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The Reply

We are aligned with Drs Olmos and Roque that there should be comprehensive medical crisis management as shown in the 4 pillars of pandemic response in the Figure.[1] Human severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection begins as a mild upper respiratory tract infection with a prehospital therapeutic window of opportunity, and there is an important "second pillar" of pandemic response that has the objective of reducing to the "hard outcomes" of COVID-19, hospitalization and death. For patients at high-risk of contracting coronavirus disease 2019 (COVID-19) and are acutely ill at home, contagion control is too late and the hospital is not an adequate safety net. Late-stage hospitalization as the only opportunity for initial treatment results in unacceptably high mortality.[2] Thus, in the context of a crisis, therapeutic decisions are made based on pathophysiological principles and the totality of available evidence. Because most serious viral infections require multidrug regimens, we can only expect signals of efficacy or safety with single agents from randomized and observational studies of COVID-19. Clinical judgment is required to assemble therapeutic combinations that address viral replication, cytokine storm, and thrombosis.[1] Since the time of the original publication in ***The American Journal of Medicine***, we are better supported from inpatient studies on the application of aspirin as well as anticoagulation that have established safety profiles.[3] Meizlish et al[4] found in a multicenter study ($N = 2785$) that aspirin administration was independently associated with a 69% reduction in mortality ($P = .001$). Billet et al[5] ($N = 3625$) demonstrated a significant decrease in adjusted mortality with prophylactic use of apixaban (odds ratio = 0.46, $P = .001$) and enoxaparin (odds ratio = 0.49, $P = .001$). We encourage Drs Olmos and Roque to overcome the fear of relying on clinical judgment before confirmatory large-scale multidrug, placebo-controlled, randomized trials. To our knowledge no such trials are forthcoming. Empiric regimens based on clinical judgment are not as "dangerous" as leaving patients untreated for many days only to succumb to calamitous hospitalization

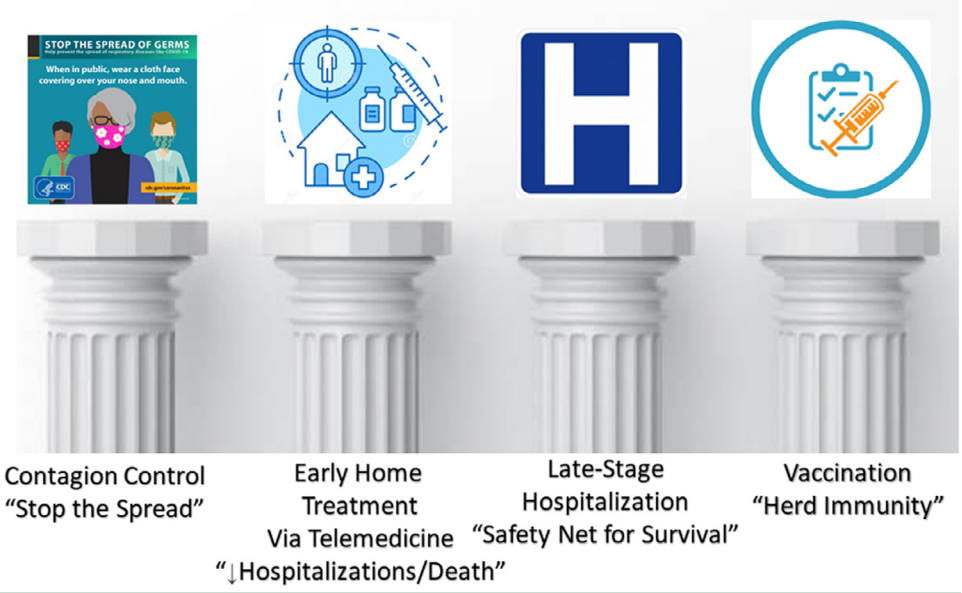

Figure The 4 pillars of pandemic response to the severe acute respiratory coronavirus 2 (SARS-CoV-2) pandemic crisis, reproduced with permission from McCullough et al.[1]

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or death. Courageous doctors and researchers have innovated and found that sequenced, multidrug regimens are associated with ~85% reductions in COVID-19 morbidity and mortality with no signals of harm.[6,7,8]

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