Two Key Takeaways From a Year of Pandemic Research

The achievements realized in the last year of coronavirus disease 2019 (COVID-19) research are nothing short of astonishing; the virus was sequenced, clinical tests were established, the epidemiology was characterized, numerous therapeutics were tested, and a number of different vaccines were developed and approved. Gains that would typically take years were realized in months, with progress documented through tens of thousands of scholarly publications disseminated globally, most of them available for free. This impressive rate of progress has also been evident in research directed specifically toward COVID-19 in its most severe form, with the global critical care community embarking on an unprecedented, coordinated project to generate new insights into the biology, treatment, and prevention of life-threatening COVID-19. These efforts rapidly generated evidence that has already changed practice. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial provided rapid, emphatic evidence that hydroxychloroquine (1) and lopinavirritonavir (2) were ineffective, and then that dexamethasone could reduce the risk of death in the sickest patients (3). Randomized, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) confirmed that another steroid, hydrocortisone, was also effective (4) and then discovered persuasive evidence of benefit from specific inhibitors of interleukin-6 (5). We learned that other treatments such as systemic anticoagulation and interferon therapy (5) may be harmful in this group but could confer benefit in those less sick. We also learned that the propensity to develop severe COVID19 was associated with clinical risk factors like age, hypertension, and diabetes (6–8), as well as specific genetic features related to innate viral defences and lung inflammation (9–11).

Just as stunning as the speed of discovery in the COVID-19 era is its stark contrast with the era of critical care that preceded it. Prior to 2020, randomized trials in the ICU showing a significant difference between treatment groups were very much the exception, rather than the rule. Paradoxically, many of these studies were done in the very syndromes that characterize severe COVID-19, namely sepsis and the acute respiratory distress syndrome (ARDS). Why have these syndromes, so long resistant to the identification of effective treatments, suddenly given way to a wellspring of definitive results? We suggest that recent successes are the result of two key factors: the biological homogeneity of severe, late-stage COVID-19, and the unprecedented international collaboration enabling recruitment at scale. The first of these considerations speaks to a growing recognition that critical illness syndromes are biologically heterogeneous (12–14). Evidence of subtypes in these conditions is rapidly mounting, including in sepsis (15–18), ARDS (19–21),

and pancreatitis (22). This heterogeneity means that patients enrolled in randomized controlled trials based on syndromic criteria constitute a mix of physiologic states. In the case of an effective therapy, this leads to heterogeneity of treatment effects; some patients benefit from the treatment, others are unaffected, and others still may be harmed. On balance, the average effect is neutral, and the trial is interpreted as showing no benefit. COVID-19 is different. Although there is tremendous heterogeneity in the biological response to infection with the severe acute respiratory syndrome coronavirus 2 virus and considerable variation in the characteristics of those presenting to hospital (23), those who progress to the need for ICU care and mechanical ventilation likely represent a group with more homogenous underlying biology (8). Patients with ARDS may have acquired this condition due to pneumonia, aspiration, trauma, or other conditions. Similarly, patients with sepsis may have infections of various different organs and body sites, arising from various different pathogens. By contrast, patients with severe COVID-19 share a common triggering event that mostly results in single-system organ failure characterized by severe, prolonged hypoxemia. Briefly stated, the ICU acts as a sort of filter in COVID-19; the heterogeneity that leads some patients to improve quickly and others to experience a milder course is abrogated, leaving a more biologically uniform subset of critically ill patients. This filtering function is less evident in non-COVID critical illness,

which may be triggered by a wide range of insults, and progress to a wide range of clinically and biologically heterogeneous states. A 20 years old with pyelonephritis and an 80 years old with bacterial pneumonia might both be admitted to an ICU with septic shock, but this does little to filter out the heterogeneity inherent in that condition. These two patients have vastly different prognoses and may have different underlying biological processes driving their illness. They are all but certain to have different risk-benefit profiles for any effective treatments. In contrast, the biological homogeneity in COVID-19 leads to greater homogeneity of treatment effects and a higher likelihood that well designed studies will yield positive results. Admission to ICU in COVID-19 thus exemplifies both prognostic enrichment and predictive enrichment, which stand to vastly enhance the efficiency of randomized trials. The second consideration—international cooperation on an unprecedented scale—impacts not only on sample

