The COVID-19 ibuprofen controversy: A systematic review of NSAIDs in adult acute lower respiratory tract infections

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Aims: In light of the recent safety concerns relating to NSAID use in COVID-19, we sought to evaluate cardiovascular and respiratory complications in patients taking NSAIDs during acute lower respiratory tract infections.

Methods: We carried out a systematic review of randomised controlled trials and observational studies. Studies of adult patients with short-term NSAID use during acute lower respiratory tract infections, including bacterial and viral infections, were included. Primary outcome was all-cause mortality. Secondary outcomes were cardiovascular, renal and respiratory complications.

Results: In total, eight studies including two randomised controlled trials, three retrospective and three prospective observational studies enrolling 44,140 patients were included. Five of the studies were in patients with pneumonia, two in patients with influenza, and one in a patient with acute bronchitis. Meta-analysis was not possible due to significant heterogeneity. There was a trend towards a reduction in mortality and an increase in pleuro-pulmonary complications. However, all studies exhibited high risks of bias, primarily due to lack of adjustment for confounding variables. Cardiovascular outcomes were not reported by any of the included studies.

Conclusion: In this systematic review of NSAID use during acute lower respiratory tract infections in adults, we found that the existing evidence for mortality, pleuro-pulmonary complications and rates of mechanical ventilation or organ failure is of extremely poor quality, very low certainty and should be interpreted with caution. Mechanistic and clinical studies addressing the captioned subject are urgently needed, especially in relation to COVID-19.

Keywords
cardiovascular cardiology, meta-analysis statistics and study design, respiratory medicine, systematic review statistics and study design

1 Introduction

Lower respiratory tract infections resulting in pneumonia and bronchiolitis are extremely common and, in 2016, accounted for...
COX-2 is induced at the site of injury by blocking inflammatory prostanooids produced by the enzyme cyclooxygenase-2 (COX-2). COX-2 is induced at the site of inflammation where it mediates swelling and pain and by both bacterial and viral mimetics where it mediates fever. A prospective study in France found that at least 50% of patients with pneumonia received an NSAID prescription. Furthermore, this number is likely to be an underestimate as NSAIDs are readily available and can be purchased over the counter.

With the recent outbreak of COVID-19, NSAIDs have been in the spotlight as French health officials recommended avoiding NSAIDs such as ibuprofen over concerns of worsening the course and outcome of COVID-19 infection. This led to substantial controversy, with several experts suggesting that NSAIDs were best avoided in patients with COVID-19 given the drugs’ safety profile. However, a response by the European Medicines Agency (EMA) stated that there was no scientific evidence establishing a link between ibuprofen and worsening of COVID-19. This is not the first time the safety of NSAIDs during pandemics has been brought into question—it has been hypothesised that the high fatality rate during the 1918 influenza pandemic, especially amongst young adults, might have been partly due to the use of the NSAID aspirin. Early deaths often presented with “wet” pneumonia received an NSAID prescription. Furthermore, this number is likely to be an underestimate as NSAIDs are readily available and can be purchased over the counter.

While we do not yet know of the respiratory effects of therapeutic doses caused by NSAIDs in infections such as COVID-19, these drugs are associated with cardiovascular, renal and gastrointestinal side effects and in people with a specific sensitivity, they can cause asthma. Given that NSAIDs are a mainstay of symptomatic relief therapy in respiratory infections, it is now important to elucidate if short-term NSAID use is detrimental to not only those with COVID-19, but also for patients with lower respiratory tract infections in general. In light of the ibuprofen–COVID-19 debate and the rapidly unfolding situation of the current pandemic, the author group collaborated to systematically assess the evidence pertaining to the safety of short-term NSAID use in lower respiratory tract infections. Our objective was to evaluate cardiovascular and respiratory complications in patients taking NSAIDs during an acute lower respiratory tract infection.

