Federatie
Medisch
Specialisten

# Leidraad Corticosteroïden voor behandeling van astma/ COPD tijdens COVID-19 pandemie

# Inhoudsopgave

## Samenstelling van de werkgroep

Het is onduidelijk wat het effect is van corticosteroïden voor de behandeling van astma of COPD op het beloop van COVID-19. Er is een werkgroep samengesteld om hierover een leidraad te formuleren. Alle werkgroepleden zijn door de wetenschappelijke verenigingen gemandateerd voor deelname aan deze werkgroep.

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## Disclaimer

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**Looptijd**
Deze leidraad is geldig vanaf 17 november 2020.

Deze leidraad kan tussentijds worden bijgewerkt en/of gewijzigd. De meest actuele versie is de versie die staat op de website van de Federatie Medisch Specialisten.

# Introductie

**Probleembeschrijving**
Het is onduidelijk wat het effect is van corticosteroïden voor de behandeling van astma of COPD op het beloop van een COVID-19 infectie. In de tweede lijn is er dan ook behoefte aan aanbevelingen over het gebruik van corticosteroïden bij astma of COPD (onderhoud en exacerbatie) tijdens de COVID-19 pandemie.

**Totstandkoming leidraad**
Voor deze leidraad is een systematische literatuursearch uitgevoerd (zie review). Vanwege de beperkte literatuur is de leidraad voornamelijk gebaseerd op overwegingen van de werkgroep. De werkgroep heeft de overwegingen gebaseerd op de beschikbare literatuur over het onderwerp en aangevuld met ervaringen uit de kliniek tijdens de COVID-19 pandemie.

**Literatuur corticosteroïden en COVID-19**
Er is een systematische review uitgevoerd naar het effect van de behandeling met corticosteroïden bij patiënten met astma en COPD op het beloop van een COVID-19 infectie (zie bijlage 1; literatuur search 1 juli 2020). De literatuur in deze patiëntenpopulatie is zeer beperkt. Er zijn twee retrospectieve observationele studies geïdentificeerd (Cchiba, 2020; Schultze, 2020 (preprint; not yet peer-reviewed)). De bewijskracht van de studies is zeer laag vanwege de relatief kleine patiëntenpopulatie en het overschrijden van de grenzen voor klinische besluitvorming (imprecisie). Hierdoor is het onduidelijk wat het effect is van corticosteroïden bij patiënten met astma of COPD (voor wie corticosteroïden zijn geïndiceerd) op het beloop van COVID-19 en de symptomen van de chronische aandoening. Er is behoefte aan studies die het effect van corticosteroïden bij patiënten met astma of COPD op het beloop van een COVID-19 infectie onderzoeken.

## Overwegingen

In deze leidraad worden adviezen gegeven over het gebruik van corticosteroïden voor behandeling van astma of COPD tijdens COVID-19 pandemie.

De volgende vragen worden beantwoord om hierover een advies te geven:

- Hebben astma/ COPD-patiënten een verhoogd risico op COVID-19?
- Hebben astma/CODP-patiënten een ernstiger beloop bij COVID-19 infectie?
- Geeft type 2 inflammatie een verhoogd risico op COVID-19?
- Geven inhalatiecorticosteroïden een verhoogd risico op COVID-19?
- Kunnen inhalatiecorticosteroïden worden gecontinueerd tijdens een aangetoonde COVID-19 infectie?
- Hoe om te gaan met exacerbaties tijdens COVID-19 en het gebruik van een stootkuur orale corticosteroïden (OCS)?

*Astma/ COPD en het risico op COVID-19*

Uit Chinese, Europese en Amerikaanse cohorten lijken patiënten met astma of COPD ten opzichte van mensen zonder deze aandoeningen geen hoger risico te hebben op het krijgen van een COVID-19 pneumonie (Guan, 2020; Carli, 2020). De meest genoemde risicofactoren voor een COVID-19 pneumonie zijn adipositas, diabetes mellitus, hypertensie, geslacht en leeftijd (Wang, 2020; Zhang, 2020).

*Astma/ COPD en het beloop van COVID-19 infectie*

In diverse observationele studies komt er geen duidelijke relatie naar voren tussen astma/COPD en een ernstiger beloop van COVID-19 (Wang, 2020; Zhang, 2020; Huang, 2020; Liu, 2020). In een recentelijke meta-analyse van zeven studies wordt echter wel een associatie gevonden tussen COPD en een ernstiger beloop van een COVID-19 infectie (Lippi, 2020). Resultaten van deze beknopte meta-analyse tonen aan dat COPD geassocieerd is met een meer dan vijfvoudig verhoogd risico op een ernstige COVID-19-infectie. Tevens toont Alqahtani (2020) aan dat rokers en patiënten met COPD een verhoogd risico hebben op ernstigere complicaties en een hogere mortaliteit bij SARS-CoV-2 infectie. Concluderend lijken er wel aanwijzingen te zijn voor een verhoogd risico op ernstiger beloop bij COPD, maar niet bij astma. COPD-patiënten dienen zodoende te worden aangemoedigd om zich strikt aan de vigerende maatregelen te houden om mogelijke blootstelling aan SARS-CoV-2 tot een minimum te beperken.

