



Home as the new frontier for the treatment of COVID-19: the case for anti-inflammatory agents

Norberto Perico*, Monica Cortinovis*, Fredy Suter*, Giuseppe Remuzzi

COVID-19, caused by SARS-CoV-2, is characterised by a broad spectrum of symptom severity that requires varying amounts of care according to the different stages of the disease. Intervening at the onset of mild to moderate COVID-19 symptoms in the outpatient setting would provide the opportunity to prevent progression to a more severe illness and long-term complications. As early disease symptoms variably reflect an underlying excessive inflammatory response to the viral infection, the use of anti-inflammatory drugs, especially non-steroidal anti-inflammatory drugs (NSAIDs), in the initial outpatient stage of COVID-19 seems to be a valuable therapeutic strategy. A few observational studies have tested NSAIDs (especially relatively selective COX-2 inhibitors), often as part of multipharmacological protocols, for early outpatient treatment of COVID-19. The findings from these studies are promising and point to a crucial role of NSAIDs for the at-home management of people with initial COVID-19 symptoms.

Introduction

The COVID-19 pandemic continues to pose major threats to global public health.¹ The more transmissible variants of SARS-CoV-2 were responsible for the four major waves of infections that spread across the globe starting in early 2020, with omicron (B.1.1.529) becoming the dominant variant after the summer of 2021, followed by the emergence of other omicron sublineages in 2022 (BA.2, BA.3, BA.4, and BA.5).^{1,2}

As a result, communities and hospitals around the world have been pushed to their limits.³ In a global effort that is unparalleled in modern history, there has been a race to find drugs and biological treatments to save the lives of patients who are hospitalised or severely ill and to develop vaccines.^{4,5} Indeed, COVID-19 vaccines have contributed to the reduced risk of SARS-CoV-2 infection, and provide protection against severe disease caused by the SARS-CoV-2 variants, including omicron.⁶ Nonetheless, to reduce severe COVID-19-related illness, overcrowding of hospitals, and treatment costs,⁷ there has also been a focus on how primary care physicians can treat initial mild to moderate symptoms in outpatients with COVID-19. This approach would provide an opportunity to intervene before infected individuals develop severe illness. Since mild to moderate symptoms of COVID-19 might reflect an underlying excessive inflammatory response to the viral infection, the use of anti-inflammatory drugs in the community during the early stage of COVID-19 appears to be a valuable therapeutic option. However, anti-inflammatory therapy for managing people with COVID-19 at home continues to be a matter of debate, in terms of effectiveness and possible important side-effects.

In this Review, we briefly describe the pathogenic mechanisms underlying the inflammatory processes of early stage COVID-19 and discuss the rationale for using non-steroidal anti-inflammatory drugs (NSAIDs), as well as evidence regarding their risk-to-benefit balance in the home and community setting. We also examine whether outpatient pharmacological interventions with corticosteroids could mitigate the ongoing inflammatory

process, potentially protecting against the risk of progression towards more severe illness.

Maladaptive hyperinflammatory response to SARS-CoV-2 infection

As with other coronaviruses, the human-to-human transmission of SARS-CoV-2 occurs primarily through direct or indirect respiratory tract exposure to infected droplets or aerosols generated during sneezing and coughing.⁸ To enter target cells, the spike subunit of SARS-CoV-2 engages the host protease ACE2 as an entry receptor, after being primed by the cellular serine protease TMPRSS2.⁹ Lysis of infected cells and SARS-CoV-2 replication in the host cells are associated with the release of inflammatory cytokines (such as TNF- α , IL-6, and IL-8) and free radicals, the induction of IFN- γ , and the recruitment and activation of leukocyte subsets, which in turn further release cytokines, chemokines, and other inflammatory mediators that determine the early inflammatory response.¹⁰ It has been hypothesised that the inflammatory environment of SARS-CoV-2 infection could also be sustained by the enhanced availability of angiotensin-II as the result of the net downregulation of ACE2, due to continuous recycling of this receptor upon viral cell entry.¹¹ Since ACE2 degrades angiotensin-II, ACE2 deficiency causes angiotensin-II accumulation, which in turn (by binding to the angiotensin-I receptor) triggers inflammatory processes by stimulating proliferation of mononuclear cells and promoting the recruitment of proinflammatory cells.^{11,12} Moreover, the uptake of an antibody-opsonised virus by the Fc γ receptors of monocytes and macrophages results in inflammatory cell death, which halts the production of infectious virus but causes systemic inflammation that contributes to COVID-19 pathogenesis.¹³

Later in the disease course, viral replication can occur in the lower respiratory tract.¹⁴ The apoptotic death response of the infected epithelial cells is associated with vascular leakage within alveoli, which induces initial local inflammation and the recruitment of immune cells to eliminate extracellular virus and destroy virus-infected

Lancet Infect Dis 2023; 23: e22–33

Published Online
August 25, 2022
[https://doi.org/10.1016/S1473-3099\(22\)00433-9](https://doi.org/10.1016/S1473-3099(22)00433-9)

*Contributed equally

Istituto di Ricerche Farmacologiche Mario Negri, IRCCS, Bergamo, Italy (N Perico MD, M Cortinovis BiotechD, Prof G Remuzzi MD); Azienda Socio-Sanitaria Territoriale (ASST) Papa Giovanni XXIII, Bergamo, Italy (Prof F Suter MD, Prof G Remuzzi)

Correspondence to: Prof Giuseppe Remuzzi, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Centro Anna Maria Astori, Parco Scientifico Tecnologico Kilometro Rosso, 24126 Bergamo, Italy (giuseppe.remuzzi@marionegri.it)

cells.¹⁵ Proinflammatory cytokines further recruit leukocytes within the lung, contributing to the propagation of the inflammatory response, as shown in patients with COVID-19 progression to severe disease.¹⁶ Furthermore, evidence indicates that proinflammatory CD68 macrophages bearing ACE2 on their surface can be directly infected by SARS-CoV-2,¹⁷ and their virus-induced activation appears to be relevant to the initiation and spread of the hyperinflammatory response.¹⁸ Notably, CD163 monocyte-derived macrophages also accumulate in the lungs.¹⁹ As shown in patients with COVID-19-related acute respiratory distress syndrome, although these cells further contribute to inflammation in the

lung, they are also reprogrammed by the virus towards a profibrotic transcriptional and proteomic phenotype, resulting in pulmonary fibrosis.¹⁹

Together, the available evidence highlights the crucial role of the dysregulation of the innate and adaptive immune response, and the associated maladaptive hyperinflammatory response, in the initiation and exacerbation of COVID-19 disease (figure 1). Thus, the timing of intervention is likely to be an important determinant in the therapeutic response. Although monoclonal antibodies^{20–22} or polyclonal convalescent plasma²³ have been shown to reduce the incidence of disease progression and hospitalisation when given to outpatients with COVID-19 within 5–9 days of disease onset, these therapies are sometimes unavailable or scarce (such as in low-income and middle-income countries) or ineffective because of antibody-resistant variants.²⁴ Therefore, a different option would be to target the inflammatory processes underlying the mild to moderate symptoms at COVID-19 onset with currently available anti-inflammatory drugs.

Rationale for using NSAIDs in the treatment of early stage COVID-19 Prostanoids and COVID-19

NSAIDs are one of the most commonly used classes of medicines worldwide—taken to reduce pain, control fever, and treat a broad range of inflammatory diseases, including osteoarthritis and rheumatoid arthritis.²⁵ The principal therapeutic effect of NSAIDs relates to their capability to inhibit the cyclooxygenase activity of two enzymes, PTGS1 and PTGS2 (also known as COX-1 and COX-2).²⁶ This inhibition of COX-1 and COX-2 eventually suppresses the formation of prostanoids—metabolites of arachidonic acid, a fatty acid present in cell membrane phospholipids (figure 2).²⁷ Prostanoids, which include prostaglandin E₂ (PGE₂), D₂ (PGD₂), and F_{2α} (PGF_{2α}), thromboxane A₂ (TxA₂), and prostacyclin (PGI₂), elicit a wide variety of biological effects involved in homeostatic and normal tissue function after binding to their receptors. These biological effects include vascular tone, platelet function, kidney function, and gastrointestinal protection, but also effects implicated in pathophysiological processes including infection, thrombosis, and inflammation.²⁸ Several initial small studies have shown that concentrations of PGE₂, PGF_{2α}, and TxA₂ in biological samples from inpatients with COVID-19 are higher than in healthy controls, although no data are available regarding prostanoid concentrations in outpatients with SARS-CoV-2 infection.^{29–32} Nonetheless, caution should be taken in interpreting these findings, which could be skewed by the use of questionable assays and an insufficient consideration of factors that influence prostanoid concentrations, including the use of NSAIDs, corticosteroids, or other drugs, besides possible artifacts created during sample collections.³³

