EDITORIAL

# Critical Illness in Patients With COVID-19
## Mounting an Effective Clinical and Research Response

Deborah J. Cook, MD, MSc; John C. Marshall, MD; Robert A. Fowler, MDCM, MS

**Dedicated, impassioned, and exhausted** clinicians the world over are collaborating to report the emerging profile of the coronavirus disease 2019 (COVID-19) pandemic. The unparalleled need for intensive care during this period challenges clinicians to bring their best efforts to the bedside, while advising health care leaders on the optimal management of resources to deliver that care in each jurisdiction. A renewed sense of community is avowed among critical care clinicians who share their early observations through traditional and social media, such that learnings from one group of patients can inform the care of the next.

Related article

The multicenter report by Grasselli and colleagues in *JAMA* provides sobering evidence about the burden of critical illness associated with COVID-19 in Lombardy, Italy.[1] Of the 1591 predominantly older, male patients with comorbid conditions admitted to the intensive care units (ICUs) of 72 hospitals from February 20 to March 18, 2020, the majority had moderate to severe acute respiratory distress syndrome (ARDS). Overall, of the 88% of patients who underwent endotracheal intubation and mechanical ventilation, the median level of positive end-expiratory pressure (PEEP) was 14 cm $H_2O$. In this cohort, 11% received noninvasive ventilation, exposure to which may have been even more extensive outside the ICU, in original or repurposed high-dependency units for patients with COVID-19, and 27% received early prone ventilation, reflecting the growing reports of using this strategy. By the end of the follow-up period, 26% of patients had died while 58% remained in the ICU. As reported in other series, older patients appeared to have the worst outcomes.[1]

The demographic characteristics of the Italian population in this study differ in some respects from earlier experiences in China. Both countries reported male sex, older age, and hypertension as risk factors for severe COVID-19 disease. However, more patients in this series received invasive ventilation, which may reflect inherent differences in clinical presentation, ICU admission criteria, or approaches to management. The massive and acute strain on normally limited ICU resources is striking. Over a period of 28 days, close to 1600 patients, most of whom required ventilatory support, were admitted to 72 Italian ICUs, an average of 22 patients per ICU. Moreover, the median ICU length of stay was 9 days. This demand far exceeds the capacity of even the best-resourced health care system and points to the potential morbidity and mortality awaiting in less-resourced areas.

Transparency in reporting the experience of patients and physicians in some parts of the world helps to telegraph what could lie ahead in other parts. Thus, pandemic-focused studies that document the presentation, clinical characteristics, and prognosis of patients with COVID-19, such as this one from northern Italy,[1] helps inform patient care elsewhere. Efforts by this consortium to gather data by telephone augmented the real-time data collection and retrospective review of hospital records that formed the basis of this report. Observations from Lombardy also inform investigators planning much-needed interventional trials by considering rates of life support utilization, fatality, and the frequency and severity of morbidity outcomes for patients with COVID-19–related critical illness. Context matters in this regard, because illness trajectories are dependent on each setting and circumstance.

Worldwide, an imperative to quickly design and conduct pandemic-focused treatment studies is understood. That clinical research is a societal good is particularly germane in these times. However, there are many barriers to research implementation in the ICU during a pandemic.[2,3] These include treatment under uncertainty and surge conditions, the understandable urge to use untested interventions, employee and equipment shortages, risk of health care worker infection, and research staff deployment to provide clinical care. The influenza A (H1N1) pandemic was an unwelcome reminder of the need to reduce regulatory redundancy and develop protocols, including "sleeper trials" in advance of when they would be required, to accelerate the acquisition of answers once a pandemic arrives.[4] Even in settings with preparedness planning, the pace of the COVID-19 pandemic may preclude some newly coordinated trials from culminating in robust results. Early efforts have already been published, such as the randomized trial by Cao and colleagues that tested the combined protease inhibitors lopinavir and ritonavir.[5] Many other trials are forthcoming.

