Glucocorticoids

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Summary

Synthetic glucocorticoids are a group of drugs with antiinflammatory, immunosuppressant, metabolic, and endocrine effects. These drugs are structurally and functionally similar to the endogenous glucocorticoid hormone cortisol. Glucocorticoids have immediate effects (e.g., vasoconstriction) that do not depend on DNA interaction. However, they exert their main antiinflammatory and immunosuppressive actions by binding to glucocorticoid receptors, which causes complex changes in gene transcription. These genomic effects only begin to manifest after several hours. Similarly, glucocorticoids bind to mineralocorticoid receptors, but, for most glucocorticoid drugs, high doses are required for a significant mineralocorticoid effect. Systemic glucocorticoids are used for hormone replacement therapy (e.g., in Addison disease), for acute or chronic inflammatory diseases (e.g., rheumatoid arthritis), and for immunosuppression (e.g., after organ transplants). Local glucocorticoids are used to treat conditions like dermatoses, asthma, and anterior uveitis. Adverse effects include metabolic and endocrine disturbances, weight gain, skin reactions, hypertension, and psychiatric disorders; using the lowest dose possible for the shortest period of time, patient education, and regular screening can help lower the incidence of adverse effects and ensure early detection if they do occur. Contraindications for systemic glucocorticoids include systemic fungal infections and, in the case of dexamethasone, cerebral malaria. Status asthmaticus is a contraindication for inhaled glucocorticoids. Topical and ophthalmic glucocorticoids are usually contraindicated if there are preexisting local infections.

This article describes the pharmacology of synthetic glucocorticoids in detail; accordingly, glucocorticoids refer here to the drug class rather than the endogenous hormone.

Definition

- **Corticosteroids**: a class of steroid hormones that includes glucocorticoids and mineralocorticoids [1]
- **Endogenous corticosteroids**: hormones synthesized from cholesterol in the **adrenal cortex** [2]
  - Endogenous glucocorticoids (e.g., cortisol): synthesized in the zona fasciculata with antiinflammatory, immunosuppressant, metabolic, and endocrine effects
  - Endogenous mineralocorticoid (i.e., aldosterone): synthesized in the zona glomerulosa and primarily functions to regulate the renin-angiotensin system and maintain electrolyte and water balance
- **Synthetic corticosteroids**: structural and functional analogs of endogenous corticosteroids that are used in the treatment of a variety of conditions [3]

Overview

- **Systemic corticosteroids**
  - Corticosteroids that are administered orally, intravenously, or intramuscularly
  - Act systemically as they are distributed throughout the body
  - Examples: See table below.
- **Local corticosteroids** (local glucocorticoids)
  - Corticosteroids that are administered topically, intraarticularly, as eye/ear drops, or are aerosolized and inhaled (inhaled corticosteroids)
  - Act primarily at the site administered; a fraction is systemically absorbed [4]
  - Examples: beclomethasone, budesonide, clobetasol, and fluticasone
- Potency **of** systemic corticosteroids [3]
  - Hydrocortisone is the synthetic equivalent of endogenous cortisol and its glucocorticoid and mineralocorticoid potency is considered to be “1” (see table below).

- Relative to hydrocortisone, systemic corticosteroids differ in potency of their glucocorticoid effects (relative glucocorticoid potency) and mineralocorticoid effects (relative mineralocorticoid potency) for a given dose.

Relative potency of systemic corticosteroids [1][3]

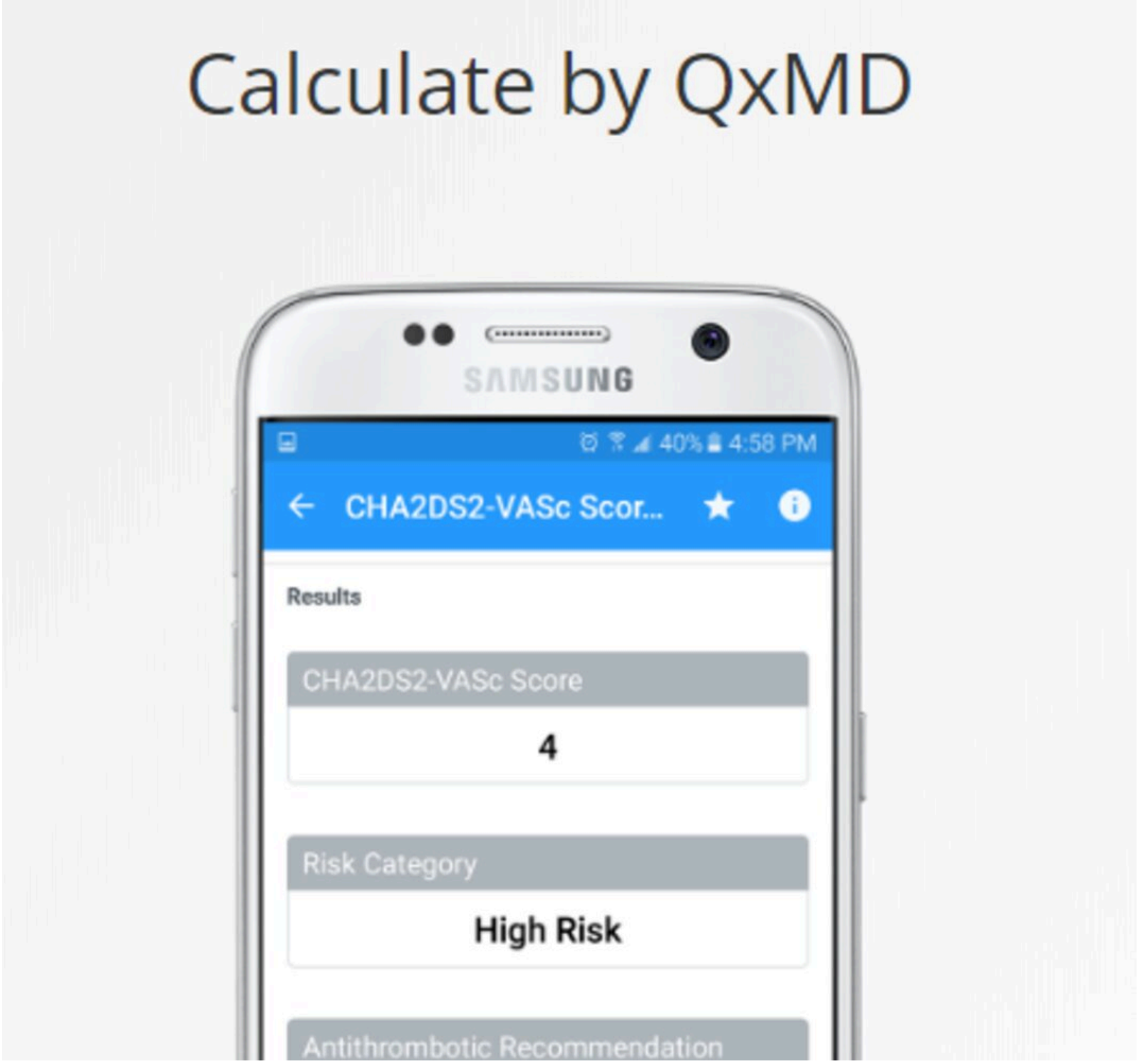
Duration of action	Drug	Common routes of administration	Relative glucocorticoid potency	Relative mineralocorticoid potency
Systemic glucocorticoids				
Short-acting (8–12 hours)	**Hydrocortisone**	• Oral • Injectable • Topical	• 1	• 1
	Cortisone	• Oral • Injectable	• 0.8	• 0.8

