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Reducing the global burden of sepsis: a positive legacy for the COVID-19 pandemic?

The European Society of Intensive Care Medicine (ESICM), The Global Sepsis Alliance (GSA)* and The Society of Critical Care Medicine (SCCM)

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The emergence of the SARS-CoV-2 virus in December 2019 and the subsequent coronavirus disease 2019 (COVID-19) pandemic has presented the world with the most serious health threat in living memory. The resultant pandemic has caused millions of deaths and unprecedented social and economic disruption. The response to the pandemic has also been unprecedented; countries have closed their borders, some have instituted draconian but effective public health measures, and the global scientific community has come together to produce robust research evidence and novel vaccines in record time. Mass vaccination programs are now underway, and while it is too early to know clearly their effectiveness in ending the pandemic, we can hope that this marks the beginning of the end.

The pandemic has put intensive care units, ventilators, vaccines, corticosteroids, and immunotherapies into the headlines of print and television news and all forms of digital and social media. The progress in response to COVID-19 stands in stark contrast to that of intensive care practitioners' signature condition, namely sepsis. Sepsis, defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" [1], is an umbrella term describing the clinical syndrome which can arise from infections caused by bacteria, viruses, fungi, and other micro-organisms. Recently, estimates for global, regional, and national sepsis incidence and mortality were published by the Global Burden of Disease Study [2]. In 2017, sepsis was estimated to affect

close to 50 million people and to cause or contribute to 11 million deaths, with over 3 million of those deaths being in children or adolescents [2]. Despite these harrowing statistics, decades of scientific enquiry, and literally billions of euros spent on clinical trials, there are currently no specific treatments effective for sepsis in general. Current efforts to reduce the global burden of sepsis are focused on improving public and healthcare worker awareness to avoid delays in diagnosis and treatment, and rapid treatment using appropriate antibiotics and bundles of supportive care focused on the common bacterial causes of sepsis [3].

Patients critically ill with COVID-19 satisfy the diagnostic criteria for sepsis and exhibit a phenotype and pathology with both similarities and differences to that of sepsis caused by other pathogens. Patients with severe COVID-19 suffer from multi-organ dysfunction, including acute respiratory distress syndrome (ARDS), vasodilatory shock, acute kidney injury, coagulation, brain, heart, and gastrointestinal dysfunction, representing the common manifestations that characterise sepsis. In fact, management guidelines for COVID-19 have been directly developed from similar sepsis guidelines [4].

COVID-19-induced sepsis also has features that appear unique. While children may develop multi-system inflammatory syndrome [5], they rarely suffer from severe COVID-19 in marked contrast to other forms of sepsis that result in the deaths of over 3 million children each year. Childhood deaths from sepsis occur mainly in low and middle-income countries, particularly in sub-Saharan Africa, and many are due to sepsis in relation to respiratory infections and diarrhoeal diseases [2]. SARS-CoV-2 overwhelmingly causes sepsis from respiratory infections whereas, although respiratory infections are the commonest cause of fatal non-COVID sepsis,

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infections at other sites cause a substantial proportion of non-COVID sepsis [2]. Other features differentiating COVID-19 include direct viral toxicity [6], pulmonary vascular injury, and a more marked hypercoagulable state [7]. The identification of these features has been made possible by the intense study of millions of cases of sepsis caused by this one unique and readily identifiable pathogen. Similar differentiating features may exist in subsets of patients with sepsis due to other individual pathogens that have not been subject to the same intense investigation, and which are not readily apparent in studies of heterogeneous populations infected with a wide variety of sepsis-inducing microorganisms. Another feature of COVID-19 to attract attention is the prolonged morbidity beyond the acute illness that has been termed “long COVID” [8]. This occurs not only in those who have been critically ill but is also reported in patients with much milder disease. That patients who survive other forms of sepsis suffer similar longer term ill effects is not well recognised [9]. Recent studies demonstrate up to 50% of sepsis survivors will suffer from a post-sepsis syndrome characterized by persisting physical, cognitive and psychological sequelae [9]. This ongoing morbidity represents an important but poorly quantified component of the global burden of sepsis.

