IN THE NAME OF GOD

Side Effects and Potency of Corticosteroids

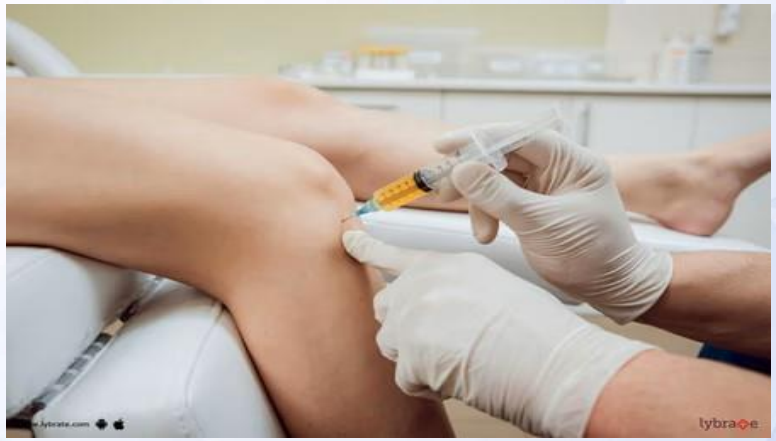
Dr. Shabnam Hajiani Ghotbabadi
Assistant professor of pediatric Rheumatology diseases of Shiraz University of medical sciences May 2024

Glucocorticoid Drugs

- Glucocorticoid drugs are the most potent anti-inflammatory agents used in the treatment of rheumatic diseases.
- They are structural variants of the naturally occurring glucocorticoid, cortisol.
- Prednisone and cortisone are therapeutic compounds that undergo hepatic biotransformation to form a hydroxyl at C11 resulting in prednisolone and hydrocortisone, respectively, that are therapeutically active forms of the drug.

Glucocorticoid Drugs

- Topical glucocorticoids, such as dexamethasone, or those administered by intraarticular injection (e.g., triamcinolone), already have a hydroxyl group at C11 and are thus in active form.



Pharmacology and mechanism of action

- Prednisone is converted to prednisolone in the liver and reaches a *peak plasma concentration* within 2 hours.
- Orally administered glucocorticoids are rapidly absorbed.
- Prednisolone has a large volume of distribution; about two-thirds is taken up by muscle.
- After metabolism in the liver, excretion occurs principally via the bile.
- Glucocorticoids are synthetic analogs of endogenous molecules that perform important physiological and pharmacological functions through glucocorticoid receptors (GRs) and genomic and nongenomic mechanisms.

Pharmacology and mechanism of action

- Glucocorticoids have anti-inflammatory and immunosuppressive effects and inhibits:
  - Early stages of inflammation (e.g., edema, fibrin deposition, capillary dilation, migration of lymphocytes into inflamed areas, phagocytic activity)
  - Later manifestations (e.g., proliferation of capillaries and fibroblasts, deposition of collagen).

Pharmacology and mechanism of action

- Glucocorticoid effects on the immune system are mediated principally through T lymphocytes.
- Administration of hydrocortisone produces a 70% decline in circulating lymphocytes.
- T lymphocytes are affected more than B lymphocytes, and CD4+ T cells are affected more than CD8+ T cells.

Pharmacology and mechanism of action

- Corticosteroids have been shown to result in a profound and transient lymphocytopenia, maximal at 4 hours after the dose.
- It is resolved by 24 hours, because of a redistribution of these cells to the bone marrow, although *drug-induced apoptotic cell death* may also be involved.
- There is also a 90% decline in circulating monocytes within the initial 6 hours.

Pharmacology and mechanism of action

- Glucocorticoids cause an increase in the number of blood neutrophils by:
  - Increasing the release of cells from the marginated neutrophil pool
  - Prolonging their stay in the circulation
  - Reducing chemotaxis of neutrophils to sites of inflammation

Safety/ Toxicity

- The risk/benefit ratio must be carefully weighed when considering glucocorticoid use in children with rheumatic diseases, as these agents can cause substantial toxicity when used systemically in long term.
- The overall aim is to limit the dose and duration of steroid therapy as much as possible while achieving disease control.
- Two categories of adverse effects of therapeutic use of systemic glucocorticoids are:
  - Exposure-dependent effects resulting from prolonged use of large doses.
  - Effects resulting from withdrawal of therapy.