Intermediate-acting (12–36 hours)	**Prednisolone**	• Prednisone: oral
		• Prednisolone:
		  ◦ Oral
		  ◦ Injectable
			• 4	• 0.8

	Prednisone			
	Methylprednisolone	• Oral • Injectable	• 5	• 0.5
	Triamcinolone	• Injectable [5][6][7] • Topical	• 5	• 0
Long-acting 36–72 hours	**Dexamethasone**	• Oral • Injectable • Topical	• 30	• 0
	Betamethasone	• Oral • Injectable • Topical	• 30	• 0
Systemic mineralocorticoid				
Intermediate-acting 12–36 hours	**Fludrocortisone**	• Oral	• 10–15	• 125–150

- **Summary of effects of** systemic corticosteroids
  - Glucocorticoids with minimal mineralocorticoid activity: triamcinolone, dexamethasone, betamethasone
  - Glucocorticoids with some mineralocorticoid activity: hydrocortisone, prednisolone
  - Synthetic corticosteroid with **predominantly** mineralocorticoid **activity:** fludrocortisone

Fludrocortisone is not used for glucocorticoid activity but as a mineralocorticoid substitute in the management of adrenal insufficiency. [3][8]



Pharmacodynamics

1. **Antiinflammatory and** immunosuppressive
   - **Acute effects** (within minutes)
     - ↓ Vasodilation and ↓ capillary permeability
     - ↓ Leukocyte **migration** to inflammatory foci
   - **Long-term effects** (within hours) : Glucocorticoids bind to cytoplasmic **glucocorticoid receptors** (GRs)
     - Inhibition of neutrophil apoptosis and demargination (loss of neutrophil binding to adhesive endothelial integrin molecules) → **neutrophilic leukocytosis**
     - Promotion of sequestration and apoptosis of eosinophils, monocytes, and lymphocytes → lymphopenia and eosinopenia

- ↑ Inhibition of phospholipase A2, which decreases the production of arachidonic acid derivatives → ↓ production of leukotrienes and prostaglandins
- ↑ Inhibition of transcription factors (e.g., NF-κB) → ↓ **expression** of pro-inflammatory genes (e.g., TNF-α gene, interleukin-2 gene)
- Translocation to the cell nucleus and binding to glucocorticoid responsive elements (GREs) within the promoters of antiinflammatory genes (e.g., interleukin-10 gene) → ↑ **expression** of antiinflammatory genes
- Suppression of B cells and T cells (T cell apoptosis)
- Inhibition of histamine release from mast cells
- Permissive effect on epinephrine and norepinephrine via upregulation of α1-adrenergic receptors on arterioles

2. Mineralocorticoid **properties**
    - Cortisol can bind to mineralocorticoid receptors at high concentrations [9]
    - Effects include, e.g., reduced sodium excretion, increased potassium excretion
3. **Antiproliferative**: triggers cell apoptosis, and inhibits fibroblast proliferation [10]
4. Anabolic-androgenic effects **with steroid abuse** : increase in muscle mass and strength

Both acute and long-term effects of glucocorticoids lead to inhibition of inflammatory processes and to immunosuppression.

References:[11][12][13][14][15]

Adverse effects

Systemic glucocorticoids

Glucocorticoid toxicity depends on the dose that is administered over a certain period of time. Therefore, even low doses can have toxic effects if administered long-term. If glucocorticoids are administered once or only briefly (e.g., for treatment of anaphylactic shock), there are usually no significant adverse effects even at high doses.

