

# COVID-19 Scientific Advisory Group Rapid Response Report

## Key Research Topic: Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in COVID-19 Patients

1. Should patients who are on prescribed NSAIDs as chronic therapy stop taking these drugs if they develop COVID-19?
2. Should NSAIDs be used for anti-pyretic therapy or other indications in patients with COVID-19?

### Context

- There has been ongoing controversy in the media regarding the use of NSAIDs (eg. ibuprofen, aspirin, naproxen, diclofenac, etc.) in COVID-19 patients after comments from the French health minister and corresponding statements from the World Health Organization (WHO) that have since been retracted.
- The initial source for the possible detrimental effect of ibuprofen appears to be a letter published in The Lancet in March 2020 by Fang, Karakiulakis & Roth (2020). This letter observed that patients with diabetes mellitus, hypertension, and coronary heart disease were at increased risk of being hospitalized for COVID-19. The treatments for these groups of patients were not assessed in the study, however, these three conditions are often treated with angiotensin-converting enzyme (ACE) inhibitors. From these two observations, it was hypothesized that the increased expression of ACE2 (by ibuprofen, for example) could facilitate infection and worsen COVID-19 (Fang, Karakiulakis & Roth, 2020). Conversely, in a large retrospective cohort study, COVID-19 patients admitted to hospital who were already taking ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB) for hypertension had a significantly lower risk of all-cause mortality than those who were on different antihypertensive medication or on no medication (Zhang, Zhu, Cai et al., 2020)
- Numerous professional associations and health authorities have offered guidance to reassure their stakeholders, however, the guidance appears to be based on experience and practice rather than pandemic specific science.

### Key Messages from the Evidence Summary

- The evidence for this topic is gathered entirely from existing guidance and literature reviews. No primary studies were identified that support or refute the safety of NSAIDs in COVID-19 treatment.
- Guidance from Canadian sources and the European Medicines Agency state that patients who take prescribed NSAIDs prior to developing COVID-19 should continue to take their medication.
- Canadian, British, and American guidance almost unanimously suggest that acetaminophen should be used as the first-line treatment for fever. This is recommended out of an abundance of caution due to the absence of evidence regarding ibuprofen.

### Committee Discussion

The committee accepted the recommendations put forward and suggested the addition of a recommendation to address the risk of acute kidney injury due to NSAIDs for patients who are acutely unwell in an acute inpatient hospital setting, especially when other risk factors for acute kidney injury are present (Zhang, Donnan, Bell et al., 2017).

## Recommendations

1. For patients with mild COVID-19 illness who are being treated in an outpatient setting and are receiving NSAIDs as chronic therapy, there is no high quality evidence to suggest a risk of harm associated with NSAID use should the patient be infected with COVID-19. Therefore, patients on chronic NSAIDs who develop COVID-19 should not have treatment stopped for the sole purpose of preventing worsening outcomes.
2. For all hospitalized patients who are acutely unwell, including COVID-19 patients, consideration should be given to temporarily holding chronic NSAID therapy during their admission, particularly for those at increased risk of acute kidney injury.
3. For anti-pyretic therapy or other indications in patients with COVID-19, there is no high quality evidence to suggest a risk of harm associated with NSAID therapy. However, given the observational evidence, as a precautionary measure, NSAID use in patients with COVID-19 should be considered to be second line therapy after acetaminophen, reserved for patients that do not respond to acetaminophen therapy or where acetaminophen is contraindicated.

## Summary of Evidence

Literature for this review was collected from a database search covering OVID MEDLINE, LitCovid, PubMed, TRIP PRO, WHO COVID-19 Database, BMJ Best practice, Centre for Evidence Based Medicine (CEBM), National Collaborating Centre for Methods and Tools, European Centre for Disease Prevention and Control (ECDC), CADTH, Cambridge Coronavirus Free Access Collection, Cochrane, medRxiv, Google and Google Scholar. The search was limited to articles published after 2019. 242 articles were identified from the initial search. These were split into articles obtained from PubMed (154) and Other Sources (88). 16 articles were included in this review after screening according to the inclusion and exclusion criteria and critical appraisal requirements. The search was limited by the searched time period and the article language – although language was not an exclusion criterion, articles published in languages other than English (such as Chinese or Italian) were not included. Editorials, opinion pieces, and commentary articles were excluded from this review.

