McMaster University | Family Medicine

COVID 19 and NSAIDs Evidence Tables. M Howard and D Mangin

“News”

Non-prescription drugs containing either anti-inflammatory agents or acetaminophen were moved behind the counter in France in January. This shift had nothing to do with COVID-19. It came about because of government concern around several known risks of the medications, including the complication of infections.

In Canada, where these medications remain available on store shelves, the Public Health Agency of Canada has recommended that anyone in self-isolation during the COVID-19 pandemic have both acetaminophen and ibuprofen with them in case of fever.

The World Health Organization has said that there is no specific medicine recommended for treating the virus at this point. Its advice notes that acetaminophen, ibuprofen and aspirin all "may mask symptoms of infection" but does not specifically recommend that any be taken or avoided in a specific situation.

Article	**Virus / drug**	**Pop**	**Study design**	**Results**
Bally M et al Risk of Acute Myocardial Infarction With NSAIDs in Real World Use: Bayesian Meta-Analysis of Individual Patient Data *BMJ Clinical Ed 2017 357, j1909*	NSAID (any)	General and older adults Mean age around 70 in studies in 3	Systematic review: A cohort of 446 763 individuals including 61 460 with acute myocardial infarction was acquired	Taking any dose of NSAIDs for one week, one month, or more than a month was associated with an increased risk of myocardial infarction. With use for one to seven days the probability of increased myocardial infarction risk (posterior probability of odds ratio >1.0) was 92% for celecoxib, 97% for ibuprofen, and 99% for diclofenac, naproxen, and rofecoxib. The corresponding odds ratios (95% credible intervals) were 1.24 (0.91 to 1.82) for celecoxib, 1.48 (1.00 to 2.26) for ibuprofen, 1.50 (1.06 to 2.04) for diclofenac, 1.53 (1.07 to 2.33) for naproxen, and

		countires and 58 in 4th (CDN)		1.58 (1.07 to 2.17) for rofecoxib. Greater risk of myocardial infarction was documented for higher dose of NSAIDs. With use for longer than one month, risks did not appear to exceed those associated with shorter durations. This may be a "depletion of susceptibles" effect
Cardiovascular Outcomes There is other abundant evidence of the association of NSAIDS and Acute Myocardial Infarction (AMI). See Bally above. Below are studies in resp illness.				
Wen YC, Hsiao FY, Chan KA, Lin ZF, Shen LJ, Fang CC. Acute Respiratory Infection and Use of Nonsteroidal Anti-Inflammatory Drugs on Risk of Acute Myocardial Infarction: A Nationwide Case-Crossover Study. J Infect Dis. 2017;215(4):503-9. doi: 10.1093/infdis/jiw603	Acute respiratory infection		Retrospective observational. Case crossover design NSAID use during ARI episodes	NSAID use during ARI was associated with a 3.4-fold increased risk of AMI (adjusted odds ratio [aOR] = 3.41; 95% confidence interval [CI] = 2.80-4.16), ARI without NSAIDs use was associated with a 2.7-fold increased risk (aOR = 2.65; 95% CI = 2.29-3.06), NSAIDs use without ARI was associated with a 1.5-fold increased risk (aOR = 1.47; 95% CI = 1.33-1.62). **note: consistent with Bally meta-analysis
Warren-Gash C. 2017 Respiratory Tract Infections, Nonsteroidal Anti-inflammatory Drugs and Acute Myocardial Infarction: Is Understanding Interaction Between Risk Factors the Key to Personalizing Prevention? https://doi.org/10.1093/infdis/jiw604	NSAIDs in acute respiratory infections		Case crossover study-Taiwan national health insurance database. ARI determined by clinical diagnosis not testing	Acute respiratory infections treated with NSAIDs had a stronger association with AMI than ARIs not treated with NSAIDs or NSAID treatment alone. AMI risk was higher with NSAID use for influenza-related ARIs compared to other ARIs
Wen YC, Hsiao FY, Lin ZF, Fang CC, Shen LJ. Risk of stroke associated with use of nonsteroidal anti-inflammatory drugs during acute respiratory infection episode. Pharmacoepidemiology and drug safety. 2018. doi: 10.1002/ppul.23041.	ARI	A	Case crossover design (exposure time to NSAIDS 1-7 days prior to hospital admission from stroke)	Multivariable conditional regression models were used to estimate odds ratios adjusting potential confounders. The results suggested that NSAIDs use during ARI episodes was associated with a 2.3-fold increased risk of stroke (ischemic: adjusted odds ratio, aOR 2.27, 95% confidence interval, 95% CI, 2.00-2.58; hemorrhagic: aOR 2.28, 95% CI, 1.71-3.02). We also determined that parenteral NSAIDs were associated with much higher risk of stroke in patients with ARI.