Organ/System of organs	Effects
Skin	• Poor wound healing, **skin atrophy**, and **stretch marks** due to impaired fibroblast activity and thus, impaired collagen synthesis • Purpura • **Steroid acne** • **Hypertrichosis** • Increased risk of squamous and basal cell carcinomas

Cardiovascular system	• **Hypertension**, most likely due to
	  ◦ Increased sensitivity to catecholamines due to the upregulation of alpha-1 receptors
	  ◦ Mineralocorticoid activity at high concentrations

Metabolism, electrolytes and endocrine system	• **Weight gain** with truncal obesity, **buffalo hump**, and **moon face** (**Cushingoid appearance**) • Proteolysis and lipolysis: proteolysis contributes to hyperglycemia whereas lipolysis leads to hyperlipidemia and eventually to redistribution of fat tissue towards the trunk. • Increased gluconeogenesis, lipolysis, and proteolysis • **Hyperglycemia** and ↑ insulin resistance → glucocorticoid-induced diabetes • Decreased glucose utilization in skeletal muscle and white adipose tissue (due to antagonization of insulin response) • Hypocalcemia → PTH activation → secondary **osteoporosis**
GI system	• Increased appetite

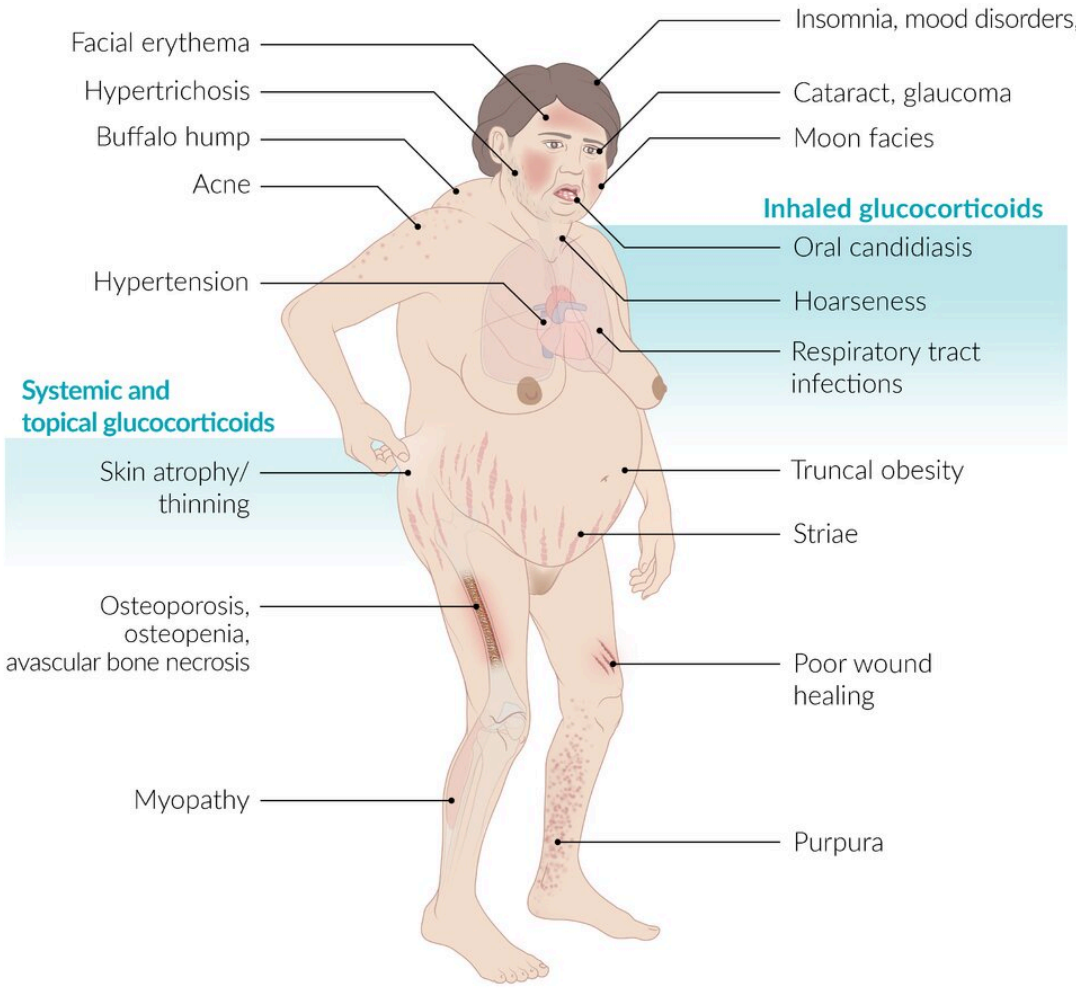
	• **Peptic ulcers** and gastrointestinal hemorrhage • Possibly pancreatitis [16]
CNS and psyche	• Mood disorders • Cognitive disorders • **Psychosis**
Eyes	• **Cataract** • Glaucoma

Other	• **Adrenocortical** atrophy
	• **Acute adrenal insufficiency** (predominantly when glucocorticoids are discontinued suddenly after chronic intake)
	• **Avascular bone necrosis** [17]
	• Glucocorticoid-induced osteoporosis, **osteopenia**: chronic glucocorticoid use → **RANKL-mediated** activation of osteoclasts and apoptosis of osteoblasts → decreased bone formation and increased bone resorption [18]
	• **Corticosteroid-induced myopathy** [19]
	  ◦ Acute: generalized muscle weakness
	  ◦ Chronic
	  ▪ Classic form of steroid myopathy
	  ▪ Progressive weakness of **proximal limb muscles**, myalgia
	• Venous thromboembolism
	• Growth inhibition in children
	• **Immunosuppression**
	  ◦ Can result in the reactivation of latent infectious diseases (e.g., CMV, tuberculosis) and opportunistic infections (e.g., candidiasis)
	  ◦ Blood test may show leukocytosis since white blood cells get demarginalized.
	• Specific to anabolic-androgenic steroid abuse
	  ◦ Endocrine/reproductive
	  ▪ Women: e.g., amenorrhea, **hirsutism**, breast atrophy, deep voice, androgenic alopecia
	  ▪ Men: e.g., **gynecomastia**, acne, small testes, **low sperm density** (due to inhibition of the hypothalamic-pituitary-gonadal axis)
	  ◦ Cardiovascular: ↑ **heart rate**, ↑ **blood pressure**
	  ◦ Hematologic: ↑ LDL, ↓ HDL, ↑ **hematocrit**
	  ◦ Neuropsychiatric: e.g., **aggressive behavior**
	  ◦ Tendon **ruptures**
	  ◦ **Hepatic damage**

Many of the adverse effects listed above are also features of iatrogenic Cushing syndrome.

