**Immuno-suppressive therapy**

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**Introduction:**
- promote acceptance of a graft (induction therapy),
- to reverse episodes of acute rejection (rejection therapy),
- to prevent rejection (maintenance therapy)

1. Besides immunosuppressive effects, ~
   - immunodeficiency toxicity (e.g., infection and malignancy), and
   - nonimmune toxicity (e.g., nephrotoxicity, diabetes mellitus, or neurotoxicity).
2. ~ only be prescribed and administered by physicians and nurses

**The main indications for immunosuppressive Rx are:**
- organ transplantation
- malignancy
- rheumatoid arthritis
- psoriasis
- inflammatory bowel disease

**I. Glucocorticoids**
- immunosuppressive and anti-inflammatory.
- mechanisms of action: include inhibition of cytokine transcription, induction of lymphocyte apoptosis, down-regulation of adhesion molecule and major histocompatibility complex expression, and modification of leukocyte trafficking.

**II. Antiproliferative agents**
- Azathioprine
- Mycophenolate mofetil (MMF)

**Azathioprine**
- purine analog that is metabolized by the liver to 6-mercaptopurine.
- Azathioprine inhibits the synthesis of DNA and thereby suppresses the proliferation of activated lymphocytes.
- Toxicity: myelosuppression, which is reversible after dose reduction or discontinuation of the drug.
III. Calcineurin inhibitors bind to immunophilins (intracellular binding proteins).

- Inhibits a key phosphatase that is involved in transducing the signal from the T-cell receptor to the nucleus.
- The net effect is blockade of interleukin-2 and other cytokine transcription, leading to inhibition of T-lymphocyte activation and proliferation.

- Cyclosporine A
- Tacrolimus (FK 506)

Cyclosporine A

- Is a cyclic 11-amino acid peptide derived from a fungus.
- Its major nonimmune side effect is nephrotoxicity due to afferent arteriolar vasoconstriction.
- Other adverse effects include gingival hyperplasia, hirsutism, tremor, hypertension, glucose intolerance, hyperlipidemia, hyperkalemia, and rarely thrombotic thrombocytopenic purpura.
- CsA has a narrow therapeutic window, and doses are adjusted based on blood levels (recommended maintenance trough levels of 100–300 ng/ml and 2-hour peak levels < 1200 ng/ml).

IV. Biological agents

- Polyclonal antibodies: Antithymocyte globulin (ATGAM); Thymoglobulin; Monoclonal antibodies

V. Newer immunosuppressive agents

- Sirolimus (rapamycin)
- Anti–interleukin-2 receptor monoclonal antibodies

Corticosteroid Therapy

Introduction

- Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex. Corticosteroids are involved in a wide range of endocrine systems such as stress response, immune response and regulation of carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.
- Glucocorticoids such as cortisol control carbohydrate, fat and protein metabolism and are anti-inflammatory by preventing phospholipid release, decreasing eosinophil action and a number of other mechanisms.
- Mineralocorticoids such as aldosterone control electrolyte and water levels, mainly by promoting sodium retention in the kidney.
History

- As early as in 1855, Addison wrote that the destruction of the cortex of the adrenal glands has serious consequences for our organism.
- T. Reichstein, E. C. Kendall and P.S. Hench were awarded the Nobel Prize for in 1950 for their work on hormones of the adrenal cortex which culminated in the isolation of cortisone.

Mechanism of action

- Enter cells where they combine with steroid receptors in cytoplasm.
- Combination enters nucleus where it controls synthesis of proteins, including enzymes that regulate vital cell activities over a wide range of metabolic functions including all aspects of inflammation.
- Formation of a protein that inhibits the enzyme phospholipase A2, which is essential for the formation of inflammatory mediators.
- Also act on cell membranes to alter ion permeability.
- Also modify the production of neurohormones.

Actions

- Important to distinguish between physiological effects (replacement therapy) and pharmacological effects (occur at higher doses).
- Normal daily secretion of hydrocortisone is 10-30 mg. Exogenous daily dose that completely suppresses cortex is 40-80 mg (or prednisolone 10-20 mg).

Mineralocorticoid effects

- Na retention by renal tubule.
- Increased K excretion in urine.

