Systemic steroids and Pulse methyl Prednisolone.

(Unlike the chapter on *topical steroids*, the Wolverton Chapter on *Systemic Corticosteroids* is excellent and is a "MUST READ" along with the Bolognia Chapter on the same topic)

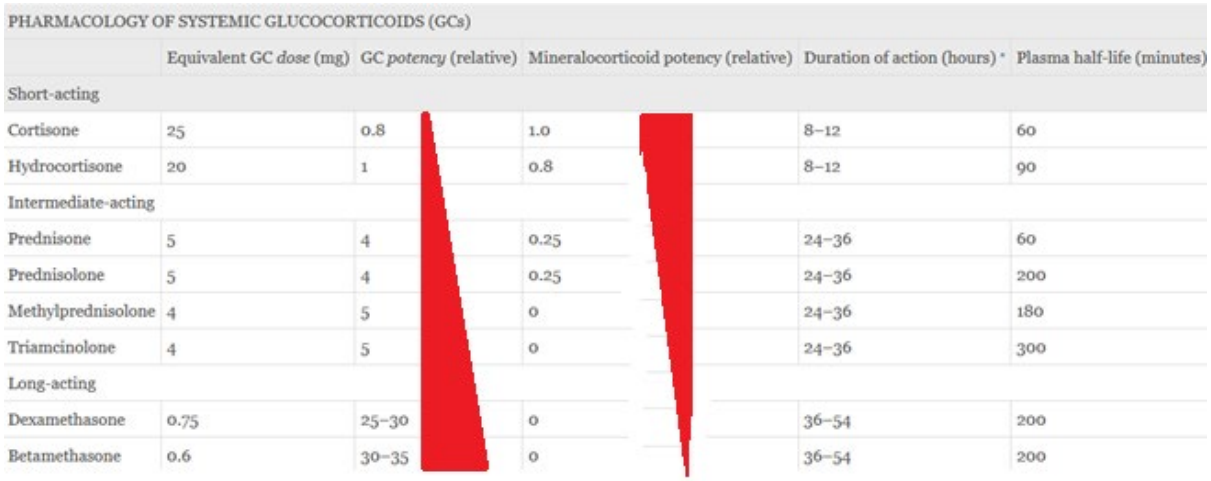
In Australia Prednisolone is the oral steroid of choice is Dermatology.

Prednisone is widely used in the USA.

Prednisone needs hepatic conversion into the active form Prednisolone.

Oral, IM and IV steroids used in Australia

Oral, IM and IV steroids (commonly) used in Australia	
Prednisolone	Oral, Tablets = 1mg, 5mg, 25g
Dexamethasone	Oral, IM or IV
Hydrocortisone	Oral, IM or IV
Methylprednisolone	IM or IV



PHARMACOLOGY OF SYSTEMIC GLUCOCORTICOIDS (GCs)

	Equivalent GC *dose* (mg)	GC *potency* (relative)	Mineralocorticoid potency (relative)	Duration of action (hours) *	Plasma half-life (minutes)
Short-acting					
Cortisone	25	0.8	1.0	8–12	60
Hydrocortisone	20	1	0.8	8–12	90
Intermediate-acting					
Prednisone	5	4	0.25	24–36	60
Prednisolone	5	4	0.25	24–36	200
Methylprednisolone	4	5	0	24–36	180
Triamcinolone	4	5	0	24–36	300
Long-acting					
Dexamethasone	0.75	25–30	0	36–54	200
Betamethasone	0.6	30–35	0	36–54	200

5mg of Prednisolone = 4mg of Triamcinolone = 0.7mg of Dexamethasone = 20mg of Hydrocortisone

Corticosteroid potency converter /calculator:

https://globalrph.com/medcalcs/corticosteroid-converter-based-on-anti-inflammatory-potency/

Course	Duration	Risks of adverse effects
Short	<3 weeks	Very low
Intermediate	>3weeks to 6 weeks	Low
Long	>6weeks	Moderate to High (Dose and Duration dependent)

Prednisolone dose	Risk of side effects in *Long term courses*
Dose <2.5 mg	Very low
Dose 2.5 to 7.5mg (Physiological Replacement)	Low
Dose > 7.5 mg	Moderate to High (dose & duration dependent)

Typical short course used in Dermatology: always give mane to reduce HPA axis suppression and reduce sleep disturbance.

