



INFLAMMATION

New York Certification Course

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★ Guidelines for Prednisone for Chronic Uveitis ★

Parameter	Suggested Guideline
Initial dose	1 mg/kg/day*
Maximum adult oral dose	60-80 mg/day
Maintenance dose (adult)	≤10 mg/day
Tapering schedule	Over 40 mg/day, decrease by 10 mg/day every 1-2 weeks 40-20 mg/day, decrease by 5 mg/day every 1-2 weeks 20-10 mg/day, decrease by 2.5 mg/day every 1-2 weeks 10-0 mg/day, decrease by 1 to 2.5 mg/day every 1-4 weeks
Monitor	Blood pressure, weight, glucose every 3 months Lipids (cholesterol and triglycerides) annually
Supplemental treatment	Bone density within first 3 months and annually thereafter Calcium 1500 mg daily and vitamin D 800 IU daily Estrogens and antiresorptive agents as needed

*In selected situations, where an immediate effect is needed, some investigators will begin with intravenous methylprednisolone at a dosage of 1 giv/day for 3 days and then start oral prednisone.

Part III – Learning Objectives

1. To understand the arachidonic acid pathway.
2. To understand the mechanism of action, ocular effects, and adverse reactions of NSAIDs
3. To recognize the types of conditions in which NSAIDs are useful in eyecare.
4. To understand the feedback loop utilized in the adrenocortical system.
5. To understand the general physiological and pharmacological effects of corticosteroids.
6. To understand the principles of ocular corticosteroid therapy.
7. To know appropriate dosing of corticosteroids and tapering of corticosteroids.
8. To understand the treatment of the ocular conditions in which steroids are needed.

The Cardinal Signs of Inflammation

Dolor (it hurts), Calor (its warm), Rubor (its red), Tumor (its swollen), Functio laesa (it doesn't work)



The Need for Inflammation

- **Dolor**
 - Alert for potential harm
 - Abruptly remove affected area from offending stimulus
 - Memory for future reference
- **Calor**
 - May speed up chemical reactions
- **Rubor**
 - Vasodilation to allow transudation of fluid and movement of cytokines, leukocytes, fibrin, platelets into tissue to promote healing/prevent/manage infection
- **Tumor**
 - The solution to pollution
 - Promotes function laesa
- **Functio laesa**
 - Immobilization promotes healing



Stimuli for Acute Inflammation

- Infections
- Physical and chemical agents
 - Trauma
 - Heat/cold
 - Ionizing radiation
 - Acids/bases
 - Bacterial toxins
- Tissue necrosis
- Foreign bodies
- Immune reactions
- SAID ANOTHER WAY

ACUTE INFLAMMATION IS GENERALLY A NON-SPECIFIC CLINICAL FINDING



Inflammation

- Destroys injurious agents
- Heal and reconstitutes the damaged tissue
- Keeps infection in check



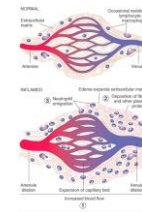
Inflammation

- Acute
 - Rapid onset (seconds or minutes)
 - Short duration (minutes-days)
 - Transudation of fluid and plasma proteins
 - Emigration of neutrophils (predominantly)
- Chronic
 - Pain beyond expected recovery period (~>3 months)
 - Can occur as a function of chronic disease (e.g. arthritis)



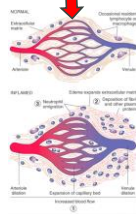
Acute Inflammation Physiology

- Vascular Changes
- Vasoconstriction
- Increased Regional Blood Flow
 - Vasodilation
 - Induced by histamine, nitric oxide, etc.
- Increased Vascular Permeability
 - Structural changes in the microvascular that permit fluids, proteins and leukocytes to leave the circulation to produce inflammatory exudates



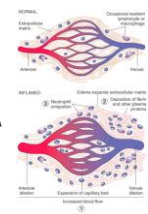
Acute Inflammation Physiology Eicosanoids at every turn

