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

Acknowledgment: The authors thank all investigators of the LYMPHONIE study group, the CIC-EC1432 (Alexandra Lamotte-Felin, Lydie Rossie, and Delphine Pecqueur), the Intensive Care Medicine Research team (Solenne Villot and Mathilde Audry), Serge Monier from the Cytometry core facility, and Shaliha Bechoua from the Centre de Ressource Biologique. They also thank the patients.

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Role of IL-6 in Severe Inflammation

To the Editor:

We read with interest the recent article investigating coronavirus disease (COVID-19) inflammatory cytokine profiles by McElvaney and colleagues, in which, in critically ill patients requiring intensive care, circulatory IL-6 was elevated (1), as recent reports have indicated this cytokine as the strongest predictor of the need for mechanical ventilation (2). However, we would like to raise a potential problem with the authors' interpretation of the results before discussing the application to IL-6–regulating medicines, as we think that it is not clear that IL-6 is a key molecule of severe inflammation like other proinflammatory cytokines, such as tumor necrosis factor and IL-1. There are several reports advocating both the proinflammatory and antiinflammatory potential of IL-6 against acute inflammatory responses, including acute respiratory distress syndrome and sepsis (3, 4). Using genetically engineered animals (IL-6–deficient B6J129Sv mouse strain), we previously demonstrated that IL-6 serves as a protector in pulmonary hemorrhagic injury induced by bacterial endotoxins (LPS), at least partly through the regulation of proinflammatory cytokines and chemokines (5). However, in this study, interestingly, we also observed that IL-$6^{-/-}$ mice show devastating lung injury compared with littermate wild-type mice 3 days after intraperitoneal administration of LPS, whereas mortality at Day 7 was higher in wild-type than in IL-$6^{-/-}$ mice (repeated three times; K. Inoue and colleagues, unpublished data), suggesting that IL-6 can have opposite effects depending on the pathological phase of the host. We imagine that IL-6 has multiple roles in the inflammatory pathway, as proposed by Qiu and colleagues (6), although the role may differ according to animal species and strain and inflammation type. Indeed, we have confirmed that this cytokine is not valuable in acute oxidative lung injury induced by diesel exhaust particles in mice with the same genetic background as in the LPS experiments.

Further research is needed to clarify the role of IL-6 in severe inflammatory conditions, including COVID-19–related conditions, and explore novel therapeutic options. ■

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

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Supported by CREST (CE19055-10).

Originally Published in Press as DOI: 10.1164/rccm.202007-3001LE on September 21, 2020

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Reply to Blot *et al.* and to Inoue *et al.*

From the Authors:

We thank Blot and colleagues for their interest in our article and for raising an important question regarding the suitability of IL-6 as a therapeutic target in coronavirus disease (COVID-19).

In their correspondence, Blot and colleagues provide data on IL-6 levels measured in patients with a diagnosis of COVID-19 versus non–COVID-19 pneumonia. Although we believe the data presented by Blot and colleagues are valid, we suggest that the IL-6 levels depicted are, by virtue of sample timing, processing methodology, and patient severity of disease, not comparable to ours and should be interpreted in context.

In the study conducted by Blot and colleagues, patients were sampled during the first 48 hours of their hospital admission, following confirmation of their diagnosis by RT-PCR. In contrast, our patients were matched for time from onset of symptoms (1). Had we not taken this approach, we risked confounding our data by sampling patients who had the same disease severity but who were merely at different points in the course of their illnesses. Moreover, the criteria for admission and the availability of testing, both locally and internationally, have shifted repeatedly throughout the current pandemic, making comparisons between studies that use admission as a starting point challenging. COVID-19 is widely regarded as a biphasic illness (2), with a later "hyperinflammatory phase" occurring 7 days from the onset of symptoms.

Blot and colleagues matched patients for disease severity by using the Pa_{O_2}:FI_{O_2} ratio. However, the Pa_{O_2}:FI_{O_2} readings and blood sampling were performed at different time points in the patient's hospital stay, with approximately three-quarters of the Pa_{O_2}:FI_{O_2} ratios for the COVID-19 group calculated later, after these individuals had progressed to the ICU. In our study, blood and physiological measurements were performed simultaneously. In addition, all of our patients with COVID-19 were receiving invasive mechanical ventilation, whereas 15% of the COVID-19 ICU group described by Blot and colleagues were not. Mechanical ventilation influences the Pa_{O_2}:FI_{O_2} ratio, such that patients who are not receiving invasive ventilation have lower Pa_{O_2}:FI_{O_2} ratios and appear sicker than patients who are ventilated with high levels of positive end-expiratory pressure and optimal lung recruitment.

The effects of sample timing and severity of illness are crucial when cytokine levels are being assessed. To illustrate this point, the mean daily difference in IL-6 levels for the COVID-19 group described by Blot and colleagues ranged from 10,000 to 14,000 pg/ml.

The study protocol used by Blot and colleagues allowed up to 4 hours to elapse before samples underwent initial processing. This delay is relevant, as IL-6 and other cytokines are released spontaneously from blood cells over time (3, 4). In contrast, our samples were processed immediately using protective centrifugation speeds without temperature shifts.

Unlike our study, Blot and colleagues did not match for markers of severity of inflammation, such as C-reactive protein, nor did they account for the diurnal variation in circulating IL-6 levels by standardizing their time of sample collection. Additionally, a large number of the patients with COVID-19 included by Blot and colleagues were already receiving therapies such as corticosteroids that are known to influence cytokine levels. In our study, these patients were excluded.

The non–COVID-19 severe community-acquired pneumonia (CAP) group recruited by Blot and colleagues was also different from ours, with a predominance of atypical pathogens. Indeed, *Streptococcus pneumoniae*, the most common CAP pathogen, was detected in only 2 of the 36 patients with non–COVID-19 severe CAP described. Furthermore, four of the severe CAP group in the Blot study had positive bacterial blood cultures. Patients with bacteremia and/or septicemia were excluded from our study because of their high likelihood of generating outlier levels of blood cytokines.

These factors may go some way in explaining the degree of variation in the IL-6 levels reported by Blot and colleagues The greater than 1,000-fold difference in IL-6 levels within their non–COVID-19 pneumonia group is still unusual, however, and levels approaching or in excess of 100,000 pg/ml in several patients would prompt consideration of alternative or concomitant diagnoses.

We agree strongly with Inoue and colleagues that blanket inhibition of IL-6 in COVID-19 should be approached with caution given the complex biology of this cytokine.

To achieve signal transduction, IL-6 first binds IL-6R (IL-6 receptor, a cell surface receptor). After this binding event, the IL-6/IL-

O.J.M. received support from the Elaine Galwey Memorial Research Bursary and the American Thoracic Society (ATS) in the form of an ATS International Trainee Scholarship award and an ATS abstract scholarship award.

Originally Published in Press as DOI: 10.1164/rccm.202008-3169LE on September 21, 2020