### *Evidence Challenges and Gaps*

The evidence for this topic is very low quality. No primary studies were identified that examined the safety of ibuprofen in the context of COVID-19. One review from the CEBM examined the safety of ibuprofen in other acute respiratory infections (ARI), but this has limited applicability to the topic at hand due to the interaction of ibuprofen with the receptor for cellular entry used by SARS-CoV-2 (ACE2) (Zhang, Penninger, Li et al., 2020; Fang, Karakiulakis & Roth, 2020).

All the relevant evidence collected in this search is either secondary literature (such as reviews) or grey literature (such as guidance). Primary sources identified by reviews suffer from the novelty of COVID-19 and so rely on SARS and MERS data, while guidance published by health authorities and professional associations appears to be based on the premise that the absence of evidence implies that practice should continue as before.

There were many opinion, editorial and commentary articles on this topic. While they are not necessarily incorrect, they represent a body of evidence that is not peer-reviewed and may not have the methodological rigour of systematic or accepted narrative reviews. Further, many of these articles seek to explain the theory behind the initial hypothesis but do not add anything to the body of knowledge.

### *Evidence from the grey literature*

Grey literature and secondary literature make up the body of evidence for this review. Within these, NSAIDs as antipyretic treatment was the dominant guidance offered.

*Should patients who are on prescribed NSAIDs as chronic therapy stop taking these drugs if they develop COVID-19?*

Four pieces of guidance were identified that address this question. All four references advise that people taking NSAIDs as a pre-existing prescription should continue to take them. (Public Health Ontario, 2020; Health Canada, 2020; Canadian Pharmacists Association (CPhA), 2020; European Medicines Agency, 2020). The CPhA (2020) was the only body that noted the confounding factors in COVID-19 risk and the absence of evidence supporting or refuting the safety of ibuprofen, thus recommending that when NSAID use is unavoidable they should be used at the lowest effective dose and for the shortest duration (Canadian Pharmacists Association, 2020). Public Health Ontario (2020) and Health Canada (2020) both advise continuing NSAID medication but also note that concerned patients should consult with their healthcare professional.

*Should NSAIDs be used for anti-pyretic therapy or other indications in patients with COVID-19?*

Advice relating to NSAIDs for anti-pyretic therapy was found in 16 of the included references. The absence of evidence on the safety or harm of ibuprofen was often noted as reason to be cautious, but not as a reason to stop using NSAIDs altogether. Almost unanimously, the articles included in this review suggested using acetaminophen as the first-line medication for fever.

Guidance from England aligned with the findings of a review conducted by the National Institute for Health and Care Excellence (NICE). The review concluded that the absence of evidence is not a strong reason to continue or discontinue the status quo, and recommended caution in prescribing NSAIDs (NICE, 2020). The practical implication of this finding is that guidance from NHS England, English professional associations, and reviews originating in England all advise that paracetamol (acetaminophen) is preferred as anti-pyretic treatment for both children and adults out of an abundance of caution (Park et al., 2020; Heneghan & Brassey, 2020; British Thoracic Society, 2020; Royal College of Paediatrics and Child Health, 2020; NHS England, 2020).

Canadian guidance flows from Health Canada, which supports the judgement of clinicians in prescribing antipyretics (Health Canada, 2020). In August 2019, Health Canada initiated a yet-unpublished safety review of ibuprofen and the risk of certain serious bacterial infections in children with chicken pox and has recently concluded there was no link (Health Canada, 2020). Canadian guidance, therefore, is equivocal in that it doesn't advise against using ibuprofen and other NSAIDs but suggests using acetaminophen as the first-line antipyretic (Public Health Ontario, 2020; Canadian Pharmacists Association, 2020; Canadian Pediatric Society, 2020).

