

STEROIDS: THE GOOD, THE BAD AND THE UGLY!

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CONFLICT OF INTEREST, DISCLOSURES

Conflict of interest: None

Disclosures:

I prescribe steroids and have for 31 years

I will be discussing off label uses of steroids

OUTLINE

- History of steroids in asthma
- Steroids: Types, preparations, routes of administration
- “The Good”: Benefits of steroids in asthma
- “The Bad and the Ugly”: Risks and side effects of steroids in asthma
- How to mitigate the risks of steroids when used in asthma

DISEASES TREATED WITH CORTICOSTEROIDS

Inflammatory

- Asthma
- Anaphylaxis
- Hypersensitivity pneumonitis
- ABPA
- Urticaria (hives)
- Eczema

Immune Suppression

- Cancer

Autoimmune Connective Tissue

- Systemic Lupus erythematosus (Lupus)
- Sarcoid, Systemic sclerosis, MCTD
- Inflammatory Bowel Disease
- Vasculitis, Myositis
- Bullous dermatitis

Other

- Adrenal insufficiency/Addison's

CONTRAINDICATIONS FOR SYSTEMIC STEROIDS

Absolute

- Systemic fungal infection
- Herpes simplex keratitis
- Hypersensitivity

Relative

- Hypertension and Congestive Heart Failure
- Psychosis or depression
- Active peptic ulcer disease
- Active TB
- Diabetes mellitus
- Osteoporosis
- Cataracts, glaucoma
- Recent intestinal anastomoses

HOW STEROIDS WORK

At the cell level:

- Suppress multiple inflammatory genes that are activated in asthmatic airways by reversing histone acetylation of the activated inflammatory genes
- Induce apoptosis of **eosinophils**
- Upregulate beta-receptors

HISTORY OF STEROIDS FOR ASTHMA/ALLERGY

- 1900: Cortisone discovered (not used for years)
- 1955: Prednisone FDA approved
- 1956: Metered dose inhaler
- 1960s: Albuterol
- 1970s: Inhaled steroid (Beclomethasone-Vanceril™ or Beclovent™)
- 1987: Rx intranasal steroid (Vancenase™)
- 2000: ICS/LABA (Advair™)
- 2013: OTC intranasal steroid (Flonase™)

STEROIDS: ROUTE OF ADMINISTRATION

Oral:

Prednisone	5 mg
Methylprednisolone (Medrol™)	4 mg
Dexamethasone (Decadron™)	0.75 mg

Injectable: IV or IM (Solumedrol™)

Inhaled: small vs large particle, dry powder, nebulizer

Nasal: watery vs aerosol

Ocular: drops, gels, ointments

Skin: (low potency to super-high potency) cream, ointment

ASTHMA

- Chronic inflammatory disorder of the airways:
 - 315 million world wide
 - 25.7 million in U.S. 82,000 in MT
 - 1.8 million ER visits in U.S. 2300 ER visits in MT
 - 439,000 hospitalizations in U.S. 400 hosp in MT
 - 3,400 people die in U.S. 13 Montanans die each yr
- Mild, moderate and severe (5 to 10%):
- Severe asthma: 32 to 45% rely on frequent or daily oral steroids

<https://dphhs.mt.gov/Asthma/data>

<https://asthma.net/basics/statistics/>

CLINICAL GUIDELINES: 2007 NHLBI (U.S.) VS 2018 GINA (GLOBAL)

- Corticosteroids: most effective treatment for asthma
- Inhaled steroids: first line treatment in all ages with persistent symptoms (in GINA, consider even in level 1 asthma)
- Should be initiated ASAP after diagnosis:
 - Early low dose ICS, leads to greater improvement in lung fxn vs waiting 2-4 yrs
 - Pt not on ICS with severe attack, have greater long term decline in lung fxn

DETAILS ON CORTICOSTEROIDS:

- Comparative pharmacology
- Bioavailability
- Pharmacokinetics
- Pharmacodynamics
- Therapeutic Index

