



# The use of ibuprofen to treat fever in COVID-19: A possible indirect association with worse outcome?

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## ABSTRACT

Fever has been reported as a common symptom occurring in COVID-19 illness. Over the counter antipyretics such as ibuprofen and acetaminophen are often taken by individuals to reduce the discomfort of fever. Recently, the safety of ibuprofen in COVID-19 patients has been questioned due to anecdotal reports of worsening symptoms in previously healthy young adults. Studies show that ibuprofen demonstrates superior efficacy in fever reduction compared to acetaminophen. As fever may have benefit in shortening the duration of viral illness, it is plausible to hypothesize that the antipyretic efficacy of ibuprofen may be hindering the benefits of a fever response when taken during the early stages of COVID-19 illness.

## Background

Recently, controversy concerning use of ibuprofen in patients with COVID-19 has arisen. The concern was initially expressed after an anecdotal report of 4 cases of worsening symptoms of COVID-19 in France that occurred after early treatment with ibuprofen in young people with no underlying health problems [1]. As a result, the WHO initially cautioned against the use of ibuprofen for symptoms of COVID-19. This initial recommendation was revised and now the European Medicines Agency and the WHO, citing the absence of clinical or population data, do not recommend nonsteroidal anti-inflammatory drugs (NSAIDs) be avoided when clinically indicated [2].

The concern related to ibuprofen use has centered on the pharmacological property of the drug and whether inhibition of the release of prostaglandins will interfere with the adaptive immune system [3]. However, aside from the direct anti-inflammatory effects of NSAIDs, there are also indirect confounding factors when ibuprofen is used to reduce fever. In the situation of early viral illness, the use of ibuprofen and acetaminophen in the home environment is often as an antipyretic. Since fever has been observed in up to 99% of COVID-19 cases [4], many patients may self treat their discomfort of an elevated temperature with over the counter agents such as ibuprofen or acetaminophen thereby unwittingly interfere with the benefits of fever in the natural course of the disease.

## Assessing ibuprofen safety in COVID-19

There are important factors which may be confounders in assessing causality of ibuprofen with possibly worse COVID-19 illness. First, fever has been shown to be beneficial toward a reduction in the duration of viral illness and the mortality associated with illness [5]. Outside of reducing patient discomfort, there is little evidence to support administration of antipyretics to reduce fever results in better overall outcomes in previously healthy patients [6]. To the contrary, in several studies, the use of antipyretics has been associated with an increase in mortality and morbidity [7]. It is therefore a concern of whether these agents may suppress the natural mechanism of the body to fight infection.

Secondly, there is evidence to support that ibuprofen is superior to acetaminophen in reducing fever. In a randomized controlled trial in children comparing ibuprofen and acetaminophen at equipotent doses, ibuprofen provided a larger temperature decrease and a longer duration of response [8]. Meta analyses have also shown that ibuprofen has a larger temperature reduction effect compared to acetaminophen in children [9] and in adults [10]. Thus, a superior antipyretic effect may be related to ibuprofen more effectively hindering the beneficial effect of fever in COVID-19 viral illness.

## Possible benefits of fever in COVID-19

To the extent a direct relationship between the fever response and a number of consequential impacts on healing processes in progress

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exists, these findings suggest allowing the natural response to occur is essential. Febrile temperatures have been shown to work as a systemic alert system activating the immune system during a challenge by invading pathogens [11]. Suppressing the fever response also blunts the associated hyperemic response, increased lymphocyte activity, and related oxygenation of organ tissues which leads to multiple organ failure in the COVID-19 patient. A recent study shows that COVID-19 proteins ORF8 and surface glycoproteins bind with the heme component of hemoglobin rendering it incapable of oxygen and CO<sub>2</sub> transport resulting in hypoxemia [12]. A physiologic fact is also that oxygen is more easily unloaded from hemoglobin to deliver it to tissues in need when temperature is increased [13].

## Conclusion

In conclusion, it is plausible to hypothesize that the antipyretic efficacy of ibuprofen may be hindering the benefits of a fever response. The difference in perceived safety of these agents in COVID-19 illness could be related to the more potent efficacy to reduce fever with ibuprofen compared to acetaminophen. Compelling data on the benefit of fever warrant further research and review to determine when to treat or withhold ibuprofen for early stage fever for COVID-19 and other related viral illnesses.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.109880>.

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