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.

Correspondence and Replies

Subcutaneous terbutaline as an alternative to aerosolized albuterol

To the Editor:

In their well-written and comprehensive article regarding contingency planning for the COVID-19 epidemic, Shaker et al[1] discuss the treatment of exacerbation of asthma. During the COVID-19 epidemic, asthmatics will continue to have exacerbations, frequently requiring emergency care in a physician's office, an urgent care center, or an emergency department of a hospital.

It is recommended that asthmatics continue to be managed according to asthma guideline–based recommendations.[2] Nebulizer use is discouraged unless essential during this pandemic because nebulized therapy is more likely to aerosolize SARS-CoV-2 and increase the risk of contagion. As such, asthma therapy delivered by a metered dose inhaler would be more appropriate in the health care setting.[3] Nevertheless, some patients are so tight that using a metered dose inhaler, even with a spacer, might be problematic, particularly if they have uncontrolled coughing, have severe life-threatening asthma, or are uncooperative or unable to follow the directions required for a metered dose inhaler with a spacer.

A recent report[4] demonstrated in a prospective study that 85 patients treated with subcutaneous terbutaline significantly improved after already receiving multiple albuterol treatments with either nebulized aerosol or albuterol metered dose inhaler. Terbutaline is readily accessible and inexpensive to use. This drug would obviate the need to use a nebulizer, thus decreasing the chance of spreading SARS-CoV-2 during this evolving pandemic.

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Reply to "Subcutaneous terbutaline as an alternative to aerosolized albuterol"

To the Editor:

We appreciate the comments and perspective expressed by Dr. Strauss regarding our recent pandemic contingency guidance,[1] and we agree that in the setting of *acute severe asthma* or impending respiratory failure, both nebulized albuterol and subcutaneous terbutaline are important clinical considerations. Although evidence suggests that inhaled albuterol through a metered dose inhaler can be as effective as nebulized albuterol, alternative bronchodilator delivery may be needed in some situations.[2,3] Although subcutaneous terbutaline may be an option, if nebulized therapy is required due to patient impairment and ineffective drug delivery by the metered dose inhaler, it would be an appropriate consideration if felt to be essential in patient management. In this context, for a patient with potential SARS-CoV-2 infection, it would be appropriate to consider administering nebulized therapy in a negative pressure room with appropriate airborne precautions—complete personal protective equipment (PPE) including an N95 respirator.[1] In the setting of acute severe asthma, it is important to ensure availability of emergency medical services and/or additional intensive care resources that may be required for patient management, including supplemental oxygen, aggressive bronchodilator therapies (both intramuscular and intravenous beta-agonists, anticholinergics, and other smooth muscle inhibitors including magnesium sulfate), anti-inflammatory medications including early administration of corticosteroids, and supportive measures such as noninvasive positive pressure ventilation and helium-oxygen gas mixtures.[4]

Terbutaline is a beta-agonist that preferentially stimulates beta-2 receptors in the bronchi to a greater degree than beta-1 receptors in the heart. Although terbutaline is effective at a dose of 0.5 mg (0.5 mL) subcutaneously in adult patients presenting with acute severe asthma, it is also notable that epinephrine at a dose of 0.5 mg (0.5 mL) has been shown to have similar benefit with a comparable adverse effect profile.[5,6] Dosing of subcutaneous terbutaline and subcutaneous epinephrine is similar (0.01 mg/kg/dose), with an adult dose of 0.25 mg for terbutaline and 0.3 to 0.5 mg for epinephrine every 20 minutes for 3 doses recommended by the 3rd Expert Panel Report (EPR3).[7,8] Notably, when administered subcutaneously, evidence suggests that terbutaline loses its beta-selectivity and offers little advantage over epinephrine,[6] which may be more readily available in many office settings; however, terbutaline subcutaneously may be preferred over subcutaneous epinephrine in pregnancy.[9] In addition, if both subcutaneous epinephrine and terbutaline are available, terbutaline may be preferred as its effect on forced expiratory volume in 1 second and forced vital capacity may be more pronounced and of longer duration as a result of its slower rate of inactivation, because it is not metabolized by either catechol-o-methyl transferase or monoamine oxidase as is

