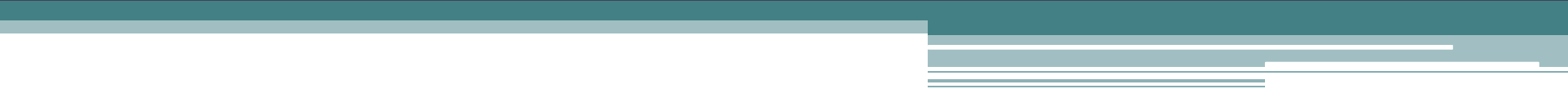


Steroids Use and Abuse

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Synthesis of Corticosteroids

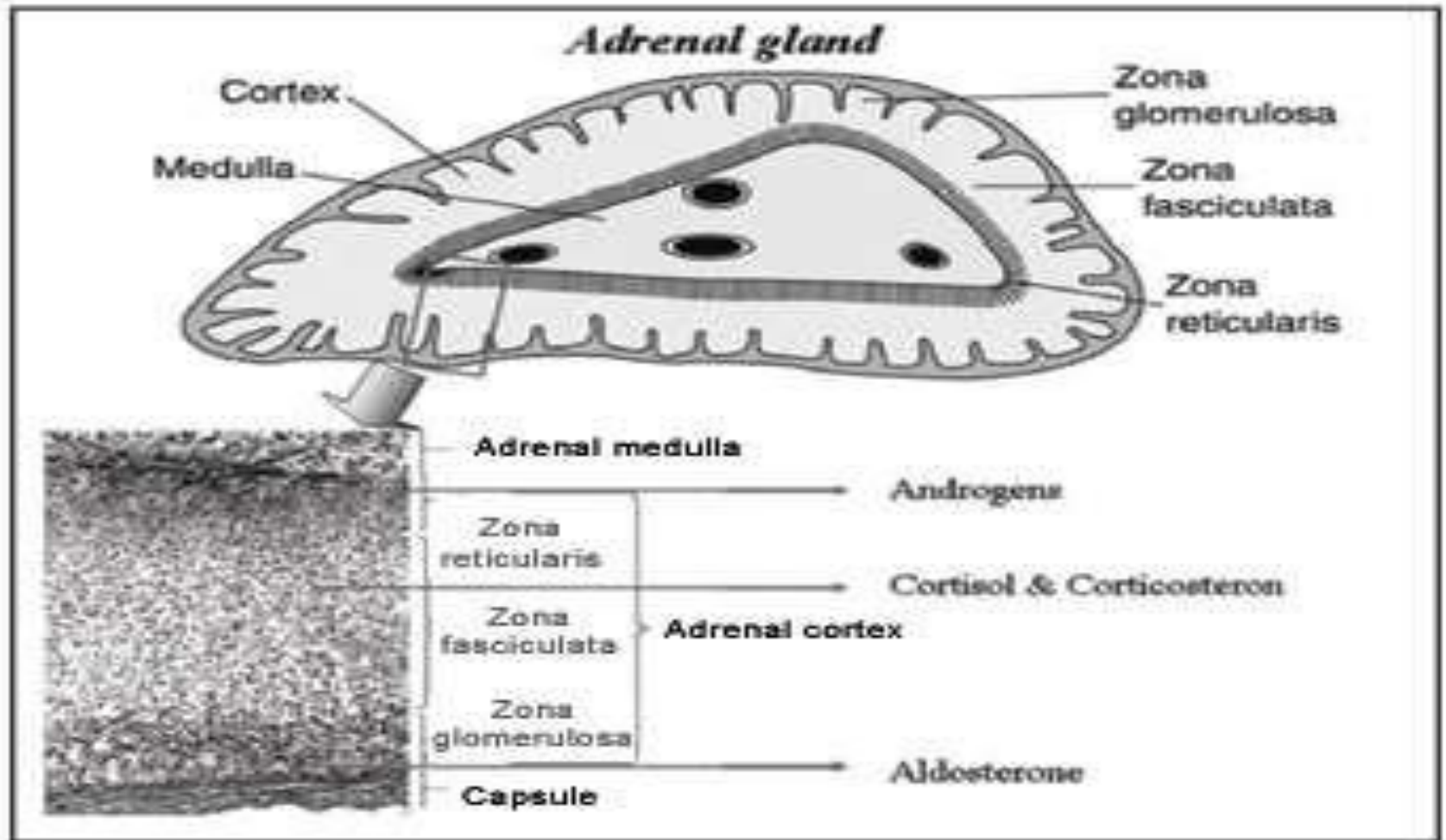


Figure 1 – Main Hormones Secreted by Cortex of Adrenal Gland

Types of Corticosteroids

Medscape®

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Corticosteroid	Relative Antiinflammatory Activity	Relative Mineralocorticoid Activity	Equivalent Dose (mg)	Plasma Half-life (min)
Cortisone	0.8	0.8	25	30
Hydrocortisone	1.0	1.0	20	90
Prednisone	4.0	0.8	5	60
Prednisolone	4.0	0.8	5	200
Triamcinolone	5.0	0.0	4.0	300
Methylprednisolone	5.0	0.0	4.0	180