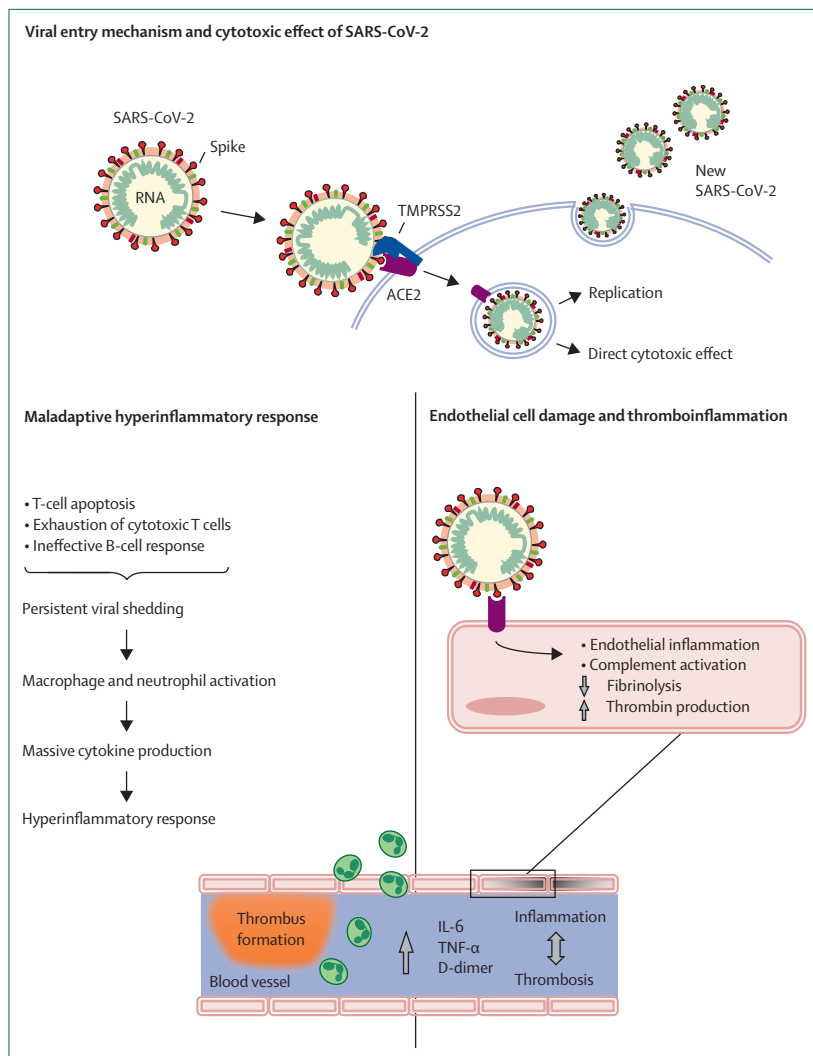


Figure 1: Proposed maladaptive hyperinflammatory response to SARS-CoV-2 infection
SARS-CoV-2 enters target host cells by interacting through its spike subunit with ACE2, after being primed by TMPRSS2. The virus induces cell damage through direct cytotoxic effects and after newly formed virions are released by exocytosis into the extracellular compartment. In addition, a dysregulated immune response eventually leads to the recruitment and activation of macrophages and neutrophils, with the release of cytokines, chemokines, and other inflammatory mediators determining hyperinflammation. At the same time, activation of the complement system and excessive cytokine production activate endothelial cells and disrupt vascular integrity leading to microthrombi deposition and microvascular dysfunction.

Coronaviruses, including SARS-CoV-2, enhance the expression of genes encoding for COX-1, COX-2, and cytosolic prostaglandin E synthase (PTGES).³⁴ For example, SARS-CoV-2 infection upregulates COX-2 expression *in vivo* in the K18-hACE2 strain of mice, as well as *in vitro* in human cells.³⁵ Similarly, COX-1, COX-2, and PTGES have been shown to be upregulated in peripheral blood mononuclear cells isolated from patients with COVID-19 compared with healthy controls.³⁶

However, cyclooxygenase enzymes trigger the cell release of prostanoids with varying effects on host immune function, at least as reported in experimental models of coronavirus infections.³⁷ Pharmacological inhibition of the PGE₂ receptors EPr₂ and EPr₄ improved survival after influenza A virus infection, an effect attributed to prevention of PGE₂-induced inhibition of type I interferon production and apoptosis in macrophages, thereby directly allowing mouse and human macrophages to restrict viral replication.³⁷ However, the differences between the various PGE₂ receptors allow for adaptable patterns of response by various cell types at different stages of immunity.³⁸ Indeed, EPr₂ and EPr₄ mediate the anti-inflammatory and immune-suppressive activity of PGE₂, whereas antigen-induced mast cell degranulation and IL-6 production are enhanced by PGE₂ in a mechanism involving EPr₁ and EPr₃.³⁹ Nonetheless, the biology of PGE₂ and its receptors in the broader context of infectious diseases (such as acute *vs* chronic virus infections) and its pathogen-specific effects remain to be determined.⁴⁰ PGD₂ acts through its two receptors, DPr1 and DPr2.⁴¹ DPr1 inhibition enhanced the migration of dendritic cells to the lungs and lymph nodes, and subsequent T-cell proliferation, which increased survival in older but not younger mice after SARS-CoV infection.⁴²

Although these findings are very preliminary, they suggest that prostanoids play a role in SARS-CoV-2 infection and support the hypothesis that therapies that modulate prostanoid biosynthesis could be beneficial, particularly during the early phase of COVID-19.

Do NSAIDs enhance susceptibility to SARS-CoV-2 infection?

Early on in the COVID-19 pandemic, there was debate on whether the use of NSAIDs, particularly ibuprofen, would enhance susceptibility to SARS-CoV-2 infection and exacerbate COVID-19 symptoms.⁴³ The potential mechanism whereby NSAIDs could theoretically harm people with COVID-19 is through the upregulation of ACE2. This speculation arose from minimal findings in rats with streptozotocin-induced diabetes treated with ibuprofen.⁴⁴ More recent *in-vitro* studies from the past 2 years, however, have highlighted the antiviral activity of some NSAIDs, albeit only at high concentrations, which could contribute to their efficacy in treating COVID-19, besides their anti-inflammatory and analgesic properties. For example, naproxen has been shown to prevent SARS-CoV-2 nucleoprotein oligomerisation and to inhibit

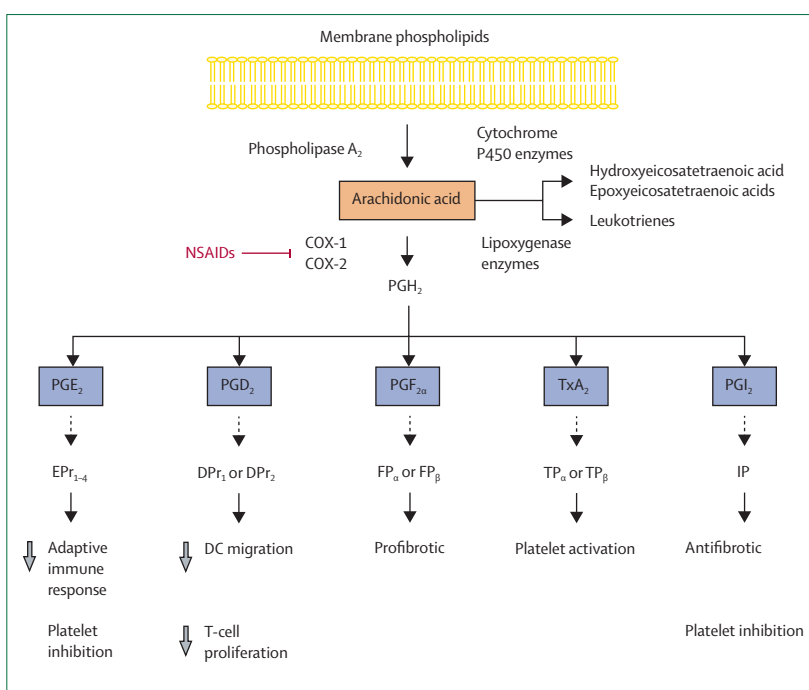


Figure 2: Prostanoid production and NSAIDs

The 20-carbon fatty acid arachidonic acid is released from membrane phospholipids by phospholipase A₂, which is activated by physical, chemical, and inflammatory stimuli. Arachidonic acid is converted by COX-1 and COX-2 to the unstable intermediate PGH₂. By tissue-specific isomerases, PGH₂ is metabolised to bioactive prostanoids, which include PGE₂, PGD₂, PGF_{2α}, TxA₂, and PGI₂. After binding to their receptors (EPr₁₋₄, DPr₁, DPr₂, FP_α, FP_β, TP_α, TP_β, and IP), prostanoids elicit a wide variety of biological effects involved in homeostatic and normal tissue function but also implicated in pathophysiological processes including infection, thrombosis, and inflammation. The principal therapeutic effect of NSAIDs is related to their capability to inhibit the cyclooxygenase activity of COX-1 and COX-2 enzymes, eventually suppressing the formation of prostanoids. DC=dendritic cell. NSAIDs=non-steroidal anti-inflammatory drugs.

viral replication in Vero E6 cells and human pulmonary epithelium.⁴⁵ Other reports from *in silico* analyses from transcriptomic databases of kidney tissue from rats treated with various NSAIDs found that naproxen, nimesulide, diclofenac, meloxicam, and piroxicam markedly reduced ACE2 expression.⁴⁶ Moreover, high concentrations of ibuprofen and flurbiprofen reduced SARS-CoV-2 replication *in vitro*.⁴⁷ Data based on small population cohorts and observational and retrospective studies have consistently shown no association between ongoing NSAID therapy and increased mortality⁴⁸⁻⁵¹ or worsening of clinical outcomes^{48,49,51-53} in people with COVID-19 in the general population (ie, inpatient and outpatient population; appendix p 1). Similarly, in people with pre-existing rheumatic disease who were chronically exposed to NSAIDs, the ongoing use of these medicines did not increase the risk of hospitalisation for COVID-19 or COVID-19-related death compared with non-users.^{50,54} Consistently, in people with osteoarthritis, chronic NSAID treatment was not associated with an increased risk of SARS-CoV-2 infection.⁵⁵ There was also no evidence of increased risk of mortality associated with NSAIDs in small retrospective studies of hospitalised patients with COVID-19 who chronically used these

