MSIC CONSENSUS STATEMENT: CORTICOSTEROIDS FOR COVID-19

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MSIC Working Group

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Severe COVID-19 is associated with a hyperinflammatory response resulting in acute respiratory distress syndrome and multi-organ dysfunction in some patients. Generally, this occurs after 7 days of symptom onset.

Prior to the COVID-19 pandemic, studies on the use of corticosteroids in critically ill patients with ARDS remain inconclusive due to limited sample size, various dosing strategies and inconsistent outcomes. Pulse dose methylprednisolone is currently not recommended in ARDS.[1,2] Similarly, evidence is also lacking in the administration of pulse methylprednisolone for 'cytokine storm' in COVID-19.

The WHO Guideline Development Group made a strong recommendation on the use of systemic corticosteroids therapy for 7 to 10 days in patients with severe and critical COVID-19[3]. The prospective meta-analysis by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT[4]) pooled data from 7 trials and concluded that administration of systemic corticosteroids was associated with a lower 28-day all-cause mortality compared with usual care or placebo. The RECOVERY[5] trial done in the UK contributed the highest weightage to this meta-analysis, where patients in the intervention arm received dexamethasone 6 mg daily for 10 days or upon discharge from hospital. The corticosteroids administered in the other trials varied in dosages, formulations and durations of treatment: dexamethasone 20 mg daily for 5 days followed by 10mg daily for 5 days (CoDEX[6] and DEXA-COVID 19); methylprednisolone 40 mg 12 hourly for 5 days (Steroids-SARI); hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days, and then 50 mg daily for 2 to 3 days (CAPE-COVID[7]); hydrocortisone 200 mg daily for 7 days (REMAP-CAP[8] and COVID STEROID).

The above data suggest that the benefit is a general class effect of glucocorticoids and not specific to any particular corticosteroid. However, because most of the participants (59%) in this meta-analysis were from the RECOVERY trial, it is likely that the benefits observed were mostly associated with dexamethasone.

Limitations on the RECOVERY trial included no data on the severity of hypoxaemia, the FiO2 or PEEP in patients who were mechanically ventilated. Higher doses may thus be appropriate in patients with moderate or severe ARDS as indicated by the CoDEX trial which demonstrated that the use of dexamethasone was associated with a higher number of ventilator-free days compared with those receiving standard care alone. Due to its early termination upon the publication of the RECOVERY trial, it was underpowered to detect mortality difference.

Dose and duration

Oxygen therapy	Steroid	Dose	Comment
Nil	Not indicated		Increases risk of mortality[4]
Nasal prongs or Facemask 5-8 L/min	IV Dexamethasone	6 mg daily x 7 – 10 days	7 days of therapy to be considered in patients who improve rapidly
HFNC/ NIV* or Mechanical ventilation	IV Dexamethasone	20 mg daily x 5 days then 10 mg daily for 5 days	Shorter duration of treatment may be considered. This may be guided by clinical condition and inflammatory markers** Rule out other causes of hypoxaemia when patient deteriorates e.g. pulmonary oedema or embolism, heart failure, etc.

***** *HFNC: high flow nasal cannula * NIV: non-invasive ventilation*

** *Inflammatory markers: CRP, D-dimer, serum ferritin and LDH*

Alternative glucocorticoids such as methylprednisolone, prednisone or hydrocortisone can be used at equivalent dose of dexamethasone. The total daily equivalent dose for intravenous dexamethasone of 6 mg is 32 mg of methylprednisolone, 40 mg of prednisone and 150 mg hydrocortisone.

Results of studies using higher doses of corticosteroids (> 1 to 1.5 mg/kg/day of methylprednisolone) have to be interpreted with caution as sample size is usually small and heterogeneity of study population. The true incidence of adverse effects with the use corticosteroids such as secondary infections, delirium and avascular necrosis is not known, for most of the randomised trials are of open label, pragmatic design with minimal reporting of adverse events and only reporting short-term outcomes (28-day mortality).

Pregnancy

In pregnant patients with COVID-19 requiring oxygen therapy, glucocorticoid is recommended.[9,10]

However, repetitive doses of antenatal glucocorticoids maybe associated with adverse neurological outcomes, small head circumference, foetal growth restriction and increase risk of neonatal hypoglycaemia. Dexamethasone has high placental transfer while the other glucocorticoids has reduced transfer. Dexamethasone is routinely administered to accelerate foetal lung maturity in patients at risk of preterm delivery.

Dose and duration

Weeks of pregnancy	Steroid	Comment
24 – 34 weeks	IV Dexamethasone 6 mg 12 hourly x 2 days[11] then either Prednisolone 40 mg daily x 8 days or Hydrocortisone 80 mg 12 hourly x 8 days	Dexamethasone required for foetal lung maturity
< 24 weeks or > 34 weeks	Prednisolone 40 mg daily x 10 days or Hydrocortisone 80 mg 12 hourly x 10 days	

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