Rational use of corticosteroids

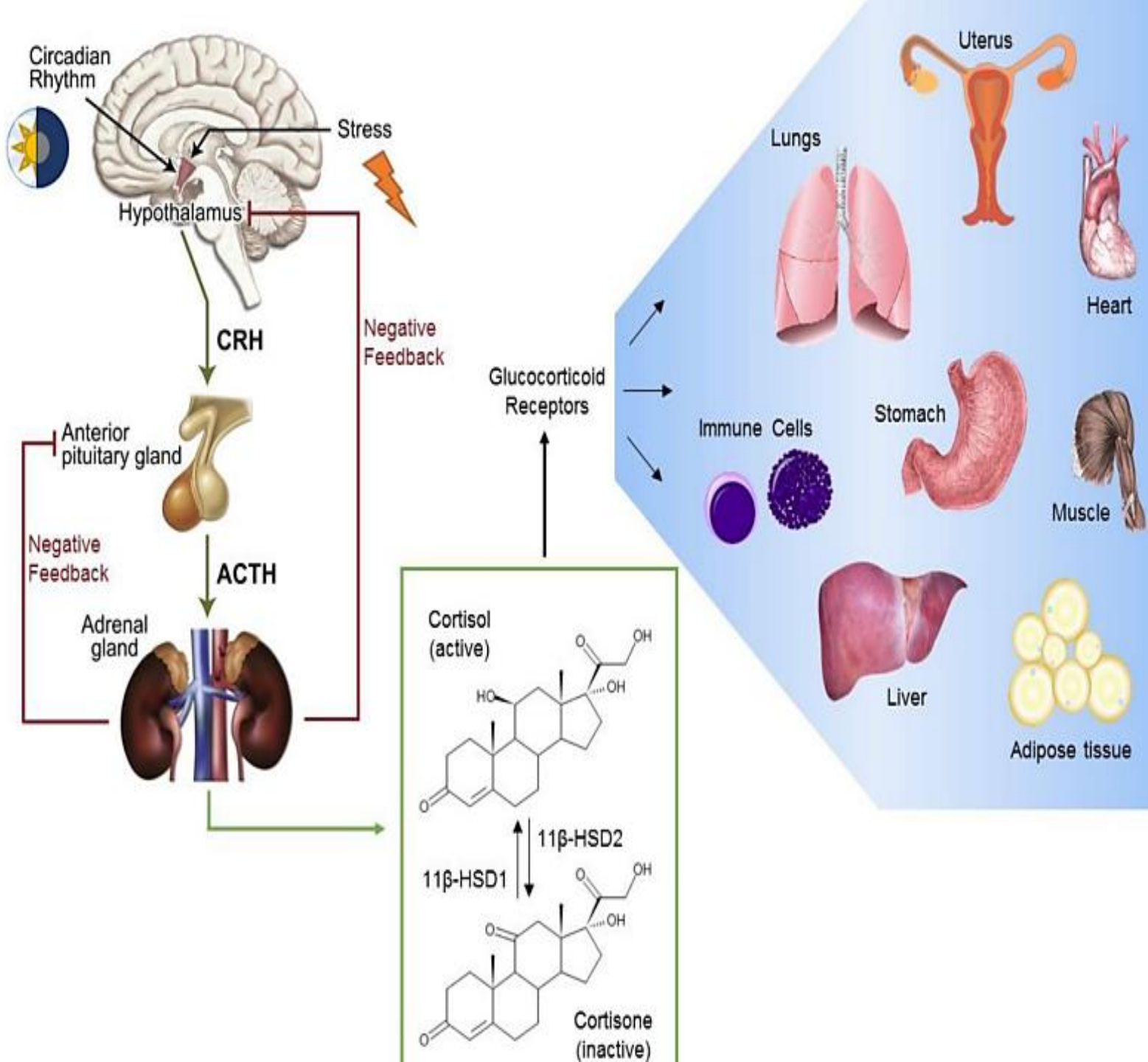
Dr Ghadrdan

Introduction

Glucocorticoids are a group of cholesterol-derived hormones secreted from the adrenal glands

The adrenal cortex synthesizes two different groups of hormones: the glucocorticoids and mineralocorticoids, which, among other things, regulate the carbohydrate and mineral metabolism.

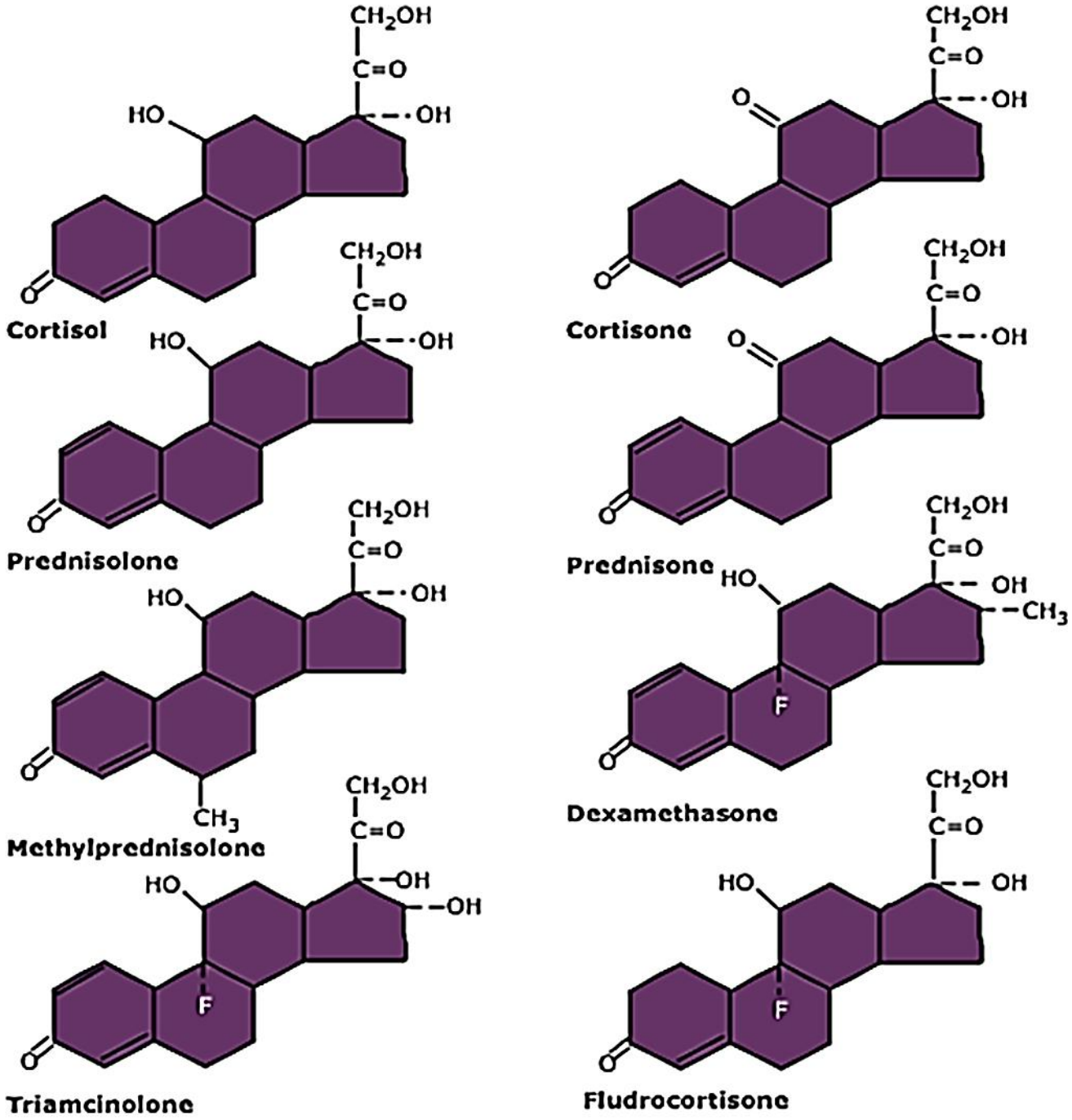
They are involved in a wide array of metabolic, anti-inflammatory, immunosuppressive, and cognitive signaling

