Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

HSE Interim Guidance for the use of Systemic Corticosteroids in the Management of Hospitalised Patients with Severe COVID-19 Disease

This document is intended for use by healthcare professionals only.

This guidance is specific to the management of hospitalised patients with confirmed severe COVID-19 disease.

While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgment or specialist consultation.

This guidance should be read in conjunction with the National HSE Infection Prevention and Control (IPC) Guidance for Possible or Confirmed COVID-19 .

Protocol: Interim Guidance for the use of Systemic Corticosteroids in the Management of Hospitalised Patients with Severe COVID-19 Disease.		Published: 17 Sep 2020 Review: 28 May 2021	Version number:1
Protocol Code: COVID19-CORTICOSTEROIDS	Approved by: Dr Vida Hamilton, HSE National Clinical Advisor and Group Lead, Acute Hospitals	Contributors: Prof C Bergin, Prof P Browne, Prof P Murray, Prof M O'Dwyer, Dr D Murphy, Dr M Power, Dr L Bacon, Prof J Laffey, Prof A Nichol, Dr R Adams, F King, P Gilvarry.	Page 1 of 6

The following HSE interim guidance and advisory statements should also be considered for the management of patients with COVID-19, as appropriate:

- *COVID-19 Interim Clinical Guidance - VTE protocol and patient information for acute hospitals (available from: https://hse.drsteevenslibrary.ie/c.php?g=679077&p=4866382)*
- *The following interim guidance and advisory statements available from https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/:*
    - *HSE Interim Guidance for the Use of Antiviral Therapy in the Clinical Management of Acute Respiratory Infection with SARS-CoV-2 (COVID-19)*
    - *HSE Interim Position Statement on the Use of Human Normal Intravenous Immunoglobulin (IVIg) in the Management of COVID-19.*
    - *Interim Guidance for the use of Tocilizumab in the Management of Patients who have Severe COVID-19 with Suspected Hyperinflammation*

Section 1: Summary Guidance for the use of Systemic Corticosteroids in the Management of Patients with Severe COVID-19.

1. Emerging high quality evidence, including randomised controlled trials[1-4] and one meta-analysis of randomised trials[5], suggests that corticosteroids may provide benefit in the management of severe COVID-19. There is evidence of no benefit, and possible harm, for the use of corticosteroids in patients with non-severe COVID-19 not requiring respiratory support.

2. A meta-analysis of seven randomised trials (1,703 patients) published by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group concluded that administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in hospitalised, critically ill patients with COVID-19.[5]

3. The corticosteroids used in the trials included in the WHO meta-analysis were dexamethasone (3 trials, 1,282 patients), hydrocortisone (3 trials, 374 patients) and methylprednisolone (1 trial, 47 patients).[5] Further details of the meta-analysis are available online at: https://jamanetwork.com/journals/jama/fullarticle/2770279

4. The results of a subgroup analysis of the RECOVERY trial for dexamethasone suggests that the relative effects of systemic corticosteroids is related to the level of respiratory support received at randomisation. Evidence of benefit was limited to patients with severe COVID-19 requiring respiratory support. The RECOVERY trial reported that dexamethasone did not provide benefit over usual care in patients not receiving respiratory support at randomisation (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55) and the results were consistent with possible harm in this subgroup.[1]

5. The potential for adverse events resulting from systemic corticosteroid therapy must be considered before initiating therapy in patients with COVID-19. The WHO REACT Working Group did not conduct a meta-analysis of serious adverse events as there were inconsistencies in the reporting and definitions used in the clinical trials included in the meta-analysis.[5] The WHO clinical guideline panel concluded that "harms, in the context of the mortality reduction in severe COVID-19, are minor".[6]

6. The HSE recommend that the use of systemic corticosteroids in a defined cohort of patients* infected with COVID-19 should only be considered after consultant-level discussion in a multidisciplinary setting (*see **Section 2**).

7. This guidance does not apply to the use of systemic corticosteroids for indications other than COVID-19 (e.g. exacerbations of asthma or COPD). Patients currently taking corticosteroids for other indications should continue to do so unless advised by their doctor to discontinue. For further information on the use

of corticosteroids for indications other than COVID-19, and in both asthma and COPD patients with COVID-19, please refer to the *HSE COVID-19: Interim Clinical Guidance: Immunosuppressant Therapy,* available from: https://hse.drsteevenslibrary.ie/ld.php?content_id=32936271 .