The tibia is **BIG**g**A** than the **FIB**ula: cortisol **increases B**lood pressure, **I**nsulin resistance, **G**luconeogenesis, and **A**ppetite; and **decreases F**ibroblast activity, **I**mmune response, and **B**one formation.

Adverse effects of glucocorticoids



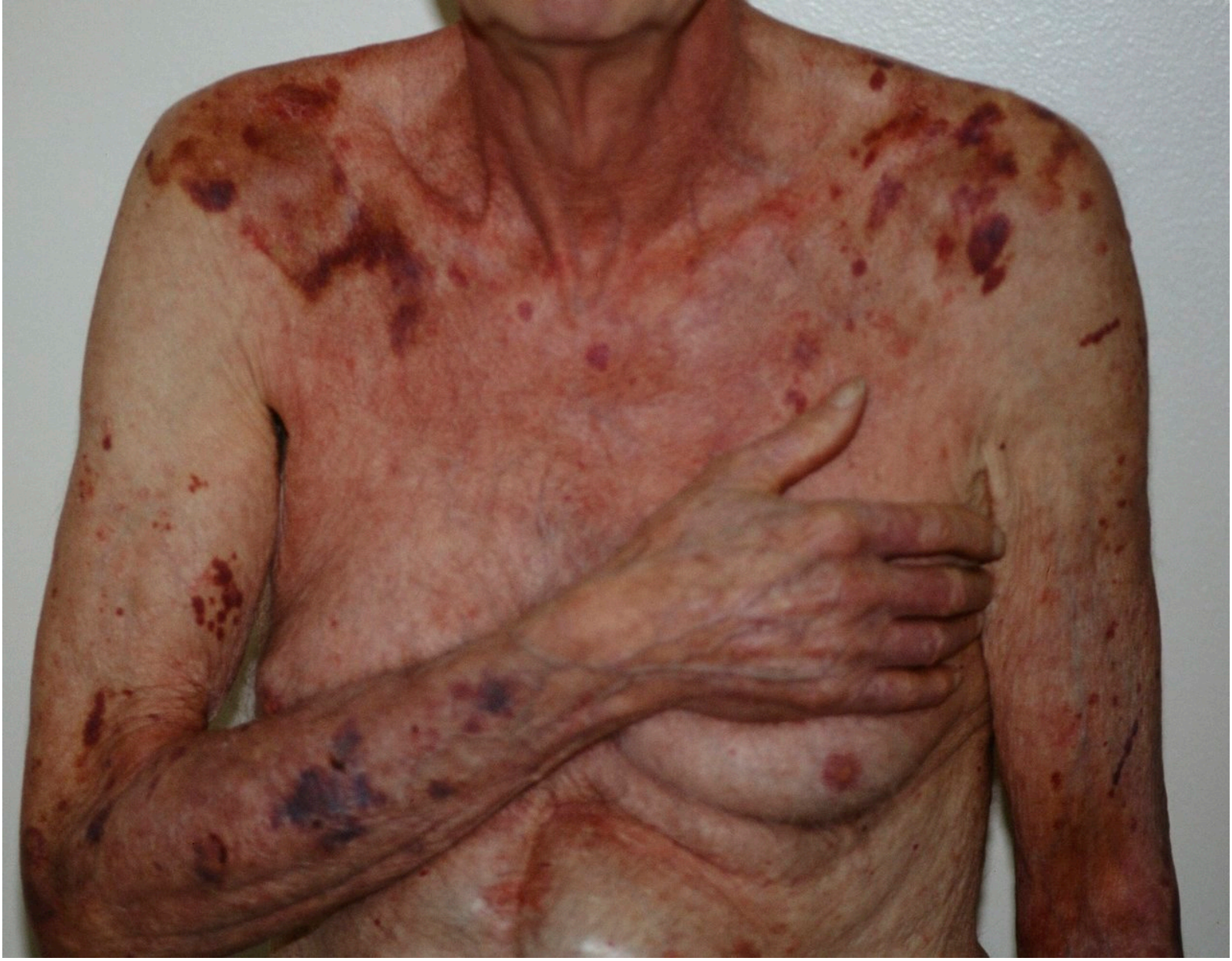
Other adverse effects

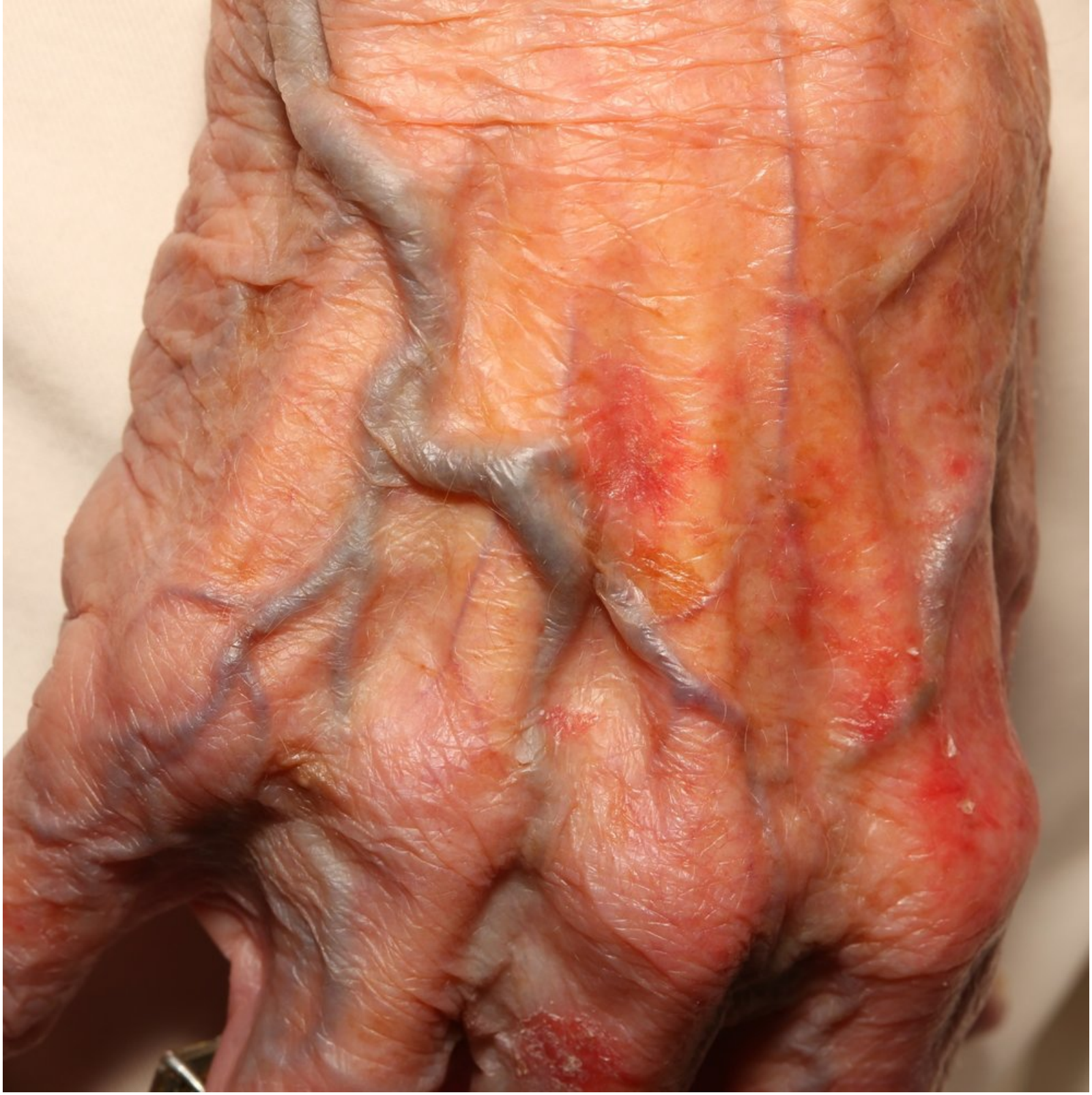
Immune system

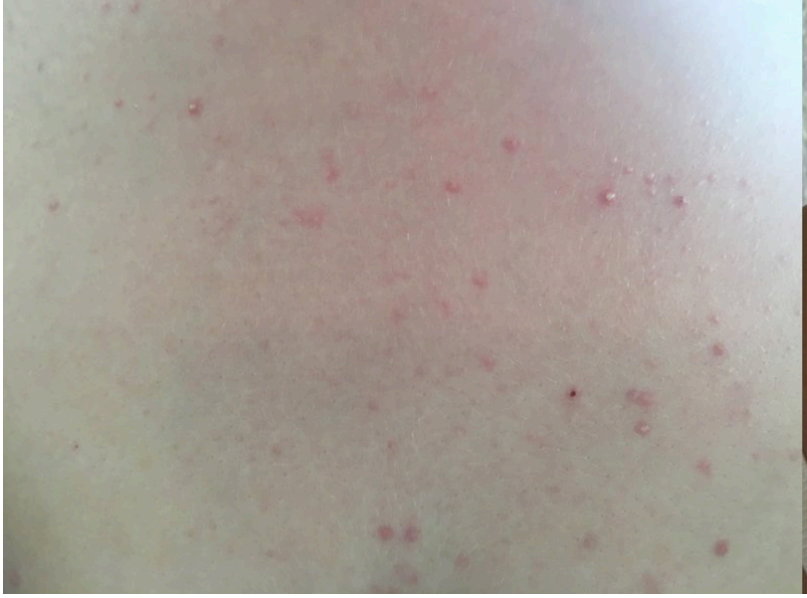
- Neutrophilic leukocytosis
- Immunosuppression