See Online for appendix

drugs before admission,^{56,57} or in ibuprofen users before SARS-CoV-2 infection.⁴⁹ In contrast with a retrospective cohort study of 1824 adults hospitalised with COVID-19 in South Korea,⁵⁸ findings from a matched, prospective, multicentre cohort study based on the International Severe Acute Respiratory and Emerging Infection Consortium Clinical Characterisation Protocol UK dataset documented that in 8410 patients hospitalised with a PCR-confirmed or highly suspected SARS-CoV-2 infection, NSAID use (including ibuprofen) in the 2 weeks preceding admission was not associated with higher in-hospital mortality or increased COVID-19 severity compared with no NSAID use.⁵⁹ Furthermore, a systematic review and meta-analysis of 40 comparative studies that evaluated over 4.8 million adult cases substantiated that the use of NSAIDs (such as COX-2 inhibitors, ibuprofen, or aspirin) was not significantly associated with a higher risk of SARS-CoV-2 infection, or a greater probability of intensive care unit admission, mechanical ventilation, or administration of supplemental oxygen.⁶⁰

In summary, growing evidence is becoming available and most of it concludes that for patients with COVID-19 NSAID use does not enhance susceptibility to SARS-CoV-2 infection, nor does it appear to confer an increased risk of worse outcomes.

Relatively selective COX-2 inhibitors for early COVID-19 symptoms

COX-2 is a crucial enzyme involved in several physiological and pathological processes.⁶¹ It plays a central role in viral infections and regulates the expression rates of several serum proteins.⁶² In a model of H3N2 influenza A viral infection, mice knocked-out for the gene encoding for COX-2 had less severe infection (as evidenced by the blunted inflammatory and cytokine response), attenuated weight loss, and improved survival compared with wild-type mice.⁶³ Similarly, hyperinduction of COX-2 has been documented in the epithelial cells of autoptic lung tissue samples of patients who died of avian influenza H5N1 infection, along with increased concentrations of TNF- α and other pro-inflammatory cytokines.⁶⁴

NSAIDs inhibit both COX-1 and COX-2 enzymes.⁶⁵ The COX-2 selectivity of a particular drug is a continuous variable in relation to the relative drug concentration required to inhibit COX-1 and COX-2 enzymes in whole blood assays by 50%.⁶⁵ In a small prospective study of 44 patients with next-generation sequencing-confirmed or PCR-confirmed COVID-19 admitted to hospital (82% of whom had moderate symptoms), the administration of the relatively selective COX-2 inhibitor celecoxib for 7–14 days as adjuvant therapy prevented clinical deterioration and improved chest CT grading compared with standard therapy.²⁹ Similarly, in a retrospective study of hospitalised patients with COVID-19 and pneumonia, a median of

3 days of treatment with etoricoxib reduced the risk of disease progression compared with the control group.⁶⁶ Although these findings were observed in hospitalised patients, some of them had mild or moderate COVID-19 symptoms at admission, a condition similar to that of non-hospitalised people with early mild or moderate symptoms of SARS-CoV-2 infection, thus supporting the use of relatively selective COX-2 inhibitors also for outpatients with COVID-19.

Substantial overlap in COX-2 selectivity is found among some COX-2 inhibitors (eg, celecoxib) and some traditional NSAIDs (eg, nimesulide).^{65,67} The experimental evidence that celecoxib decreased cytokine concentrations (TNF- α , G-CSF, and IL-6) in bronchoalveolar lavage fluid in mice with influenza A infection,⁶⁸ and the overlap in COX-2 selectivity between this COX-2 inhibitor and nimesulide, provided the rationale for recommending these two drugs for early outpatient treatment of COVID-19 symptoms if not contraindicated.⁶⁹ Moreover, compared with other COX-2 inhibitors (including etoricoxib, rofecoxib, valdecoxib, and robenacoxib), celecoxib has higher lipophilicity, which would predict higher biological activity⁷⁰ and, therefore, should be the preferential COX-2 inhibitor for at-home treatment of early COVID-19 symptoms.

In an observational matched-cohort study, we looked at the outcomes of 90 consecutive consenting patients with mild to moderate COVID-19 treated at home by their family physicians according to a treatment algorithm based on NSAIDs (with a priority for relatively selective COX-2 inhibitors), and compared them with outcomes for 90 age-matched, sex-matched, and comorbidities-matched patients who received other therapeutic regimens.⁷¹ Early treatment according to the proposed recommendation regimen almost completely prevented the need for hospitalisation due to a progression to more severe illness (two of 90 patients), compared with patients in the control cohort who were treated according to their family physician's assessments (13 of 90 patients). This result translated into a reduction of over 90% in the overall number of days of hospital stay and related treatment costs. Moreover, symptoms (such as anosmia, ageusia, or dysgeusia) persisted less frequently and for a shorter period in the recommended algorithm cohort than in the control cohort.⁷¹ These results were substantiated by a further matched-cohort study in 216 outpatients with mild to moderate COVID-19, managed by their family doctors, showing that the adoption of the outpatient treatment algorithm based on relatively selective COX-2 inhibitors during the early phase of the illness reduced the incidence of subsequent hospitalisation (primary outcome) and related costs.⁷² Nonetheless, future randomised studies will be required to consolidate these positive observational findings.

Although more selective inhibition of COX-2 is desirable to reduce the gastrointestinal toxicity seen with

less selective COX-2 inhibitors, physicians might be aware that NSAID use has been associated with higher rates of cardiovascular events compared with placebo.⁷³ Moreover, nimesulide has been associated with a risk of hepatotoxicity; however, this risk is low when the drug is administered at the recommended time and daily dose.⁷⁴ Furthermore, long-term NSAID treatment could cause nephrotoxicity, which is exacerbated by fever and dehydration.^{75,76} This risk is particularly true for people older than 65 years, who might already have reduced kidney function related to ageing or concomitant chronic kidney disease, and for whom the maintenance of renal blood flow is highly dependent on vasodilator prostaglandins. Thus, family physicians should counsel older patients to hydrate adequately while taking NSAIDs and use these drugs for the shortest time possible.

Other NSAIDs for early stage COVID-19

Anecdotal observations from researchers in Egypt reported that 17 people with PCR-confirmed or rapid IgM test-confirmed or suspected COVID-19 who were managed at home and took ibuprofen or diclofenac—NSAIDs with similar inhibitory activity of COX-1 and COX-2 enzymes^{65,77}—recovered from most early symptoms (sore throat, dry cough, mild dyspnoea, fever <38°C) within 5 days.^{78,79} However, a prospective cohort study reported that ibuprofen, given to 40 people with COVID-19, did not lower their risk of hospitalisation compared with that of 357 non-NSAID users.⁴⁸ Yet, the possibility that people with more severe symptoms were more likely to initiate ibuprofen, and thus be at higher risk of worse disease outcomes, cannot be excluded.

The data regarding indometacin are more convincing. A powerful NSAID that non-selectively inhibits COX-1 and COX-2 enzymes,⁸⁰ indometacin has mostly been used to treat musculoskeletal inflammatory conditions.⁸¹ In vitro studies have shown both the antiviral effect of indometacin against several viruses, including SARS-CoV,^{82–84} and its ability to lower thrombin-induced production of IL-6,⁸⁵ a cytokine that is upregulated during COVID-19.⁸⁶ Notably, it has been speculated that indometacin could also modulate bradykinin effects in people with COVID-19, possibly improving the COVID-19-induced dry cough or other symptoms related to the biological activity of bradykinin.⁸⁷ Using real-world data, Gordon and colleagues first reported the beneficial outcome in a cohort of 103 people with PCR-confirmed SARS-CoV-2 infection who happened to start a course of indometacin compared with a matched group who started a prescription of celecoxib (n=103).⁸⁸ New users of indometacin were less likely than the matched new users of celecoxib to require hospitalisation or inpatient services. Similarly, in another real-world retrospective study involving 158 participants with a PCR-confirmed diagnosis of early stage COVID-19, early treatment at home (within 3 days of symptom onset vs later) with a

multipharmacological regimen (including indometacin) shortened symptom duration and reduced the risk of hospitalisation.⁸⁹ Although these findings could not be attributed to indometacin specifically, given the multipharmacological treatment, they further highlight the value of early COVID-19 patient management with therapy including NSAIDs. An open-label randomised clinical trial in India evaluated the efficacy and safety of indometacin for patients hospitalised with COVID-19 with mild to moderate symptoms including fever, cough, and myalgia at admission.⁹⁰ None of the 103 patients randomly assigned to indometacin developed desaturation (SpO₂ ≤93%); however, desaturation did occur in 20 of the 107 patients allocated to paracetamol. Patients who received indometacin also had more rapid symptom relief than those given paracetamol, with most symptoms disappearing in half the time. Although the trial involved only hospitalised patients, the mild to moderate symptoms at admission are those commonly seen in the early phase of COVID-19, so the beneficial effect of indometacin could also be expected for outpatients with COVID-19. Nonetheless, neither indometacin nor paracetamol was administered as a stand-alone treatment, but along with a standard of care including ivermectin and other adjuvant therapies.

