In Response

Thank you for the opportunity to respond to the letter by Dr Subedi wherein he has raised some very important points about managing the coronavirus disease 2019 (COVID-19) pandemic when working in a low-resource environment.

It seems that Nepal has been very effective in coping with the pandemic thus far. Nevertheless, as in other countries, there are huge stresses placed on all health care workers (HCWs), both physically and mentally. As he says, governments need to recognize them for their commitment and loyalty to their patients. Certainly, the general populations in many countries have done so as evidenced by the singing (Italy), playing of musical instruments (Spain), and even banging of pots and pans (United States and Canada). But HCW, and others maintaining systems during the crisis, need more than that. He outlines some of the important things, such as proper sleep, food, and connections with loved ones. We could add others such as peer support and professional support when necessary. National and international anesthesia societies have also addressed this issue as have publications in journals such as *Anesthesia & Analgesia.*

Another interesting point raised by Dr Subedi is that of the role of private hospitals versus public during the pandemic. Each country will have come to its own solution on this problem. The Republic of Ireland chose a different route which certainly gained public support coordination between the 2 sectors. The Republic of Ireland, for example, has been an example of excellent management of supplies and services. Each country will have come to its own solution on this problem, but was not without its challenges. In low-income countries, there are huge stresses placed on all health care workers (HCWs), both physically and mentally. As he says, governments need to recognize them for their commitment and loyalty to their patients. Certainly, the general populations in many countries have done so as evidenced by the singing (Italy), playing of musical instruments (Spain), and even banging of pots and pans (United States and Canada). But HCW, and others maintaining systems during the crisis, need more than that. He outlines some of the important things, such as proper sleep, food, and connections with loved ones. We could add others such as peer support and professional support when necessary. National and international anesthesia societies have also addressed this issue as have publications in journals such as *Anesthesia & Analgesia.*

Another interesting point raised by Dr Subedi is that of the role of private hospitals versus public during the pandemic. Each country will have come to its own solution on this problem. The Republic of Ireland chose a different route which certainly gained public support coordination between the 2 sectors. The Republic of Ireland, for example, has been an example of excellent management of supplies and services. Each country will have come to its own solution on this problem, but was not without its challenges. In low-income countries, private hospitals may be much better equipped than public hospitals; in such cases, governments will need to negotiate with them as to how they may best serve their nation’s needs.

Finally, there is the issue of inadequate supplies of personal protective equipment (PPE). This has been a problem almost everywhere but nowhere more so than in low-resource environments. Governments have rapidly reduced barriers to local production. Companies have been very creative but still the deficit exists. Much has been written about how to extend the life of PPE. Use of proper PPE is essential in protecting HCWs everywhere but especially in countries where they are a scarce commodity to be treasured and safeguarded. As noted in our article, the loss of HCWs after an epidemic can be substantial and can have long-lasting effects on the health care systems they serve.

The pandemic of COVID-19 is challenging governments, health care systems, and HCWs as never before. We need to support each other as we find our way through this. It seems that the old advice of Semmelweis to wash our hands frequently and the new advice of public health to work together by staying apart will serve us all well.

**Choon-Looi Bong, MBChB, FRCA**

Duke-National University of Singapore (NUS) Medical School
Singapore

Yong Loo Lin School of Medicine
Singapore

Department of Paediatric Anaesthesia
KK Women’s and Children’s Hospital
Singapore

**Christopher Brasher, MBBS, FANZCA**

University of Melbourne
Melbourne, Victoria, Australia

Department of Anaesthesia and Pain Management
Royal Children’s Hospital
Melbourne, Victoria, Australia

**Edson Chikumba, MBChB, MMed (Anaesthesia)**

Department of Anaesthesia and Critical Care Medicine
College of Health Sciences
University of Zimbabwe
Harare, Zimbabwe

**Robert McDougall, MBBS, FANZCA**

University of Melbourne
Melbourne, Victoria, Australia

Department of Anaesthesia and Pain Management
Royal Children’s Hospital
Melbourne, Victoria, Australia

**Angela Enright, MBCh BA, FRCP**

Department of Anaesthesia
University of British Columbia
Royal Jubilee Hospital
Vancouver, British Columbia, Canada
acenright1@gmail.com