Glucocorticoid effects

- CHO metabolism: increased gluconeogenesis, ± peripheral glucose uptake may be decreased with resultant hyperglycaemia ± glycosuria.
- Protein metabolism: anabolism is decreased but catabolism continues unabated or is increased resulting in negative N balance and muscle wasting. Osteoporosis occurs; growth slows in children; skin atrophies (together with increased capillary fragility leads to bruising and striae), healing and fibrosis delayed.
- Fat deposition: increased on shoulders, face and abdomen.

Glucocorticoid effects

- Inflammatory response depressed.
- Allergic response depressed.
- Antibody production reduced by large doses.
- Lymphoid tissue reduced (including leukaemic lymphocytes).
- Decreased eosinophils.
- Renal urate excretion increased.
- Euphoria or psychotic states may occur. ? due to CNS electrolyte changes.
**Glucocorticoid effects**

- anti-vitamin D action
- reduction of hypercalcaemia (chiefly where this is due to increased absorption from gut: vit D intoxication, sarcoidosis)
- increased urinary Ca excretion. Renal stones may form
- growth reduction where new cells are being added (eg in children) but not where they are replacing cells as in adult tissues
- suppression of hypopituitary-pituitary-adrenal (HPA) axis. Although steroid suppressed adrenal continues to secrete aldosterone

**Individual steroids**

<table>
<thead>
<tr>
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<th>Relative potencies</th>
<th>Glucocorticoid</th>
<th>Mineralocorticoid</th>
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<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
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<td>1</td>
<td></td>
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<tr>
<td>Prednisolone</td>
<td>4</td>
<td>0.8</td>
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<tr>
<td>Methylprednisolone</td>
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</tr>
<tr>
<td>Dexamethasone</td>
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<tr>
<td>Fludrocortisone</td>
<td>15</td>
<td>150</td>
<td></td>
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</tbody>
</table>

**Prednisolone** is standard choice for anti-inflammatory therapy. Can be given orally or IM

- methylprednisolone used for IV pulsed therapy
- dexamethasone longer acting.
- fludrocortisone used to replace aldosterone where the adrenal cortex has been destroyed
- beclomethasone and budesonide used by inhalation for asthma.

**Pharmacokinetics**

**Administration:**

- PO
- IM
- IV
- intra-articular
- topical
- inhaled

Absorption after oral administration is rapid. Maximum biological effect seen after 2-8 h

**Distribution:**

- high plasma protein binding (95% in case of hydrocortisone) to transcortin
- when transcortin is saturated, then binds to albumin (80% in the case of hydrocortisone)
- concentration of transcortin is increased by oestrogens (eg. pregnancy, oral contraceptives)
- in patients with very low serum albumin doses should be reduced due to reduced binding capacity

**Elimination:**

- hepatic and renal.
- t1/2 of most steroids 1-3 h.
- Prolonged in renal and hepatic disease
- shortened by hepatic enzyme induction
Adverse effects

- In general serious unwanted effects are unlikely if daily dose is:
  - < 50 mg hydrocortisone or
  - > 10mg of prednisolone or equivalent

Iatrogenic Cushing’s syndrome

- General physical features:
  - Tendency to gain weight, esp. abdomen, face (moon face), neck and upper back (buffalo hump);
  - Thinning and weakness of the muscles of the upper arms and upper legs;
  - Thinning of the skin, with easy bruising and pink or purple stretch marks (striae) on the abdomen, thighs, breasts and shoulders;
  - Increased acne, facial hair growth, and scalp hair loss in women;
  - Children will show obesity and poor growth in height.

Symptoms:

- Fatigue, weakness, depression, mood swings, increased thirst and urination, and lack of menstrual periods in women.

Common findings:

- Elevated white blood count, a high blood sugar (often into the diabetic range), and a low serum potassium.

Hypopituitary-pituitary-adrenal (HPA) axis suppression

- Dependent on steroid used, dose, duration of administration and time of administration
- E.g. single morning dose of <20mg prednisolone does not usually cause suppression while 5mg in evening suppresses early morning activation of HPA axis
- For up to twelve months after the steroids are stopped, the lack of steroid response to stress can be detected

Osteoporosis

- Particularly in smokers, postmenopausal women, underweight or immobile elderly
- May result in fractures of the spine, ribs or hip joint with minimal trauma.
- These occur after the first year in 10-20% of patients treated with more than 7.5mg prednisone daily. It is estimated that up to 50% of patients using oral corticosteroids will develop bone fractures.
- Preventative treatment: calcium, vitamin D, oestrogen and bisphosphonates. Treatment is most effective when started at the same time as the steroids as most bone loss occurs within the first three months.

