Discussion

This study is the first to analyze the test characteristics of Light's criteria in a cohort of neutropenic patients using the clinical diagnosis as the reference standard. Light's criteria demonstrated similar sensitivity but worse specificity compared with prior studies (2, 12), particularly with more profound and longer duration neutropenia. Specificity could suffer in particular due to nonspecific systemic LDH elevations in inflammatory conditions wherein neutropenia is common (12). Pleural fluid protein >2.9 g/dl and pleural fluid/serum protein >0.5 had robust LR+ in this population, which is similar to other studies (7). Within exudates, pleural fluid neutrophil percentage distinguished those due to infection versus malignancy despite the presence of peripheral neutropenia. In clinical practice, clinicians should feel confident diagnosing a transudate in a patient with neutropenia when none of Light's criteria are met; however, when Light's criteria are met, we suggest additionally using pleural fluid protein >2.9 g/dl or a pleural fluid/serum protein ratio >0.5 as more specific indicators of an exudative effusion.

Strengths of this study include independent case adjudication and clinical diagnosis as case definition. Limitations include cohort size, variable etiologies and duration of neutropenia, and limited pleural cholesterol values. Future studies could utilize a similar approach but focus on a particular etiology of neutropenia. ■

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

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Not All Inhaled Medicines Are Equal

To the Editor:

We read with interest the perspective by Dr. Rabin and colleagues on "opportunities to transform the inhaler market to address an important source of GHG (greenhouse gas) emissions" (1). Their conclusions include that the use of metered dose inhalers (MDIs) containing hydrofluoroalkanes (HFA) should be minimized because of the carbon footprint, and prescribing should be systemically directed away from these products, and "would represent a major symbolic victory". We differ on some key points.

While the potential environmental impact of current MDIs is important, perspective is needed. According to a 2018 United Nations committee report, the carbon footprint of 2 puffs of albuterol HFA 134a is between that of manufacturing 250 ml of orange juice and 300 ml of cola (2). A 2021 European Respiratory Society statement recognizes the environmental impact of MDIs, but points to the need to focus on patient safety and choice rather than just the device (3). The statement reported that medical aerosols account for <0.1% of GHG in Europe. They state restricting MDIs would be "a retrograde step for the respiratory care community".

New, low-carbon footprint propellants for MDIs are currently in development—specifically HFO (hydrofluoroolefin) 1234ze and HFA-152a, with an environmental impact similar to dry powder inhalers. A recent Phase 1 study in healthy volunteers of a current triple therapy MDI with HFO-1234ve reported it as bioequivalent and safe (3). Additional studies are required to bring this product and others to market, but they appear promising.

As suggested by the authors, society, government, manufacturers, and healthcare should drive the process for low-impact inhalers. Critically, the U.S. Food and Drug Administration

has no published guidance on this topic nor has a U.S. respiratory society published a strategy.

There is a disconnect between prescribers of inhalers and clinical aerosol science. Pulmonologists primarily rely on pharmacology when prescribing inhalers, less so the inhalational device (4). This is largely due to lack of training on this topic from medical school forward as well as too often limited medication formulary access. As part of a quality improvement project in 2018, we conducted an electronic survey in 50 pulmonary fellows from six U.S. programs regarding knowledge of aerosol devices and how they were educated—24 reported learning on their own (R.A. Pleasants, unpublished results). When searching Pubmed with "aerosol drug delivery" (July 11, 2022), there were 4,910 citations—reflecting the tremendous amount of published science in this area.

While we can point out clinical and device advantages of MDIs over other inhalers, there are some pragmatic problems with excluding MDIs from mainstream use. One example is Maintenance and Reliever Therapy with budesonide/formoterol that is now recommended by the Global Initiative for Asthma (GINA) (5)—this medication combination is only available as an MDI in the United States. Theoretically, the majority of asthmatics could qualify for such therapy. There is no soft mist inhaler containing inhaled corticosteroid (ICS). If restricting ICS to DPIs, fluticasone propionate and fluticasone furoate would be the dominant ICSs used in the United States. The former is increasingly used because of generic availability and additional brand name inhalers. We believe overall evidence is compelling that fluticasone propionate, particularly over extended periods and at high doses, has substantial risks of systemic (6) and topical adverse effects (7). We do not believe it is in the best interest of patients to drive prescribing toward this ICS.

We believe an approach that permits use of current MDIs until such time we have different propellants and products is in the best interest of patients and healthcare providers. An inclusive and comprehensive strategy that prioritizes patients should be developed and employed as soon as possible to minimize the impact on inhalers on the environment. ■

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

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Reply: Not All Inhaled Medicines Are Equal

From the Authors:

We thank Drs. Pleasants and Tilley for highlighting several important issues pertaining to an inhaler device transition in the United States (1). We agree with the authors that reducing the use of inhaler propellants with high global warming potential is but one step toward minimizing the environmental harms of healthcare delivery. Reducing hospital energy use, cutting medical waste, and decarbonizing supply chains are vitally important to the cause. Nonetheless, if we are in a climate emergency (2), why not look critically at all sources of greenhouse gas emissions, particularly those that can be easily modified with the stroke of a pen or the click of a mouse?

We know that acting in an emergency, even one as dire as our planet faces, does not mean acting recklessly. A poorly executed device transition, as occurred after implementation of the Montreal Protocol, left Americans with fewer medication options at higher cost (3). With history as our guide, we favor an approach that prioritizes patient outcomes and cost while also weighing environmental impacts. To that end, we agree that regulatory guidance from the U.S. Food and Drug Administration and input from respiratory organizations such as the American Thoracic Society are sorely needed in the face of an eventual hydrofluorocarbon phasedown (4).