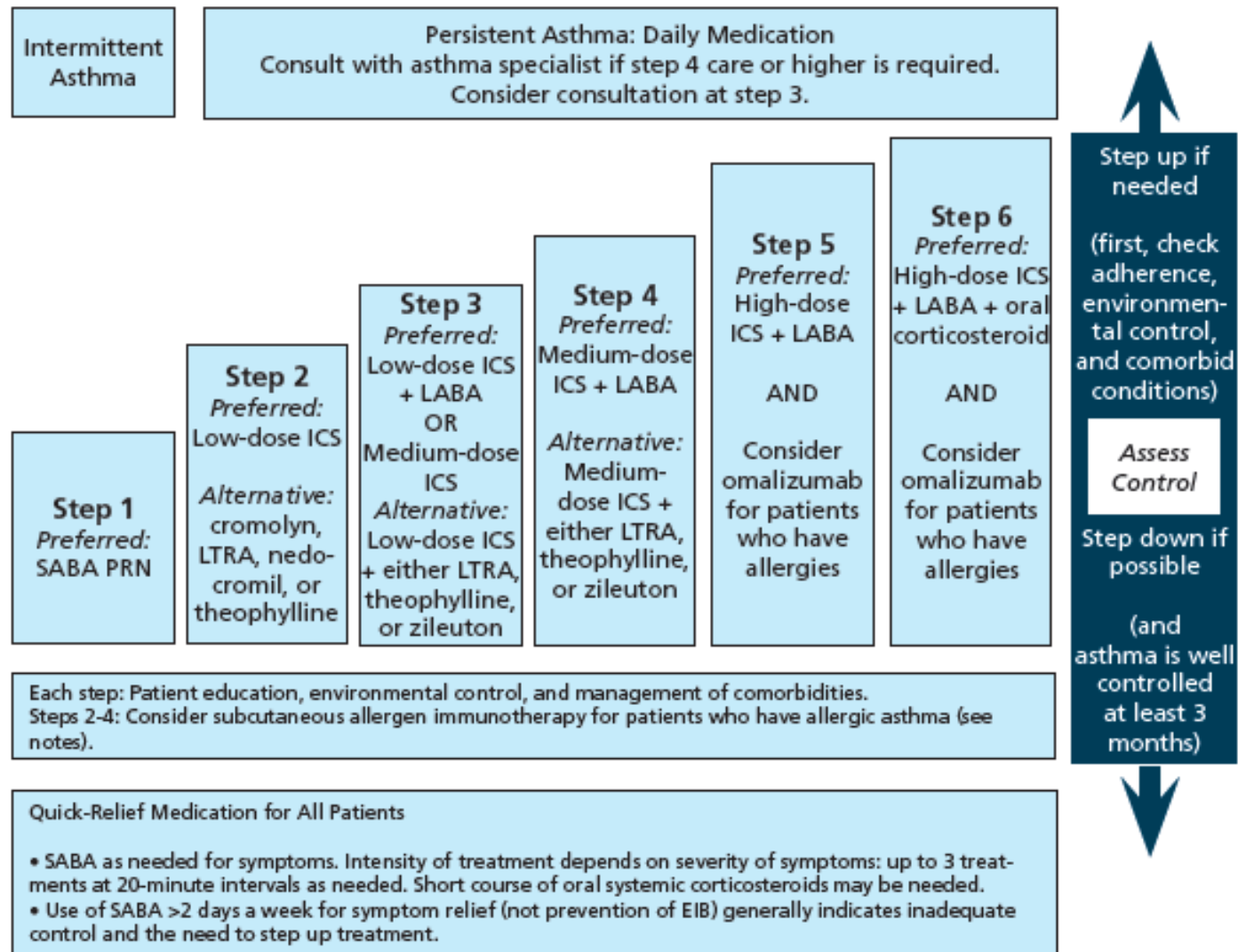
“THE GOOD”: CLINICAL BENEFITS OF STEROIDS IN ASTHMA

- Improve symptoms
- Improve lung function
- Improve quality of life
- Reduce exacerbations
- Decrease mortality
- Most of benefit: at **low to medium** doses!
- Unfortunately: Do not alter asthma progression

WAYS TO USE: INHALED STEROIDS

- Low dose
- High dose
- Regularly
- Seasonally
- Combination with LABA
- Intermittently (GINA guidelines): single reliever and controller therapy—
off label

FIGURE: STEPWISE APPROACH TO ASTHMA TREATMENT⁹



Key: Alphabetical order is used when more than 1 treatment option is listed within either preferred or alternative therapy. EIB = exercise-induced bronchospasm; ICS = inhaled corticosteroid; LABA = long-acting inhaled beta₂-agonist; LTRA = leukotriene-receptor antagonist; SABA = inhaled short-acting beta₂-agonist

