Aspirin in Coronavirus Disease 2019–Related Acute Respiratory Distress Syndrome: An Old, Low-Cost Therapy With a Strong Rationale

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GLOSSARY

ACE-2 = angiotensin-converting enzyme-2; **ARDS** = acute respiratory distress syndrome; **COVID-19** = coronavirus disease 2019; **COX-1** = cyclo-oxygenase-1; **COX-2** = cyclo-oxygenase-2; **ICU** = intensive care unit; **LIPS-A** = Lung Injury Prevention Study with Aspirin; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus-2

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused >1 million deaths and is responsible for a worldwide pandemic.[1,2] Most patients affected with coronavirus disease 2019 (COVID-19) have a favorable prognosis. However, between 20% and 67% of patients admitted to the hospital develop acute respiratory distress syndrome (ARDS) criteria according to the Berlin definition.[3] In these patients, hospital mortality ranges from 35% to 46% depending on ARDS severity.[4]

Nearly 10 months after the COVID-19 pandemic, therapeutic options remain limited. Until now the major treatments have focused on neutralizing the virus through passive immunity (ie, convalescent-phase plasma or monoclonal antibodies), inhibiting viral replication (ie, remdesivir), or decreasing the immune response (ie, glucocorticoids). However, recently 2 double-blind, placebo-controlled trials have respectively demonstrated no significant differences in clinical status or overall mortality between COVID-19 patients treated with convalescent plasma[5] and those who received placebo and between COVID-19 patients treated with tocilizumab compared with placebo.[6]

Although the pathophysiology of severe COVID-19 pneumonia is incompletely understood, patients with COVID-19 are characterized by a prothrombotic status, coagulopathy, and increase in plasmatic D-dimer concentrations.[7] In addition, several studies have suggested that ARDS associated with COVID-19 represents a specific phenotype characterized by severe hypoxemia initially associated with relatively well-preserved lung mechanics and lung gas volume.[8,9]

One explanation for the high dead space and impaired oxygenation in the absence of significant decrease in pulmonary compliance is endothelial dysfunction and microvascular thrombosis.[7] In addition, evidence of COVID-19–associated hypercoagulability has been demonstrated by viscoelastic coagulation testing, by elevated D-dimer and fibrinogen concentrations in patients with COVID-19–associated ARDS, and by autopsy findings that report an incidence of alveolar capillary microthrombosis 9 times higher than in influenza patients.[7,10]

This triad of infection, inflammation, and coagulopathy are all consistent with the proposed pathophysiology of COVID-19.

SARS-CoV-2 binds to angiotensin-converting enzyme-2 (ACE-2) to gain cellular entry. After endocytosis of the viral complex, surface ACE-2 is downregulated, resulting in unopposed angiotensin-2 activity. Angiotensin-2 causes vasoconstriction and lung injury, leading to tissue factor expression, endothelial injury, and coagulation cascade activation. SARS-CoV-2 further causes lung injury via activation of residential macrophages, in which triggers a

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cytokine storm.[11] Inflammatory exudate enters the alveolar space, followed by the formation of fibrin and hyaline membranes. In conclusion, COVID-19 induces microvascular endothelial damage leading to increased permeability, expression of tissue factor with coagulation activation, and thrombus formation.[12]

Existing evidence suggests that systemic anticoagulation with heparin reduces hospital mortality in mechanically ventilated COVID-19 patients. In a retrospective review of 2773 patients from Mount Sinai in New York, anticoagulated patients had a considerably lower mortality (29% than those who were not anticoagulated [62.7%] and a negligible difference in major bleeding events [3% vs 1.9%]).[13]

In light of these data and due to its antiplatelet and anti-inflammatory properties, it is reasonable to hypothesize that the cyclo-oxygenase-1 (COX-1) inhibitor aspirin plays a therapeutic role in COVID-19 infection.

Clinical evidence regarding aspirin in ARDS patients, however, is mixed. Aspirin has been already demonstrated to have beneficial effects. A 2017 meta-analysis of 3 independent observational cohort studies found that aspirin was associated with an overall reduced incidence of ARDS in critically ill patients.[14] In contrast, the 2016 Lung Injury Prevention Study with Aspirin (LIPS-A) clinical trial, randomized 390 patients at high risk of ARDS to receive placebo or aspirin and found no effect of aspirin on the ARDS onset at 7 or 28-day survival.[15] Although the reason for these divergent results are not clear, one possibility is that patients in the LIPS-A trial had a broad spectrum of risk factors for ARDS (sepsis, pancreatitis, pneumonia, and trauma) which confounded the effect of aspirin.

In this issue of *Anesthesia & Analgesia*, Chow et al[16] examine the association between aspirin and clinical outcomes in patients with ARDS related to COVID-19. Chow et al[16] retrospectively reviewed the clinical course of 412 patients from a multicenter registry, 98 of which (23.7%) received aspirin within 24 hours of admission or 7 days before admission. Although patients who received aspirin had significantly higher rates of hypertension, renal insufficiency, diabetes mellitus, and coronary artery disease, they were less likely to need mechanical ventilation (35.7% vs 48.4%) and intensive care unit (ICU) admission (38.8% vs 41%) than patients who did not receive aspirin. In-hospital mortality was similar (26.5% vs 23%). Furthermore, after multivariable adjustment for 9 confounding variables, aspirin was independently associated with a reduced risk of mechanical ventilation, ICU admission, and in-hospital mortality.[16]

Although intriguing, Chow et al's[16] data are limited by the observational design, the absence of inflammatory marker measurement to inform potential mechanisms, and the unusual time frame for aspirin administration (7 days before to 24 hours after hospitalization) that may have helped create a heterogeneous aspirin group, mitigating the results of the study. In fact, patients on aspirin could present with less severe illness because of a tighter relationship with the health care system and no propensity analysis can account for all covariates.

However, Chow et al's[16] findings do provide fertile ground for prospective study. A strong pathophysiological rationale supports the administration of aspirin in COVID-19. Aspirin decreases interleukin-6 and C-reactive protein production by the inhibition of cyclooxygenase-2 (COX-2) and by inhibiting COX-1 reduces thromboxane A2 synthesis, platelet aggregation, and thrombus formation. These mechanisms play a larger role in ARDS due to COVID-19 as a primary mechanism of COVID-19–induced ARDS is endothelial dysfunction leading to inflammation and hypercoagulability.

In light of the lack of effective therapeutic tools for treating COVID-19 pneumonia, how should the clinician interpret the findings of Chow et al?[16] The downsides seem low, although aspirin use for primary prevention of cardiovascular disease increases bleeding risk.[17] However, in this study, a significant increase in major bleeding was not found, possibly because patients were hypercoagulable at baseline. Similarly, Paranjpe et al[13] in hospitalized patients with COVID-19 treated with anticoagulation dose of heparin reported a low risk of bleeding (2%–3%).

Although not based on large data, the administration of aspirin in patients affected with ARDS related to COVID-19 seems a low-cost therapy with a good safety profile that, however, needs randomized controlled trails to confirm its potential benefits.

DISCLOSURES

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