Adverse Effects of Glucocorticoid Drugs

Cushing syndrome

Growth suppression

Effects on bone: osteoporosis, avascular necrosis

Immunosuppression

Lymphopenia and neutrophilia

Central nervous system effects: mood and behavioral disturbances, psychosis

Cataracts and glaucoma

Metabolic effects: impaired carbohydrate tolerance, protein wasting, metabolic alkalosis

Myopathy hypertension

Side effects of inhaled steroids

Side effects of inhaled steroids are generally mild, which is why doctors often prescribe them. In most cases, the benefits of the steroids outweigh any possible side effects.

Common side effects of inhaled steroids include:

- hoarseness
- cough
- sore throat
- oral thrush

If you're taking a high dose or have used inhaled steroids for a long time, you may experience weight gain due to an increase in appetite.

Those who take inhaled steroids for long-term management have an increased risk of developing pneumonia.

Generally, inhaled steroids have very few side effects because the medicine goes directly into the lungs.

Table 185.16 Risk Assessment for Corticosteroid Adverse Effects

	CONDITIONS	RECOMMENDATIONS
Low risk	(≤1 risk factor*) Low- to medium-dose ICS (see Table 185.13)	Monitor blood pressure and weight with each physician visit Measure height annually (stadiometry); monitor periodically for declining growth rate and pubertal developmental delay Encourage regular physical exercise Ensure adequate dietary calcium and vitamin D with additional supplements for daily calcium if needed. Avoid smoking and alcohol Ensure TSH status if patient has history of thyroid abnormality
Medium risk	(If >1 risk factor,* consider evaluating as high risk) High-dose ICS (see Table 185.13) At least four courses of OCS per year	As above, *plus*: Yearly ophthalmologic evaluations to monitor for cataracts or glaucoma Baseline bone densitometry (DEXA scan) Consider patient at increased risk for adrenal insufficiency, especially with physiologic stressors (e.g., surgery, accident, significant illness)
High risk	Chronic systemic corticosteroids (>7.5 mg daily or equivalent for >1 mo) ≥7 OCS burst treatments per year Very-high-dose ICS (e.g., fluticasone propionate ≥800 µg/day)	As above, *plus*: DEXA scan: if DEXA *z* score ≤1.0, recommend close monitoring (every 12 mo) Consider referral to a bone or endocrine specialist Bone age assessment Complete blood count Serum calcium, phosphorus, and alkaline phosphatase determinations Urine calcium and creatinine measurements Measurements of testosterone in males, estradiol in amenorrheic premenopausal women, vitamin D (25-OH and 1,25-OH vitamin D), parathyroid hormone, and osteocalcin Urine telopeptides for those receiving long-term systemic or frequent OCS treatment Assume adrenal insufficiency for physiologic stressors (e.g., surgery, accident, significant illness)

*Risk factors for osteoporosis: presence of other chronic illness(es), medications (corticosteroids, anticonvulsants, heparin, diuretics), low body weight, family history of osteoporosis, significant fracture history disproportionate to trauma, recurrent falls, impaired vision, low dietary calcium and vitamin D intake, and lifestyle factors (decreased physical activity, smoking, alcohol intake).