- Vascular Changes
- Vasoconstriction → **PROSTACYCLINE (PGI₂) and THROMBOXANE (TXA₂)—are released quickly after the injury**
- Increased Regional Blood Flow
 - Vasodilation
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Acute Inflammation Physiology

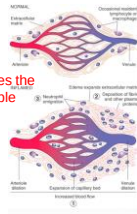
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- Increased Regional Blood Flow
 - Vasodilation → **Then TXA₂ mediates the release of vasodilators**
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Acute Inflammation Physiology

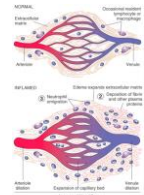
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LEUCOTRIENE LT/B4 makes the blood vessels more permeable



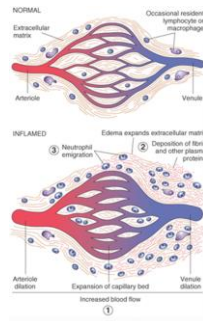
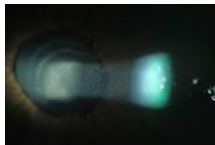
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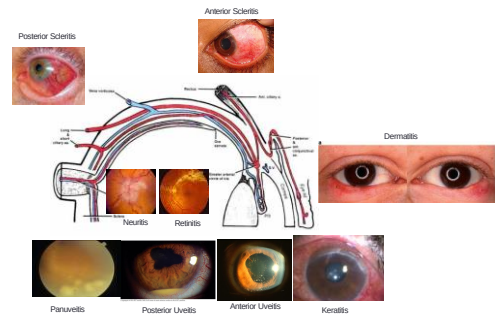


Increase COX-2 which increases Prostaglandin PG/E2 → sensitizing pain neurons
PG/E2 is also a potent pyretic agent

Acute Inflammation Clinical Presentation

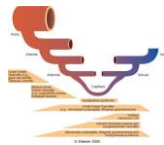


Blood Supply in the Eye: Anatomical Tour of Eye Related Inflammation



Primary Systemic Vasculitides

- Giant cell arteritis (IV)
- Takayasu's arteritis (IV)
- Churg-Strauss syndrome (I)
- Cutaneous leukocytoclastic angitis
- Henoch-Schönlein purpura (III)
- Kawasaki disease (II)
- Microscopic polyangiitis (II)
- Polyarteritis nodosa (III)
- Primary vasculitis
- Wegener's granulomatosis (IV)

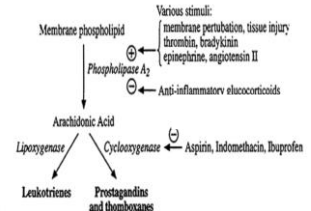


Immunopathological Pathways of Vasculitides Based on Immune and Cell Reactions

Type I Anaphylactic Type	Type II Cytotoxic Type	Type III Immune-complex Type	Type IV Cell-mediated type
Churg-Strauss Syndrome	Wegener's Granulomatosis	Polyarteritis nodosa	Giant cell (temporal) arteritis
	Microscopic polyangiitis	Henoch-Schönlein purpura	Takayasu arteritis
	Kawasaki disease	Essential cryoglobulinemia	Wegener's Granulomatosis

Inflammation and Pain

- A localized inflammatory response induces the release of free arachidonic acid (AA) from membrane phospholipids
- Converted into Eicosanoids