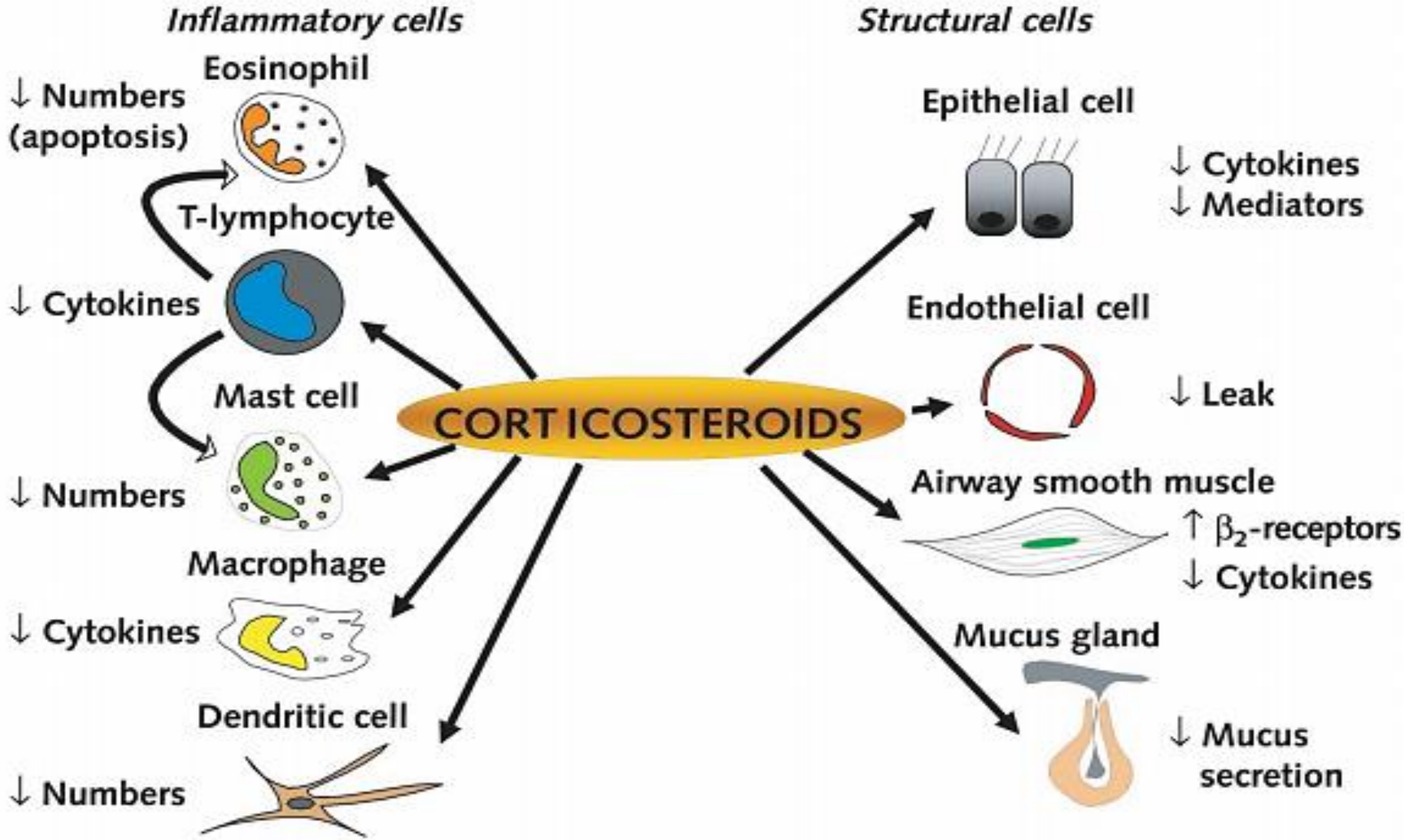


Corticosteroid: Any of a class of steroids (aldosterone, cortisone & hydrocortisone) related to steroids naturally synthesized by the adrenal cortex. Includes
both **glucocorticoids** (e.g. cortisol, prednisone) & **mineralocorticoids** (e.g. aldosterone) that have selectivities for different intracellular receptors affecting gene transcription.

synthetic glucocorticoids often bind to the GR with a higher affinity and thus have much more potent glucocorticoid actions on the HPA axis, the immune system, and energy metabolism than the naturally occurring hormones.

All synthetic glucocorticoids are structurally related to hydrocortisone (cortisol) and corticosterone. Most of them are 21-carbon polycyclic compounds with a steroid structure




Inflammatory cells
Structural cells
Eosinophil
↓ Numbers (apoptosis)
T-lymphocyte
↓ Cytokines
Mast cell
↓ Numbers
Macrophage
↓ Cytokines
Dendritic cell
↓ Numbers
CORTICOSTEROIDS
Epithelial cell
↓ Cytokines
↓ Mediators
Endothelial cell
↓ Leak
Airway smooth muscle
↑ β2-receptors
↓ Cytokines
Mucus gland
↓ Mucus secretion

Indication

1

- ✓ Establish the diagnosis and cause of Cushing's syndrome
- ✓ Treatment of adrenal insufficiency
- ✓ Treatment of congenital adrenal hyperplasia

2

- ✓ Treatment of patients with inflammatory, allergic, and immunological disorders
- ✓ Hematology: hemolytic anemia, leukemia, lymphoma, ITP
- ✓ Other: organ transplantation, antenatal lung maturation, nephrotic syndrome, cerebral edema, MS

- **Low to moderate doses:** Low to moderate doses of prednisolone are doses up to 1 mg/kg per day of prednisone in children or 40 mg per day in adults
- **Higher doses**: Doses >1 mg/kg per day in children or >40 mg daily in adults can be considered higher doses for the purpose of immune function.
- High doses of glucocorticoids can be administered for a few days with little risk.
- **Medical emergencies**
- **Chronic use**

Comparison of representative glucocorticoid preparations

	Equivalent doses* (mg)	Relative anti-inflammatory activity	Duration of action (hours)
Glucocorticoids			
Short acting			
Hydrocortisone (cortisol)	20	1	8 to 12
Cortisone acetate	25	0.8	8 to 12
Intermediate acting			
Prednisone	5	4	12 to 36
Prednisolone	5	4	12 to 36
Methylprednisolone	4	5	12 to 36
Triamcinolone	4	5	12 to 36
Long acting			
Dexamethasone	0.75	30	36 to 72
Betamethasone	0.6	30	36 to 72
Mineralocorticoids			
Fludrocortisone	Not used for an anti-inflammatory effect ¶		12 to 36

The **mineralocorticoid effect** of commonly administered glucocorticoids may be estimated as follows:

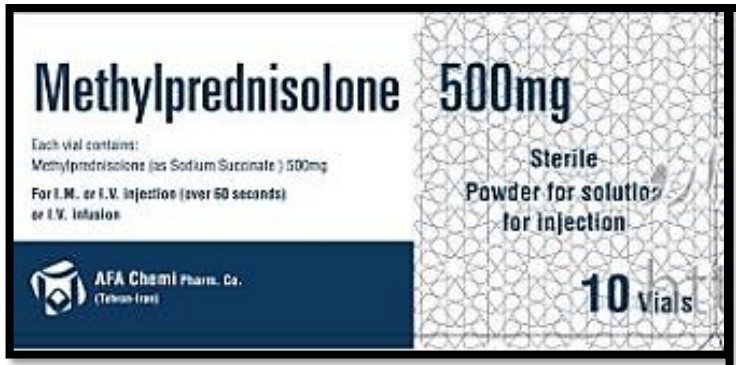
- When given at replacement doses, triamcinolone, dexamethasone, and betamethasone have no clinically important mineralocorticoid activity.
- 20 mg hydrocortisone and 25 mg of cortisone acetate each provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg fludrocortisone.
- Prednisone or prednisolone given at antiinflammatory doses ≥50 mg per day provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg of fludrocortisone.