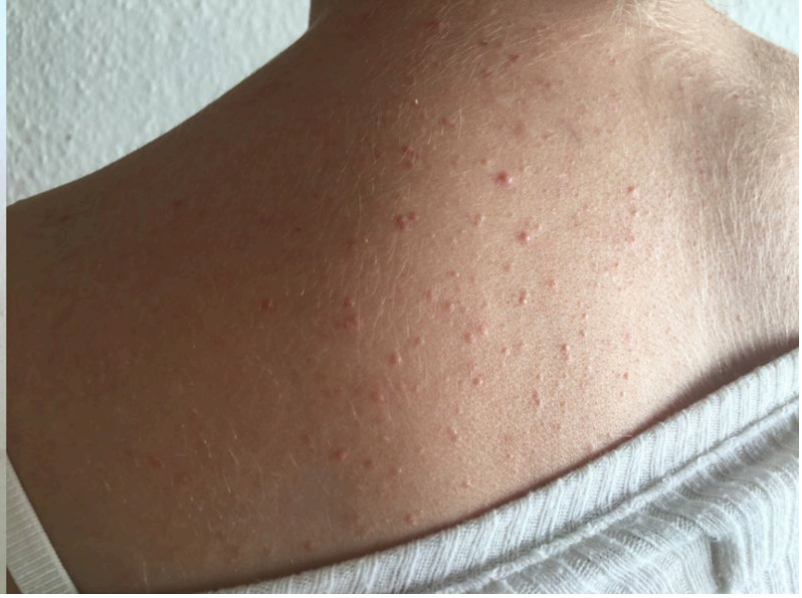
Abdominal organs

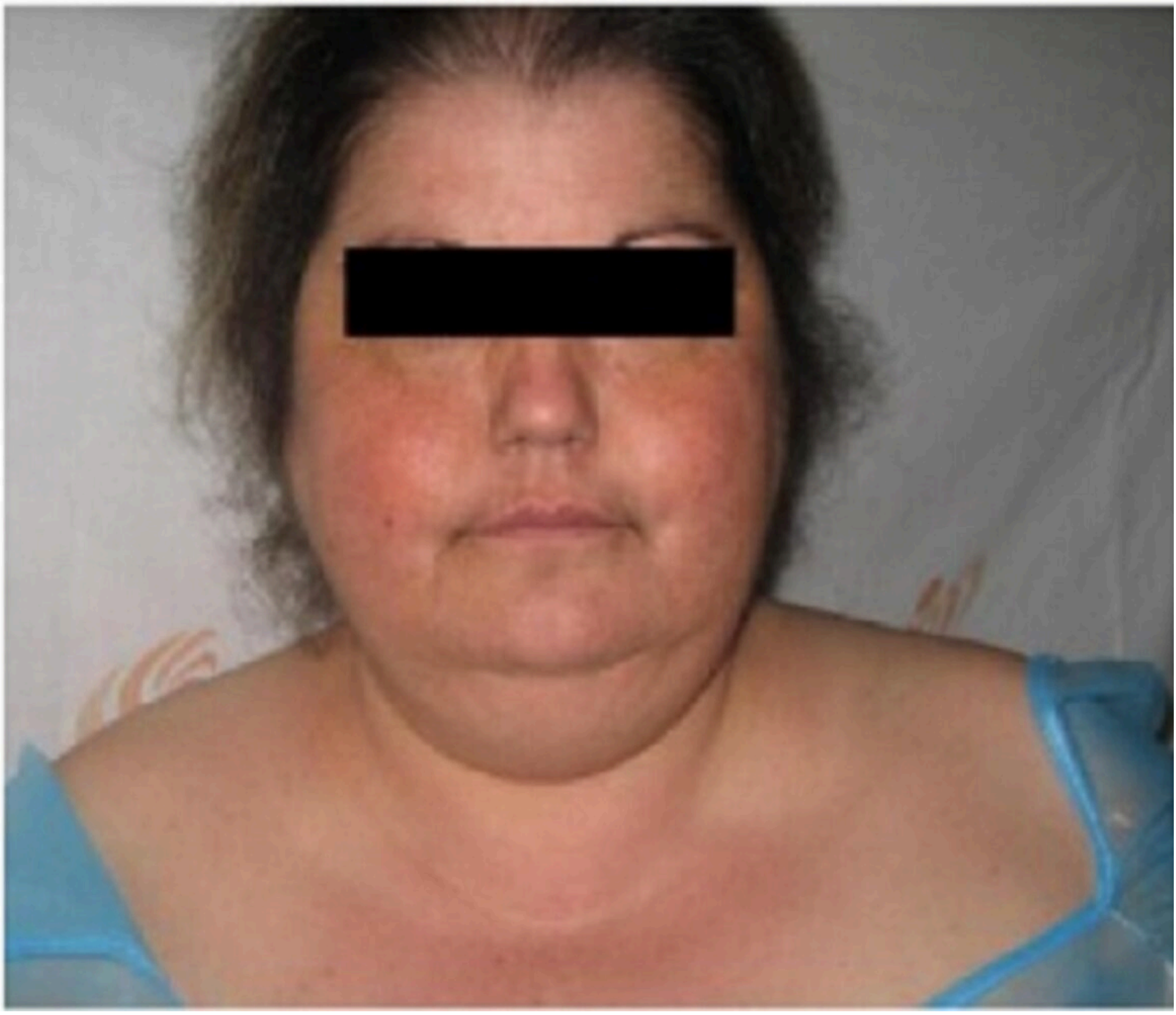
- Peptic ulcers, gastrointestinal hemorrhage
- Hyperglycemia (may progress to diabetes)
- Hepatic damage
- Adrenocortical atrophy, acute adrenal insufficiency (in sudden glucocorticoid withdrawal)







