USE OF DEXAMETHASONE FOR COVID-19 IN HOSPITALISED ADULTS, ADOLESCENTS and CHILDREN DRUG GUIDELINE

This guideline aims to provide supportive information for clinicians if they decide to prescribe dexamethasone in hospitalised patients with COVID-19. This guideline requires endorsement by your local Drug and Therapeutics Committee (DTC) prior to implementation.

Dexamethasone is registered in Australia for a wide range of indications. The National COVID-19 Clinical Evidence Taskforce's Living Guidelines recommend use in adults with COVID-19, including pregnant and breastfeeding women, ***who are receiving oxygen (including mechanically ventilated patients)****. There is a conditional recommendation for children and adolescents with COVID-19 receiving oxygen (including those mechanically ventilated).[1] Current evidence suggests that there is no benefit in giving dexamethasone to patients who do not require oxygen (or mechanical ventilation).*

Use of dexamethasone for COVID-19 is ***not recommended*** *in the Hospital in the Home setting or in community-based patients with COVID-19.*

Drug Class

Corticosteroid

Authorised Prescribers

Any medical doctor caring for the hospitalised patient with COVID-19

Indication for applying this guidance

At the treating clinician's discretion, dexamethasone is recommended for patients with confirmed SARS-CoV2 (or known contact of a confirmed case with COVID-19) and **receiving oxygen (including mechanically ventilated patients)** for the following patient groups:

- adults, not including pregnant and breast-feeding women (recommended)
- pregnant and breast-feeding women (recommended)* and
- children and adolescents (conditional recommendation)*.

*See discussion under *Special Patient Population Considerations* below.

Do not routinely use dexamethasone to treat COVID-19 in patients who do not require oxygen.

The current evidence available shows no benefit and possible harm including secondary infection, hyperglycaemia, neurological adverse effects and adrenal suppression.[2, 3]

Contraindications

- Hypersensitivity to dexamethasone or to any excipients of the tablet or injection or to other corticosteroids
- Concomitant administration of live virus vaccines (the risk of severe systemic infection)

Relative Contraindications / Precautions [4, 5]

Many of the listed precautions below may not apply when dexamethasone is used short-term in the treatment in COVID-19.

**The treating doctor needs to assess if treatment with dexamethasone puts the patient at substantial risk due to concurrent (non-COVID) infection. This assessment must not delay treatment with dexamethasone.

Precaution	Effect
Use in infection**	Corticosteroids can mask the signs of infection, suppress the immune system and increase the risk and severity of infections. While immunosuppression is most likely to occur in patients on long-term, high-dose systemic corticosteroid treatment, patients receiving moderate doses for short periods may also be at risk. Consider screening for pre-existing infections where reactivation may occur but do not delay treatment with corticosteroids (e.g. Strongyloides[6], tuberculosis, hepatitis B, Pneumocystis jirovecii pneumonia etc.).
Peptic ulcer disease	Corticosteroids may increase risk of peptic ulcers; consider co-administration with a proton pump inhibitor.
Diabetes	Corticosteroids may cause hyperglycaemia and dose adjustments of antihyperglycaemic medications may be necessary.
Hypertension, heart failure	May worsen; note that mineralocorticoid activity (sodium and water retention) of dexamethasone is lower than that of other corticosteroids.
Psychiatric disorders	May worsen. Most psychiatric adverse effects resolve after dose reduction or withdrawal.
Glaucoma	Intraocular pressure may increase; continue anti-glaucoma therapy.
Myasthenia gravis	May increase muscle weakness.
Phaeochromocytoma	May precipitate a crisis.
Epilepsy	Latent epilepsy can manifest during corticosteroid treatment
Hepatic impairment	Use with caution in severe impairment (Childs Pugh C); the elimination half-life may be prolonged. Frequent monitoring and a reduction of dexamethasone dosage may be necessary.[7]

