DEFINITIONS AND PRINCIPLES

Corticosteroids are produced by the cortex of the adrenal glands\(^{(1)}\). There are two main forms - glucocorticoids and mineralocorticoids\(^{(1)}\). The actions of glucocorticoids include gluconeogenesis, fat deposition, sodium retention, decreased protein synthesis and decreased immune response\(^{(1)}\). Examples of glucocorticoids include Cortisol (Hydrocortisone), Prednisolone and Dexamethasone\(^{(1)}\). Mineralocorticoids, such as Fludrocortisone, mainly act on the extracellular balance of sodium and potassium in the distal tubule of the kidney\(^{(1)}\).

Glucocorticoids are commonly used within palliative care in a variety of doses to tackle both specific and non-specific symptoms of advanced cancer\(^{(2)}\). They are commonly referred to as steroids although as explained above they are one form of several corticosteroids\(^{(1)}\). The corticosteroid used most commonly in palliative care is Dexamethasone, see below\(^{(3)}\). The use of corticosteroids within the general medical population is extremely closely monitored and there have been some concerns within the literature that this is not appropriately translated into palliative care patients\(^{(4,5)}\).

These guidelines are designed for all specialist clinicians caring for Palliative Care patients.

PHARMACOLOGY OF CORTICOSTEROIDS

The corticosteroid of choice within palliative care is Dexamethasone but Prednisolone is used at times\(^{(3)}\). Below is a table of approximate anti-inflammatory equivalencies of several corticosteroids\(^{(6)}\).

<table>
<thead>
<tr>
<th>NAME</th>
<th>DOSE (mg)</th>
<th>DURATION OF ACTION (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>20mg</td>
<td>8-12</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5mg</td>
<td>12-36</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75mg</td>
<td>36-54</td>
</tr>
</tbody>
</table>

Dexamethasone has several advantages for patients with malignancy\(^{(6)}\)
- Lower sodium retention potency and hence reduced likelihood of fluid retention
- Ability to administer larger dose with small number of tablets.
- Tablets dispersed in small volumes of water.
- Available as subcutaneous injection.
SIDE EFFECTS

- Doses >4mg od are likely to lead to significant side effects after several weeks\(^{(3)}\).
- Doses <4mg od are often tolerated in patients with a prognosis of months\(^{(3)}\).

*Early effects – days\(^{(6)}\)*
Diabetes mellitus (steroid induced or worsening of established type 1 or type 2 diabetes)
Oral thrush
Fluid retention
Hunger
Mental disturbance – insomnia, agitation, euphoria, paranoia
Additive risk of GI bleed when used with NSAIDS

*Later effects – weeks\(^{(6)}\)*
Cushingoid appearance – moon facies, central obesity, buffalo hump.
Thinning of skin
Increased susceptibility to infection
Proximal muscle wasting and weakness

*Longer term effects - months to years\(^{(6)}\)*
Avascular bone necrosis
Osteoporosis
**PRESCRIBING CORTICOSTEROIDS**

### General Points
- Always clearly document reasons for prescribing steroids\(^{(4,6,7)}\).
- Review treatment regularly and discontinue if no benefit after one week, ensure patients are aware of principle of aiming for short courses of steroids-not long-term medication\(^{(6,7)}\).
- Patients should be made aware of side-effects and the need to report to GP or ward staff if less well on steroids\(^{(6,7,8)}\). They should be given a steroid card\(^{(6)}\).
- Give steroids before 1400hrs to minimize risk of sleep disturbance\(^{(3,8)}\).
- Non-diabetics should be advised to check urinalysis weekly approx 2hrs after lunch and record on monitoring sheet, appendix 1 \(^{(7,11,12,13,14,15)}\). If clinistick demonstrates 3++ glycosuria or patient symptomatic of hyperglycaemia, request patient contact GP/DN for BM check. Diabetic patients will need increased monitoring and adjustment to their usual regimen.
  (For management of steroid induced hyperglycaemia see below.)
- Give gastric protection if also taking NSAIDS, aspirin, oral bisphosphonates or previous GI bleed\(^{(7,9,10)}\).
- Consider prophylactic oral anti-fungals e.g. Nystatin 1ml QDS, if any present or prior symptoms\(^{(5)}\).
- Doses may need to be doubled if patients are also taking enzyme-inducers eg. Phenytoin, Carbamazepine\(^{(3,7)}\). In addition, Carbamazepine and Phenytoin levels can be reduced by corticosteroids and may need to be adjusted\(^{(7)}\).
- Consider switching to Prednisolone if proximal myopathy develops but benefit is still being achieved on Dexamethasone\(^{(5)}\)
- Consider prophylaxis against osteoporosis (eg; Risendronate 35mg once weekly) if patient is on steroids for >3months and prognosis felt to be at least 6 months\(^{(3,16)}\).

### Reduction/Discontinuation\(^{(3,6,8,17)}\)
- If taken <4mg Dexamethasone for <3 weeks, it is generally safe to stop steroids abruptly UNLESS:
  - Patients have had repeated courses of systemic corticosteroids, particularly if taken for >3 weeks.
  - 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.
- If taken Dexamethasone for more than 3 weeks, reduction should not be abrupt but should largely be guided by whether the disease is likely to relapse as steroids are reduced.
  - If the latter is likely to occur, reduce steroids more slowly.
  - If not suggested guidance below:
    - Dexamethasone>2mg daily – reduce the dose by half every 3-5 days.
    - then/or
    - Dexamethasone <2mg daily(near physiological dose) – reduce dose by 0.5mg every 5-7 days or on alternate days to stopping.
Anorexia\(^{(1,3,6,7)}\)
- Is a universal symptom in the dying - often this concerns carers more than the patient.
- Careful discussion and reassurance that deterioration in condition is due to disease process can relieve anxieties about limited food intake.
- If the patient is concerned about poor intake, it may be appropriate to have a trial of steroid therapy.
- If the patient has no appetite undue pressure to eat will cause distress and or nausea.

