How sepsis parallels and differs from COVID-19

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“Nothing in life is to be feared. It is only to be understood.”

Marie Curie-Sklodowska

A recent meta-analysis indicated that the majority of severely ill COVID-19 patients (78%) met the Sepsis 3.0 criteria for sepsis/septic shock with acute respiratory distress syndrome (ARDS), as the most frequent organ dysfunction (88%). Thus, it is suggestive that COVID-19 in hospitalized patients should be inherently considered as sepsis. This perception is not widely shared, and varying views of COVID-19 and sepsis syndromes cloud the understanding of their pathophysiology. Given that Sepsis 3.0 definition is relatively inclusive, it is imperative to understand the similar and distinctive phenotypic features of both conditions, to maximize treatment benefits and reduce harm.

In the context of COVID-19, ARDS is a prominent contention element. Namely, to what extent a SARS-CoV-2-induced ARDS is comparable/dissimilar to a bacterial-origin ARDS. Both ARDS forms are paralleled by a decreased lung compliance, inflammation, hypoxemia, hypercarbia and endothelial injury. Conversely, COVID-19 ARDS features a robust alveolar thrombosis accompanied by an excessive fibro-proliferative lung tissue remodeling. Another phenomenon for COVID-19 respiratory failure, not observed in other etiologies, is the so-called “silent hypoxemia” (a critically low pO2 accompanied by mild dyspnea). Silent hypoxemia is especially detrimental, as it delays timely therapeutic management and facilitates multi-organ failure. Coagulopathy is frequent in both illnesses, yet COVID-19 derangements are far from the typical disseminated intravascular coagulation (DIC) encountered in bacterial sepsis. COVID-19-associated coagulopathy features highly elevated circulating fibrinogen, high D-dimers accompanied by a typically non-apparent thrombocytopenia and mildly affected clotting times. Both of those new manifestations constitute a medical terra incognita and require charting of new therapeutic maps.

Nearly three years of research have shed some light on the intricacies of the immuno-inflammatory response to COVID-19. It is apparent that the captivating “cytokine storm” label should be downgraded to a “cytokine drizzle”, as the levels of circulating proinflammatory cytokines (e.g. IL-6, IL-8, TNF) are at a fraction of the concentrations recorded in an non-SARS-CoV-2 sepsis/septic shock. In contrast to the systemic response, the lung compartment in the severely ill COVID-19 patients typically undergoes a robust, protracted inflammation. At the COVID-19 management level, there is no dominant break-through strategy, which would dramatically differ (apart from the antimicrobials/antivirals) from the established sepsis treatment bundle by the US National Institutes of Health guidelines. One important exception is the dissimilar efficacy of glucocorticoids (GCs). While the current sepsis guidelines feature a weak recommendation for GCs, their use for severe SARS-CoV-2 pneumonia is unequivocally beneficial. Biological mechanisms behind this disparity should be elucidated as the underlying reasons may galvanize a renaissance of GCs in bacterial sepsis and critical care in general.

There is a striking parallel between bacterial sepsis and COVID-19 phenotypes: the long-term sequelae. In both patient groups, the hospital discharge does not equal full recovery, but it is frequently followed by protracted, incapacitating consequences. While in bacterial sepsis, the post-discharge complications are referred to as post-sepsis syndrome and/or Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS), whereas, in SARS-CoV-2 infected patients, they are known as “long-COVID”. Long-COVID is not very different from post-sepsis syndrome. The most common persistent symptoms include fatigue, muscle pain, poor sleep, cardiac and cognitive disturbances (e.g. arrhythmias, short-term memory loss). Remarkably, a new, troubling difference exists: unlike in sepsis, long-COVID is frequently diagnosed in mildly SARS-CoV-2 infected patients (i.e. no hospital stay). The presence of the “long-phenotype” in both illnesses strongly indicates a severe and protracted deregulation of the immune-inflammatory (with clear immunosuppression features) and organ homeostasis. In the context of the slowly subsiding severe COVID-19 manifestations, we should re-focus on the long-term sequelae to evaluate a potential risk of increase in chronic debilitating in individuals.
repeatedly exposed to the virus, as SARS-CoV-2 becomes seasonal/endemic.

A comparison of the pre-clinical research in sepsis and COVID-19 brings several important lessons. A subjective (and largely undeserved) disappointment in pre-clinical bacterial sepsis studies has not been shared by COVID-19 modeling. On the contrary, despite logistic challenges, modeling of SARS-CoV-2 infection has demonstrated its robust utility. One of the key advantages of pre-clinical COVID-19 research is the rich palette of species (including non-human primates), while >90% of bacterial sepsis studies are performed in mice and rats. A multi-species approach considerably enhances reproducibility and translatability concurrently reducing idiosyncratic findings. Animal COVID-19 models were well-predictive of both successes (e.g. anti-SARS-CoV-2 monoclonal antibodies, remdesivir, vaccines) and failures (e.g. hydroxychloroquine, lopinavir/ritonavir) of clinically-tested substances. Given intuitive drive for benefits, the latter should not be underappreciated; “negative” findings hold a valuable life-/time and cost-saving potential. Notably, anti-TNF treatment in a clinically relevant mouse model of cecal ligation and puncture sepsis predicted failure of that therapy three years before the failed clinical trials. A clear pre-clinical parallel for sepsis and COVID-19 models exist: they both can be employed to cover identical research niches: i) mild-to-severe disease phenotypes, ii) defined cohort targeting, iii) selected pathophysiological insights (e.g. compartmentalization of responses). Furthermore, long-term sequelae can be effectively investigated in both bacterial sepsis and COVID-19 models.

Given that bacterial sepsis and COVID-19 parallels heavily intertwine with contrasts, it is critical to carefully dissect them into defined, manageable pieces of pathophysiological evidence (e.g. by a given system, compartment) before any further therapeutic action is recommended. Equally important is that we avoid a reflexive transplantation of ready-to-use preconceptions (eg, “cytokine storm”) from an existing disease while dealing with any new entity. Well-designed pre-clinical studies can aid in a translationally valid verification of virtually any of the above concepts at the fraction of time/costs required for a clinical trial execution.

Contributors
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Declaration of interests
None to declare.

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