Special Patient Population Considerations

- **Pregnant and/or breastfeeding women** [8]
  - Dexamethasone crosses the placental barrier and appears in breast milk in small quantities:
    - Most studies have shown no increased risk of major congenital malformations following maternal use of corticosteroids.[9]
    - Published reports describing the use of dexamethasone during breastfeeding are not available. An alternate corticosteroid may be preferred, especially while nursing a newborn or preterm infant.
  - A harm: benefit assessment for use of corticosteroids and choice of corticosteroid to optimise the mother's outcomes is recommended.
  - The RECOVERY protocol on which the recommendation for use is based, advised that pregnant and breastfeeding women would receive oral prednisolone 40 mg or intravenous hydrocortisone 80 mg twice daily; it was permitted to switch between the two routes of administration according to clinical circumstances. Both these medications have lower foetal concentrations as a result of either limited placental crossing (prednisolone) or rapid placental metabolism (hydrocortisone). Six pregnant or breastfeeding women were included in the RECOVERY analyses; however, it is unclear to which treatment arm they were assigned.
  - No adverse effect have been reported in breastfed infants with maternal use of any corticosteroid during breastfeeding. With high maternal doses, avoiding breastfeeding for 4 hours after a dose

should markedly decrease the dose received by the infant. However, this strategy is not necessary with short-term use. High doses might occasionally cause temporary loss of milk supply.[10, 11]
  - Advice from the pharmacy department or medicines information service, if available, or specialist maternity drug information, obstetric or specialist lactation advice may be sought on a case by case basis in conjunction with patient and/or family consultation. See also Australian guidelines for the clinical care of people with COVID-19 for more information.

- **Children and adolescents** [2, 12]
  - The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment in paediatric patients including use in those with multisystem inflammatory syndrome in children (MIS-C) have not been sufficiently evaluated.
  - The results from the RECOVERY trial should be interpreted with caution for patients aged <18 years as there were low numbers of paediatric patients included in the preliminary analysis and mortality rates were significantly lower for paediatric patients with COVID-19 (and hence RECOVERY continues to investigate dexamethasone use in children).

- **Patients already on corticosteroid therapy for chronic conditions** [2, 13]
  Those with primary or secondary adrenal insufficiency, rheumatologic and other chronic conditions treated with corticosteroids including patients on inhaled corticosteroids for asthma or COPD may not be able to mount a normal stress response in the event of COVID-19 infection. Administration of physiologic stress doses of corticosteroids should be considered in all cases to avoid potentially fatal adrenal failure.

- **Patients with septic shock**
  Some patients with COVID-19 may develop a bacterial superinfection resulting in septic shock. In patients with septic shock who are refractory to vasopressors, corticosteroids e.g. hydrocortisone 200 mg daily, as 50 mg IV every six hours, for up to 7 days are often used.[14, 15] In the scenario of a COVID-19 patient with septic shock from bacterial superinfection, a substitution with hydrocortisone or continuation of dexamethasone may be considered. As dexamethasone 6mg provides an equivalent glucocorticoid effect to hydrocortisone 160 mg, patients who are switched to hydrocortisone should receive at least 160 mg/day for up to 10 days as used in the RECOVERY trial [16]

- **COVID-19 patients with acute respiratory distress syndrome (ARDS) or hyper-inflammatory syndromes**
  Specialist advice should be sought regarding the use of corticosteroids and what dose and duration to use in these patients.

Drug Interactions

Dexamethasone is a moderate inducer of CYP3A4 and P-glycoprotein (P-gp) [5, 7] and a substrate for CYP3A4. Use with CYP3A4 inhibitors may increase dexamethasone concentrations and the risk of adverse effects, while use with CYP3A4 inducers may decrease dexamethasone concentrations and efficacy.

The effects of anticoagulant agents are usually decreased (but may be increased in some patients) with concurrent corticosteroid treatment. Close monitoring of the INR or prothrombin time is recommended.[2]

Concomitant use of drugs that irritate the gastro-intestinal lining with dexamethasone may increase the risk of peptic ulceration and bleeding.[13]

There is an increased risk of myopathies if dexamethasone is used with hydroxychloroquine or chloroquine, noting that current guidelines do not support the use of these medicines in COVID-19.[7] Although not listed in other references (e.g. Liverpool Drug Interaction Checker, Micromedex) there is a potential drug interaction involving the concurrent administration of interferon-beta and dexamethasone in patients with COVID-19.[17] Consider using more than one drug interactions resource to check for drug interactions.

Dose

- ***For adults use*** dexamethasone 6 mg intravenously (IV)* or orally ONCE DAILY for up to 10 days.
  Can be discontinued when the patient is discharged from hospital even if a 10 day course has not been completed. (The median duration in the RECOVERY trial was 7 days).

  ***Use 1.5 mL of 4 mg/mL or 8 mg/2mL injectable products to obtain 6 mg.** Consensus following consideration of salt form, equivalence with oral formulation if stepped down and bioavailability of oral formulation has determined 1.5 mL of injectable product to be most appropriate.

- ***For children and adolescents*** the RECOVERY protocol states a dose of 0.15 mg/kg/day of dexamethasone **base** to a maximum of 6 mg/day.[16]

See Special Patient Population Considerations section for dosing considerations in patients with septic shock, ARDS or hyper-inflammatory syndromes.