3 Week Course: 37.5mg for 7 days then, 25mg for 7 days then, 12.5mg for 7 days then STOP.

Or

2 Week Course: 25mg for 7 days then, 12.5mg for 7 days then STOP.

These use 25 mg tablets which come in quantities of 30 tablets /bottle (enough in one bottle for a full course)

Or

20 mg for 5days then 15 mg for 5 days then 10 mg for 5 days then 5 mg for 5 days then stop

This uses 5 mg tablets which come in bottle of 60 tablets. (enough in bottle for a full course)

Short term side effects of Prednisolone

SIDE EFFECTS OF SHORT-TERM SYSTEMIC GLUCOCORTICOID THERAPY
• Mood changes, anxiety, insomnia • Gastrointestinal intolerance (e.g. nausea, vomiting) • Hyperglycemia • Fluid/sodium retention • Increased appetite, weight gain • Acneiform eruptions • Increased infections • Amenorrhea • Muscular weakness, muscle effects • Impaired wound healing

DANGEROUS SHORT-TERM EFFECTS

TABLE 12-10 CORTICOSTEROID COMPLICATIONS THAT MAY RARELY BE FATAL

COMPLICATION	COMMENTS
ADRENAL CRISIS	DISTINCTLY UNCOMMON CURRENTLY PERHAPS DUE TO HEIGHTENED AWARENESS, AGGRESSIVE EMERGENCY ROOM OR POSTOPERATIVE PREVENTIVE AND THERAPEUTIC MEASURES
BOWEL PERFORATION	BEST TREATMENT IS PREVENTION; CAN HAVE CATASTROPHIC OUTCOME IF LATE DIAGNOSIS
PERFORATED PUD	TYPICALLY FACTORS SUCH AS NSAID, KNOWN HISTORY OF PUD PRESENT; GASTRIC ULCERS AND PERFORATION MORE COMMON THAN DUODENAL
PANCREATITIS	PRIMARILY A RESULT OF TRIGLYCERIDE ELEVATIONS >800 MG/DL; POSSIBLE ROLE OF INCREASED VISCOSITY OF PANCREATIC SECRETIONS LEADING TO OBSTRUCTION
SEVERE HYPERGLYCEMIA	RISK PRIMARILY IF DIABETIC KETOACIDOSIS OR HYPEROSMOLAR NON-KETOTIC COMA RESULTS; OVERALL THESE COMPLICATIONS ARE RARE, PERHAPS DUE IN PART TO HOME GLUCOSE MONITORING
OPPORTUNISTIC INFECTIONS*	STRIKINGLY UNCOMMON IN DERMATOLOGIC THERAPY; GREATER RISK WITH MULTIDRUG IMMUNOSUPPRESSIVE REGIMENS COMMON WITH ORGAN TRANSPLANTATION
'Opportunistic' malignancies	Primarily with CS in multidrug immunosuppression regimens in transplantation settings; Kaposi's sarcoma may be an exception with CS use alone

Other Short-term effects

Long term side effects of Prednisolone

How to minimize Long term side effects of Prednisolone

Use in Pregnancy and Lactation: Pregnancy (In Australia Category A)

Pulse Methyl Prednisolone: How, When and What are the risks?