Betamethasone	25.0	0.0	0.75	100–300
Dexamethasone	25–30	0.0	0.75	100–300
Fludrocortisone	10	125	—	200

Source: Pharmacotherapy © 2007 Pharmacotherapy Publications

Actions of Corticosteroids

- **Metabolic**
- **Anti-inflammatory**
- **Immunosuppressive**

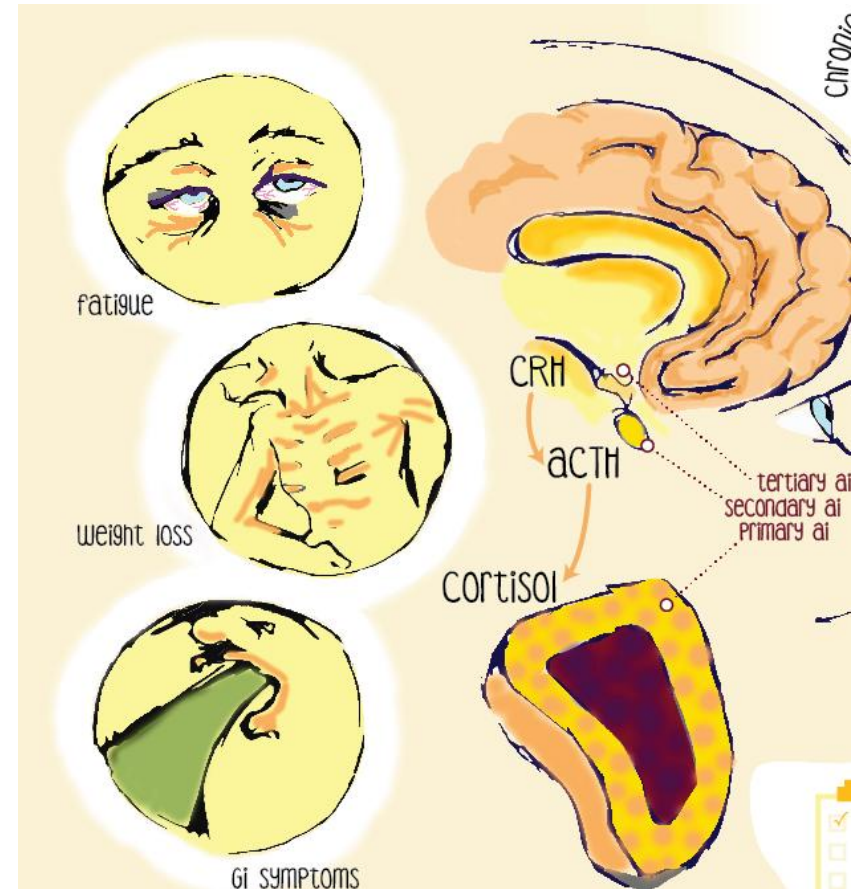
Uses Of Steroids

- Replacement therapy:

Adrenocortical Insufficiency:

a) Chronic adrenal insufficiency:

About 15-25 mg of hydrocortisone must be given PO daily in divided doses, with increased amounts during periods of stress. It must be supplemented with 100-150 mcg/day of fludrocortisone acetate for salt retention activity.



