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COVID-19 infection: Are we doing more harm than  
good?**

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## Use of proton pump inhibitors in patients with COVID-19 infection: Are we doing more harm than good?

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### Abstract

**Purpose:** The purpose of this paper was to highlight the use of proton pump inhibitors (PPIs) in the supportive treatment of COVID-19 infection and the potential effects associated with their use.

**Methodology:** This was a theoretical paper.

**Findings:** COVID-19 pandemic has had a profound negative impact worldwide on the economic and healthcare machinery. PPIs are important drugs used as supportive therapy for various medical conditions like heart-burn and acid peptic disease. There is an on-going deliberation regarding the probable useful versus deleterious effects of PPI use in patients with COVID-19 infection. Some authorities believe in their usefulness as anti-oxidant and anti-inflammatory agents, while others prove with evidence the potential harm caused by their use in terms of increased vulnerability to infections.

**Recommendation:** Given their possible side-effects, prudent usage of PPI therapy is warranted in patients with active COVID-19 infection.

**Keywords:** *Pandemic, COVID-19, SARS-CoV-2, proton pump inhibitors.*

Coronavirus (COVID-19) infection, (also known as SARS-CoV-2), is predominantly a disease of the respiratory tract, ranging from asymptomatic disease to very severe and life-threatening pneumonia with septic shock leading to secondary multi-organ failure. The virus causing this illness primarily spreads through direct contact or respiratory droplets, although some experts believe it can also be transmitted as an airborne infection. Ever since the World Health Organization (WHO) declared coronavirus (COVID-19) infection as a public health emergency in late January 2020, the pandemic has had devastating effects on global economy and healthcare system. Millions of people across the world have been infected, and despite the recovery rate being satisfactory, thousands have already succumbed to the illness.

In the absence of a definitive anti-viral therapy, mass vaccination may be the only way to prevent the spread of disease. However, the quest for a safe and effective vaccine for COVID-19 infection is still continuing, and authorities are skeptical regarding the availability of one by the end of 2020 (1). So far, standard precautions and social distancing seem to be the only effective measures to inhibit infection transmissibility. This short article provides a crisp overview, based on available data, regarding the potential risks and benefits of using drugs like proton pump inhibitors (PPIs) in patients with COVID-19 infection.

PPIs are the undoubtedly one of the commonest class of drugs which, over the past few years, have been prescribed by physician community across the globe for the management of conditions related to hyper-acidity, namely gastro-esophageal reflux disease (GERD) and peptic ulcer disease (2). However, there is enough evidence to suggest that these medications are being over-prescribed by healthcare practitioners, without keeping specific indications in mind (3). Additionally, it has been hypothesized that hypochlorhydria produced by long-term PPI therapy weakens the immune system of the human body, especially as the gastric juice is considered to be the first line of defense against major pathogens (4). For this reason, there have been growing apprehensions over the grave side effects of PPI therapy, which include increased risk of various infections like pneumonia and clostridium difficile colitis, dementia, chronic renal failure and fractures secondary to osteoporosis, which can even lead to increased morbidity and mortality (5).

SARS-CoV-2 virus, besides infecting the respiratory system, can also involve the gastrointestinal (GI) tract (6). Although murine models clearly suggested that infectivity of Middle East respiratory syndrome coronavirus (MERS-CoV) was reduced in the normal pH of stomach, similar results have so far not been extrapolated for the similar SARS-CoV-2 virus (7). Having said that, it can well be assumed that increasing the stomach pH by using PPIs can also theoretically intensify the virulence of COVID-19 infection. Also, there is a possibility of the virus spreading from the GI tract to other systems of the body, especially the respiratory system (8). The use of PPI can also make an individual susceptible to bacterial infections, and investigators have shown that concomitant bacterial infection is clearly associated with increased mortality (9). Contrary to the above theory, many authorities believe that PPI co-therapy in patients with COVID-19 disease may have therapeutic benefits, as PPIs can reduce cellular oxidative stress and in turn prevent inflammation and fibrosis (10). Hence, there is an on-going debate as to whether or not PPIs should be administered in patients with COVID-19.

The most robust evidence of the potentially detrimental effects of PPI use in patients with COVID-19 infections comes from a large Korean cohort of 1,32,316 subjects, out of which 4,785 tested

positive for SARS-CoV-2 infection (11). In this study, 20,405 individuals were either actively taking PPI therapy or had taken therapy in the past. Adverse outcome measures included intensive care unit (ICU) admission, requirement of mechanical ventilation or death. The study revealed that although patients receiving PPI therapy may not be at increased risk of acquiring SARS-CoV-2 infection, they do have a more severe clinical course as compared to those who are not on PPIs (even when these drugs were used in the short-term). These results, the authors hypothesized, could be due to increased risk of bacterial co-infections in patients continuously using PPIs, as well as increased propensity of developing the cytokine storm. Therefore, the investigators recommended judicious use of these drugs by physicians especially when dealing with COVID-19 positive patients. Similarly, another retrospective study, despite its limitations, showed that PPIs significantly increase the development of adult respiratory distress syndrome (ARDS) in hospitalized patients with COVID-19 disease (12).

One must be mindful of the fact, however, that there are certain circumstances where use of PPI therapy becomes inevitable. Patients with moderate to severe COVID-19 infection may be prone to develop thromboembolic events (13). These complications can occur even while patients are on prophylactic anti-coagulation. To counter this, hospitals managing these critical patients have developed protocols which include therapeutic anti-coagulation therapy. As GI bleeding is a frequent problem with anti-coagulants, many patients will require therapeutic endoscopic procedures for control of bleeding. In this regard, along with other factors, the role of intravenous (and subsequently oral) treatment with a PPI cannot be undermined (14). Furthermore, it is important to identify patients who are at a higher risk of GI bleeding, and commence PPI therapy early in the course of the disease.

Can we avoid using PPIs in COVID-19 patients with low risk for GI bleeding, and use alternatives like histamine-2 receptor antagonists (H2RAs) instead? Interestingly, there is emerging early data on the potential benefit of famotidine (H2RA) in hospitalized patients of COVID-19 in terms of favorable clinical outcome, and maybe recovery (15). The evidence is nevertheless not convincing so far, and more data is needed in the form of randomized trials to prove this association, as H2RAs also suppress gastric acidity, albeit not as potently as PPIs (16, 17).

### **Conclusion**

PPIs are very valuable, economical and readily available drugs for managing common GI disorders. The jury is still out on the possible role of this group of medications and how it can affect the severity of COVID-19 disease. Administering PPI in patients with GI bleeding or those at high bleeding risk may be necessary, however in non-bleeding scenarios clinicians should be cognizant of the possible side-effects and negative implications of PPI therapy before prescribing them to such patients.

### **Recommendations**

1. In patients with SARS-CoV-2 infection, a detailed drug history, including use of PPI should be inquired by the treating physicians and all unnecessary medications should be stopped.
2. Safer options like H2RAs should be tried in patients without GI bleeding.

3. Even if a definitive indication has been established in such patients, PPI should be commenced if the potential benefit outweighs the risk, ideally with the lowest possible dose and for a pre-defined time period.

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