Summary of Clinical Guideline for the Use of Corticosteroids in Haematology

Indications for corticosteroid therapy
- Autoimmune haemolytic anaemia
- Idiopathic thrombocytopenic purpura
- Prevention of Graft versus Host Disease
- Thrombotic thrombocytopenic purpura
- Cryoglobulinaemia
- Treatment of lymphoid malignancies
- Infectious mononucleosis

Absolute contra-indications to Steroids
- Known sensitivity to prednisolone
- Systemic infection (unless specific anti-microbial therapy given)

Relative contra-indications
- Adrenal suppression
- Infection
- Children and adolescents
- Elderly (close supervision required)
- Tuberculosis (close supervision required)
- Hypertension (close supervision required)
- Recent myocardial infarction (cardiac rupture reported)
- Congestive cardiac failure
- Fluid retention
- Liver failure
- Renal impairment
- Diabetes mellitus
- Osteoporosis
- Glaucoma
- Hyperthyroidism
- Pregnancy and breast feeding

Investigations prior to corticosteroid therapy

History to exclude
- Tuberculosis
- Pregnancy
- Chronic infection - consider amoebiasis and strongyloidiasis
- Ocular infections and glaucoma

Investigations
- Full blood count
- U & E, creatinine and LFTs, blood glucose and/or urine dipstick for glucose
- Thyroid function
- Blood glucose and/or urine dipstick for glucose
- Chest X-ray
- Antibody levels for chicken-pox
- Consider initial and sequential bone densitometry in those at risk of osteoporosis
Dose and Administration

Give the lowest doses and shortest course needed to control the disease. Discuss the major side effects with the patients. Pharmacy will give them a copy of the manufacturer’s patient information leaflet and a steroid card. Patients should carry the steroid card for one year after finishing treatment. Start with prednisolone at 0.5-1 mg/kg. In severe disease treatment may be started with i.v. methylprednisolone 0.5-1.0 g daily for three days followed by oral prednisolone once a day in the morning. Remember carbemazipine, phenytoin, phenobarbitone and rifampicin reduce efficacy of steroids.

Prevention of gastro-intestinal bleeding – give lansoprazole 30 mg o.d. if concurrent NSAIDs are used or if daily dose of corticosteroids > 30 mg prednisolone.

Chicken Pox – if exposed to chickenpox, patients who are receiving systemic corticosteroids or have received them in the last three months and have not had chicken pox and/or had no detectable antibody should be given passive anti-varicella-zoster immunoglobulin.

Measles – patients should avoid exposure to measles and to seek medical advice urgently if exposed. Prophylaxis with normal immunoglobulin may be needed.

Monitor for side effects

- rapidly evident side effects are hyperglycaemia, mental disturbance and insomnia
- gastro-intestinal disturbance
- proximal myopathy, osteoporosis
- adrenal suppression, menstrual irregularities and Cushing's syndrome, hirsutism, weight gain and increased appetite
- increased susceptibility to infection including ophthalmic infections
- ophthalmic effects including glaucoma, papillodema, posterior cataracts and corneal thinning
- hypertension

For long-term treatment

- Reduce pituitary adrenal suppression by giving steroids once daily in the morning or alternate days.
- Reduce glucocorticoid side effects by adding a small dose of another immunosuppressive drug e.g. azothioprine.
- In those taking > 7.5 mg prednisolone per day for more than 3 months, assessed and reduce osteoporosis by giving biphosphonate such as alendronate or risedronate, calcitriol or hormone replacement (HRT in women, testosterone in men) as appropriate.

Withdrawal of steroids

- The Committee of Safety of Medicines has recommended that gradual withdrawal of systemic steroids should be considered in those whose disease is unlikely to relapse and have
  - Recently received repeated courses
  - Taken a short course within one year of stopping long term therapy.
  - Have other causes of adrenal suppression e.g. iron overload
  - Received more than 40 mg prednisolone per day or equivalent for more than three weeks
  - Been given repeated doses in the evening

During withdrawal of corticosteroids the dose may be rapidly reduced to physiological doses, equivalent to prednisolone 7.5 mg per day and then reduce more slowly.
Oxford Haematology Department

Clinical Guideline for the use of Corticosteroids in Haematology patients

Aims of Treatment

Glucocorticoids have profound anti-inflammatory activities and have been used for over fifty years to suppress abnormal and unwanted immune reactions and to treat leukaemia. These drugs bind to specific receptors in lymphocytes and reduce expression of the c-myc and so induce apoptosis in these cells.

All corticosteroids have both mineralocorticoid and glucocorticoid activity. Prednisolone has predominantly glucocorticoid activity and is the most commonly used oral corticosteroid for long-term disease suppression.

Prednisone has a similar level of activity but is only active after conversion in the liver to prednisolone and is therefore not recommended for use.

In terms of equivalent anti-inflammatory effects 5 mg of prednisolone has the same effect as 20 mg of hydrocortisone, 4 mg of methylprednisolone and 0.75 mg of dexamethasone. There is some evidence that dexamethasone has a greater lymphocytotoxic activity than prednisolone in relation to their glucocorticoid activity.