Evidence for switching between corticosteroids is not available. However, an equivalent corticosteroid with glucocorticoid activity may be substituted if dexamethasone is unavailable or not appropriate.[4] The total daily dose equivalencies to dexamethasone 6 mg (IV/oral) are [2]:

- prednisolone 40 mg oral (once daily or in 2 divided doses daily)
- methylprednisolone 32 mg IV (once daily or in 2 divided doses daily) (*use sodium succinate*)
- hydrocortisone 160 mg IV (in 2 to 4 divided doses daily)

Dexamethasone has a long-half life and rebound effects from short-term dexamethasone should not occur when ceased. Use of other corticosteroids may require tapering over approximately 3 days.

Australian marketed formulations* [4]

Form	Brand	Strength*	Description
Tablet**	Dexmethsone®	0.5 mg 4 mg	Plain white tablets.
Ampoule	DBL Dexamethasone Sodium Phosphate Solution for Injection®#	4 mg/mL (1 mL ampoule)	Clear colourless and preservative free solution.
Vial	DBL Dexamethasone Sodium Phosphate Solution Injection®#	4 mg/mL (1 mL vial) 8 mg/2mL (2 mL vial)	Clear and colourless solution.
	Dexamethasone (Mylan) Solution for Injection®#	4 mg/mL (1 mL vial) 8 mg/2mL (2 mL vial)	Clear and colourless solution.

#Contains dexamethasone phosphate as dexamethasone sodium phosphate.
**Note that dexamethasone injectable formulations available overseas do not necessarily contain 4 mg/mL dexamethasone phosphate. Check formulations and strengths carefully if Australian marketed products become unavailable. (4 mg dexamethasone phosphate is equivalent to 3.3 mg dexamethasone base.)*
***Oral liquid forms in various strengths are available either through the Special Access Program or may be compounded. Contact your pharmacy department.*

Preparation and administration [18]

Oral tablet [5]	Give tablets orally in the morning with food to minimise gastrointestinal upset.
Intravenous Injection [18]	Inject slowly over 3 to 5 minutes. May be diluted with 10 mL of sodium chloride 0.9% to facilitate slow injection.
Intravenous infusion [18]	Dilute with 50–100 mL of a compatible fluid and infuse over 15 minutes. (Infusion may be preferred if injection causes pain and tingling or burning sensations). Compatible fluids: Glucose 5% , Plasma-Lyte 148 via Y-site , sodium chloride 0.9%

Adverse Effects [5]

Many known corticosteroid adverse effects are unlikely to occur when it is used short-term i.e. less than 2 weeks, such as in the treatment in COVID-19.

Incidence of adverse effects is usually related to dose and duration of treatment with short courses of high-dose systemic treatment causing fewer adverse effects than prolonged courses of lower doses.

Below are some common adverse effects that may occur with short term use of dexamethasone:

- transient itching, burning or tingling in perineal area (after high dose rapid IV bolus)
- infection, hypernatraemia*, hypervolaemia, hypertension, hypokalaemia, hyperglycaemia*, increased appetite, dyspepsia, delayed wound healing, bruising, facial flushing, myopathy, muscle weakness*, psychiatric effects (euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour. Delirium or psychosis are less common).

  *A recent Cochrane review of corticosteroids for treating sepsis in children and adults identified treated patients are at increased risk from these adverse events.(15) There is probably no increased risk of superinfection and little or no effect on risk of GI bleeding, neuropsychiatric events, stroke or cardiac events.

Monitoring Requirements [2]

Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects including muscle weakness, electrolyte disturbances, hyperglycemia, secondary infections (including reactivation of pre-existing or latent infections), neuropsychiatric effects, and hypertension. (See adverse effects section above).

Reporting adverse effects

At the time of writing this guideline, the trial on which the recommendation for dexamethasone use in COVID-19 is based (RECOVERY), has not yet reported adverse events.[16] It is important to document and report serious adverse effects (from possible to confirmed) to inform its safety and current/future use in patients with COVID-19.

The prescribing clinician is responsible for reporting medication errors and adverse drug reactions occurring as a result of treatment with dexamethasone.

- Clinically significant adverse events related to dexamethasone should be reported to the TGA, the hospital IMS+ or RiskMan system.
- Hospitals may wish to consider the collection and analysis of patient outcomes and systematic monitoring of medicines use (including dexamethasone) for COVID-19 patients.

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