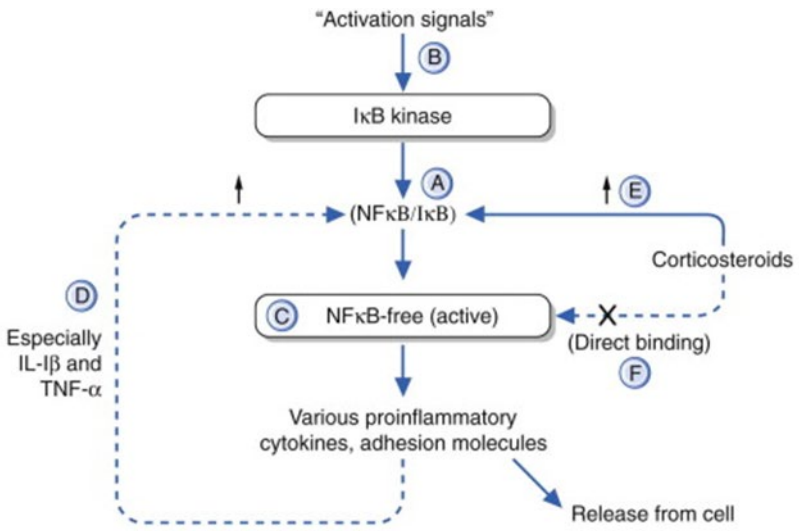
Mechanism of action

Corticosteroid action	**Mechanism and biologic result**
Effects on glucocorticoid receptor (GCR)	

Corticosteroid action	Mechanism and biologic result
Normal response	Upon binding of the Endogenous Cortisol or Synthetic Corticosteroid (CS) to the Glucocorticoid Receptor (GCR), the GCR is activated and translocates to the nucleus, binding to glucocorticoid-response elements of multiple genes. CS can function as an agonist or antagonist for these genes – GCR is ubiquitous throughout body.
Resistance	Generally a dynamic, temporary, relative resistance, with mechanisms not fully known; usually no evidence of GCR mutations or polymorphisms
Transcription factor effects	
NFκB inhibition	Increased IκB production, direct NFκB binding; net result ↓ production of multiple cytokines such as IL-1, TNF-α, adhesion molecules, growth factors, etc.
AP-1 inhibition (AP-1 = Activator Protein -1)	Decreased production of multiple cytokines; similar cytokine spectrum to NFκB
Apoptosis induction	
Lymphocyte apoptosis	Apoptosis of autoreactive T cells (in autoimmune disorders) and neoplastic T cells (in various lymphomas); AP-1 and caspase cascade probably involved in process
Eosinophil apoptosis	Apoptosis of eosinophils with potential implications for various allergic disorders
Signal transduction	
Phospholipase A_2 inhibition	CS effect probably mediated indirectly via ↑ lipocortin-1 (now called 'annexin')
↓ 'downstream' eicosanoids	As a result of phospholipase A_2 inhibition, ↓ production of various prostaglandins, leukotrienes, 12-HETE and 15-HETE inflammatory mediators
Cyclo-oxygenase 2 inhibition (COX-2)	↓ eicosanoid production generated by this inducible (with inflammation) enzyme; CS effect on COX-2 >> COX-1
Effects on various WBC subsets and other immunologic cells	
B-cells	With higher CS doses significant B-cell effect, reduced immunoglobulin production
T-cells	Greater CS effect on T-cells (CD4 > CD8 effect) at lower doses compared to above B-cell effect; net result ↓ IL-2 production and resultant amplification effect