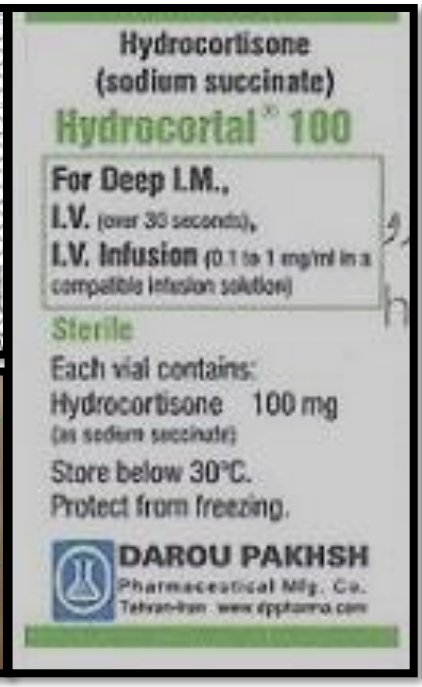
Route of administration

- **Parenteral therapy:** Parenteral administration of high doses may be warranted in emergencies, such as septic shock and severe acute asthma. Intravenous ("pulse") bolus doses of 1 to 2 g of methylprednisolone have been used to treat transplant rejection and some autoimmune diseases such as rheumatoid arthritis
- **Oral administration**: Oral preparations are usually used for chronic therapy. They are absorbed within approximately 30 minutes
- **Nonsystemic administration :** When possible, nonsystemic glucocorticoid therapy should be used in an attempt to deliver higher local concentrations while minimizing systemic exposure. Intraarticular injection for joint inflammation, inhalation therapy for asthma, and topical application for inflammatory skin disorders are examples.

Parenteral corticosteroids

Methylprednisolone succinate 250, 500mg
Methylprednisolone acetate 40mg/1ml
Hydrocortisone 100mg
Betamethasone Disodium phosphate 4mg/1ml
Betamethasone Disodium phosphate / betamethasone acetate 3/3
Dexamethasone 8mg/2ml
Triamcinolone acetonide 40mg/1ml





Oral dose administration

- Usually given as a single dose early in the morning, does not suppress the circadian peak in cortisol secretion the next morning. Thus, the patient is exposed to the sum of the exogenous prednisone plus his own normal or near-normal cortisol production.

- Administer tablets after meals or food or milk to decrease GI upset.


۱۰۰ قرص خط دار
پردنیزولون ۵
هر قرص حاوی:
پردنیزولون ۵ میلی گرم
دستور پزشک:
LOT 5060
EXP 2022.02.01


۱۰۰ قرص خط دار
پردنیزولون ۵۰
هر قرص حاوی:
پردنیزولون ۵۰ میلی گرم
دستور پزشک:
ساخت شرکت داروسازی ابوریحان (سهامی عام)
IFDA
http://irc.fda.gov.ir/nfi


Budegit
Budesonide
3mg
90 Delayed Release Capsules
Each Capsule contains
Budesonide 3 mg
B.No
D/P
سازمان غذا و دارو
http://irc.fda.


۱۰۰ قرص خط دار
دگزامتازون ۴
هر قرص خط دار حاوی:
۴ میلی گرم دگزامتازون
ساخت شرکت داروسازی ابوریحان


۱۰۰ قرص
دگزامتازون ۰/۵
هر قرص حاوی:
دگزامتازون ۰/۵ میلی گرم
ساخت شرکت داروسازی ابوریحان (سهامی عام) تهران - ایران


۱۰۰ قرص خط دار
هیدروکورتیزون
هر قرص حاوی:
هیدروکورتیزون ۱۰ میلی گرم
ساخت شرکت داروسازی ابوریحان (سهامی عام) تهران - ایران


۱۰۰ قرص خط دار
بتامتازون
هر قرص حاوی:
بتامتازون ۰/۵ میلی گرم
ساخت شرکت داروسازی ابوریحان (سهامی عام)


۱۰۰ قرص خط دار
فلودروکورتیزون
هر قرص حاوی:
فلودروکورتیزون استات ۰/۱ میلی گرم
دستور پزشک
تهران - ایران

Topical corticosteroids

- Vehicles : rapid delivery of the drug to the stratum corneum and into the lower layers of the skin
- Vehicles are usually a combination of several chemicals, including emollients, humectants, emulsifying agents (eg, polysorbates), solvents, penetration enhancers, and preservatives.
- Oils act as emollients and, because of their occlusive properties, often enhance drug penetration. Liquids in vehicles evaporate, providing a cooling, soothing sensation, and may aide exudative lesions to dry.
- If the wrong formulation is used, the response to therapy may be delayed, inadequate, or, in some cases, worsened.

Formulation	
Ointment	This type of vehicle facilitates **heat retention**, decreases transepidermal **water loss**, provides enhanced medication **absorption**, and is semiocclusive. Ointments are generally the most **potent formulations** due to their occlusive effect, but patient acceptance and adherence to treatment may be low because they are greasy, sticky, and generally unsuitable for application to large body areas or to hairy areas.
Cream	Creams are semisolid emulsions of 20 to 50 percent oil in water. They are cosmetically appealing and can be washed off with water. For the same topical corticosteroid, cream formulations are **usually stronger than lotions** but less potent than ointments.
Lotions	Lotions consist of suspensions or solutions of medication in water, alcohol, or other liquids. Thus, patients must **shake** the container before use. Lotions (as well as foams and solutions) are especially useful in **hairy areas** and in conditions where large areas have to be treated. In addition, as lotions evaporate, they provide a cooling and drying effect, making them useful for treating **moist dermatoses** and/or **pruritus**. Like creams, lotions can be washed off with water.
Gels	Gels are an oil-in-water emulsion with alcohol in the base, and they dry in a thin, greaseless, nonstaining film. Gel formulations combine the best therapeutic advantages of ointments with the best cosmetic advantages of creams, and they are cosmetically attractive to many patients . They are easily absorbed and are an efficient method for delivering topical corticosteroids **to hair-bearing areas**.
Foams	Particularly for **inflamed** skin and for **scalp** dermatoses. Unlike other vehicles, foams depend on the vehicle delivery system for the physical delivery of the drug. Because of the complexities in designing vehicle delivery systems, foam preparations tend to be more **expensive** than other vehicles.

Topical therapy: Vehicle selection for specific body sites

Vehicle	Smooth, nonhairy skin; thick, hyperkeratotic lesions	Hairy areas	Palms, soles	Infected areas	Between skin folds; moist, macerated lesions
Ointment	+ + +		+ + +		
Cream	+ +	+	+ +	+	+ +
Lotion		+ +		+ +	+ +
Solution		+ + +		+ + +	+ +
Gel		+ +		+	+
Foam	+ +	+ + +	+ +	+ +	+ +

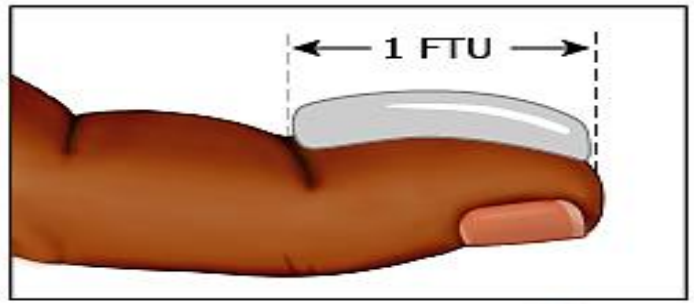
+: infrequently used; + +: acceptable vehicle; + + +: preferred vehicle.

