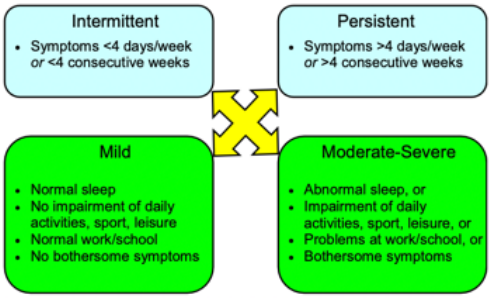
PHARMACOLOGIC MANAGEMENT OF ALLERGIC RHINITIS IN CHILDREN & ADULTS

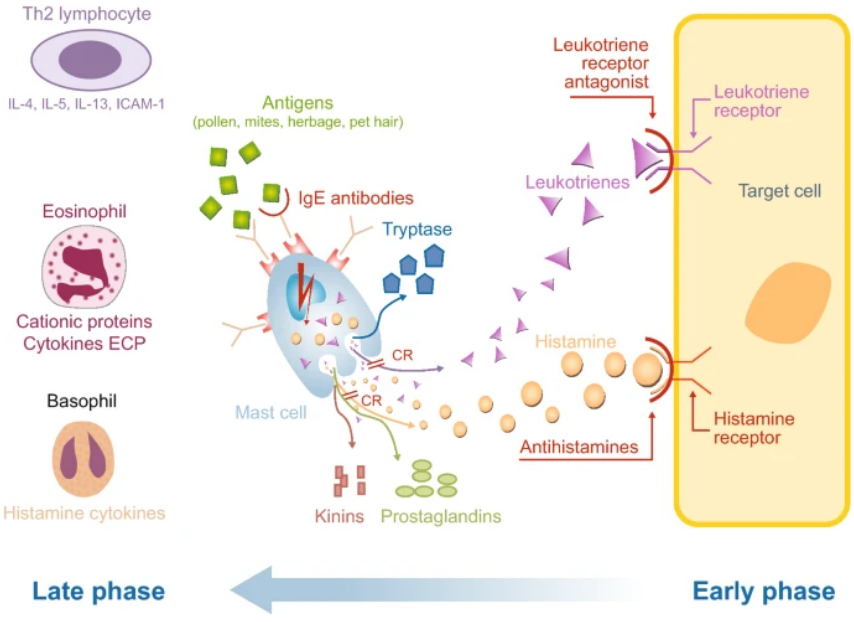
General Considerations

- Rhinitis, defined as inflammation of the nasal mucosa, is a common disorder affecting up to 40% of the population and is often undetected in the primary-care setting.
- Allergic rhinitis, affecting 10-20% of the population, is strongly linked to asthma and conjunctivitis.
  - Allergic reactions in the upper airways (i.e., nose, nasal cavity, paranasal sinuses, pharynx, and larynx) may lead to inflammatory processes in the lower airways (i.e.., trachea, bronchial tubes, bronchioles and lungs) --> hyper-responsiveness of lower airways --> bronchospasm
- Allergic rhinitis symptoms: sneezing, rhinorrhea, nasal obstruction, pruritis of nose and palate, postnasal drip, cough, irritability, and fatigue.
  - Severe allergic rhinitis is associated with significant impairments in quality of life, sleep, & work performance
- The management of allergic rhinitis is influenced by the frequency of severity symptoms, the age of the patient, and the presence of concurrent conditions.



Pathophysiology

- In allergic rhinitis, mast cells, CD4-positive T cells, B cells, macrophages and eosinophils infiltrate the nasal lining upon exposure to an allergen.
- The T cells infiltrating the nasal mucosa are T helper 2 (Th2) that release cytokines (e.g., IL-3, IL-4, IL-5, IL-13) and promote IgE antibody production by plasma cells. (IgE antibodies are bound to mast cells)
- When an allergen binds to IgE receptors on mast cells, it triggers the release of histamine and leukotrienes, resulting in arteriolar dilation, increased vascular permeability, itching, rhinorrhea, mucous secretion, and smooth muscle contraction in the lung.



