



Non-steroidal anti-inflammatory drugs (NSAIDs) and the increased risk of complications during infections

A literature review

19 March 2020

Edited by the Section of Clinical Pharmacology of the Italian Society of Pharmacology

GIORGIO RACAGNI
Presidente

GIUSEPPE CIRINO
Presidente Eletto

GIAMBATTISTA BONANNO
NICOLETTA BRUNELLO
ROMANO DANESI
ANNAMARIA DE LUCA
PATRIZIA HRELIA
MARCO PISTIS
Consiglieri

CARLA GHELARDINI
Segretario

ALESSANDRO MUGELLI
Past President

On March 16th, 2020, the French Minister of Health has recommended the use of paracetamol for the treatment of fever in patients with suspected of Coronavirus Disease 2019 (COVID-19) instead of ibuprofen or oral cortisone [1]. In this circumstance, the French Authorities have announced that NSAIDs may worsen the clinical condition of patients with COVID-19 based on the evaluation of 4 young patients affected by a severe and sustained COVID-19, with no comorbidity, and with the NSAID treatment identified as the only risk factor. Immediate was the reply from the Spanish Agency of Medicines and Medical Devices (AEMPS), which underlined that there are no scientific data to support a worsening of the infection with ibuprofen or other NSAIDs. They also announced that the relationship between the infection exacerbation and the use of ibuprofen or ketoprofen is currently evaluated by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) [2], and it will be available the next May.

In the literature, conflicting results are available on the association between NSAIDs and infections. Some observational studies showed an increased risk of complications in pediatric patients with flu or infections who take NSAIDs [3,4]. A case series, published on BMJ in 2015, described two cases of H1N1 flu and history of NSAIDs abuse that developed type 1 respiratory failure, which required access to the intensive care [5]. Another study, published on BMJ in 2009, showed that the use of NSAIDs could worsen symptoms of H1N1 infection and predispose to the development of multi-organ failure [6]. The main explanation to this result is that the NSAIDs administration, through the alleviation of inflammatory symptoms (fever and pain), could impede the prompt recognition of pneumonia, delaying its diagnosis and treatment [7].

The infective inflammatory process starts with the activation of polymorphonuclear neutrophils, recruited at the site of infection, which release

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it



SOCIETÀ ITALIANA DI FARMACOLOGIA

Riconosciuta con D.M. del MURST del 02/01/1996
Iscritta Registro Persone Giuridiche Prefettura di Milano n. 467 pag 722 vol. 2°
C.F.: 97053420150 – P.I.: 11453180157



GIORGIO RACAGNI
Presidente

GIUSEPPE CIRINO
Presidente Eletto

GIAMBATTISTA BONANNO
NICOLETTA BRUNELLO
ROMANO DANESI
ANNAMARIA DE LUCA
PATRIZIA HRELIA
MARCO PISTIS
Consiglieri

CARLA GHELARDINI
Segretario

ALESSANDRO MUGELLI
Past President

reactive oxygen species (ROS), proteolytic enzymes, and antimicrobial peptides. This response also involves the cyclooxygenase type 2 (COX) [8-11].

Many studies have instead demonstrated that COX could have a protective role during infections. Specifically, Chen and colleagues showed that non-selective NSAIDs (aspirin and indomethacin) and the selective NSAID (celecoxib) inhibit the virus replication through an increase of nitric oxide levels in a model of vesicular stomatitis [12]. Other studies have demonstrated that COX-2 levels are increased in patients with an active viral infection [13-15], suggesting a possible role for COX-2 inhibitors in the control of viral infection [16, 17]. Finally, Amici and colleagues have conducted a preclinical study to evaluate the effect of indomethacin on the replication of Severe acute respiratory syndrome-coronavirus (SARS-CoV). This study showed an important anti-viral activity of indomethacin that is independent from the COX inhibition [18].

In conclusion, today, there is no clear evidence that supports the worsening of clinical conditions in patients with COVID-19 and treated with NSAIDs.

No Regulatory Authority, apart from the French one, has contraindicated the use of ibuprofen or other NSAIDs for the treatment of flu symptoms. These drugs must be used according to their approved information and at the lower dose that allows a symptom reduction.