Rising to the challenge of rapidly launched and interpreted treatment trials, adaptive trial designs can accelerate the evaluation of COVID-19 therapies.[3] Adaptive trials hold the promise of minimizing harm to participants by exposing fewer patients to the treatment burdens and risks, while maximizing treatment benefits for the greatest number of participants.[6] Protocol modifications are expected rather than discouraged while adaptive trials are underway, such as enriching, refining, or repressing enrollment of patients with particular genetic, biological, physiological, or clinical profiles. Anticipated modification to the interventions being evaluated in adaptive trials are additions (newly identified auspicious therapies); adjustments (changes to or deletion of unfavorable drugs or devices); and abandonment (for reasons of benefit, harm, futility, or supply shortages).

The Randomized Embedded Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP), for example, was conceived in the wake of the 2009 H1N1 influenza pandemic for the express purpose of having a randomized trial actively recruiting patients at the onset of the next pandemic.[7] REMAP-CAP has now shifted its focus to COVID-19 and is actively recruiting patients in the European Union, UK, Canada, Australia, New Zealand, and Saudi Arabia. New domains relevant to the emerging understanding of COVID-19 disease are being developed and integrated. With hope and a leap of faith in this pandemic, participants will consent to eventualities that neither they, nor the investigators, may fully envision. Trials not yet launched will benefit from early decisions made in adaptive trials already launched. Data and safety monitoring boards will shoulder difficult decisions. In this light, open data sharing will take on a renewed sense of purpose.

Many other national and international research efforts are underway. Leaders of international investigator-led clinical research consortia[8] and critical care clinicians[9] have joined to promote a scientifically rigorous, geopolitically inclusive, and academically collegial response to this pandemic challenge. Rather than driven by individual investigators or a small number of consortia, the blueprint for another adaptive randomized global platform trial is now established and a growing number of countries have committed to contribute to this alliance by merging with this World Health Organization–led trial, aptly named SOLIDARITY.[10] Effectiveness will be examined through frequent interim analyses so that the most promising therapies will continue to be evaluated while the least effective are discarded. This "continually learning trial" may prove to be one of the largest international platform trials conducted in a pandemic period and represents an aspirational approach of universally coordinated efforts to help treat those affected by COVID-19.

As described by Grasselli et al,[1] the number of critically ill patients presenting to Italian hospitals—as in China, Iran, Europe, and now many cities in the US—highlights the fragility of health care systems to care for the most severely ill patients in even the wealthiest countries. It has been estimated that, just over a century ago, approximately 3% of the world's population died as a result of the 1918 pandemic influenza.[11] In modern times, many of these patients would survive if they could be treated in an ICU. Much of the world still lacks that resource[12] and patients fare worse in pandemic periods in such settings.[13] However, without space in hospitals, and with insufficient ventilators and other life support measures, personnel, and protective equipment, the ability to support patients with COVID-19 is threatened everywhere. The moral distress of rationing health care resources is inevitable in many corners of the world during this pandemic.[14]

Pandemics do not affect all locations with the same intensity at the same time. By calling forth shared humanity in the face of COVID-19–related morbidity and mortality, supporting close and distant neighbors reciprocally, and encouraging practical, creative solutions,[15] the pandemic burden may be attenuated. Taking this road less traveled demands a different kind of solidarity: care without borders to help those in need when they need it most.

Months ago, there was no clear indication that COVID-19 was coming. Today there is no clear indication of how or when it will end. An extraordinary ferment of courage, compassion, and collaboration will be essential to fuel an effective multifaceted response to this devastating pandemic.

## ARTICLE INFORMATION

**Author Affiliations:** Medicine (Critical Care), Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada (Cook); St Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada (Marshall); Sunnybrook Hospital, University of Toronto, Toronto, Ontario, Canada (Fowler).

**Corresponding Author:** Deborah J. Cook, MD, MSc, McMaster University, Department of Epidemiology & Biostatistics, 1200 Main St W, Hamilton, ON L8N 3A5, Canada (debcook@mcmaster.ca).

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**Additional Information:** Dr Cook is a Research Chair of the Canadian Institute of Health Research.

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