Section 2: Patient Selection (with input from specialist multidisciplinary team)

1. Systemic corticosteroid therapy should only be considered for the management of COVID-19 disease in hospitalised patients requiring:

    - Mechanical ventilation
      OR
    - Supplemental oxygen but who are not mechanically ventilated

    (The above definitions correspond to the HSE National Clinical Programme for Respiratory Medicine/Irish Thoracic Society COVID Respiratory Scale (CRS) categories B, C or D; the CRS is available from https://hse.drsteevenslibrary.ie/c.php?g=679077&p=4866795#appendix1%20021)

    *Systemic corticosteroids should **not** be used for the management of patients with COVID-19 who do not require respiratory support, unless another indication for corticosteroid therapy exists*

    AND

2. Exclusion of contraindications to systemic corticosteroid therapy including acute severe infection from sources other than SARS-CoV2.

    AND

3. If treatment is being considered, it must only be initiated after consultant-level discussion in a multidisciplinary setting.

Section 3: Prescribing Information (Refer to Summary of Product Characteristics of respective medicinal products for full prescribing information)

Table 1. Key Prescribing Recommendations

Prescribing Recommendations (Adapted from WHO Clinical Guideline: *Corticosteroids for COVID-19*)[6]
Systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. dexamethasone orally or intravenously or hydrocortinsone intravenously) for 7 to 10 days.
Table 1 continued on next page.

Recommended Dexamethasone Dose Schedule:	Dexamethasone 6mg orally daily for 7 to 10 days. **OR** Dexamethasone phosphate 8mg (equivalent to dexamethasone 6.6mg) intravenously daily for 7 to 10 days [#] *[#]In the RECOVERY trial dexamethasone was prescribed as dexamethasone base.*[7] *Dexamethasone phosphate (salt) 4mg in 1ml injection is equivalent to dexamethasone (base) 3.3mg in 1ml injection.*[8,9] *Check with local pharmacy department for formulation available.* *No conversion is required for oral formulations of dexamethasone*.
Recommended Hydrocortisone Dose Schedule:	Hydrocortisone 50mg every 6 to 8 hours intravenously for 7 to 10 days.[6,10]
Considerations for Route of Administration Based on Level of Care (*All patients must satisfy the criteria for systemic corticosteroids detailed in* ***Section 2*** *regardless of level of care)*	- Intensive Care Unit (ICU) Patients: Hospitalised patients requiring escalation to ICU within 24 hours of admission and not already commenced on dexamethasone should be considered for treatment with intravenous hydrocortisone. - Non-ICU Patients: Hospitalised patients not requiring admission to an ICU should be considered for treatment with parenteral corticosteroids (dexamethasone or hydrocortisone) for the first 48hours followed by a review to oral therapy. (*Expert Opinion of Guideline Development Group*)

Additional Considerations

1. The optimal dose and duration of treatment was not assessed in the WHO Group meta-analysis. There was no evidence suggesting that [$]higher doses of corticosteroids were associated with greater benefit than lower dose corticosteroids.[5]

   [$]The WHO Group applied the following a priori cut-offs to define high-dose corticosteroids: dexamethasone 15mg per day, hydrocortisone 400mg per day, and methylprednisolone 1mg/kg per day.[5]

2. The evidence for use of corticosteroids in the management of paediatric or pregnant patients with severe COVID-19 disease is lacking and specialist advice should be sought for the appropriate clinical management of these patients.

3. Suspected co-infection with pathogens other than SARS-CoV2 should be investigated and treated empirically as per local antimicrobial policy with consideration of the principles of antimicrobial stewardship (Further information available from: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/guidance/infectionpreventionandcontrolguidance/antimicrobialstewardship/ .

4. For patients prescribed systemic corticosteroids at the time of hospital admission, the dose should be increased to a dose therapeutically equivalent to that detailed in **Table 1**. Corticosteroid anti-inflammatory dose equivalencies[11] are:
   a. Dexamethasone base 6 mg
   b. ≡ Hydrocortisone 160 mg
   c. ≡ Methylprednisolone 32 mg
   d. ≡ Prednisolone 40 mg

Once the course of treatment with systemic corticosteroids indicated for COVID 19 is completed, assess clinical need to recommence the previous corticosteroid prescription.

5. Response to systemic corticosteroid therapy should include monitoring of relevant laboratory markers of inflammation and clinical parameters.

6. Patients with COVID-19 who are receiving corticosteroids must be monitored for adverse effects (e.g. hyperglycaemia, secondary infections; see Summary of Product Characteristics for full information on adverse events). Consideration needs to be given to the need for appropriate gastroprotection according to local hospital policy.

7. Use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus, herpes viruses, and tuberculosis).

8. The safety and efficacy of corticosteroids in combination with other COVID-19 therapies (e.g. remdesivir) is not confirmed.

9. Co-administration of dexamethasone and remdesivir has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.[12]

   Refer to the Summary of Product Characteristics and drug-drug interaction databases (e.g. Stockley's Interaction Checker) to check for drug-drug interactions. The University of Liverpool have developed an online database for checking drug-drug interactions with the experimental COVID-19 specific medicinal products; available online at www.covid19-druginteractions.org .

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