*Relatie inflammatie astma/COPD en ACE2 receptor expressie*

Type 2 inflammatie, dat bij 80% van de astmapatiënten aanwezig is, lijkt mogelijk een remmende werking te hebben op de expressie van de ACE2 receptoren (Jackson, 2020). Dit zou kunnen samenhangen met een verhoogd risico op een ernstige COVID-19 infectie in patiënten met astma. Klinische studies hebben dit verband vooralsnog niet aangetoond. Een overzichtsartikel van Lipworth (2020) suggereert dat gecontroleerd astma geen risicofactor is voor COVID-19 pneumonie noch dat COPD een risicofactor is (Chibba, 2020). Evenmin zijn er aanwijzingen voor een ernstiger beloop bij astma of COPD. In tegenstelling tot andere luchtwegvirussen lijkt het SARS-CoV-2 virus ook geen astma of COPD-exacerbaties te induceren (Zhang, 2020). Astma-gerelateerde factoren die het beloop van een COVID-19 infectie zouden kunnen beïnvloeden zijn onder andere systemische inflammatie (hoog IL-6), astma fenotype (type 2-laag astma), ernstig astma: GINA step 5, verminderde longfunctie, ongecontroleerd astma, frequente exacerbaties en orale corticosteroïd-kuren (Maes 2020). Jacobs (2020) vond recent een hogere expressie van ACE2 zowel op mRNA als op eiwit niveau in de longen van rokers als in die van patiënten met GOLD III-IV (Jacobs, 2020).
Tevens tonen Wan (2020) en Toru (2020) aan dat expressie van de ACE2 receptor, die introductie van het SARS-CoV-2 faciliteert, verantwoordelijk is voor COVID-19 (Halpin, 2020). Meer onderzoek zal

moeten uitwijzen welke subgroepen mogelijk een verhoogd risico op een ernstige COVID-19 infectie hebben.

*ICS en het risico op COVID-19*
ICS worden gebruikt als anti-inflammatoire onderhoudstherapie bij astma en dikwijls ook bij COPD. Bij een virale luchtweginfectie kunnen SCS zoals prednisolon mogelijk schadelijk zijn, vanwege stimulering van virusreplicatie, vertraagde virale klaring en een verhoogde kans op een secundaire bacteriële infectie. De systemische opname van ICS is echter relatief laag in vergelijking met SCS. Bij COVID-19 is vooralsnog niet aangetoond dat ICS het risico op het krijgen van COVID-19 verhogen (Lipworth, 2020; Schultze, 2020 (preprint; not yet peer-reviewed)). Het is dus van belang dat bij een onderliggende obstructieve longziekte de patiënt optimaal wordt behandeld en dat (inhalatie) medicatie wordt gecontinueerd om exacerbaties te voorkomen.

*ICS continueren tijdens COVID-19*
Er zijn geen aanwijzingen voor een ernstiger beloop van een COVID-19 infectie bij gebruik van ICS (Chhiba, 2020; Schultze, 2020 (preprint; not yet peer-reviewed)). Er zijn labexperimentele overwegingen dat ICS een gunstig effect zou kunnen hebben op het COVID-19 beloop door onderdrukking van lokale cytokine expressie, vermindering van ACE2 genexpressie en remming van virusreplicatie in vitro (Lipworth, 2020). Hoewel een recente studie laat zien dat er een gunstig effect is bij gebruik van dexamethason bij COVID-19 patiënten opgenomen op de ICU (Horby, 2020), is er echter geen bewijs dat systemische corticosteroïden (SCS) een gunstig effect hebben op COVID-19 in geval van een milder beloop (Abdolahi, 2020). Vooralsnog dienen bij patiënten met astma/COPD en COVID-19 inhalatie of orale corticosteroïden gecontinueerd te worden (GOLD COVID-19 GUIDANCE, 2020).

*Exacerbatie behandeling astma/ COPD tijdens COVID-19*
Wanneer er klinisch aanwijzingen zijn voor een exacerbatie van astma wordt aangeraden om ook bij verdenking of bewezen COVID-19 een prednisolon stootkuur geven. Het is verstandig om het aantal bloedeosinofielen mee te nemen in de afweging van het wel of niet starten van SCS bij astma. Bij een laag aantal bloedeosinofielen (< 150 x 10E9/L) lijkt SCS minder zinvol en moeten andere behandelopties worden overwogen, bijvoorbeeld antibiotica. Bij een milde longaanval van astma verdient het de voorkeur om eerst ICS op te hogen dan wel ophogen van ICS/LABA tot de maximale dosering. Indien er sprake is van een chronisch ongecontroleerd astma dan graag de stappen van de GINA (2020) doorlopen en altijd terughoudend zijn met gebruik van OCS, zeker in de afwezigheid van T2-inflammatie (GINA, 2020). Bij een longaanval van COPD is het aangewezen de GOLD-guidelines te doorlopen (GOLD, 2020).
Bij een laag aantal bloedeosinofielen (< 100 cellen/uL) lijkt SCS minder zinvol en moeten andere behandelopties zoals antibiotica worden overwogen.

# Aanbevelingen

Astma

Volg de GINA-guideline (2020) bij patiënten met astma tijdens de COVID-19 pandemie.

