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Before and beyond Inhaled Corticosteroids

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The indications for inhaled corticosteroids (ICS) have narrowed in the past few years. One of the drivers for this change is the association between ICS and pneumonia. Prescribed for the treatment of chronic obstructive pulmonary disease (COPD) and asthma, they are only recommended as initial therapy for highly symptomatic patients with frequent exacerbations and blood eosinophil counts greater than 300 cells/dl in the former (1). In asthma, intermittent use as a rescue inhaler has been deemed noninferior to daily dosing (2).

Despite these changes, ICS continue to be among the most commonly prescribed medications in the United States. In 2018, six inhaled corticosteroid preparations made it into the top 100 list of the Center for Medicare and Medicaid services. Medicaid and Medicare Part B spent over 4 billion dollars each on ICS during the same year (3).

Pneumonia continues to be the leading infectious cause of death worldwide, and it is responsible for 1.4 million visits to the emergency department every year in the United States alone (4). *Streptococcus pneumoniae* is the main causative agent (5).

These staggering numbers underline the importance of the study in this issue of *AnnalsATS* by Torén and colleagues (pp. 1570–1575), which furthers our knowledge on the association between ICS and pneumonia on a background of ICS overutilization (6).

In this editorial, I will review some of the strengths and weaknesses of the study and the association between ICS and pneumonia. I will finish with presenting nonpharmacological interventions for the treatment of patients with airway disease and persistent symptoms or exacerbations that can prevent ICS overuse.

The authors used a case–control design, in which data were abstracted from the prospectively collected Swedish Invasive Pneumococcal Disease, National Population, Hospital Discharge, and Drug registries. Development of invasive pneumococcal disease (IPD) was the entry criteria for cases. Control subjects were obtained by matching geography, age, and sex to the general population. This approach is a strength of the study. It helped reduce unmeasured biases such as living conditions, vaccination rates, and colonization with *S. pneumoniae* in the community. It also provided a very robust sample size with over 4,000 cases in the final analysis, 71% of which with pneumonia. Their main conclusion was an increase in the risk of IPD with pneumonia in patients being treated with ICS. ICS did not impact the risk of IPD without pneumonia.

IPD was defined by a positive culture or detection of *S. pneumoniae* antigen from a sterile site. Because these diagnostic tests are usually performed only in hospitalized patients, the use of healthier control subjects from the community may have resulted in an overestimation of the risk attributable to ICS (7). Both COPD and asthma were more frequent among hospitalized cases, with 10.3% for COPD and 9.2% for asthma, than control subjects, with 0.9% for COPD and 2.3% for asthma. Smoking, the anatomical and physiological alterations of COPD, and asthma are known risk factors for IPD. In fact, in their sensitivity analysis, any use of ICS in the last 5 years remained associated with increased odds for IPD (odds ratio, 1.94; 95% confidence interval, 1.53–2.47). This finding can only be explained if ICS have very long-lasting effects or if confounding by indication is present.

One last limitation relates to the exclusion criteria. IPD affects children and the elderly disproportionately, and asthma and COPD are the main indications for ICS treatment. Asthma usually has its onset before the age of 10, and COPD increases in prevalence with age (8). The exclusion of patients aged less than 20 and greater than 65 years is problematic, as it excludes a large portion of the target population.

ICS and Risk of Pneumonia

ICS are a known risk factor for pneumonia. In a landmark population-based cohort study from the province of Québec, Canada, Ernst and colleagues (9) found that patients with an exposure to ICS had a 70% increase in their relative risk for pneumonia. Their results also substantiated a dose–response relationship, risk reduction with discontinuation of treatment, and a higher risk of mortality for patients requiring admission to the hospital who had an exposure to ICS. Their findings were independent of COPD severity (9). Similarly, secondary analysis of randomized controlled trials, including TORCH (Towards a Revolution in COPD Health), IMPACT (Informing the Pathway of COPD Treatment), INSPIRE (Investigating New Standards for Prophylaxis in Reduction of Exacerbations)

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(10–12), found an increased risk of pneumonia in the subgroup of patients receiving ICS.

What remains unknown is whether the increased risk of pneumonia is pathogen specific. None of the above cited studies reported the etiological agents of pneumonia. In this sense, the focus by Torén and colleagues on *S. pneumoniae* is a novelty. *S. pneumoniae* continues to be the most commonly isolated bacteria in community-acquired pneumonia. It accounts for 5–10% of the cases of community-acquired pneumonia in the United States and 25–40% of the cases in Europe (5, 13). The findings by Torén and colleagues are supported by previous studies that reported an increase in the rate of upper airway colonization by *S. pneumoniae* with the use of ICS and dampening of the inflammatory response required to recruit neutrophils and trigger an adaptive immune response to this particularly virulent pathogen (14, 15).

Before and beyond ICS

Overall, the available evidence supports an increase in the risk of pneumonia with the use of ICS. These findings mandate a reevaluation of the risk–benefit ratio of ICS for asthma and COPD. While we await safe and effective alternatives, maximization of available therapies and judicious use of ICS should be the norm.

Part of the problem of ICS overuse stems from a focus on inhaled pharmacotherapy. Nonpharmacological interventions are underutilized despite their known benefits. In the United States, this is exemplified by the low utilization rates of pulmonary rehabilitation in patients with COPD. A study from 2018 reported that less than 3% of Medicare beneficiaries with COPD discharged from the hospital received pulmonary rehabilitation over the following 12 months (16). Exercise training, nutritional advice to avoid the extremes of weight, and self-management education can improve symptoms and decrease the risk of exacerbations.