Other side effects

- Reduction in growth in children
- Muscle weakness, esp. shoulder and thighs
- Rarely, avascular necrosis of the femoral head (destruction of the hip joint).
- Diabetes can be precipitated or aggravated.
- Increased serum lipid levels
- Redistribution of body fat: moon face, buffalo hump and truncal obesity.
- Salt retention: leg swelling, raised blood pressure, weight increase and heart failure.
- Shakiness and tremor.
Other side effects
- Eye disease: cataract (chronic use), glaucoma (prolonged use of eye drops)
- Psychological effects including insomnia, mood changes, increased energy, excitement, delirium or depression
- Headaches
- Immunosuppression, esp. at high doses
- Peptic ulceration
- Side effects from reducing the dose: tiredness, headaches, muscle and joint aches and depression

Skin effects
- The skin is prone to the following adverse effects from prolonged courses or high doses of systemic steroids:
  - Increased risk of skin infections such as bacterial and fungal infections
  - Skin thinning resulting in easy bruising (purpura), skin tearing after minor injury, slow healing, and stretch marks (striae)
  - Acne: esp. on face, chest and upper back
  - Subcutaneous lipoatrophy from injected steroid that does not go deep enough into the muscle

Cushingoid features in a 43-yr-old man

Moon face

Easy bruising

Skin thinning
Fragile skin

Acne

Striae

Use in pregnancy
- teratogenic in animals (esp Dexomethasone)
- adrenal insufficiency due to HPA axis suppression in newborn only occurs with high maternal doses
- keep doses as low as possible in pregnancy

Indication

Endocrine Disorders:
- Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; with mineralocorticoids where applicable)
- Congenital adrenal hyperplasia.
- Nonsuppurative thyroiditis.
- Hypercalcemia associated with cancer.

Rheumatic Disorders
- Rheumatoid arthritis,
- Ankylosing spondylitis.
- Acute and subacute bursitis.
- Synovitis of osteoarthritis.
- Acute nonspecific tenosynovitis
- Acute gouty arthritis etc
Collagen Diseases:
- Systemic lupus erythematosus.
- Systemic dermatomyositis (polymyositis).
- Acute rheumatic carditis.

Dermatologic Diseases:
- Bullous dermatitis herpetiformis.
- Severe erythema multiforme (Stevens-Johnson syndrome).
- Exfoliative dermatitis.
- Severe psoriasis. etc

Ophthalmic Diseases:
- Optic neuritis
- Allergic corneal marginal ulcers.
- Herpes zoster ophthalmicus.
- Anterior segment inflammation.
- Diffuse posterior uveitis and choroiditis.
- Sympathetic ophthalmia.
- Keratitis.
- Allergic conjunctivitis.
- Chorioretinitis.
- Iritis and iridocyclitis.

Respiratory Diseases:
- Symptomatic sarcoidosis.
- Fulminating or disseminated pulmonary tuberculosis: ATT with ~
- Aspiration pneumonitis.

Hematologic Disorders:
- Idiopathic thrombocytopenic purpura in adults.
- Secondary thrombocytopenia in adults.
- Acquired (autoimmune) hemolytic anemia.
- Erythroblastopenia (RBC anemia).
- Congenital (erythroid) hypoplastic anemia.

Allergic States:
- Bronchial asthma
- Seasonal or perennial allergic rhinitis.
- Drug hypersensitivity reactions.
- Serum sickness.
- Contact dermatitis.
- Atopic dermatitis.
Neoplastic Diseases

- Leukemias and lymphomas in adults.
- Acute leukemia of childhood.

Edematous States: To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in:
- Ulcerative colitis.
- Regional enteritis.

Nervous System: Acute exacerbations of multiple sclerosis

Miscellaneous

- Tuberculous meningitis with subarachnoid block or impending block: ATT with ~
- Trichinosis with neurologic or myocardial involvement.