Cushing Syndrome

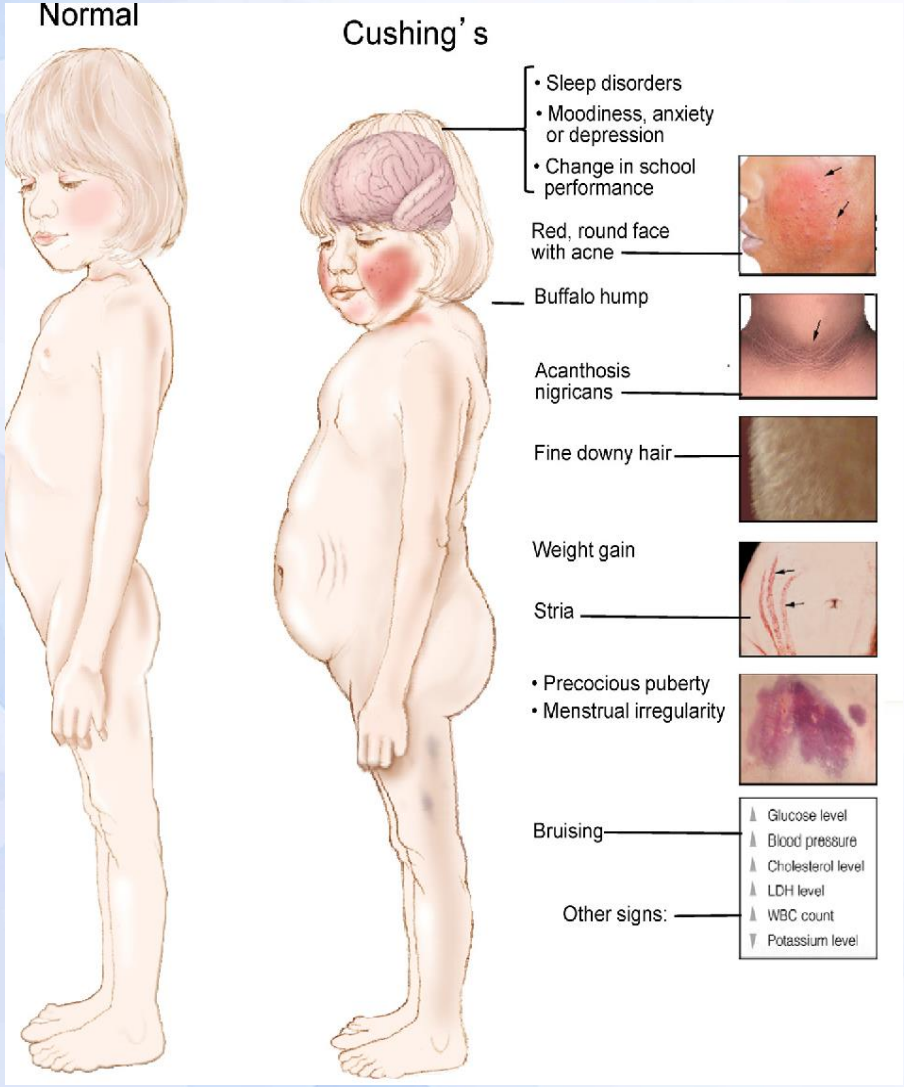
- Cushing syndrome can be induced by prolonged glucocorticoid administration.
- It is characterized *biochemically* by high plasma glucocorticoid levels and suppression of the hypothalamic–pituitary–adrenal axis.

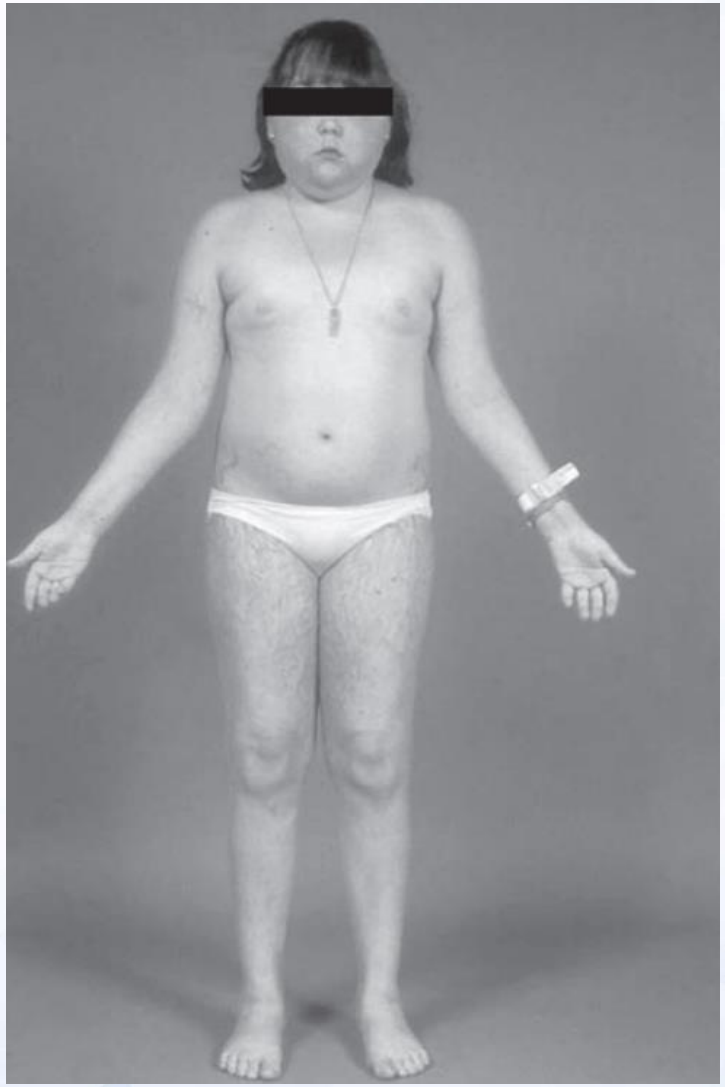
Clinical manifestations:

