Maes and colleagues (1) fail to point out the inhibitory *in vitro* effects of ICS on local and systemic production of IL-6 (5, 6), this being the strongest predictor for impending respiratory failure in severe coronavirus disease (COVID-19) (7). Finally, a more specific suppressive effect from ICS on SARS-CoV-2 replication has been described with ciclesonide and mometasone furoate but not with budesonide, beclomethasone, or fluticasone (8).

We believe that, taken together, these observations reinforce the need for patients with eosinophilic asthma and COPD to continue receiving their controller therapy containing ICS, as that will provide optimal disease control and perhaps also confer protection against viral triggers, perhaps including SARS-CoV-2. ■

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Reply to Lipworth *et al.*

From the Editorialists:

We totally agree with the letter by Lipworth and colleagues in response to our editorial emphasizing that patients with asthma need to continue using their inhaled corticosteroid (ICS)-containing controller therapy during the coronavirus disease (COVID-19) pandemic, as this provides optimal asthma control and also confers some protection against viral triggers, perhaps including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). They also highlight several interesting papers, published after the publication of our editorial, which address two key research questions: *1*) are subjects with asthma at increased risk of COVID-19 infection and related illness? and *2*) does ICS use modulate this risk? Because asthma is a very heterogeneous disease, we hypothesize that asthma phenotypes and the type of underlying airway and systemic inflammation need to be taken into account to answer these questions correctly (*see* Table 1).

In children with asthma, allergic sensitization and other type 2 biomarkers (such as fractional exhaled nitric oxide and epithelial expression of IL-13, which increases the expression of inducible nitric oxide synthase) were inversely related to ACE2 (angiotensin-converting enzyme 2), the cellular receptor for SARS-CoV-2 (2). Moreover, in ICS-naive adults with mild allergic asthma, segmental allergen bronchoprovocation significantly reduced ACE2 expression in the bronchial epithelium. In contrast, nonatopic asthma was not associated with reduced ACE2 expression, which is in line with the findings by Peters and colleagues (3), demonstrating no difference in ACE2 gene expression in induced sputum of subjects of the SARP-3 (Severe Asthma Research Program-3) as compared with healthy control subjects, as atopy is less prevalent in adults with severe asthma. In addition, in samples from bronchial brushes and biopsies, there were similar levels of ACE2 mRNA expression in healthy volunteers and adult subjects with mild-to-moderate asthma or

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Table 1. Heterogeneity of Asthma and Potential Risk of Severe COVID-19

Characteristic of Subject with Asthma	No Increased Risk of COVID-19 (or Decreased Risk)	Increased Risk of COVID-19
Age	Children and adolescents	Older subjects
Asthma phenotype	Type 2–high asthma	Type 2–low asthma
Airway gene expression	Type 2 cytokines (e.g., IL-13)	IFN-stimulated genes
Systemic inflammation	Low IL-6	High IL-6
Comorbidities	Allergic sensitization	Obesity, diabetes, or hypertension
Asthma severity	Mild-to-moderate asthma: GINA steps 1–4	Severe asthma: GINA step 5
Lung function	Normal	Impaired
Asthma control	Well controlled	Uncontrolled
Exacerbation frequency	No exacerbations	Frequent exacerbations
Controller treatment	ICS	OCS: repetitive bursts or OCS maintenance treatment

Definition of abbreviations: COVID-19 = coronavirus disease; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroids; OCS = oral corticosteroids.

severe asthma (4). Again, an inverse correlation between ACE2 and T-helper cell type 2 cytokine–dependent gene expression was observed. Indeed, IL-13 treatment of primary airway epithelial cells significantly reduced ACE2 expression but increased expression of TMPRSS2 (transmembrane protease serine 2) (5). Importantly, ACE2 has been identified as an IFN-stimulated gene in human airway epithelial cells and lung type II pneumocytes (6). Because IFNs are key mediators of our host defense against viral infections and because ACE2 is supposed to provide tissue-specific protection during lung injury, this implies that SARS-CoV-2 could exploit IFN-driven upregulation of ACE2 to propagate infection, leading to severe acute respiratory distress syndrome, respiratory failure, and mortality. Intriguingly, increased expression of IFN-stimulated genes has also been demonstrated in samples from airway brushings and in blood cells of patients with mild or severe type 2–low asthma, respectively (7). Lastly, elevated levels of systemic IL-6, most commonly seen in those with concurrent obesity and asthma, are not only associated with more severe asthma (8) but also predict the need for mechanical ventilation in severe cases of COVID-19 (9).