Aspirin is an affordable, globally available drug that at low doses irreversibly inhibits the COX-1 enzyme. In addition to being a key enzyme in the synthesis of pro-inflammatory prostaglandins, COX-1 is responsible for the production of TxA₂, which promotes platelet aggregation.⁹¹ Thus, in patients with COVID-19, low-dose aspirin has mainly been proposed as a preventive approach against the thromboembolic risk associated with this disease, and the related increased mortality.^{92,93} Available studies on the use of aspirin as an antithrombotic drug for COVID-19 mainly involve hospitalised patients with varying disease severity. Consistent with small retrospective studies in China⁹⁴ and Iran,⁹⁵ a large propensity-score matched study reported a lower cumulative incidence of in-hospital death for patients with COVID-19 given low-dose aspirin during hospitalisation than for those who received no antiplatelet therapy.⁹⁶ Similarly, the beneficial effect of short-term use of low-dose aspirin is supported by the findings of a retrospective cohort study involving 412 adult patients hospitalised with COVID-19-related acute respiratory distress syndrome, showing that aspirin administration, started within 24 h of admission or 7 days before hospital admission, was independently associated with a reduced risk of mechanical ventilation, intensive care unit admission, and in-hospital mortality.⁹⁷ A meta-analysis of ten retrospective studies, including 56 696 hospitalised patients with COVID-19,^{94,97–102} indicated a lower likelihood of dying for those who had taken aspirin than for non-aspirin users.¹⁰³ Moreover, in contrast to findings of the large RECOVERY trial (n=7351),¹⁰⁴ an observational cohort study of 111 269 US

	Exposure	Timing of exposure	Total patients	Age, years*	Sex, %	Primary outcome	Inhaled corticosteroid group	Control group	Between-group difference, p value
Ramakrishnan et al (2021); ¹³⁴ STOIC (open-label)	Inhaled budesonide (1600 µg/day) until self-reported symptom recovery or primary outcome achievement	≤7 days from symptom onset	146	45 (13)	57% female, 43% male	Combined endpoint of COVID-19-related emergency department assessment or hospital admission	Two (3%) of 73 patients	11 (15%) of 73 patients	Difference in proportions 12.3% (95% CI 3.3 to 21.3); p=0.009
Yu et al (2021); ¹³⁵ PRINCIPLE (open-label)	Inhaled budesonide (1600 µg/day) for 14 days	≤14 days from symptom onset	1856	64.2 (7.6)†	52% female, 48% male†	Time to first self-reported recovery by 28 days; combined endpoint of hospital admission or death by 28 days	11.8 days (95% BCI 10.0 to 14.1); 6.8% (95% BCI 4.1 to 10.2)	14.7 days (95% BCI 12.3 to 18.0); 8.8% (95% BCI 5.5 to 12.7)	HR 1.21 (95% BCI 1.08 to 1.36); HR 0.75 (95% BCI 0.55 to 1.03)
Ezer et al (2021); ¹³⁶ CONTAIN (placebo-controlled)	Inhaled (1200 µg/day) and intranasal (200 µg/day) ciclesonide for 14 days	≤6 days from symptom onset	203	35 (27–47)	54% female, 46% male	Resolution of symptoms by day 7	42 (40%) of 105 patients	34 (35%) of 98 patients	Adjusted risk difference 5.5% (95% CI –7.8 to 18.8), p=NS‡
Clemency et al (2022); ¹³⁷ Covis Pharma (placebo-controlled)	Inhaled ciclesonide (640 µg/day) for 30 days	Positive SARS-CoV-2 test ≤72 h	400	43.3 (16.9)	55% female, 45% male	Time to alleviation of COVID-19-related symptoms by day 30	19.0 days (95% CI 14.0 to 21.0)	19.0 days (95% CI 16.0 to 23.0)	HR 1.08 (95% CI 0.84 to 1.38), p=NS‡
Duvignaud et al (2022); ¹³⁸ COVERAGE (open-label)	Inhaled ciclesonide (640 µg/day) for 10 days	≤7 days from symptom onset	217	63 (59–68)	51% female, 49% male	Combined endpoint of hospital admission, oxygen therapy at home, or death by day 14	18 (16%) of 110 patients	13 (12%) of 107 patients	p=NS§

BCI=Bayesian credible interval. HR=hazard ratio. NS=not significant. *Data are mean (SD) or median (IQR). †Data refer to SARS-CoV-2-positive participants. ‡Significance threshold was 0.05. §Significance threshold was not specified.

Table 1: Randomised controlled trials that examined inhaled corticosteroids for outpatient treatment of COVID-19

adults hospitalised with moderate COVID-19 showed that early aspirin use was associated with a lower risk of in-hospital mortality after 28 days than was no aspirin use.¹⁰⁵ Together, these studies on aspirin use as an antithrombotic agent in patients hospitalised for COVID-19 are encouraging, although not conclusive. However, the observation that the beneficial effects of aspirin were also documented in patients with moderate COVID-19¹⁰⁵ suggests a usefulness of this anti-inflammatory drug even for managing outpatients with early stage COVID-19. In this setting, aspirin could be considered an alternative treatment to relatively selective COX-2 inhibitors, indometacin, or other NSAIDs when signs of toxicity or contraindications to these drugs are brought to the attention of family doctors. Indeed, aspirin has been shown to reduce the plasma concentrations of cytokines in patients with chronic stable angina,¹⁰⁶ and even to have antiviral activity against RNA viruses in the respiratory tract.¹⁰⁷ Thus, these aspirin properties could help to reduce the mild or moderate symptoms induced by the underlying inflammatory processes.

Corticosteroids for early stage COVID-19

Synthetic corticosteroids are widely available medications used to treat chronic inflammatory and autoimmune diseases. At the cellular level, they exert

anti-inflammatory actions mainly through inhibition of the NF-κB pathway.¹⁰⁸ The effects of corticosteroids on type I interferons, which play a key role in host immune response to viral infections, remain incompletely characterised. Routine doses of oral corticosteroids do not appear to suppress type I interferon production in patients with systemic lupus erythematosus.¹⁰⁹ However, there is in vitro evidence that these medications impair the antiviral immune response in human airway cells by interfering with the type I interferon signalling pathway, thereby enhancing viral replication.^{110,111} Corticosteroids also dampen cellular immunity by inhibiting the development of type 1 helper T cells, CD8 T cells, and natural killer cells.¹¹²

Evidence from preclinical studies suggests that corticosteroids can directly modulate endothelial function, with effects depending on the inflammatory environment. In particular, under physiological conditions, corticosteroids could lead to endothelial function impairment by reducing vascular nitric oxide availability.^{113,114} By contrast, under inflammatory conditions, they were found to exert protective effects on the inflammation-associated endothelial cell dysfunction, possibly by reducing IL-6 and TNF-α expression.¹¹⁵ Thus, timing and inflammatory milieu seem to influence responses to corticosteroid treatment.

Chronic use of corticosteroids in autoimmune or obstructive pulmonary diseases and in COVID-19

Chronic use of systemic or inhaled corticosteroids has been associated with increased odds of hospitalisation⁵⁴ or mortality^{116–119} in people with COVID-19 and rheumatic diseases, inflammatory bowel disease, asthma, or chronic obstructive pulmonary disease. However, the more serious outcomes observed in patients on corticosteroids could be confounded by treatment indication, whereby underlying disease activity or severity could itself negatively affect COVID-19 sequelae.^{119–121} Thus, uncertainty remains around the effects of chronic use of corticosteroid on COVID-19 outcomes.

Systemic corticosteroids for COVID-19 management

Based on evidence from previous coronavirus outbreaks (eg, SARS-CoV and MERS-CoV), the use of systemic corticosteroids in COVID-19 was initially discouraged due to the potential risk of secondary infections, long-term complications, and delayed viral clearance.¹²² However, the RECOVERY trial, published in 2021, showed reduced mortality with dexamethasone in patients hospitalised with COVID-19 who required mechanical ventilation or supplemental oxygen, but not among those receiving no respiratory support.¹²³ Largely based on these findings, WHO guidance strongly recommended systemic corticosteroids in patients with severe and critical COVID-19.¹²⁴ Data regarding the use of these drugs during the initial phase of COVID-19, when patients are not hospitalised, are scant. Anecdotal evidence from case reports and observational studies suggests that early outpatient treatment with systemic corticosteroids at the time of viral replication (ie, within the first few days of symptoms onset) is associated with an increased risk of delayed recovery and worse clinical outcomes.^{125–129} Systemic corticosteroids cause widespread immunosuppression, which could be useful during the late inflammatory phase of severe COVID-19 but cause harm in the early disease phase by suppressing host antiviral responses.¹³⁰ Nonetheless, further studies are needed to pinpoint the optimal timing of corticosteroid initiation during the disease course.