NHLBI: STEROIDS BY STEPWISE APPROACH IN 2007

CURRENTLY AVAILABLE ICS:

Fluticasone furoate: Arnuity:



Fluticasone propionate (FP): Flovent



Budesonide: Pulmicort



BDP (beclomethasone):
Qvar Redihaler



mometasone
furoate: Asmanex



Ciclesonide:
Alvesco



Flunisolide: Aerobid

COMPARATIVE DAILY DOSAGES OF INHALED CORTICOSTEROIDS*

Steroid	Low Dose (μg , Child [†] /Adult)	Medium Dose (μg , Child [†] /Adult)	High Dose (μg , Child [†] /Adult)
Beclomethasone HFA	80–160/80–240	>160–320/>240–480	>320/>480
Mometasone, DPI	110/220	220-440/440	>440/>440
Budesonide			
DPI	180–360/180–540	>360–720/>540–1,080	>720/>1,080
Nebules	500/UK	1,000/UK	2,000/UK
Ciclesonide	80–160/160–320	>160–320/>320–640	>320/>640
Flunisolide HFA	160/320	320/320–640	>640/>640
Fluticasone prop			
HFA MDI	88–176/88–264	>176–352/>264–440	>352/>440
DPIs	100–200/100–300	>200–400/>300–500	>400/>500
Fluticasone furoate	100		200

Abbreviations: BDP = beclomethasone dipropionate; BUD = budesonide; CIC = ciclesonide; DPI = dry-powder inhaler; FLU = flunisolide; FP = fluticasone propionate; HFA = hydrofluoroalkanes; MDI = metered-dose inhaler; MF = mometasone furoate; UK = unknown. *Data from Reference 4. †Five to 11 yr of age, except for BUD nebulas (2–11 yr of age).

ICS/LABA COMBINATIONS



Advair=Fluticasone propionate+ salmeterol



Symbicort=
Budesonide+
formoterol



Dulera=
Mometasone+
formoterol



Breo Ellipta=Fluticasone
furoate+ vilanterol

No more “Black Box” warning on LABAs used in asthma

SYGMA: (SYMBICORT GIVEN AS NEEDED IN MILD ASTHMA)

Trial 1

- N=3849 pts, age >12 yr
- 1 year of:
 - Placebo bid + prn SABA
 - Placebo bid + prn Symbicort
 - Symbicort (200/6) bid + SABA prn
- Outcome: asthma control

Trial 2

- N=4215 pts, age >12 yr
- 1 year of:
 - Symbicort prn
 - Symbicort (200/6) bid + SABA prn
- No reminders to use meds
- Outcome: rate of severe attacks

CONCLUSIONS OF SYGMA TRIALS:

- Maintenance group:
 - Asthma control: 44% vs prn ICS/LABA (34%) vs prn SABA (31%)
 - Adherence: 79%
 - Steroid exposure (avg per day): 340 mcg vs 57 mcg in prn ICS/LABA
 - Lung function and ACT: maint group > prn ICS/LABA > prn SABA
- No difference in reducing asthma attacks (prn vs maint ICS/LABA)
 - As needed approach: reduces avg daily ICS dose (66 mcg vs 267 mcg)
- Option to use prn ICS/LABA in mild asthma is RADICAL!
 - May lead to better adherence and decreased pharmacy \$\$

TREATMENT OF ASTHMA EXACERBATIONS

- Adult:
 - Prednisone 40 to 50 mg (GINA) po daily (max 60 mg-NHLBI) x 5 to 7 days
- Children:
 - Prednisone 1-2 mg/kg/day, (max 60 mg/day) *for 3 - 10 days (NHLBI)*
 - Prednisone 1-2 mg/kg/day (max 40 mg/day) for 3 - 5 days (GINA)
 - Dexamethasone 0.3 to 0.6 mg/kg x 1 to 5 days
 - [Can Fam Physician](#). 2009 Jul; 55(7): 704–706.
- Taper not needed if less than 2 weeks

“THE BAD”: STEROID SIDE EFFECTS

- Inhaled steroids:
 - Local
 - Systemic at high dose
- Oral/injectable steroids:

Raissy HH, Kelly HW, Harkins M, Szeffler SJ. Inhaled corticosteroids in lung diseases. *Am J Respir Crit Care Med.* 2013;187:798–803

Roland. *Chest* 2004; 126(1):213.

