Information Sheet and FAQs About Proton Pump Inhibitors (PPIs) and Risk of COVID-19

About this Document

On July 7th, 2020, *The American Journal of Gastroenterology* released the following study examining the relationship between use of PPIs and risk of COVID-19:

> Almario CV, Chey WD, Spiegel BMR. Increased risk of COVID-19 among users of proton pump inhibitors. *Am J Gastroenterol* 2020 (pre-print posted online July 7, 2020)

In this document, members of the American College of Gastroenterology (ACG) leadership team partnered with the study authors to prepare a brief overview of the research, discuss its findings, and address potential implications for clinical care. The full study in pre-print format can be found at this link.

What are the main results of the study?

This study was an online population-based survey of 53,130 English-speaking adult Americans. Respondents were asked about any current PPI and/or histamine-2 receptor antagonist (H_2RA) use and were also asked about whether they have tested positive for COVID-19. The authors then performed a regression analysis to test the relationship between anti-secretory use and risk of COVID-19 while adjusting for a wide range of potential confounders, including demographic, socioeconomic, lifestyle, and comorbidity variables.

The authors found that PPI use was independently associated with increased odds for COVID-19. Moreover, there was a dose-response relationship between the amount of acid suppression and the risk of COVID-19 that fell along a biological gradient. Compared to those not using PPIs, those taking twice-daily PPIs registered a 3.7-fold increased odds of COVID-19, whereas those using PPIs up to once daily had a 2.2-fold increase. In contrast, people taking less powerful H_2RAs were not at increased risk for COVID-19. Of note, the risk of PPIs remained significant regardless of duration of use, including those who had been on PPIs for six months or greater, before the start of the pandemic. In addition to PPI usage, males, current smokers, non-Hispanic blacks, and Latinxs were significantly more likely to report being positive for COVID-19, consistent with previous research.

Do patients need to stop their PPIs right now because of this study?

As always, the decision about whether, when, and how to modify PPIs dosing should be based on a thoughtful assessment of the risk-benefit ratio for individual patients. This study does not definitively prove that PPIs increase the risk for COVID-19. As with any medication, the lowest effective dose should be used when clinically indicated, and, when appropriate and consistent with best-practice guidelines, H_2RAs may also be considered as an alternative treatment for acid-related conditions.

How might you use the results of this study to advise patients taking PPIs?

The main result of this study is that use of PPIs, particularly twice-daily PPIs, appears to increase the risk of COVID-19. Although the relative risk is notable, with an adjusted odds ratio of 3.7 for twice-daily dosing, the *absolute risk* is still small for any individual patient using PPIs.

For patients using PPIs for an appropriate indication who are concerned about COVID-19, the best way to reduce personal risk is to practice regular hand washing, practice social distancing, and wear a mask when around others. These practices will have a much greater impact on personal risk of COVID-19 than manipulating PPI dosing. *If nothing else, the discussion about PPI risk could save lives simply by reminding users to closely adhere with CDC guidelines given the potential increased risk conferred by PPIs.*

Beyond the critical point of emphasizing adherence with CDC guidelines, clinicians should consider whether twice-daily PPI dosing is necessary for their patients, particularly those who are especially vulnerable for severe COVID-19 (e.g., elderly or comorbid patients). Twice-daily PPI use can lead to 24-hour median intragastric pH >6 and sustain pH >4 for more than 20 hours.[1-3] *Moreover, meta-analysis suggests that in general, twice daily PPI does not offer clinically meaningful benefits over once daily dosing for gastroesophageal reflux disease.* Although individual patients may certainly benefit from twice-daily dosing, it is always useful to re-evaluate the need for high-dose PPIs, particularly during a pandemic when the population prevalence of COVID-19 remains high.

It is important to emphasize that this study extends upon previously published research: that PPIs increase the risk of gastrointestinal infection. Although the absolute risk of any PPI-induced infection is low, previous research has shown a clear link between PPI use and an increased odds of gastrointestinal infections.[4-6] The current study's novelty lies in the extension of this knowledge to COVID-19. It is reasonable to make sure there is a clear indication in all patients taking a PPI. When a PPI is indicated, clinicians should inform their patients about the association between PPIs and enteric infections, now including COVID-19, just as it would be useful to review potential side effects whenever prescribing any other medicine. The benefits and risks of PPI therapy should be carefully considered and balanced to arrive at an individualized decision for each individual patient.

Why was this study performed?

PPIs have been linked to a variety of side effects over the years, many of which remain to be adequately confirmed. However, prospective, randomized controlled data have previously shown that PPI use increases the odds for enteric infection by 33%, likely from PPI-induced hypochlorhydria.[4] Moreover, it is known that pH ≤3 impairs the infectivity of the SARS-CoV-1 virus and likely has the same effect on SARS-CoV-2, the virus that causes COVID-19.[5] Thus, it is possible that inhibiting gastric acid might allow a larger inoculum of SARS-CoV-2 to gain entry into the gastrointestinal tract and replicate within the gut epithelium, leading to gut symptoms and inflammation and perhaps enabling spread of the virus beyond the GI tract. This is especially relevant because SARS-CoV-2 can infect the digestive system via the angiotensin-converting enzyme 2 (ACE-2) receptor, which is widely expressed throughout the gastrointestinal tract.[6] Therefore, it is important to understand if PPI-induced hypochlorhydria is an independent risk factor for acquiring COVID-19.

What are the limitations of the study?

It is always possible that people taking PPIs are systematically different from people who are not using PPIs, and those differences might explain the varying risk of COVID-19. For example, it is

possible that people using PPIs are older, have more comorbidities, or carry other risk factors such as obesity which have been associated with COVID-19. For that reason, the authors controlled for a wide range of potentially confounding demographic, socioeconomic, lifestyle, and comorbidity variables. It is also notable that the PPI effect followed a dose-response gradient, and that a control group H_2RA users did not reveal the same link to COVID-19. Nonetheless, it is impossible to completely eliminate residual confounding from an observational study.

It is also possible that people started a PPI *because* they had COVID-19, possibly to treat COVID-19-related digestive symptoms. For that reason, the authors classified patients who only started the PPI after their diagnosis as non-users, and they also performed additional analyses examining both short-term and long-term use of PPIs.

Importantly, this is not a prospective, randomized controlled trial. Therefore, this observational study, although prospectively designed to test a hypothesis and featuring a large sample size, *cannot definitely prove that PPIs increase the risk for COVID-19.* The study only demonstrates a dose-response relationship between PPIs and COVID-19 and also suggest that H_2RAs do not increase risk. We need additional prospective research to examine these associations further.

References

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