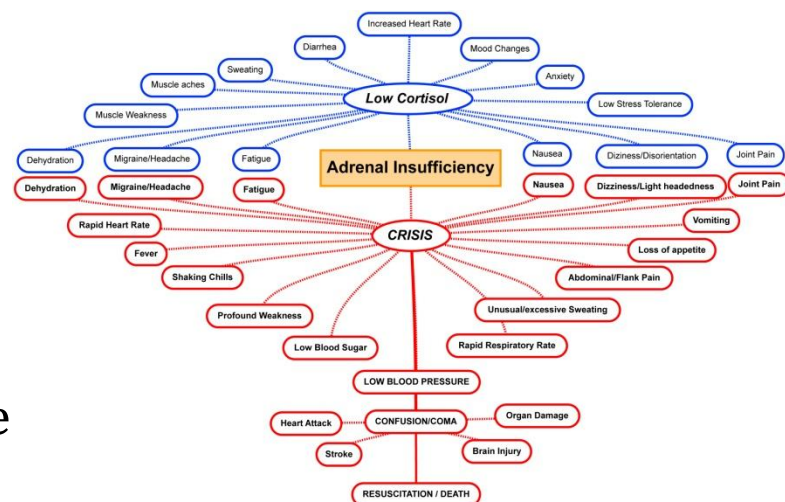
Uses Of Steroids

- Replacement therapy:

Adrenocortical Insufficiency:

Acute (Addisonian Crisis): Bolus injection of 100 mg hydrocortisone, followed by the administration of 100–200 mg hydrocortisone over 24 h, either by continuous infusion or provided by several IV or IM injections.

Mineralocorticoid replacement can be initiated once the daily hydrocortisone dose has been reduced to <50 mg because at higher doses hydrocortisone provides sufficient stimulation of mineralocorticoid receptors. As the patient stabilizes, the hydrocortisone dose may be decreased to 25 mg every 6-8 hours.



Congenital Adrenal Hyperplasia:

The typical oral dose of hydrocortisone in children is 1-1.5 times the normal cortisol production (about 10-15 mg/m² daily) in two or three divided doses.

The mineralocorticoid used is fludrocortisone acetate (0.05-0.2 mg/day). Therapy is guided by gain in weight and height, by plasma levels of 17-hydroxyprogesterone, and by blood pressure.

In adults, prednisone may be given in lowest possible dose to suppress excess androgen production.

To suppress fetal adrenal androgen production effectively and consequent virilization, glucocorticoid therapy (e.g., dexamethasone, 20 mcg/kg taken daily orally by mothers at risk) must be initiated before 10 weeks of gestation, before a definitive diagnosis of CAH can be made.

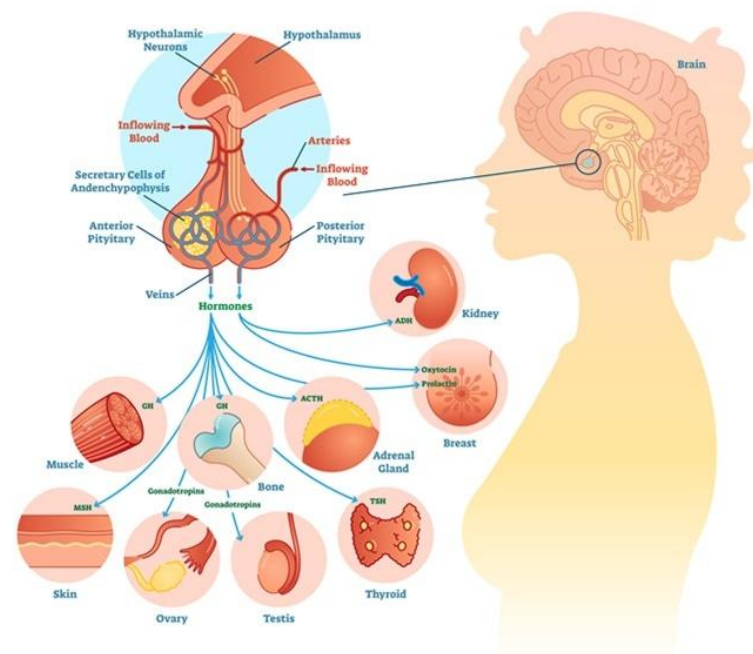
Cushing's disease (Post adrenalectomy)

Upto 300 mg of hydrocortisone is given as continuous infusion on the day of surgery. The dose must be tapered gradually to normal replacement level thereafter.

Sheehan's Syndrome

Glucocorticoids should be replaced before thyroid hormone. Estrogen is given alone if patient has gone under hysterectomy otherwise in combination with progesterone. Future pregnancies may be possible with combined preparations of LH and FSH.

PITUITARY GLAND



Non Endocrine Uses

Allergic reactions

In severe disease, intravenous glucocorticoids (methylprednisolone, 125 mg intravenously every 6 hours, or equivalent) are appropriate.