Systemic Effects of Eicosanoids

Cyclooxygenase derived

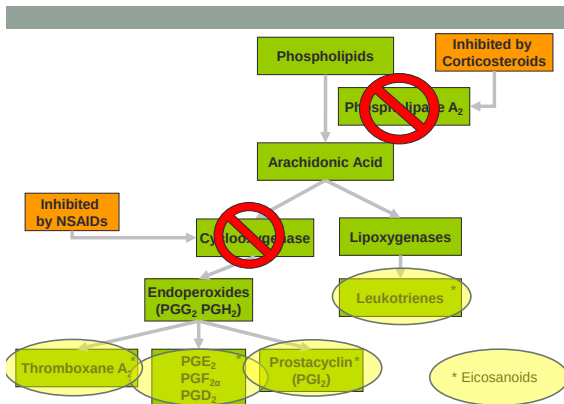
- Thromboxane
 - Clotting
 - Vasoconstriction
- Prostacyclins
 - Vasodilation
- Prostaglandins
 - Vascular smooth muscle
 - Platelet aggregation
 - Pain
 - Inflammation

Lipoxygenase derived

- Leukotrienes
 - Inflammatory response
- Increased Vascular Permeability
- Structural changes in the microvascular that permit fluids, proteins (eg. cytokines: interferon, interleukin, growth factors) and leukocytes to leave the circulation to produce inflammatory exudates

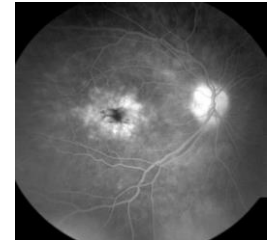
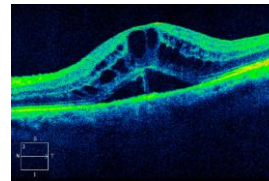
Management of Inflammation

- NSAIDS
- Steroids
- Biologicals/Antimetabolites
- Immunologics
 - Immunosuppressants
 - Interferons
 - Immunoglobulins
- Disease Modifying Anti-Rheumatic Drugs (DMARDs)



NSAID most common use is topical: eg. pre/post op ECCE/CME

- Pre/post op ECCE to prevent CME
- Utility as an adjunct in the treatment of macular edema



CME TREATMENT

Topical nonsteroidal medications
Acular (ketorolac, Allergan) and Voltaren (diclofenac, Novartis Ophthalmics)

Topical corticosteroid drops such as Pred Forte (prednisolone acetate, Allergan) and Lotemax (loteprednol, Bausch & Lomb).

Common dosing ranges from qid to q2h. Often a loading dose of q2h is indicated, and then rapidly dropped to qid after several days.

http://www.revoptom.com/HANDBOOK/oct02_sec5_1.htm

Examples of Topical NSAIDs

- Acular, Acular I.S. Acular PF
- Acuvail
- Bromday
- Ilevro
- Nevanac
- Ocufen
- Prolensa
- Voltaren
- Xibrom



Oral NSAIDS

- Generally ineffective as primary treatment for ocular inflammatory disease
- Exception
 - Non-necrotizing anterior scleritis



Rx'd NSAID Examples

- **Generic names/common brand names**
- Celecoxib (Celebrex®)
- Diclofenac (Voltaren®)
- Fenoprofen (Nalfon®)
- Indomethacin (Indocin®)
- Ketorolac tromethamine (Toradol®)

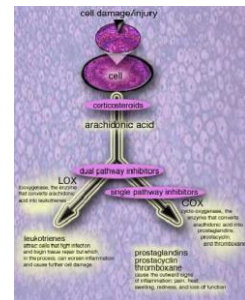


Rx'd NSAID Examples

- **Generic names (no brands)**
- Meclofenamate sodium
- Diflunisal
- Tolmetin
- Ketoprofen
- Flurbiprofen

COX-1 vs. COX-2

- There are two separate forms, or isoenzymes, of cyclo-oxygenase: COX-1 and COX-2.
- Both work on arachidonic acid to form prostaglandins and the other pro-inflammatory products.



COX-1

- **Maintenance of stomach lining, kidney, liver** and a variety of other tissues
 - Ensure adequate blood flow
 - **Protect stomach lining from acid damage**
- **CONSTITUTIVE** – Functions in the absence of inflammation
- Role in the inflammatory process in pain perception

Theoretically....

- NSAIDS that do not inhibit beneficial COX-1 in stomach, liver, kidney and other non-inflamed tissues, potentially have fewer side effects than nonselective NSAIDS.