Four peer-reviewed review articles were identified and included in this report. Each acknowledges the absence of evidence relating to the safety of ibuprofen in COVID-19, and supports using caution when treating fever in COVID-19 (Gupta et al., 2020; Kakodkar et al., 2020; Favalli et al., 2020; Russell et al., 2020). The American Society for Critical Care Medicine also acknowledges the lack of evidence and recommend using acetaminophen over no treatment (Alhazzani et al. 2020).

No evidence was identified that actively discouraged the used of ibuprofen as an antipyretic in COVID-19.

*Evidence from the primary literature*

No primary evidence was identified relating to this topic.

## Evolving Evidence

The media furor over the safety of ibuprofen has relented somewhat over the past two weeks. However, the question has still spurred reviews and guidance to reassure clinicians. A search of [clinicaltrials.gov](https://clinicaltrials.gov) on April 18, 2020 identified four registered clinical trials evaluating outcomes of COVID-19 symptom management using Aspirin (2), ibuprofen (1), and naproxen (1).

Date question received by advisory group: April 16, 2020

Date report submitted to committee: April 21, 2020

Date of first assessment: April 22, 2020

## Authorship and Committee Members

This review was written by Rachael Erdmann and Ania Kania-Richmond, and scientifically reviewed by Jeremy Slobodan, Christopher Mody (external reviewer), Kelly Zarnke (external reviewer), and Susanne Benseler (external reviewer). The full Scientific Advisory Group was involved in discussion and revision of the document: Lynora Saxinger (co-chair), Braden Manns (co-chair), John Conly, Alexander Doroshenko, Shelley Duggan, Nelson Lee, Elizabeth MacKay, Andrew McRae, Jeremy Slobodan, James Talbot, Brandie Walker, and Nathan Zelyas.

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## Appendix

### List of Abbreviations

ACE: Angiotensin-converting enzyme

ACEI: Angiotensin-converting enzyme inhibitor

AHS: Alberta Health Services

ARB: Angiotensin receptor blocker

CEBM: Centre for Evidence-Based Medicine

COVID-19: Coronavirus Disease-2019

CPhA: Canadian Pharmacists Association

EMA: European Medicines Agency

KRS: Knowledge Resource Services

MERS: Middle East Respiratory Syndrome

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NSAID: Non-steroidal anti-inflammatory drug

SAG: Scientific Advisory Group

SARS: Severe Acute Respiratory Syndrome

WHO: World Health Organization

### Literature Search Details

A literature search was conducted by Rachel Zhao from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. KRS searched databases for articles published 2019 and included: OVID MEDLINE, LitCovid, PubMed, TRIP PRO, WHO COVID-19 Database, BMJ Best practice, Centre for Evidence Based Medicine (CEBM), National Collaborating Centre for Methods and Tools, European Centre for Disease Prevention and Control (ECDC), CADTH, Cambridge Coronavirus Free Access Collection, Cochrane, medRxiv, Google and Google Scholar. Briefly, the search strategy involved combinations of keywords and subject headings including:

- Novel coronavirus / SARS-CoV-2 / COVID-19
- Non-steroidal anti-inflammatory drugs (MeSH term)

242 articles were identified from the initial search. These were split into articles obtained from PubMed (154) and Other Sources (88). 19 articles were included in this review after screening according to the inclusion and exclusion criteria and critical appraisal. Following the title and abstract screen, 6 articles were retained from the PubMed search and 30 were retained from the search of the other databases and sources. 4 articles were

identified by ad hoc inclusion of relevant studies from reference lists. 21 articles were excluded following full-text screening. In total, 16 articles were included in this review.