In less severe disease, antihistamines are the drugs of first choice.

In allergic rhinitis, intranasal steroids are now viewed as the drug of choice by many experts.

•**Bronchial Asthma:**

- Intravenous administration of 60-120 mg methylprednisolone (or equivalent) every 6 hours is used initially for an acute attack. Prednisone or prednisolone 30-45 mg PO once daily for 5-10 days is used thereafter.

Inhaled Corticosteroids (ICS) are the most effective controllers for asthma (mild persistent, moderate persistent and severe persistent).

Chronic Obstructive Pulmonary Disease

For stable patients: Available data suggest that inhaled glucocorticoids reduce exacerbation frequency by ~25%.

For Acute exacerbation: The GOLD guidelines recommend 30-40 mg of oral prednisolone or its equivalent for a period of 10-14 days.

•**Stimulation of Lung Maturation in the Fetus:**

- Betamethasone (12 mg intramuscularly every 24 hours for two doses) or dexamethasone (6 mg intramuscularly every 12 hours for four doses) is administered to women with definitive signs of premature labor between 26 and 34 weeks of gestation.

Connective Tissue Disorders:

Rheumatoid Arthritis:

Glucocorticoids may serve in several ways to control disease activity in RA. First, they may be administered in low to moderate doses to achieve rapid disease control before the onset of fully effective DMARD therapy.

Second, a 1-2 week burst of glucocorticoids may be prescribed for the management of acute disease flares.

Cont...

- Chronic administration of low doses(5-10 mg/d) of prednisone may also be warranted to control disease activity in patients with an inadequate response to DMARD therapy.
- In the setting of an acute exacerbation, higher doses of glucocorticoids may be employed (typically 20-40 mg/day of prednisone or equivalent), with rapid taper thereafter.

Cont...

- Symptomatic effect of small reductions in dose (decreases of perhaps 1 mg/day of prednisone every 2- 3 weeks) should be tested frequently while concurrent therapy with other measures is continued, to maintain the lowest possible prednisone dose.

- **Systemic Lupus Erythematosus (SLE):**

In non life threatening disease, if quality of life is inadequate inspite of treatment with NSAIDS and Hydroxychloroquine, treatment with low doses (0.07-0.3mg/kg per day) of systemic glucocorticoids may be necessary.

In life threatening SLE (proliferative form of lupus nephritis), 0.5-1 mg/kg per day PO or 1000mg of methylprednisolone I/V daily for 3 days followed by 0.5-1 mg/kg of daily prednisone or equivalent is given.

•Giant cell arteritis(Temporal Arteritis) and Polymyalgia Rheumatica:

- Treatment begins with prednisone 40-60 mg/day for ~ 1 month, followed by gradual tapering. When ocular signs and symptoms occur, consideration should be given for the use of methylprednisolone 1000 mg daily for 3 days to protect vision. Symptom recurrence during prednisone tapering develops in 60-85% of pts, requiring a dose increase.

Patients with isolated polymyalgia rheumatica respond promptly to prednisone, which can be started at a lower dose of 10-20 mg/d.

Vasculitis syndromes

- **Takayasu's Arteritis:** Although glucocorticoid therapy in doses of 40-60 mg prednisone per day alleviates symptoms, there are no convincing studies that indicate that they increase survival.
- **Idiopathic cutaneous vasculitis:** therapy started as prednisone 1 mg/kg per day with rapid tapering where possible, either directly to discontinuation or by conversion to an alternate day regimen followed by ultimate discontinuation.
- **Granulomatosis with polyangiitis(Wegener's):** Along with Cyclophosphamide and Rituximab for disease remission.

Cont...

- **Churg Strauss Syndrome** : Glucocorticoids alone appear to be effective in many patients. Dosage tapering is often limited by asthma, and many pts require low dose prednisone for persistent asthma many years after clinical recovery from vasculitis.
- **Polyarteritis nodosa**: In combination with cyclophosphamide.
- **Henoch – Schonlein Purpura**: Prednisone 1mg/kg per day and tapered according to clinical response has been shown to be useful in decreasing tissue edema, arthralgias and abdominal discomfort.
- **Microscopic Polyangiitis**: Similar to Wegener's.

Behcet's syndrome: Uveitis and CNS – Behcet's syndrome require systemic glucocorticoid therapy(prednisone, 1 mg/kg per day).