Attention to and mitigation of environmental and occupational exposures is another intervention often overlooked. Besides tobacco smoke, indoor and outdoor air pollution have been associated with worsening respiratory symptoms, exacerbations, and progression of asthma and COPD. Avoidance of biomass fuels, allergens, and improvements in housing and home ventilation systems can all be helpful (17). At a higher degree, COPD and asthma affect minorities and lower socioeconomic groups. Interventions to address disparities in exposures to pollutants and access to health care could also be beneficial (18).

Comorbidities are common in chronic respiratory patients and have a profound impact on quality of life. They should also be targeted for treatment. As an example, esophageal and pharyngeal dysmotility leading to aspiration can trigger exacerbations. Coronary and peripheral vascular disease can mimic exacerbations of asthma and COPD and can impact exercise tolerance and quality of life. In the face of a predictable set of comorbidities, pulmonary practices should at least ensure care pathways for their evaluation and management (19).

Finally, we need to acknowledge the limitations of diagnostic classifications created more than 100 years ago. These classifications are dichotomous; a patient can be healthy or ill, and overlap between different airway diseases is not considered. Realization of these limitations opens the door to considering overlap between COPD, asthma, bronchiectasis, interstitial lung disease, and other airway and parenchymal lung diseases. This, in turn, opens new horizons in terms of treatments available to alleviate patients' symptoms.

In conclusion, the article by Torén and colleagues provides new epidemiological evidence of the link between ICS and IPD with pneumonia, a reminder that a new inhaler prescription might not be the right response for every patient. ■

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

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COVID-19 and Pulmonary Arterial Hypertension: Early Data and Many Questions

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Coronavirus disease (COVID-19), first described in Wuhan, China, in December 2019, is caused by a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of August 2020, the pandemic has impacted more than 21 million individuals worldwide, with those with underlying chronic health conditions, mainly hypertension and cardiovascular diseases, being at risk of developing more severe disease.

Early in the pandemic, there was speculation in the pulmonary vascular community regarding a perceived low risk for severe COVID-19 in patients with pulmonary arterial hypertension (PAH) (1). Anecdotally, PAH centers in areas hit hard by the pandemic were not observing as many patients with PAH with COVID-19 as they had anticipated. Several potential explanations were advanced. Could the disease itself or maybe PAH-specific medications be protective against COVID-19 (*see* Figure 1)? These speculations were suggested by autopsy findings of SARS-CoV-2 infecting endothelial cells with associated vascular injury, thrombosis, and inflammation (2, 3). In addition to the pathological features of endotheliitis in COVID-19, the angiotensin-converting enzyme 2 (ACE-2), key to the entry of SARS-CoV-2 into cells, is known to be downregulated in PAH (4, 5). The ACE-2 receptor, a member of the renin–angiotensin system, is essential for not only the coronavirus' entry into the cells but also its replication. In fact, ACE-2 knockout mice have lower levels of SARS-CoV and low numbers of SARS-CoV spike RNA (6). Angiotensin II, which contributes to injury and inflammation in the lungs, is converted to angiotensin (1–7) by ACE-2 (7). Angiotensin (1–7) has antiinflammatory and vasodilatory properties. Upregulation of angiotensin II and low angiotensin (1–7) levels in COVID-19 could lead to increased pulmonary vasoconstriction and dysregulation of hypoxic vasoconstrictive mechanisms. Recombinant ACE-2, pulmonary overexpression of ACE-2, and the use of small-molecule ACE-2 activators were shown to attenuate PAH through increased production of angiotensin (1–7) (5). Whether reduced ACE-2 in PAH is protective or could promote lung injury in COVID-19 disease remains unclear. Given SARS-CoV-2's tendency to infect the endothelium (2, 8) it was also proposed that the abnormal endothelium in the remodeled arteries of patients with PAH and the immune cellular landscape might limit viral replication and suppress the deleterious cytokine response induced by SARS-CoV-2. Another hypothesis advanced was that perhaps PAH-targeted therapies could have protective effects against COVID-19, through improving endothelial function and ventilation–perfusion mismatch. Studies have shown cross-talk between the endothelin system and renin–angiotensin system. In fact, endothelin-1 can downregulate ACE-2 expression in the lung epithelial cells, whereas endothelin receptor antagonists inhibit angiotensin II–induced vasoconstriction and lung injury (9, 10). Other studies showed that angiotensin (1–7) attenuates the actions of endothelin-1 on endothelial cells, mainly inflammation and growth (11). Endothelin-1 is upregulated in PAH, and endothelin receptor antagonists, frequently used to treat PAH, could be beneficial in the treatment of COVID-19 lung injury. Enhancing the nitric oxide (NO) pathway via phosphodiesterase type 5 inhibitors or soluble guanylate cyclase stimulators is another commonly used PAH-targeted therapeutic avenue. During the 2003 SARS outbreak, inhaled NO was shown to have antiviral activity against the coronavirus. Inhaled NO reversed pulmonary hypertension, improved severe hypoxia, and shortened the length of ventilatory support compared with matched control patients with SARS-CoV (12). *In vitro* studies demonstrated that NO donors increased the survival rate of

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