Corticosteroid action	**Mechanism and biologic result**
Other lymphocyte subsets	↓ natural killer (NK) cell activity, ↓ antibody-dependent cellular cytotoxicity mediated by K-cells
PMN	↓ PMN marginisation, ↓ chemotaxis, small effect on microbicidal respiratory burst; also ↓ apoptosis of PMN (in contrast with T-cells and eosinophils above)
Mast cells	Inhibit degranulation, with resultant ↓ release histamine, kinins, other mediators
Monocytes, Macrophages	↓ monocyte maturation; ↓ access to inflammatory sites, ↓ IL-1 and IFN-γ release
Langerhans cells	↓ characteristic surface markers, impaired antigen processing and presentation
Eosinophils, Basophils	Reduced numbers and function both cell types, ↓ recruitment to inflammatory sites
Fibroblasts	↓ production of collagen, ground substance, fibronectin and collagenase
Membrane stabilization	Both lysosomal and cell membrane stabilization; probable role in mast cell, PMN, other inflammatory cell effects
Bottom line *generalizations*	CS overall effects – cell trafficking > cellular function; cellular immunity > humoral immunity; major portion of effects mediated via above cytokine alterations
Vascular effects	
Angiogenesis	↓ angiogenesis in wound healing and with proliferative lesions (hemangiomas)
Vasoconstriction	Net result of vasocortin and vasoregulin, potentiate response to catecholamines (remember Vasoconstrictor Assay used for Potency)
Decreased permeability	Decreased vascular smooth muscle response to histamine and bradykinin

Corticosteroid action	Mechanism and biologic result



A "Normally" NFκB is bound by IκB (inhibitor κB) and rendered inactive as a transcription factor.
B Many "activation signals" (see text) which incite an inflammatory response lead to ↑ production of IkB kinases, resulting in ↑ free (active) NFκB.
C The free form of NFκB serves as a transcription factor for a multitude of proinflammatory cytokines and adhesion molecules (see text).
D Among the cytokines produced are IL-1α and TNF-α which form a (+) feedback loop further stimulating release of free NFκB.
E **Corticosteroids** ↑ production of IκB, resulting in ↓ free NFκB.
F **Corticosteroids** also directly bind to free NFkB, inhibiting the transcription factor.

Mechanism of Side effects

Adverse effect	Proposed mechanisms
HPA axis effects	
Adrenal crisis	Reduced GC and MC reserves – normally there are adequate compensatory mechanisms for GC and MC effects such that major complications are very rare in dermatologic therapy
Metabolic effects	
Hyperglycemia	GC effects – ↑ hepatic glucose/glycogen production, ↑ gluconeogenesis via protein catabolism, induce insulin resistance producing ↓ glucose entry into cells
Hypertension	MC effects – sodium retention; also in part due GC-induced vasoconstriction

Adverse effect	Proposed mechanisms
Congestive heart failure	MC effects – ↑ sodium retention, resultant fluid overload in predisposed individuals
Hyperlipidemia	GC effects – overall result of catabolic state, in part initiated by ↑ lipoprotein lipase
Cushingoid changes	Altered fat distribution, uncertain mechanism; result of overall fat catabolism
Bone effects	
Growth impairment	Due to ↓ growth hormone and IGF-1 production; net result delayed skeletal maturation
Osteoporosis *	↑ osteoclast activity, ↓ osteoblast activity, ↓ GI absorption of calcium, ↑ renal excretion of calcium; resultant secondary hyperparathyroidism and bone resorption
Osteonecrosis	↑ marrow fat deposition, compression of interosseous vessels; hypercoagulability due to endogenous disorders or exogenous factors such as smoking, alcohol, trauma
Gastrointestinal effects	
Bowel perforation	GC catabolic effects producing ↓ wound healing after recent bowel anastomosis
Peptic ulcer disease	↓ mucus production, ↑ acid production; CS not a direct gastric irritant
Other adverse effects	
Cataracts	Altered lens proteins, with uncertain mechanism (typically posterior subcapsular)
Agitation/psychosis	Possibly due to electrolyte shifts, altered nerve excitability, possibly mild cerebral edema
Opportunistic infections	Impaired immunologic responses – see previous section
Myopathy	↓ glucose and amino acid uptake by muscles, leading to muscle atrophy/wasting

* Greatest CS effect on bone resorption at sites of high trabecular bone content such as ribs, vertebral bodies and flat bones of pelvis –correspond to sites with greatest risk of fractures.