2 METHODS

2.1 Selection of studies for inclusion

His systematic review and meta-analysis was performed according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA guidelines. The full review protocol was registered on PROSPERO (CRD42020176168) prior to data extraction. A systematic electronic search of Embase, Medline, Cochrane Controlled Register of Trials (CENTRAL) and Clinical Trials. Gov was performed to identify relevant publications from inception to 21 March 2020. The full details of the search terms can be found in Appendix A. Citations were screened by title and abstract by two independent reviewers from a pool of six. Any disagreements were resolved by a third reviewer. Relevant full texts were then retrieved for screening by two independent reviewers from a pool of six. Any disagreements were resolved by a third reviewer and reasons for exclusion were documented. Any non-English articles were translated. References of included studies and review articles were manually screened for further eligible studies. Authors were contacted when necessary.

2.2 Types of studies for inclusion

We included clinical randomised controlled trials (RCTs) assessing the safety profile of NSAID use during an acute lower respiratory tract infection. The search was extended to include the following quasi experimental and observational studies: controlled pre/post intervention, prospective and retrospective cohort, cross-sectional and case-control studies. We excluded case reports, pharmacodynamic or pharmacokinetic studies that did not report clinical outcomes and studies with less than five patients.

2.3 Participants/population

The search was limited to studies that reported the safety profile of any NSAID used during an acute lower respiratory tract infection in adults (age ≥18 years). The lower respiratory tract was defined as a distal airway infection including either the trachea, bronchi or lungs. Types of infections included viral, typical and atypical bacterial. We excluded chronic lung infections, aspiration pneumonia and fungal infections. Acute infections in patients with chronic lung diseases as specified by authors of identified studies, e.g. acute infections in patients with chronic obstructive pulmonary disease, were included. Patients with chronic NSAID use were excluded as we were primarily interested in short-term NSAID use.

2.4 Interventions/comparator

The interventions included any non-steroidal anti-inflammatory drug including but not limited to: aspirin, ibuprofen, naproxen, diclofenac and celecoxib. The comparators included non-exposed group including placebo, alternative NSAID or any other drug.
2.4.1 | Outcome domains of interest

Our primary outcome was all cause mortality and longest available follow-up period. Our secondary outcomes included major adverse cardiac and cerebrovascular events (MACCE), renal complications and respiratory complications (including adult respiratory distress syndrome [ARDS], mechanical ventilation, tracheostomy, abscess/empyema). We did not include gastrointestinal complications.

2.4.2 | Data extraction

Data from included studies was extracted onto an online form using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Data relating to summary estimates of baseline characteristics and the outcomes stated were extracted by two independent authors from a pool of six with any disagreements being resolved by consensus or consulting a third reviewer. The risk of bias for each included study was independently assessed by two review authors from a pool of six with any disagreements resolved by consensus or consulting a third reviewer. For RCTs, criteria from the Cochrane Handbook for Systematic Reviews of Interventions14 was used and the ROBINS-I tool16 for observational studies. The risk of bias from each study was taken into consideration when discussing any treatment effects.

2.4.3 | Subgroup analysis

We had planned to carry out the following subgroup analysis:

- Types of NSAID used (e.g. Ibuprofen vs Aspirin)
- Type of infection (e.g. viral vs bacterial)
- Effect of any co-morbidities (e.g. smoking, hypertension) using meta-regression.

However, we did not perform any planned subgroup analysis as there was an insufficient number of studies identified for inclusion and we were unable to adjust for confounding using meta-regression.

2.4.4 | Data analysis

Due to significant heterogeneity and the poor quality of included studies, we were unable to pool data and conduct any meaningful meta-analysis and instead the data has been described narratively. Relative risks (RR) with 95% confidence intervals (CI) for the individual studies were presented and calculated using the modified Wald method.

Although analyses of the number needed to treat for an additional harm was planned, it was omitted in the final analysis as the authors felt this could be misleading for readers in view of all studies having a high risk of bias. Since less than ten studies were included, publication bias was not assessed.

Two independent review authors independently judged the overall quality of the evidence using the five GRADE criteria (study limitations, consistency of effect, imprecision, indirectness, and publication bias).37 All P-values were two-sided, and P < 0.05 were considered statistically significant.

