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CURRENT CLINICAL CONTROVERSY

PPIs and Beyond: A Framework for Managing Anticoagulation-Related Gastrointestinal Bleeding in the Era of COVID-19

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Abstract
Coronavirus disease of 2019 (COVID-19) can be associated with high morbidity and mortality; patients with severe clinical manifestations may develop significant coagulopathy as well as unexpected thromboembolic complications. In response, centers are increasingly treating selected patients with intermediate-dose prophylactic or even therapeutic dose anticoagulation in order to prevent potentially catastrophic thrombotic complications. With this changing practice, the authors suspect that inpatient gastrointestinal consult teams across the country will be frequently managing COVID-19 patients with gastrointestinal bleeding (GIB). In order to reduce potentially avoidable hospital readmissions for GIB while improving patient outcomes, it is imperative to appropriately risk-stratify patients prior to initiation of anticoagulation. In this review, we discuss how to appropriately identify high-risk patients for GIB and how to mitigate GIB risk with proton-pump inhibitor co-therapy, medication reconciliation, and *Helicobacter pylori* testing and treating in this complex and morbid population.

Keywords Gastrointestinal bleeding · Anticoagulation · Thrombosis · COVID-19

Introduction

The coronavirus disease of 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected over 5 million patients around the world as of May 2020 [1]. Clinical manifestations of COVID-19 infection can be heterogeneous, ranging from a mild respiratory illness to a more severe, systemic disease characterized by acute respiratory distress syndrome (ARDS), shock, and multiple organ dysfunction [2, 3]. Emerging studies from Wuhan, China, have demonstrated that patients with severe COVID-19 may have subclinical or overt coagulation abnormalities [4] along with an increased risk of thromboembolic events [5], a pattern that is now commonly seen globally. Unfortunately, these thromboembolic complications can occur despite administration of prophylactic anticoagulation [6]. With increasing experience in caring for COVID-19 patients, many hospitals are now initiating empiric intermediate intensity or even therapeutic dosing of anticoagulation in high-risk patients as a means to decrease thromboembolic complications. As gastrointestinal bleeding (GIB) is a common complication of anticoagulation, gastroenterologists should expect to see an increase in the number of COVID-19 patients requiring endoscopic intervention. To improve quality-of-care and ensure patient safety, clinicians should risk-stratify patients prior to initiation of anticoagulation and consider *Helicobacter pylori* testing and the use of PPI co-therapy in those at highest risk for GIB.

Coagulation Parameters in COVID-19

Elevated D-Dimer levels have been a consistent observation among patients with COVID-19, particularly in those with more progressive disease [7]. Other laboratory findings in COVID-19, such as mild prolongation of the prothrombin time and elevated activated partial thromboplastin time, appear similar to sepsis-associated disseminated intravascular coagulopathy (DIC). Yet, studies have identified the coagulopathy in COVID-19 to be distinctly different from DIC, with more prothrombotic rather than hemorrhagic consequences [7–9]. Although the cause of these laboratory abnormalities remains unknown, patients with COVID-19

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and coagulopathy appear to have an inferior prognosis [10, 11]. D-dimer levels > 1000 ng/mL are an independent risk factor for in-hospital mortality, with one study demonstrating up to an 18× increased risk of death [12].

These coagulation changes seen in COVID-19 suggest the presence of a hypercoagulable state [3]. Combined with other risk factors including prolonged immobilization and possible endotheliopathy [7, 13], it is not surprising that several studies have demonstrated a relatively high rate of thromboembolic complications in COVID-19. In a study of 184 patients with COVID-19, the composite incidence of deep vein thrombosis, pulmonary embolism, ischemic stroke, myocardial infarction, and systemic arterial events was 31% [14]. Other recently published studies showed a 25–69% incidence of venous thromboembolic (VTE) complications in patients with COVID-19 [5, 14, 15]. Although these studies did not report rates of thromboembolic complications in a control (non-COVID-19) population, historical data have reported a lower VTE incidence of 5–33% in critically ill patients [16–19].

Anticoagulation Management in COVID-19

These disproportionally high rates of thromboembolic complications in COVID-19 persist in some cases despite prophylactic or even therapeutic dose anticoagulation [15, 20]. In a prospective study of 150 COVID-19 patients admitted to the ICU for ARDS, a significantly higher proportion of patients developed pulmonary embolism despite anticoagulation when compared with a non-COVID-19 ARDS cohort (11.7% vs. 2.1%, $p < 0.008$) [21]. In this study, 77% of patients were receiving prophylactic dosed anticoagulation and 21% received therapeutic dosed anticoagulation.