Indien er sprake is van chronisch ongecontroleerd astma bij een verdenking op of bewezen COVID-19 infectie:

- Doorloop de stappen van de GINA-guideline
- Wees altijd terughoudend met het gebruik van OCS, zeker in afwezigheid van T2-inflammatie

Indien er sprake is van een milde exacerbatie astma en een verdenking op of bewezen COVID-19 infectie:

- Verhoog eerst ICS dan wel ICS/LABA tot de maximale dosering, alvorens over te gaan naar de onderstaande stap

Indien er sprake is van matig/ernstige exacerbatie bij astma en een verdenking op of bewezen COVID-19 infectie:

- Onderzoek het aantal bloedeosinofielen om een behandeloptie te kiezen:
  - Bij een hoog aantal bloedeosinofielen (≥ 150 x 10E9/L):
    - Overweeg behandeling met systemische corticosteroïden 6 mg dexamethason of equivalent prednisolon per dag
  - Bij een laag aantal bloedeosinofielen (< 150 x 10E9/L):
    - Overweeg andere behandelopties, bijvoorbeeld antibiotica

COPD

Volg de GOLD-guideline (2020) bij patiënten met COPD tijdens de COVID-19 pandemie.

Indien er binnen een jaar sprake is van *twee of meer moderate exacerbaties of ziekenhuisopname(s) vanwege een exacerbatie(s)** bij COPD en een verdenking op of bewezen COVID-19 infectie:

- Doorloop de stappen van de GOLD-guideline
- Onderzoek het aantal bloedeosinofielen om een behandeloptie te kiezen:
  - Bij een hoog aantal bloedeosinofielen (> 300 cellen/uL) en/of astma in voorgeschiedenis:
    - Overweeg behandeling met inhalatiecorticosteroïden
  - Bij bloedeosinofielen (100-300 cellen/uL) en een milde exacerbatie:
    - Overweeg behandeling met inhalatiecorticosteroïden
  - Bij een laag aantal bloedeosinofielen (<100 cellen/uL) en pneumonie of mycobacteriële infectie in voorgeschiedenis:
    - Continueer behandeling met LAMA/LABA, geef geen ICS

Indien er sprake is van klinische aanwijzingen voor een exacerbatie bij COPD en een verdenking op of bewezen COVID-19 infectie:

- Start met orale corticosteroïden 6 mg dexamethason of equivalent prednisolon per dag

Indien er sprake is van onderliggend chronisch obstructieve luchtwegaandoening bij een verdenking op of bewezen COVID-19 infectie:

- Continueer behandeling met inhalatie of orale corticosteroïden om een exacerbatie te voorkomen

*Afkortingen: GINA: Global Initiative for Asthma; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: inhalatiecorticosteroïden; LABA: langwerkende bèta-agonist (LABA – long acting beta agonist); LAMA: long-acting muscarinic antagonist; OCS: orale corticosteroïden; T2: Type 2 inflammatie*

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**Bijlage 1: Review**

# ‘Behandeling met inhalatie of lokale injectie corticosteroïden bij reumatische aandoening, pijn en astma/COPD in de context van COVID-19’

Datum: 14-10-2020
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**Inhoud**

**Inleiding**
Het is onduidelijk of behandeling met (gluco)corticosteroïden bij patiënten met chronische aandoeningen (musculoskeletale aandoeningen waaronder reumatische aandoeningen, (chronische) pijn en astma/COPD) effect heeft op het beloop van een COVID-19 infectie.

**Klinische vraag**
Wat is de plaats van behandeling met corticosteroïden bij patiënten met reumatische aandoeningen, (chronische) pijn, of astma/COPD tijdens de COVID-19 pandemie?

A review of the literature was performed to answer the following question:
What is the effect of corticosteroid treatment compared to no corticosteroid treatment on COVID-19 disease severity or chronic disease severity in patients with musculoskeletal/rheumatic disease, (chronic) pain or asthma/COPD (for which corticosteroid treatment is indicated) and a (asymptomatic, presumed or confirmed) COVID-19 infection?

**PICO:**
P: patients with a musculoskeletal/rheumatic disease, (chronic) pain or asthma/COPD for which corticosteroid treatment is indicated, and a (asymptomatic, presumed or confirmed) COVID-19 infection
I: corticosteroid treatment
C: no corticosteroid treatment
O: COVID-19 disease severity, chronic disease severity

<u>Relevant outcome measures</u>
COVID-19 disease severity was considered as a critical outcome measures for decision making and chronic disease severity was considered an important outcome measure. A priori, the workgroup did not define the outcome measures listed above, but used the definitions that were described in the individual studies.
The working group defined a difference of 25% clinically relevant for dichotomous variables (RR, HR, OR <0.8 or >1.25).

<u>Search and select (Methods)</u>
The databases and online sources (PubMed, Embase, Google Scholar, MedRxiv) were searched with relevant search terms until July 2nd, 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 860 hits. Title/abstracts were screened for studies meeting the PICO. 32 publications were full-text screened and reference lists were checked for additional relevant studies. 3 studies were included, and information was extracted and summarized. 29 publications were excluded; see Table 3 for publications and reason for exclusion.

**(Chronic) pain**

Description of studies

No studies investigating the effect of corticosteroid treatment compared to no corticosteroid treatment on COVID-19 disease severity or chronic disease severity in patients with (chronic) pain (for which corticosteroid treatment is indicated) and a (asymptomatic, presumed or confirmed) COVID-19 infection were identified.

Results

No studies investigating the effect of corticosteroid treatment compared to no corticosteroid treatment on COVID-19 disease severity or chronic disease severity in patients with (chronic) pain and a (asymptomatic, presumed or confirmed) COVID-19 infection were identified.