- The pathophysiology of allergic rhinitis consists of an early-phase and late-phase allergic response.
- The early phase reaction is characterized by mast cell degranulation and the rapid onset of acute nasal symptoms (i.e., sneezing, rhinorrhea) and ocular symptoms (i.e., itching, redness, watering) caused by histamine, leukotrienes (LTs), prostaglandins (PGs), cytokines, and kinins. --> increase in vascular permeability and edema.
- The late phase reaction develops over 4-6 hours after allergen exposure and is characterized by cellular recruitment of basophils, neutrophil, T-lymphocytes, monocytes and eosinophils and by the release of cytokines, PGs, and LTs --> causes tissue remodeling and perpetuates mucosal inflammatory and edema --> causes nasal congestion (i.e., most troublesome symptom of allergic rhinitis) and hyper-responsiveness of airway in asthma.
  - Nasal congestion is associated with sleep disruption and impaired sleep quality --> daytime sedation and reduced productivity.

Pharmacologic Agents in Mild-Moderate Rhinitis

Oral Antihistamines

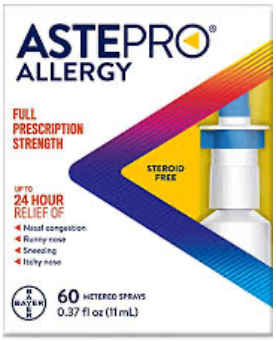
- MOA: Antihistamines bind to H_1 receptors and downregulate their activity by shifting the equilibrium from the active form to the inactive form.
  - Antihistamines have been reclassified as "inverse agonists," rather than H_1 receptor antagonists.
- H_1 antihistamines are divided into 1st and 2nd generation agents.
  - 1st generation antihistamines
    diphenhydramine (Benadryl), chlorpheniramine (Chlor-Trimeton), hydroxyzine (Atarax, Vistaril), cyproheptadine, promethazine (Phenergan).
  - 2nd generation antihistamines
    cetirizine (Zyrtec), loratadine (Claritin), fexofenadine (Allegra), desloratadine (Clarinex), levocetirizine (Xyzal)

Drug	Dose	Preparations	Duration of action	Common adverse reactions	Considerations
Chlorpheniramine (Aller-chlor®, Ahist™, Chlor-Trimeton®)	4 mg PO q4h-q6h or sustained release 8–12 mg PO q8h-q12h, maximal oral dose 24 mg/day; 5–40 mg IM, IV or SC as a single dose, maximum parenteral dose 40 mg/day	4 mg (Aller-Chlor®), 12 mg (Ahist™, Chlor-Trimeton®), SR 8 mg and 12 mg tablets (PO); 10 mg/mL (IV)	3–6 hours	Cardiac dysrhythmias, constipation, drowsiness, dizziness, epigastric discomfort, hypotension, increased bronchial secretions, urinary retention, somnolence	No specific advantages, available without prescription
Diphenhydramine hydrochloride (Benadryl®)	25–50 mg PO q4h-q6h, maximal oral dose 300 mg/day; 10–50 mg IV/ IM or IV q2h-q3h, maximal parenteral dose 400 mg/day	25 mg, 50 mg tablets (PO); 50 mg/mL (IV)	4–6 hours	Dizziness, drowsiness, photosensitivity, paradoxical excitement, tachycardia, thickened bronchial secretions, urinary retention	Most sedating antihistamine, useful for insomnia, available without prescription
Hydroxyzine (Vistaril®)	25 mg PO TID-QID; 25–100 mg IM q4–6h	10 mg, 25 mg, 50 mg tablets (PO); 50 mg/mL (IM)	4–6 hours	Agitation, drowsiness, dizziness, dry mouth, weakness	IV route not recommended due to digital gangrene, possible psychological effects of withdrawal, requires prescription
Cyproheptadine (generic)	4 mg PO TID- QID, maximal dose 0.5 mg/kg per day	4 mg tablets (PO)	6–9 hours	Abdominal discomfort, dry mouth diarrhea, nausea, rash, urticaria, photosensitivity, weight gain	Serotonin antagonist, requires prescription
Promethazine (Phenergan®)	6.25–12.5 mg PO QD; 12.5–25 mg IV q4h-q6h	12.5 mg, 25 mg, 50 mg tablets (PO); 25 mg/mL (IV)	4–6 hours	Drowsiness, dermatitis, photosensitivity, somnolence	Effective antiemetic and adjunct for post-operative pain, requires prescription