LOCAL SIDE EFFECTS: INHALED STEROIDS

Side Effects

- Oral thrush
- Dysphonia: Hoarseness
- Unusual:
 - Perioral dermatitis
 - Tongue hypertrophy
 - Increased thirst

Myth: Tooth staining

How to Mitigate

- Rinse and spit
- Use holding chambers
- Use lower doses

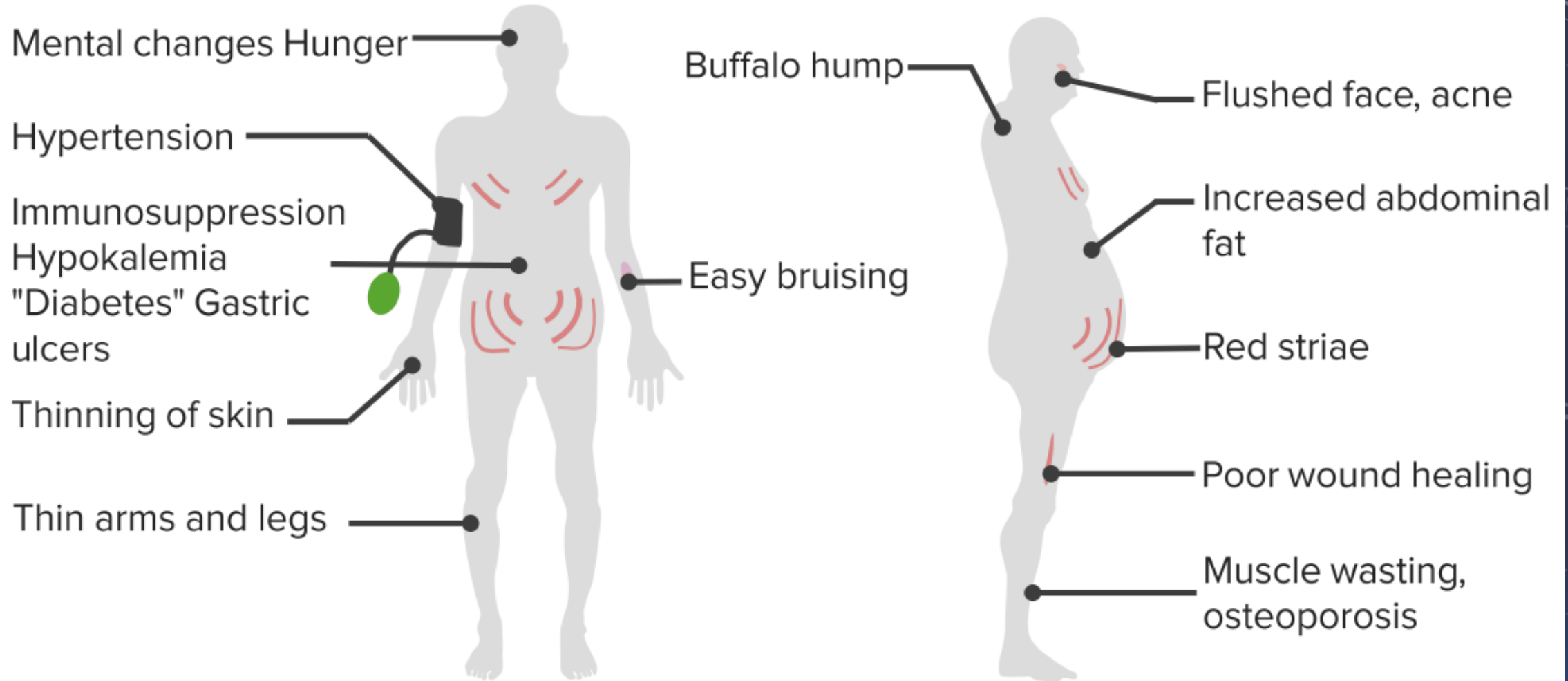
“THE BAD”: SIDE EFFECTS OF PREDNISONE

- Mood and personality changes: high, low, rage
- Headache, dizziness, insomnia, memory loss, confusion, delirium
- Appetite: increase or decrease
- Weight gain: round abdomen, small arms and legs
- Skin: acne, thin/fragile skin, increased sweating, hair growth
- GI: nausea, vomiting, heartburn, ulcers
- Fat redistribution: “Moon face,” “Buffalo Hump”
- Fluid retention: feet swelling