Therefore, patients in chronic treatment with ibuprofen or other NSAIDs must continue their treatment as long as the PRAC does not conclude the referral on this potential association [19]. The EMA has recently published some information on the use of NSAIDs in patients affected by COVID-19 underlining the necessity of epidemiological studies to provide evidence to confute/confirm the hypothesis on the protective/damaging role of NSAIDs in patients with COVID-19 [19].

References

1. <https://ansm.sante.fr/S-informer/Actualite/COVID-19-l-ANSM-prend-des-mesures-pour-favoriser-le-bon-usage-du-paracetamol>.
2. <https://gacetamedica.com/politica/espana-no-desaconseja-tomar-ibuprofeno-frente-al-covid-19/>

Segreteria Organizzativa:

Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente:

Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto:

Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario:

Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it



SOCIETÀ ITALIANA DI FARMACOLOGIA

Riconosciuta con D.M. del MURST del 02/01/1996
Iscritta Registro Persone Giuridiche Prefettura di Milano n. 467 pag 722 vol. 2°
C.F.: 97053420150 – P.I.: 11453180157



GIORGIO RACAGNI
Presidente

GIUSEPPE CIRINO
Presidente Eletto

GIAMBATTISTA BONANNO
NICOLETTA BRUNELLO
ROMANO DANESI
ANNAMARIA DE LUCA
PATRIZIA HRELIA
MARCO PISTIS
Consiglieri

CARLA GHELARDINI
Segretario

ALESSANDRO MUGELLI
Past President

3. François P, Desrumaux A, Cans C, Pin I, Pavese P, Labarère J. Prevalence and risk factors of suppurative complications in children with pneumonia. *Acta Paediatr.* 2010 Jun;99(6):861-6. doi: 10.1111/j.1651-2227.2010.01734.x.
4. Le Bourgeois M, Ferroni A, Leruez-Ville M, Varon E, Thumerelle C, Brémont F, Fayon MJ, Delacourt C, Ligier C, Watier L, Guillemot D; Children, Antibiotics, Nonsteroidal Anti-inflammatory Drugs and Childhood Empyema (ChANCE) Study Group. Nonsteroidal Anti-Inflammatory Drug without Antibiotics for Acute Viral Infection Increases the Empyema Risk in Children: A Matched Case-Control Study. *J Pediatr.* 2016 Aug;175:47-53.e3. doi: 10.1016/j.jpeds.2016.05.025.
5. Prower E, Hasnain O, Oscier C. H1N1 pneumonitis associated with long-term non-steroidal anti-inflammatory drug abuse. *BMJ Case Rep.* 2015;2015:bcr2014205237. Published 2015 Apr 13. doi:10.1136/bcr-2014-205237
6. Hama R. A/H1N1 flu. NSAIDs and flu. *BMJ* 2009;338:b2345 10.1136/bmj.b2345
7. Voiriot G, Philippot Q, Elabbadi A, Elbim C, Chalumeau M, Fartoukh M. Risks Related to the Use of Non-Steroidal Anti-Inflammatory Drugs in Community-Acquired Pneumonia in Adult and Pediatric Patients. *J Clin Med.* 2019;8(6):786. Published 2019 Jun 3. doi:10.3390/jcm8060786
8. Kaplan H.B., Edelson H.S., Korchak H.M., Given W.P., Abramson S., Weissmann G. Effects of non-steroidal anti-inflammatory agents on human neutrophil functions in vitro and in vivo. *Biochem. Pharmacol.* 1984;33:371–378. doi: 10.1016/0006-2952(84)90228-4.
9. Ip M., Lomas D.A., Shaw J., Burnett D., Stockley R.A. Effect of non-steroidal anti-inflammatory drugs on neutrophil chemotaxis--An in vitro and in vivo study. *Br. J. Rheumatol.* 1990;29:363–367. doi: 10.1093/rheumatology/29.5.363.
10. Serhan C.N. Pro-resolving lipid mediators are leads for resolution physiology. *Nature.* 2014;510:92–101. doi: 10.1038/nature13479.
11. Fukunaga K., Kohli P., Bonnans C., Fredenburgh L.E., Levy B.D. Cyclooxygenase 2 plays a pivotal role in the resolution of acute lung injury. *J. Immunol. Baltim. Md* 1950. 2005;174:5033–5039. doi: 10.4049/jimmunol.174.8.5033.