- Truncal obesity
- Osteoporosis
- Thinning of the subcutaneous tissues
- Hypertension (usually mild but occasionally requires treatment or reduction of the glucocorticoid dose)
- Distribution of fat predominantly in the subcutaneous tissue of the abdomen, upper back *(buffalo hump)* and in the face *(moon facies)*
- Purple striae
- Hirsutism and acne

Except for skin striae, all the physical features are reversible after cessation of glucocorticoid therapy.

Cushing Syndrome





An 11-year-old girl with severe systemic-onset JIA, requiring high-dose corticosteroid treatment. Cushingoid features shown include moon facies, truncal obesity, and cutaneous striae.

Growth Suppression

- Growth suppression can occur in young children who receive prolonged therapy in dosages equivalent to 3 mg/day of prednisone, and it increases with higher dosages.
- The mechanism of glucocorticoid-associated growth suppression in children with arthritis remains controversial.
- Alternate-day dosing regimens have been shown to minimize this adverse effect.
- Increased height velocity and catch-up growth has been seen in patients who received growth hormone, and achievement of their genetically determined target height was observed in JIA patients.
- The optimal dose and time to initiate growth hormone have yet to be determined and the potential for metabolic complications requires routine monitoring.

Effects on Bone

- Glucocorticoids have been associated with a reduction in bone formation primarily attributed to osteoblast inhibition and apoptosis.
- They can also increase bone resorption mediated through inhibition of gut absorption of calcium and increased urinary calcium excretion which can result in *secondary hyperparathyroidism*.
- The extent of bone loss is related to the dose and duration of glucocorticoid therapy, although these factors do not have a consistent relationship with fracture risk.
- Significant bone loss occurs with dosages of 7.5 mg/day or greater in most adults.
- In adults, bone loss is predominantly trabecular (e.g., spine and ribs) rather than cortical, whereas in children the osteoporotic effects of glucocorticoids are more generalized.

Effects on Bone

- Bone loss seems to occur rapidly within the first 6 to 12 months of therapy and then reaches a plateau.
- Alternate-day glucocorticoid therapy may not be protective.
- Not all patients exposed to long-term glucocorticoid therapy develop bone loss.

Screening:

- Bone densitometry may be used to screen children who are at high risk for osteoporosis, although there are challenges with misinterpretation because of adult norms.
- There are limited guidelines on what frequency to perform densitometry and controversy on the utility of other types of imaging modalities.