Inhaled corticosteroids for COVID-19 management

Inhaled corticosteroids have been proposed as an early COVID-19 treatment on the basis of their targeted anti-inflammatory effects in the lung and their antiviral properties.^{131–133} To date, five randomised controlled trials have explored treatment with inhaled corticosteroids in outpatients with COVID-19 within 7–14 days of the onset of mild to moderate symptoms (table 1). The STOIC study showed that among 146 outpatients with mild COVID-19, inhaled budesonide reduced the composite endpoint of emergency department assessment or hospitalisation, and improved time to recovery, compared with usual care.¹³⁴ The larger PRINCIPLE study found that in 1856 outpatients with

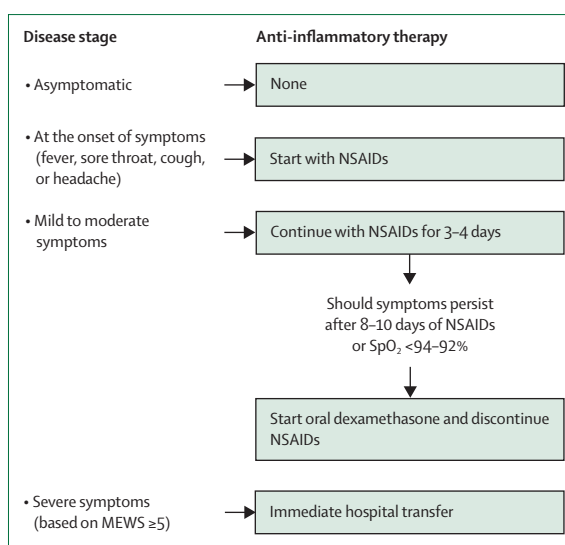


Figure 3: Options for at-home anti-inflammatory therapy in adults with COVID-19 depending on disease stage

MEWS=Modified Early Warning Score (an international, universal scoring scale from multiple parameters including respiratory rate, SpO₂, heart rate, systolic blood pressure, consciousness). NSAIDs=non-steroidal anti-inflammatory drugs. SpO₂=oxygen saturation.

COVID-19 at high risk of disease progression, inhaled budesonide improved time to recovery and reduced the combined endpoint of hospital admission or death compared with usual care, although statistical significance was not achieved for the combined endpoint.¹³⁵ The COVERAGE study, which aimed to test inhaled ciclesonide in outpatients with COVID-19 at risk of disease aggravation, was prematurely stopped after the first interim analysis revealed no efficacy with regard to reducing the primary composite endpoint of a need for oxygen therapy at home, hospitalisation, or death.¹³⁸ Notably, these randomised controlled trials had an open-label design, and inhaled medications are known to have placebo effects in respiratory diseases,¹³⁹ which could have introduced bias in subjective endpoints. Two double-blind, placebo-controlled, randomised controlled trials have examined the effects of inhaled ciclesonide in patients with early stage COVID-19 in the community. An industry-sponsored study involving 400 people with mild to moderate COVID-19 disease found that inhaled ciclesonide did not decrease time to symptom alleviation, but it did reduce the combined endpoint of emergency department visit or hospitalisation.¹³⁷ Instead, the CONTAIN study showed that among 203 young outpatients (median age of 35 years) with COVID-19, the combination of inhaled and intranasal ciclesonide did not improve the resolution of symptoms, nor did it reduce the incidence of hospitalisation.¹³⁶ Overall, evidence from randomised controlled trials suggests that the use of inhaled corticosteroids in outpatients with COVID-19 does not adversely affect clinical

	When to use	Dosage	Time of exposure
NSAIDs			
Relatively selective COX-2 inhibitors			
Nimesulide	At the onset of symptoms (fever, cough, sore throat, headache)	100 mg orally twice a day	For 3–4 days, if symptoms persist, continue for a maximum of 12 days
Celecoxib	At the onset of symptoms (fever, cough, sore throat, headache)	Initial oral dose of 400 mg followed by a second dose of 200 mg on the first day; in the following days, 200 mg/day up to a maximum of 400 mg/day	For 3–4 days, if symptoms persist, continue for a maximum of 12 days
Other NSAIDs			
Ibuprofen	At the onset of symptoms (fever, cough, sore throat, headache)	400 mg orally twice a day	For 3–4 days
Aspirin	At the onset of symptoms (fever) or with laboratory signs of hepatotoxicity associated with nimesulide or contraindications to celecoxib	500 mg orally twice a day	For 3–4 days, if symptoms persist, continue for a maximum of 8 days
Corticosteroids*			
Dexamethasone	Should fever persist after 8–10 days of NSAID treatment, or when oxygen saturation <94–92% occurs	8 mg orally for 3 days, then tapered to 4 mg for a further 3 days, and then to 2 mg for 3 days	Duration of treatment depends on the clinical evolution of the disease
The recommended drugs can be used unless contraindicated according to summary of product characteristics. *At the start of corticosteroid treatment, NSAIDs should be discontinued. NSAID=non-steroidal anti-inflammatory drug.			

Table 2: Recommendations for anti-inflammatory agents for early COVID-19 symptoms in adults

outcomes nor does it increase the risk of side-effects compared with usual care or placebo. Nonetheless, the effectiveness of these medications in early COVID-19 management remains ill-defined.

Discussion and conclusions

Several recommendations on how to treat people at home with COVID-19 with mild to moderate symptoms have been proposed, starting with the use of anti-inflammatory drugs.^{69,140–142} The main recommended NSAIDs are relatively selective COX-2 inhibitors, indometacin, ibuprofen, and aspirin—often as part of a multipharmacological protocol. Some of the recommendations suggest paracetamol as a safe therapy for the early management of pain and fever in people with COVID-19. However, one should consider that (besides being a negligible anti-inflammatory drug)¹⁴³ at relatively low doses paracetamol reduces plasma and tissue glutathione concentrations, which might exacerbate COVID-19.^{144,145} Very few researchers have formally tested their proposed recommendations for outpatients with symptomatic COVID-19 through observational studies, although those that have show encouraging results.^{71,72,89,146} In particular, findings from our studies^{71,72} have corroborated the treatment protocol recommendations for early outpatient treatment of COVID-19 we have previously proposed on the basis of growing knowledge on the pathophysiology underlying the mild to moderate symptoms encountered at disease

Search strategy and selection criteria

References for this Review were identified through searches of PubMed for articles published from Jan 1, 2020, to May 25, 2022, with the terms “COVID-19”, “SARS-CoV-2”, “anti-inflammatory agents”, “non-steroidal anti-inflammatory drugs”, “NSAIDs”, “COX-2 inhibitors”, “corticosteroids”, “glucocorticoids” “pathogenesis”, and “hyperinflammation”. All articles published in English and Italian resulting from these searches, and relevant references cited in those articles, were reviewed.

onset (figure 3).⁶⁹ These treatment recommendations are based on three pillars: intervene at the very onset of symptoms at home; start therapy as early as possible after the family doctor has been contacted by the patient (without waiting for the results of a nasopharyngeal swab); and rely on NSAIDs, especially relatively selective COX-2 inhibitors (table 2). The overlap in COX-2 selectivity between celecoxib and nimesulide was the rationale for recommending these two drugs for the early outpatient treatment of COVID-19 symptoms (table 2). Aspirin or ibuprofen are the alternative treatments to these relatively selective COX-2 inhibitors, if these COX-2 inhibitors are not available or when signs of toxicity or contraindications to these drugs are evident according to clinical characteristics and the medical history of the patient. Treatment with NSAIDs should continue for 3–4 days, but if symptoms persist it could be extended for a maximum of 8–12 days, if not contraindicated (table 2). Moreover, given the metabolic pathway of these NSAIDs involving, among others, the cytochrome 3A4, family physicians should consider the risk of potential drug interactions, especially for patients with COVID-19 who started antiviral therapy with remdesivir or ritonavir-boosted nirmatrelvir. In this case, potential strategies include adjusting the NSAID dose, increasing monitoring for potential adverse reactions, or temporary NSAID withholding. These NSAIDs should be given to treatment-naïve patients who are older than 65 years for the shortest time possible, and under adequate hydration. They can be prescribed to pregnant women but only in the first few months of gestation, according to the summary of product characteristics.¹⁴⁷ Celecoxib, ibuprofen, and nimesulide should be avoided in children younger than 12 years, whereas aspirin should be taken only under prescription and at the dose recommended by the family doctor.

Overall, our studies and other observational studies indicate that anti-inflammatory therapy, especially NSAIDs, is crucial for the management of outpatients with early symptoms of COVID-19, since the mitigation of these symptoms protects against progression towards a more severe illness that would eventually require hospitalisation, placing a huge burden on the hospital system (appendix p 1).

Contributors

NP and MC did the data search for this Review. All authors wrote the text, reviewed and edited the manuscript, and made substantial contributions to discussions of the content.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank Kerstin Mierke (Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Italy) for her help with English language editing of the manuscript. We would also like to thank Martinelli Ginetto for their support realising the study. Finally, we would like to express our sincere gratitude to Fondazione MEI Onlus for their generous contribution to this study.