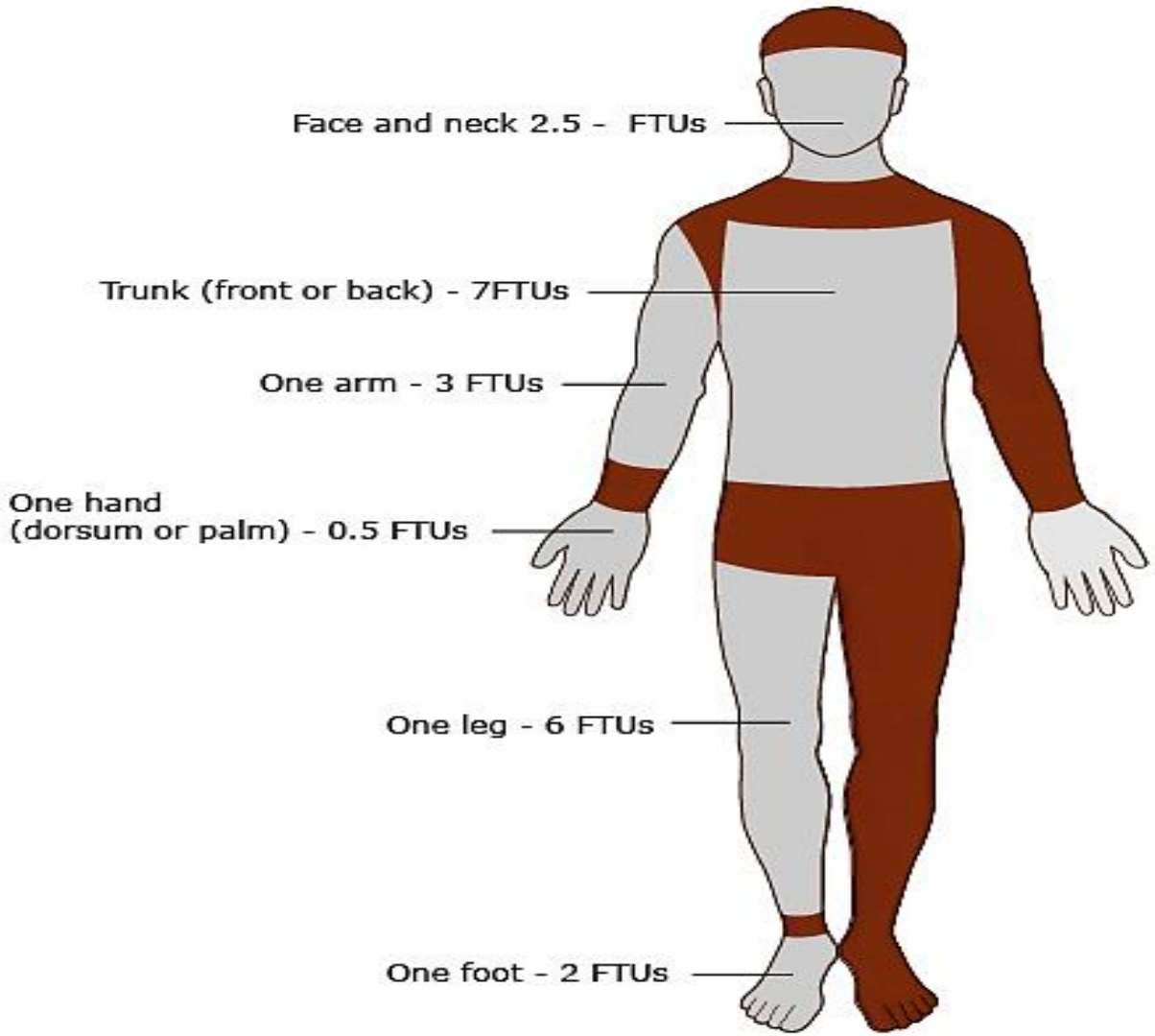
Topical corticosteroids

- The area of the body on which it is applied (eg, intertriginous areas > forehead > scalp > face > forearm)
- Whether the vehicle contains **urea**, **dimethylsulfoxide**, or other agents (eg, salicylic acid) that increase absorption
- Whether the area is covered with an **occlusive dressing**, which may increase absorption as much as 10-fold
- The skin integrity; glucocorticoids are absorbed through **areas of inflammation** and desquamation better than normal skin
- The patient's age; infants and young children, whose stratum corneum is much thinner than that of adults, absorb topical steroids more readily

Topical corticosteroids

- Amount
  A single application to the whole body of an adult will require 30 of product. An area of one hand (palm and digits) will require 0.3 g per application. No more than 45 g/week of potent or 100 g/week of a moderately potent topical steroid should be applied if systemic absorption is to be avoided. In children, the amounts should be smaller.
- Application once or twice daily is usually sufficient, but frequency may increase when treating areas where the preparation can easily be wiped off (for example palms and soles).
- The shortest course of treatment is recommended for acute diseases, although small recalcitrant lesions may need to be treated for longer. **Treatment should not be longer than two weeks on the face and 3–4 weeks on the rest of the body**. For longer treatment periods, intermittent therapy such as every other day, weekend-only application or a resting period of 1–2 weeks between cycles may be an option.





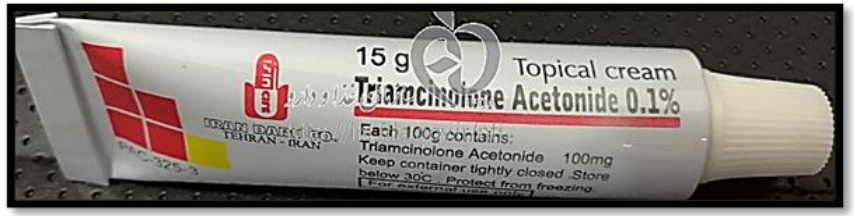
One FTU is equal to 0.5 grams. The suggested dose of FTU is dependent upon the body region being treated. On average, the number of FTUs needed in certain body areas are as follows:

- Face and neck – 2.5
- Trunk (front or back) – 7
- One arm – 3
- One hand (dorsum or palm) – 0.5
- One leg – 6
- One foot – 2

قدرت بسیار بالا	کلوبتازول پروپیونات ۰.۰۵٪
قدرت بالا	بتامتازون پروپیونات
	مومتازون ۰.۱٪
قدرت متوسط	تریامسینولون ۰.۱٪
قدرت کم	فلئوسینولون
	بتامتازون والرات ۰.۱ ٪
قدرت خیلی کم	هیدروکورتیزون (پماد و کرم)

	Presentations available		
	Ointment	Cream	Lotion
Superpotent – Class 1 USA, Class I UK			
Betamethasone dipropionate 0.05% in optimised vehicle	X		
Clobetasol propionate 0.05%	X		
High potency – Class 2/3 USA, Class II UK			
Betamethasone dipropionate 0.05%	X		
Betamethasone valerate 0.1%	X		
Mometasone furoate 0.1%	X	X	
Moderate potency – Class 4/5 USA, Class III UK			
Betamethasone dipropionate 0.05%		X	X
Betamethasone valerate 0.05%	X	X	
Triamcinolone acetonide 0.1%		X	
Methylprednisolone aceponate 0.1%	X	X	X
Clobetasone 0.05%		X	
Low potency – Class 6/7 USA, Class IV UK			
Hydrocortisone or hydrocortisone acetate 0.5%, 1%	X	X	X
Desonide 0.05%	X	X	X

Hydrocortisone 1% Cream/ ointment
Triamcinolone 0.1% Cream/ ointment
Mometasone Furoate 0.1% Cream/ ointment/ lotion
Betamethasone valerate 0.1% Cream/ ointment/ lotion
Clobetasol propionate 0.05% Cream/ ointment/ lotion
Fluocinolone acetonide 0.025% Cream/ ointment



Rectal corticosteroids

Enema
60 mL

انـــــما
۶۰ میلی لیتر

Hydrocortisone 100 - Emad

هیدروکورتیزون ۱۰۰ - عمـــــاد

Hydrocortisone

هیدروکورتیزون

- Each 60 mL contains:
  Hydrocortisone 100 mg

- هر ۶۰ میلی لیتر محتوی :
  هیدروکورتیزون ۱۰۰ میلی گرم

فقط برای استعمال داخل مقعدی است.

- دور از دید و دسترس اطـــفال نگهـــداری شود.
- در دمای کمتر از ۳۰ درجه سانتیگراد، دور از نور نگهداری و از یخ زدگی محافظت شود.
- قبل از مصرف ظرف را خوب تکان دهید.