**REFERENCES**


Hypotension, Systemic Inflammatory Response Syndrome, and COVID-19: A Clinical Conundrum

To the Editor

Clinicians who have treated large numbers of critically ill patients with coronavirus disease 2019 (COVID-19) would generally agree on several core observations: (1) intensive care unit (ICU) admissions for COVID-19 patients occurred almost exclusively for worsening respiratory failure; (2) doses of sedatives and analgesics to facilitate mechanical ventilation in COVID-19 patients were substantial elevations when compared with critically ill patients without COVID-19; and (3) systemic hemodynamics of most COVID-19 patients, including those with acute respiratory distress syndrome (ARDS), were remarkably preserved, unless heart failure, an acute thrombotic event, or superimposed bacterial sepsis complicated the disease.

The first clinical description of ICU admissions for COVID-19 in the United States concluded that “most patients did not present with evidence of shock.” This is supported by a larger study from ICUs in New York City area where median lactate value of 223 studied critically ill patients was 1.5 mmol/L. Isolated cases of COVID-19-induced shock continue to be discussed as case reports.

Hence, the most typical clinical picture of a critically ill patient with COVID-19 that one encounters in the ICU is a patient who is deeply sedated and sometimes paralyzed, has a severely impaired alveolar gas exchange, and requires none or relatively low doses of intravenous vasopressors (eg, norepinephrine at rates typically lower than 5 μg/min). These mild degrees of hypotension can often be attributed to high doses of sedatives, positive pressure ventilation with high levels of positive end-expiratory pressure (PEEP), restrictive fluid management, and aggressive diuresis. In the absence of elevated lactate, these physiologic characteristics do not fulfill criteria for shock. In our experience, many patients in fact required resumption of their home antihypertensives while being mechanically ventilated.

These observations of preserved hemodynamics and the absence of shock in a syndrome that has been characterized by “cytokine storm” with markedly elevated levels of certain interferons, interleukins, and chemokines are curious and stand in contrast to other cohorts of critically ill patients with ARDS who commonly present with distributive shock and require fluid resuscitation and higher levels of hemodynamic support.

Due to significant increases in plasma levels of interleukin (IL)-6 in COVID-19, similarities have recently been drawn to cytokine release syndrome and acute lung injury that sometimes occur after chimeric antigen receptor (CAR) T-cell therapy. Consequently, trials targeting IL-6 are ongoing in patients with COVID-19. Having managed patients after CAR T-cell infusions ourselves, we must question these proposed similarities between COVID-19 disease and CAR T-cell therapy—CAR T-cell patients with cytokine release syndrome often require large amounts of fluid resuscitation due to capillary leak, resulting in pulmonary or even airway edema, and hypotension is often present even in milder cases of cytokine release resulting in the need for vasopressor support in the ICU.

With these observations and data as a backdrop, one now needs to reconcile the following: we have historically attributed the hypotension of ICU patients with sepsis and ARDS to the “systemic inflammatory response syndrome (SIRS)” after ensuring that patients are euvolemic and their cardiac function is adequate. We have believed that SIRS drives vasodilation, capillary leak, and hypotension. Critically ill COVID-19 patients with ARDS who commonly present with distributive shock and require fluid resuscitation often have high levels of inflammatory markers (eg, ferritin, C-reactive protein) and proinflammatory cytokines. Distributive shock, however, is rare compared to other patients with similar inflammatory cytokine elevations (non-COVID sepsis, ARDS, CAR T-cell therapy). In addition, lactate levels have been only rarely reported in large COVID-19 observational studies, and we may only hypothesize that this is due to their generally normal values.

While COVID-19–related ARDS has been proposed to be a “unique type of ARDS” (due to extensive microcapillary thrombosis, pulmonary angiogenesis, preserved respiratory system compliance in a subset of patients), it is also important to investigate why this hyperinflammatory syndrome is accompanied by a remarkably preserved hemodynamic picture. Clearly not all severe systemic inflammatory responses are equal.

Dusan Hanidziar, MD, PhD
Edward A. Bittner, MD, PhD

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