
MICHAEL ZACHARISEN, MD.
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

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

**Immune Suppression**
- Cancer

**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/ALLERGENCY

• 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 TREATMENT**

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Preferred: SABA PRN</th>
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</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>Preferred: Low-dose ICS</td>
</tr>
<tr>
<td>Alternative: cromolyn, LTRA, nedocromil, or theophylline</td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td>Preferred: Low-dose ICS + LABA</td>
</tr>
<tr>
<td>OR Medium-dose ICS</td>
<td></td>
</tr>
<tr>
<td>Alternative: Low-dose ICS + either LTRA, theophylline, or zileuton</td>
<td></td>
</tr>
<tr>
<td>Step 4</td>
<td>Preferred: High-dose ICS + LABA AND</td>
</tr>
<tr>
<td>Step 5</td>
<td>Consider omalizumab for patients who have allergies</td>
</tr>
<tr>
<td>Step 6</td>
<td>Preferred: High-dose ICS + LABA + oral corticosteroid AND</td>
</tr>
<tr>
<td>Consider omalizumab for patients who have allergies</td>
<td></td>
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</tbody>
</table>

**Step up if needed**
(first, check adherence, environmental control, and comorbid conditions)

**Step down if possible**
(and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

**Quick-Relief Medication for All Patients**
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

**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
CURRENTLY AVAILABLE ICS:

BDP (beclomethasone): Qvar Redihaler

Fluticasone furoate: Arnuity

Fluticasone propionate (FP): Flovent

Budesonide: Pulmicort

Mometasone furoate: Asmanex

Ciclesonide: Alvesco

Flunisolide: Aerobid
### COMPARATIVE DAILY DOSAGES OF INHALED CORTICOSTEROIDS*

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Low Dose (μg, Child†/Adult)</th>
<th>Medium Dose (μg, Child†/Adult)</th>
<th>High Dose (μg, Child†/Adult)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mometasone, DPI</td>
<td>110/220</td>
<td>220–440/440</td>
<td>&gt;440/&gt;440</td>
</tr>
<tr>
<td>Budesonide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPI</td>
<td>180–360/180–540</td>
<td>&gt;360–720/&gt;540–1,080</td>
<td>&gt;720/&gt;1,080</td>
</tr>
<tr>
<td>Nebules</td>
<td>500/UK</td>
<td>1,000/UK</td>
<td>2,000/UK</td>
</tr>
<tr>
<td>Flunisolide HFA</td>
<td>160/320</td>
<td>320/320–640</td>
<td>&gt;640/&gt;640</td>
</tr>
<tr>
<td>Fluticasone prop</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPIs</td>
<td>100–200/100–300</td>
<td>&gt;200–400/&gt;300–500</td>
<td>&gt;400/&gt;500</td>
</tr>
<tr>
<td>Fluticasone furoate</td>
<td>100</td>
<td></td>
<td>200</td>
</tr>
</tbody>
</table>

**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 nebules (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
- Taper not needed if less than 2 weeks
“THE BAD”: STEROID SIDE EFFECTS

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


# LOCAL SIDE EFFECTS: INHALED STEROIDS

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>How to Mitigate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral thrush</td>
<td>Rinse and spit</td>
</tr>
<tr>
<td>Dysphonia: Hoarseness</td>
<td>Use holding chambers</td>
</tr>
<tr>
<td>Unusual:</td>
<td>Use lower doses</td>
</tr>
<tr>
<td>Perioral dermatitis</td>
<td></td>
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<tr>
<td>Tongue hypertrophy</td>
<td></td>
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<tr>
<td>Increased thirst</td>
<td></td>
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<tr>
<td>Myth: Tooth staining</td>
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</tbody>
</table>

“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

Mental changes
Hunger

Hypertension

Immunosuppression
Hypokalemia
"Diabetes" Gastric ulcers

Thinning of skin

Buffalo hump

Flushed face, acne

Increased abdominal fat

Red striae

Easy bruising

Poor wound healing

Muscle wasting, osteoporosis

Thin arms and legs
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)
STEROID SPARING EFFECT OF LAMA (TIOTROPIUM)

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

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

http://dx.doi.org/10.1136/archdischild-2011-301570
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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Mepo</th>
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</thead>
<tbody>
<tr>
<td>90 to 100% reduction</td>
<td>11%</td>
<td>23%</td>
</tr>
<tr>
<td>75 to 90% reduction</td>
<td>8%</td>
<td>17%</td>
</tr>
<tr>
<td>50 to 75% reduction</td>
<td>15%</td>
<td>13%</td>
</tr>
<tr>
<td>0 to 50% reduction</td>
<td>11%</td>
<td>10%</td>
</tr>
</tbody>
</table>

50% reduction in Nucala group vs. 0 in placebo
32% decrease in attacks and improved ACQ score
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

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