Table 1. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> <li>- Chronic use of NSAID in COVID-19</li> <li>- NSAID as an anti-pyretic in COVID-19 (non-chronic usage)</li> <li>- SARS-CoV-2</li> <li>- Aspirin (ASA/acetylsalicylic acid) and baby aspirin</li> <li>- Advil (ibuprofen)</li> <li>- Aleve (naproxen)</li> <li>- Voltaren (diclofenac)</li> <li>- Describes adverse events or complications</li> <li>- Describes positive or negative patient outcomes</li> <li>- Guidelines, systematic reviews, meta-analysis, clinical trials, abstracts, letters narrative reviews (anything with a methodology)</li> <li>- Any jurisdiction</li> </ul>	<ul style="list-style-type: none"> <li>- Non-NSAID</li> <li>- NSAID not listed in inclusion criteria</li> <li>- Virus other than SARS-CoV-2</li> <li>- No outcomes or adverse events described</li> <li>- Non-clinical research</li> <li>- Commentary, opinion, editorial, news article</li> </ul>

## Critical Appraisal

Critical appraisal was conducted using an adapted Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). References were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. This modified MMAT method allows for a quick appraisal of the evidence and provides a yes/no decision for inclusion based on quality. However, it does not provide a ranking of the studies or detailed analysis of the aspects of quality. The table below summarizes the results of the critical appraisal and includes sources flagged by SAG members as receiving public attention or determined by the writer/reviewers to be relevant to the question.

Table 2. Summary of quality assessment results for articles included in this review

	Reference	Quality Appraisal Criteria
1.	Alhazzani, 2020	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, opinion, editorial, preprint <input checked="" type="checkbox"/> Guideline: Society for Critical Care Medicine <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
2.	British Thoracic Society, 2020	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, opinion, editorial, preprint

		<input checked="" type="checkbox"/> Guideline: British Paediatric Respiratory Society <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
3.	Canadian Paediatric Society, 2020	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, opinion, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input checked="" type="checkbox"/> Other: Position Statement 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
4.	Canadian Pharmacists Association, 2020	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, opinion, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input checked="" type="checkbox"/> Other: Backgrounder 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
5.	DTB Select, 2020	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, opinion, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input checked="" type="checkbox"/> Other: Bulletin 2a) Are there clear research questions or a clearly identified issue? <input type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
6.	Favalli, 2020	1) <input checked="" type="checkbox"/> Peer-reviewed: Narrative review <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, opinion, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue?

		<input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
7.	Gupta, 2020	1) <input checked="" type="checkbox"/> Peer-reviewed: Narrative review <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, opinion, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
8.	Health Canada, 2020	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, opinion, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input checked="" type="checkbox"/> Other: Recall/Alert 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
9.	Heneghan, 2020	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, opinion, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input checked="" type="checkbox"/> Other: CEBM Rapid Review 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
10.	Kakodkar, 2020	1) <input checked="" type="checkbox"/> Peer-reviewed: Literature review <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, opinion, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?



		<input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
11.	NHS England, 2020	<p>1) <input type="checkbox"/> Peer-reviewed: &lt;specify study type&gt;  <input checked="" type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Commentary, opinion, editorial, preprint  <input checked="" type="checkbox"/> Guideline: NHS England  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
12.	NICE, 2020	<p>1) <input type="checkbox"/> Peer-reviewed: &lt;specify study type&gt;  <input checked="" type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Commentary, opinion, editorial, preprint  <input checked="" type="checkbox"/> Guideline: National Institute for Health and Care Excellence  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
13.	Park, 2020	<p>1) <input type="checkbox"/> Peer-reviewed: &lt;specify study type&gt;  <input checked="" type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Commentary, opinion, editorial, preprint  <input type="checkbox"/> Guideline: &lt;Specify source &gt; (AHS, PHAC, WHO, Reputable research group, other)  <input checked="" type="checkbox"/> Other: CEBM Rapid Review</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
14.	Public Health Ontario, 2020	<p>1) <input type="checkbox"/> Peer-reviewed: &lt;specify study type&gt;  <input checked="" type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Commentary, opinion, editorial, preprint  <input checked="" type="checkbox"/> Guideline: Public Health Ontario  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
15.	Royal College of Paediatrics and Child Health, 2020	<p>1) <input type="checkbox"/> Peer-reviewed: &lt;specify study type&gt;  <input checked="" type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Commentary, opinion, editorial, preprint  <input checked="" type="checkbox"/> Guideline: Royal College of Paediatrics and Child Health</p>

		<input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
16.	Russell, 2020	1) <input checked="" type="checkbox"/> Peer-reviewed: Systematic Review <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, opinion, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)

## Reference List

Alhazzani, W., Møller, M. H., Arabi, Y. M., Loeb, M., Gong, M. N., Fan, E., ... & Du, B. (2020). Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive care medicine*, 1-34. Retrieved from: <https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-U>. Accessed 19 April 2020.