References

- Johns Hopkins Center for Systems Science and Engineering. COVID-19 map—Johns Hopkins Coronavirus Resource Center. <https://coronavirus.jhu.edu/map.html> (accessed June 16, 2022).
- US Centers for Disease Control and Prevention. Omicron variant: what you need to know. <https://www.cdc.gov/coronavirus/2019-ncov/variants/omicron-variant.html> (accessed June 16, 2022).
- Perico N, Fagioli S, Di Marco F, et al. Bergamo and COVID-19: how the dark can turn to light. *Front Med* 2021; **8**: 609440.
- Kupferschmidt K, Cohen J. Race to find COVID-19 treatments accelerates. *Science* 2020; **367**: 1412–13.
- Tregoning JS, Flight KE, Higham SL, Wang Z, Pierce BF. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. *Nat Rev Immunol* 2021; **21**: 626–36.
- Danza P, Koo TH, Haddix M, et al. SARS-CoV-2 infection and hospitalization among adults aged ≥ 18 years, by vaccination status, before and during SARS-CoV-2 B.1.1.529 (omicron) variant predominance—Los Angeles County, California, November 7, 2021–January 8, 2022. *MMWR Morb Mortal Wkly Rep* 2022; **71**: 177–81.
- Fagioli S, Lorini FL, Remuzzi G. Adaptations and lessons in the province of Bergamo. *N Engl J Med* 2020; **382**: e71.
- Hui KPY, Cheung M-C, Perera RAPM, et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. *Lancet Respir Med* 2020; **8**: 687–95.
- Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; **181**: 271–80.e8.
- Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. *Nat Rev Nephrol* 2021; **17**: 46–64.
- Vaduganathan M, Vardeny O, Michel T, McMurray JVV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med* 2020; **382**: 1653–59.
- Ruiz-Ortega M, Lorenzo O, Suzuki Y, Rupérez M, Egido J. Proinflammatory actions of angiotensins. *Curr Opin Nephrol Hypertens* 2001; **10**: 321–29.
- Junqueira C, Crespo Á, Ranjbar S, et al. FcγR-mediated SARS-CoV-2 infection of monocytes activates inflammation. *Nature* 2022; **606**: 576–84.
- Hou YJ, Okuda K, Edwards CE, et al. SARS-CoV-2 reverse genetics reveals a variable infection gradient in the respiratory tract. *Cell* 2020; **182**: 429–46.e14.
- Shi Y, Wang Y, Shao C, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ* 2020; **27**: 1451–54.
- Yang Y, Shen C, Li J, et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. *J Allergy Clin Immunol* 2020; **146**: 119–27.e4.
- Wang C, Xie J, Zhao L, et al. Alveolar macrophage dysfunction and cytokine storm in the pathogenesis of two severe COVID-19 patients. *EBioMedicine* 2020; **57**: 102833.
- Pedersen SF, Ho Y-C. SARS-CoV-2: a storm is raging. *J Clin Invest* 2020; **130**: 2202–05.
- Wendisch D, Dietrich O, Mari T, et al. SARS-CoV-2 infection triggers profibrotic macrophage responses and lung fibrosis. *Cell* 2021; **184**: 6243–61.e27.
- Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. *N Engl J Med* 2021; **384**: 238–51.
- Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus etesevimab in mild or moderate COVID-19. *N Engl J Med* 2021; **385**: 1382–92.
- Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med* 2021; **385**: 1941–50.
- Sullivan DJ, Gebo KA, Shoham S, et al. Early outpatient treatment for COVID-19 with convalescent plasma. *N Engl J Med* 2022; **386**: 1700–11.
- Callaway E. COVID antibody drugs work best when given as early as possible. *Nature* 2022; published online March 30. <https://doi.org/10.1038/d41586-022-00893-y>.
- Wolfe F, Zhao S, Lane N. Preference for nonsteroidal antiinflammatory drugs over acetaminophen by rheumatic disease patients: a survey of 1,799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. *Arthritis Rheum* 2000; **43**: 378–85.
- Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs—differences and similarities. *N Engl J Med* 1991; **324**: 1716–25.
- Samuelsson B. An elucidation of the arachidonic acid cascade. Discovery of prostaglandins, thromboxane and leukotrienes. *Drugs* 1987; **33** (suppl 1): 2–9.
- Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. *Arterioscler Thromb Vasc Biol* 2011; **31**: 986–1000.
- Hong W, Chen Y, You K, et al. Celebrex adjuvant therapy on coronavirus disease 2019: an experimental study. *Front Pharmacol* 2020; **11**: 561674.
- Kazancioglu S, Yilmaz FM, Bastug A, et al. Assessment of galectin-1, galectin-3, and prostaglandin E2 levels in patients with COVID-19. *Jpn J Infect Dis* 2021; **74**: 530–36.
- Yalçın Kehribar D, Cihangiroğlu M, Sehmen E, et al. The assessment of the serum levels of TWEAK and prostaglandin F2α in COVID-19. *Turk J Med Sci* 2020; **50**: 1786–91.
- Archambault A-S, Zaid Y, Rakotoarivelo V, et al. High levels of eicosanoids and docosanoids in the lungs of intubated COVID-19 patients. *FASEB J* 2021; **35**: e21666.
- Grosser T, Naji A, FitzGerald GA. Urinary prostaglandin metabolites: an incomplete reckoning and a flush to judgment. *Circ Res* 2018; **122**: 537–39.
- Theken KN, FitzGerald GA. Bioactive lipids in antiviral immunity. *Science* 2021; **371**: 237–38.
- Chen JS, Alfajaro MM, Chow RD, et al. Non-steroidal anti-inflammatory drugs dampen the cytokine and antibody response to SARS-CoV-2 infection. *J Virol* 2021; **95**: e00014–21.
- Yan Q, Li P, Ye X, et al. Longitudinal peripheral blood transcriptional analysis reveals molecular signatures of disease progression in COVID-19 patients. *J Immunol* 2021; **206**: 2146–59.
- Coulombe F, Jaworska J, Verway M, et al. Targeted prostaglandin E2 inhibition enhances antiviral immunity through induction of type I interferon and apoptosis in macrophages. *Immunity* 2014; **40**: 554–68.
- Kalinski P. Regulation of immune responses by prostaglandin E2. *J Immunol* 2012; **188**: 21–28.
- Gomi K, Zhu FG, Marshall JS. Prostaglandin E2 selectively enhances the IgE-mediated production of IL-6 and granulocyte-macrophage colony-stimulating factor by mast cells through an EP1/EP3-dependent mechanism. *J Immunol* 2000; **165**: 6545–52.
- Sander WJ, O'Neill HG, Pohl CH. Prostaglandin E₂ as a modulator of viral infections. *Front Physiol* 2017; **8**: 89.
- Hata AN, Breyer RM. Pharmacology and signaling of prostaglandin receptors: multiple roles in inflammation and immune modulation. *Pharmacol Ther* 2004; **103**: 147–66.
- Zhao J, Zhao J, Legge K, Perlman S. Age-related increases in PGD(2) expression impair respiratory DC migration, resulting in diminished T cell responses upon respiratory virus infection in mice. *J Clin Invest* 2011; **121**: 4921–30.
- FitzGerald GA. Misguided drug advice for COVID-19. *Science* 2020; **367**: 1434.
- Qiao W, Wang C, Chen B, et al. Ibuprofen attenuates cardiac fibrosis in streptozotocin-induced diabetic rats. *Cardiology* 2015; **131**: 97–106.