Effects on Bone

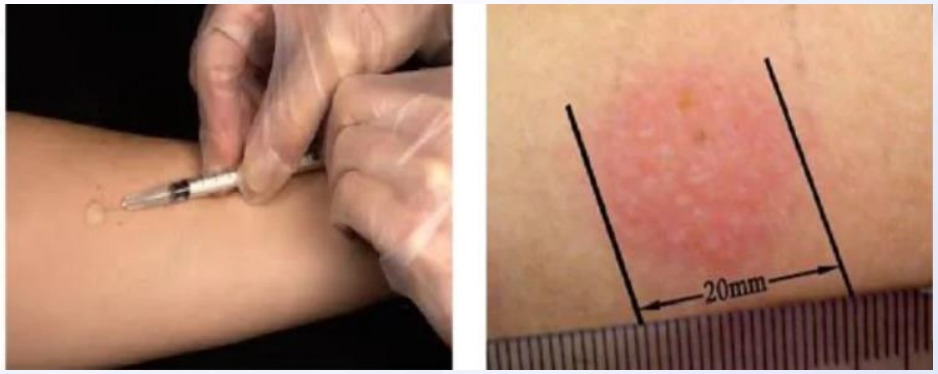
- High-dose glucocorticoids have also been associated with avascular necrosis of bone (AVN), although the exact mechanism is unknown.
- Intramedullary vascular compromise may result from increased osteocyte apoptosis and adipocyte differentiation induced by glucocorticoids.
- Reduced blood flow and bony ischemia can be caused by the absence of the clearance of apoptotic osteocytes and enhanced fat infiltration in the marrow.
- Glucocorticoids also increase the expression of endothelin-1, which may also lead to reduced intramedullary blood flow.
- The most common and clinically significant location for AVN is the *femoral head*, and the underlying disease process (such as in SLE), in addition to age, can be a contributing factor.

Infection and immunity

- Glucocorticoids interfere with the ability to resist infection by acting as immunosuppressives and unpredictably decreasing the patient's resistance to viral and bacterial infections; they are anti-inflammatory agents and thus can mask the signs and symptoms of infection.
- The minimal dose and duration of systemic steroids that result in immunosuppression in a healthy child are not well defined.
- Effects of the underlying disease and concurrent immunosuppressive therapies also affect the overall extent of immunosuppression in children with rheumatic diseases.

Infection and immunity

- Patients receiving high doses of glucocorticoids for a prolonged period are prone to infections that are associated with defects of delayed hypersensitivity (e.g., tuberculosis).
- *Mantoux test* (purified protein derivative [PPD], 5 tuberculin units) or *QuantiFERON-TB Gold test* should be performed before initiation of long-term glucocorticoid therapy.



Infection and immunity

- The risk of complications of varicella infection must also be considered.
- A susceptible child being treated with glucocorticoids who is exposed to chickenpox should receive varicella-zoster immune globulin (VariZIG) as soon as possible (up to 10 days after exposure), and it is only effective in prevention or modification of the disease course if administered before the disease is established.
- If VariZIG is unavailable, IV immunoglobulin (IVIG) can also be used at a dose of 400 mg/kg IV up to 10 days after exposure.
- If acutely infected, IV acyclovir should be used to prevent dissemination, as oral acyclovir has poor oral bioavailability.

Central Nervous System

- The effect of glucocorticoids on the CNS results from changes in the concentration of plasma glucose, circulatory dynamics, and electrolyte balance, reflected by changes in mood, behavior, and electroencephalographic (EEG) studies.
- Glucocorticoid-induced psychoses:
  - have an acute onset,
  - are related to high doses,
  - occur within 96 hours after initiation of medication.
- *Pseudotumor cerebri* is rare but may occur after rapid dose reduction.
- A prospective cohort study of the adverse effects of high-dose intermittent IV glucocorticoids in 213 children with rheumatic diseases found behavioral changes in 21 (10%).

Cardiovascular System

- Glucocorticoids can cause hypertension and dyslipidemia.
- The mechanisms by which these side effects occur are complex, but they are related to:
  - the regulation of renal sodium excretion,
  - induction of angiotensin II receptors,
  - increased plasma renin or antidiuretic hormone activity,
  - glucocorticoid effects upon capillaries, arterioles, and the myocardium.
- Dyslipoproteinemia and accelerated coronary atherosclerosis have been observed in patients, especially those with SLE, after prolonged administration of glucocorticoids.
- The pathogenesis of coronary artery disease in these patients is multifactorial, as uncontrolled disease activity likely also plays a role.

Acute adrenal insufficiency (addisonian crisis)

- The use of pharmacological doses of glucocorticoids for a 2-week period may result in transient suppression of endogenous cortisol production, and prolonged therapy may lead to suppression of pituitary–adrenal function that can be slow in returning to normal.
- This is potentially the *most serious and life-threatening* adverse effect associated with glucocorticoid therapy.
- The actual doses and duration of therapy that are associated with suppression and the length of the recovery period after cessation of therapy are not well defined.
- If not recognized, suppression of the hypothalamic–pituitary–adrenal axis places a child at risk for vascular collapse, adrenal crisis, and death in situations that demand increased availability of cortisol.