Anticoagulation may be associated with improved outcomes in this population [22, 23]. In an observational study of over 2700 hospitalized COVID-19 patients, 28% received systemic anticoagulation during their hospital course [22]. In the subset of patients requiring mechanical ventilation ($n = 395$), in-hospital mortality was 29% with a median survival of 21 days for those treated with anticoagulation, compared with 63% mortality with a median survival of 9 days in those who did not receive anticoagulation. Unfortunately, the limitations of this observational trial were significant and included confounding by indication, and in particular lack of adjustment for immortal time bias [24]. Although results of controlled trials to prove the benefit of empiric anticoagulation are pending, medical centers have proposed intermediate and therapeutic dosed anticoagulation in a subset of COVID-19 patients, particularly those with elevated D-dimer levels, in order to prevent potentially catastrophic thromboembolic complications [8, 23, 25, 26]. Thus, a detailed discussion on the risks of this strategy in regards to GIB is warranted.

Identification of Patients with COVID-19 at High Risk of GIB

GIB is already the most common reason for hospitalization in the United States due to a digestive disorder, with approximately 500,000 annual admissions [27]. Although the majority of patients with upper and lower GIB do well, GIB can have a devastating impact on older patients with comorbid illnesses [28–30]. Furthermore, the risk of GIB increases with the use of systemic anticoagulation, occurring with an estimated annual risk of 4.5–8% [31–33]. As more centers adapt to intermediate dose, therapeutic dose, or longer duration anticoagulation protocols, we anticipate an increase in the number of COVID-19 cases complicated by GIB in the coming months.

To effectively manage these complex patients and prevent hospital readmissions for GIB, risk-stratification prior to initiation of anticoagulation is essential. Although there are limited data on the incidence or risk factors associated with GIB in patients with COVID-19, we can extrapolate data from historical studies. Risk factors for GIB in patients initiated on anticoagulants have included older age, a prior history of GIB, chronic renal impairment, *H. pylori* infection, concomitant use of antiplatelet drugs, and preexisting gastrointestinal tract lesions [34–37]. As the number of risk factors increase, so does the risk of GIB [38].

Current Evidence-Based Practice of Proton-Pump Inhibitor Prophylaxis

Proton-pump inhibitors (PPI) reduce gastric acid secretion, promote ulcer healing, and prevent ulcer recurrence, and can help mitigate the risk of GIB in these high-risk populations [39, 40]. Several studies have demonstrated an overall benefit with the use of prophylactic PPI, particularly in patients taking dual antiplatelet therapy (DAPT) and/or concomitant anticoagulation. Nevertheless, careful selection of appropriate patients for PPI prophylaxis is necessary in order to decrease unintended complications of PPI therapy [41].

The protective effect of PPI in selected patients was demonstrated in a retrospective study of Medicare beneficiaries by Ray et al. [39]. Patients receiving several types of oral anticoagulants with or without PPI were stratified by GIB risk scores and evaluated for GIB hospitalizations. There was a significant protective association with PPI co-therapy for all patients receiving anticoagulation, except for those in the lowest risk decile for GIB. This was further demonstrated in a retrospective study of patients receiving warfarin. PPI

co-therapy with warfarin was associated with a 24% reduction in risk of upper GIB compared to those without PPI co-therapy (HR 0.76, 95% CI 0.63–0.91, $p=0.0035$) [42]. The greatest reduction in risk for upper GIB was seen in patients receiving concomitant antiplatelet drugs or NSAIDS [42], further highlighting the gastroprotective effect of PPI in high-risk patients receiving anticoagulation.

Concomitant Medications and Risk of GIB

Prior to initiation of anticoagulation and possible co-therapy with PPI, it is imperative to perform a careful medication reconciliation and evaluate the need for other antiplatelet therapies. Concomitant antiplatelet drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) and dual antiplatelet therapy (DAPT) pose a higher risk of GIB in patients and should be avoided (if appropriate) when initiating anticoagulation.