epinephrine.[6] The recently released GINA guidelines[10] and EPR3[8] recommend nebulized or inhaled short-acting beta-agonists for the initial treatment of acute asthma exacerbation; EPR3 stated that injected epinephrine or terbutaline had "no proven advantage" compared with aerosol therapy.[8] Properly designed studies demonstrating superior therapeutic utility of terbutaline for acute asthma are required to alter this recommendation; however, in the setting of the current SARS-CoV-2 pandemic and the need to implement droplet and situational airborne precautions, administration of injected bronchodilator therapy may merit consideration. The benefits of using subcutaneous terbutaline or subcutaneous epinephrine in acute severe asthma may outweigh the increased risks of SARS-CoV-2 infection by nebulizer therapy, especially in an increasingly common scenario of PPE shortages throughout North America. Importantly, when delivering bronchodilator therapy in the setting of acute asthma, supplemental oxygen may be needed because approximately one-third of patients may experience a decrease in PaO_2, and patients who are already hypoxic may be at greater risk due to ventilation-perfusion mismatch.[6] In this setting, beta-agonists may increase perfusion relative to ventilation through cardiac output and pulmonary vasodilation.[6] In the context of supplemental oxygen therapy, recommendations for PPE for patients with suspected SARS-CoV-2 infection would also apply.[1]

During the COVID-19 pandemic, each clinician must treat the patient in front of him or her, managing each unique situation in its appropriate context. Although subcutaneous beta-agonists may have a role in managing some asthma exacerbations during the pandemic, COVID-19 is not an absolute contraindication to any medication or management strategy urgently needed in delivering optimal care. Still, Dr. Strauss highlights an important and often overlooked aspect in the management of acute asthma exacerbations and we greatly appreciate this insight.

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Debate on drugs that may aggravate COVID-19

To the Editor:

The Journal of Allergy and Clinical Immunology: *In Practice* published a contingency planning article by Shaker et al[1] to guide the allergists/immunologists through the coronavirus disease 2019 (COVID-19) pandemic. They provided suggestions for a logical approach to quickly adjust our services to mitigate risk to both medical staff and patients during the pandemic, while social distancing is being encouraged. In this context, there is an ongoing worldwide debate regarding the use of angiotensin-converting enzyme (ACE) inhibitors and ibuprofen in patients with COVID-19. The concern is that these drugs could worsen the prognosis of patients with the infection.[2]

The 2 coronaviruses of the "severe acute respiratory syndrome," China, 2002/2003, and of the "Middle East respiratory syndrome," Middle Eastern countries, 2012, use angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4, respectively, as their receptors to infect human cells.[3] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the coronavirus involved in COVID-19, also depends on ACE2 for cell entry.[4]

Drugs that inhibit ACE paradoxically upregulate ACE2 expression on the cell surface and could theoretically facilitate coronavirus infection and progression.[5] There is no definitive evidence that this effect is clinically relevant, but some retrospective observational studies suggest an association between the use of these drugs and a worse outcome of COVID-19.[6] A cause-effect association cannot be confirmed, and ACE inhibitors could be confounding factors that indicate comorbidities, such as cardiopathy, hypertension, and diabetes, besides advancing age, which are well-recognized risk factors for worse outcome of COVID-19. Myocardial injury, indicated by increased serum levels of troponin T, and cardiovascular disease had a significant association with fatal outcomes of COVID-19.[6] Moreover, withdrawal of ACE inhibitors could aggravate an underlying disease and make patients more unstable to overcome a coronavirus infection.

Coincidentally or not, the receptors of coronavirus, ACE2 and dipeptidyl peptidase 4, are enzymes that break down bradykinin in addition to their main functions. After SARS-CoV-2 binding to ACE2, the viral complex undergo endocytosis and surface ACE2 is downregulated (Figure 1). ACE also degrades bradykinin and drugs that inhibit this enzyme lead to an increase in tissue bradykinin and may even trigger cough and angioedema in hypersensitive individuals. We speculate whether the excess of bradykinin in patients taking ACE inhibitors could complicate coronavirus infection, because of its effects of vasodilation, increase in vascular permeability, and cough reflex exacerbation.[7] However, no study has been done investigating this hypothesis and current data do not justify the discontinuation of ACE inhibitors in patients at risk or with COVID-19.

Some experts' opinions and unpublished French cases suggested an association between the use of ibuprofen and a worse outcome of COVID-19,[8] but there are no studies supporting this hypothesis. A recent publication stated that ibuprofen also increases ACE2 expression, but the authors did not provide the reference that supports this statement.[2] Ibuprofen use could be a marker of disease severity and not necessarily the cause of a worse prognosis. Patients more toxemic and symptomatic, having fever, asthenia, and myalgia, are more prone to use nonsteroidal