2.4.5 | Patient and public involvement

It was not possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,18 and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.19

3 | RESULTS

3.1 | Description of literature search and study selection

From the 4725 studies identified in our initial search, 4187 were excluded following title screen and 408 were duplicates. After full text review, a further 124 articles were excluded. Two further articles were identified when screening references and eight studies were included in the final analysis (Figure 1). A search on ClinicalTrials.gov identified 37 studies. After the eight studies were retrieved for final analysis, two additional trials pertaining to the subject of this meta-analysis were logged:

- The ENACOVID trial (NCT04325633), which is an ongoing single-centre randomised controlled trial (RCT) comparing the use of naproxen versus standard care in patients with COVID-19 in France; at the time of writing, the trial had not yet officially begun recruiting.
- The LIBERATE Trial (NCT04334629), which is an ongoing multi-centre RCT comparing the use of lipid ibuprofen versus standard care for acute hypoxemic respiratory failure due to COVID-19; the trial has begun recruitment.

3.2 | Characteristics of included studies

A total of eight studies including two RCTs, three retrospective and three prospective observational studies enrolling 44 140 patients were included

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in the final analysis. Five of the studies were in patients with pneumonia, two in patients with influenza and one in a patient with acute bronchitis. Only three of the eight included studies defined the type of NSAID used, with only one study reporting on the use of aspirin.

Eight studies were included in the final analysis (Table 1).

### 3.3 Risk of bias of the included studies

All six observational studies were deemed to have an overall high risk of bias, primarily driven by lack of adjustment for confounding and bias in selection of the reported result. The two RCTs were also deemed to have a high risk of bias. A summary for each domain is presented in Figure 2.

### 3.4 Outcomes

A summary of the included studies and outcomes is presented in Table 1.

### 3.5 Mortality

Five studies reported mortality of which one was an RCT. The mortality data in Basille et al.27 included data for chronic NSAID use and was therefore excluded from the analysis. Hung et al.20 reported a reduction in 30 day mortality; RR 0.11 (95% CI 0.01–0.89). It is important to note that the study investigated the effects of both clarithromycin and naproxen in combination with oseltamivir and therefore any benefits seen may be due to the use of concomitant antibiotics and not NSAID use. Basille et al.26 and Voiriot et al.28 reported an uncertain effect on 30 day mortality, Messika et al.22 reported an uncertain effect on in-hospital mortality, and Epperly et al.24 reported an uncertain effect on 90 day mortality. Although the mortality data could not be pooled due to heterogeneity, the overall direction of effect suggests there may be a trend towards a reduction in mortality.

### 3.6 Cardiovascular complications

Cardiovascular complications were not reported in any of the included studies. Whilst screening references of included studies, two case-crossover design studies were identified and reported myocardial infarction29 and stroke.30 The authors made a decision not to include these as they used unconventional methodology in the study design.

### 3.7 Respiratory complications

#### i. Pleuro-pulmonary complications

Pleuro-pulmonary complications were reported in five studies, all of which were observational studies and in patients with pneumonia. Four of the included studies reported a significant increase in pleuro-pulmonary complications. The largest study in the analysis (Basille et al.,27 n = 47,266) was from registry data and we extracted data from a subgroup of new NSAID users with an exposure within the last 7 days. A single study by Kotsiou et al.21 reported an uncertain effect on the rates of empyema. Overall, there is a trend towards an increase in the reported rates of pleuro-pulmonary complications with NSAID use; however, this must be interpreted with caution given the lack of adjustment for confounding and the risk of publication bias.

#### ii. Mechanical ventilation

The need for mechanical ventilation was reported as an outcome in three studies of which one was an RCT, all of which reported an uncertain effect on the need for mechanical ventilation.