- 2nd generation antihistamines are minimally sedating and are preferred over 1st generation agents because they have similar efficacy and fewer CNS and anticholinergic adverse effects.
  - 1st generation antihistamines are lipophilic --> readily cross the BBB (blood-brain barrier) --> bind to H_1 receptors in CNS --> sedation.
  - 1st generation antihistamines are associated with paradoxical agitation in children --> impair school performance.
  - 1st generation antihistamines are associated with anticholinergic side effects: dry mouth and eyes, urinary hesitancy, constipation, etc…
- Although the 2nd generation antihistamines are less sedating than the 1st generation agents, cetirizine (Zyrtec) causes some sedation in 10% of pts.
- General considerations of oral antihistamines:
  (1) Oral antihistamines reduce itching, sneezing, rhinorrhea; but are less effective for nasal congestion than glucocorticoid (GC) nasal sprays.
  (2) "Onset of action" of oral antihistamines is within 1 hour and "time to peak" (i.e., max effects) are achieved in 2-3 hours.
  (3) 2nd generation antihistamines are dosed once or twice daily and are equally efficacious.
  (4) When higher than recommended doses of 2nd generation antihistamines are used for severe symptoms of rhinitis, they are associated with sedation.
  (5) 2nd generation oral antihistamines are effective in patients with mild or intermittent symptoms of rhinitis. Glucocorticoid nasal sprays are preferred in patients with chronic and moderate-severe symptoms due to greater efficacy.
  (6) Drug tolerance does not develop to antihistamines.

Antihistamines
Anticholinergic effects
Dry mouth and eyes
Impotence
Urinary hesitancy
Glaucoma
Central nervous system effects
Sedation
Rarely stimulation (usually children)
Confusion (older patients)
Cognitive impairment
Miscellaneous effects
Weight gain
Hypersensitivity
Prolonged QT interval
Ventricular arrhythmias
Decongestants
Nervousness
Irritability
Insomnia
Headache
Urinary hesitancy
Tachycardia/palpitations
Hypertension
Nausea

<u>Antihistamine Nasal Sprays (OTC)</u>: Azelastine (AstePro) and Olopatadine (Patanase)



- Antihistamine nasal sprays have some anti-inflammatory effects and can relieve nasal congestion.
- General considerations of antihistamine nasal sprays:
  (1) Rapid onset of action (< 15 mins) indicates that antihistamine nasal sprays may be used "on demand" and "PRN."
  (2) Azelastine and olopatadine have similar efficacy.
  (3) Glucocorticoid (GC) nasal sprays are preferred over antihistamine nasal sprays for greater efficacy in chronic and moderate-severe rhinitis.
  (4) Antihistamine nasal sprays are available OTC and are FDA-approved for infants (azelastine) and pediatrics (azelastine and olopatadine).