Contraindications

- **Absolute**
- ***Relative*** †

- Systemic fungal infections
- Herpes simplex keratitis
- Hypersensitivity (occasionally noted with IV preparations)
- Cardiovascular: hypertension, CHF
- Central nervous system: prior psychosis, severe depression
- Gastrointestinal: active PUD, recent anastomosis
- Infections: active TB, positive tuberculin skin test
- Metabolic: diabetes mellitus
- Musculoskeletal: osteoporosis
- Ocular: cataracts, glaucoma
- Pregnancy: in Australia Pregnancy Category is A, can use if Risk < Benefit, animal studies have shown cleft lip and palate but not in humans. Avoid in 1st Trimester if possible.

Adverse effects

- **HPA axis**
- Steroid withdrawal syndrome
- Addisonian crisis
- **Metabolic**
-
    - **Glucocorticoid effects**
    - Hyperglycemia
    - Increased appetite (and weight)
    - **Mineralocorticoid effects (due to sodium retention, potassium loss)**
    - Hypertension
    - Congestive heart failure
    - Excessive weight gain
    - Hypokalemia
    - **Lipid effects (↑ lipolysis & altered deposition)**
- **Gastrointestinal**
- Peptic ulcer disease
- Bowel perforation
- Fatty liver changes
- Esophageal reflux
- Nausea, vomiting
- **Ocular**
- Cataracts
- Glaucoma
- Infections especially staphylococcal
- Refraction changes (from CS-induced hyperglycemia)
- **Psychiatric**
- Psychosis
- Agitation or personality change
- **Infectious**
- Tuberculosis reactivation
- Opportunistic – deep fungi, others
- Prolonged herpes virus infections
- **Muscular**
- Myopathy (with muscle atrophy)
- **Pediatric**
- Growth impairment
- **Cutaneous**
- **See list below**
- **Pulse therapy**
- Electrolyte shifts

- Hypertriglyceridemia
- Cushingoid changes
- Menstrual irregularity

- **Bone**
- Osteoporosis
- Osteonecrosis
- Hypocalcemia (indirectly)
- Depression
- (Prednisone phobia or dependency)
- **Neurologic**
- Pseudotumor cerebri
- Epidural lipomatosis
- Peripheral neuropathy
- Cardiac dysrhythmias
- Seizures
- **Other**
- 'Opportunistic' malignancies
- Teratogenicity – doubtful in humans

Cutaneous adverse effects from systemic corticosteroids

Category	**Mechanism**	**Adverse effects**
Wound healing and related changes	↓ collagen, ground substance; ↓ re-epithelialization, angiogenesis	Non-healing wounds, ulcers, striae, atrophy, telangiectasias
Pilosebaceous	*Pityrosporum ovale,* androgenicity	'Steroid acne', 'steroid rosacea'
Vascular	Catabolic effects on vascular smooth muscle (see above)	Purpura, including actinic purpura
Cutaneous infections	Various Immunological effects	Staphylococcal, herpes virus infections in particular
Hair effects	Uncertain for telogen effluvium	Telogen effluvium, hirsutism
Injectable CS	Lipolysis of subcutaneous fat	Fat atrophy; crystallization of injectable material
Other skin effects	↓ CS immunosuppression (taper) Insulin resistance	Pustular psoriasis flare, rebound of poison ivy/oak Acanthosis nigricans

HPA Axis: critical facts

Basal production in *prednisone equivalents* – 5–7.5 mg daily

Maximal stress production in *prednisone equivalents* – 75 mg daily

'Minor stress' production of cortisol – probably 2–3 times basal production: 15 to 25mg *prednisone equivalents.*

ALTERNATE-MORNING GLUCOCORTICOID THERAPY

"Off" days allow recovery of hypothalamic–pituitary–adrenal (HPA) axis

Decreases risks of:

- - Growth suppression
- - Myopathy
- - Hypertension
- - Opportunistic infections
- - Neuropsychiatric effects
- - Electrolyte imbalances (e.g. hypokalemia, hypocalcemia)

Does *not* substantially alter risks of osteoporosis or cataracts

Fluctuations in glucose levels can make diabetes mellitus more difficult to manage