- 45 Terrier O, Dilly S, Pizzorno A, et al. Antiviral properties of the NSAID drug naproxen targeting the nucleoprotein of SARS-CoV-2 coronavirus. *Molecules* 2021; **26**: 2593.
- 46 Saheb Sharif-Askari N, Saheb Sharif-Askari F, Mdkhana B, et al. Effect of common medications on the expression of SARS-CoV-2 entry receptors in liver tissue. *Arch Toxicol* 2020; **94**: 4037–41.
- 47 de Bruin N, Schneider A-K, Reus P, et al. Ibuprofen, flurbiprofen, etoricoxib or paracetamol do not influence ACE2 expression and activity in vitro or in mice and do not exacerbate in-vitro SARS-CoV-2 infection. *Int J Mol Sci* 2022; **23**: 1049.
- 48 Abu Esba LC, Alqahtani RA, Thomas A, Shamas N, Alswaidan L, Mardawi G. Ibuprofen and NSAID use in COVID-19 infected patients is not associated with worse outcomes: a prospective cohort study. *Infect Dis Ther* 2021; **10**: 253–68.
- 49 Rinott E, Kozler E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. *Clin Microbiol Infect* 2020; **26**: 1259.e5–7.
- 50 Wong AY, MacKenna B, Morton CE, et al. Use of non-steroidal anti-inflammatory drugs and risk of death from COVID-19: an OpenSAFELY cohort analysis based on two cohorts. *Ann Rheum Dis* 2021; **80**: 943–51.
- 51 Lund LC, Kristensen KB, Reilev M, et al. Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: a Danish nationwide cohort study. *PLoS Med* 2020; **17**: e1003308.
- 52 Kragholm K, Gerds TA, Fosbøl E, et al. Association between prescribed ibuprofen and severe COVID-19 infection: a nationwide register-based cohort study. *Clin Transl Sci* 2020; **13**: 1103–07.
- 53 Choi MH, Ahn H, Ryu HS, et al. Clinical characteristics and disease progression in early-stage COVID-19 patients in South Korea. *J Clin Med* 2020; **9**: E1959.
- 54 Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020; **79**: 859–66.
- 55 Chandan JS, Zemedikun DT, Thayakaran R, et al. Nonsteroidal antiinflammatory drugs and susceptibility to COVID-19. *Arthritis Rheumatol* 2021; **73**: 731–39.
- 56 Imam Z, Odish F, Gill J, et al. Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. *J Intern Med* 2020; **288**: 469–76.
- 57 Bruce E, Barlow-Pay F, Short R, et al. Prior routine use of non-steroidal anti-inflammatory drugs (NSAIDs) and important outcomes in hospitalised patients with COVID-19. *J Clin Med* 2020; **9**: E2586.
- 58 Jeong HE, Lee H, Shin HJ, Choe YJ, Filion KB, Shin J-Y. Association between nonsteroidal antiinflammatory drug use and adverse clinical outcomes among adults hospitalized with coronavirus 2019 in South Korea: a nationwide study. *Clin Infect Dis* 2021; **73**: e4179–88.
- 59 Drake TM, Fairfield CJ, Pius R, et al. Non-steroidal anti-inflammatory drug use and outcomes of COVID-19 in the ISARIC Clinical Characterisation Protocol UK cohort: a matched, prospective cohort study. *Lancet Rheumatol* 2021; **3**: e498–506.
- 60 Zhou Q, Zhao S, Gan L, et al. Use of non-steroidal anti-inflammatory drugs and adverse outcomes during the COVID-19 pandemic: a systematic review and meta-analysis. *EClinicalMedicine* 2022; **46**: 101373.
- 61 Baghaki S, Yalcin CE, Baghaki HS, Aydin SY, Daghan B, Yavuz E. COX2 inhibition in the treatment of COVID-19: review of literature to propose repositioning of celecoxib for randomized controlled studies. *Int J Infect Dis* 2020; **101**: 29–32.
- 62 Liu L, Li R, Pan Y, et al. High-throughput screen of protein expression levels induced by cyclooxygenase-2 during influenza A virus infection. *Clin Chim Acta* 2011; **412**: 1081–85.
- 63 Carey MA, Bradbury JA, Seubert JM, Langenbach R, Zeldin DC, Germolec DR. Contrasting effects of cyclooxygenase-1 (COX-1) and COX-2 deficiency on the host response to influenza A viral infection. *J Immunol* 2005; **175**: 6878–84.
- 64 Lee SMY, Cheung C-Y, Nicholls JM, et al. Hyperinduction of cyclooxygenase-2-mediated proinflammatory cascade: a mechanism for the pathogenesis of avian influenza H5N1 infection. *J Infect Dis* 2008; **198**: 525–35.
- 65 FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; **345**: 433–42.
- 66 Ong SWX, Tan WYT, Chan Y-H, et al. Safety and potential efficacy of cyclooxygenase-2 inhibitors in coronavirus disease 2019. *Clin Transl Immunology* 2020; **9**: e1159.
- 67 Singla AK, Chawla M, Singh A. Nimesulide: some pharmaceutical and pharmacological aspects—an update. *J Pharm Pharmacol* 2000; **52**: 467–86.
- 68 Carey MA, Bradbury JA, Reboloso YD, Graves JP, Zeldin DC, Germolec DR. Pharmacologic inhibition of COX-1 and COX-2 in influenza A viral infection in mice. *PLoS One* 2010; **5**: e11610.
- 69 Suter F, Perico N, Cortinovis M, Remuzzi G. A recurrent question from a primary care physician: how should I treat my COVID-19 patients at home? An update. *Clin Med Invest* 2020; **5**: 1–9.
- 70 Starek M, Plenis A, Zagrobelna M, Dąbrowska M. Assessment of lipophilicity descriptors of selected NSAIDs obtained at different TLC stationary phases. *Pharmaceutics* 2021; **13**: 440.
- 71 Suter F, Consolaro E, Pedroni S, et al. A simple, home-therapy algorithm to prevent hospitalisation for COVID-19 patients: a retrospective observational matched-cohort study. *EClinicalMedicine* 2021; **37**: 100941.
- 72 Consolaro E, Suter F, Rubis N, et al. A home-treatment algorithm based on anti-inflammatory drugs to prevent hospitalization of patients with early COVID-19: a matched-cohort study (COVER 2). *Front Med (Lausanne)* 2022; **9**: 785785.
- 73 Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; **382**: 769–79.
- 74 Donati M, Conforti A, Lenti MC, et al. Risk of acute and serious liver injury associated to nimesulide and other NSAIDs: data from drug-induced liver injury case-control study in Italy. *Br J Clin Pharmacol* 2016; **82**: 238–48.
- 75 Zhang X, Donnan PT, Bell S, Guthrie B. 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 Nephrol* 2017; **18**: 256.
- 76 Clavé S, Rousset-Rouvière C, Daniel L, Tsimaratos M. The invisible threat of non-steroidal anti-inflammatory drugs for kidneys. *Front Pediatr* 2019; **7**: 520.
- 77 Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc Natl Acad Sci USA* 1993; **90**: 11693–97.
- 78 Kelleni MT. Early use of non-steroidal anti-inflammatory drugs in COVID-19 might reverse pathogenesis, prevent complications and improve clinical outcomes. *Biomed Pharmacother* 2021; **133**: 110982.
- 79 Kelleni M. Breakthrough: ibuprofen/nitazoxanide/azithromycin: a battle changer personalized COVID-19 telemedicine five days protocol. 2020. <https://www.authorea.com/users/318758/articles/460853-breakthrough-ibuprofen-nitazoxanide-azithromycin-a-battle-changer-personalized-covid-19-telemedicine-five-days-protocol?commit=52337e49b98b96fae21dab166828780e5f544a80> (accessed June 16, 2022).
- 80 Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *Am J Med* 1998; **104**: 413–21.
- 81 Nalamachu S, Wortmann R. Role of indomethacin in acute pain and inflammation management: a review of the literature. *Postgrad Med* 2014; **126**: 92–97.
- 82 Amici C, Di Caro A, Ciucci A, et al. Indomethacin has a potent antiviral activity against SARS coronavirus. *Antivir Ther* 2006; **11**: 1021–30.
- 83 Schröer J, Shenk T. Inhibition of cyclooxygenase activity blocks cell-to-cell spread of human cytomegalovirus. *Proc Natl Acad Sci USA* 2008; **105**: 19468–73.
- 84 Bahrami H, Daryani NE, Haghpanah B, et al. Effects of indomethacin on viral replication markers in asymptomatic carriers of hepatitis B: a randomized, placebo-controlled trial. *Am J Gastroenterol* 2005; **100**: 856–61.
- 85 Bour AM, Westendorp RG, Laterveer JC, Bollen EL, Remarque EJ. Interaction of indomethacin with cytokine production in whole blood. Potential mechanism for a brain-protective effect. *Exp Gerontol* 2000; **35**: 1017–24.