Relapsing Polychondritis: Prednisone 40-60 mg/d is effective in suppressing disease activity. It is tapered gradually once disease is controlled.

Systemic Sclerosis: Glucocorticoids may be useful for alleviating stiffness and aching in early stage diffuse cutaneous SSc. Their use in high doses is associated with an increased risk of scleroderma renal crisis.

Sarcoidosis: Corticosteroids are indicated therapy for patients with debilitating symptoms or life-threatening forms of sarcoidosis. Patients who are symptomatic with multiple organs involvement are treated with 20- 40 mg per day of prednisone, or an equivalent dose of alternative steroids, to induce remission.

Maintenance doses, which often are required for long periods of time, is usually 5-10 mg/day of prednisone.

Osteoarthritis: Intraarticular injections of glucocorticoids relieves local inflammation and pain.

Acute Gouty arthritis: Glucocorticoids given I / M or orally , e.g., prednisone 30-50 mg/day as the initial dose and gradually tapered with the resolution of the attack, can be effective in polyarticular gout. For a single joint or a few involved joints, intraarticular triamcinolone acetonide, 20-40 mg, or methylprednisolone, 25-50 mg, have been effective and well tolerated.

Immune Thrombocytopenia: In immune thrombocytopenia, prednisone (0.5 mg/kg) is used to decrease the bleeding tendency. In more severe cases, and for initiation of treatment of idiopathic thrombocytopenia, daily doses of prednisone (1-1.5 mg/kg) are employed. Patients with refractory idiopathic thrombocytopenia may respond to pulsed high-dose glucocorticoid therapy.

Autoimmune hemolytic anemia: Patients with autoimmune destruction of erythrocytes (i.e., hemolytic anemia with a positive Coombs test) are treated with prednisone (1 mg/kg per day). In the setting of severe hemolysis, higher doses may be used, with tapering as the anemia improves. Small maintenance doses may be required for several months in patients who respond.

Skin Graft and Organ transplant: In organ transplantation, high doses of prednisone (50-100 mg) are given at the time of transplant surgery, in conjunction with other immunosuppressive agents, and most patients are kept on a maintenance regimen that includes lower doses of glucocorticoids.

Malignancies: Glucocorticoids are used in the chemotherapy of ALL and lymphomas because of their antilymphocytic effects. Most commonly, glucocorticoids are one component of combination chemotherapy administered under scheduled protocols. Glucocorticoids once were frequently employed in the setting of hypercalcemia of malignancy, but more effective agents, such as the bisphosphonates, now are the preferred therapy.

Renal Diseases

- **Nephrotic Syndrome:** Patients with nephrotic syndrome secondary to minimal change disease generally respond well to steroid therapy, and glucocorticoids clearly are the first-line treatment in both adults and children. Initial daily doses of prednisone are 1-2 mg/kg for 6 weeks, followed by a gradual tapering of the dose over 6-8 weeks, although some nephrologists advocate alternate-day therapy. Objective evidence of response, such as diminished proteinuria, is seen within 2-3 weeks in 85% of patients, and >95% of patients have remission within 3 months.

Cont...

- Studies with other forms of renal disease, such as membranous and membranoproliferative glomerulonephritis and focal sclerosis, have provided conflicting data on the role of glucocorticoids. In clinical practice, patients with these disorders often are given a therapeutic trial of glucocorticoids with careful monitoring of laboratory indices of response.
- In the case of membranous glomerulonephritis, many nephrologists recommend a trial of alternate-day glucocorticoids for 8-10 weeks (e.g., prednisone, 120 mg every other day), followed by a 1 to 2 month period of tapering.

Gastrointestinal diseases

- **Inflammatory Bowel Diseases:** Prednisone is usually started at doses of 40-60 mg/d for active Ulcerative Colitis that is unresponsive to 5-ASA therapy.
- Parenteral glucocorticoids may be administered as hydrocortisone, 300mg/d or methylprednisolone, 40-60 mg/d.
- Topically applied glucocorticoids are also beneficial for distal colitis and may serve as adjunct in those having rectal involvement.
- Hydrocortisone enema or foam may control active disease, although they have no proven role as maintenance therapy.

Cont...