British Thoracic Society. (2020). Guidance for the clinical management of children admitted to hospital with suspected COVID-19. Retrieved from: <https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/bprs-guidance-on-children-admitted-to-hospital-with-covid-19/>. Accessed 19 April 2020.

Canadian Paediatrics Society. (2020). Can NSAIDs be used in children when COVID-19 is suspected?. Retrieved from: <https://www.cps.ca/en/documents/position/can-nsaids-be-used-in-children-when-covid-19-is-suspected>. Accessed 19 April 2020.

Canadian Pharmacists Association. (2020). Use of NSAIDs in patients with COVID-19: what is the evidence?. Retrieved from: <https://www.pharmacists.ca/cpha-ca/assets/File/cpha-on-the-issues/Use-of-NSAIDs-in-patients-with-COVID-19-FINAL-EN.pdf>. Accessed 19 April 2020.

DTB Select. (2020). EMA advice on the use of NSAIDs for Covid-19. *Drug and Therapeutics Bulletin*. Retrieved from: <https://dtb.bmj.com/content/early/2020/03/31/dtb.2020.000021.full>. Accessed 19 April 2020.

Fang, L., Karakiulakis, G., & Roth, M. (2020). Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?. *The Lancet. Respiratory medicine*, 8(4), e21. Retrieved from: [https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(20\)30116-8/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30116-8/fulltext). Accessed 18 April 2020.

Favalli, E. G., Ingegnoli, F., De Lucia, O., Cincinelli, G., Cimaz, R., & Caporali, R. (2020). COVID-19 infection and rheumatoid arthritis: Faraway, so close!. *Autoimmunity reviews*, 102523. Retrieved from: <https://www.sciencedirect.com/science/article/pii/S1568997220300781>. Accessed 19 April 2020.

Gupta R, Misra A. (2020). Contentious issues and evolving concepts in the clinical presentation and management of patients with COVID-19 infection with reference to use of therapeutic and other drugs used in Co-morbid

diseases (Hypertension, diabetes etc). *Diabetes Metab Syndr.* 14(3):251-254. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102586/>. Accessed 19 April 2020.

Health Canada. (2020). No scientific evidence that ibuprofen worsens COVID-19 symptoms. Health Canada Recalls and Alerts. Retrieved from: <https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2020/72633a-eng.php>. Accessed 19 April 2020.

Heneghan, C., Brassey, J. (2020). COVID-19: NSAIDs in Acute Respiratory Infection. *Oxford COVID-19 Evid Serv.* Retrieved from: <https://www.cebm.net/oxford-covid-19/nsaids-in-acute-respiratory-infection>. Accessed 19 April 2020.

Hong, Quan Nha et al. (2018). The Mixed Methods Appraisal Tool (MMAT) Version 2018 for Information Professionals and Researchers'. 1 Jan. 2018 : 285 – 291. Retrieved from: [http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/attach/127916259/MMAT\\_2018\\_criteria-manual\\_2018-08-01\\_ENG.pdf](http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/attach/127916259/MMAT_2018_criteria-manual_2018-08-01_ENG.pdf)

Kakodkar P, Kaka N, Baig MN. (2020). A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID-19). *Cureus.* 12(4):e7560. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7138423/>. Accessed 19 April 2020.

NHS England. (2020). Clinical guide for the management of palliative care in hospital during the coronavirus pandemic. Retrieved from: <https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/C0081-Speciality-guide-Palliative-care-and-coronavirus-FINAL-02.04.20.pdf>. Accessed 19 April 2020.