**Level of evidence of the literature**

No studies investigating the effect of corticosteroid treatment compared to no corticosteroid treatment on COVID-19 disease severity or chronic disease severity in patients with (chronic) pain for which corticosteroid treatment is indicated) and a (asymptomatic, presumed or confirmed) COVID-19 infection were identified.

**Lung diseases**

Description of studies

Two retrospective observational studies investigating COVID-19 disease severity with or without inhalation corticosteroid treatment in patients with asthma or COPD were identified.

**1**

Chhiba (2020) described a retrospective analysis, primarily investigating the prevalence of asthma among confirmed COVID-19 patients. In addition, hospitalization associated with asthma and/or inhaled corticosteroid use was assessed. Medical records were screened by a computer algorithm first, follow-up by a manual chart review of all asthma patients to confirm diagnosis and medication. The length of follow-up was not reported. In total, 1,526 patients with confirmed COVID-19 were included in the analysis, of which 220 (14.4%) had diagnosis of adult asthma. Of the asthma patients, 114 (51.8%) did not use maintenance inhalers and 106 (48.2%) did use inhaled corticosteroids (ICS) or ICS combined with long-acting beta-agonists at the time of COVID-19 diagnosis or hospitalization. The majority of included patients was between 40 and 69 years of age (55.3%) and 53% was female. Groups were comparable at baseline, except for concurrent diagnoses (COPD, allergic rhinitis and rhinosinusitis more often in intervention group).

Schultze (2020; preprint not yet peer reviewed) described a retrospective analysis, investigating the association between inhaled corticosteroids and COVID-19 related death in COPD and asthma patients. Primary care records were used through the OpenSAFELY platform and were linked to death data from the Office for National Statistics. In total, 148,488 people with COPD and 817,973 people with asthma were included in the analysis. Of the COPD cohort, 105,210 (71%) patient received prescriptions for ICS+LABA or ICS+LABA/LAMA in the four months before index, and 43,278 patients (29%) received a LABA/LAMA prescription. Of the asthma cohort, 608,583 patients (74%) had a prescription for low/medium dose ICS in the four months prior to index date, 101,010 (12%) prescriptions for high dose ICS and 108,380 (13%) were prescribed SABA only.

*Abbreviations - ICS: inhaled corticosteroids; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting beta agonist*

Results

*COVID-19 disease severity – Hospitalization*

Chhiba (2020) assessed the risk difference for hospitalization between asthma patients with and

without maintenance inhalers. The risk ratio was 1.39 (95% CI: 0.90 to 2.15) in the fully adjusted model, in favour of the patients without maintenance inhalers. This finding indicates that the risk for hospitalization is 39% higher in the group using maintenance inhalers. This difference is clinically relevant.

*COVID-19 disease severity – COVID-19 related death*
Schultze (2020 –; preprint not yet peer reviewed) assessed the hazard ratio for COVID-19 related death, adjusted for age, gender and remaining comorbidities.
Compared to COPD patients that were prescribed only LABA and/or LAMA, COPD patients that were prescribed ICS alone or in combination with LABA/LAMA, had an increased risk for COVID-19 related death (adjusted HR = 1.38; 95% CI = 1.08 – 1.75). This is a clinically relevant difference.
Asthma patients that were prescribed low-medium ICS had an increased risk for COVID-19 related death, compared to asthma patients that were prescribed SABA only (adjusted HR = 1.10, 95% CI = 0.82 – 1.49). This difference is not clinically relevant.
Asthma patients that were prescribed high-dose ICS had an increased risk for COVID-19 related death compared to asthma patients that were prescribed SABA only (adjusted HR = 1.52, 95%CI = 1.08 – 2.14). This is a clinically relevant difference.

*Chronic disease severity*
No studies investigating the effect of corticosteroid treatment compared to no corticosteroid treatment on chronic disease severity in patients with lung diseases for which corticosteroid treatment is indicated) and a (asymptomatic, presumed or confirmed) COVID-19 infection were identified.

**Level of evidence of the literature**
*COVID-19 disease severity (hospitalization and COVID-19 related death)*
The observational nature of the study implies a low level of evidence. In addition, based on the small number of participants (Chhiba 2020) and imprecision (crossing threshold for clinical relevance; Chhiba, 2020; Schultze, 2020 (preprint – not yet peer reviewed), the level of evidence is downgraded to 'very low', hindering the possibility to draw conclusions based on these studies.

*Chronic disease severity*
No studies investigating the effect of corticosteroid treatment compared to no corticosteroid treatment on chronic disease severity (for which corticosteroid treatment is indicated) in patients with lung diseases and a (asymptomatic, presumed or confirmed) COVID-19 infection were identified.

**Musculoskeletal / rheumatic diseases**
Description of studies
One retrospective observational study (Gianfrancesco, 2020) investigating COVID-19 disease severity and corticosteroid treatment in patients with a rheumatic disease was identified.