NSAIDs have long been associated with increased risk of GIB, particularly in older patients (> 65 years), in patients with previous complicated ulcers, and in those receiving high-dose NSAIDs or concomitant anticoagulation, aspirin or steroids [43]. As such, NSAIDs should be completely avoided in COVID-19 patients who are started on intermediate dosed or therapeutic dosed anticoagulation. If NSAIDs are deemed medically necessary and cannot be stopped while receiving anticoagulation, PPI co-therapy can decrease the risk of GIB in this population [44–46].

The use of DAPT with anticoagulants poses a significant additional risk of GIB [47, 48] and should be avoided. While aspirin alone confers a risk of bleeding, when combined with a thienopyridine, the risk of GIB increases by 2 to 3-fold, and further increases when combined with anticoagulation (triple therapy) [38]. While the optimal approach would be to avoid anticoagulation in patients receiving DAPT, there may be clinical situations when triple therapy is required. As a result, the American College of Cardiology, American College of Gastroenterology, and American Heart Association released a consensus statement in 2010 recommending PPI in high-risk patients receiving DAPT, particularly in those with concurrent use of anticoagulants, steroids or NSAIDS, *H. pylori* infection, older age, or with previous GIB history [38].

Although the risk of bleeding is highest when receiving triple therapy, PPI co-therapy can also reduce bleeding in patients receiving single antiplatelet therapy and anticoagulation. In a recent randomized controlled trial, Moayyedi et al. [49] demonstrated that while routine use of PPI in patients receiving low-anticoagulation and/or aspirin did not significantly reduce the primary endpoint of composite clinical upper gastrointestinal events, PPI did reduce overt bleeding from gastroduodenal lesions by approximately 50% (HR 0.52, 95% CI 0.28–0.94, $p=0.03$), highlighting the protective effect of PPI. Therefore, if patients with COVID-19 receiving either single or dual antiplatelet therapy are placed on anticoagulation, we strongly recommend consideration of co-therapy with PPI (Fig. 1).

H. Pylori, Colorectal Neoplasia, and Risk of GIB

Helicobacter pylori, a chronic gastric bacterial infection, has been associated with peptic ulcer disease (PUD) [50], and eradication of *H. pylori* can reduce the risk of ulcer recurrence and subsequent GIB. [51]. As a result, the American College of Gastroenterology recommends *H. pylori* testing in all patients with active PUD or in those with a past history of PUD, and conditionally recommends *H. pylori* testing in patients taking long-term aspirin in order to prevent the risk of ulcer bleeding [50]. Based on these recommendations, we encourage clinicians to test for (and eradicate if positive) *H. pylori* in COVID-19 patients with a history of GIB or PUD prior to initiation of anticoagulation. Similarly, testing for *H. pylori* in high-risk patients, including those patients who must continue aspirin, DAPT, or NSAIDs, may attenuate the risk of anticoagulation-related GIB. Note that the commonly used stool antigen test can yield false negatives if the patient has taken PPIs within 2 weeks of providing the stool sample.

Colorectal neoplasia has also been identified as a risk factor for GIB in patients initiated on anticoagulation. Using data from the Randomized Evaluation of Long-Term Anticoagulation study, 546 cases of unique major gastrointestinal bleeding events were identified in patients receiving dabigatran or warfarin, and 8.1% of GIB cases were secondary to previously undiagnosed luminal gastrointestinal cancer [52]. While there are few intervenable aspects to gastrointestinal malignancy during an acute hospitalization for COVID-19, one of the most common causes of GIB in patients initiated on anticoagulation can be occult neoplasia. Prompt recognition can lead to early diagnosis and management.

Protocol for Assessment of GIB in COVID-19 Patients Started on Anticoagulation

We suggest risk-stratifying COVID-19 patients receiving intermediate dosed or therapeutic anticoagulation by considering the following factors (see Fig. 1 for suggested protocol):

1. *Past medical history* History of PUD or previous GIB is associated with a higher risk of GIB. We recommend PPI prophylaxis in this high-risk group as well as *H.*