#### iii. Acute respiratory distress syndrome (ARDS)

A single study by Voiriot et al.28 reported no difference in risk of developing ARDS following NSAID use; RR 0.9 (0.75–1.09).
### Table 1: An overall summary of each included study

| Study            | Design                  | Disease                                          | Setting     | Intervention                                                                 | Control                                                                 | Outcome summary                                                                                                                                                                                                 |
|------------------|-------------------------|--------------------------------------------------|-------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hung et al.¹⁸    | Randomised control trial| Influenza (H3N2)                                 | Hospital    | Oseltamivir 75 mg 5 days + clarithromycin 500 mg BD 2 days + naproxen 200 mg BD 2 days (n = 107) | Oseltamivir 75 mg 5 days (n = 110)                                     | Intervention group had reduced 30 day mortality; RR 0.11 (95% CI 0.01–0.89). Uncertain effect on the need for mechanical ventilation; RR 0.34 (95% CI 0.07–1.66) |
| Kotsiou et al.²¹ | Prospective cohort      | Pneumonia and parapneumonic effusion             | Hospital    | NSAID (n = 36)                                                                | No NSAID (n = 21)                                                       | NSAID use was associated with no significant difference in rates of empyema; RR 1.5 (95% CI 0.75–2.98)                                                                                       |
| Messika et al.²² | Retrospective cohort study | Pneumococcal pneumonia                            | ICU         | NSAID (n = 20)                                                                | No NSAID (n = 86)                                                       | Uncertain effect on in-hospital mortality; RR 0.23 (95% CI 0.03–1.6). Increase in pleuro-pulmonary complications in NSAID group; RR 3.58 (95% CI 1.81–7.1). Uncertain effect on mechanical ventilation RR 0.7 (95% CI 0.4–1.2) |
| Llor et al.²³    | Randomised control trial| Acute bronchitis                                 | Primary care | Ibuprofen (n = 136)                                                          | Co-amoxiclav (n = 143) or placebo (n = 143)                             | Uncertain effect on adverse events; RR 1.8 (95% CI 0.55–6.15)                                                                                                                                   |
| Epperly et al.²⁴ | Retrospective cohort study | Influenza (pH1N1)                               | ICU         | NSAID (n = 88) or aspirin (n = 101)                                          | No NSAID (n:595) or no aspirin (n:582)                                  | Uncertain effect on 90 day mortality; RR 0.99 (95% CI 0.68–1.44)                                                                                                                                    |
| Voiriot et al.²⁵ | Prospective cohort study | Pneumonia                                        | ICU         | NSAID (n = 32)                                                                | Control (n = 58)                                                       | Uncertain effect on 30 day mortality; RR 0.26 (95% CI 0.01–4.8). Increase in pleuro-pulmonary complications with NSAID use; RR 5.44 (95% CI 1.91–15.48). Uncertain effect on mechanical ventilation; RR 2.7 (95% CI 0.48–15.4) |
| Basile et al.²⁶  | Prospective cohort study | Pneumonia (influenza or bacterial)               | Hospital    | NSAID (n = 24)                                                                | No NSAID (n = 197)                                                     | Uncertain effect on 30 day mortality; RR 0.48 (95% CI 0.06–3.4). Increase in pleuro-pulmonary complications with NSAID use; RR 2.05 (95% CI 1.07–3.93) |
| Basile et al.²⁷  | Retrospective registry   | Pneumonia                                        | Hospital    | New NSAID user (n = 2294)                                                    | NSAID non-user (n = 40 548)                                           | Increase in pleuro-pulmonary complications with NSAID use; RR 2.72 (95% CI 2.29–3.23)                                                                                                                   |

NSAID, non-steroidal anti-inflammatory drug.  
RR, relative risk (95% confidence intervals).  
ICU, intensive care unit.
3.8 | Dialysis

Two small observational studies in patients with pneumonia reported the need for dialysis. Both Messika et al.\(^{22}\); RR 1.1 (95% CI 0.1–9.1) and Voiriot et al.\(^{28}\); RR 0.8 (95% CI 0.2–2.8) reported an uncertain effect on the need for dialysis. Such small sample sizes and the extremely wide 95% CI barred any clinically meaningful conclusions to be drawn.