In the absence of specific effective treatments, supportive therapies for organ dysfunction remain the mainstay of the treatment of non-COVID sepsis, and uncertainty remains about the safety and efficacy of many widely used adjunctive treatments. In contrast, the global research effort encompassing basic science and laboratory investigation together with rapidly-recruiting clinical trials has already provided robust evidence for and against the use of specific treatments for COVID-related sepsis. The demonstrated benefit of corticosteroids in reducing mortality from COVID-19 [10, 11], stands in stark contrast to the investigation of corticosteroids to treat non-COVID Sepsis where more than five decades of research and at least 40 clinical trials have resulted in equivocal evidence of their effectiveness [12].

There are clear, understandable, and justifiable reasons for the global response to COVID-19 being much greater than that for endemic sepsis. The virus is easily and rapidly transmissible causing many millions of cases and deaths in a short period of time. This has the potential to overwhelm health care systems and to cause unprecedented societal and economic

disruption. Nevertheless, looking toward the control of the pandemic is the appropriate time to consider how the response to the pandemic can inform efforts to substantially reduce the current and future global burden of sepsis. One of the most important aspects of COVID-19 has been the rapid generation of reliable evidence by platform trials, such as REMAP-CAP [13] as well as new clinical outcomes targets developed by the WHO [14]. Broad acceptance of these newer trial designs and outcome targets has facilitated research in COVID-19 that may also be applied in sepsis research.

The COVID-19 pandemic has dramatically illustrated the crucial role of policymakers in enacting public health regulations to control the spread of the virus, this success depends not only on close collaboration between clinicians but also on effective public messaging to achieve compliance. Public health measures targeted at preventing infection, notably vaccination and the provision of clean water and hygienic health care have the potential to dramatically reduce the burden of sepsis, particularly maternal sepsis and sepsis in children in low and middle-income countries. Additionally, policymakers actively supporting the embedding of clinical research into routine care, notably in the United Kingdom [15], has been crucial in generating public trust and engagement in clinical research. These are all recommended actions of the 2017 World Health Assembly resolution on improving the prevention, diagnosis, and clinical management of sepsis [16].

Similar to cancer, sepsis is a valuable overall term that could become recognizable to the public. Also similar to cancer, sepsis will benefit from more precise molecular definitions and identifying phenotypes more likely to respond to new therapeutics.

Recognising that sepsis results from a dysregulated host response to infection and the failure of prior research efforts to identify specific treatments, the research infrastructure, notably international adaptive platform trials, set up or adapted to rapidly investigate treatments for COVID-19 should be maintained and supported beyond the end of the pandemic. With an estimated 50 million cases of sepsis occurring each year, including even a small proportion of affected patients in such trials would allow us to determine which patients and which forms of sepsis are amenable to treatment with immunomodulators and other treatments, and to investigate how to prevent and treat the longer-term health effects of sepsis.

Planning for post-pandemic sepsis research and policy should start now. Reducing the global burden of sepsis, particularly in resource-poor settings, would be a fitting legacy for the tragedy of this global pandemic.

Specific actions based on the pandemic that will reduce the global burden of sepsis:

Recognition that sepsis, like cancer, is a valuable umbrella term describing a heterogeneous syndrome with a core underlying mechanism; a dysregulated immune response to infection

Recognition that sepsis caused by different pathogens and in different populations may respond to different treatment approaches

Fostering the understanding that increasing awareness of sepsis, education of the public and health care professionals on the prevention, early recognition, the need to manage sepsis as an emergency, and good training in supportive care will reduce sepsis mortality from all causes

Maintaining political and policymaker focus on public health measures that can reduce the global burden of sepsis and by following the requests of the WHO sepsis resolution to integrate sepsis in the national health strategies of all member states

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