دستـور پزشـک:

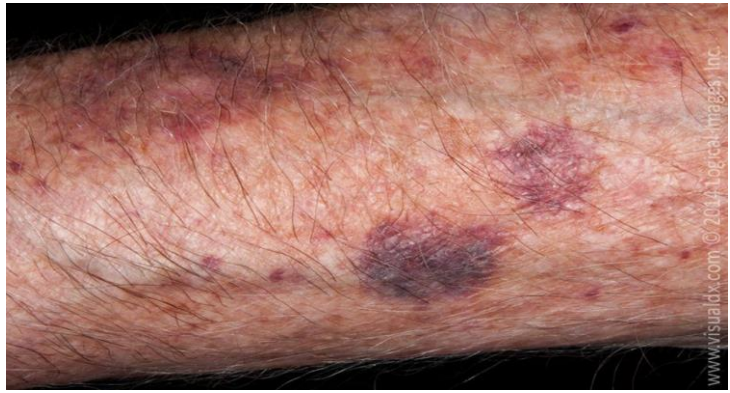
Ear and eye products

Adverse effects

- Ophthalmologic effects
- Cardiovascular effects
- Gastrointestinal effects
- Bone and muscle effects
- Neuropsychiatric effects
- Metabolic and endocrine effects
- Immune system effects
- Dermatologic effects

Dermatologic effects

- Many clinically relevant adverse effects of glucocorticoids on the skin and appearance that have been observed even at **lower doses** include skin **thinning** and **ecchymoses**, **Cushingoid appearance**, acne, weight gain, mild hirsutism, facial erythema, and striae
- **Skin thinning and ecchymoses:** **Most common**, even at low doses, Antiproliferative GC effect on fibroblasts & keratinocytes, resulting in dermal atrophy.
- The ecchymoses or purpura associated with glucocorticoid use often affects the **sun-exposed areas** of the dorsum of the hand and forearm
- **Cushingoid features:** Redistribution of body fat with truncal obesity, buffalo hump, and moon face, **dose- and duration-dependent** and can develop within the **first two months** of therapy
- **Weight gain**: fluid retention and appetite stimulation

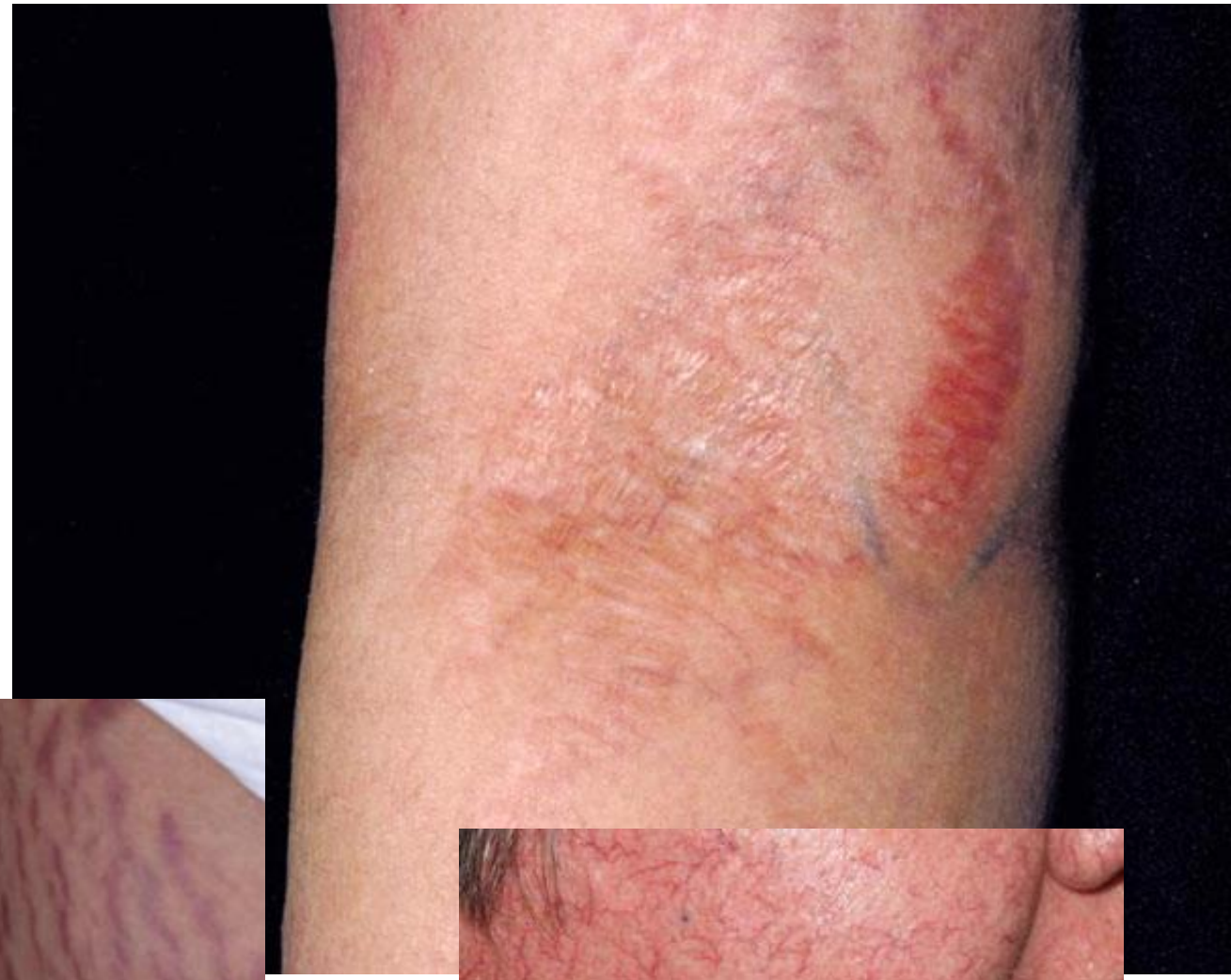


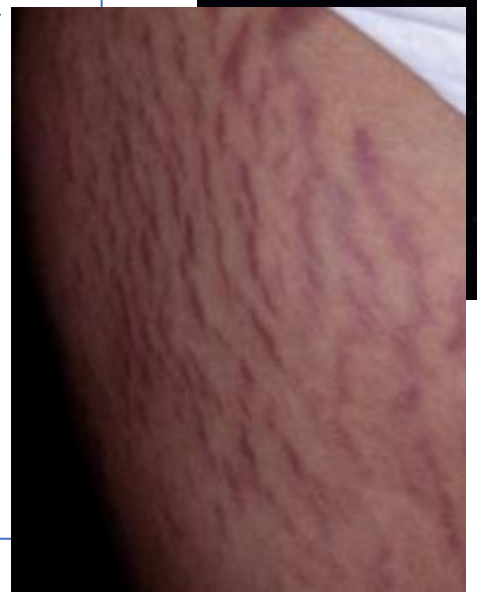
Adverse effects

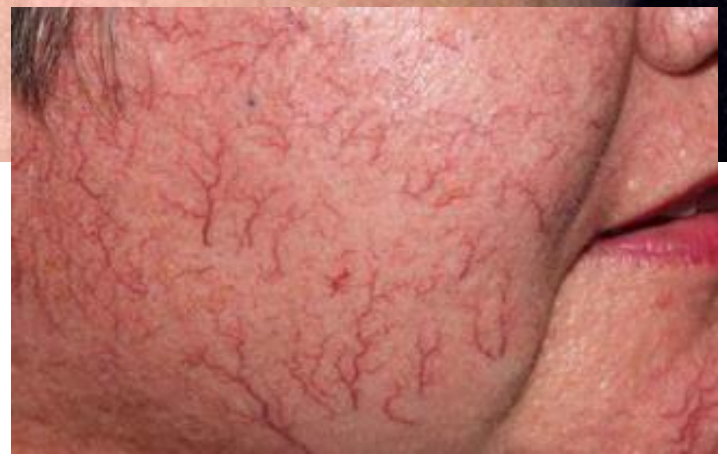
- **Atrophy, telangiectasia, striae**

Superpotent and potent topical corticosteroids may induce atrophy, telangiectasia, and striae as early as two to three weeks following daily application

Intertriginous and thin-skinned, highly penetrable areas (eg, eyelid, face in general, genitals) are particularly susceptible to atrophy