Theoretically....

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COX-2 inhibitor

- The only COX-2 inhibitors available in the U.S
- Other COX-2 inhibitors have been taken off the U.S. market because of safety concerns.
- Rofecoxib (Vioxx®) was linked to increases in heart attacks and strokes.
- Valdecoxib (Bextra®) was linked to an increase in heart attacks and stroke in people who had cardiac bypass surgery. It was also linked to a rare, fatal skin reaction.
- Lumiracoxib (Prexige®) was found to cause severe liver damage in a small number of people.



NSAIDs: Metabolism and Elimination

- NSAIDs are rapidly and completely absorbed and are highly protein bound.
- Elimination of NSAIDs is through hepatic biotransformation.
- NSAIDs metabolites are excreted via the kidney.

Approved Uses of NSAIDs (include but not limited to):

- | | |
|---------------------------------|-------------------------|
| • Rheumatoid arthritis | • Acute gout |
| • Osteoarthritis | • Fever |
| • Ankylosing spondylitis | • Sunburn |
| • Mild to moderate pain | • Migraine |
| • Primary dysmenorrhea | • Cluster headaches |
| • Juvenile rheumatoid arthritis | • Menorrhagia |
| • Tendinitis | • Premenstrual syndrome |
| • Bursitis | • Cystoid macular edema |

Common Side Effects of NSAIDs

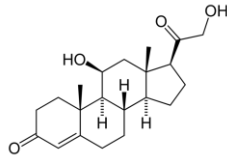
- | | |
|---------------------------|----------------------------|
| • Gastrointestinal | • Other |
| • Nausea | • Dizziness |
| • Vomiting | • Headache |
| • Diarrhea | • Vertigo |
| • Constipation | • Drowsiness |
| • Abdominal distress | • Tremor |
| • Cramps and pain | • Psychic disturbances |
| • Dyspepsia | • Mental confusion |
| • Flatulence | • Congestive heart failure |
| • Anorexia | • Hypotension |
| • Stomatitis | • Hypertension |
| | • Kidney failure |
| | • Dermatologic problems |
| | • Respiratory problems |

Serious Reactions to NSAIDs

- | | |
|------------------------------------|------------------------------|
| • GI bleed | • Anaphylaxis |
| • GI ulceration/perforation | • Bronchospasm |
| • MI | • Exfoliative dermatitis |
| • Stroke | • Stevens-Johnson |
| • Thromboembolism | • Toxic epidermal necrolysis |
| • HTN | • Anemia |
| • CHF | • Blood dyscrasia |
| • Nephrotoxicity | • Prolonged bleeding time |
| • Hepatotoxicity | |

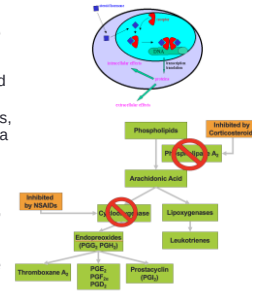
Corticosteroids

- Naturally produced in the adrenal cortex
 - Glucocorticoids – mimic cortisol
 - Mineralocorticoids – mimic aldosterone
- Normal physiology
 - Stress response
 - Inflammatory response
 - Carbohydrate and protein metabolism
 - Blood electrolyte levels
 - Behavior

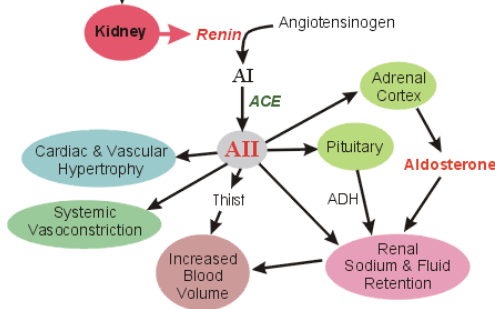


Corticosteroids and Inflammation

- Non-specific – no regard to cause
- Work at level of cell nucleus
 - Reduction of capillary permeability and exudation.
 - Inhibition of degranulation of mast cells, basophils, and neutrophils, leading to a reduction of inflammatory mediators.
 - Suppression of lymphocyte proliferation.
 - Inhibition of phospholipase A synthesis, resulting in decreased production of prostaglandins and leukotrienes.
 - Inhibition of the cell-mediated immune response.

