

Conditions Favoring Increased COVID-19 Morbidity and Mortality: Their Common Denominator and Treatment

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To the Editor,

Morbidity and mortality with coronavirus disease-2019 (COVID-19) has been found to be increased in patients with at least one of the following five conditions: diabetes, obesity, chronic obstructive airways disease (COAD), advanced age, and male gender. A literature search revealed that the common denominator of all these diverse groups is a tendency toward a lower than normal urine or interstitial fluid pH.

Although plasma and interstitial fluid contain similar amounts of bicarbonate buffer, blood has, in addition, powerful pH buffering protein molecules such as hemoglobin and albumin, which keep the pH of the blood strictly between 7.35–7.45. Interstitial fluids, however, contain few pH buffering protein molecules, with the result that the pH of interstitial fluids is more variable than that of plasma [1].

Consequently, in conditions with mild but not severe acidosis such as in the five groups I listed, while arterial blood pH is tightly controlled within the normal

range, the pH of interstitial fluids may be lower than that of the blood.

Urine pH reflects acid–base balance and is readily measurable. Urine pH is normally slightly acidic, with values of 6.0–7.5. In all the five groups however, urine pH has been found to be, on average, toward the lower side, possibly reflecting a lower than normal interstitial fluid pH.

Low interstitial fluid pH adversely affects the prognosis in COVID-19 infection in two ways:

- Low pH enhances viral fusion and entry into cells via the endosomal route, thereby facilitating viral multiplication [2]
- Low pH increases the production of inflammatory cytokines, exacerbating the cytokine storm and the dire consequences thereof [3]

VIRAL FUSION

For all enveloped viruses such as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a critical event during the entry of the virus into cells is the fusion of the viral envelope with the membrane of the host cell. This process is enhanced by a low pH [4].

INFLAMMATORY CYTOKINES AND LOW pH

There is strong evidence favoring the existence of links between acid–base balance and cytokine concentrations with low pH as a potential factor for the

trigger threshold of the inflammatory response [3].

Acidosis is among the most common abnormalities seen in patients presenting with critical illness. Its etiologies are multiple, and treatment of the underlying condition is usually the mainstay of therapy. However, growing evidence suggests that acidosis itself has profound effects on the host, particularly in the area of immune function.

If viral multiplication and cytokine production could be reduced by increasing pH, it would without doubt improve survival rates and reduce morbidity and mortality in at-risk COVID-19 patients.

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Capsule

Obesity and inflammation

Obesity is associated with chronic inflammation, which can trigger other diseases such as atherosclerosis, type 2 diabetes, and even cancer. There appears to be a genetic component to excess fat accumulation, and studies suggest that inflammatory gene variants may contribute. Karunakaran and colleagues found that single-nucleotide polymorphisms in the human receptor-interacting serine/threonine-protein kinase 1 gene (*RIPK1*) increase its expression and are causally associated with obesity.

RIPK1 is a key regulator of inflammatory responses and cell death. Silencing of *Ripk1* in mice on a high-fat diet reduced fat mass, body weight, and inflammatory responses in adipose tissue. This finding suggests that *RIPK1*-mediated inflammation (and possibly other functions) contribute to obesity and that *RIPK1* could be a therapeutic target.

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