3.9 | Other adverse events (excluding gastrointestinal complications)

Two observational studies in pneumonia patients reported uncertain effects on rates of organ failure. Llor et al.\(^{22}\) reported uncertain effects on rates of adverse events; RR 1.8 (95% CI 0.55–6.15), although the majority of these were reported as mild.

3.10 | Summary

An overall summary of the treatment effects for each outcome measure with GRADE quality of evidence is presented in Table 2.

4 | DISCUSSION

In this systematic review of NSAID use during acute lower respiratory tract infections in adults, we found that the existing evidence for mortality, pleuro-pulmonary complications, rates of mechanical ventilation and need for dialysis or organ failure is of extremely poor quality and very low certainty, with most reports being observational/registry data with high risks of bias due to lack of adjustment for confounding variables. Moreover, we found no studies, subject to our selection criteria, where cardiovascular outcomes were documented. The apparent lack of quality clinical studies addressing benefits and risk of these drugs in acute lower respiratory tract infections was unexpected considering the frequency of NSAID use and the known cardio-renal and gastrointestinal side effect of NSAIDs.

The included studies demonstrated a trend towards higher rates of pleuro-pulmonary complications following short-term NSAID use. Although this review focused on adults, these findings have been echoed in paediatric studies.\(^{31–36}\) There are essentially two hypotheses that may explain these findings, both of which warrant further investigation:

1. Indirect:
a. NSAIDs mask major symptoms of inflammation leading to patients presenting with more advanced disease; and/or that
b. Confounding by indication—patients who develop pleuro-pulmonary complications are more likely to take NSAIDs due to pain from pleurisy; and/or that

2. Direct/mechanistic: Through blocking COX activity, NSAIDs remove protective (in this setting) prostanoids, slowing immune responses, resolution and/or augmenting organ dysfunction.

Nevertheless, the observed differences in pleuro-pulmonary complications did not translate to differences in short-term mortality. It is important to note that the included studies only reported short-term mortality with the longest reported follow-up of 90 days in a single study. Although there may be a trend towards a reduction in mortality, individual studies reported wide confidence intervals and so there remains significant uncertainty of the effects of NSAIDs on mortality in lower respiratory tract infections. Furthermore, the lack of relationship between pleuro-pulmonary complications and mortality may also reflect the possibility of confounding by indication, as mentioned above. While initial reports suggested that NSAIDs may worsen the course and outcomes of COVID-19, the World Health Organisation and Public Health England stated otherwise. Our results appear to support the latter as there is insufficient evidence to support an association of NSAID use and worsening of outcomes in acute lower respiratory tract infections. All included studies exhibited high risks of bias, particularly due to lack of adjustment for confounding. Furthermore, there is a risk of protopathic bias and NSAID exposure could be a marker for pleuro-pulmonary infections rather than a cause. Caution should therefore be applied to interpretation of these results, which highlight the urgent need for further clinical and mechanistic studies in this area.

NSAIDs are associated with renal dysfunction but in our analysis we found insufficient evidence to draw any meaningful conclusions. Data relating to only 196 patients with 15 events in total across two studies were included, so this should also be interpreted cautiously, especially since the nephrotoxicity of NSAIDs is well known. Importantly, none of the studies identified in this review reported cardiovascular events. This is unexpected since, with the exception of aspirin, all NSAIDs including older (traditional) drugs such as ibuprofen and newer COX-2 inhibitors, such as celecoxib, are known to increase cardiovascular risks and that the increased risk of myocardial infarction is seen as early as after 1–2 weeks of use. It is therefore crucial that further studies consider cardiovascular and renal side effects.