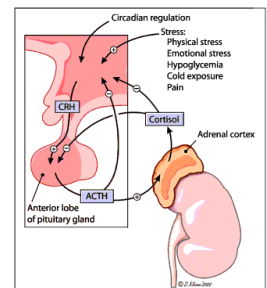


Sympathetic Stimulation
Hypotension
Decreased Sodium Delivery



Hypothalamic-Pituitary-Adrenal Axis

- H: Corticotropin Releasing Hormone
- P: Adrenocorticotropic Hormone
- A: Cortisol
- H: (-) feedback



Prescribing Oral Corticosteroids – Alternate Day Therapy

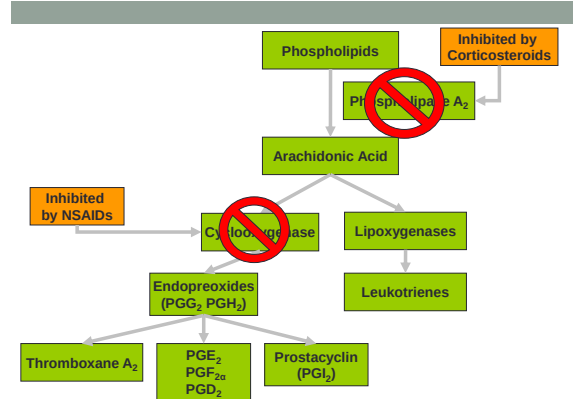
- Attempt to mimic the normal circadian rhythm of steroid production
- Double the dosage and take alternate days in the AM
- Only useful with intermediate acting steroids

Prescribing Oral Corticosteroids-Tapering

- Purpose
 - To allow recovery of pituitary-adrenal responsiveness to secretion of endogenous corticosteroids without exacerbation of disease state
- “Recommended” tapering schedule
 - Depending on dosage, duration, and disease, decrease dosage by 2.5 to 5 mg pred every 3-7 days until reaching a dosage of 5 mg pred. Then perform a challenge to determine extent of recovery.
 - Symptoms of adrenal insufficiency
 - HA, dizziness, fainting, fatigue, lethargy, myalgia, joint pain, dyspnea, orthostatic hypotension, nausea, vomiting, anorexia, weight loss, fever, hypoglycemia, desquamation of skin

Contraindications

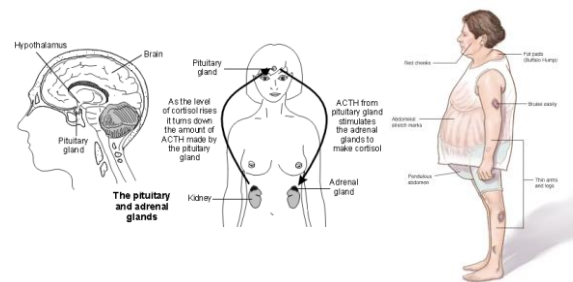
- Untreated serious infection
 - CXR to r/o active TB
- Caution in setting of
 - Liver dysfunction
 - Healing open wounds
 - h/o stomach or duodenal ulcers
 - May need co-therapy
 - Osteoporosis
 - Recent MI, heart failure, HTN
- DM
 - May need to adjust insulin dose
- Epilepsy
- Pregnancy
 - 1st 12 weeks small risk of cleft lip/palate
- Category C
- Risk-benefit
- Breastfeeding
 - Wait > 4 hours s/p dose