NICE. (2020). COVID-19 rapid evidence summary: acute use of non-steroidal anti-inflammatory drugs (NSAIDs) for people with or at risk of COVID-19. Retrieved from: <https://www.nice.org.uk/advice/es23/resources/covid19-rapid-evidence-summary-acute-use-of-nonsteroidal-antiinflammatory-drugs-nsaids-for-people-with-or-at-risk-of-covid19-pdf-1158174128581>. Accessed 19 April 2020.

Park, S., Brassey, J., Heneghan, C., Mahtani, K. (2020). Managing Fever in adults with possible or confirmed COVID-19 in primary care. *Oxford COVID-19 Evid Serv.* Retrieved from: <https://www.cebm.net/covid-19/managing-fever-in-adults-with-possible-or-confirmed-covid-19-in-primary-care/>. Accessed 19 April 2020.

Public Health Ontario. (2020). COVID-19 What We Know So Far About...Use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs). Retrieved from: <https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/what-we-know-nsaids.pdf?la=en>. Accessed 19 April 2020.

Royal College of Paediatrics and Child Health. (2020). COVID-19 - guidance for paediatric services. Retrieved from: <https://www.rcpch.ac.uk/resources/covid-19-guidance-paediatric-services>. Accessed 19 April 2020.

Russell, B., Moss, C., George, G., Santaolalla, A., Cope, A., Papa, S., & Van Hemelrijck, M. (2020). Associations between immune-suppressive and stimulating drugs and novel COVID-19—a systematic review of current evidence. *ecancermedicalscience*, 14. Retrieved from: <https://ecancer.org/en/journal/article/1022-associations-between-immune-suppressive-and-stimulating-drugs-and-novel-covid-19-a-systematic-review-of-current-evidence>. Accessed 29 April 2020.

Zhang, X., Donnan, P. T., Bell, S., & Guthrie, B. (2017). Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis. *BMC nephrology*, 18(1), 256. Retrieved from: <https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-017-0673-8>. Accessed 21 April 2020.

Zhang, H., Penninger, J. M., Li, Y., Zhong, N., & Slutsky, A. S. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive care medicine*, 1-5. Retrieved from: <https://link.springer.com/article/10.1007/s00134-020-05985-9>. Accessed 20 April 2020.

Zhang, P., Zhu, L., Cai, J., Lei, F., Qin, J. J., Xie, J., ... & Xia, M. (2020). Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19. *Circulation Research*. Retrieved from: <https://www.ahajournals.org/doi/pdf/10.1161/CIRCRESAHA.120.317134>. Accessed 20 April 2020.

## Search Strategy

### Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to April 15, 2020

#	Searches	Results
1	exp Coronavirus/ or exp Coronavirus Infections/ or coronaviru*.mp. or "corona virus*".mp. or ncov*.mp. or n-cov*.mp. or "novel cov".mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-COV-2.mp. or SARSCOV-2.mp. or SARSCOV2.mp. or SARSCOV19.mp. or Sars-Cov-19.mp. or SarsCov-19.mp. or SARSCOV2019.mp. or Sars-Cov-2019.mp. or SarsCov-2019.mp. or "severe acute respiratory syndrome cov 2".mp. or "2019ncov".mp. or "2019ncov".mp.	23331
2	exp Anti-Inflammatory Agents, Non-Steroidal/	196204
3	antipyretics/	2654
4	(anti-inflammatory analgesic* or anti-inflammatory agent* or aspirin like agent* or nsaid or nsaid or antiinflammatory agent* or anti-inflammatory drug* or aspirin like drug* or nsaid or nsaid or antiinflammatory drug*).kf,tw.	63319
5	("4,5-Dihydro-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-amine" or 66000-40-6 or "bw 755c" or bw755c).kf,tw.	680
6	(aspirin or acetysal* or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin or acetylsalicylic acid).kf,tw.	55812
7	(diclofenac or dichlofenal or "diclonate p" or diclophenac or dicrofenac or feloran or novapirina or orthofen or orthophen or ortofen or voltaren or voltarol).kf,tw.	11797
8	(diflunisal or dolobid or dolobis or dolocid).kf,tw.	731
9	(fenoprofen or nalfon or nalgesic).kf,tw.	418
10	(flurbiprofen or ansaid or cebutid or dobrofen or flubiprofen or flugalin or fluriproben or froben or neo artrol or novo flurprofen or ocufen or strefen).kf,tw.	2395