- Steroids are also effective for treatment of moderate to severe Crohn's disease and induce a 60-70 % remission.
- Controlled ileal-release budesonide has been nearly equal to prednisone for ileocolonic CD. Budesonide is used for 2-3 months at a dose of 9 mg/d, then tapered. Budesonide 6 mg/d is effective in reducing relapse rates.
- Once clinical remission has been induced, steroids should be tapered usually at a rate of no more than 5 mg/week.

Hepatic Diseases

- **Autoimmune Hepatitis:** Therapy is initiated with prednisone 60 mg/day. This dose is tapered successively over the course of a month down to a maintenance level of 20 mg/d according to fall in serum transaminases levels. An alternative approach is to begin with half the prednisone dose (30 mg/d) along with azathioprine. Prednisone is then tapered over the course of a month to 10 mg/d.
- **Alcoholic Hepatitis:** Pts with severe disease should be given prednisone 40 mg/d or prednisolone 32 mg/d for 4 weeks followed by tapering.

Neurological Diseases

1. Reduction of Cerebral Edema:

Corticosteroids are of value in the reduction or prevention of cerebral edema associated with parasites (Neurocysticercosis) and neoplasms.

In Brain tumours, glucocorticoids are highly effective at reducing perilesional edema and improving neurologic function, often within hours of administration.

Dexamethasone has been the glucocorticoid of choice because of its relatively low mineralocorticoid activity. Initial doses are typically 12 mg to 16 mg a day in divided doses given orally or IV (both are equivalent). Consequently, a taper is indicated as definitive treatment is administered and the patient improves.

Cont...

- **Acute Bacterial Meningitis:** The rationale for giving dexamethasone 20 min before antibiotic therapy is that dexamethasone inhibits the production of TNF-alpha by macrophages and microglia only if it is administered before these cells are activated by endotoxin. Therapy with dexamethasone should ideally be started 20 min before, or not later than concurrent with, the first dose of antibiotics.
- **Tuberculous Meningitis:** Dexamethasone therapy is recommended for HIV-negative patients with tuberculous meningitis. The dose is 12–16 mg per day for 3 weeks, then tapered over 3 weeks.

Table. Recommended dosage regimens of corticosteroids in extrapulmonary TB.^{41,42} (*Adapted from Thwaites et al¹¹*)

Clinical Condition	Regimen
Tubercular meningitis (Stage 1)*	<i>Total duration 6 weeks</i> Inj. Dexamethasone 0.3 mg/kg i.v. Day 1-7; 0.2mg/kg i.v. Day 8-14; 0.1 mg/kg i.v. Day 15-21 Followed by Tab. Dexamethasone 3 mg/day orally Days 22-28; 2 mg/day orally Day 29-35; 1 mg/day orally Day 36-42
Tubercular meningitis (Stages 2 and 3)*	<i>Total duration 8 weeks</i> Inj. Dexamethasone 0.4 mg/kg i.v. Day 1-7; 0.3 mg/kg i.v. Day 8-14; 0.2 mg/kg i.v. Day 15-21; 0.1 mg/kg Day 22-28 Followed by Tab. Dexamethasone 4 mg/day orally Days 29-35; 3 mg/day orally Day 36-42; 2 mg/day orally Day 43-49; 1 mg/day orally Day 50-56
Tubercular pericardial effusion	<i>Total duration 11 weeks</i> Tab. Prednisolone 60 mg/day[†] orally Day 1-28; 30 mg/day[†] orally Day 29-56; 15 mg/day[†] orally Day 57-70; 5 mg/day orally Day 71-77

*=Stage 1, Glasgow coma scale (GCS) score 15 and no focal neurological deficits; Stage 2, GCS score 11-14 or focal neurological deficits present; Stage 3, GCS score less than 11

[†]=Administered as three divided doses in the Transkei trials;^{14,15} i.v.=intravenous.

Cont...

- **Multiple Sclerosis:** For acute attacks or initial demyelinating episodes, intravenous methylprednisolone, 500–1000 mg/d for 3–5 days, either without a taper or followed by a course of oral prednisone beginning at a dose of 60–80 mg/d and gradually tapered over 2 weeks is given.
- **Bell's Palsy :** A course of glucocorticoids, given as prednisone 60–80 mg daily during the first 5 days and then tapered over the next 5 days, modestly shortens the recovery period and improves the functional outcome.

Cont...