### 4.1 Strengths and limitations

This systematic review represents the most up-to-date data of the captioned subject and should have immediate relevance in informing clinicians worldwide of the evidence of using NSAIDs in patients with acute lower respiratory tract infection. The main limitation of our findings is the poor quality of the included studies. Also, none of the included studies focused on COVID-19. Thus, our findings may not extrapolate well to COVID-19. Moreover, both bacterial and viral infections were included, and subgroup analysis by pathogen was impossible due to small sample sizes and lack of pathogen-specific outcome reporting. We focused on short-term NSAID use, and the effects of prior NSAID exposure or chronic NSAID use were not explored. Finally, as the included studies had significant

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**TABLE 2** Summary of treatment effects for each outcome measure and GRADE quality of evidence

| Outcome (number of studies) | Overall treatment effect | GRADE | Reasons for downgrading |
|-----------------------------|--------------------------|-------|-------------------------|
| Mortality (5)               | Uncertain effect on mortality although there may be a trend towards a reduction. | Very low | Majority observational studies Risk of bias Imprecision Publication bias |
| Cardiovascular complications (0) | Not reported in any of the included studies | No evidence | No evidence |
| Pleuro-pulmonary complications (5) | Four of the five included studies reported a significant increase in rates of pleuro-pulmonary complications with NSAID use. | Very low | All observational studies Risk of bias Publication bias |
| Need for mechanical ventilation (3) | Uncertain effect on the need for mechanical ventilation in all studies | Very low | Majority observational studies Risk of bias Imprecision Publication bias |
| Need for dialysis (2)       | Uncertain effects of need for dialysis. Low sample sizes and wide confidence intervals prohibits any meaningful conclusions | Very low | All observational studies Risk of bias Imprecision Publication bias |
| Major organ failure (2)     | Uncertain effects on major organ failure. | Very low | All observational studies Risk of bias Imprecision Publication bias |

NSAID, non-steroidal anti-inflammatory drug.
heterogeneity, we were unable to pool the data and conduct any meaningful meta-analysis. Despite these, until more data become available including from the ongoing ENACOVID trial (NCT04325633) and The LIBERATE Trial (NCT04334629), this report represents a summary of the best available evidence that is clinically relevant to frontline staff.

5 | CONCLUSION

In this systematic review of NSAID use during acute lower respiratory tract infections in adults, we found that the existing evidence for mortality, pleuro-pulmonary complications and rates of mechanical ventilation or organ failure is of extremely poor quality and very low certainty. Cardiovascular or renal complications could not be adequately addressed. There may be an overall trend towards an increase in pleuro-pulmonary complications but a reduction in mortality. However, these results must be interpreted with extreme caution given the high risk of bias of the included studies, the very low quality of evidence and the results’ generalisability to COVID-19 is unclear. Despite this, the summary represents the best available evidence for NSAID use in adult patients with acute lower respiratory tract infections. Mechanistic studies and clinical studies, especially pertinent to NSAID use-non-steroidal-anti-inflammatories-covid-19, are urgently required.

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COMPETING INTERESTS

J.A.M. is on the scientific advisory board for Antibe Therapeutics. The other authors declare that they have no competing interests.

CONTRIBUTORS

R.V., N.K. and J.M. conceived the idea. R.V., L.J.R., A.H., J.C. and J.M. developed the protocol. R.V., J.C., A.H., L.J.R., H.G. and P.F. screened and extracted data. R.V., J.C., A.H. and L.J.R. performed data analysis. R.V., J.C., P.F. and L.J.R. wrote the manuscript. H.G., N.K., A.H. and J.M. edited the final manuscript. The guarantor for this article is Dr Ricky Vaja. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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APPENDIX A: Search terms

Search of Embase, Medline, Cochrane Controlled Register of Trials (CENTRAL) and Clinical Trials. Gov from inception to 21 March 2020

1. exp anti-inflammatory agents, non-steroidal/ or aspirin/ or celecoxib/ or diclofenac/or ibuprofen/or naproxen/
2. *bronchitis/ or *common cold/ or *empyema, pleural/ or *influenza, human/ or *lung abscess/or *pneumonia/or *severe acute respiratory syndrome
3. SARS.mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
4. COVID.mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
5. respiratory distress syndrome.mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
6. 2 or 3 or 4 or 5
7. 1 and 6