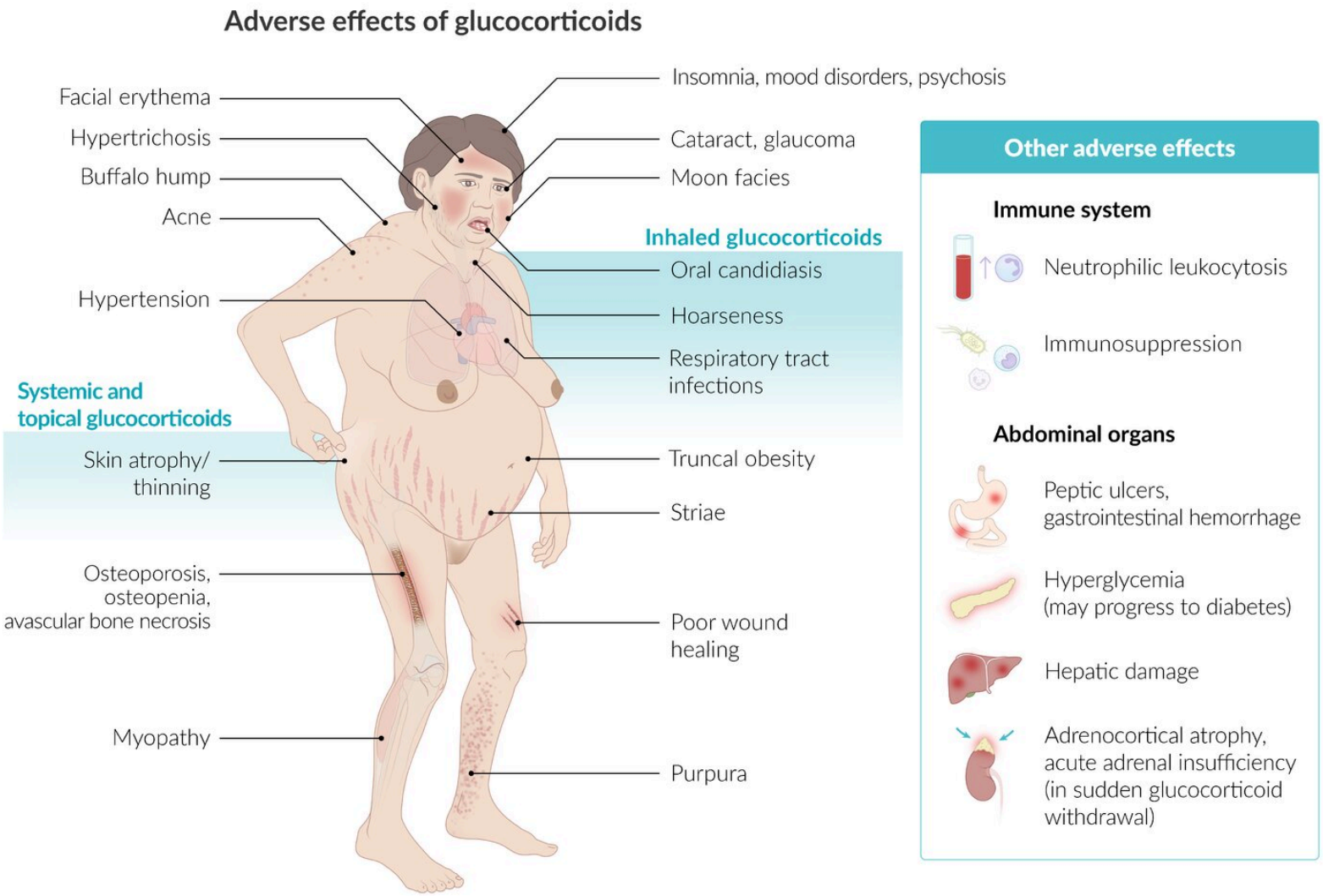




Local glucocorticoids [20]

	Topical glucocorticoids	Inhaled glucocorticoids
Local effects	• Skin manifestations as in systemic glucocorticoids • Allergic dermatitis	• **Oral candidiasis** (can be prevented by using a spacer or by rinsing out the mouth after inhalation) • Lung infections • Hoarseness • Allergic dermatitis
Eyes	• As in systemic glucocorticoids	• Ocular reactions
Other	-	• Growth inhibition • **Osteoporosis** • **Adrenal suppression**

Local side-effects of inhaled glucocorticoids can be avoided by reducing the dose to the lowest effective amount, rinsing with mouthwash after each puff, improving the inhalation technique and compliance, and keeping vaccinations up to date.



We list the most important adverse effects. The selection is not exhaustive.

Indications

- **Replacement therapy**
  - Adrenocortical insufficiency (**Addison disease**)
  - Congenital adrenal hyperplasia
  - Hypopituitarism
- **Systemic symptomatic treatment**
  - Acute
    - Allergic reactions and anaphylactic shock
    - **Asthma**
    - Antiemetic treatment (e.g., nausea due to cytostatic treatment)
    - Toxic pulmonary edema [21]
    - Acute exacerbation of autoimmune diseases (e.g., multiple sclerosis, psoriasis)
    - Acute exacerbation of COPD
    - Gout, calcium pyrophosphate deposition disease
    - Cerebral edema
    - Thyroid storm:cortisol inhibits the peripheral conversion of T_4 to T_3 (the inactive byproduct of T_4, rT_3, increases)
    - Acute pericarditis
  - Long-term
    - Chronic, inflammatory diseases (e.g., asthma, chronic obstructive pulmonary disease, inflammatory bowel disease, vasculitides)
    - Rheumatic diseases (e.g., sarcoidosis, Sjogren syndrome)
    - Graves ophthalmopathy
    - Malignancy (e.g., CLL, non-Hodgkin lymphoma)
- **Local symptomatic treatment**: anterior uveitis, dermatoses, tenosynovitis, and osteoarthritis or juvenile idiopathic arthritis
- **Prophylactic**
  - Organ transplant
  - **Preterm delivery**: Glucocorticoids are given to the mother prenatally to induce fetal lung maturity.

Contraindications

- **General**: hypersensitivity
- **Systemic**
  - Systemic fungal infections
  - Intrathecal administration
  - Cerebral malaria (dexamethasone)
  - Concomitant live or live attenuated virus vaccination (if glucocorticoids are used in immunosuppressive doses)
  - Use in premature infants (formulations containing benzyl alcohol)
- **Topical**
  - Dermatological: bacterial, viral or fungal infection of the mouth or throat (triamcinolone)
  - Ophthalmic
    - Systemic fungal infection (triamcinolone)
    - Acute untreated purulent ocular infections (prednisolone)
    - Fungal or mycobacterial ocular infections, viral conjunctivitis, or keratitis (prednisolone, dexamethasone)

- **Inhalation**: status asthmaticus or acute asthma episode requiring intensive measures (beclomethasone, budesonide)
- **Relative contraindications**: Glucocorticoids should be avoided in certain conditions due to increased risk of toxicity.
  - Adrenocortical atrophy
  - Cushing syndrome
  - Diabetes mellitus (steroid diabetes), hyperglycemia
  - Amenorrhea
  - Osteoporosis
  - Avascular necrosis (e.g., of the femoral head)
  - Peptic ulcers
  - Cataracts
  - Psychosis

References:[22]

We list the most important contraindications. The selection is not exhaustive.

