13: Considerations for Certain Concomitant Medications in Patients with COVID-19

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Summary Recommendations
• Patients with COVID-19 who are receiving concomitant medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], statins, systemic or inhaled corticosteroids, nonsteroidal anti-inflammatory drugs, acid-suppressive therapy) for underlying medical conditions should not discontinue these medications during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition (**AIIa** for ACE inhibitors and ARBs; **AIII** for other medications). • The COVID-19 Treatment Guidelines Panel **recommends against** using medications off-label to treat COVID-19 if they have not demonstrated safety and efficacy in patients with COVID-19, except in a clinical trial **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Individuals with underlying medical conditions such as cardiovascular disease, pulmonary disease, diabetes, or malignancy are at higher risk of severe illness with COVID-19. These patients are often prescribed medications to treat their underlying medical conditions. It is unclear whether these concomitant medications have a positive or negative impact on the treatment and outcomes of COVID-19.

The following section reviews the available data on the use of certain concomitant medications for comorbid conditions in patients with COVID-19 and discusses the considerations clinicians should be aware of when evaluating a patient's concomitant therapy. When prescribing medications for the treatment of COVID-19, clinicians should always assess the patient's current medications for potential drug interactions and adverse effects. The decision to continue or change medication therapy should be based on an individual patient's condition.

Patients with COVID-19 who are treated with concomitant medications for an underlying medical condition should not discontinue these medications during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition **(AIII)**. Several commonly used medications have been proposed to have direct effects on SARS-CoV-2 or to impact the pathogenesis of COVID-19. This section will address considerations for using these medications as potential treatments for COVID-19 if data are available.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Recommendations

- Patients with COVID-19 who are receiving **angiotensin-converting enzyme (ACE) inhibitors** or **angiotensin receptor blockers (ARBs)** for cardiovascular disease (or other non-COVID-19 indications) should not discontinue these medications unless discontinuation is otherwise warranted by their clinical condition **(AIIa)**.
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **ACE inhibitors** or **ARBs** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

These recommendations are in accord with a joint statement of the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology.[1]

ACE2 is the cell surface receptor for SARS-CoV-2. It has been hypothesized that using ACE inhibitors or ARBs to modulate ACE2 could suppress or enhance SARS-CoV-2 replication.[2,3] Meta-analyses and an ongoing systematic review have not found an association between the use of ACE inhibitors or ARBs and the likelihood of a positive result on a SARS-CoV-2 test or the severity of COVID-19.[4,5]

In a multicenter, open-label randomized trial, hospitalized patients with COVID-19 (n = 659) who were receiving chronic ACE inhibitor therapy or ARB therapy were randomized to continue or discontinue their therapy for 30 days. Treatment of COVID-19 followed local standards of care, and the use of alternative therapies to replace the discontinued medications was at the discretion of the treating physician. The study did not enroll any patients who required invasive mechanical ventilation or who had hemodynamic instability or multiple organ failure.

Overall, there was no difference between the arms in the primary endpoint of days alive and out of the hospital; the mean number of days alive and out of the hospital was 21.9 days in the discontinuation arm and 22.9 days in the continuation arm (mean ratio 0.95; 95% CI, 0.90–1.01). No differences were observed in the secondary endpoints of the percentages of patients who experienced death, cardiovascular events, or COVID-19 progression. Subgroup analyses identified an interaction between the treatment effect and the subgroup of patients with greater severity of COVID-19 (those with oxygen saturation <94%, pulmonary infiltrates >50%, or a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] <300 mm Hg). There may be a clinical benefit to continuing ACE inhibitor therapy or ARB therapy in these patients. Because of limitations in the available data, it is difficult to interpret these findings in subsets of patients with certain comorbid conditions, severe or critical illness, and pre-existing diagnoses of heart failure.[6]

Additional investigations of the role of ACE inhibitors, ARBs, and recombinant human ACE2 in the management of COVID-19 are underway.[1] Please see *ClinicalTrials.gov* for the latest information.

Corticosteroids

Recommendation

- Patients with COVID-19 who are receiving **inhaled or systemic corticosteroids** for an underlying condition should not discontinue these medications unless discontinuation is otherwise warranted by their clinical condition **(AIII)**.

Systemic treatment with dexamethasone or other corticosteroids is recommended for certain populations of patients with COVID-19. See Therapeutic Management of Adults With COVID-19, Corticosteroids, and Special Considerations in Pregnancy for specific recommendations.

Oral corticosteroid therapy prescribed for an underlying medical condition (e.g., primary or secondary adrenal insufficiency, rheumatological diseases) should be continued in patients after the diagnosis of COVID-19.[7] Supplemental or stress-dose steroids may be indicated in individual cases.