Acute adrenal insufficiency (addisonian crisis)

- Under conditions of stress (e.g., serious infection, trauma, surgery), all children who may be at risk for hypothalamic–pituitary–adrenal axis suppression require additional glucocorticoids.
- The *"stress dose"* regimen is based on the body's requirements for hydrocortisone during stress.
- Hydrocortisone (6 to 9 mg/m2/day divided three times daily) is needed for physiological maintenance.
- For febrile or severe illnesses, hydrocortisone requirements increase to 40 mg/m2/day.
- With induction of anesthesia or in a resuscitation situation, 100 mg/m2 IV of hydrocortisone is required initially, and then 25 mg/m2 IV every 6 hours for the following 24 to 48 hours.

Acute adrenal insufficiency (addisonian crisis)

- If the patient is currently receiving glucocorticoids such as prednisone or prednisolone at a dosage equivalent to or greater than 40 mg/m2/day of hydrocortisone then the current glucocorticoid dose prescribed for disease management may be enough for febrile or severe illnesses.

- As steroids are weaned or discontinued after prolonged use, glucocorticoid replacement may be required to prevent adrenal crisis if the body's corticosteroid needs exceed the dose prescribed for disease management.

TABLE 13.3 Relative Doses and Equivalent Potencies of Glucocorticoids (Compared with Hydrocortisone)

Glucocorticoid*	Equivalent Dose† (mg)	Relative Anti-Inflammatory Potency	Relative Sodium Retaining Potency
Short Acting			
Hydrocortisone	20	1	1
Deflazacort	6	4	1
Intermediate Acting			
Prednisone	5	4	0.8
Prednisolone	5	4	0.8
Methylprednisolone	4	5	0.5
Long Acting			
Dexamethasone	0.75	25	0

*Biological half-life, short-acting, 8 to 12 hours (deflazacort, ~1.5 hours); intermediate-acting, 12 to 36 hours; long-acting, 36 to 72 hours.

†Oral or intravenous administration only.

Adapted from Goodman and Gilman (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics, eighth ed., Pergamon Press, New York, 1990. Reproduced with permission of the McGraw-Hill Companies.

Other toxicities

- Subcapsular cataracts can occur with glucocorticoid therapy.
- The risk of cataract development becomes significant when a dosage of prednisone equal to or greater than 9 mg/ m2/day has been maintained for longer than 1 year.
- Children should also be monitored for glaucoma.
- Muscle wasting on high-dose glucocorticoid administration is associated with atrophy of muscle fibers, especially type IIB fibers.
- Steroid-induced myopathy usually affects proximal muscles, is seldom painful, and is usually associated with normal serum levels of muscle enzymes and an electromyogram suggestive of myopathy.
- Glucocorticoid-induced hypokalemia may also lead to muscular weakness and fatigue.
- Excess glucocorticoid may also cause polycythemia, glucose intolerance and glycosuria, and peptic ulceration.

Minimizing toxicity

- The deleterious effects of glucocorticoids can be minimized by choosing a drug with a short half-life.
- Prednisone is the drug most often given for oral therapy, as its prominent glucocorticoid and minimal mineralocorticoid actions give it the *lowest risk/benefit* ratio of any of the analogs in general use.
- The anti-inflammatory effect and the toxicity of glucocorticoids increase with larger doses and more frequent administration.
- Short-acting glucocorticoids given in the morning do not suppress the pituitary as much as glucocorticoids given later in the day (which suppress the normal surge of adrenocorticotropic hormone [ACTH] that occurs during sleep), so once daily administration should preferably be in the morning.