“UGLY” SIDE EFFECTS OF STEROIDS

- Growth effects (children): dose related; oral > ICS
- Vaccine failure
- High blood pressure (in 20%)
- Eye: cataracts and glaucoma
- Myopathy
- Poor wound healing
- Adrenal suppression
- Diabetes
- Reactivation of Herpes, TB
- Bone
 - Osteopenia
 - Osteoporosis
 - Osteonecrosis
 - Fractures: vertebral, femur

CUSHINGOID

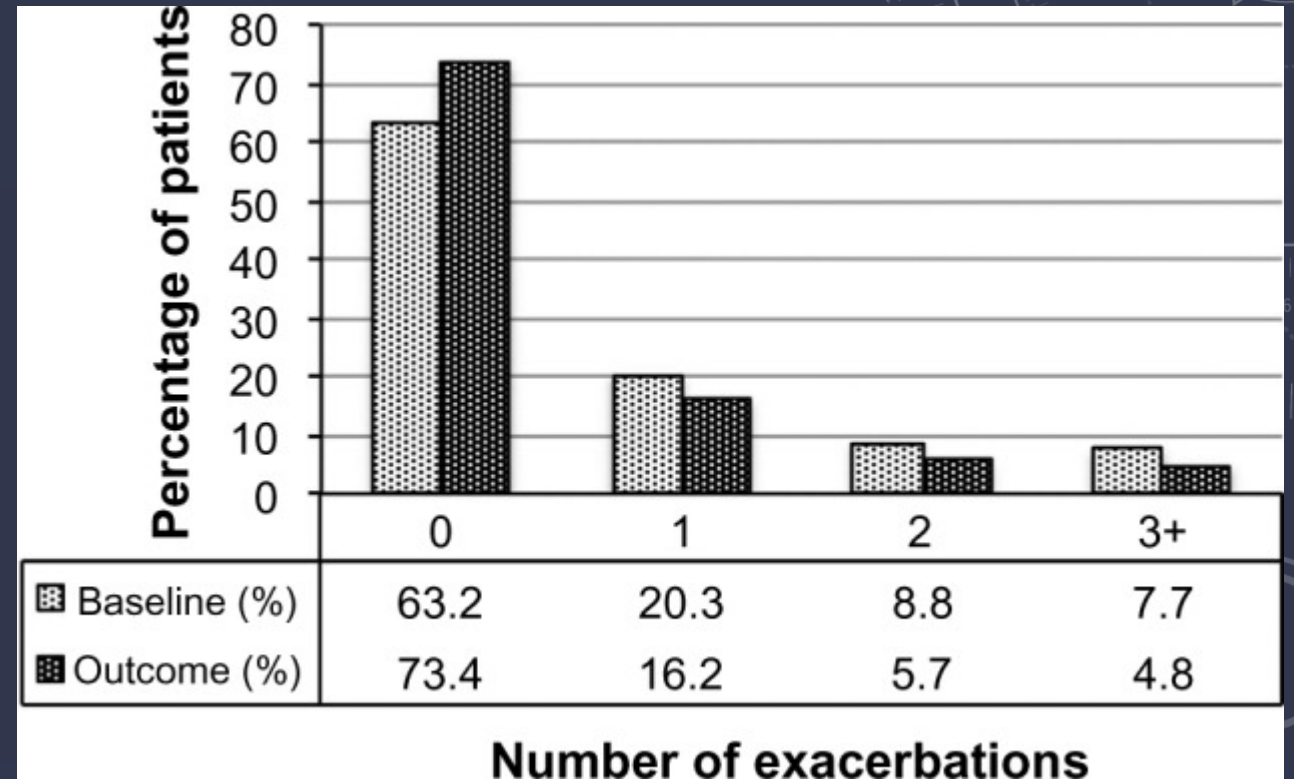


HOW TO MINIMIZE STEROID RISKS/SIDE EFFECTS

- Use least amount necessary for shortest time possible
- Keep prednisone courses to less than once a year
- Optimize avoiding asthma triggers and consider allergy injections
- Add steroid-sparing medications
 - LABA (long-acting beta-agonists)
 - LTRA (Leukotriene receptor antagonists): montelukast
 - LAMA: (long acting muscarinic antagonists)
 - Biologics (anti-IgE, anti-IL-5, anti-IL5-rc, anti-IL 4/13)

