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-Skłodowska

A recent meta-analysis[1] 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[2] 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.[3] Another phenomenon for COVID-19 respiratory failure, not observed in other etiologies, is the so-called "silent hypoxemia" (a critically low pO_2 accompanied by mild dyspnea).[4] 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.[4] 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.[5] 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.[6]

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).[7] 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).[8] 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 sequalae to evaluate a potential risk of increase in chronic debilitations in individuals,

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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.[9] 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.[10] 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 sequalae 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 (eg, 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

MFO and AH conceptualised the content/format of the commentary together; MFO provided the final editing. Both authors read and approved the final version of the manuscript.

Declaration of interests

None to declare.

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