Segreteria Organizzativa:

Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente:

Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto:

Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario:

Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it



SOCIETÀ ITALIANA DI FARMACOLOGIA

Riconosciuta con D.M. del MURST del 02/01/1996
Iscritta Registro Persone Giuridiche Prefettura di Milano n. 467 pag 722 vol. 2°
C.F.: 97053420150 – P.I.: 11453180157



GIORGIO RACAGNI
Presidente

GIUSEPPE CIRINO
Presidente Eletto

GIAMBATTISTA BONANNO
NICOLETTA BRUNELLO
ROMANO DANESI
ANNAMARIA DE LUCA
PATRIZIA HRELIA
MARCO PISTIS
Consiglieri

CARLA GHELARDINI
Segretario

ALESSANDRO MUGELLI
Past President

12. Chen N, Warner JL, Reiss CS. NSAID treatment suppresses VSV propagation in mouse CNS. *Virology*. 2000 Oct 10;276(1):44-51.
13. Alfajaro MM, Choi JS, Kim DS, Seo JY, Kim JY, Park JG, Soliman M, Baek YB, Cho EH, Kwon J, Kwon HJ, Park SJ, Lee WS, Kang MI, Hosmillo M, Goodfellow I, Cho KO. Activation of COX-2/PGE2 Promotes Sapovirus Replication via the Inhibition of Nitric Oxide Production. *J Virol*. 2017 Jan 18;91(3). pii: e01656-16. doi: 10.1128/JVI.01656-16.
14. Kirkby NS, Zaiss AK, Wright WR, et al. Differential COX-2 induction by viral and bacterial PAMPs: Consequences for cytokine and interferon responses and implications for anti-viral COX-2 directed therapies. *Biochem Biophys Res Commun*. 2013;438(2):249–256. doi:10.1016/j.bbrc.2013.07.006
15. Fitzgerald D.W., Bezak K., Ocheretina O., Riviere C., Wright T.C., Milne G.L., Zhou X.K., Du B., Subbaramaiah K., Byrt E., Goodwin M.L., Rafii A., Dannenberg A.J. The effect of HIV and HPV coinfection on cervical COX-2 expression and systemic prostaglandin E2 levels. *Cancer Prev. Res*. 2012;5:34–40.
16. Nunez O., Fernandez-Martinez A., Majano P.L., Apolinario A., Gomez-Gonzalo M., Benedicto I., Lopez-Cabrera M., Bosca L., Clemente G., Garcia-Monzon C., Martin-Sanz P. Increased intrahepatic cyclooxygenase 2, matrix metalloproteinase 2, and matrix metalloproteinase 9 expression is associated with progressive liver disease in chronic hepatitis C virus infection: role of viral core and NS5A proteins. *Gut*. 2004;53:1665–1672
17. Carey M.A., Bradbury J.A., Seubert J.M., Langenbach R., Zeldin D.C., Germolec D.R. Contrasting effects of cyclooxygenase-1 (COX-1) and COX-2 deficiency on the host response to influenza A viral infection. *J. Immunol*. 2005;175:6878–6884.
18. Amici C, Di Caro A, Ciucci A, Chiappa L, Castilletti C, Martella V, Decaro N, Buonavoglia C, Capobianchi MR, Santoro MG. Indomethacin has a potent antiviral activity against SARS coronavirus. *Antivir Ther*. 2006;11(8):1021-30. PubMed PMID: 17302372.
19. https://www.aifa.gov.it/documents/20142/847374/2020.03.18_IT_Comunicazione_EMA_Ibuprofen.pdf/1eb7a327-e922-972e-b4b5-01d1ed643a21

Segreteria Organizzativa:

Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente:

Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto:

Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario:

Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it