Using international registry data, Gianfrancesco (2020) compared characteristics of hospitalized (N=277) versus non-hospitalized (N=323) individuals with rheumatic diseases and a presumed or confirmed COVID-19 infection. Amongst other, type of rheumatic disease, comorbidities and treatment for rheumatic disease were compared. The length of follow-up was at least 14 days from symptom onset or until the end-point of the study (symptom resolution or death) was reached. The most common rheumatic disease diagnosis was rheumatoid arthritis (230/600; 38%). 71% of patients was female and the median age was 56 years (IQR 45–67). Compared to the non-hospitalised group, the hospitalised group was older, had more comorbidities, more frequently used NSAIDs (25% vs. 16%, p=0.02). The non-hospitalised group more often received high doses of glucocorticoids (16% vs 7% for doses ≥10mg/day, p=0.01). Sex, antimalarial therapy and days from symptom onset to symptom resolution or death were comparable between the study groups.

Results

*COVID-19 disease severity - Hospitalization*

Gianfrancesco (2020) compared the rate of hospitalization in patients with and without medication prior to COVID-19 diagnosis. Of individuals that used prednisone-equivalent glucocorticoid of 1–9mg/day or ≥10mg/day, respectively 54% (67/125) and 67% (43/64) was hospitalized. 40% (162/403) of individuals that did not use glucocorticoids was hospitalized. The use of 1–9mg/day was associated with a higher odds for hospitalization (adjusted OR 1.03 (0.64 to 1.66), but this difference is not clinically relevant. The use of >10mg/day prednisone-equivalent glucocorticoid was associated with a higher odds for hospitalization (adjusted OR 2.05 (95%CI 1.06 to 3.96). This results indicates that a dose of prednisone-equivalent glucocorticoid >10mg/day was associated with a higher risk of hospitalization. This difference is clinically relevant.

*Chronic disease severity*

No studies investigating the effect of corticosteroid treatment compared to no corticosteroid treatment on chronic disease severity in patients with musculoskeletal / rheumatic diseases (for which corticosteroid treatment is indicated) and a (asymptomatic, presumed or confirmed) COVID-19 infection were identified.

**Level of evidence of the literature**

*COVID-19 disease severity - Hospitalization*

The observational nature of the study implies a low level of evidence. In addition, based on the small number of participants and imprecision (crossing the threshold of clinical relevance), the level of evidence is downgraded to ‘very low’, hindering the possibility to draw conclusions based on these studies.

*Chronic disease severity*

No studies investigating the effect of corticosteroid treatment compared to no corticosteroid treatment on chronic disease severity in patients with musculoskeletal / rheumatic diseases (for which corticosteroid treatment is indicated) and a (asymptomatic, presumed or confirmed) COVID-19 infection were identified.

**Conclusions**

Chronic pain

*COVID-19 disease severity, symptoms of chronic disease*

| | |
|---|---|
| **no GRADE** | No literature was available regarding the effect of corticosteroid treatment compared to no corticosteroid treatment on *COVID-19 disease severity* or *symptoms of chronic disease* in patients with (chronic) pain (for which corticosteroid treatment is indicated) and a (asymptomatic, presumed or confirmed) COVID-19 infection.<br><br>*Sources: -* |

Asthma/COPD

*COVID-19 disease severity*

| | |
|---|---|
| **very low GRADE** | It is unclear whether corticosteroid treatment compared to no corticosteroid treatment results in a difference in *COVID-19 disease severity* in patients with asthma or COPD (for which corticosteroid treatment is indicated) and a (asymptomatic, presumed or confirmed) COVID-19 infection.<br><br>*Sources: Cchiba 2020, Schultze 2020 (preprint – not yet peer reviewed)* |

*Symptoms of chronic disease*

| | |
|---|---|
| **no GRADE** | No literature was available regarding the effect of corticosteroid treatment compared to no corticosteroid treatment on *symptoms of chronic disease* in patients with COPD or asthma (for which corticosteroid treatment is indicated) and a (asymptomatic, presumed or confirmed) COVID-19 infection.<br><br>*Sources: -* |

Musculoskeletal/rheumatic diseases

*COVID-19 disease severity*

| | |
|---|---|
| **very low GRADE** | It is unclear whether corticosteroid treatment compared to no corticosteroid treatment results in a difference in *COVID-19 disease severity* in patients with musculoskeletal/rheumatic diseases (for which corticosteroid treatment is indicated) and a (asymptomatic, presumed or confirmed) COVID-19 infection.<br><br>*Sources: Gianfrancesco 2020* |

*Symptoms of chronic disease*

| | |
|---|---|
| **no GRADE** | No literature was available regarding the effect of corticosteroid treatment compared to no corticosteroid treatment on *COVID-19 disease severity* or *symptoms of chronic disease* in patients with musculoskeletal/rheumatic diseases (for which corticosteroid treatment is indicated) and a (asymptomatic, presumed or confirmed) COVID-19 infection.<br><br>*Sources: -* |

**Literatuurlijst**

Chhiba KD, Patel GB, Vu THT et al. Prevalence and characterization of asthma in hospitalized and non-hospitalized patients with COVID-19, Journal of Allergy and Clinical Immunology, 2020. ISSN 0091-6749, https://doi.org/10.1016/j.jaci.2020.06.010.

Gianfrancesco M, Hyrich KL, Al-Adely S on behalf of the COVID-19 Global Rheumatology Alliance, 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. Annals of the Rheumatic Diseases 2020;79:859-866.