- **Chronic Inflammatory Demyelinating Disease (CIDP) :** 60–80 mg prednisone PO daily for 1–2 months, followed by a gradual dose reduction of 10 mg per month as tolerated.
- **Myasthenia Gravis:** The initial dose is relatively low (15–25 mg/d) . The dose is increased stepwise, as tolerated by the patient (usually by 5 mg/d at 2- to 3- day intervals), until there is marked clinical improvement or a dose of 50–60 mg/d is reached. This dose is maintained for 1–3 months and then is gradually modified to an alternate-day regimen over the course of an additional 1–3 months

Cont...

- **Spinal Cord Injury:** A meta-analysis of several randomized, controlled trials (Bracken, 2002) demonstrated significant decreases in neurological defects in patients with acute spinal cord injury treated within 8 hours of injury with large doses of methylprednisolone sodium succinate (30 mg/kg initially followed by an infusion of 5.4 mg/kg per hour for 23 hours).
- **Duchene's Muscular Dystrophy:** Glucocorticoids, administered as prednisone in a dose of 0.75 mg/kg per day significantly slow progression of Duchenne's dystrophy for up to 3 years.

Infectious Diseases

- **Septic shock:** Hydrocortisone (50 mg IV every 6 h) should be given; if clinical improvement occurs over 24– 48 h, most experts would continue hydrocortisone therapy for 5–7 days before slowly tapering and discontinuing it.
- In AIDS patients with *Pneumocystis carinii* pneumonia and moderate to severe hypoxia, addition of glucocorticoids to the antibiotic regimen increases oxygenation and lowers the incidence of respiratory failure and mortality. Similarly, glucocorticoids clearly decrease the incidence of long-term neurological impairment associated with *Haemophilus influenzae* type b meningitis in infants and children 2 months of age.

Thyroid Disorders

- **Thyrotoxicosis/thyroid storm** : Dexamethasone, 2 mg every 6 hrly .
- **Malignant exophthalmos**: High-dose glucocorticoids e.g., prednisone, 40–80 mg daily is given. Doses are tapered by 5 mg every 2 weeks. Pulse therapy with IV methylprednisolone (e.g., 500–1000 mg of methylprednisolone in 250 mL of saline infused over 2 h daily for 1 week) followed by an oral regimen is also used.
- **Subacute thyroiditis**: The usual starting dose is 40–60 mg prednisone, depending on severity. The dose is gradually tapered over 6–8 weeks, in response to improvement in symptoms and the ESR.

Skin Diseases

- Glucocorticoids are remarkably efficacious in the treatment of a wide variety of inflammatory dermatoses. A typical regimen for an eczematous eruption is 1% hydrocortisone ointment applied locally twice daily.
- Glucocorticoids are administered systemically for severe episodes of acute dermatological disorders and for exacerbations of chronic disorders. The dose in these settings is usually 40 mg/day of prednisone. Systemic steroid administration can be lifesaving in pemphigus, which may require daily doses of up to 120 mg of prednisone.

Ocular Diseases

- Glucocorticoids frequently are used to suppress inflammation in the eye and can preserve sight when used properly. They are administered topically for diseases of the outer eye and anterior segment and attain therapeutic concentrations in the aqueous humor after instillation into the conjunctival sac.
- For diseases of the posterior segment, intraocular injection or systemic administration is required. A typical prescription is 0.1% dexamethasone sodium phosphate solution (ophthalmic), 2 drops in the conjunctival sac every 4 hours while awake, and 0.05% dexamethasone sodium phosphate ointment (ophthalmic) at bedtime.
- For inflammation of the posterior segment, typical doses are 30 mg of prednisone or equivalent per day, administered orally in divided doses.

Uses Of Androgens

- **Male hypogonadism:** Testosterone esters are administered typically at doses of 75–100 mg intramuscularly every week or 150–200 mg every 2 weeks.
- **As anabolic steroids**
- **Osteoporosis**
- **As growth stimulators** in boys with delayed puberty
- **Male Senescence**
- **Gynecological disorders** like endometriosis and breast tumours.