CAP Course and Complications				
Basille D, Plouvier N, Trouve C, Duhaut P, Andrejak C, Jounieaux V. Non-steroidal Anti-inflammatory Drugs may Worsen the Course of Community-Acquired Pneumonia: A Cohort Study. Lung. 2017;195(2):201-8. doi: 10.1007/s00408-016-9973-1	Development of pleuroparenchymal complications in community-acquired pneumonia / NSAIDS	A	Prospective cohort of 221 non-immunocompromised patients hospitalized for pneumonia	In multivariate analyses, two factors were independently associated with the development of pleuroparenchymal complications: NSAIDs intake [Odds Ratio (OR) = 2.57 [1.02-6.64]; p = 0.049] and alcohol abuse (OR = 2.68 [1.27-5.69]; p = 0.01)
Voiriot G, Dury S, Parrot A, Mayaud C, Fartoukh M. Nonsteroidal antiinflammatory drugs may affect the presentation and course of community-acquired pneumonia. Chest. 2011;139(2):387-94. doi: 10.1378/chest.09-3102.	nonimmunocompromised inpatients with community-acquired pneumonia (CAP) admitted to the ICU / NSAID prior to hospital admission	A	Prospective cohort 90 patients	more often developed pleuropulmonary complications, such as pleural empyema and lung cavitation (37.5% vs 7%; P = .0009), and had a trend to more-invasive disease, with a higher frequency of pleural empyema (25% vs 5%, P = .014) and bacteremia, especially in those not having received concomitant antibiotics (69% vs 27%, P = .009). Nevertheless, the patients in the NSAID group had no more severe systemic inflammation or remote organ dysfunction. In multivariable analyses, NSAID exposure was independently associated with the occurrence of pleuropulmonary complications (OR, 8.1; 95% CI, 2.3-28)
Kotsiou OS, Zarogiannis SG, Gourgoulianis KI. Prehospital NSAIDs use prolong hospitalization in patients with pleuro-pulmonary infection. Respir Med. 2017;123:28-33. doi: 10.1016/j.rmed.2016.12.005.	Pneumonia with effusion in adults		Prospective study n=57 consecutive patients	72% of the cases were smokers. Prehospital use of NSAIDs >6 days was positively associated with prolonged hospitalization extending out for approximately 10 days. Immunosuppression was an independent risk factor for prolonged hospitalization of more than 5 days. This group of patients also had more complicated pleural effusions and were more difficult to treat. In the immunocompetent group of patients, there was a negative inverse correlation of duration of NSAIDs use with pleural fluid pH and glucose. The longer medication with NSAIDs correlated with lower values of C-reactive protein, and ESR. Earlier prehospital antibiotic use significantly prevented the development of empyema.
Messika J, Sztrymf B, Bertrand F, Billard-Pomares T, Barnaud G, Branger C, et al. Risks of nonsteroidal antiinflammatory drugs in undiagnosed intensive care unit pneumococcal pneumonia: younger and more severely affected patients. Journal of critical care.	Pneumococcal pneumonia in Intensive Care	A		One hundred six confirmed pneumococcal CAP were identified, 20 received NSAIDs within 4 (2-6) days before admission. Nonsteroidal antiinflammatory drug-exposed patients were younger (43.3 vs 62.2 years; P < .0001), had less frequently at least one chronic comorbid condition (40% vs 75%; P = .003), had more often complicated pleural effusions (20% vs 2.3%; P = .01), and more frequent pleuropulmonary complications (odds ratio: 5.75 [1.97-16.76]). Nonsteroidal antiinflammatory drug patients required more often noninvasive