Schultze A, Walker AJ, MacKenna, B et al. on behalf of the The OpenSAFELY Collaborative. Inhaled corticosteroid use and risk COVID-19 related death among 966,461 patients with COPD or asthma: an OpenSAFELY analysis. MedRXiV 2020 [preprint, **not** yet peer-reviewed]

## Tables

### Table 1: Evidence table of comparative observational studies

| Study reference | Study characteristics | Patient characteristics [2] | Intervention (I) | Comparison / control (C) [3] | Follow-up (FU) | Outcome measures and effect size [4] | Comments |
|---|---|---|---|---|---|---|---|
| Chronic pain | | | | | | | |
| n.a. | | | | | | | |
| Lung diseases | | | | | | | |
| Chhiba et al. 2020<br><br>Link<br><br>[in press, pre-proof] | Type of study: Retrospective analysis<br><br>Setting and country: 10 hospitals affiliated with Northwestern Medicine health system; USA<br><br>Funding and conflicts of interest: Funding was not reported; authors report no relevant conflicts of interest. | Inclusion criteria:<br>• confirmed COVID-19 infection<br>• all ages<br>• adult asthma diagnosis<br><br>Exclusion criteria:<br>• no confirmed COVID-19 infection<br>• no adult asthma diagnosis<br><br>N total at baseline: 220<br>I: 106<br>C: 114<br><br>Groups at baseline: Groups were comparable at baseline, except for concurrent diagnoses (COPD, allergic rhinitis and rhinosinusitis more often in intervention group). Model 2 adjusted for these variables. | Inhaled corticosteroids alone, of combined with long-acting beta-agonists at the time of COVID-19 diagnosis or hospitalization | No inhaled corticosteroids at the time of COVID-19 diagnosis or hospitalization | Length of FU: n.a.<br><br>Loss-to-FU: n.a. | Hospitalization<br>Model 1:<br>RR 1.22 (95% CI 0.84 to 1.76)<br>Model 2:<br>RR 1.39 (95% CI: 0.90 to 2.15) | • This is a retrospective, descriptive study, comparing characteristics of asthma patients with confirmed COVID-19<br><br>• Model 1 was adjusted for age, gender, race/ethnicity<br>• Model 2 was adjusted for age, gender, race/ethnicity, smoking, obesity, comorbidities<br><br>Authors conclusion: Despite a substantial prevalence of asthma in our COVID-19 cohort, asthma was not associated with an increased risk of hospitalization. Similarly, the use of ICS with or without systemic corticosteroids was not associated with COVID-19-related hospitalization. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Schultze, 2020<br><br>[preprint, **not** yet peer-reviewd]<br><br>LINK | Type of study: Retrospective analysis, cohort study<br><br>Setting and country: national register study, UK<br>Index date: 01 Mar 2020; follow-up lasted until 06 May 2020<br><br>Funding and conflicts of interest:<br>This work was supported by the Medical Research Council MR/V015737/1; ink to disclosure forms present | **COPD**<br>Inclusion criteria:<br>• age >35y<br>• COPD<br>• current or former smoking recorded any time before the index date<br>Exclusion criteria:<br>• prior diagnoses of other chronic respiratory conditions<br>• asthma in 3y before the index date<br>• receiving nebulised COPD medications in 12M before index date<br>• leukotriene receptor antagonist (indicating potential asthma) in the 4M before index date<br>• missing data for gender, index of multiple deprivation (IMD), or <1Y primary care records<br><br>**Asthma**<br>Inclusion criteria:<br>• age >18y<br>• asthma recorded 3 years prior to index date<br>Exclusion criteria:<br>• COPD or other chronic respiratory condition prior to index date (indicates possible COPD)<br>• missing data for gender, index of multiple deprivation (IMD), or | **COPD**<br>**ICS+(LAMA)/LABA**<br>= at least one ICS prescription within 4 months prior to the index date either in combination with LABA or LAMA/LABA, or as single therapy provided there was also at least one prescription record of a LABA,<br><br>**Asthma**<br>**ICS**<br>= prescribed high dose ICS and low/medium-dose ICS during the 4 months before index date<br><br>Exposure for people prescribed both high and low/medium dose ICS was assigned according to their most recent prescription. Inhalers were assigned to low/medium or high dose based on OpenPrescribing.net | **COPD**<br>**LABA/LAMA**<br>= prescription for a LABA/LAMA (combined or as separate single therapy prescriptions) only<br><br>**Asthma**<br>**SABA**<br>= prescribed SABA only | Length of FU:<br>n.a.<br><br>Loss-to-FU:<br>n.a. | **COPD**<br><br>**Asthma**<br><br>COVID-19 related death;<br>*adjusted for age, gender and remaining comorbidities*<br>**COPD**<br>adjusted HR = 1.38<br>(95% CI = 1.08 – 1.75).<br>**Asthma**<br>High dose:<br>adjusted HR = 1.52<br>(95%CI = 1.08 – 2.14)<br>low-medium dose:<br>adjusted HR = 1.10<br>(95% CI = 0.82 – 1.49) | Abbreviations:<br>• ICS: inhaled corticosteroids<br>• LABA: long-acting beta agonist<br>• LAMA: long-acting muscarinic antagonist<br>• SABA: short-acting beta agonist<br><br>Additional information:<br>• COPD patients receiving LAMA monotherapy were not included, as a greater clinical comparability between the LAMA/LABA and ICS-based therapy groups was expected<br><br>Comments<br>• This is a retrospective study based on register data.<br><br>• Authors: Quantitative bias analyses indicated that an unmeasured confounder of only moderate strength of association with exposure and outcome could explain the observed associations in both populations.<br><br>Authors conclusion:<br>These results do not support a major role of ICS in protecting against COVID-19 related deaths. Observed increased risks |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | <1Y primary care records<br><br>**COPD**<br>N total, baseline: 148,588<br>I: 105,210<br>C: 43,278<br><br>**Asthma**<br>N total, baseline: 817,973<br>I:<br>low-medium dose:<br>608,583<br>High-dose:<br>101,010<br>C: 108,380<br><br>Groups at baseline: | | | | | of COVID-19 related death among people with COPD and asthma receiving ICS can be plausibly explained by unmeasured confounding due to disease severity. |
| Musculoskeletal /rheumatic diseases | | | | | | | |
| Gianfrancesco, 2020<br><br>Link | Type of study:<br>Case series; retrospective comparison<br><br>Setting and country:<br>International register<br><br>Funding and conflicts of interest:<br>no specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors; competing interest reported per author | Inclusion criteria:<br>presumed or confirmed COVID-19 infection<br>Exclusion criteria:<br>-unknown hospitalisation status<br><br>N total at baseline: 592<br>Interv I: 125 (21%)<br>Interv II: 64 (11%)<br>Control: 403 (68%)<br><br>Groups at baseline:<br>Baseline comparison based on hospitalization status; hospitalized patients older, more comorbidities<br><br>Not hospitalized<br>Interv I: 58 (18%)<br>Interv II: 21 (7%)<br>Control: 241 (75%)<br>Hospitalized:<br>Interv I: 67 (25%)<br>Interv II: 43 (16%)<br>Control: 162 (60%) | Prednisone-equivalent glucocorticoids:<br><br>Interv-I: 1–9mg/day<br>Interv-II: >10mg/day | No prednisone-equivalent glucocorticoids | Length of FU:<br>n.a.<br><br>Loss-to-FU:<br>n.a. | Hospitalization, *n/N (%)*<br>Interv-I: 67/125 (54%)<br>Interv-II: 43/64 (67%)<br>Control: 162/403 (40%)<br>*Unadjusted OR*<br>Interv-I: 1.72 (1.15 to 2.57)<br>Interv-II: 3.05 (1.74 to 5.32)<br><br>*Adjusted OR*<br>Interv-I: 1.03 (0.64 to 1.66)<br>P=0.91<br>Interv-II: 2.05 (1.06 to 3.96)<br>P=0.03 | Comments:<br>• This is a retrospective study based on register data.<br>• The adjusted logistic regression included variables that differed at baseline between hospitalized and non-hospitalized patients.<br><br>Authors conclusion:<br>We found that glucocorticoid exposure of ≥10 mg/day is associated with a higher odds of hospitalisation and anti-TNF with a decreased odds of hospitalisation in patients with rheumatic disease. Neither exposure to DMARDs nor NSAIDs were associated with increased odds of hospitalisation. |

1. Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures
2. Provide data per treatment group on the most important prognostic factors [(potential) confounders]
3. For case-control studies, provide sufficient detail on the procedure used to match cases and controls
4. For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders

**Table 2: Quality assessment of comparative observational studies**

| Study reference | Bias due to a non-representative or ill-defined sample of patients?[1] | Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2] | Bias due to ill-defined or inadequately measured outcome ?[3] | Bias due to inadequate adjustment for all important prognostic factors?[4] |
|---|---|---|---|---|
| **Chronic pain** | | | | |
| n.a. | | | | |
| **Lung diseases** | | | | |
| Cchiba, 2020 | Unlikely<br><br>Sample well-defined, and stratified analyses carried out | Unlikely<br><br>Retrospective study, outcome of interest available for all subjects | Unlikely<br><br>Well-defined outcome | Unlikely<br><br>Multivariable adjusted analysis, including variables that differed between groups at baseline. |
| Schultze, 2020 (preprint – not yet peer reviewed) | Unlikely<br><br>Sample well-defined, and stratified analyses carried out | Unlikely<br><br>Retrospective study, outcome of interest available for all subjects | Unclear<br><br>Well-defined outcome 'mortality'. However, unclear whether this outcome reflects the risk both of becoming infected as well as the risk of developing severe disease and dying.<br>*"It is possible that ICS use has a different effect on the risk of infection and on disease severity."* | Unlikely<br><br>Multivariable adjusted analysis, including variables that differed between groups at baseline. |
| **Musculoskeletal diseases** | | | | |
| Gianfrancesco, 2020 | Unlikely<br><br>Sample well-defined, and sensitivity analyses carried out | Unlikely<br><br>Retrospective study, outcome of interest available for all subjects | Unlikely<br><br>Well-defined outcome | Unlikely<br><br>Multivariable adjusted analysis, including variables that differed between groups at baseline. |

1. Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.
2. Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.
3. Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4. Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.