size (best exemplified by the World Health Organization– led Solidarity trial) but also on the generalizability and global acceptance of results. In our experience, clinicians who participate in a trial are more likely to change their practice based on the results. Perhaps, the best demonstration of this is in the RECOVERY trial, which initially only recruited in the United Kingdom. Practice across the United Kingdom changed immediately when the dexamethasone result was revealed by press release (24). In contrast, clinicians in other countries understandably waited for the preprint, or the peer-reviewed article, before prescribing steroids for COVID-19 patients. Power calculations for critical care trials in the past have reflected both optimism and pragmatism on the part of the investigators, who often hypothesize an outsize effect of the therapies they are studying, leading to more manageable sample sizes needed to complete enrollment (25). The large effect sizes seen with anti-inflammatory treatment for COVID-19 suggest that this optimism may in fact be warranted; there is potential for similar effect sizes in other critical illness syndromes, if only we can get the diagnoses right. Likewise, the pace of recruitment into many COVID-19 trials shows how we might allay some of the pragmatic concerns around recruitment through the deployment of coordinated national and international networks. Progress has been made in this regard, but it is slow. ICU studies of thousands of patients are increasingly common, but it typically takes years to accrue the sample, often with broad inclusion criteria that exacerbate the first problem of biological heterogeneity. Building on a longstanding tradition of collaboration and cooperation in critical care research and on specific preparation for outbreaks (26), investigators studying severe COVID-19 have been able to rapidly stand up large networks both within and across international borders (27). The Genetics of Mortality in Critical Care (GenOMICC) study has been recruiting patients in the United Kingdom since 2016 with a view to examining the genetic underpinnings of critical illness. Designed as an “open source” trial, documents related to grant applications, research ethics, patient and caregiver consent, and study protocols are all freely available, enabling investigators worldwide to launch a fully compatible effort in other jurisdictions. GenOMICC is now enrolling in Canada, with other countries soon to follow, and recently identified a number of genetic loci associated with severe, lifethreatening COVID-19 (11).

The REMAP-CAP platform is one of the most illustrative examples of a globally coordinated interventional study, in which multiple therapeutic domains have been rapidly studied through harmonized clinical trial protocols and centralized data analysis (28). Results regarding the effectiveness of antivirals and immunomodulators came quickly, and preexisting clinical trials were seamlessly incorporated into the platform, thanks to the dedication, openness, and collegiality of their investigators. In one illustrative case of this cooperation, investigators from the Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC), Antithrombotics for Adults Hospitalized With COVID-19 (ACTIV-4), and REMAP-CAP studies—all of which have been examining the efficacy of systemic anticoagulation in COVID-19—decided to harmonize their protocols and data, leading to

the rapid accrual of more than 5,000 patients, and actionable findings about the utility of anticoagulation in both moderate and severe COVID19. These results speak to the tremendous potential of international collaboration, which also confers an added benefit; studies enrolling diverse cohorts in disparate locales are more robust and more likely to generate lasting, generalizable findings. The response to the COVID-19 crisis charts a course for critical care research in the coming decades that stands to quell an earlier sense of nihilism in the critical care community. With two key takeaways from the pandemic in mind, actionable, timely evidence can be generated. First, efficient studies will enroll biologically homogenous disease states, and second, they will do so by leveraging multinational networks that can recruit on a massive scale. Of course, all of this will be easier said than done. Global collaboration is fast becoming part of the fabric of critical care research, but challenges persist related to differences in regulatory, legal, and research ethics environments. The collection and harmonization of multijurisdictional data is also an important technical challenge. Finding biologically homogeneous states to study might also prove difficult. Sepsis and ARDS may be the most obvious examples of heterogeneity in critical care, but they are not the only ones; delirium can be both hypoactive and hyperactive, acute kidney injury can be both oliguric and nonoliguric, patients with the same type of blunt trauma can progress in vastly different ways, and so on. Reassuringly, subtype discovery in critical care continues to mature, leveraging large datasets from molecular and genomic studies, electronic health records, and physiologic monitoring systems. Once identified, these subtypes can be factored into the design of pragmatic randomized trials. Although these are challenges that must be addressed, the pandemic has shown us how they can be overcome. A crisis like the current global pandemic unearths new and urgent needs, reveals new truths, and presents new challenges, which if surmounted stand to confer benefit not just in resolving the crisis itself but well into the future. The critical care research response to COVID-19 has done just this, providing invaluable tools in dealing with the current pandemic, while also showing through its successes how critical care research might extend its recent string of breakthroughs in the postpandemic era