Prednisolone is used in a number of regimes including CHOP and its derivative, methylprednisolone, in CVAMP for myeloma. Dexamethasone is used in chemotherapy regimes VAD and alone. A comparison of the efficacy of dexamethasone and prednisolone in the treatment of ALL in children is in progress. However, prednisolone remains the drug of choice for immunosuppression in non-malignant conditions.

These beneficial effects of steroid therapy must always be balanced against the predictable and sometimes serious side effects of these drugs. In other diseases, e.g. rheumatoid arthritis, long term steroid use is an independent predictor of mortality.

Suppression of normal adrenal function may have devastating consequences during intercurrent illness or surgical emergency. The lack of normal adrenal function in a patient who has taken long term steroids may cause fever, myalgia, arthralgia, runny nose, itchy skin, weight loss and fatigue and under stress, such as infection, may cause hypotension and shock.

Anaesthetists must therefore be aware of steroid therapy to avoid peri- or post-operative hypotension and shock. So patients must carry cards giving details of the dosage of steroids and potential complications (Appendix 1).

Following concerns about susceptibility to chicken-pox in patients taking long-term systemic steroid the CSM has issued a notice that every patient prescribed systemic corticosteroids should receive patient information leaflets supplied by the manufacturer (Appendix 2).
Indications for corticosteroid therapy

Corticosteroids are used to reduce disease activity and to restore normal blood cell counts in:

- **Autoimmune haemolytic anaemia** – response rate is 70%-90%, the remainder of patients receive no benefit. Sustained response after stopping steroids is seen in 20%-30% of patients, while 60% of patients require maintenance and/or experience repeated relapse. The response is almost always evident by one week.

- **Idiopathic thrombocytopenic purpura** – clinical response is seen in 70-90% of patients. Complete remission with normal platelet count is seen in 50-60% of patients. Fewer patients experience sustained remission. Response is usually seen in 1-2 days but occasionally seen after 1-2 months (one wonders here whether this is actually related to steroid therapy).

- **Prevention of Graft versus Host Disease** – used according to protocol.

- **Thrombotic Thrombocytopenic Purpura** – given as an immunosuppressive dose of prednisolone 1mg/kg from initiation of plasmapheresis according to clinical guidelines for the treatment of TTP in the Department of Haematology.

- **Cryoglobulinaemia** – In addition to therapy of underlying disease in patients with progressive renal disease, neurological involvement or disabling manifestations.

- **Malignant Disease** - Steroids are used in the treatment of acute lymphocytic leukaemia, chronic lymphocytic leukaemia, lymphoma and plasma cell myeloma according to established chemotherapy protocols.

- **Infectious mononucleosis** – steroids are indicated when infectious mononucleosis is complicated by AIHA, ITP, progressive neurological involvement or incipient airways obstruction. Resolution of fever, reduction of lymphoid hyperplasia occurs in 24 hours.

- **Steroids** have been used in a number of haematological conditions but their use is ill defined in:
  - Hypercalcaemia due to malignant disease
  - DIC
  - “Lupus” inhibitors
  - Antibodies to factor VIII
  - Radiation pneumonitis

**Absolute Contra-Indications to Steroids**

- Known sensitivity to prednisolone
- Systemic infection (unless specific anti-microbial therapy given)
Relative contra-indications

- Adrenal suppression
- Infection
- Children and adolescents
- Elderly (close supervision required)
- Tuberculosis (close supervision required)
- Hypertension (close supervision required)
- Recent myocardial infarction (cardiac rupture reported)
- Congestive cardiac failure
- Fluid retention
- Liver failure
- Renal impairment
- Diabetes mellitus
- Osteoporosis
- Glaucoma
- Hyperthyroidism
- Pregnancy
- Breast feeding

Pregnancy and Breast Feeding

Corticosteroids vary in ability to cross the placenta. Betamethasone and dexamethasone cross the placenta readily but 90% of prednisolone is inactivated as it crosses the placenta. The clinical effects of steroids in pregnancy are summarised as follows:

- there is no convincing evidence of congenital abnormalities following steroid administration
- short courses of steroids, for example those given as prophylaxis against neonatal respiratory distress, show no signs of causing side effects
- intrauterine growth can be reduced by prolonged or repeated corticosteroid administration during pregnancy
- adrenal suppression in the neonate following pre-natal exposure usually resolves spontaneously after birth and is rarely clinically important
- prednisolone appears in small amounts in breast milk but doses up to 40 mg are unlikely to cause systemic effects in infants.

For AIHA, ITP and NAIT, intravenous immunoglobulin would be an alternative treatment to steroids.

While prednisolone appears to be the best-tolerated and safest corticosteroid in pregnancy, clearly pregnancy and lactation are relative contra-indications to the use of this medicine.

Investigations prior to corticosteroid therapy

History to exclude

- Tuberculosis
Pregnancy
Chronic infections - consider amoebiasis and strongyloidiasis
Ocular infections
Chicken-pox

Investigations

- Full blood count
- U & E, creatinine and LFTs
- Thyroid function
- Blood glucose and/or urine dipstick for glucose
- Chest X-ray
- Antibody levels for chicken-pox
- Consider initial and sequential bone densitometry in those with history of osteoporosis, men over 50 and post-menopausal women

Dose and Administration

For malignant conditions prednisolone is given according to protocol and administration will not be discussed further.

