Dexamethasone for CAP

Intervention

Dexamethasone 6mg by mouth, nasogastric tube or intravenously for 10 days or until discharge, whichever is sooner.

Pregnant women should receive oral prednisolone 40mg once daily or intravenous hydrocortisone 80mg twice daily instead of dexamethasone.

Information on dexamethasone for CAP

RECOVERY and other randomised trials have demonstrated the benefit of corticosteroids in patients with COVID-19 pneumonia.[1,2] However, the potential role of corticosteroids in community-acquired pneumonia (CAP) caused by other pathogens remains uncertain. Randomised trials have demonstrated that corticosteroids improve time to clinical stability and discharge in patients hospitalised with CAP, but this may simply relate to suppression of fever and inflammatory markers rather than a true improvement in disease outcomes.[3,4]

Previous trials have produced conflicting results on mortality, but have mostly been underpowered for this outcome, and in aggregate they are consistent with no significant effect of corticosteroids on mortality, or with a reduction of a third.[5] The recent CAPE COD trial reported a significant reduction in mortality associated with corticosteroid use in ICU patients, but no effect was observed in the similar ESCAPe trial.[6,7] The role of corticosteroids in CAP remains unclear and use in clinical practice is variable. Corticosteroid treatment is not recommended in current US or UK CAP treatment guidelines.[8,9] European guidelines for severe CAP suggest the use of corticosteroids if shock is present.[10] An adequately powered randomised trial is needed to resolve this uncertainty.

Eligibility

- Hospitalised adults with an acute pneumonia syndrome, in general based on:
  a) typical symptoms of new respiratory infection, and
  b) objective evidence of acute lung disease, (e.g. compatible imaging [plain X-ray, CT or ultrasound], clinical examination, or new hypoxia), and
  c) alternative causes considered unlikely
- Clinical diagnosis of community acquired pneumonia with planned antibiotic treatment.

Exclusions

- Use of systemic corticosteroids for >24h during the current illness with a glucocorticoid-equivalent of ≥10mg prednisolone per day (equivalent to ≥1.5mg dexamethasone or ≥40mg hydrocortisone).
- Current or expected indication for systemic corticosteroids as determined by the patient's managing clinician (e.g. COPD, septic shock).
- Any contraindication to corticosteroids as determined by the managing clinician.
- Suspected or confirmed infection with SARS-CoV-2, influenza, *Pneumocystis jirovecii* (PCP/PJP) or active pulmonary tuberculosis (testing for these pathogens is not required unless clinically indicated).
- Hospital-acquired pneumonia (e.g. hospital inpatient within the last 10 days before current admission, or pneumonia starting after current admission).

Dexamethasone for CAP

Frequently asked questions

1. ***Can patients receiving regular low-dose systemic corticosteroids be enrolled?***
   Yes, if the dose is lower than that specified in the exclusions.
2. ***Can patients who have received a higher dose of systemic corticosteroids be enrolled?***
   Yes, but only if they have received this for <24 hours and there is no indication for continued treatment.
3. ***Can patients receiving inhaled or topical corticosteroids be enrolled?***
   Yes, and this can continue regardless of treatment allocation.
4. ***Can patients who require corticosteroids equivalent to ≥10mg prednisolone for a co-existing medical condition (e.g. COPD) be enrolled?***
   No. They should receive corticosteroids as clinically indicated.
5. ***Can patients with diabetes be enrolled?***
   Yes, but it may not be appropriate for patients with unstable diabetes or acute complications of diabetes.

   Regular glucose monitoring will be required in line with usual clinical practice, with possible adjustment of diabetic therapy to prevent/treat hyperglycaemia. Dexamethasone may be stopped if causing uncontrollable hyperglycaemia.
6. ***Can patients with hepatic impairment be enrolled?***
   Yes, and no dose adjustment is needed.
7. ***Can patients with renal impairment be enrolled?***
   Yes, and no dose adjustment is needed.
8. ***Can pregnant and breast-feeding women be enrolled?***
   Yes, but prednisolone (40mg once daily) or hydrocortisone (80mg twice daily IV) should be used instead of dexamethasone to reduce fetal/infant exposure. Inclusion should be discussed with an obstetric specialist (see protocol appendix 4)
9. ***Can children (age <18) be enrolled?***
   No. Children are excluded in all countries.
10. ***Is screening for endemic infections (e.g. Strongyloides) required?***
    No, but this can be done if required by local practice.
11. ***Are patients with a planned/pending influenza/SARS-CoV-2 test eligible?***
    No. If an influenza and/or SARS-CoV-2 test is planned (which may be the policy for all acute respiratory admissions in winter), then do not recruit the patient to the CAP comparison until a negative result has been returned. If the initial test results are indeterminate/inhibited and the local policy is to repeat it, do not randomize the patient until a negative result has been returned. If testing for these viruses is not part of routine care or retesting in case of inconclusive results is not applicable, then the patient is potentially eligible and a test is not required for trial purposes.