Additional considerations

- **Systemic administration**
  - **Tapering** to avoid toxicity
    - Short-term administration (≤ 3 weeks): usually no tapering necessary
    - Long-term administration (> 3 weeks): tapering regimen based on patient age and condition and on duration/dose of prior glucocorticoid administration → e.g., tapering over 2 months
  - Sudden discontinuation after chronic use should be avoided because of the risk of adrenal insufficiency (adrenal crisis) secondary to long-term hypothalamic-pituitary-adrenal axis suppression.
- **IM application**
  - Indications include antenatal induction of fetal lung maturity and adrenal crisis
  - For other conditions, IM application is generally avoided as it can result in localized atrophies and disturbances in the endogenous release of glucocorticoids

If the Cushing threshold is exceeded over a longer period of treatment, the glucocorticoid dose should be gradually decreased to minimize the risk of adrenocortical insufficiency.

An intratendinous injection carries the risk of bacterial spread and iatrogenic bacterial arthritis.

References:[2][23]

Preventing complications of glucocorticoid therapy

Complications are most common with long-term systemic treatment but can also occur with higher-dose topical and inhaled steroids. The risk of complications can be reduced by keeping treatment durations short or doses low. [24]

Approach [25]

- Choose short-term higher-dose pulse therapy if possible.
- If continuous treatment is necessary, aim for the lowest possible daily dose. [26]
  - Low dose: equivalent to < 2.5 mg prednisolone/day

- Moderate dose: equivalent to 2.5–7.5 mg prednisolone/day
- High dose: equivalent to > 7.5 mg–29 mg prednisolone/day
- Very high dose: equivalent to ≥ 30 mg prednisolone/day

- Assess risk factors for complications of glucocorticoid therapy.
- Initiate measures to prevent complications of glucocorticoid therapy.
- When discontinuing long-term steroid regimens:
  - Advise patients not to stop the medication suddenly because of the risk of adrenal suppression.
  - Taper under medical supervision in courses lasting > 3 weeks. [27]

Risk assessment

Risk factors for complications of glucocorticoid therapy	
Adrenal suppression and adrenal insufficiency [28][29][30]	• Any systemic, high-dose topical, or high-dose inhaled corticosteroid therapy
Osteoporosis [24]	• Systemic therapy at any dose ≥ 3 months
Peptic ulcer disease [31]	• Systemic therapy for at least 7–28 days increases the risk of bleeding.
Diabetes and hyperglycemia [32][33][34]	• Increased risk of hyperglycemia within 24–48 hours of starting systemic treatment
Infections [35]	• Systemic therapy for at least 2–4 weeks at doses > 20 mg/day
Cardiovascular disease [36][37][38][39][40]	• Hypertension can result from any medium- to high-dose systemic steroid regimen. • Alterations to lipid levels usually require at least 2 weeks of systemic therapy.
Ocular disease [41][42]	• Glaucoma can result from several weeks of any form of steroid administration. • The risk of cataracts increases after > 1 year of high-dose systemic therapy.
Psychiatric complications [43][44]	• Typically within 2 weeks of starting systemic therapy, particularly with very high-dose therapy

Measures to prevent complications

Measures to prevent complications of glucocorticoid therapy		
Complication to prevent	**Before therapy**	**During therapy**
Adrenal suppression and adrenal insufficiency [3][45]	• Educate patients on sick day rules. • Provide patient with a steroid card/bracelet. • Provide an emergency hydrocortisone kit for injection. [46]	• See "Stress-dose steroids" for information on prevention of adrenal crisis in acute illness, after trauma, or perioperatively.

Osteoporosis [26]	• Assess fracture risk. [26]
	• Offer bone mineral density testing.
	• Promote patient education on modifiable risk factors.
		• For all patients taking ≥ 2.5 mg/day prednisone (or equivalent) for ≥ 3 months
		  ◦ Optimize bone health
		  ▪ Calcium intake > 1,000–1,200 mg/day
		  ▪ Vitamin D supplementation
		  ▪ Encourage physical activity.
		  ◦ Start pharmacotherapy for glucocorticoid-induced osteoporosis for patients with moderate or high risk for osteoporosis

Peptic ulcer disease [47]	• Screen patients for risk factors for peptic ulcer disease.	• Avoid concurrent NSAID use. • Consider PPIs, e.g., omeprazole in patients with risk factors for peptic ulcer disease.
Diabetes and hyperglycemia [24]	• Obtain baseline HbA1c. [24] • Consider home glucometer for patients on long-term moderate- and high-dose steroids.	• Regularly monitor patients. [33][34][48] • Educate patients on early recognition of the symptoms of diabetes • See "Glucocorticoid-induced hyperglycemia" in "Inpatient management of hyperglycemia"

Infections	• Screening
	  ◦ Screen for HIV, hepatitis B, and hepatitis C. [24][35][49][50]
	  ◦ Consider TB screening for patients with risk factors for tuberculosis. [51][52]
	• Vaccinations: Give missing or indicated vaccinations to patients before initiating therapy planned to last > 14 days.
	  ◦ Live vaccines: ≥ 4 weeks prior to starting therapy, if possible [35][53]
	  ◦ Inactive vaccinations: > 2 weeks prior to starting therapy [54]
		• Avoid live vaccines during treatment and for at least 1 month after completion.
		• Routine recommended inactivated vaccines (e.g., influenza) should be given during treatment but may be less effective.

Cardiovascular disease [24]	• Obtain baseline blood pressure measurement and lipid panel.	• Regular blood pressure measurements to identify arterial hypertension • Regular lipid panels to identify lipid disorders
Ocular disease [24][41][55]	• Screen patients for a history of cataracts or glaucoma.	• Regular eye examinations [42] • Educate patients on the symptoms of glaucoma.

Measures to prevent complications of glucocorticoid therapy		
Complication to prevent	**Before therapy**	**During therapy**
Psychiatric disease [3] [24]	• Screen patients for psychiatric comorbidities, e.g., depression. [24]	• Review within a week of initiating steroid therapy for mood changes. [43] • Avoid split-dose regimens to prevent sleep disruption.

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