For non-malignant haematological conditions systemic treatment is of course essential. Give the lowest dose and shortest course needed to control the disease. Discuss the major side effects with the patients. Pharmacy will give them a copy of the manufacturer’s patient information leaflet and a steroid card. Patients should carry the steroid card for one year after finishing treatment.

Start with prednisolone at 0.5-1 mg/kg. In severe disease treatment may be started with a short course of i.v. methylprednisolone 0.5-1.0g daily for three days followed by oral prednisolone once a day in the morning.

The initial prednisolone dose is continued treatment for two weeks. If the response is poor, reassess and confirm the diagnosis and where appropriate consider adding or changing immunosuppressive therapy. Once remission is achieved reduce the dose over 1-3 months depending on the severity of the initial disease to 7.5 mg per day and then more slowly and where possible on alternate days (see below).

Prevention of gastro-intestinal bleeding with proton pump inhibitors (PPI).

Corticosteroids may increase the risk of gastro-intestinal bleeding. Give PPI (lansoprazole 15-30 mg o.d.) if concurrent NSAIDs are used or if daily dose of corticosteroids > 30 mg prednisolone.

Chicken Pox

Patients taking corticosteroids are susceptible to severe chicken pox. They are at risk of serious disease unless they have had previous infection. Susceptible patients may present with pneumonia, hepatitis, or DIC. Rash may not be prominent. Passive anti-varicella-zoster immunoglobulin should be given to patients exposed to chicken pox and who are receiving systemic corticosteroids or have received them in the last three months and have not had chicken-pox and/or had no detectable antibody. This risk should be made clear to patients at the start of therapy.
Patients taking systemic corticosteroids are also at risk of severe measles. Patients should be advised to take particular care to avoid exposure to measles and to seek medical advice urgently if exposed. Prophylaxis with normal immunoglobulin may be needed.

For long-term treatment

- Reduce pituitary adrenal suppression by giving steroids once daily in the morning or alternate days. This has been used in the management of inflammatory bowel disease but no randomised controlled trials have been published for alternate day use of steroids in haematological conditions.

- Reduce glucocorticoid side effects by adding a small dose of another immunosuppressive drug e.g. azathioprine.

- The greatest risk of bone mineral loss is in the first 6-12 months of therapy. Patients taking > 7.5 mg prednisolone per day for more than 3 months should be assessed and where necessary given treatment. Reduce osteoporosis by giving biphosphonate such as alendronate or risedronate, calcitriol or hormone replacement (HRT in women, testosterone in men) in those who are deficient.

Withdrawal of steroids

- The Committee of Safety of Medicines has recommended that gradual withdrawal of systemic steroids should be considered in those whose disease is unlikely to relapse and have
  - Recently received repeated courses
  - Taken a short course within one year of stopping long term therapy
  - Have other causes of adrenal suppression e.g. iron overload
  - Received more than 40 mg prednisolone per day or equivalent for more than three weeks
  - Been given repeated doses in the evening.

Systemic steroids may be stopped abruptly in those whose treatment is unlikely to relapse and have received treatment for three weeks or less and are not in the groups described above. In practice most patients receiving steroids for treatment of an immunohaematological condition will have received several weeks therapy at high dose and thus gradual withdrawal of steroid should be implemented.

During withdrawal of corticosteroids the dose may be rapidly reduced to physiological doses, equivalent to prednisolone 7.5 mg per day and then reduce more slowly. Clearly the activity of the disease has to be monitored carefully to detect a relapse.

Side effects

Monitor for side effects

Rapidly evident side effects are hyperglycaemia and mental disturbance

Other side effects appearing over weeks to years are:
• Gastrointestinal - including dyspepsia, peptic ulcer and perforation, abdominal distension, acute pancreatitis and candidiasis

• Musculoskeletal including proximal myopathy, osteoporosis

• Endocrine including adrenal suppression, menstrual irregularities and Cushing's syndrome, hirsutism, weight gain and increased appetite

• Increased susceptibility to infection

• Neuropsychiatric effects including euphoria or depression, paranoia, insomnia, increasing intracranial pressure and on withdrawal include frank psychosis and aggravation of epilepsy

• Ophthalmic effects including glaucoma, papillodema, posterior cataracts corneal thinning and exacerbation of ophthalmic viral or fungal infections

• Other effects - impaired healing, skin atrophy and bruising, myocardial rupture after recent infarction, leukocytosis thromboembolism, nausea, malaise and hiccups

• Mineralocorticoid side effects including hypertension, sodium and water retention and potassium loss occur only slightly with prednisolone and close relatives

Drug Interactions

Remember carbemazipine, phenytoin, phenobarbitone and rifampicin increase the metabolism of corticosteroids and reduce their efficacy.

References

Acute Lymphoblastic Leukaemia 97 Protocol, Medical Research Council, UK.


Immunosuppressive drugs and their complications. Drugs Therp Bull 1994 32:66-70