**Tabel 3: Exclusietabel**

| Author and year | Reason for exclusion |
|---|---|
| Attaway, 2020 | No clinical study, no COVID-19 literature |
| Ayobami, 2020 | No clinical study, no COVID-19 literature |
| Beaney, 2020 | No clinical study, no COVID-19 literature |
| Cohen, 2020 | No clinical study, no COVID-19 literature |
| Costi, 2020 | No clinical study, no COVID-19 literature |
| Favalli, 2020 | No clinical study, no COVID-19 literature |
| Ferro, 2020 | No clinical study, no COVID-19 literature |
| Gazzaruso, 2020 | No clinical study, no COVID-19 literature |
| Georgiev, 2020 | No clinical study, no COVID-19 literature |
| Ghai, 2020 | No clinical study, no COVID-19 literature |
| Gill, 2020 | No clinical study, no COVID-19 literature |
| Gupta, 2020 | Descriptive study, survey among rheumatologists |
| Halphin, 2020 | No clinical study, no COVID-19 literature |
| Kowalski, 2020 | No clinical study, no COVID-19 literature |
| Lewandowski, 2020 | No clinical study, no COVID-19 literature |
| Lipworth, 2020 | No clinical study, no COVID-19 literature |
| Lu, 2020 | No clinical study, no COVID-19 literature |
| Misra, 2020 | No clinical study, no COVID-19 literature |
| Monti, 2020 | Descriptive study |
| Morais-Almeida, 2020 | No clinical study |
| Nasonov, 2020 | No clinical study, no COVID-19 literature |
| Peters, 2020 | No clinical study, not on PICO treatment and outcome |
| Pope, 2020 | No clinical study, no COVID-19 literature |
| Ragni, 2020 | No clinical study, no COVID-19 literature |
| Richez, 2020 | No clinical study, no COVID-19 literature |
| Robinson, 2020 | No clinical study, no COVID-19 literature |
| Scioscia, 2020 | No clinical study, no COVID-19 literature |
| Sharmeen, 2020 | No clinical study, no COVID-19 literature |
| Veeranpandiyan, 2020 | No clinical study, no COVID-19 literature |

**Zoekverantwoording**

Search below was updated at July 1st, 2020.

History

| Search | Query | Items found |
|---|---|---|
| #1 | Search **("COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR (("Coronavirus"[MeSH Terms] OR "Coronavirus Infections"[Mesh:NoExp] OR pneumonia virus*[tiab] OR cov[tiab]) AND (outbreak[tiab] OR wuhan[tiab] OR novel[all] OR 19[tiab] OR 2019[tiab] OR epidem*[tiab] OR epidemy[all] OR epidemic*[all] OR pandem*[all] OR new[tiab])) OR coronavirus*[tiab] OR corona virus*[tiab] OR ncov[tiab] OR 2019ncov[tiab] OR covid19[tiab] OR "covid 19"[tiab] OR "sars cov 2"[tiab] OR sars2[tiab] OR "ncov 2019"[tiab] OR "sars coronavirus 2"[tiab] OR "sars corona virus 2"[tiab] OR "severe acute respiratory syndrome cov 2"[tiab] OR "severe acute respiratory syndrome cov2"[tiab] OR severe acute respiratory syndrome cov*[tiab] OR cov2[tiab]) AND ("2019/12"[Date - Entrez] : "3000"[Date - Entrez])** | 10797 |
| #8 | Search **#1 AND #7** | 161 |
| #7 | Search **corticosteroid*[tiab] OR glucocorticoid*[tiab] OR beclomethason*[tiab] OR fluticason*[tiab] OR triamcinolon*[tiab] OR budesonid*[tiab] OR mometason*[tiab] OR dexamethason*[tiab] OR flunisolide[tiab] OR ciclesonide[tiab]) OR (((((("Anti-Inflammatory Agents"[Mesh:noexp]) OR "Anti-Inflammatory Agents"[Pharmacological Action]) OR ("Adrenal Cortex Hormones"[Mesh])) OR (("Anti-Inflammatory Agents"[Mesh:noexp]) OR "Anti-Inflammatory Agents"[Pharmacological Action])) NOT ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh])) OR "Steroids"[Mesh] OR steroid*[tiab] OR "Adrenal Cortex Function Tests"[Mesh] OR "Adrenal Cortex Hormones" [Pharmacological Action]** | 1290699 |

Embase Session Results (7 May 2020)

| No. | Query | Results |
|---|---|---|
| #10 | #8 AND #9 | **174** |
| #9 | (('coronavirinae'/exp OR 'coronavirus infection'/de OR coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'pneumonia virus*':ti,ab,kw OR cov:ti,ab,kw OR ncov:ti,ab,kw) AND (outbreak:ti,ab,kw OR wuhan:ti,ab,kw) OR covid19:ti,ab,kw OR 'covid 19':ti,ab,kw OR ((coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw) AND 2019:ti,ab,kw) OR 'sars cov 2':ti,ab,kw OR sars2:ti,ab,kw OR 'coronavirus*':ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'ncov 2019':ti,ab,kw OR ncov:ti,ab,kw OR 'sars coronavirus 2':ti,ab,kw OR 'sars corona virus 2':ti,ab,kw OR 'severe acute respiratory syndrome cov 2':ti,ab,kw OR 'severe acute respiratory syndrome cov2':ti,ab,kw) AND [2019-2020]/py | **8283** |
| #8 | corticosteroid*:ti,ab,kw OR glucocorticoid*:ti,ab,kw OR beclomethason*:ti,ab,kw OR fluticason*:ti,ab,kw OR triamcinolon*:ti,ab,kw OR budesonid*:ti,ab,kw OR mometason*:ti,ab,kw OR dexamethason*:ti,ab,kw OR flunisolide:ti,ab,kw OR ciclesonide:ti,ab,kw OR 'adrenal cortex hormone':ti,ab,kw OR 'adrenal cortex hormones':ti,ab,kw OR 'corticosteroid'/exp | **1030562** |