A Call for Rational Intensive Care in the Era of COVID-19

To the Editor:

As intensive care physicians, we have been trained to treat viral pneumonia and its attendant complications of acute respiratory distress syndrome (ARDS) and multiorgan failure. The coronavirus disease (COVID-19) pandemic has challenged our profession to revisit its paradigms. Specifically, do mechanical ventilation strategies optimized in ARDS trials still apply to this disease? Is our policy of waiting for proof of benefit before instituting novel therapeutics still sensible? In this commentary, we make the case that the ICU is already optimized for the care of patients with COVID-19 and that departures from our standard of care require evidence, not vice versa.

We have learned from decades of critical care research and experience that protocol-driven, physiologically based management strategies result in improved patient outcomes, particularly for ARDS (1). The Berlin Definition established criteria for ARDS based on its acute clinical presentation in the presence of hypoxemia and radiographic pulmonary edema not arising entirely from hydrostatic mechanisms (2). We, along with other intensivists, have observed that some patients with COVID-19–induced ARDS exhibit higher than expected lung compliance that seems out of proportion to the degree of shunt physiology. Importantly, although experience has shown that stiff lungs are a common finding in patients with ARDS in general, measures of static respiratory system compliance are not included in the Berlin Definition. ARDS is a syndrome, not a disease, and is heterogeneous by its nature. Regardless, findings in COVID-19 have led some to believe that COVID-19–related respiratory failure is an ARDS variant (3). A worrisome corollary of this belief is that the accumulated database of proven ARDS management strategies (e.g., intubation and low-tidal-volume ventilation, prone positioning, and surveillance for nosocomial infections) can be disregarded. In fact, the patients enrolled in the ARMA (Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress) trial of low-tidal-volume ventilation and the PROSEVA (Proning Severe ARDS Patients) trial of prone positioning exhibited myriad etiologies, compliances, and shunt fractions but nevertheless benefited from the targeted interventions (4, 5). We should not deny the benefits proven by rigorous randomized controlled trials to our patients with COVID-19.

Biological plausibility is insufficient justification to administer a medication to a critically ill patient outside of a clinical trial. Indeed, our specialty's history is littered with examples of agents that carried a strong mechanistic rationale and even positive *in vitro* signals yet failed or were shown to be harmful in clinical trials, such as surfactants, N-acetylcysteine, statins, and β-agonists, to name a few in ARDS alone (6). Currently, numerous agents are being administered to patients with COVID-19 outside of controlled trials, including hydroxychloroquine, azithromycin, doxycycline, remdesivir, lopinavir-ritonavir, heparin, low-molecular-weight heparin, tissue plasminogen activator, glucocorticoids, tocilizumab, eculizumab, IFN-β, IFN-γ, IL-1 inhibitors, mesenchymal stem cells, convalescent plasma, nitric oxide, vitamin C, and others. We do not suggest that physicians never use unproven medications off-label or off-trial; in the ICU, we frequently must give therapies based on strong signals in disease processes that are similar to the one in front of us. In contrast, the routine use of the agents listed above for COVID- 19—outside of controlled trials—strains credulity. Many of these compounds have failed in trials of viral infection and ARDS. Continued use of lopinavir-ritonavir is even more shocking in light of a negative randomized controlled trial in COVID-19 that was published early in the pandemic (7).

Why are physicians abandoning standards of critical care in the era of COVID-19? Emotion, stress, fatigue, and political proclamations amplify our innate desire to help our patients and try something—anything—that might provide benefit and give hope to providers and patients alike. This data-free approach will ultimately harm more patients than it helps, as one-off administration of medications ruins clinical equipoise about their use. When a medication is administered to a patient who then improves, the natural human bias is to believe that the drug caused the improvement. Nevertheless, if the patient succumbs to the disease, our biases do not confirm the counterfactual logic. Instead, we believe that the disease was too severe for the drug to overcome, while we minimize the possibility that the drug was ineffective or toxic. The only known strategy to overcome these biases lies in the scientific method and the application of controlled trials to determine whether an agent is effective and the degree to which it is harmful. The possibility of persistent COVID-19 is real, and the emergence of new viral pandemics in the future is certain. For our patients' sake, we need to know what works and what does not. The straw man argument—that patients with COVID-19 improve with protocol-driven supportive care—needs to serve as a null hypothesis to be rejected or accepted in controlled trials. To act as if we know otherwise is irrational, hubristic, and reckless. Pending data from ongoing clinical trials, we must resist the innate human desire to act on emotion and instead rely on our creed: first, do no harm. ■

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Upregulation of CD32 in T Cells from Infants with Severe Respiratory Syncytial Virus Disease: A New Costimulatory Pathway?