In conclusion, the risk of severe COVID-19 in subjects with asthma is influenced by multiple factors, including demographics (age and sex), ethnicity, genetics, treatment (e.g., ICS treatment), asthma severity, lung function, level of asthma control, exacerbation frequency, asthma phenotype (type 2–high vs. type 2–low asthma) and comorbidities (*see* Table 1). Large-scale epidemiologic studies, clinical trials, and mechanistic studies are needed to disentangle the relative importance of these and other risk or protective factors in modulating the susceptibility of those with asthma to SARS-CoV-2 infection and severe COVID-19. ■

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Fungal Infection during COVID-19: Does *Aspergillus* Mean Secondary Invasive Aspergillosis?

To the Editor:

We read with great interest the letter "COVID-19–associated Pulmonary Aspergillosis" by van Arkel and colleagues (1). The authors report a high incidence of presumed invasive pulmonary aspergillosis (6 of 31; 19.4%) among patients with coronavirus disease (COVID-19) admitted to intensive care.

In light of the recent studies revealing the high incidence of influenza-associated pulmonary aspergillosis (2), it seems natural to expect similar complications in severe forms of COVID-19 pneumonia. However, we would like to discuss some particular points.

Among the six patients presented by the authors, two had chronic obstructive pulmonary disease (COPD), another had asthma with inhaled corticoid therapy, and a fourth received oral prednisone. The association between aspergillosis and COPD is well known; in a recent prospective study, 14% of patients with COPD exacerbations had respiratory samples with *Aspergillus* spp. of unclear clinical significance (3). Corticosteroid therapy is also a known risk factor for *Aspergillus* colonization (4). Furthermore, these four patients had an *A. fumigatus*–positive culture on a single respiratory sample, and aspergillosis was diagnosed within 3–5 days after ICU admission. Because no previous negative respiratory sample was available, the preexisting presence of *Aspergillus* cannot be ruled out. Finally, the fifth patient had only a single positive galactomannan on a BAL.

Eight years ago, Blot and colleagues proposed criteria for defining invasive aspergillosis in critically ill patients using histopathology-controlled cases as references (5). For immunocompetent patients, the direct examination of hyphae in respiratory samples was mandatory to classify the case as putative, which would have excluded all the presented cases. Criteria have evolved since then and are now similar to those suggested by the authors for the diagnosis of COVID-19–related aspergillosis, that is, *Aspergillus* spp. cultured from BAL (without direct examination) or a galactomannan index of 1 or greater on BAL or 0.5 or greater on serum. However, diagnosing an invasive aspergillosis in an immunocompetent individual solely on a single positive respiratory specimen culture or a single galactomannan index might be adventuresome. Indeed, this generates a risk of artificially increasing the incidence of aspergillosis and the overuse of antifungal treatments.

To illustrate this point, we present two cases of patients hospitalized for severe COVID-19 in our institution. Following the same criteria, secondary invasive aspergillosis would have been diagnosed in them. Nevertheless, they presented favorable outcomes without any antifungal treatment, which from our point of view makes the diagnosis refutable.

The first patient was a 66-year-old immunocompetent man with type 2 diabetes who was hospitalized for 21 days in our ICU. A BAL performed on Day 7 was positive for galactomannan (index = 3.2). Antifungal treatment was not administered because the direct examination, the *A. fumigatus* PCR, and the culture were negative, as were the serum galactomannan and β-D-glucan. The patient presented a favorable outcome and was later discharged from the hospital.

The second patient was a 38-year-old woman with obesity, hypertension, type 2 diabetes, and rheumatoid arthritis treated with methotrexate. She required venovenous extracorporeal membrane oxygenation and was therefore hospitalized in our ICU for 11 days. Several colonies of *A. niger* were found on a protected distal respiratory sample performed on Day 4 but not on later samples. This patient did not receive any antifungal treatment, but her respiratory state improved nonetheless.

The diagnosis of invasive aspergillosis is difficult and based on a body of arguments. This is especially true for critically ill patients in whom clinical arguments are not discriminant and computed tomographic scan is either lacking or difficult to analyze. This is why mycological arguments play a crucial role in the diagnostic approach. Consequently, we ask ourselves whether the use of more stringent criteria that are not limited to a single mycological argument would be preferable.

Also, careful attention should be paid to clearly differentiate aspergillosis as a subsequent complication of severe COVID-19 pneumonia from aspergillosis in patients with underlying chronic respiratory diseases (that may be occult noninvasive forms preexisting COVID-19).

We acknowledge that COVID-19 might be an independent risk factor for subsequent aspergillosis. It is also possible that underlying pulmonary conditions may favor COVID-19–associated aspergillosis. We also fully agree with the authors that classifying aspergillosis cases is very challenging, especially in the ICU setting. Common efforts should therefore be made to further assess the pathogenic nature of the presence of *Aspergillus* in respiratory samples in ICU patients with severe COVID-19. ■

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