<u>Azelastine (0.1%, 0.15%) Nasal Spray</u> (AstePro)
- Infants <u>≥</u> 6 months and children < 6 yrs --> 0.1% Soln: 1 spray per nostril BID
- Children 6 to < 12 years: 0.1% or 0.15% Soln: 1 spray per nostril BID
- Children > 12 years and adults: 0.15% Soln: 2 sprays per nostril BID

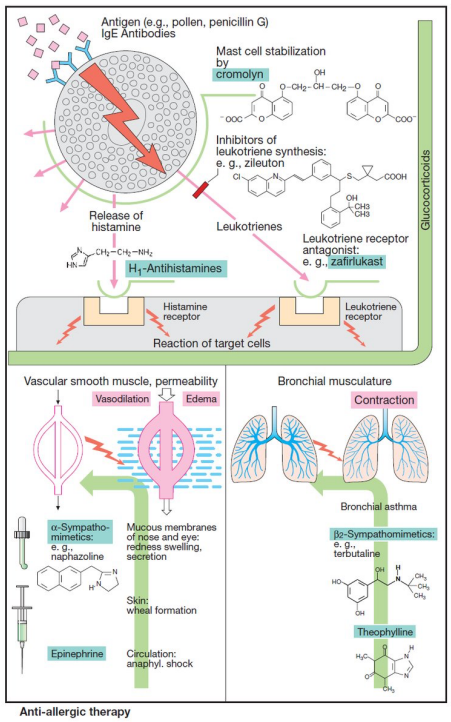
<u>Olopatadine (0.6%) Nasal Spray</u> (Patanase)
- Children (6 to < 12 years): 1 spray per nostril BID
- Children <u>≥</u> 12 years and adults: 2 sprays per nostril BID

(5) A combination of antihistamine/glucocorticoid nasal spray is available by prescription for patients who have not obtained sufficient relief with one agent.

<u>Dymista Nasal Spray</u> (azelastine-fluticasone 137 mcg – 50 mcg)
- Dymista is approved for children > 6 years-old
- Dosage: 1 spray each nostril BID

<u>Cromolyn Sodium Nasal Spray</u>
(Nasacrom)

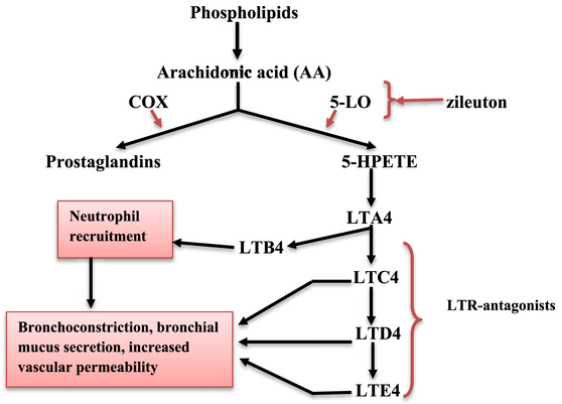
- MOA: Cromolyn sodium is a mast cell stabilizer --> inhibits mast cell release of histamine, leukotrienes, and other inflammatory mediators.
- Efficacy: cromolyn is less effective than glucocorticoid nasal sprays and less effective than 2nd generation antihistamines (oral and nasal).
  - In allergic rhinitis, it is most effective when initiated 2-3 weeks prior to pollen season or exposure to allergens, rather than after symptoms begin.
  - Dosing: 1-2 sprays TID-QID is required to maintain efficacy in allergic rhinitis.
- Safety: cromolyn is very safe when used during pregnancy and is very safe in pediatrics.
- Cromolyn is generally recommended when patients are unable to tolerate adverse effects associated with other agents.