11	(advil or ibuprofen or brufen or ibumetin or motrin or nuprin or rufen or salprofen or trauma dolgit gel).kf,tw.	13384
12	(indomethacin or amuno or indocid or Indocin or metindol or osmosin).kf,tw.	35751
13	(indoprofen or dexindoprofen).kf,tw.	197
14	(ketoprofen or alrheumat or alrheumum or benzoylhydratropic acid or orudis or profenid).kf,tw.	3845
15	ketorolac.kf,tw.	2866
16	(acular or toradol).kf,tw.	153
17	(masoprocol or meso nordihydroguaiaretic acid or actinex or dihydronorguaiaretic acid).kf,tw.	15
18	(meclofenamic acid or meclofenamate or meclomen).kf,tw.	1286
19	(mefenamic acid or apo mefenamic or contraflam or coslan or dysman or mefac or mefacit or mefenaminic acid or mefic or nu mefenamic or parkemed or pinalgesic or ponalar or ponalgic or ponmel or ponstan or ponstan forte or ponstel or ponsyl or pontal).kf,tw.	1372
20	(naproxen or anaprox or aleve or methoxypropioicin or naprosin or naprosyn or proxen or Synflex).kf,tw.	6132
21	(niflumic acid or donalgin or flunir or niflactol or niflugel or nifluril).kf,tw.	1100
22	(olopatadine or patanol).kf,tw.	336
23	(oxaprozin or danoprox or daypro or dayrun).kf,tw.	157
24	(oxyphenbutazone or diflamil or hydroxyphenylbutazone or oxyphenylbutazone or tanderil).kf,tw.	863
25	(phenylbutazone or butacote or butadion or butadiene or butapirazol or butapyrazole or butazolidin or diphenylbutazone or fenilbutazon).kf,tw.	8503
26	(piroxicam or feldene).kf,tw.	3000
27	(salicylates or salicylic acids).kf,tw.	3289
28	sodium salicylate.kf,tw.	2406
29	(sulfasalazine or asulfidine or azulfadine or azulfidine or pleon or salazopyrin or salazosulfapyridine or salicylazosulfapyridine or sulfasalazin-heyl or sulfasalazin medac or sulphasalazine or ucine or ulcol).kf,tw.	5000
30	(sulindac or sulindal or aclin or apo sulin or apo-sulin or arthrobid or arthrocline or chibret or clinoril or copal or kenalin or klinoril or novo-sundac).kf,tw.	2004
31	suprofen.kf,tw.	288

32	tolmetin.kf,tw.	417
33	(cyclooxygenase inhibitor* or prostaglandin synthesis antagonist* or cyclo oxygenase inhibitor* or cyclooxygenase inhibitor* or prostaglandin endoperoxide synthase inhibitor* or prostaglandin synthase inhibitor*).kf,tw.	5870
34	(celecoxib or celebrex).kf,tw.	6267
35	(etodolac or etodolic acid or lodine or ramodar or ultradol).kf,tw.	673
36	(etoricoxib or arcoxia).kf,tw.	710
37	(meloxicam or masflex or meloxicam or mobec or Mobic or mobicox or movalis or movicox or parocin or reumoxicam or uticox).kf,tw.	2075
38	(nabumetone or apo-nabumetone or aponabumetone or arthrxan or gen-nabumetone or listran or mebutan or nabucox or nabumeton or Relafen or relif or relifex).kf,tw.	460
39	(antipyretic or antifebrile or anti-pyretic or anti-febrile).kf,tw.	4366
40	or/2-37	277884
41	1 and 40	47
42	limit 41 to (english language and yr="2019 -Current")	22