2014;29(5):733-8. doi: 10.1016/j.jcrc.2014.05.021				ventilatory support (25% vs 4.6%; P = .003). Intensive care unit length of stay and mortality were similar.
Viral illness outcomes and symptom control (usly vs acetaminophen = paracetamol)				
Little P, Moore M, Kelly J, Williamson I, Leydon G, McDermott L, et al. Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care: pragmatic randomised factorial trial. BMJ. 2013;347:https://www.bmj.com/content/347/bmj.f6041.	patients aged ≥3 with acute respiratory tract infections		RCT: advice on analgesia (take paracetamol, ibuprofen, or both), dosing of analgesia (take as required *v* regularly), and steam inhalation (no inhalation *v* steam inhalation).	Compared with paracetamol, symptom severity was little different with ibuprofen (adjusted difference 0.04, 95% confidence interval −0.11 to 0.19) or the combination of ibuprofen and paracetamol (0.11, −0.04 to 0.26). Ibuprofen: evidence of reduced symptoms severity benefit in the subgroup with chest infections (ibuprofen −0.40, −0.78 to −0.01; combination −0.47; −0.84 to −0.10), equivalent to almost one in two symptoms rated as a slight rather than a moderately bad problem. Reconsultations with new/unresolved symptoms or complications were documented in 12% of those advised to take paracetamol, 20% of those advised to take ibuprofen (adjusted risk ratio 1.67, 1.12 to 2.38), and 17% of those advised to take the combination (1.49, 0.98 to 2.18).
Little P, Stuart B, Andreou P, McDermott L, Joseph J, Mullee M, et al. Primary care randomised controlled trial of a tailored interactive website for the self-management of respiratory infections (Internet Doctor). BMJ open. 2016;6(4):e009769. doi: 10.1136/bmjopen-2015-009769	Adults age 18+ with respiratory infection		RCT of tailored internet advice on paracetomol/ibuprofen-followed for 24 weeks	The estimate of slower symptom resolution in the intervention group was attenuated when controlling for whether individuals had used web pages which advocated ibuprofen use (length of illness 0.22 days, −0.51 to 0.95, p=0.551; moderately bad or worse symptoms 0.36 days, −0.08 to 0.80, p=0.105). There was no evidence of increased hospitalisations (risk ratio 0.13; 0.02 to 1.01; p=0.051).
Graham NMH https://doi.org/10.1093/infdis/162.6.1277 (full article not available)	Healthy volunteers (n=60) challenged with rhinovirus: 1. aspirin 2. Acetaminophen 3. Ibuprofen 4. placebo		Double-blind placebo controlled RCT	Aspirin and acetaminophen suppressed serum neutralizing antibody response vs placebo (p<.05) Aspirin and acetaminophen increased nasal symptoms (p<.05) No significant difference in viral shedding- trend for longer in aspirin and acetaminophen vs placebo
Amici C. 2006 PMID: 17302372	SARS-CoV /Indomethicin		In-vitro studies in monkey VERO cells and human lung cells	Does not affect binding or entry into host cells- works by blocking viral RNA synthesis-