Inhaled corticosteroids that are used daily by patients with asthma and chronic obstructive pulmonary disease to control airway inflammation should not be discontinued in patients with COVID-19. A large, retrospective study of adult patients with chronic obstructive pulmonary disease and asthma found that those who were prescribed high doses of inhaled corticosteroids had a higher risk of mortality than those who received other inhaled medications without corticosteroids; however, the study had limitations.[8] In fact, the authors suggested that this association may have been due to differences between the groups in the severity of the underlying disease, rather than a harmful effect of the inhaled corticosteroids. For patients with COVID-19 who require nebulized corticosteroids, precautions should be taken to minimize the potential for transmission of SARS-CoV-2 in the home and in health care settings.[9,10]

The use of corticosteroids has been associated with delayed viral clearance and/or worse clinical outcomes in patients with other viral respiratory infections.[11-13] Some studies have suggested that systemic corticosteroids slow SARS-CoV-2 clearance, especially when given earlier in the course of infection.[14-18] There is insufficient evidence to identify a relationship between inhaled corticosteroid use and the speed of viral clearance.

HMG-CoA Reductase Inhibitors (Statins)

Recommendations

- Patients with COVID-19 who are receiving **statin therapy** for an underlying condition should not discontinue these medications unless discontinuation is otherwise warranted by their clinical condition **(AIII)**.
- The Panel **recommends against** the use of **statins** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

HMG-CoA reductase inhibitors, or statins, affect ACE2 as part of their function in reducing endothelial dysfunction. It has been proposed that these agents have a potential role in managing patients with severe COVID-19.[19]

A large observational study in China found that the use of statins in hospitalized patients with COVID-19 was associated with a lower risk of all-cause mortality compared with patients who did not receive statins (aHR 0.63; 95% CI, 0.48–0.84; $P = 0.001$).[20] In contrast, a retrospective, multicenter study of critically ill patients with COVID-19 in Italy found no association between the long-term use of statins and mortality (aHR 0.98; 95% CI, 0.81–1.20; $P = 0.87$).[21] Similarly, recent receipt of statin therapy was not associated with a higher mortality risk (aHR 0.96; 95% CI, 0.78–1.18) or the severity of disease (aHR 1.16; 95% CI, 0.95–1.41) in a national cohort study of 4,842 patients with COVID-19 in Denmark.[22]

More data are needed to clarify the impact of statin therapy on COVID-19. Clinical trials that are evaluating the therapeutic impact of statins as an adjunctive therapy for COVID-19 are currently underway. Please see *ClinicalTrials.gov* for the latest information.

Nonsteroidal Anti-Inflammatory Drugs

Recommendations

- Patients with COVID-19 who are receiving **nonsteroidal anti-inflammatory drugs (NSAIDs)** for an underlying medical condition should not discontinue therapy unless discontinuation is otherwise warranted by their clinical condition **(AIII)**.
- Strategies for using **antipyretic therapy** (e.g., acetaminophen, NSAIDs) in patients with COVID-19 should remain similar to the approaches used in other patients **(AIII)**.

In March 2020, news agencies promoted reports that anti-inflammatory drugs may worsen COVID-19. It has been proposed that NSAIDs such as ibuprofen can increase the expression of $ACE2^2$ and inhibit antibody production.[23] Shortly after these reports, the Food and Drug Administration stated that there is no evidence linking the use of NSAIDs with worsening of COVID-19 and advised patients to use NSAIDs as directed.[24]

In a national cohort study of patients who tested positive for SARS-CoV-2 infection in Denmark, no association was found between a history of NSAID use and the need for hospitalization, the risk of mortality, or the severity of illness.[25]

Acid-Suppressive Therapy

Recommendations

- Patients with COVID-19 who are receiving **acid-suppressive therapy** for an underlying condition should not discontinue these medications unless discontinuation is otherwise warranted by their clinical condition **(AIII)**.
- The Panel **recommends against** the use of **famotidine** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Acid-suppressive therapies, such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), increase gastric pH. Low gastric pH is proposed to be a protective mechanism against infection with viruses that can enter the body through the gastrointestinal tract (e.g., enteric viruses, SARS-CoV).[26] Observational studies that have evaluated the relationship between the use of acid-suppressive therapy and the acquisition of SARS-CoV-2 or COVID-19 disease severity have produced mixed results.

A propensity-matched cohort study in South Korea observed that current PPI use was not associated with a higher risk of testing positive for SARS-CoV-2, but it was associated with a higher risk of severe illness.[27] An online survey conducted in the United States identified no association between the use of H2RAs and the risk of SARS-CoV-2 infection, while PPI therapy was associated with higher odds of receiving a diagnosis of SARS-CoV-2 infection, especially in those who received twice-daily doses of PPIs.[26] However, these studies had the inherent limitations of observational studies and studies that rely on surveys, and they likely had multiple confounding factors.

The impact of the H2RA famotidine on the outcomes of COVID-19 has been evaluated in observational studies. In a retrospective study of 878 hospitalized patients, receipt of famotidine (n = 83) was associated with lower odds of death.[28] In another retrospective study of 84 patients who received famotidine and a matched comparator group of 420 patients who did not, the use of famotidine was associated with a reduction in the composite outcome of death or intubation.[29] Only a small proportion of the patients enrolled in these studies received famotidine, and it is unclear what the indications for famotidine therapy were or whether there were other confounding factors. These limitations make it difficult to draw conclusions about the efficacy of using famotidine to treat patients with COVID-19.

Results from ongoing clinical trials will provide more insights into the role of famotidine in the treatment of COVID-19. Please see *ClinicalTrials.gov* for the latest information.

In patients with COVID-19 who require PPI therapy, the American College of Gastroenterology suggests using the lowest effective dose of the PPI.[30]

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