- 86 Russell B, Moss C, George G, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19—a systematic review of current evidence. *Ecancermedicalscience* 2020; **14**: 1022.
- 87 Alkotaji M, Al-Zidan RN. Indomethacin: can it counteract bradykinin effects in COVID-19 patients? *Curr Pharmacol Rep* 2021; **7**: 102–06.
- 88 Gordon DE, Hiatt J, Bouhaddou M, et al. Comparative host-coronavirus protein interaction networks reveal pan-viral disease mechanisms. *Science* 2020; **370**: eabe9403.
- 89 Fazio S, Bellavite P, Zanolin E, McCullough PA, Pandolfi S, Affuso F. Retrospective study of outcomes and hospitalization rates of patients in Italy with a confirmed diagnosis of early COVID-19 and treated at home within 3 days or after 3 days of symptom onset with prescribed and non-prescribed treatments between November 2020 and August 2021. *Med Sci Monit* 2021; **27**: e935379.
- 90 Ravichandran R, Mohan SK, Sukumaran SK, et al. An open label randomized clinical trial of indomethacin for mild and moderate hospitalised COVID-19 patients. *Sci Rep* 2022; **12**: 6413.
- 91 Warner TD, Nylander S, Whatling C. Anti-platelet therapy: cyclooxygenase inhibition and the use of aspirin with particular regard to dual anti-platelet therapy. *Br J Clin Pharmacol* 2011; **72**: 619–33.
- 92 Klok FA, Kruij MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. *Thromb Res* 2020; **191**: 148–50.
- 93 Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020; **18**: 1995–2002.
- 94 Liu Q, Huang N, Li A, et al. Effect of low-dose aspirin on mortality and viral duration of the hospitalized adults with COVID-19. *Medicine (Baltimore)* 2021; **100**: e24544.
- 95 Haji Aghajani M, Moradi O, Amini H, et al. Decreased in-hospital mortality associated with aspirin administration in hospitalized patients due to severe COVID-19. *J Med Virol* 2021; **93**: 5390–95.
- 96 Meizlish ML, Goshua G, Liu Y, et al. Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: a propensity score-matched analysis. *Am J Hematol* 2021; **96**: 471–79.
- 97 Chow JH, Khanna AK, Kethireddy S, et al. Aspirin use is associated with decreased mechanical ventilation, intensive care unit admission, and in-hospital mortality in hospitalized patients with coronavirus disease 2019. *Anesth Analg* 2021; **132**: 930–41.
- 98 Yuan S, Chen P, Li H, Chen C, Wang F, Wang DW. Mortality and pre-hospitalization use of low-dose aspirin in COVID-19 patients with coronary artery disease. *J Cell Mol Med* 2021; **25**: 1263–73.
- 99 Merzon E, Green I, Vinker S, et al. The use of aspirin for primary prevention of cardiovascular disease is associated with a lower likelihood of COVID-19 infection. *FEBS J* 2021; **288**: 5179–89.
- 100 Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res* 2020; **191**: 9–14.
- 101 Alamdari NM, Afaghi S, Rahimi FS, et al. Mortality risk factors among hospitalized COVID-19 patients in a major referral center in Iran. *Tohoku J Exp Med* 2020; **252**: 73–84.
- 102 Sahai A, Bhandari R, Koupenova M, et al. SARS-CoV-2 receptors are expressed on human platelets and the effect of aspirin on clinical outcomes in COVID-19 patients. *Res Sq* 2020; published online Dec 23. <https://doi.org/10.21203%2Frs.3.rs-119031%2Fv1> (preprint).
- 103 Srivastava R, Kumar A. Use of aspirin in reduction of mortality of COVID-19 patients: a meta-analysis. *Int J Clin Pract* 2021; **75**: e14515.
- 104 Abani O, Abbas A, Abbas F, et al. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2022; **399**: 143–51.
- 105 Chow JH, Rahnavard A, Gomberg-Maitland M, et al. Association of early aspirin use with in-hospital mortality in patients with moderate COVID-19. *JAMA Netw Open* 2022; **5**: e223890.
- 106 Ikonomidis I, Andreotti F, Economou E, Stefanadis C, Toutouzias P, Nihoyannopoulos P. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation* 1999; **100**: 793–98.
- 107 Glatthaar-Saalmüller B, Mair KH, Saalmüller A. Antiviral activity of aspirin against RNA viruses of the respiratory tract—an in vitro study. *Influenza Other Respir Viruses* 2017; **11**: 85–92.
- 108 De Bosscher K, Vanden Berghe W, Haegeman G. The interplay between the glucocorticoid receptor and nuclear factor-kappaB or activator protein-1: molecular mechanisms for gene repression. *Endocr Rev* 2003; **24**: 488–522.
- 109 Guiducci C, Gong M, Xu Z, et al. TLR recognition of self nucleic acids hampers glucocorticoid activity in lupus. *Nature* 2010; **465**: 937–41.
- 110 Thomas BJ, Porritt RA, Hertzog PJ, Bardin PG, Tate MD. Glucocorticosteroids enhance replication of respiratory viruses: effect of adjuvant interferon. *Sci Rep* 2014; **4**: 7176.
- 111 Marcellini A, Swieboda D, Guedán A, et al. Glucocorticoids impair type I IFN signalling and enhance rhinovirus replication. *Eur J Pharmacol* 2021; **893**: 173839.
- 112 Shimba A, Ikuta K. Control of immunity by glucocorticoids in health and disease. *Semin Immunopathol* 2020; **42**: 669–80.
- 113 Schäfer SC, Wallerath T, Closs EI, et al. Dexamethasone suppresses eNOS and CAT-1 and induces oxidative stress in mouse resistance arterioles. *Am J Physiol Heart Circ Physiol* 2005; **288**: H436–44.
- 114 Rogers KM, Bonar CA, Estrella JL, Yang S. Inhibitory effect of glucocorticoid on coronary artery endothelial function. *Am J Physiol Heart Circ Physiol* 2002; **283**: H1922–28.
- 115 Goodwin JE, Feng Y, Velazquez H, Sessa WC. Endothelial glucocorticoid receptor is required for protection against sepsis. *Proc Natl Acad Sci USA* 2013; **110**: 306–11.
- 116 Brenner EJ, Ungaro RC, Geary RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology* 2020; **159**: 481–91.e3.
- 117 Strangfeld A, Schäfer M, Gianfrancesco MA, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2021; **80**: 930–42.
- 118 Shin YH, Shin JI, Moon SY, et al. Autoimmune inflammatory rheumatic diseases and COVID-19 outcomes in South Korea: a nationwide cohort study. *Lancet Rheumatol* 2021; **3**: e698–706.
- 119 Schultze A, Walker AJ, MacKenna B, et al. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. *Lancet Respir Med* 2020; **8**: 1106–20.
- 120 Schäfer M, Strangfeld A, Hyrich KL, et al. Response to: “Correspondence on factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician reported registry” by Mulhearn et al. *Ann Rheum Dis* 2021; published online March 1. <http://dx.doi.org/10.1136/annrheumdis-2021-220134>.
- 121 Brain O, Satsangi J. Therapeutic decisions in inflammatory bowel disease in the SARS-Cov-2 pandemic. *Gastroenterology* 2021; **160**: 1883–84.
- 122 Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020; **395**: 473–75.
- 123 Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021; **384**: 693–704.
- 124 Lamontagne F, Agoritsas T, Siemieniuk R, et al. A living WHO guideline on drugs to prevent COVID-19. *BMJ* 2021; **372**: n526.
- 125 Arora K, Panda PK. Steroid harms if given early in COVID-19 viraemia. *BMJ Case Rep* 2021; **14**: e241105.
- 126 Ordinola Navarro A, Lopez Luis BA. Corticosteroids prescription for mild-moderate COVID-19 in primary care. *J Infect Dev Ctries* 2021; **15**: 1813–15.
- 127 Okoye C, Rogani S, Franchi R, et al. Pitfalls of early systemic corticosteroids home therapy in older patients with COVID-19 pneumonia. *Geriatrics (Basel)* 2022; **7**: 21.
- 128 Aggarwal A, Mittal A, Soneja M, et al. Role of systemic corticosteroids in preventing hypoxia among patients with mild COVID-19: an observational study. *Drug Discov Ther* 2021; **15**: 273–77.

- 129 Callejas Rubio JL, Aomar Millan I, Moreno-Higueras M, Martín Ripoll L, Yuste Osorio E, Ríos-Fernández R. Caution with the use of dexamethasone in patients with COVID-19 in its initial phases. *Rev Clin Esp (Barc)* 2021; **221**: 592–95.
- 130 Matthay MA, Wick KD. Corticosteroids, COVID-19 pneumonia, and acute respiratory distress syndrome. *J Clin Invest* 2020; **130**: 6218–21.
- 131 Nicolau DV, Bafadhel M. Inhaled corticosteroids in virus pandemics: a treatment for COVID-19? *Lancet Respir Med* 2020; **8**: 846–47.
- 132 Halpin DMG, Faner R, Sibila O, Badia JR, Agusti A. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? *Lancet Respir Med* 2020; **8**: 436–38.
- 133 Pinna SM, Scabini S, Corcione S, Lupia T, De Rosa FG. COVID-19 pneumonia: do not leave the corticosteroids behind! *Future Microbiol* 2021; **16**: 317–22.
- 134 Ramakrishnan S, Nicolau DV Jr, Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *Lancet Respir Med* 2021; **9**: 763–72.
- 135 Yu L-M, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet* 2021; **398**: 843–55.
- 136 Ezer N, Belga S, Daneman N, et al. Inhaled and intranasal ciclesonide for the treatment of COVID-19 in adult outpatients: CONTAIN phase II randomised controlled trial. *BMJ* 2021; **375**: e068060.
- 137 Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of inhaled ciclesonide for outpatient treatment of adolescents and adults with symptomatic COVID-19: a randomized clinical trial. *JAMA Intern Med* 2022; **182**: 42–49.
- 138 Duvignaud A, Lhomme E, Onaisi R, et al. Inhaled ciclesonide for outpatient treatment of COVID-19 in adults at risk of adverse outcomes: a randomised controlled trial (COVERAGE). *Clin Microbiol Infect* 2022; **28**: 1010–16.
- 139 Wechsler ME, Kelley JM, Boyd IOE, et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *N Engl J Med* 2011; **365**: 119–26.
- 140 Donno DR, Grattagliano I, Rossi A, et al. How to treat COVID-19 patients at home in the Italian context: an expert opinion. *Infect Dis Rep* 2021; **13**: 251–58.
- 141 WHO. Home care for patients with suspected or confirmed COVID-19 and management of their contacts. Interim guidance. Aug 12, 2020. [https://www.who.int/publications/i/item/home-care-for-patients-with-suspected-novel-coronavirus-\(ncov\)-infection-presenting-with-mild-symptoms-and-management-of-contacts](https://www.who.int/publications/i/item/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts) (accessed June 16, 2022).
- 142 Pandolfi S, Chirumbolo S, Ricevuti G, et al. Home pharmacological therapy in early COVID-19 to prevent hospitalization and reduce mortality: time for a suitable proposal. *Basic Clin Pharmacol Toxicol* 2022; **130**: 225–39.
- 143 Ghanem CI, Pérez MJ, Manautou JE, Mottino AD. Acetaminophen from liver to brain: new insights into drug pharmacological action and toxicity. *Pharmacol Res* 2016; **109**: 119–31.
- 144 Khanfar A, Al Qaroot B. Could glutathione depletion be the Trojan horse of COVID-19 mortality? *Eur Rev Med Pharmacol Sci* 2020; **24**: 12500–09.
- 145 Sestili P, Fimognari C. Paracetamol-induced glutathione consumption: is there a link with severe COVID-19 illness? *Front Pharmacol* 2020; **11**: 579944.
- 146 D'Amato G, Acanfora L, Delli Paoli L, D'Amato M. Preventive home therapy for symptomatic patients affected by COVID-19 and followed by teleconsultations. *Multidiscip Respir Med* 2021; **16**: 748.
- 147 US National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. <https://www.covid19treatmentguidelines.nih.gov> (accessed June 16, 2022).

Copyright © 2022 Elsevier Ltd. All rights reserved.