Indomethacin has a potent antiviral activity against SARS coronavirus.				The results identify INDO as a potent inhibitor of coronavirus replication and suggest that, having both anti-inflammatory and antiviral activity, INDO could be beneficial in SARS therapy.
Gwaltney JM Jr. 2002 https://doi.org/10.1016/S0002-9343(01)01062-2	Rhinovirus challenge / NSAIDs		Refers to 2 double blind placebo controlled trials	In several clinical trials, drugs representative of their class were tested in the rhinovirus challenge model using the Jackson method of scoring illness. Naproxen, as a representative of NSAIDs, was tested in doses of 200 or 500 mg 3 times a day.6 At the higher dose, significant reductions were observed in the severity of headache and malaise, and a strong, favorable trend occurred with chilliness **(Figure 1)**. Also, severity of cough was reduced. Other studies have reported a beneficial effect of NSAIDs on cough.7, 8 On the other hand, the severity of the nasal symptoms, sneezing, nasal obstruction, and rhinorrhea was not reduced. Viral concentrations in nasal secretions were the same in the naproxen and control groups.
Rainsford, KD. 2006 Influenza ("Bird Flu"), inflammation and anti-inflammatory/analgesic drugs https://doi.org/10.1007/s10787-006-0002-5 Review article	Review of drugs for treating inflammatory symptoms of influenza			NSAIDs can increase risk of adverse events in severe influenza. NSAIDs at OTC levels may have some benefit in controlling inflammation in mild-moderate influenza. RCT patients age 65+ with influenza A, serum anti-body titers were greater with aspirin, especially in age 75+. Aspirin and other NSAIDs may reduce proliferation of influenza
Other infections				
Mikaeloff Y, Kezouh A, Suissa S. Nonsteroidal anti-inflammatory drug use and the risk of severe skin and soft tissue complications in patients with varicella or zoster disease. Br J Clin Pharmacol. 2008;65(2):203-9. doi: 10.1111/j.1365-2125.2007.02997.x	Varicella or zoster / NSAID		Nested case-control study	The rate ratio of complications associated with exposure to NSAIDs was 1.6 (95% CI 1.1, 2.4). In both conditions, there was no increased risk of complication associated with a current exposure to paracetamol.
Pediatric Context				
Le Bourgeois M, Ferroni A, Leruez-Ville M, Varon E, Thumerelle C, Bremont F, et al. Nonsteroidal Anti-	Empyema after acute viral infection / NSAIDS	P	Matched case-control	multivariable analysis retained an increased risk of empyema associated with NSAIDs exposure (aOR 2.79, 95% CI 1.4-5.58, P = .004), and a decreased risk associated with antibiotic use (aOR

Inflammatory Drug without Antibiotics for Acute Viral Infection Increases the Empyema Risk in Children: A Matched Case-Control Study. The Journal of pediatrics. 2016;175:47-53.e3. doi: 10.1016/j.jpeds.2016.05.025.			At least 6 days antibiotic use and at lest one day NSAID use, 3 days or more after onset of illness	0.32, 95% CI 0.11-0.97, P = .04). The risk of empyema associated with NSAIDs exposure was greater for children not prescribed an antibiotic and antibiotic intake diminished that risk for children given NSAIDs
Souyri C, Olivier P, Grolleau S, Lapeyre-Mestre M. Severe necrotizing soft-tissue infections and nonsteroidal anti-inflammatory drugs. Clinical and experimental dermatology. 2008;33(3):249-55. DOI:10.1177/106002809703100914	necrotizing fasciitis in adults and children NSAID	P /A	Case control study created from pharmacovigilance reports n=38 cases 10 adults 28 children	Thirty-three cases were identified, of which 10 were fatal. Over two-thirds of the patients were younger than 40 years. Thirty (91%) had a possible portal of entry for infection. Most received NSAIDs for acute conditions including varicella (26/28) for most of the peds cases, trauma, and postoperative or postpartum pain; 7 received an NSAID by intramuscular injection. Higher OR for use of NSAIDs in children. Numbers and NSAIDS exposure too low to draw a conclusion in adults. Reporting in paper poor. Numbers did not add up. Authors conclusion: indication bias with NSAIDs masking Sx leading to delayed treatment.
Krenke K, Krawiec M, Kraj G, Peradzynska J, Krauze A, Kulus M. Risk factors for local complications in children with community-acquired pneumonia. The clinical respiratory journal. 2018;12(1):253-61. doi: 10.1111/crj.12524.	parapneumonic effusion/pleural empyema, necrotizing pneumonia, and lung abscess) in children with community-acquired pneumonia (CAP) / ibuprofen and acetominophen	P	203 children, prospective cohort	Asymmetric chest pain as well as prehospital treatment with ibuprofen and acetaminophen were significantly more common in patients with complicated CAP (P < .001, P = .02 and P = .003, respectively). Preadmission cumulative dose of ibuprofen exceeding 78.3 mg/kg (median dose for the entire group) was associated with 2.5-fold higher odds ratio (OR) for CAP complications [OR 2.54 CI (1.31-4.94); P = .008)]. In contrast, pneumococcal vaccination was associated with lower odds ratio [OR.03 CI (.23-.89); P = .03] for local complications.
Elemraid MA, Thomas MF, Blain AP, Rushton SP, Spencer DA, Gennery AR, et al. Risk factors for the development of pleural empyema in children. Pediatr Pulmonol. 2015;50(7):721-6. doi: 10.1002/ppul.23041.				Children with empyema were more frequently prescribed Ibuprofen prior to admission to hospital than those without (82% vs. 46.2%; OR 1.94, 97.5% credible interval 0.80-3.18). Bacterial infection was strongly associated with the development of empyema (OR 3.34, 97.5% credible interval 1.70-5.14).
Francois P, Desrumaux A, Cans C, Pin I, Pavese P, Labarere J. Prevalence and risk factors of		P		Of 767 children with community-acquired pneumonia, 90 had suppurative complications: 83 cases of pleural empyema and seven cases of lung abscess. The mean prevalence of complicated pneumonia