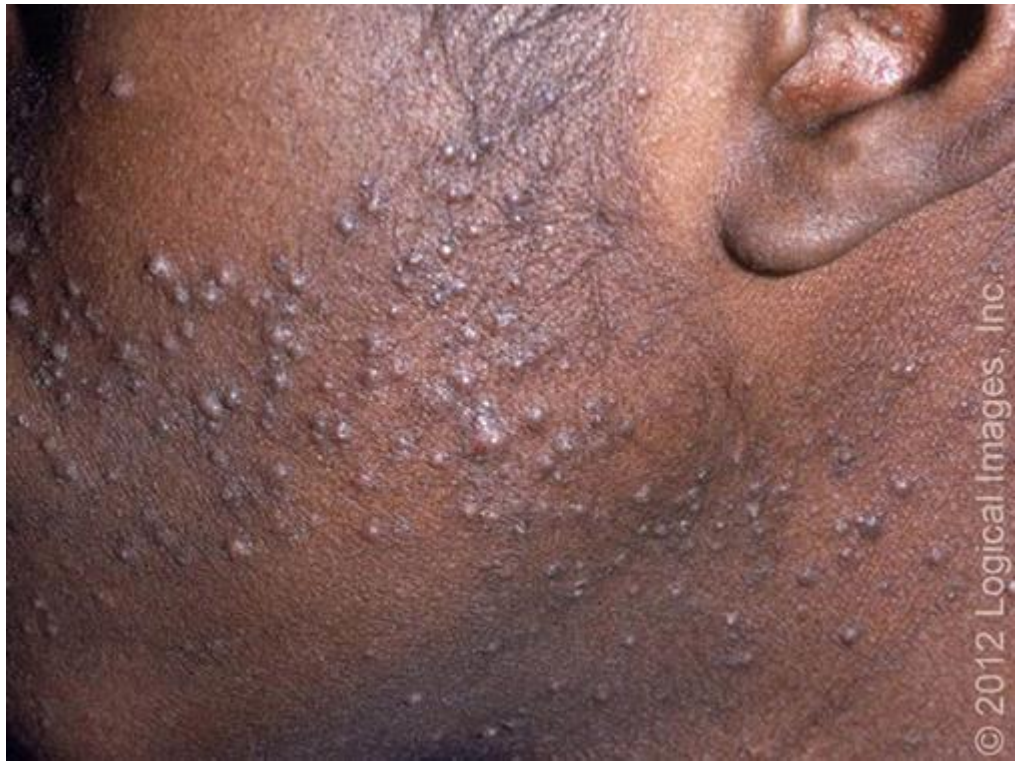




Acneiform eruption

Prolonged use of topical corticosteroids may induce an acneiform eruption that resolves with discontinuance of corticosteroid treatment.

Chronic application of topical corticosteroids to the face may also cause a dry, scaly eruption with scattered, follicular pustules around the mouth (perioral dermatitis), and use of potent topical corticosteroids on the face can cause a facial eruption that is indistinguishable from rosacea



Allergic sensitization

Vehicles or **preservatives** are most often the sensitizing agents, although contact allergy against the steroid moiety itself is possible.

Topical glucocorticoid-induced contact allergy should be suspected in patients with chronic dermatoses that appear to be exacerbated by therapy.

Cross-reactions between different topical corticosteroids are determined by their chemical structure. Cross-reactivity between groups is not uncommon.

Class C topical corticosteroids have the lowest rate of allergenicity.

Class	
A	Hydrocortisone, prednisolone, methylprednisolone
B	Triamcinolone, budesonide
C	Betamethasone, dexamethasone,
D	Beclomethasone, clobethasone, fluticasone, mometasone,

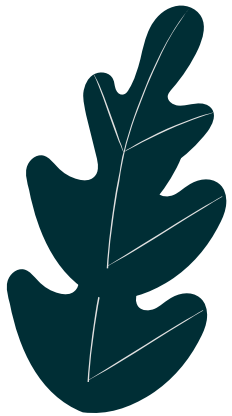
Ophthalmologic effects

Cataracts

- Dose-related
- Commonly occur after **prolonged** use (more common with prednisolone doses greater than 10 mg/day or with medications that have been administered for more than one year)
- Usually bilateral and develop slowly

Glaucoma

- Dose-related
- The mechanism is not well established but is thought to be related to reduced outflow at the trabecular meshwork.
- Glucocorticoid preparations (ie, ocular, oral, inhaled, and periocular dermatologic preparations) can raise IOP in open-angle glaucoma patients
- Most commonly in patients who use glucocorticoid eye drops, although it has been observed in chronic and, to a lesser extent, acute systemic glucocorticoid use
- **Two-week** (or longer) course of glucocorticoids is required before an increase in IOP is seen.



Cardiovascular effects

- Glucocorticoid use has been associated with a variety of adverse cardiovascular effects including fluid retention, premature atherosclerotic disease, and arrhythmias.
- Cardiovascular disease risk is **dose-dependen**t and may be low or absent in patients on low-dose glucocorticoid therapy
- Premature atherosclerotic disease: Glucocorticoid use has been associated with increased rates of myocardial infarction, stroke, heart failure
- Arrhythmias: atrial fibrillation and flutter, Serious adverse cardiovascular toxicities, including sudden death, have been reported in occasional patients who have been given pulse infusions of glucocorticoids

Hypertension

- In patients receiving low doses of glucocorticoids (eg, 10 mg/day of prednisone), significant hypertension may be better explained by age and initial blood pressure than by the glucocorticoids themselves.
- Hypertension: Increased peripheral vascular sensitivity to adrenergic agonists , Increased hepatic production of renin substrate (angiotensinogen) ,Increased mineralocorticoid activity
- Corticosteroids with strong mineralocorticoid effects, such as fludrocortisone and hydrocortisone, produce the greatest amount of fluid retention.
- Fludrocortisone causes significant blood pressure increases and, thus, is useful in treating patients with postural hypotension

Gastrointestinal effects

- Gastritis, ulcer formation, and gastrointestinal bleeding

- Glucocorticoid use is associated with a nearly twofold increased risk of a gastrointestinal adverse effect among patients also taking NSAIDs when compared with those who use NSAIDs alone

Bone and muscle effects

Myopathy :

- weakness induced by the catabolic effects of excess glucocorticoid on skeletal muscle. Hypokalemia can accentuate the weakness.
- Myopathy is an infrequent complication of glucocorticoid therapy. It presents as painless proximal motor weakness in both the upper and lower extremities.
- Usually develop over several weeks to months.
- Higher doses can lead to a more rapid onset.
- Myalgias and tenderness of the muscles are typically not seen.
- Symptoms will typically improve and then resolve at 3 to 4 weeks after discontinuing the corticosteroid

Myopathy

- **Risk factors:** dose (>10 mg/day of prednisone), systemic glucocorticoid, **fluorinated** preparations, such as dexamethasone and triamcinolone, compared with nonfluorinated preparations, such as prednisone and prednisolone
- The diagnosis is generally established by demonstrating improved strength within **three to four weeks** after sufficient dose reduction, which is usually to doses of less than 10 mg/day of prednisone or its equivalent.
- Minimizing the dose and duration of glucocorticoid exposure is the most important intervention.
- In patients treated with a fluorinated preparation, such as dexamethasone, substituting a nonfluorinated preparation, such as prednisone, can be tried if the patient cannot be weaned from glucocorticoid therapy

Glucocorticoid-induced osteoporosis

- Glucocorticoid therapy is associated with risk of bone loss and fracture risk
- Osteoporosis: Corticosteroids increase catabolism of 25(OH) vitamin D and 1,25(OH) 2vitamin D
- Glucocorticoids may increase bone resorption by decreasing secretion of androgens and estrogens, mediated primarily by inhibition of gonadotropin secretion

Prevention

- The dose and the duration of glucocorticoid therapy should be as low as possible because even what are thought to be replacement doses or chronic inhaled glucocorticoids can cause bone loss
- Topical therapy
- Weight bearing exercises
- Avoid smoking and excess alcohol
- **Calcium and vitamin D:** ACR suggests that all patients taking glucocorticoids (any dose with an anticipated duration of ≥3 months) maintain a total calcium intake of 1000 to 1200 mg/day and vitamin D intake of 600 to 800 international units/day through either diet and/or supplements

