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 Reply

A limitation regarding the association between intranasal corticosteroid use and better COVID-19 outcomes: Nasal symptoms matter

To the Editor:

We read with great interest the article by Strauss et al.[1] Their study investigated the possible association between intranasal corticosteroid (INCS) therapy and risk for hospitalization, intensive care unit admission, or death owing to COVID-19. One strength of the study is that the authors analyzed a large-scale database about COVID-19 and adjusted for many clinically relevant confounding factors using a causal inference method (ie, propensity score matching). In addition, they confirmed the robustness of results by performing sensitivity analyses that accounted for the use of prescription inhaled corticosteroids, blood absolute eosinophil count, and allergic rhinitis. Although the results may support the potential effectiveness of INCS use in COVID-19 outcomes, we point to a possible limitation that might influence the interpretation of study results. We have an additional suggestion regarding this study.

The limitation is regarding preexisting nasal symptoms such as rhinorrhea and nasal congestion. Because this study is a retrospective observational design, most INCS users in this study experienced some kind of nasal symptom. Under such a condition, this study examined only the association between INCS use for preexisting nasal symptoms and COVID-19 outcomes, not the effectiveness of INCS on COVID-19 outcomes. Importantly, patients with mild COVID-19 present with nasal congestion or rhinorrhea as well as cough or hyposmia.[2] Thus, it might be that early nasal symptoms caused by COVID-19 rather than INCS potentially predict better COVID-19 outcomes. To clarify the effectiveness of INCS use in COVID-19 outcomes, a consideration is needed of the association between nasal symptoms and COVID-19 severity. To compensate for this limitation, we have a simple suggestion. If available, the authors should both describe and adjust for nasal symptoms (eg, rhinorrhea, nasal congestion), which are clearly distinguished from flu-like symptoms in clinical presentations. Because preexisting nasal symptoms are the common cause of both INCS use and COVID-19 outcomes,[2] these may be an important residual confounding factor that require adjustment.[3] Hence, if the authors could identify and adjust for preexisting nasal symptoms among COVID-19 patients who used INCS, they could clarify the association between INCS users and COVID-19 outcomes, considering the presence of nasal symptoms.

We could not entirely interpret ICNS use to be associated with good COVID-19 outcomes, although this study is well-designed. This limitation might be attributed to the observational study design. Therefore, randomized controlled trials are essential to prove the causal effects of INCS use on COVID-19 outcomes. However, we believe that considering the limitation and suggestion mentioned here will help clinicians and future researchers interpret this study accurately.

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Reply to "A limitation regarding the association between intranasal corticosteroid use and better COVID-19 outcomes: Nasal symptoms matter"

To the Editor:

We thank the editors for the opportunity to respond to the comments by Maeda et al[1] regarding our article, and appreciate their positive comments. We acknowledge that our article was limited by its retrospective design and the information available in the Cleveland Clinic COVID-19 Research Registry (CCCRR). Despite this, the significant associations between intranasal corticosteroid (INCS) and improved COVID-19 outcomes highlight the need for a randomized controlled trial (RCT) to determine whether INCS are effective in treating or preventing COVID-19.

Maeda et al[1] hypothesized that the association of early nasal symptoms with improved COVID-19 outcomes was confounded by INCS therapy and recommended repeat analysis adjusting for nasal symptoms. Although we appreciate their recommendation, the CCCRR does not include data on nasal symptoms. Nonetheless, adding nasal symptoms as a covariate to our models, although helpful, does not preclude the need for a prospective cohort study or an RCT to corroborate our findings.

We note that observational studies of nasal symptoms in COVID-19 have been limited by small sample sizes and missing data. Kim et al[2] demonstrated that both nasal congestion (34.3%) and rhinorrhea (26.2%) were relatively common in a cohort of

172 symptomatic patients with COVID-19. However, larger studies, including a systematic review of 1,770 patients with a positive COVID-19 test, showed that nasal congestion (4%) and rhinorrhea (2%) were relatively uncommon in COVID-19.[3] Rhinorrhea (1% to 6.8%) and nasal congestion (3% to 4.8%) were also uncommon in two additional systematic reviews.[4,5] These conflicting results and the low prevalence of nasal symptoms support our concern that data on nasal symptoms, extracted from electronic health records, are frequently incomplete and misleading. Hence, a prospective observational study or an RCT is needed to test the hypothesis raised by Maeda et al.[1]