STERIOD SPARING EFFECT OF LAMA (TIOTROPIUM)

- Adding: LAMA (tiotropium)
- Improves symptoms
- Decreases exacerbations and oral steroid use



[Price. Et al. J Asthma Allergy. 2015; 8: 1–13.](#)

Long-acting muscarinic antagonist use in adults with asthma: real-life prescribing and outcomes of add-on therapy with tiotropium bromide

STEROID SPARING EFFECTS OF BIOLOGICS

- Omalizumab (Xolair): SQ antibody against IgE
- Reslizumab (Cinqair): IV antibody against IL-5 rc
- Mepolizumab (Nucala): SQ antibody against IL-5 rc
- Benralizumab (Fasenra): SQ antibody against alpha subunit of IL-5 rc
- Dupilumab (Dupixent): SQ antibody against IL-4 and IL-14

STEROID-SPARING EFFECT OF OMALIZUMAB (XOLAIR)

- Open label
- N=12 adults, Prednisone 22.5 mg
- 4 off Pred, 7 on Pred 4 mg/day (all <10 mg), 1 no response
- ---
- N=34 children (age 12), Pred 20 mg, 16 weeks of Tx
- Result: decreased Pred to 5 mg, 7 completely off Pred
- No change in FEV1

Feb 2013 Vol 131, Issue 2,
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<http://dx.doi.org/10.1136/archdischild-2011-301570>

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STEROID-SPARING EFFECT OF MEPOLIZUMAB (NUCALA)

Random DB trial. N=135 pt with severe eos asthma on
Pred 12.5 mg daily

Mepolizumab vs placebo SQ q month x 20 weeks

Outcome: pt reduction of steroids Placebo Mepo

90 to 100% reduction	11%	23%
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75 to 90% reduction	8%	17%
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50 to 75% reduction	15%	13%
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0 to 50% reduction	11%	10%
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50% reduction in Nucala group vs. 0 in placebo

32% decrease in attacks and improved ACQ score

NEJM. 2014; 371:1189

STEROID-SPARING EFFECT OF BENRALIZUMAB (FASENRA)

- 28 week, RDBPC trial of Benralizumab vs placebo in 220 adults with severe eosinophilic asthma (med eos 400 to 500)
- On Pred 7.5 to 40 mg, avg 10 mg for at least 6 months
- Protocol: decreased pred by 2.5 to 5 mg each week
- Results
 - Decreased oral steroid doses by 75% vs 25% in placebo
 - >50% of pt on drug: completely off oral steroids vs 19% placebo
 - Decreased asthma exacerbation rate but no change in FEV1

Nair. NEJM. 2017.
376:25;2448

STEROID SPARING EFFECT OF DUPILUMAB (DUPIXENT)

- Quest and Venture Trials
- Reduced the risk of severe asthma attacks
- Improved lung function
- Reduced oral corticosteroids.

PHENOTYPE-SPECIFIC ASTHMA THERAPEUTIC TARGETING

Pathology	Phenotype	Therapeutic Intervention
Non-Eosinophilic	Paucigranulocytic / Neutrophilic	IL-17 antagonists Macrolide antibiotics, methotrexate, phosphodiesterase IV inhibitors
Eosinophilic	Allergen-Exacerbated	Allergen avoidance and immunotherapy Anti-IgE IL-4 antagonists IL-13 antagonists IL-4/IL-13 dual antagonists
	Idiopathic eosinophilic	Corticosteroids IL-5/IL-5R antagonists
	Aspirin-exacerbated respiratory disease	Leukotriene modifiers Aspirin desensitization

SCREENING/TREATMENT FOR SIDE EFFECTS OF STEROIDS

Screening

- Monitor growth in children
- Adrenal insufficiency:
 - Am cortisol
 - Low/high dose ACTH stimulation
- DEXA scan: bone mineral density

Treatment

- Calcium +Vitamin D
- Bisphosphonates

GIO: Glucocorticoid-induced osteoporosis
American College of Rheumatology

CONCLUSIONS AND TAKE HOME POINTS:

- Use lowest possible dose for the shortest possible duration of time
- ICS better than oral; steroid specific (low-medium-high dose)
- No one specific dose for each person (individualize)
- If need prednisone more than once a year----TOO MUCH
- Use steroid-sparing approach/medications:
 - Avoidance, allergy shots, LABA, LTRA, LAMA, biologics