In Response

We thank the author for the interest in our article.[1,2] We agree that additional human studies would better characterize the net benefit of angiotensin II (Ang-2) administration in the setting of Coronavirus Disease 2019 (COVID-19)–related shock. However, the author's argument that exogenous Ang-2 may worsen cytokine release, complement system activation, and lung injury from "unopposed" renin-angiotensin-aldosterone system (RAAS) activation hinges on both a review article that did not discuss severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and 2 case reports that neither measured any components of the RAAS nor reported any hemodynamic outcomes. While ACE2 deletion may impair renal and cardiac function in a mouse model, findings in one species do not always translate to human physiology. Furthermore, the effects of certain therapies implemented during times of health do not necessarily translate to similar effects during times of illness and, in particular, during times of critical illness when severe physiologic derangements affect all aspects of a person's response.

To be clear, we do not support Ang-2 administration for either prevention of SARS-CoV-2 or in COVID-19 patients without shock. However, in those with shock, any potential risk of lung injury resulting from Ang-2–induced ACE2 depletion is dwarfed by the combined adverse effects of SARS-CoV-2–mediated lung injury (which Ang-2 may lessen by decreasing ACE2 entry sites into cells) and septic shock–induced hemodynamic collapse resulting from vascular endothelial injury–induced ACE dysfunction. The large, multinational, double-blinded, placebo-controlled, randomized ATHOS-3 trial, in which patients had a mean APACHE score of 28 (correlating to a >66% predicted in-hospital mortality), and its numerous subgroup analyses of Ang-2 for vasodilatory shock found significant mortality benefit, not harm, from Ang-2 hormonal repletion.[3,4] Moreover, septic shock–induced endothelial ACE dysfunction may disproportionately benefit from Ang-2 administration.[5] Human data specifically in COVID-19 patients suggest that Ang-2 is safe and effective in treating SARS-CoV-2–induced shock.[6–8] A recently published report from Italy describes 16 patients who received Ang-2 for the treatment of SARS-CoV-2–related shock, 10 of whom received Ang-2 as a first-line vasopressor.[8] After 48 hours of treatment, those treated with Ang-2 had significant improvements in F_{IO_2}, PEEP, and S_{PO_2}:F_{IO_2} ratio. Despite the high mortality rate reported in the critically ill population, 88% of Ang-2 recipients were alive at the time of publication.[8]

We fully support the notion that the treatment of all patients should be evidence-based. Understanding the difficulty in performing randomized controlled trials during this pandemic, we support employing all available data sources (including those from small animal studies) to direct our medical decision-making. However, when high-quality studies already support certain therapies for life-threatening conditions, and when basic physiologic data may further support such therapies during novel pandemics, smaller case series[6–8] must help guide our management of SARS-CoV-2–induced vasodilatory shock while we await more definitive high-quality trials.

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Conflicts of Interest: J.H.C. serves on the Speaker's Bureau for La Jolla Pharmaceutical Company.

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