Our analysis sought to exclude acute INCS therapy during COVID-19, as noted by a median (interquartile) time between INCS prescription and COVID-19 testing of 379 (147-679) days. To address this further, we repeated the analysis after excluding patients (n = 837) who had an INCS prescription within 14 days of COVID-19 test date and found similar results, including lower risk for COVID-19 related hospitalization (adjusted odds ratio [OR] [95% confidence interval [(CI)]: 0.77 [0.71-0.83]), admission to the intensive care unit (0.74 [0.63-0.87]), and in-hospital mortality (0.72 [0.57-0.89]).

Compared with non-users, INCS users reported more age-adjusted comorbidities and an increased use of medications at baseline. The INCS users were more likely to have asthma, and reported more respiratory symptoms during acute COVID-19, consistent with united airway disease when upper and lower airways are considered a united morphologic and functional unit.[6] Despite this, our adjusted analysis associated INCS independently with improved COVID-19 outcomes. The association we demonstrate is founded on plausible biologic mechanisms,[7] sound statistical methods, and a large sample size. Our findings are also supported by a recent study that associated fluticasone propionate with *ACE2* gene suppression in human nasal epithelial cells.[8] Given these results, we believe it is time for an RCT to determine the role of INCS in the management of COVID-19.

J.G. Zein, R. Strauss, and A.H. Attaway made substantial contributions to the conception or design of the work; J.G. Zein acquired, analyzed, and interpreted the data for the work; R. Strauss, and A.H. Attaway contributed to drafting the work or revising it critically for important intellectual content; J.G. Zein agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; and J.G. Zein, R. Strauss, and A.H. Attaway gave the final approval of the version to be published.

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Features of nephrotic syndrome in infants with severe combined immunodeficiency

To the Editor:

We read with great interest the recent article by Tsilifis et al[1] on a child with interleukin-7Rα–severe combined immunodeficiency (SCID) who developed features of nephrotic syndrome secondary to maternofetal graft-versus-host disease. At our center at Chandigarh, North India, we have diagnosed and managed 95 cases of SCID in last 30 years.[2] We share our experience on 2 infants with SCID who developed features of nephrotic syndrome.

In Case 1, a 1.5-month-old female born to a fourth-degree consanguineous couple presented with generalized anasarca noted since day 10 of life. On examination, she had a dry, nonerythematous rash over the trunk and extremities and gross ascites. She had nephrotic range proteinuria (albumin 4+) and protein-creatinine ratio greater than 2. Blood investigation showed high triglycerides of 627 mg/dL and serum cholesterol of 200 mg/dL with albumin of 2.6 g/dL suggestive of nephrotic syndrome. Flow cytometry was suggestive of T-B-NK-SCID with Omenn syndrome (OS) (Table I). A renal biopsy could not be performed because she succumbed to illness. Adenosine deaminase (ADA) 1 enzymatic activity was suggestive of ADA-deficiency SCID and genetic analysis showed a novel mutation in *ADA* gene at exon 5 c.407G>A (homozygous).

In Case 2, a 6-month-old male child born to a nonconsanguineous married couple presented with febrile illness and erythematous macular rash for 1.5 months and loose stools and rapid breathing**.** He has been treated elsewhere with multiple antimicrobials. His elder sister and brother expired at 3 to 4 months of age with a similar illness. On examination, he was failing to thrive and had pallor, generalized edema, diffuse hyperpigmented rash, respiratory distress, oral thrush, and hepatosplenomegaly. He had lymphopenia with increased T cells and absent B cells and low immunoglobulin G (Table I). He had nephrotic range of proteinuria and his serum cholesterol was elevated (310 mg/dL). He succumbed to illness due to multiorgan dysfunction. Diagnosis of SCID was confirmed on autopsy with a markedly atrophic thymus that was devoid of lymphocytes and totally depleted peripheral lymphoid organs. Renal histopathology showed evidence of mesangial sclerosis. Also noted were necrotizing pneumonia