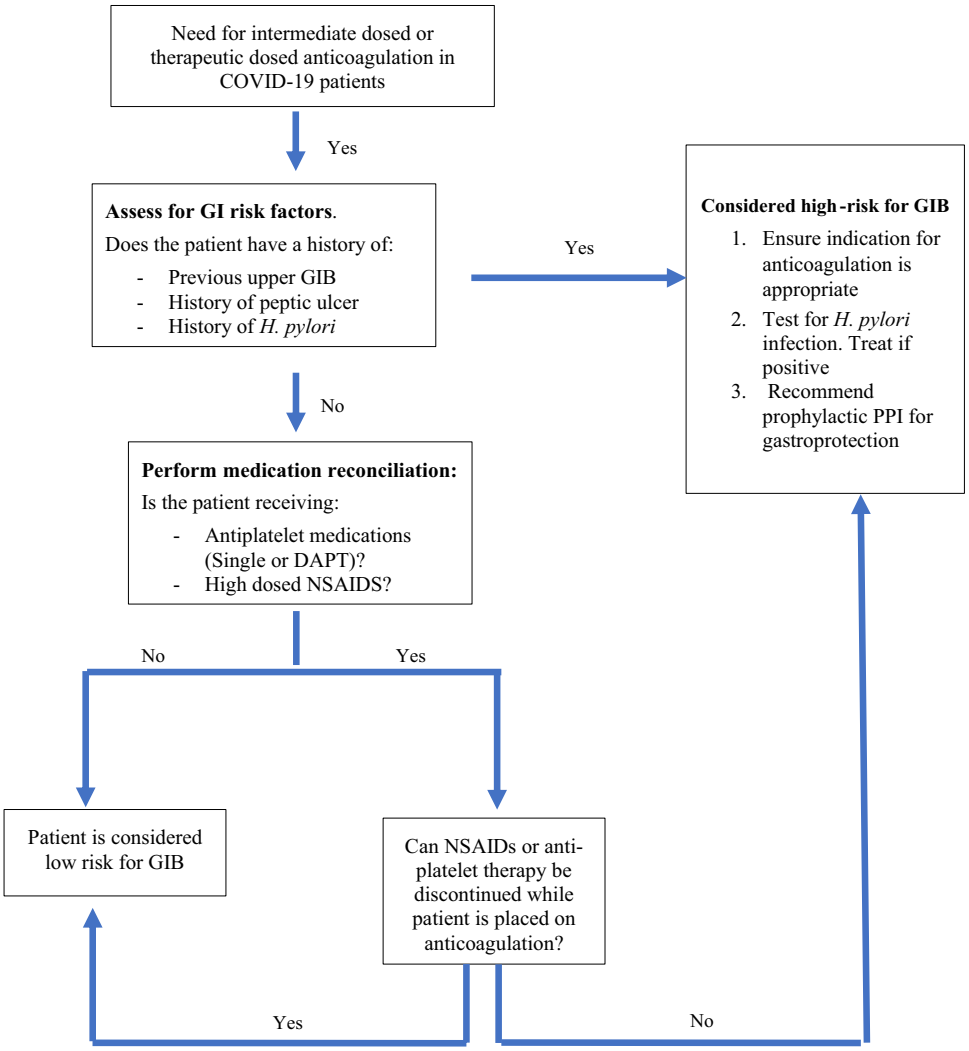

Fig. 1 Proposed algorithm to assess risk of GIB in COVID-19 patients undergoing intermediate dosed or therapeutic dosed anticoagulation

pylori testing in those with a history of PUD or previous GIB,

2. *Medications* High-dose NSAIDs, single antiplatelet therapy, and DAPT are considered risk factors for GIB and pose an additional risk when given concomitantly with anticoagulation. If medically appropriate and feasible, we recommend temporarily discontinuing these medications if therapeutic anticoagulation is pursued. If unable to discontinue these medications (i.e. DAPT should not be discontinued if there was a recent cardiac stent placement or acute coronary syndrome), we recommend testing for *H. pylori* and employment of PPI co-therapy.

Conclusion

Although no randomized controlled trial evidence is currently available to support empiric anticoagulation in COVID-19, more centers may adapt to an intermediate dose, therapeutic dose or prolonged duration of anticoagulation in patients given the high incidence of thromboembolic disease. As such, the incidence of readmissions for anticoagulation-associated GIB will likely rise. Given the morbidity and resource utilization associated with GIB, it will be important to mitigate the risk of bleeding by using *H. pylori* testing and eradication, PPI co-therapy, and limited antiplatelet drug use in appropriately selected patients. In a fragile patient population faced with an unprecedented infection with devastating manifestations, we must take action to reduce preventable complications, such as GIB.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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