Impact of prior corticosteroids therapy for airway diseases on COVID-19 clinical trajectory

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The coronavirus disease 2019 (COVID-19) outbreak has now infected over 35 million people worldwide. As SARS-CoV-2 infection spreads among the population, a breath of outcomes of the infection are becoming apparent, from asymptomatic individuals to severely ill and dying, from complete recovery to long-lasting symptoms1,2 . With a second wave of infection ongoing, it is more important than ever to rapidly assess the risks of COVID-19 complications and their consequences, which may not be as benign as first anticipated. Understanding the key elements that determines the outcome of the infection is essential in identifying at risk individuals and improving disease management.

Acute and chronic inflammation damages tissues that can lead to dysfunctions that can have drastic consequences on health. Accordingly, in COVID-19 there is a strong pro-inflammatory response combined to an ineffective anti-viral response3 . This leads to a hyperinflammatory state in a subset of COVID-19 adult patients with severe and often deadly complications4 . This hyperinflammation in severe COVID-19 patients includes elevated levels of C-reactive protein (CRP), ferritin, fibrinogen, interleukin (IL)-6 and D-dimers5–7 . Both IL-6 and CRP are important modulator of neutrophilic inflammation, that we and others have proposed as key regulators of thrombosis in COVID-19 5,8,9 (Fig. 1). This suggests that neutrophilic inflammation is a mediator of complications in COVID-19 that involves activation of innate immune signalling pathways that can be tractable therapeutic targets.

Corticosteroids (CS) have long been the main-stay therapy in many hyperinflammatory syndromes, including airway diseases. Their rapid immunosuppressive effects have, throughout the years, made them the ideal candidate for immuno-modulation in Acute Respiratory Distress Syndrome (ARDS) as they have been shown to improve oxygen saturation and inflammatory markers amongst improvements in other clinical manifestations10 . Given that lung injuries and ARDS are associated with adverse outcomes in coronaviruses infection, the use of CS have been proposed. Dexamethasone has been recommended to treat severely ill COVID-19 patients in intensive care unit, requiring respiratory support11 . However, the impact of CS on early infection is not fully known. At the early stage of SARS-CoV-2 infection, the host inflammatory response may be important in limiting viral progression. Therefore, at this early stage, CS therapy may have a negative impact on the COVID-19 clinical trajectory. Additionally, response to CS varies amongst individuals, suggesting that host factors (including genetic factors) may influence the complex interaction between SARS-CoV-2 in the presence of CS. To address this question, we will study participants to two provincial biobanks that suffer from airway diseases that involves CS therapy (severe asthma and chronic obstructive pulmonary disease (COPD)) to identify the various

endophenotypes present within the CS therapy subgroup that can influence COVID-19 trajectory. This will determine whether CS therapy prior or concomitant to infection impacts COVID-19 clinical trajectory in all the endophenotypes identified or just some particular groups.

We propose to apply a systems biology approach that uses an advanced computational pipeline to quickly and efficiently stratify individuals diagnosed with COVID-19 that are taking CS therapy, leveraging whole-genome data, transcriptome, and proteomic data from well-phenotyped biosamples of the “Biobanque Québécoise de la COVID-19” (BQC19, www.bqc19.ca). This will identify several endophenotypes present in COVID-19 that may be associated with different clinical outcomes. We will determine whether within the full landscape of COVID-19 clinical trajectories, some endophenotypes in the CS therapy subgroups have worst outcomes than others. Moreover, the molecular signature associated with the most at-risk group will provide insight into molecular mechanisms of CS therapy impact on COVID-19.