Appetite / wellbeing\(^{(1,3,6,7)}\)
- Steroids can increase appetite, food intake and sense of wellbeing, although this is usually a short term benefit.
- If appetite not improved steroids should be rapidly tailed off. Progestogens e.g Megestrol Acetate up to 160mg bd, may be prescribed for appetite stimulation or Mirtazapine 15-45mg.

Anti-emetic\(^{(1,3,6,7)}\)
- Thought to enhance anti-emetic tone in medulla.

Pain\(^{(1,3,6,7)}\)
- Mechanism of action not entirely clear but thought to be combination of:
  - an anti-inflammatory effect
  - a reduction in oedema and pressure e.g. nerve compression or raised ICP
  - action on pain transmission through C-fibres.

Dyspnoea\(^{(1,3,6,7)}\)
- Mechanism unclear but some evidence of benefit in lymphangitis carcinomatosis, radiotherapy pneumonitis and airways obstruction.

SVCO/Cord Compression\(^{(1,3,6,7)}\)
- Both are medical emergencies and should be treated with high dose steroids on the basis of clinical suspicion.

NB: See also care guidelines for above symptoms.
MANAGEMENT OF STEROID INDUCED HYPERGLYCAEMIA

- Corticosteroids are known to cause hyperglycaemia and it is recognized that the severity of this is dose related. The peak effect is seen on postprandial glucose and specifically 1-2 hours after meals. Glucose levels normalize overnight without treatment.
- There is a lack of evidence relating to its management in palliative patient population.
- Known diabetics will need adjustment of their regimen and if on a diet/oral regimen possibly conversion to insulin.
- Suggested strategy of monitoring and managing blood sugars for non-diabetic patients on corticosteroids:
  - Monitor urinalysis 1-2hrs after lunchtime meal weekly when commenced on dexamethasone. Monitoring can be relaxed after 6 weeks (median time to development of steroid-induced diabetes) but random checks should continue e.g. twice a month
  - If persistent hyperglycaemia >15mmol/L or symptomatic hyperglycaemia.
    I. Consider reduction in steroid dose, aim for lowest required dose.
    II. Consider benefit/burden of treatment:
      - If treatment indicated – general aim is to avoid hypoglycaemic episodes and minimize symptomatic hyperglycaemia aiming for post-prandial BM 8-15mmol/L.
        (This range may need to be tighter in certain patients e.g. if prognosis months-years.)

TREATMENT OPTIONS:
- Sulphonylureas (24hr secretagogues) e.g. gliclazide can be used but with caution, particularly if poor oral intake/liver metastases, due to long half-life. Monitor and adjust according to postprandial BM 1-2hrs after lunch checked 1-2xweekly.
- Once daily insulin administered in the morning and titrated to response, e.g. Glargine/Insulatard - common starting dose 10 units daily. Adjust dose according to postprandial blood sugars – 1-2hrs after lunch checked 1-2xweekly.
- If insulin unacceptable/impractical, consider pre-meal insulin secretagogue e.g nateglinide before breakfast and lunch only. The dose can be omitted if meal missed. Monitor postprandial blood sugars – 1-2hrs after lunch checked 1-2xweekly.

ALWAYS review regularly and remember reduction in steroids will reduce requirements for hypoglycaemic agents.

STEROIDS AT THE END OF LIFE
There is a lack of evidence over discontinuation of steroids at the end of life and each case should be considered in terms of the reason for taking the steroids, dose and duration along with burden of administering the steroids either orally or subcutaneously. Ideally the decision should be discussed with the patient and/or relatives.
STANDARDS

1. Dexamethasone is the corticosteroid of choice.
2. Corticosteroids should be prescribed for a recognised indication.
3. Before prescribing corticosteroids, the benefits and possible side effects should be discussed with the patient where possible.
4. Corticosteroids should be administered before 1400hrs to avoid sleep disturbance.
5. Clinical response, side effects and dose should be reviewed at regular intervals to ensure the MINIMUM effective dose is used.
6. Patients on corticosteroids should carry a steroid card.
7. Patients should have urinalysis checked 1-2hours after lunch weekly for at least 6 weeks after starting steroids or dose increase.
8. Gastric protection should be prescribed for all patients with a history of peptic ulcer disease or if they are also taking NSAID’s, aspirin or oral bisphosphonates.
9. Bisphosphonate prophylaxis should be considered for any patients who have been on corticosteroids for more than 3months and who are felt to have a prognosis of 6months.
REFERENCES

12. Braithwaite SS, Barr WG, Rahman A, Quddusi S. MANAGING DIABETES DURING GLUCOCORTICOID THERAPY How to avoid metabolic emergencies Postgraduate Medicine: Volume 104: No.5
APPENDIX 1.

Attach to patients steroid card for recording their urinalysis.

<table>
<thead>
<tr>
<th>DATE (1-2hrs after lunch)</th>
<th>STEROID DOSE</th>
<th>URINALYSIS (Circle result)</th>
<th>DATE (1-2hrs after lunch)</th>
<th>STEROID DOSE</th>
<th>URINALYSIS (Circle result)</th>
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<tbody>
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<td>0 + ++ +++</td>
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IF URINALYSIS SHOWS ++++, PLEASE CONTACT YOUR GP

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