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CONFLICT OF INTEREST, DISCLOSURES AND CONFESSIONS

Conflict of interest: None
Disclosures:
I prescribe steroids and have for 31 years
I will be discussing off label uses of steroids
Confession: I’m not a pharmacist

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
QUESTION AND CASE

20 y/o male with allergic rhinitis and asthma since 4 years old.
Having mild cough every day and wheeze 3 nights a week
Taking albuterol twice a week. Spirometry: FVC 80%, FEV1 56%

- What is the best steroid treatment strategy?
  A. Short course of oral steroids
  B. Inhaled steroids
  C. Inhaled steroid/LABA combination
  D. Kenalog™ injection

TYPES OF STEROIDS:
- Sex steroids: estrogen, progesterone, testosterone (Anabolic)
- Corticosteroids:
  - Glucocorticoids (cortisol): regulates immune function
  - Mineralocorticoids (aldosterone) regulates balance of electrolytes
- Secosteroids: (Vitamin D) helps regulate many biological functions
- Neurosteroids: (DHEA) aids synthesis of male and female hormones
- Sterols (Cholesterol): help maintain cell membrane integrity

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

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**ASTHMA**

- Chronic inflammatory disorder of the airways:
  - 315 million worldwide
  - 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/

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**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
CURRENTLY AVAILABLE ICS:


COMPARATIVE DAILY DOSAGES OF INHALED CORTICOSTEROIDS:

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Low Dose (μg, Child/Age)</th>
<th>Medium Dose (μg, Child/Age)</th>
<th>High Dose (μg, Child/Age)</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 DPI</td>
<td>180–360/180–540</td>
<td>&gt;360–720/360–1,080</td>
<td>&gt;720/&gt;1,080</td>
</tr>
<tr>
<td>Indacaterol (UK)</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>320–640/640</td>
<td>&gt;640/&gt;640</td>
</tr>
<tr>
<td>Fluticasone propionate DPI</td>
<td>100–200/100–300</td>
<td>&gt;200–400/300–500</td>
<td>&gt;400/&gt;500</td>
</tr>
<tr>
<td>Fluticasone furoate</td>
<td>100</td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DPI = dry-powder inhaler; HFA = hydrofluoroalkane; MDI = metered-dose inhaler; MF = mometasone furoate; UK = unknown. *Data from Reference 4. †Five to 11 yr of age, except for BU/MDI 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>Dysohphonia</td>
<td>Use holding chambers</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Use lower doses</td>
</tr>
<tr>
<td>Unusual:</td>
<td></td>
</tr>
<tr>
<td>Perioral dermatitis</td>
<td></td>
</tr>
<tr>
<td>Tongue hypertrophy</td>
<td></td>
</tr>
<tr>
<td>Increased thirst</td>
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<tr>
<td>Myth: Tooth staining</td>
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PREDNISONE

“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

“THE UGLY”
“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
Immuno suppression
Hypokalnia
"Diabetes" Gastric ulcers
Thinning of skin
Thin arms and legs

Buffalo hump
flushed face, acne
Increased abdominal fat
Red striae
Poor wound healing
Muscle wasting, osteoporosis

“THE BAD”: (CONT)

Up to 90% of pts who take steroids for >60 days. These side effects, including the more serious fractures and cataracts, occur even in patients taking low (≤7.5 mg/d) dosages.

Steroids: Pharmacology, Complications, and Practice Delivery Issues

William Ericson-Nielsen, MD, and Alan David Kaye, MD, PhD

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-IL-5 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-13
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

Feb 2013 Vol 131, Issue 2, Suppl Page AB6

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%
75 to 90% reduction 8% 17%
50 to 75% reduction 15% 13%
0 to 50% reduction 11% 10%
50% reduction in Nucala 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

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Phenotype</th>
<th>Therapeutic Intervention</th>
</tr>
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<tbody>
<tr>
<td>Non-Eosinophilic</td>
<td>Neutrophilic</td>
<td>IL-57 antagonists, Macrolide antibiotics, methotrexate, phosphodiesterase IV inhibitors</td>
</tr>
<tr>
<td>Eosinophilic</td>
<td>Allergen-Exacerbated</td>
<td>Allergen avoidance and immunotherapy, 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-3 antagonists</td>
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<tr>
<td></td>
<td></td>
<td>IL-4/IL-13 dual antagonists</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Corticosteroids, IL-5/IL-5R antagonists</td>
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<tr>
<td>Idiopathic eosinophilic</td>
<td></td>
<td>Leukotriene modifiers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin desensitization</td>
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BIOLOGIC THERAPIES FOR ASTHMA
SCREENING/TREATMENT FOR SIDE EFFECTS OF STEROIDS

<table>
<thead>
<tr>
<th>Screening</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor growth in children</td>
<td>Calcium + Vitamin D</td>
</tr>
<tr>
<td>Adrenal insufficiency:</td>
<td>Bisphosphonates</td>
</tr>
<tr>
<td>• Am cortisol</td>
<td></td>
</tr>
<tr>
<td>• Low/high dose ACTH stimulation</td>
<td></td>
</tr>
<tr>
<td>• DEXA scan: bone mineral density</td>
<td></td>
</tr>
</tbody>
</table>

GIO: Glucocorticoid-induced osteoporosis
American College of Rheumatology

CASE:

20 yr old male with allergic rhinitis and asthma since 4 years old.
Having mild cough and wheeze 3 nights a week, every other day
Taking albuterol twice a week. Spirometry: FVC 80%, FEV1 56%
• What is the best steroid treatment strategy?
A. Short course of oral steroids: with or without taper
B. Inhaled steroids: high dose
C. Inhaled steroid/LABA combination
D. Kenalog™ injection: No

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