Adults ≥40 years	• FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) with the adjustment for GC dose **and** BMD testing (if available, or with-out BMD if it is not available) as soon as possible, but **at least within 6 months** of the initiation of GC treatment.
Adults <40 years	BMD testing should be done as soon as possible but **at least within6 months** of the initiation of GC treatment if: -The patient is at high fracture risk because of a history of previous OP fracture(s) or -If the patient has other significant OP risk factors (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, smoking, alcohol use at>3units/day

Initial fracture risk assessment

FRAX® Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References | CE Mark | English

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: Iran Name/ID: el About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 62 Date of Birth: Y: M: D:
2. Sex — Male / Female
3. Weight (kg): 95
4. Height (cm): 164
5. Previous Fracture — No / Yes
6. Parent Fractured Hip — No / Yes
7. Current Smoking — No / Yes
8. Glucocorticoids — No / Yes
9. Rheumatoid arthritis — No / Yes
10. Secondary osteoporosis — No / Yes
11. Alcohol 3 or more units/day — No / Yes
12. Femoral neck BMD (g/cm^2): Select BMD

Clear | Calculate

BMI: 35.3

The ten year probability of fracture (%)

without BMD

Major osteoporotic	3.5
Hip Fracture	0.6

Weight Conversion

Pounds → kg

Convert

Height Conversion

Inches → cm

Convert

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Individuals with fracture risk assessed since 1st June 2011

Adults ≥40 years

- **Low risk** 10-year risk of hip or a major osteoporotic fracture of ≤1 and <10 percent, respectively
- **Medium risk** 10-year risk of hip or a major osteoporotic fracture >1 to <3 percent and 10 to 19 percent, respectively
- **High risk** History of a fragility fracture, a lumbar spine or hip T-score below -2.5, or 10-year risk of hip or a major osteoporotic fracture ≥3 and 20 percent, respectively

Adults <40 years

- **Low risk** No medium- or high-risk factors other than glucocorticoid treatment
- **Medium risk** Hip or spine Z-score <-3, **or** rapid bone loss (≥10 percent over one year) **and** continuing glucocorticoid treatment at ≥7.5 mg/day for ≥6 months
- **High risk** History of a fragility fracture

- lifestyle modification and calcium and vitamin D supplementation, the ACR recommend oral bisphosphonates for adults at medium or high risk of major fracture.
- If oral bisphosphonates contraindicated or not tolerated, options include IV bisphosphonates, triparatide, denosumab, and raloxifen.
- BMD q2-3Y

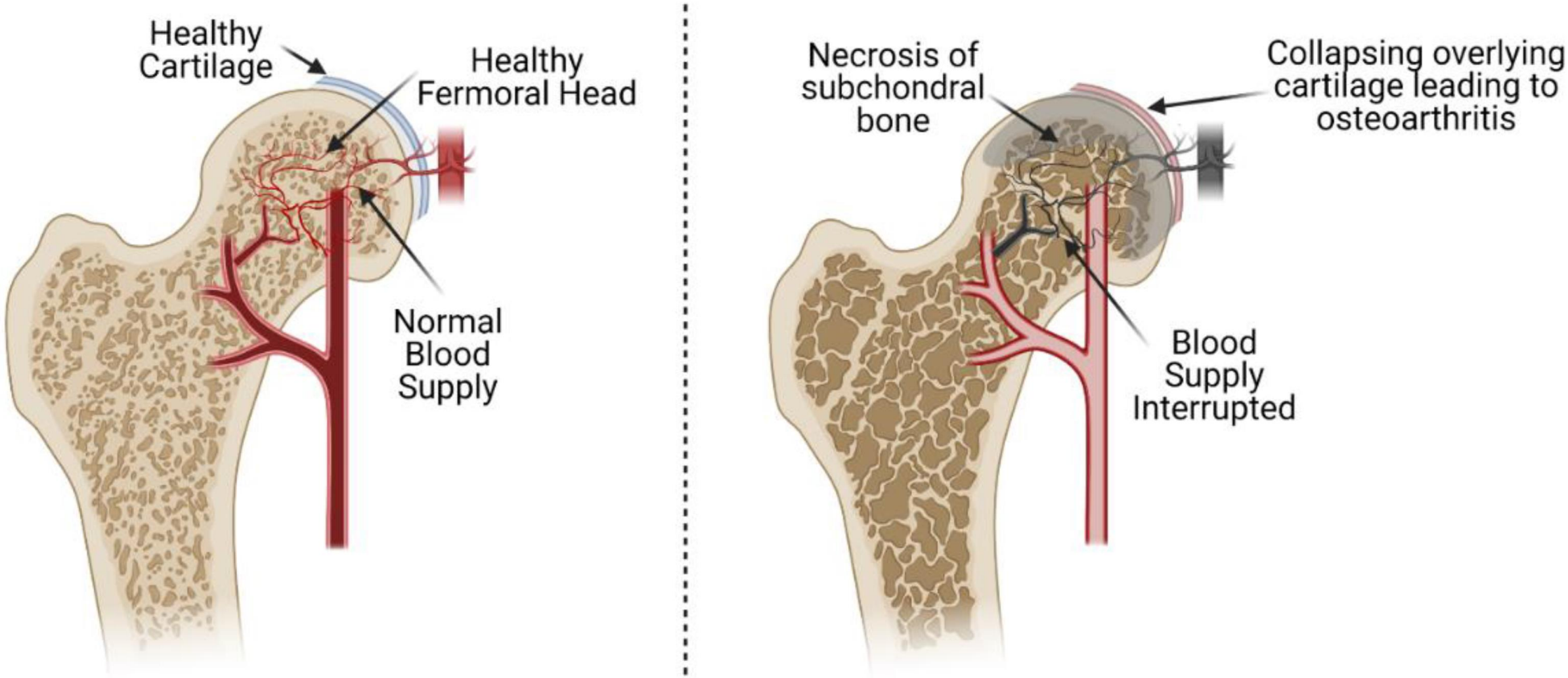
Avascular Necrosis of Femur Head

- Animal studies indicate GC-induced increased levels of serum lipids result in both increased formation of microemboli in the arteries supplying bone, and fat-related blockage of venous flow from bone. These mechanisms result in increased ischemia in bone, which most commonly affects the **femoral head**, but can occur in any skeletal site such as the knee, shoulder, ankle or hand

- AVN usually causes **significant chronic pain** and reduced mobility, with some patients requiring joint replacements.

- AVN usually occurs with **high doses** of corticosteroids over a period of a few weeks to several years. Other known risk factors for AVN include: alcoholism, infections, marrow infiltrating diseases, coagulation defects, sickle cell anemia and some autoimmune diseases.

- In the presence of a confirmed diagnosis of AVN, **stopping or interrupting** corticosteroid treatment should be considered.


Healthy Cartilage
Healthy Fermoral Head
Normal Blood Supply
Necrosis of subchondral bone
Collapsing overlying cartilage leading to osteoarthritis
Blood Supply Interrupted

Neuropsychiatric effects

Mood disorders: sense of well-being within several days of starting the medications; mild euphoria or anxiety .
Hypomanic reactions and activated states are more common early in therapy than is depression, but the prevalence of depression is greater in patients on more longstanding therapy, even on low to moderate doses

Psychosis : Corticosteroids can cause a range of psychiatric disorders, including psychosis, agitation, insomnia, irritability, hypomania, anxiety, and mood lability. Short courses of corticosteroids can produce euphoria in many individuals and progress to depressive symptoms with extended courses. Psychosis is typically only seen with **high doses** (over 20 mg prednisone/day or equivalent) at **prolonged periods**. These psychotic features may require antipsychotic treatment if they persist.