12. ***If a patient recruited to the CAP comparison subsequently tests positive for influenza, SARS-CoV-2, PCP or TB, should they be withdrawn?***
    No. They should remain in the trial and have follow up as planned. Any trial treatment should be stopped unless the responsible doctor wants this to continue as part of routine care. This situation should be avoided as far as possible, but it is not a protocol deviation if the patient met the eligibility criteria at the time of randomisation. The subsequent diagnosis will be captured on the follow up form.

13. ***If a patient recruited to the CAP comparison subsequently tests positive for influenza, are they eligible for the RECOVERY influenza comparisons?***
    No, patients cannot re-enter another RECOVERY comparison after being randomised.

14. ***Are patients eligible for the CAP comparison if a virus other than influenza or SARS-CoV-2 is detected?***
    Yes, they can be enrolled in the CAP comparison if they meet the eligibility criteria (this requires planned antibiotic treatment, so patients without a suspected bacterial component would not be eligible).

15. ***Can dexamethasone be used concomitantly with other treatments?***
    The patient's managing clinician and the investigator should decide if corticosteroids are contraindicated due to concomitant medication, based on their usual practice. No specific trial exclusions are related to this.

    Concomitant use of potent CYP3A4 inhibitors, including clarithromycin and erythromycin, is not contraindicated, but the possible risk of increased corticosteroid side-effects should be considered (note azithromycin, an alternative macrolide used for CAP, is not a potent CYP3A4 inhibitor).

    Concomitant use of other immunomodulatory therapies is not contraindicated, but the total burden of therapy should be considered.

16. ***Are tablet and liquid preparations of dexamethasone interchangeable?***
    Yes, they are dose-equivalent for the purposes of the trial.

17. ***Can liquid dexamethasone be administered down an NG tube?***
    Yes.

18. ***Are oral and IV preparations of dexamethasone interchangeable?***
    Yes, they are dose-equivalent for the purposes of the trial. An approximate 10% over or under dosing is acceptable if the IV formulation makes exact dosing is difficult.

19. ***Can dexamethasone be stopped abruptly after 10 days of treatment?***
    Yes, acute adrenal insufficiency on withdrawal is unlikely with the dose and duration used in RECOVERY. However, if the managing clinician believes the patient is at high risk for adrenal insufficiency they may choose to reduce the dose gradually according to their usual practice. If so, they should determine the appropriate withdrawal regimen.

    The SmPC advises "Abrupt withdrawal of doses of up to 6mg daily of dexamethasone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression in the majority of patients. In the following patient groups, gradual

withdrawal of systemic corticosteroid therapy should be *considered* even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks.
- When a short course has been prescribed within one year of cessation of long-term therapy (months or years).
- Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
- Patients receiving doses of systemic corticosteroid greater than 6mg daily of dexamethasone.
- Patients repeatedly taking doses in the evening"

20. Should dexamethasone be prescribed as take-home medication if the patient is discharged before day 10?

No. The trial dexamethasone is stopped on the day of hospital discharge, or at day 10 whichever is sooner.

21. Can dexamethasone be continued beyond day 10?

Use of dexamethasone beyond day 10 is outside the trial protocol, and is at the discretion of the managing clinician.

22. Can dexamethasone be stopped before day 10?

The trial regimen is dexamethasone for 10 days or until discharge. However, the managing doctor may stop treatment earlier if they think the risks of treatment outweigh any potential further benefit (for example in a patient who is medically ready to be discharged but remains in hospital for other reasons). This would not be considered a protocol deviation. If this happens then make sure that the number of days of treatment actually received is recorded on the follow up form.

23. Is dexamethasone dosing to be adjusted for weight in adults?

No, a fixed dose of 6 mg dexamethasone is to be given.

References

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