suppurative complications in children with pneumonia. Acta paediatrica (Oslo, Norway : 1992). 2010;99(6):861-6.. doi: 10.1111/j.1651-2227.2010.01734.x.				was 3% during the 1995-1998 period, and then steadily increased following a linear trend to reach 23% in 2003. Children with complicated pneumonia were older and had a longer symptomatic period preceding hospitalization. They were more likely to receive antibiotics, especially aminopenicillins ($p < 0.01$), and nonsteroidal anti-inflammatory drugs, especially ibuprofen ($p < 0.001$). In multivariable analysis, ibuprofen was the only preadmission therapy that was independently associated with complicated pneumonia [adjusted OR = 2.57 (1.51-4.35)].
STEROIDS				
A rationale for using steroids in the treatment of severe cases of H5N1 avian influenza. Carter MJ. J Med Microbiol. 2007 Jul;56(Pt 7):875-83. Review.	Steroids to reduce inflammation that leads to organ failure in severe cases of H5N1		Review article	Difficult to find the dose high enough for excess activation of inflammation, but low enough to avoid immune suppression. Although steroids cannot be used as a monotherapy in the treatment of avian influenza, there might be a potential role for their use as an adjunct treatment to antiviral therapy if appropriate dosages can be determined.
J Thorac Dis. 2018 Jul;10(Suppl 19):S2248-S2259. doi: 10.21037/jtd.2018.03.169. **Re-understanding anti-influenza strategy: attach equal importance to antiviral and anti-inflammatory therapies.**	NSAIDs and analgesics: Methods to alleviate the damage caused by a cytokine storm in response to influenza virus infection have become an important part of anti-influenza strategies.		Various studies	A retrospective study of Guangzhou SARS cases showed that corticosteroid use reduced mortality and shortened hospitalization (82). In an experimental mouse model of H1N1 infection, corticosteroid treatment ameliorated acute lung injury induced by 2009 H1N1 virus (83). However, other reports have suggested that corticosteroid therapy does not significantly improve the survival of patients with influenza A virus infection (84) and may even be associated with higher mortality in patients with severe influenza H1N1 infection (85). Among H1N1-positive patients with ARDS in particular, the early use of corticosteroids may be harmful (86). Therefore, there is no clear consensus on corticosteroid use in the treatment of severe viral pneumonia or on the timing, dosage, and course of treatment.

WHO H1N1 Guidelines 2010

Recently published retrospective observational studies suggest that corticosteroid treatment of influenza is associated with a higher likelihood of ICU admission and mortality as clinical outcomes (Jain et al., 2009; Liem et al., 2009). In addition, two observational studies demonstrate that corticosteroid use is associated with slower viral clearance, significantly increased odds of persistent viral replication 7 days after symptom onset (Lee et al., 2009), and a longer duration of viral shedding with increased corticosteroid dose (Nichols et al.,2004).

