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*Mini Review Article*

# NSAIDs and COVID-19: A New Challenging Area

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**Abstract**

Considering the recent controversies regarding the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in Coronavirus disease 2019 (COVID-19) patients, and due to the limited published data in this field, we reviewed currently available evidence for the use of NSAIDs in viral respiratory tract infections to help make decisions in this area. Currently, there is insufficient evidence to judge the safety and efficacy of NSAIDs in patients with COVID-19. According to the current evidence, acetaminophen is the choice treatment for symptomatic relief. If the patients' symptoms are not controlled by acetaminophen, naproxen may be used as an alternative therapy.

## Introduction

Coronavirus disease 2019 (COVID-19) which was first diagnosed in China, characterized as a pandemic in March 2020 due to the increasing number of affected countries all around the world.[1] Fortunately, most of the patients (approximately 81%) have mild symptoms and do not require hospital intervention. International guidelines have recommended symptomatic therapy (for fever, myalgia, etc.) in patients with mild COVID-19.[2,3] Until now, acetaminophen and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been widely used as symptomatic relief of viral infections. However, due to the current controversies over NSAIDs use in acute respiratory tract infections (RTIs), the rational use of these medications should be considered in the COVID-19 pandemic. We aimed to review the current evidence to find out whether it is safe to administer NSAIDs in patients with COVID-19 or not.

## Pharmacology

NSAIDs may have positive or negative effects on viral infections through several mechanisms, which are briefly reviewed in this section:

1. Following the innate immune response induced after the pathogen invasion in alveolar space, NSAIDs interfere with the generation of prostaglandins E2 and I2 through the cyclooxygenases (COX) pathway.[4]
2. NSAIDs can also affect polymorphonuclear neutrophils (PMNs) through COX-dependent and COX-independent pathways, which result in modifications in their recruitment, diapedesis, phagocytic activity, and degranulation.[4]
3. These medications prevent biosynthesis of pre-resolving mediators (e.g. lipoxins and resolvins) and monocyte recruitment through inhibition of COX2-induced lipid mediator class switching. Thus, NSAIDs can reduce the clearance of infection, prolong the acute phase, and delay the recovery of inflammation.[4]
4. Naproxen has shown antiviral effects against influenza A and B virus. Naproxen targets and inhibits viral nucleoproteins (NPs), which in association with the ribonucleoprotein complex (RNP) are involved in the transcription and replication of influenza virus RNA.[5,6]
5. Indomethacin inhibits protein translation and viral replication through activation of a double-stranded RNA (dsRNA)-dependent protein kinase R (PKR) and phosphorylation of the eukaryotic initiation factor-2 α-subunit (eIF2α).[7] In another study, the antiviral activity of indomethacin against canine (CCoV) and human (SARS-CoV) coronaviruses was investigated and showed that the drug did not affect the attachment or entry of the virus, but was able to significantly inhibit virus RNA replication.[8]
6. One study reported that ibuprofen and indomethacin inhibit multidrug resistance protein 4 (MRP4); thus, they can prevent host cellular mechanisms involved in drug resistance and also increase intracellular concentrations of anti-Human Immunodeficiency Virus-1 medications (especially nucleoside reverse transcriptase inhibitors).[9]
7. On the other hand, a study demonstrated that ibuprofen may increase angiotensin-converting enzyme 2 (ACE2) expression,[10] which is considered as a host cell surface receptor for some kind of viruses.[11]

## Hypotheses and evidence of NSAIDs safety and efficacy in Respiratory Tract Infections RTIs other than COVID-19

Most studies regarding the effects of NSAIDs on RTIs have been conducted on naproxen, indomethacin, and ibuprofen. The studies have reported conflicting results on the safety and efficacy of these medications (especially for ibuprofen). Given the previous in vitro and in vivo studies that reported

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beneficial antiviral effects of naproxen,[5,6] a randomized clinical trial (RCT) was performed to realize the efficacy of naproxen on patients with H3N2 influenza. According to the results of this study, mortality and hospitalization rate decreased among the intervention group receiving naproxen (200 mg twice daily for 2 days) in combination with clarithromycin and oseltamivir.[12]

