CORTICOSTEROID DOMAIN ADMINISTRATION GUIDE

REMAP-CAP CORTICOSTEROID DOMAIN

This domain aims to determine the effectiveness of systemic corticosteroid strategy in the treatment of hospitalised patients with severe lower respiratory tract infections. In this domain, patients are randomised to receive:

- No corticosteroid, including hydrocortisone or dexamethasone (without administration of placebo)
- Shock-dependent hydrocortisone while the patient is in septic shock
- Fixed duration dexamethasone for 10 days

Your site may be participating in all interventions in this domain or only two, depending on local practice. Different interventions may be offered in the Moderate and Severe Illness Severity States, or depending on age.

NO CORTICOSTEROID INTERVENTION

Intervention
Patients allocated to the *'no corticosteroid' intervention* are not to receive any systemic corticosteroid (including hydrocortisone or dexamethasone) for this respiratory tract infection or its direct complications.

Discontinuation of intervention
The withholding of corticosteroids for this episode of CAP or its complications is to continue until the end of study day 28 or hospital discharge, whichever occurs first.

SHOCK-DEPENDENT HYDROCORTISONE INTERVENTION

Intervention
Patients randomised to the *shock-dependent hydrocortisone intervention* are to receive 50mg IV hydrocortisone every 6 hours while the patient is in septic shock. This intervention is only available to patients in the Severe Illness Severity State at the time of randomization.

Commencement of intervention
The intervention is to commence as soon as septic shock is diagnosed, including immediately after randomisation if septic shock has already been diagnosed.

Definition of shock
For the purposes of this intervention, septic shock is defined as:

- Administration of any vasopressor by continuous infusion, AND
- The treating clinician believes that the vasopressor requirement is due to the respiratory tract infection, and not for another reason such as untreated hypovolaemia or solely to offset the effects of other ICU interventions (such as administration of sedation or mechanical ventilation).

The exact dose of vasopressor that defines septic shock is not defined by the protocol, but is based on the judgement of the treating clinician.

Discontinuation of intervention
Hydrocortisone administration is to cease when the clinician believes that septic shock has resolved. Septic shock would always be regarded as being resolved if vasopressor infusion has not been administered in the preceding 24 hours.
A clinician may regard septic shock to have resolved if vasopressors are being administered intermittently or at a low dose.

If, during the same ICU admission and within 28 days of randomisation, hydrocortisone is ceased and shock due to the respiratory tract infection or its direct complications reoccurs, then the intervention is to be recommenced until resolution of shock.

Hydrocortisone should be ceased prior to hospital discharge.

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FIXED DURATION DEXAMETHASONE INTERVENTION

Intervention
Patients allocated to the *fixed duration dexamethasone intervention* are to receive a course of dexamethasone 6mg (IV or enteral) daily for 10 days. The choice of enteral or IV administration is at the discretion of the treating clinician based on the patient's ability to take enteral medications and illness severity, including likely gastric absorption rates.

In children, the allocated intervention should be replaced by dexamethasone 0.15 mg/kg to a maximum dose of 6mg/day for 10 days.

In pregnancy, dexamethasone should be replaced by oral prednisolone 40mg once daily, or IV hydrocortisone 50mg every 6 hours, for 10 days.

Commencement of intervention
Administration is to commence immediately after allocation is revealed. It will be considered a protocol deviation if during the 10 day course more than two sequential doses of dexamethasone are missed, or if three or more individual doses are missed.

Discontinuation of intervention
The ten-day course will be administered until at least the end of study day 10, and no longer than the end of study day 11 (i.e. it is intended that 10 doses are administered). From completion of the 10-day course onwards, patients allocated to this intervention are not to receive any systemic corticosteroid, including hydrocortisone or dexamethasone, for this respiratory tract infection and its direct complications up until study day 28 or hospital discharge, whichever occurs first.

For patients allocated to the fixed duration dexamethasone intervention who later develop septic shock, a decision to cease dexamethasone and commence a course of hydrocortisone will be at the discretion of the treating clinician, and will not be considered a protocol deviation.

For patients discharged from hospital before the end of the ten day course, dexamethasone should be discontinued at hospital discharge.

CONCOMITANT CARE AND PROTOCOL DEVIATIONS

The administration of Etomidate after enrolment is not permitted and will be considered a protocol deviation.

For patients who are allocated to a fixed course of hydrocortisone or dexamethasone and are discharged from the randomising location (i.e. ward or ICU) before the end of the allocated course of corticosteroids, it is the responsibility of the treating clinician to prescribe the allocated corticosteroid to complete the course. However, it is not the responsibility of the treating clinician or research staff to ensure continuation of the allocated corticosteroid after discharge from the randomising location. It is not a protocol deviation if the allocated course of corticosteroids is not completed after discharge from the randomising ward or ICU, and continuation of the allocated interventions is a clinical decision at the discretion of the treating clinician in the new location.

Administration of a non-allocated systemic corticosteroid is permitted for the treatment of new illnesses that develop in the course of a patient's hospital stay (e.g. asthma, treatment of an allergic reaction, new episode of septic shock from hospital-acquired infection). For patients who have received an allocation in this domain who remain in hospital after study day 28, administration of corticosteroids is at the discretion of the treating clinician.