or long-term, fixed airflow obstruction, and the treatment of these is obviously different. A rheumatologist would not treat destroyed, burned-out joints with monoclonal agents in the hope of a resurrection from the ashes, but would instead focus on symptomatic treatment such as analgesic therapy, rehabilitation, or surgical joint replacement. Neither should we be escalating antiinflammatory treatment, no matter what the chronic symptom burden may be, in those with burned-out disease. These patients certainly have an unmet need, but trying to meet their needs with the wrong therapy is not the way forward (7). By contrast, rheumatologists initiate intensive therapy early, long before irreparable damage has been done and irrespective of current symptom burden, because they know that untreated arthritis will ultimately lead to disability unless energetically treated.

What can we learn from this approach? The domains of asthma risk include a short-term one, namely the impending risk of an asthma attack, but also, seriously, the risk of progression from mild to moderate disease to severe (or "too-late") disease. There is a huge and appropriate focus on severe asthma, but to what extent is severe asthma the consequence of inadequate earlier treatment of more mild disease and a failure to appreciate the underlying risk in some of these patients? In a recent study of asthma remission (8), still a concept for which there is no uniformly agreed-upon definition, the longer the duration of disease, the less likely remission was to be reached with any of the biological agents studied (omalizumab, anti–IL-5/IL-5 receptor, anti–IL-4 receptor-α). Remission was also likeliest in those with better lung function, fewer asthma attacks, lower oral corticosteroid exposure, and fewer symptoms. Surely this drives us to the hypothesis that the early institution of biologic agents while the disease is in the throes of early activity offers the best chance of attaining remission. If this hypothesis is correct (and of course, it must be proven prospectively or otherwise), we need markers of risk for progression to severe asthma in those with mild disease or we will bankrupt

(Received in original form December 11, 2024; accepted in final form January 21, 2025)

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

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Am J Respir Crit Care Med Vol 211, Iss 5, pp 698–699, May 2025

Originally Published in Press as DOI: 10.1164/rccm.202412-2431VP on January 21, 2025
Internet address: www.atsjournals.org

the health economy and risk poor patient engagement and inadequate treatment adherence by treating a high proportion of patients who are at low risk. The same study (8) provides the clue: remission was likeliest in those with the highest biomarker levels. We know that a high blood eosinophil count (9) and particularly a high F_{ENO} (10, 11) are predictors of accelerated deterioration in lung function, something that needs to be prevented if true asthma remission is to be attained. Another clue is from the START (inhaled Steroid Treatment as Regular Therapy in early asthma) study (12), which documented a more rapid decline in lung function in patients who had severe asthma attacks and were not prescribed inhaled corticosteroids. We propose that patients with mild to moderate asthma who have increased blood eosinophil count and F_{ENO}, especially if they are experiencing severe asthma attacks, are a high-risk group whose treatment should rapidly be escalated to biologic agents if standard therapy does not normalize the biomarkers and prevent attacks. Of course, determining whether this has resulted in the prevention of severe asthma will take years, but this aggressive approach would be justified by a much shorter-term study if attack frequency was reduced. In any case, there is plenty of scope to reduce the morbidity of so-called "mild" but highly active asthma (13, 14).

So the key question in treating the patient with asthma is, "What is the level of disease activity?" Is there active, ongoing type 2 airway inflammation that needs to be treated early and energetically to prevent short- and medium-term attacks and severe asthma, respectively, or has the disease burned out, in which case treatment targeting disease activity should be reduced? We suggest that the stepwise "treatment elevator" needs dramatic acceleration for the patient with active disease, but needs to be put into reverse or focused in a different direction for those for whom the disease has burned out. The challenge is to accept the importance of the question and perform the studies to determine prospectively if this is the right approach. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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