In numerous clinical trials, ibuprofen has been associated with increased risk of exacerbation of symptoms and subsequent complications for example empyema in both children and adults, by inhibiting the body's inflammatory response against infections. Thus, these studies recommended against routine ibuprofen use in acute RTIs unless the patients' symptoms are extremely annoying which are not controlled by acetaminophen.[13-16]

## Hypotheses and Evidence about the Safety and Efficacy of NSAIDs in Patients with COVID-19

Published data from hospitalized COVID-19 patients in Wuhan, China, demonstrated that underlying cardiovascular disease (20%) and hypertension (about 30-43%) are common risk factors in the infected population. However, none of these studies have identified previous NSAIDs use as a risk factor for the COVID-19. On the other hand, cardiac injuries (in 23% of patients) and hospital-acquired pneumonia (in 11.5% of patients) have been reported as complications of COVID-19 during ICU admissions.[17,18] Further, these two are important issues which require more attention in the use of NSAIDs in RTIs.

The only clinical recommendation for the use of NSAIDs in COVID-19 belongs to a "Chinese rapid advice guideline for the diagnosis and treatment of COVID-19", suggesting ibuprofen as an antipyretic treatment for fever higher than 38.5 (200 mg every 4-6 hours, maximum 4 doses per day).[19] All other published data in this field are hypotheses, which are based on the pathophysiology of the disease and the pharmacology of the NSAIDs. A response to an article published in BMJ,[20] has mentioned the possible role of naproxen in the prevention and treatment of COVID-19 patients in regions that have limited access to medications currently used in the world (e.g. Iran). On the other hand, a published correspondence points to the increased ACE2 expression by ibuprofen administration, which may lead to an enhanced risk of COVID-19 infection in this population.[21] In an in vivo study, the administration of ibuprofen for 8 weeks increased the expression of ACE2 in rat cardiac muscle cells,[10] confirming the hypothesis of this correspondence. Since the cellular attachment of COVID-19 may be enhanced by increased ACE2 expression,[22] the use of ibuprofen in these patients seems controversial. Given the growing concerns,[23,24] several reviews have been published based on little available evidence, most of which have failed to reach a definite conclusion. Some of them recommended not to use NSAIDs in COVID-19 as self-treatment,[25-27] and some of others declared that using NSAIDs may not lead to any trouble.[28,29]

## Conclusion

Two points to consider about the use of NSAIDs in acute RTIs include progression of symptoms or subsequent complications following administration of NSAIDs in acute RTIs,[4,16] as well as adverse cardiovascular effects of NSAIDs which are considered as risk factors for RTIs including COVID-19. Nevertheless, the frequency of adverse effects is different among NSAIDs; ibuprofen, diclofenac, and coxibs have the highest cardiovascular complications but naproxen (even high doses) has not shown significant cardiovascular problems in RCTs.[30]

Currently, there is not sufficient available evidence to judge the safety and efficacy of NSAIDs in patients with COVID-19. Based on studies conducted for other viral infections, acetaminophen is recommended as a choice treatment for fever and pain relief. The only exception is patients who are co-infected with influenza and COVID-19, which may benefit the positive effects of naproxen in influenza. If the patients' symptoms are not controlled by acetaminophen, the first choice among NSAIDs may be naproxen (given the fewer cardiovascular adverse effects and the available evidence for its efficacy in influenza) and the second one could be indomethacin (according to available in vitro and in vivo evidence for SARS).

Currently, available evidence is not conclusive to judge the patients' prognosis following ibuprofen use, and further clinical trials are required to make a definite decision. Because of higher cardiovascular adverse effects and probable risk of symptoms exacerbations or complications of other RTIs related to ibuprofen, it seems rational to limit the use of ibuprofen and replace acetaminophen or naproxen instead.

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## Conflicts of Interest

The authors declare that there are no conflicts of interest.

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