Anti-allergic therapy

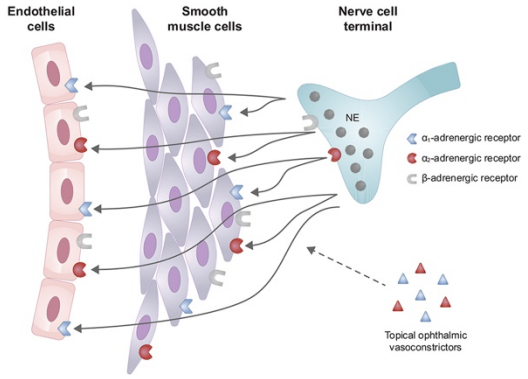
Leukotriene Antagonists: Montelukast (Singulair)

- Montelukast is indicated for the treatment of asthma and allergic rhinitis.
- Efficacy: montelukast is similar in efficacy to antihistamines, but less effective than glucocorticoid nasal sprays.
- Leukotriene antagonists (LTRAs) are considered when patients are unable to tolerate other agents and refuse intranasal glucocorticoids or antihistamines.
- Black boxed warning was added to montelukast in 2020 instructing patients to report mood changes, since montelukast has been associated with neuropsychiatric adverse effects: dream abnormalities, insomnia, anxiety, depression, suicidal thoughts.



Nasal Decongestant Sprays

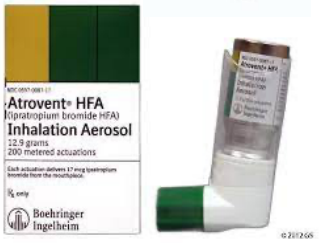
- MOA: topical nasal decongestants are alpha-1 receptor agonists --> vasoconstriction of nasal vessels --> reduce mucus production and edema --> decrease congestion.
- OTC nasal decongestant products include: phenylephrine (Neo-Synephrine), oxymetazoline (Afrin), xylometazoline, and naphazoline (Privine).
- Oxymetazoline (Afrin) nasal spray is very popular due to its 12-hour duration, compared to Q4-6H dosing schedule of the other nasal decongestants.
- Efficacy: Nasal decongestants are highly effective for nasal congestion, but they are not recommended as monotherapy in chronic allergic rhinitis since they can cause rhinitis medicamentosa after 5-7 days of continuous use. In rhinitis medicamentosa, downregulation of alpha-1 adrenergic receptors results in rebound congestion and dependency.
- In clinical trials, when oxymetazoline (Afrin) was used once daily in combination with a fluticasone (Flonase) in adults who did not respond optimally to GC nasal spray alone, there was no evidence of rhinitis medicamentosa after 4 weeks of treatment. Further studies are needed before routinely recommending long-term combined treatment. Current guidelines recommend discontinuing the vasoconstrictor sprays once symptoms are controlled with a GC nasal spray alone.
- SEs (oral and nasal decongestants): nervousness, irritability, insomnia, headache, urinary hesitancy, tachycardia/palpitations, hypertension, and nausea.
- Nasal and oral decongestants are contraindicated in patients with uncontrolled hypertension and patients with coronary artery disease.



Decongestants
Nervousness
Irritability
Insomnia
Headache
Urinary hesitancy
Tachycardia/palpitations
Hypertension
Nausea

Ipratropium Bromide (Atrovent Nasal Spray)

- MOA: Ipratropium is an anticholinergic agent which promotes bronchodilation in asthma/COPD; however, when applied to the nasal mucosa, it inhibits secretions from serous and seromucous glands --> decreases rhinorrhea.
  (Note: ipratropium bromide is a quaternary amine that minimally crosses the nasal membranes and BBB --> decreases systemic anticholinergic effects).
- Ipratropium bromide (0.03% -0.06%) nasal spray, is useful for decreasing rhinorrhea.
- Dose: 2 sprays per nostril BID-TID.
- Efficacy: Ipratropium is not recommended as a 1st-line agent for allergic rhinitis, since it is less effective than GC nasal sprays for sneezing, pruritus, or nasal obstruction. It's mainly useful in children or adults who have profuse rhinorrhea that is not adequately controlled with GC sprays.