TABLE 13.4 Systemic Administration of Glucocorticoid Drugs

Schedule	Advantages	Disadvantages
Divided daily doses	Optimal disease control	More side effects
Single daily dose	Good disease control; fewer side effects	May not control severe disease
Alternate-day dose	Fewer side effects, less chance of developing Cushing syndrome or pituitary suppression	Less disease control
Intravenous pulse therapy	Less long-term toxicity, rapid onset of action	Acute toxicities

Minimizing toxicity

- Reduction in glucocorticoid dose must be individualized for the child and the disease and is often fraught with difficulty because of the adaptation of the patient's metabolism to chronic steroid excess.
- At high dosages (e.g., 60 mg/day), reductions of 10 mg are usually well tolerated; at lower dosages (e.g., 10 mg/day), reductions of only 1 or 2 mg may be possible.
- An alternate-day regimen should be the goal to minimize toxicity, although some patients do not tolerate this regimen.
- In some children, steroid pseudorheumatism may result from a rapid dose decrease.
- These withdrawal effects gradually resolve over 1 or 2 weeks and are minimized if each decrement in daily prednisone is 1 mg or less per week (at the lower dose levels).

Minimizing toxicity

- Vitamin D and its analogs, calcitonin, and various bisphosphonates have been used for the prevention and treatment of corticosteroid-associated osteoporosis.
- Calcitriol (vitamin D3) or cholecalciferol (vitamin D), with or without calcitonin, were shown to prevent bone loss from the lumbar spine better than calcium alone.
- Treatment with calcium and vitamin D in adults who receive glucocorticoids effectively slows lumbar and forearm bone loss.
- Treatment with calcium and vitamin D supplementation has become standard practice for children with rheumatic disease who receive glucocorticoids.

Minimizing toxicity

- The following bisphosphonates have been shown in randomized controlled trials to increase lumbar spine bone mineral density in adults receiving long-term glucocorticoids for various diseases.
  - Etidronate
  - Pamidronate
  - Alendronate
  - Risedronate

- Bisphosphonates have been studied in children with osteogenesis imperfecta and seem to be beneficial in:
  - reducing bone resorption,
  - increasing bone density,
  - and reducing the chronic bone pain associated with this condition.

Minimizing toxicity

- Although there are concerns regarding their effects on growth and remodeling, bisphosphonates have been found to be useful and safe in open-label studies of children with idiopathic juvenile osteoporosis, or osteoporosis associated with connective tissue diseases or induced by glucocorticoids.
- Binding to bone and prolonged renal excretion (mean 7 years) continues to concern clinicians for long-term safety of these agents in children, necessitating larger prospective trials in children.

High-dose Intravenous glucocorticoid therapy

- IV glucocorticoid *"pulse"* therapy is sometimes used to treat more severe, acute systemic inflammation to achieve an immediate anti-inflammatory effect and to minimize toxicity related to long-term oral therapy in moderate to high daily doses.
- *Pulse methylprednisolone* has been shown to inhibit cytokine generation and dissolve in cell membranes, altering membrane-associated proteins.
- Differences are seen in the alpha-interferon gene expression signature in pediatric SLE patients receiving pulse methylprednisolone therapy compared with oral glucocorticoid therapy, which may explain an advantage for this dosing regimen over oral doses.

High-dose Intravenous glucocorticoid therapy

- *IV methylprednisolone* has been the *drug of choice*, given in a dosage of 10 to 30 mg/kg/pulse up to a maximum dose of 1 g, administered according to various protocols.
- A single administration as clinical circumstances warrant, a pulse each day for 3 to 5 days, or alternate-day pulses for three doses.
- IV glucocorticoid pulse therapy may be associated with potentially serious complications.

EBOX 13.2 Suggested Protocol for Administration of Intravenous Methylprednisolone

Dose

Methylprednisolone up to 30 mg/kg (maximum 1 g)

Preparation

Prepare drug with diluent provided with package

Calculated dose is added to 100 mL normal saline and infused over 1 to 3 hours

Monitoring

Temperature, pulse rate, respiratory rate, blood pressure before beginning infusion

Pulse and blood pressure every 15 minutes for first hour, every 30 minutes thereafter

Slow rate or discontinue infusion, and increase frequency of monitoring if there are significant changes in blood pressure or pulse rate

Side Effects/Potential Acute Toxicities

Hypertension or hypotension, tachycardia, bradycardia, cardiac arrhythmia secondary to potassium depletion, blurring of vision, hyperglycemia with or without ketosis, flushing, sweating, metallic taste in mouth, acute psychosis, behavioral changes, convulsions, anaphylaxis

