Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

NAC-mediated prevention of COPD exacerbations is through restoration of the normal antiviral innate immune response that is suppressed by cigarette smoking and perhaps in COPD.

Cigarette smoking is the major cause of COPD and predisposes patients to severe respiratory tract infections. Respiratory viral infections with rhinoviruses, influenza viruses, and respiratory syncytial virus are the main causes of COPD exacerbations, which are associated with disease progression and loss of lung function.[2] Specifically, several studies have confirmed the relationship between cigarette smoking and the risk of influenza infection.[3] Influenza infections are more severe, with more cough, acute and chronic phlegm production, breathlessness, and wheezing in smokers.[4] The mechanism of increased susceptibility to infections in smokers is likely multifactorial but clearly includes an alteration of immunologic host defenses.

We have demonstrated that cigarette smoke extract (CSE) suppresses host antiviral activity in a human lung model.[5] Thus, cigarette smoke exacerbates the susceptibility of the host to respiratory infectious diseases and the attendant pathology. We found that CSE treatment inhibited influenza-induced antiviral cytokine expression in our human model. This is associated with CSE-inhibited messenger RNA and protein expression of the major RNA virus sentinel RIG-I that is important in the antiviral host response. However, inhibition of viral-mediated RIG-I induction by CSE was prevented, and antiviral cytokine responses were restored by NAC.[5] The interactions between host immune responses and influenza virus usually determine the outcome of infection. Restoration of these responses by NAC may have been a major mechanism in the decrease in exacerbations demonstrated by Tse et al[1] in patients with COPD.

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Response

To the Editor:

We would like to thank Dr Wu and colleagues for their response to our article[1] and for raising the question about alternate mechanisms explaining the action of N-acetylcysteine (NAC) in reducing COPD exacerbations. In a human lung model[2] NAC could restore the antiviral cytokine response and prevent the inhibitory effect of cigarette smoke extract (CSE) on the viral-mediated retinoic acid-inducible gene (*RIG-I*), which is an important pattern recognition receptor that senses influenza. This dose-dependent effect of NAC on the innate immune response further supported the use of higher-dose NAC in the treatment of patients with chronic COPD, as shown in our previous The Effect of High Dose N-acetylcysteine on Air Trapping and Airway Resistance of Chronic Obstructive Pulmonary Disease—a Double-Blinded, Randomized, Placebo-Controlled Trial (HIACE).[1]

We have reservations in concluding that its effect on the innate immune system is the major mechanism for reducing COPD exacerbations. First, influenza infection is not the sole cause of COPD exacerbations; in fact, other respiratory viruses (human rhinovirus, respiratory syncytial virus, human metapneumovirus, coronavirus, and adenoviruses) were recognized during exacerbations. The majority of our patients with COPD in the HIACE[1] were ex-smokers; it is unknown whether cigarette smoking has a sustained long-term suppressive effect on the innate immune response. Moreover, at present, there are still limited clinical data in patients with COPD that demonstrate the interaction between cigarette smoking and NAC in "virus-induced exacerbation." To extrapolate the in vivo results to patients with COPD, it seems that further clinical studies are warranted, especially to demonstrate the attenuated innate immune response in patients with COPD and the clinical effect of NAC in enhancing innate response as well as reducing virus-induced exacerbations in patients with COPD.

In fact, exacerbation of COPD is multifactorial. NAC may act on various target sites, resulting in the reduction of exacerbations. In addition to its mucolytic effect, antioxidant and antiinflammatory properties of NAC could attenuate the chronic airway inflammation as well as improve small airways function and reduce air trapping. For example, patients with COPD are characterized by overexpression of adhesion molecules (eg, intercellular adhesion molecule-1, which causes excessive transmigration of neutrophils). It was shown in an in vitro study[3] that NAC could exert its anti-inflammatory effect by inhibiting cytokines that stimulated IL-8 and intercellular adhesion molecule-1 in endothelial and epithelial cells. Other effects that were demonstrated by NAC include (1) reductions of lysozyme and lactoferrin concentrations in smokers,[4] (2) reduction in the activation and number of neutrophils and macrophages in BAL fluid in smokers,[5] and (3) inhibition of the adherence of bacteria to ciliated epithelial cells in vitro.[6]

Nevertheless, the authors' comments have definitely shed light on the potential mechanism for our previous observation that NAC could reduce exacerbation in patients with COPD. Further clinical studies are warranted to confirm the hypothesis.

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Mitigating VTE in Soldiers From Operation Iraqi Freedom and Operation Enduring Freedom

To the Editor:

We read with great interest the recent article by Holley et al[1] in *CHEST* (September 2013) detailing the nature of VTE in combat soldiers. We previously published the first report to our knowledge in this same population[2] and agree that application of VTE prophylaxis in injured soldiers is often limited by bleeding risk, anatomic location of injury, and discontinuity in care arising from surgical or logistical interventions. Although it is encouraging that Holley et al[1] noted a reduction in VTE events with higher doses of enoxaparin (in contrast to our data[2]), it is somewhat contradictory that missed dosing did not appear to influence VTE rates.

In our opinion, two developments have markedly impacted the care of patients injured in the recent conflicts in Afghanistan and Iraq: an increase in the incidence and profundity of penetrating injury[3] and the impressive capability for expedited aeromedical evacuation. The emergence of the latter has decreased the time from in-theater injury to stateside ICU for injured American soldiers to <48 h in some instances. This places lengthy transport of the injured (flight times ≥ 8 h) within the time period when VTE develops and prophylaxis is likely most essential, and the vagaries of wartime transport may compromise administration of prophylaxis. Moreover, the conditions of hypobaric hypoxia seen with air travel may increase risk of VTE independently of risk associated with prolonged immobility,[4] further increasing the propensity of these patients develop clots. Although this hypobaric risk may be mitigated by low-molecular-weight heparin,[5] and aggressive thromboprophylaxis in the trauma setting is certainly justifiable, as Holley et al[1] note, the absence of data from the evacuation period remains problematic in developing a tailored and evidence-based approach to VTE prevention in this population.

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Response

To the Editor:

We appreciate the comments from Dr Jackson and colleagues regarding our recent article.[1] Although they state that they recorded relevant variables during their chart review, they do not report