### LitCovid

anti-inflammatory or aspirin or nsaid or nsaid or antiinflammatory or [naproxen](#) or anaprox or methoxypropicoin or naprosin or naprosyn or proxen or Synflex or advil or aleve or acetylsalicylic acid or ibuprofen or brufen or ibumetin or motrin or nuprin or rufen or salprofen or trauma dolgit gel or antipyretic or antifebrile or anti-pyretic or anti-febrile or cyclooxygenase inhibitors or prostaglandin synthesis antagonist or cyclo oxygenase inhibitors or cyclooxygenase inhibitors or prostaglandin endoperoxide synthase inhibitors or prostaglandin synthase inhibitors

### TRIP PRO / Google / Google Scholar

(anti-inflammatory or aspirin or nsaid or nsaid or antiinflammatory or [naproxen](#) or anaprox or methoxypropicoin or naprosin or naprosyn or proxen or Synflex or advil or aleve or acetylsalicylic acid or ibuprofen or brufen or ibumetin or motrin or nuprin or rufen or salprofen or trauma dolgit gel or antipyretic or antifebrile or anti-pyretic or anti-febrile or cyclooxygenase inhibitors or prostaglandin synthesis antagonist or cyclo oxygenase inhibitors or cyclooxygenase inhibitors or prostaglandin endoperoxide synthase inhibitors or prostaglandin synthase inhibitors) AND (coronaviru\* OR "corona virus" OR ncov\* OR n-cov\* OR COVID-19 OR COVID19 OR COVID-2019 OR COVID2019 OR SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019 OR "severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus\*" OR "2019 ncov" OR 2019ncov OR Hcov\*) from:2019

### PubMed

(("anti-inflammatory agents, non-steroidal"[MeSH Terms]) OR (antipyretics[MeSH Terms]) or anti-inflammatory[Title/Abstract] or aspirin[Title/Abstract] or nsaid[Title/Abstract]s or nsaid[Title/Abstract] or antiinflammatory[Title/Abstract] or naproxen[Title/Abstract] or anaprox[Title/Abstract] or methoxypropicoin[Title/Abstract] or naprosin[Title/Abstract] or naprosyn[Title/Abstract] or proxen[Title/Abstract] or Synflex[Title/Abstract] or advil[Title/Abstract] or aleve[Title/Abstract] or acetylsalicylic acid[Title/Abstract] or ibuprofen[Title/Abstract] or brufen[Title/Abstract] or ibumetin[Title/Abstract] or motrin[Title/Abstract] or nuprin[Title/Abstract] or rufen[Title/Abstract] or salprofen[Title/Abstract] or trauma dolgit gel[Title/Abstract] or antipyretic[Title/Abstract] or antifebrile[Title/Abstract] or anti-pyretic[Title/Abstract] or anti-febrile[Title/Abstract] or cyclooxygenase inhibitors[Title/Abstract] or prostaglandin synthesis antagonist[Title/Abstract] or cyclo oxygenase inhibitors[Title/Abstract] or cyclooxygenase inhibitors[Title/Abstract] or prostaglandin endoperoxide synthase inhibitors[Title/Abstract] or prostaglandin synthase inhibitors[Title/Abstract]) AND (((wuhan[tw] AND (coronavirus[tw] OR corona virus[tw])) OR coronavirus\*[ti] OR COVID\*[tw] OR nCov[tw] OR 2019 ncov[tw] OR novel coronavirus[tw] OR novel corona virus[tw] OR covid-19[tw] OR SARS-COV-2[tw] OR Severe Acute Respiratory Syndrome Coronavirus 2[tw] OR coronavirus disease 2019[tw] OR corona virus disease 2019[tw] OR new coronavirus[tw] OR new corona virus[tw] OR new coronaviruses[all] OR novel coronaviruses[all] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[nm] OR 2019 ncov[tw] OR nCov 2019[tw] OR SARS Coronavirus 2[all]) AND (2019/12[dp]:2020[dp]))

#### WHO COVID-19 Database

(tw:("anti inflammatory agents nonsteroidal" )) OR (tw:("anti inflammatory agents")) OR (tw:("anti inflammatories")) OR (tw:("nsaids")) OR (tw:("aspirin")) OR (tw:("ibuprofen")) OR (tw:("naproxen"))