Intraarticular steroids

- Injection of long-acting glucocorticoids directly into inflamed joints is a key treatment modality for various types of arthritis.
- IAS therapy has been used most often in children with oligoarticular disease in conjunction with, or as an alternative to, NSAID therapy.
- In polyarticular disease, multiple IAS injections at one time can be used as a temporizing measure while awaiting response to systemic agents.
- IAS may also be useful as an alternative to increasing systemic therapy in children with polyarticular disease who have significant inflammation in only a few joints.

Intraarticular steroids

- All patients experience rapid resolution of symptoms and signs of joint inflammation within a few days after injection, resulting in improved physical function.
- About two-thirds achieve remission for at least 12 months after a single injection.
- A longer duration of response has been described in children with oligoarticular JIA, and in those who are younger, with shorter disease duration.
- Early use of IAS injections have been associated with less leg-length discrepancies in patients with asymmetrical pauciarticular JIA.
- Data suggest the effectiveness of using radiographic assistance to guide IAS injections into involved temporomandibular and subtalar joints.

Type of steroid, dosage, and frequency of injection

- Various preparations are available for IAS injection.
- The most frequently studied agents in children are triamcinolone hexacetonide (TH) and triamcinolone acetonide (TA).
- These agents are completely absorbed from the site of injection over 2 to 3 weeks.
- Because of its lower solubility, TH is absorbed more slowly than TA, thereby maintaining synovial levels for a longer period and resulting in lower systemic glucocorticoid levels.
- In comparative studies in patients with JIA, at equivalent doses, TH was found to be more effective than triamcinolone acetonide, betamethasone, and methylprednisolone.

Type of steroid, dosage, and frequency of injection

- Some data indicate that higher doses of TH (about 1 mg/kg) may be associated with a better response.
- Generally, children who weigh less than 20 kg receive 20 mg of TH in large joints.
- Children weighing more than 20 kg receive 30 to 40 mg TH in the hips, knees, and shoulders, and 10 to 20 mg in the ankles and elbows.
- In smaller joints such as the wrist, midtarsal, and subtalar joints, 10 mg is used.
- TH was long the preferred agent, dosing of TA is less well described; some studies have used similar dosing as for TH, whereas others have used higher doses up to 2 mg/kg (with a max of 80 mg for large joints).
- For injections into tendon sheaths and small joints of the hands and feet, 0.25 to 0.50 mL of a combination of methylprednisolone acetate mixed 1:1 with preservative-free 1% lidocaine (Xylocaine) is recommended.

Type of steroid, dosage, and frequency of injection

- The shorter acting steroid is associated with less risk of damage to tendon sheaths or local soft tissue atrophy.
- Repeated injections into the same joint are not performed more than three times per year, although there are few data on which to base this recommendation.
- There are also no controlled studies in children that examine whether postinjection rest has a role. It is the authors' recommendation to limit strenuous activity for the first 24 hours after a joint injection.

Safety/ Toxicity

- Clinical studies indicate an overall favorable adverse-effect profile.
- Iatrogenic septic arthritis is always a potential risk, yet it occurs very rarely and can be avoided with appropriate aseptic precautions.
- Transient crystal synovitis occurs rarely but is self-limited within 3 to 5 days in most cases without any intervention.
- The most frequent adverse effects are atrophic skin changes at the site of injection, particularly of smaller joints such as wrists, ankles, and interphalangeal joints, and asymptomatic calcifications on radiographs in joints after multiple injections that generally resolve over time.

Safety/ Toxicity

- Skin changes are attributed to leakage of long-acting steroids into subcutaneous tissues and can be minimized by clearing the needle track with injection of saline or local anesthetic as the needle is withdrawn from the joint.
- Nonspecific cartilage changes have been seen in children with multiple IAS injections after long-term monitoring.
- IAS injection into the temporomandibular joint has been associated with decreased mandibular growth.
- Systemic steroid effects can occur in rare instances.


Thank You
For Your
Attention


"Only the wounded healer can truly heal."
– Irvin D. Yalom