Anabolic Steroids

- Anabolic steroids or Anabolic-androgenic steroids (AASs) are chemically modified analogues of testosterone.
- 17 β -Esters of testosterone (cypionate, enanthate, heptylate, propionate, oxandrolone, bucyclate)
- 17 α -Alkyl derivatives of testosterone (methyltestosterone, fluoxymesterone, oxadrolone, stanozolol)
- 19-Nortestosterone (nandrolone)
- 17 β -Esters of 19-nortestosterone (decanoate, phenpropionate)
- 19-Norandrostenedione
- 19-Norandrostenediol
- Tetrahydrogestrinone

Uses of Anabolic Steroids

1. Osteoporosis
2. Catabolic states
3. Renal insufficiency
4. Hereditary angioneurotic edema
5. Suboptimal growth in children
6. Hypoplastic , haemolytic and malignancy associated anemia
7. To enhance physical ability in athletes

Preparations Available and Relative Androgenic: Anabolic Activity

- Testosterone 1:1
- Methandrostenolone 1:3 Anabolex 10Mg (100tablets Rs2,809)
- Oxandrolone 1:3–1:13 Anavar 10mg (50Tablets Rs3,595)
- Nandrolone phenpropionate 1:3–1:6 Durabolin(inj 25mg 1ml Rs40.50)
- Nandrolone decanoate 1:2.5–1:4 Decadurabolin(inj 100mg 1ml Rs214.50)
- Stanozolol 1:3–1:6 (Tanzol cap 2mg 10 cap Rs 27.00)

Uses of Estrogens and Progesterone

- **Primary Hypogonadism:** 0.3 mg conjugated estrogens or 5-10 mcg ethinyl estradiol on days 1-21 each month, slowly increased to adult doses and maintained until the age of menopause.
- **Postmenopausal Replacement Therapy.**
- Endometriosis
- Oral Contraceptive pills
- Postcoital contraceptives

Diagnostic Uses of Corticosteroids

- Dexamethasone is used as a first-line agent to diagnose hypercortisolism and to differentiate among the different causes of Cushing's syndrome.
- Overnight dexamethasone suppression test: Patients are given 1 mg of dexamethasone orally at 11 P.M., and cortisol is measured at 8 A.M. the following morning. Suppression of plasma cortisol to <1.8 g/dL suggests strongly that the patient does not have Cushing's syndrome. Following determination of baseline cortisol levels for 48 hours, dexamethasone (0.5 mg every 6 hours) is administered orally for 48 hours.

Cont...

- In the high-dose phase of the test, dexamethasone is administered orally at 2 mg every 6 hours for 48 hours.
- Patients with pituitary-dependent Cushing's syndrome (i.e., Cushing's disease) generally respond with decreased cortisol levels. In contrast, patients with ectopic production of ACTH or with adrenocortical tumors generally do not exhibit decreased cortisol levels.

Adverse Effects of Steroids

- Altered distribution of fat
- Edema, hypokalemia and hypertension
- Suppression of HPA axis
- Osteoporosis and osteonecrosis
- Hyperglycemia and glycosuria
- Peptic ulcer
- Posterior subcapsular cataract and glaucoma.
- Myopathy and muscle wasting
- Susceptibility to infections
- Reversible psychological disturbances
- Weight gain, menstrual irregularities, acne, anovulation

Steroid Abuse

- Use of anabolic steroids by athletes and body builders to increase efficiency during competitive events.
- Their use is referred to as doping and banned by all major sporting bodies.
- Body weight may increase by 2–5 kg as a result of short-term (<10 weeks) AAS use, which may be attributed mainly to an increase of lean mass.
- The dose of AAS used by athletes varies considerably and is often thought to exceed 10 to 40 times the recommended therapeutic dose.

Dope test

- Doping by testosterone can be indirectly tested by measuring the ratio of urinary testosterone to epitestosterone (T/E).
- Measurements of the T/E ratio and other metabolites in urine by sensitive gas chromatography/mass spectrometry methods are used to detect androgenic anabolic steroid doping by competitive athletes.
- Administration of androgenic anabolic steroids suppresses the production and clearance of epitestosterone relative to testosterone, resulting in an elevated T/E ratio in urine.
- The World and United States Anti-Doping Agencies have set a threshold T/E ratio of greater than 4 : 1 as suspicious for anabolic steroid doping.

Most commonly detected anabolic steroids

- Testing by **International Olympic Committee** laboratories in 1993 revealed that the most commonly detected steroids are:
- Testosterone (32.5%)
- Nandrolone (23.9%)
- Stanozolol (11.4%)
- Metandienone (10.7%)
- Methenolone preparations (7.7%).

Modes of Use

- **Cycling**
 - set cycles that may have periods during which no steroids are taken
 - different anabolic steroids are rotated.
- **Stacking**
 - Use more than one type at a time.
 - Usually PO and IM
- **Pyramid stacking**
 - Up-tapering or down-tapering doses of a steroid

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