- Risk factors for neuropsychiatric effects of corticosteroids include higher dose, history of neuropsychiatric disorder, female sex, and use of long-acting formulations.
- Symptom onset is variable, but typically occurs within days to weeks of steroid use and usually **resolve** completely within days to months after steroid cessation
- Mainstay of treatment is steroid discontinuation if possible, or tapering if abrupt discontinuation is contraindicated
- Consider **pharmacologic therapy** for symptom control or mood stabilization if severe symptoms or if steroid discontinuation is contraindicated

Metabolic and endocrine effects

Hyperglycemia:

- Hepatic gluconeogenesis, inhibition of glucose uptake in adipose tissue direct suppression of insulin release
- A **dose-dependent** hyperglycemic effect occurs in patients within hours of exposure, and the effect seems to be greater on **postprandial glucose** levels than fasting glucose levels

Hypokalemia : Induced by increased mineralocorticoid activity

HPA axis suppression

- Both endogenous and exogenous glucocorticoids exert negative feedback control on the HPA axis by suppressing hypothalamic CRH production and pituitary ACTH secretion

- The time course for **recovery** of the HPA axis after stopping glucocorticoid therapy following a prolonged treatment course is variable and depends upon a variety of factors including the dose, time of day, and duration of glucocorticoid therapy

Non suppressed HPA axis

- Any patient who has been taking **any dose** of glucocorticoid for less than three weeks

- Patients who have received **morning** doses of **less** than 5 mg/day of prednisolone or its equivalent for any length of time

Suppressed HPA axis patients

- Any patient who is currently taking more than **20 mg/day of prednisolone** or its equivalent (eg, 16 mg/day of methylprednisolone, 2 mg/day of dexamethasone, or 80 mg/day of hydrocortisone) for more than three weeks
- Any patient on glucocorticoids who has **clinical Cushing's syndrome**
- These patients be treated with supplemental glucocorticoids in the perioperative period in accordance with the magnitude of the stress
- Chronic use of inhaled or high-potency, topical glucocorticoids has potential to cause HPA axis suppression.
  - ≥750 mcg daily of fludrocortisone (1500 mcg daily for other IGCs) for more than three weeks prior to surgery
  - ≥2 g/day of high potency or super high potency topical corticosteroids (class I-III) for more than three weeks prior to surgery

Intermediate patients (HPA suppression unknown)

- Patients currently taking doses of 5 to 20 mg of prednisolone (or its equivalent) for more than three weeks have considerable variability in HPA axis suppression that does not correlate well with age, sex, dose, or duration of therapy. This variability is probably due to differences in rates of glucocorticoid metabolism.

- Additionally, doses lower than the equivalent of 5 mg of prednisolone daily taken in the evening may disrupt the normal diurnal variation and the way the patient responds to surgical stress.

- We suggest that all patients in this intermediate category undergo preoperative evaluation of their HPA axis

Infection risk

- **Dose and intensity of therapy**: Infection risk is directly related to glucocorticoid dose. The risk begins to normalize as soon as high-dose therapy is complete. In contrast, the effects on phagocytic cell function with longer-term, low-dose use are minimal, but there may be some inhibition of adaptive immune responses with increasing duration of therapy

- **Patient-specific factors**: Patient specific factors that may influence infection risk include underlying disease, the presence of concomitant immunosuppressive therapies

Steroid withdrawal syndrome

- Steroid withdrawal syndrome may occur after rapid tapering or abrupt withdrawal of corticosteroid therapy
- Characterized by sleep and appetite disturbances, depression, fatigue, irritability, personality changes, decreased concentration, agitation, psychosis, and suicide
- Non-life-threatening somatic symptoms can include fever, nausea, weight loss, desquamation of the skin, arthralgias, and weakness
- Typically resolves within 2-8 weeks without corticosteroid treatment, but reinitiation of treatment with slower taper may be required if symptoms persist
- Stable decrement of 5 to 10 percent every one to four weeks

Pregnancy

- Cortisol and prednisolone, but not betamethasone and dexamethasone, are enzymatically inactivated in the placenta. Perinatally, only 10% of the maternal concentration of prednisone and prednisolone are found in the fetal blood. With betamethasone it is 30% and with dexamethasone nearly 100%
- A systemic, antiallergic, antiinflammatory or immunosuppressive treatment of the mother with glucocorticoids may also be carried out for relevant indications. **Prednisone and prednisolone** are the drugs of choice for this.
- With the rarely necessary higher dose treatment over many weeks, **fetal growth** should be observed sonographically. If this therapy continues until birth, **adrenal insufficiency** in the newborn must be considered and treated if it occurs.
- Treatment of the mother with high doses of glucocorticoids during weeks 8–11 of pregnancy may warrant an ultrsonographic evaluation of the fetal face for the detection of **clefting of the lip** and palate

Pregnancy

- There is no objection to occasional use of topical glucocorticoids or topical antiphlogistics in limited areas. Very potent steroids such as clobetasol propionate should be avoided during pregnancy. However, their use may be favored to systemic steroids if required because of disease severity
- According to the International Asthma Guidelines, ICS is the preferred treatment of choice for long-term therapy in pregnancy. More thoroughly investigated substances such as **budesonide** are to be preferred.
- Emergency treatments are obviously not subject to any dosage limitations
- The induction of lung maturation with a threatening premature birth is currently carried out with a one-time betamethasone cycle between the twenty-fourth (achievement of viability) and the thirty-fourth week of pregnancy. In individual cases, a second cycle follows after the twenty-eighth week of pregnancy has passed.

Lactation

- With maternal **inhalable corticosteroid** therapy, breastfeeding may continue without limitation. **Budesonide is the best-studied drug.**

- **Prednisolone, prednisone, and methylprednisolone** are the corticoids of choice for systemic treatment during breastfeeding. Even high doses of up to 1 g administered once or for a few consecutive days – for example, for an asthma attack or multiple sclerosis – do not require any limitation of breastfeeding. When such high doses are given repeatedly, there should be a **3–4 hour** wait for breastfeeding if that can be arranged. Other corticoids are probably also tolerated. Routine inhalation of a corticoid for asthma is no cause for concern

Drug interactions

- Glucocorticoids undergo metabolism in the liver and other tissues by **CYP 3A4** and other transformations. In vitro data suggest that **dexamethasone**, **methylprednisolone** and **prednisolone** are also substrates of **P-glycoprotein** membrane efflux transporters. Medications that strongly inhibit or induce CYP 3A4 and/or P-glycoprotein transporters may significantly alter the glucocorticoid serum concentration

- Medications that increase the systemic glucocorticoid concentration include **estrogen derivatives**, such as oral contraceptives and strong inhibitors of CYP 3A4 including some antibiotics (eg, clarithromycin, ritonavir, telaprevir, telithromycin) and antifungals (eg, posaconazole, voriconazole).

- Medications that reduce the systemic glucocorticoid concentration include aluminum/magnesium containing antacids, which decrease prednisone bioavailability due to decreased oral absorption, and strong inducers of CYP 3A4 (eg, carbamazepine, phenobarbital, phenytoin and rifampin)

Drug interaction	
Desmopressin	Do not use desmopressin with systemic or inhaled glucocorticoids. Desmopressin may be started or resumed 3 days or 5 half-lives after discontinuation of the corticosteroid, whichever is longer.
- BCG Products - Poliovirus Vaccine (Live/Trivalent/Oral) - Rubella- or Varicella-Containing Live Vaccines	This interaction applies to systemic corticosteroids at a dose equivalent to more than 2 mg/kg or 20 mg/day of prednisone (for persons over 10 kg) given for more than 2 weeks. Corticosteroids (Systemic) may enhance the adverse/toxic effect of BCG Products. Specifically, the risk of vaccine-associated infection may be increased.
Antacids	Antacids may decrease the bioavailability of Corticosteroids (Oral). Consider separating the doses of these agents by 2 or more hours.
Denosumab	Denosumab may enhance the immunosuppressive effect of Corticosteroids (Systemic), This interaction applies to systemic corticosteroids at a dose equivalent to more than 2 mg/kg or 20 mg/day of prednisone (for persons over 10 kg) given for more than 2 weeks.
warfarin	Marked INR increases have been reported and INRs should be closely monitored (daily has been recommended5) if this or other high-dose corticosteroids
Antidiabetics	The effects of systemic corticosteroid treatment in diabetics should be closely monitored and the dosage of the antidiabetic raised as necessary. Antidiabetics are sometimes needed in non-diabetic patients taking corticosteroids to reduce blood glucose levels
Midazolam	The metabolism of oral midazolam may be increased in patients receiving long-term treatment with corticosteroids.
Azole	Administration of the two drugs by 12 h
Bile-acid binding resins	The usual recommendation is to give other drugs one hour before or 4 to 6 hours after taking colestyramine, and one hour before or 4 hours after taking colestipol

Thanks