COVID-19: collaboration will keep us ahead of the curve

There have been few disruptions to life on a global scale in any of our lifetimes like SARS-CoV-2 infection, and even fewer where the response has depended so heavily on us as a medical community. The COVID-19 pandemic has not only been responsible for a significant loss of life, but also far-reaching human, social and economic devastation. It is blatantly clear that this entity is far more challenging in practice than many other serious infective threats from the recent past. The impact and pace of the pandemic consequently demand a new agility and adaptability from the health profession to modify rapidly systematic approaches to tackle it. Although many scientific advances have been made, significant knowledge gaps remain, in particular regarding immunopathogenesis and treatment, and there is an urgent need for a coordinated and collaborative response.1,2

SARS-CoV-2 is a difficult combatant. Enhanced infectivity, prolonged incubation period, asymptomatic transmission and significant mortality, in particular from the cytokine storm induced by the illness, have precipitated a global health crisis.3 COVID-19 presents a distinctly new threat, and until sufficient knowledge is progressively accumulated, health efforts have been limited by multiple factors: an as yet incomplete understanding of the pathogenesis underlying mortality in this disease, the absence of an established clinical algorithm to recognise those at greatest risk from this disease, and a paucity of medical therapies proven to influence the disease course.4 Although there is excellent work being done at an unprecedented rapid pace, success requires cross-disciplinary collaboration at the bedside and laboratory to facilitate aggregation of clinical experience and leverage upon unique subspecialty skills.

The pressing need for the exchange of knowledge and pre-existing experience among healthcare providers is visibly demonstrated when considering the role of the host immune system in COVID-19. The predisposition for SARS-CoV-2 to result in a critical illness associated with acute respiratory distress syndrome (ARDS) remains a unique clinical challenge.5 This typically occurs in the second week of infection, notably when the viral load is falling, attesting to the role of the host inflammatory response.6 When COVID-19 causes this rapid respiratory failure and multiorgan dysfunction, it parallels the clinical and laboratory features of a cytokine storm syndrome, with substantial associated mortality.6,7 Ordinarily, after the initial immune activation for the clearance of infection, homeostasis is achieved through an immune suppression phase potentially harnessing anti-inflammatory cytokines such as interleukin-10.8 In the hyperinflammatory phase of COVID-19, however, dysregulation of the host immune system appears to result from unrestricted T-cell activation by infected antigen-presenting cells and activated macrophages that have not been cleared. The resultant positive feedback loop causes hypersecretion of key proinflammatory cytokines including interleukin-1, interleukin-6 and tumour necrosis factor-alpha, responsible for much of the aggressive clinical deterioration seen in patients with COVID-19.9 The consequences of this uncontrolled systemic inflammatory response are dire: unremitting fevers, haemodynamic instability due to vascular leakage, activation of the coagulation cascade, and ARDS with resultant respiratory failure and death. This highlights one of the most dangerous and yet peculiar difficulties in COVID-19: its harm arises not only from its infective pathology but also from the discordant multisystem inflammatory response it provokes, even as the viral load diminishes.

