

COVID-19

LITERATURE REPOSITORY

Is the risk of ibuprofen or other non-steroidal anti-inflammatory drugs increased in COVID-19?

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Publication date

13 May 2020

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Discussion

Non-steroidal anti-inflammatory drugs (NSAIDs) include medications like ibuprofen (often referred to by one brand name, Nurofen™) commonly used to treat pain, inflammation and reduce fever. Recently, concerns have been circulating in both the media and medical literature regarding the use of NSAIDs in patients with COVID-19.

Where did this concern come from?

On March 14th 2020, the French Health Minister, Olivier Veran, tweeted in relation to COVID-19:

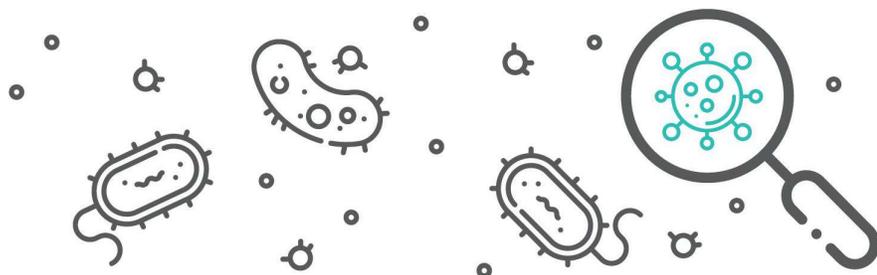
*"Taking anti-inflammatory drugs (ibuprofen, cortisone...) could be an aggravating factor of the infection. If you have a fever, take paracetamol. If you are already on anti-inflammatory drugs or in doubt, ask your doctor for advice."*¹

Later the same day, the French Ministry of Health released an official statement re-affirming Minister Veran's tweet, advising to avoid NSAID use in possible or confirmed cases of COVID-19. The statement, however, did not provide any details regarding adverse event reports, nor reference any studies as evidence for their decision. This tweet was widely circulated on social media causing lots of concern and confusion amongst healthcare professionals and the public alike.

To add to the confusion, on March 17th, the World Health Organization (WHO) released a statement advising that patients with COVID-19 avoid taking ibuprofen whilst the WHO looked into evidence of its use in this context. The following day the WHO retracted their initial advice following a systematic review², stating:

*"Based on currently available information, WHO does not recommend against the use of ibuprofen"*³.

Subsequently numerous other global authorities, including Australia's Therapeutic Goods Administration (TGA),⁴⁻⁷



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have released statements agreeing there is no reason for people with possible COVID-19 to avoid use of ibuprofen (or other NSAIDs). Based on current evidence, people already on regular NSAIDs should continue to take them (unless there is an alternative indication to stop them). It is recommended that the use of NSAIDs in each individual be reviewed with their doctor as an opportunity to stop any unnecessary use.

Unfortunately, there has been ongoing circulation of misleading and even fictitious information, particularly through social media, leading to ongoing community concern.

Is there any scientific evidence behind the concern?

Those who continue to advocate against the use of NSAIDs in COVID-19 cite a letter published in *The Lancet* on March 11th, 2020⁸. This letter discussed 3 studies which found a significant proportion of patients with COVID-19, particularly those with severe disease, had diabetes mellitus and/or hypertension (high blood pressure). The letter speculates that some medications used in managing those conditions may impact the patient's vulnerability to COVID-19 infection by raising an enzyme protein, ACE-2, which has been implicated in viral entry into cells⁹. It further hypothesises that NSAIDs such as ibuprofen may indirectly raise ACE-2 and affect disease outcomes. Of note, during the 2003 SARS-CoV outbreak, reduced ACE-2 levels were associated with severe disease and acute lung injury¹⁰ arguing against this concern. Research is ongoing in this area.

Whilst there is no clear evidence that ibuprofen is harmful in suspected or confirmed COVID-19, it is important to consider, as with any medication, whether there are patient factors which make adverse reactions more likely. There is evidence in adults with acute respiratory infections that NSAIDs may increase the risk of blood clotting, leading to acute myocardial infarction (when used for more than one week)¹¹ and stroke¹². However, these concerns are much less applicable to children.

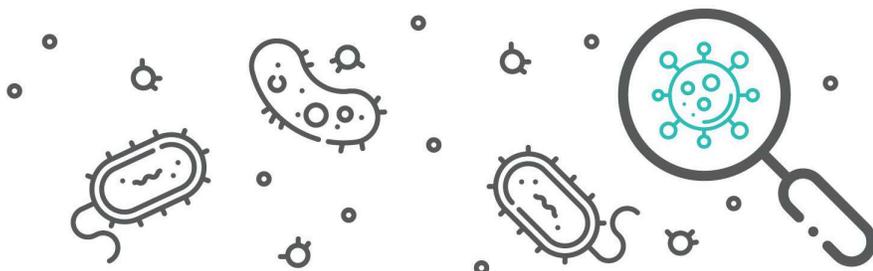
When the incidence of COVID-19 is low, the benefits of NSAIDs for a child in pain or significant discomfort will likely outweigh any theoretical harms, unless the child has an underlying risk factor such as chronic kidney impairment. When the incidence of COVID-19 is high, the risk-benefit balance is less certain; prescribers will have to weigh uncertainties and decide whether the benefits of an NSAID justify the theoretical risk.

Summary

A mildly symptomatic child with COVID-19 should be managed as per normal guidelines. There is currently no evidence to suggest that NSAID use in this population would increase their risk of severe disease from COVID-19. In very unwell children, such as those being managed in the Intensive Care Unit, careful consideration of the risk-benefit profile of all medications, including NSAIDs, should be considered based on the most recent evidence and in the context of the child's condition on a case-by-case basis.

Recommendations

1. There is no clear reason to routinely restrict the use of NSAIDs in most confirmed or suspected COVID-19 patients, particularly those with mild manifestations. Those with pre-existing conditions putting them at higher risk of stroke or myocardial infarction may benefit from avoiding NSAIDs use where able.
2. Based on current evidence, patients already on regular NSAIDs should not discontinue them over concern for COVID-19 without expert medical advice. Use this opportunity to review ongoing NSAID use in each individual, and consider ceasing in those without a clear indication.

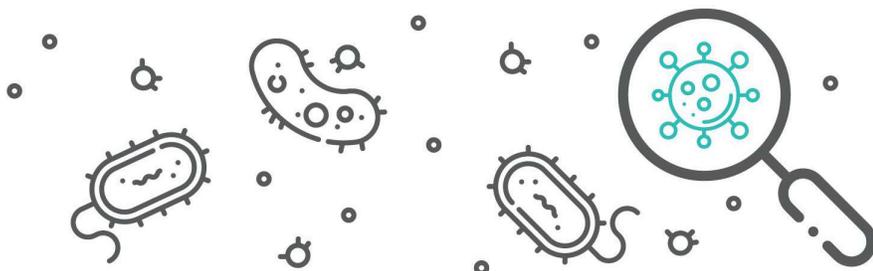


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