To the Editor:

Respiratory syncytial virus (RSV) infection is a major cause of severe respiratory disease in infants and in immunocompromised and older adults. RSV infects virtually all children by 2–3 years of age, resulting in nearly 3 million hospitalizations and 100,000 in-hospital deaths annually, mostly in developing countries (1). There is no approved vaccine against RSV infection. Passive prophylaxis with the anti-RSV antibody palivizumab is the only intervention licensed for the prevention of severe RSV disease in high-risk individuals (2, 3). RSV-specific serum IgG antibodies are present in most children and adults, reflecting the universality of RSV infection throughout life. Neutralizing antibodies remain a commonly accepted measure of protective immunity in vaccine trials (4). However, IgG antibodies might influence the course of RSV disease, not only by acting as neutralizing antibodies but also by activating effector functions through the receptors for the Fc portion of IgG (FcγRs) (5, 6). These receptors are widely expressed in myeloid and B cells. Whether T cells express FcγRs is still controversial, but recent studies strongly suggest that a minor fraction of T cells express FcγRII (CD32) (7–10). We show in the present study that severe RSV infection in infants is associated with a marked upregulation of CD32 on T cells. Moreover, we found that CD32 ligation improves the activation of $CD4^+$ and $CD8^+$ T cells from hospitalized infants.

Our study included 89 infants (median age, 6 mo [interquartile range, 3–10.5]; male, 58%) admitted to "Pedro de Elizalde" Children's Hospital, Buenos Aires, Argentina, with RSV infection confirmed by direct immunofluorescence of nasopharyngeal aspirates. The local institutional review board approved the study, and written informed consent was obtained from parents. All infants had a clinical disease severity score (modified Tal score) greater than or equal to 7 and needed O_2. Those admitted to the pediatric ICU required mechanical ventilation ($n = 5$). Blood samples were collected at enrollment, usually 2–3 days after the onset of symptoms. Age- and sex-matched infants admitted for scheduled surgery were included as healthy control subjects ($n = 43$). They had no airway infections for a 4-week period before the study or any episode of severe RSV infection in their past. Peripheral blood mononuclear cells were obtained from blood samples (0.4–0.6 ml) by using Ficoll-Hypaque gradient (GE Healthcare Life Sciences). $CD4^+$, $CD8^+$, and/or $CD3^+$ T cells were sorted with a FACSAria Fusion flow cytometer (BD Biosciences). Purity was >96%. To perform real-time qRT-PCR, total RNA was extracted using the PureLink-RNA Mini Kit (Thermo Fisher). CD32a and CD32b isoforms were quantified as described previously (9). Antibody-dependent enhancement assays were performed using RSV (subtype A, strain Long) expanded in HEp-2 cells (American Type Culture Collection) and purified by ultracentrifugation on a 20% sucrose layer. Phytohemagglutinin (PHA)-stimulated isolated T cells (1×10^6/ml, 4 μg/ml; Sigma-Aldrich) were challenged with RSV (multiplicity of infection, 0.5) previously preincubated or not with subneutralizing concentrations of intravenous immunoglobulin (2 μg/ml; Universidad Nacional de Córdoba) for 2 days. The percentage of infection was determined by flow cytometry. T-cell functional assays were performed using sorted T cells (1×10^6/ml) incubated with anti-CD32 monoclonal antibody (30 μg/ml; STEMCELL Technologies). Cross-linking of CD32 was induced by antimouse IgG $F(ab')_2$ (50 μg/ml; Jackson ImmunoResearch). Next, cells were stimulated with PHA and cultured for 3 days. Cytokines were quantified in cell supernatants (BioLegend). Degranulation of $CD8^+$ T cells was evaluated by flow cytometry. Statistical analysis was achieved using GraphPad Prism version 7 software. $P < 0.05$ was considered statistically significant.

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