Although COVID-19 is an infective threat we are still trying to understand, the process of cytokine release is a familiar foe to clinicians with inflammatory disorder experience. A similar hyperinflammatory state has been much better elucidated in more long-standing phenomena including macrophage activation syndrome in rheumatic diseases, cytokine release syndrome in CAR T-cell therapy, secondary haemophagocytic lymphohistiocytosis (HLH) in the context of other diseases, or primary HLH in a genetically susceptible individual.9–11 The unrestricted T-cell activation in COVID-19 is phenotypically and pathophysiology similar and as such, established tools, including risk stratification algorithms and cytokine-targeting therapies, should be similarly considered to mitigate the impact of the host immune response in driving rapidly progressive tissue damage and systemic organ failure. Following the established utilisation of therapies targeting the interleukin-6 and interleukin-1 pathways in these analogous clinical phenomena,12,13 there is early promise of benefit in life-threatening COVID-19.14,15 Given the pace of COVID-19, both in terms of individual patient deterioration and spread across populations, we cannot solely rely on our conventional methods of systematic knowledge accrual to manage COVID-19, and must borrow these insights from other areas of medicine to match the speed at which this new enemy is moving.
This leverage from collaboration is particularly important given the fickle yet deadly nature of these hyperinflammatory syndromes. By the time the cytopenias, coagulopathy and hyperferritinemia blossom in the cytokine storm in COVID-19, they are but downstream indicators of a process that has well and truly taken hold.16 This puts greater weight on early recognition in order to act before it is too late, a process best achieved with the more intimate understanding that collective wisdom can bring, to understand differences as well as similarities. Harnessing lived experience in identifying this phenomenon before it is well established might deliver better risk stratification algorithms and facilitate presciently early intervention for patients in danger of serious adverse outcomes, as well as delivering an appreciation of the strengths and weaknesses of potential therapeutic approaches in practice. This is not to underplay the crucial role of well designed clinical trials in providing solid evidence regarding these therapeutic approaches in due course; however, we should look to what we have learnt from similar disease processes to inform these trials and interim clinical practice. If we know that poor outcomes correlate with well established signs of a cytokine storm, and we have experience with this rapid and deadly complication, not to draw substantially from the existing knowledge pool would be to miss an opportunity to best face this existential challenge.3,17

While the cytokine storm syndrome in COVID-19 provides a prime example for the need to collaborate to find the fastest route to a solution, it is by no means the only area of COVID-19 that will benefit from this approach. Beyond the rheumatologists, clinical immunologists and haematologists who might support our critical care physicians, respiratory physicians and infectious diseases physicians, it is likely that a diverse array of specialties will be stewards of expertise important in the fight.18 To ignore that, and rely on the slow accumulation of direct experience of COVID-19 clinical care will cost lives; our ability to collate efficiently our collective relevant experience will ultimately aid our success in fighting a pandemic where we do not have the luxury of time. While critical initiatives by bright minds are underway, siloed efforts are inherently limiting. Indeed, this pandemic has the capacity to accelerate the medical community towards a positive unification of efforts, which is an upside that we should embrace, not neglect. We will be more powerful, efficient and effective against this foe when we work together, across disciplines, towards finding a collective solution to the healthcare crisis of our generation.

Received 3 May 2020; accepted 7 May 2020.

doi:10.1111/imj.14888

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Navigating shifting waters: rapid response to change in the era of COVID-19

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China in December 2019 has resulted in a global COVID-19 pandemic and a consequent rapid transformation of medical practice in 2020. Overseas, distressing reports of overwhelmed health systems, healthcare workers losing their lives and shortages of personal protective equipment (PPE) have created significant anxiety and catalysed rapid action across Australia and New Zealand. Enormous effort has been invested in developing screening clinics; redesigning general practice, hospital inpatient wards and emergency departments (and the models of care used within them) and expanding intensive care capacity. Public and private pathology services have rapidly expanded their capacity to meet the testing demand. As of 6 May, 664,756 tests for SARS-CoV-2 have been performed in Australia, representing 2611 tests per 100,000 people. Fundamental changes to general practice have also occurred rapidly; across five Australian Primary Health Networks, weekly face-to-face consultations dropped from around 300,000 to 200,000 per week from February to April 2020; in the same period, telephone/telehealth consultations in general practice rose from 0 to 120,000 per week, now representing 40% of consultations overall. As of 17 April 2020, cumulative COVID-19 related deaths reported to the World Health Organisation (WHO) from New Zealand and Australia were around 0.25 per 100,000 population (similar to those reported by Singapore, Japan, South Korea and China—all <1 per 100,000). In contrast, the cumulative reported mortality in Germany (4.6 per 100k), the United States (8.5), the United Kingdom (20.2) and Italy (36.7) ranges from 18 to 145 times that reported from Australasia. However, even these stark figures are almost certainly underestimates of total deaths attributable to COVID-19 based on analysis of excess mortality in the most affected populations. The other result is that we now have time, time to ensure the health system preparations we have put in place are ready to be activated at an unknown point in the future. The result of sacrifices made is that we have been spared the enormous morbidity and mortality experienced by most countries.