Effects/Side Effects of Corticosteroids

- Increased appetite and weight gain
- Fat deposits on back, chest, face, stomach
- Edema from salt and water retention
- Elevated blood pressure
- Elevated blood sugar
- Bruising
- Slow wound healing
- Osteoporosis
- Cataract
- Acne
- Muscle weakness
- Thinning of the skin
- Increases susceptibility to infection
- Stomach ulcers
- Increased sweating
- Mood swings
- Depression
- Adrenal crisis
- Children – growth inhibition

Effects/Side Effects of Corticosteroids – Cushing's syndrome



Risk of Side Effects

- A short course of oral steroids usually causes no side-effects (1-2 weeks)
- Side-effects are more likely to occur if you take a long course of oral steroids (more than 2-3 months), or if you take short courses repeatedly
- Dose dependent so lowest effective dose

Types of oral steroids

- **Glucocorticoids**
 - Prednisolone
 - Betamethasone
 - Dexamethasone
 - Hydrocortisone
 - Methylprednisolone
 - Deflazacort
- **Mineralocorticoids**
 - Fludrocortisone

- usually used for replacing steroids the body isn't producing itself, and the common one used

PO Steroid Indications

- Inflammatory bowel diseases
 - E.g. Crohn's disease, ulcerative colitis
- Autoimmune diseases
 - E.g. SLE
- Relapses that occur in MS
- Joint and muscle diseases
 - E.g. Rheumatoid arthritis, polymyalgia rheumatica
- Allergies
- Asthma
- Chronic obstructive pulmonary disease (COPD)
- Croup
- Hormone replacement in pituitary deficiency (Addison's disease)
- Arthritis
- Asthma
- Cancer
- Dermatitis
- Mineralocorticoid deficiency

Prescribing Oral Corticosteroids – Drug-Drug Interactions

- **Contraindicated**
 - Mifepristone
 - Blocks effects of cortisol
 - Live vaccines
- **Avoid/Use alternatives**
- **Aldesleukin (interleukin-2)**
 - Kidney/skin cancer
- **Clopidogrel**
 - Prevent MI, CVA in setting of heart d
 - Prevents blood clots (antiplatelet coagulator)
- **Blood thinners**
- **NSAIDs**

Ocular Indications for Corticosteroids

- Used for control/prevent inflammation e.g.
 - Dermatitis
 - Blepharitis
 - Episcleritis
 - HSV Stromal Keratitis
 - Uveitis
 - Pre/Post op eye surgery
 - Graft rejection



Ocular Indications for Corticosteroids

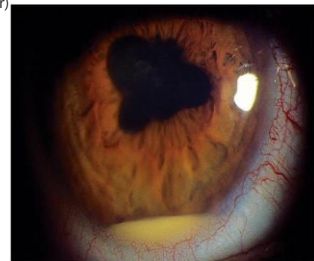
- Non-responsive uveitis
- Severe allergic reactions
- Orbital pseudotumor
- Arteritic Ischemic Optic Neuropathy
- Scleritis
- Retinitis/vitritis
- Sterile endophthalmitis

Corticosteroids in Eye Disease

- Type and location of inflammation determine which route of administration is used.
- Dosage is determined by clinical experience and should be continuously reevaluated.
- Dosage should be individualized.
- Therapy should be reduced gradually.
- The minimal effective dose for the shortest period of time should be used.
- Close supervision of the patient is needed to monitor the effect of treatment and side effects.

Corticosteroids in Eye Disease

- Mainstay of treatment in uveitis
 - topical, local injections (periocular or intraocular)
 - Oral
 - IV