Table 1.9: Clinical data for corticosteroids in influenza

Studies	Design	Population characteristics	Key results
Abdel-Ghafar 2008	H5N1 review	H5N1 cases	– Prolonged or high-dose corticosteroid therapy can result in serious adverse events, including opportunistic infections (e.g. CNS toxoplasmosis). – In a Vietnamese study, mortality was 59% among 29 recipients of corticosteroids, as compared with 24% among 38 persons who did not receive corticosteroids (*P*=0.004). – Recommends against routine use of corticosteroids.
Carter 2007	Literature review	Clinical and laboratory literature for H5N1	– Adrenal insufficiency can be overcome with prolonged (7-10 days or more) of supraphysiological steroid treatment at a high enough dose to reduce activation of NF-κB, but low enough not to cause immune suppression. – Annane (2004) sepsis review suggests a long course of low dose steroids is more protective against mortality than high dose short courses. – Few animal studies for influenza, plus it is difficult to extrapolate dosage thresholds. – Human H5N1 data are limited as there are few cases (28) and confounding complicates analysis. – Steroids should not be used as monotherapy. – Conclusion: there is weak evidence suggesting steroids have an adjunctive role in influenza.
Jain 2009	Medical chart review N= 272	Hospitalized patients with confirmed pandemic H1N1 influenza	– Fatal cases and patients admitted to an ICU were more likely to have received corticosteroids than those hospitalized on wards (52% vs. 31%, significant $p<0.05$).
Lee 2009	1-year, prospective observational study N=147	Adult patients hospitalized with influenza 37 (25.2%) using corticosteroids	– Systemic corticosteroid use for asthma or COPD was associated with slower viral clearance. – Viral RNA detected at symptom day 7: 53.8% in those using corticosteroids and 25% in those not (p=0.007). – Virus isolated at symptom day ≥4: 24.1% and 14.9% (corticosteroids vs. none) (p=0.256). – Corticosteroid use is associated with persistent viral replication at 1 week after illness onset (OR=5.44, 95% CI:1.86, 15.89, p=0.002).
Liem 2009	Retrospective review	Laboratory confirmed cases of H5N1 in	– Stratified analysis of the effect of steroid treatment on outcome, after controlling for possible confounding by the presence or absence of neutropenia at admission (as a marker of severity),

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	N=67	Vietnam	still found evidence of an increased risk of death (Mantel-Haenszel summary OR=4.11; 95% CI: 1.14, 14.83; P=0.027)
Nichols 2004	Reviewed records of 12 seasons from 1 transplant centre N= 62	Influenza after haemopoietic stem cell transplantation	– Duration of influenza virus shedding was longer in patients treated with steroid doses of >1mg/kg than among those treated with doses of <1mg/kg (mean, 15 vs. 9 days).
Quispe-Laime 2009	Prospective evaluation Uncontrolled study N=13	Suspected pandemic H1N1 acute lung injury–ARDS patients in ICU. 8 H1N1 patients, 1 Influenza A (not H1N1), and 4 influenza A negative.	– All received oseltamivir. Severe ARDS patients received methylprednidone (1mg/kg/day), others received hydrocortisone (300mg/day). – By treatment day 7: significant improvement in lung injury and multiple organ dysfunction scores ($p<0.001$). Results were similar for pandemic H1N1 positive and negative patients. – Similar impact of both corticosteroids. – Prolonged low-to-moderate dose was well-tolerated and associated with significant improvement in lung injury and organ dysfunction score.
Sessler 2008	Review	Influenza patients with ARDS	– High dose methylprednisolone (MP) (120mg/kg/day) administered early in ARDS is ineffective. – Extended course (≤28 days) of low dose (1mg/kg/day) corticosteroids are associated with reduced systemic inflammation, shorter duration of ventilation and lower mortality. – Timing is important. MP administered >13 days after ARDS onset was associated with higher mortality. Administering MP on day 7-13 was associated with lower mortality.