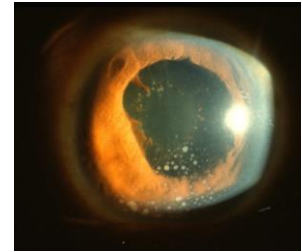
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Parameter	Suggested Guideline
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Maximum adult oral dose	60–80 mg/day
Maintenance dose (adult)	≤10 mg/day
Tapering schedule	Over 40 mg/day, decrease by 10 mg/day every 1–2 weeks 40–20 mg/day, decrease by 5 mg/day every 1–2 weeks 20–10 mg/day, decrease by 2.5 mg/day every 1–2 weeks 10–0 mg/day, decrease by 1 to 2.5 mg/day every 1–4 weeks
Monitor	Blood pressure, weight, glucose every 3 months Lipids (cholesterol and triglycerides) annually Bone density within first 3 months and annually thereafter
Supplemental treatment	Calcium 1500 mg daily and vitamin D 800 IU daily Estrogens and antiresorptive agents as needed

*In selected situations, where an immediate effect is needed, some investigators will begin with intravenous methylprednisolone at a dosage of 1 gm/day for 3 days and then start oral prednisone.

PO Steroids in Uveitis

- May be indicated when
- Vision/QOL is threatened
- Recalcitrant to topical or injection
- OU or systemic involvement



PO Steroids in Uveitis

- High dose initially
- Initial dosing of oral prednisone is typically 1–1.5 mg/kg/day
- Taper depends on effectiveness of initial Tx
- Too rapid tapering or early discontinuation of systemic steroids may lead to disease recurrence

Example of Taper Schedule

Prednisone dose (mg/day)	Decrement (mg/day)	Taper Interval	
		RAPID	STANDARD
60–30	10	2 days	weekly
30–15	5	2 days	weekly
15–7.5	2.5	2 days	weekly
<7.5	2.5–1	2–7 days	weekly-monthly

Oral Corticosteroids

- Low-dose therapy
 - 0.1 to 0.25 mg/kg of body wt.
- Moderate dose therapy
 - About 0.5 mg/kg of body weight
- High dosage
 - About 1 to 3 mg/kg of body weight
- Massive dosage
 - About 15 to 30 mg/kg of body weight

Relative Potency of Glucocorticoids

Corticosteroid	Systemic Equivalent (mg)	Relative Potency
Bethamethasone	0.6	33.0
Dexamethasone	0.75	26.0
Methylprednisolone	4	5.0
Triamcinolone	4	5.0
Prednisolone	4	5.0
Prednisone	5	4.0
Hydrocortisone	20	1.0
Cortisone	25	0.8

NSAIDs/Corticosteroid Comb

- Increases the risk of gastric ulcers; therefore, histamine-H₂ receptor antagonists or proton-pump inhibitors should be prescribed to reduce the risk

CLINICAL CASE REPORT

Thought her head was going to explode after she used a hair dye home coloring kit



Explosion Averted



- Prednisone 40 mg PO q 12 h or
- Medrol Dose Pack

Medrol dose pack

- 21 4 mg methylprednisolone tabs
- Made for easy administration and taper



Medrol Dose Pak					
Day #	TDD	Before Breakfast	After Lunch	After Supper	At Bedtime
1	6	2	1	1	2
2	5	1	1	1	2
3	4	1	1	1	1
4	3	1	1	0	1
5	2	1	0	0	1
6	1	1	0	0	0

47 year-old female

- Painful, red OS x 2 days
- Has had red OS before, but nothing like this
- VA 20/50
- IOP = 25



QQQ: Describe what you see.
 QQQ: Thoughts on pathogenesis?
 QQQ: Thoughts on how to manage it?

HSV Stromal Keratitis Treatment

- Aggressively manage inflammation
 - Frequent use of topical steroids with slow taper (months-years)....
 - Pred Forte 1% QID-q2h (if epithelium compromised, Tx first)
- Antiviral cover
 - Ganciclovir 0.15% gel 3-5x/day
 - Viroptic TID-QID with taper as steroids are tapered
- Oral antiviral (esp if uveitis present)
 - Acyclovir 400 mg BID (800 mg PO 5x/day per day, 10-14 days)
 - Valacyclovir 500 mg BID (1000 mg 3x/day, 10-14 days)
 - Famciclovir 500 mg 3X daily
- Manage IOP as needed (aqueous suppressants)
- Cycloplegia for comfort