Glucocortocoid Nasal Sprays

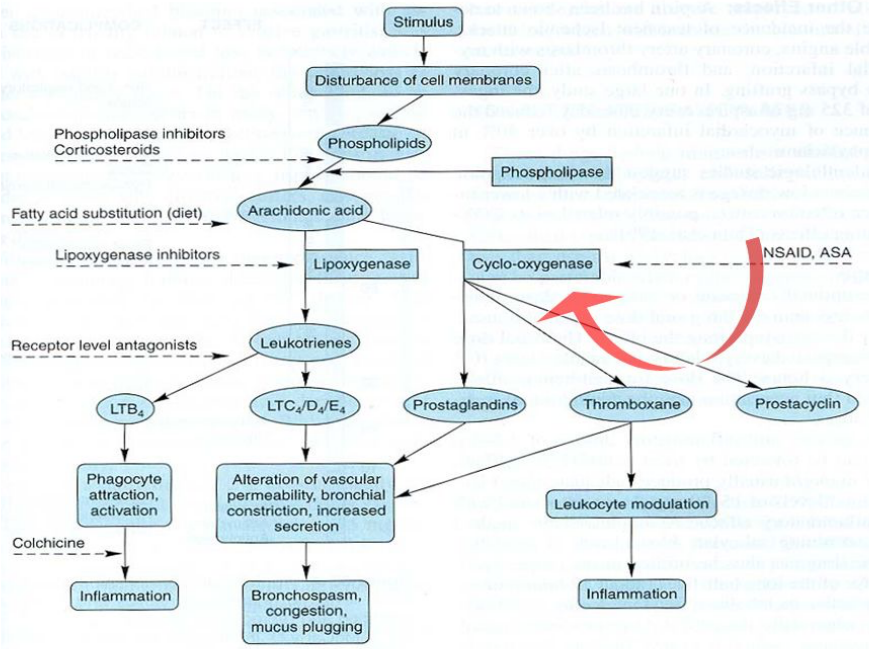
- Glucocorticoid (GC) nasal sprays are the most effective pharmacologic agents for allergic rhinitis and are recommended for moderate-severe allergic rhinitis.
- All of the glucocorticoid preparations have similar efficacy, but the 2nd generation agents are more convenient with once daily dosing and safer for long-term use because of lower bioavailability (i.e., systemic absorption).
- For patients who fail to respond to glucocorticoid nasal sprays, a 2nd agent from a different class may be added, such as (1) an antihistamine nasal spray, (2) an oral antihistamine, or (3) an antihistamine/glucocorticoid combination product.
  - Dymista (Azelastine/fluticasone) is available as a convenient combination product for patients who experience breakthrough symptoms with a glucocorticoid nasal spray.

Glucocorticoids Nasal Sprays for Treatment of Rhinitis

Name	Common brand name(s) and strength	Usual adult dose per nostril	Lower age limit when used in children (years)*	Usual pediatric dose per nostril	Type of preparation (alcohol content)¶
First-generation (systemic bioavailability 10 to 50%)					
Beclomethasone	Beconase AQ (42 mcg/spray)	One or two sprays twice daily	6 years	One or two sprays twice daily; in children 6 to 11 years, start with one spray twice daily	Aqueous suspension pump spray (0.25% alcohol)
	Pediatric: Qnasl Children's (40 mcg/spray) Adolescent/adult: Qnasl (80 mcg/spray)	Two sprays once daily using 80 mcg/spray product	4 years	4 to 11 years: One spray once daily using 40 mcg/spray product ≥12 years: Two sprays once daily using 80 mcg/spray product	Pressurized aerosol spray (8% alcohol)
Budesonide	Generic (formerly Rhinocort Allergy) (OTC) (32 mcg/spray)	One to two sprays once daily	6 years	One to two sprays once daily; in children 6 to 11 years, start with one spray twice daily	Aqueous suspension pump spray
Second-generation (systemic bioavailability <1% or undetectable)					
Ciclesonide	Omnaris (50 mcg/spray)	Two sprays once daily	2 years	2 to 11 years: One or two sprays once daily ≥12 years: Two sprays once daily	Aqueous suspension pump spray
	Zetonna (37 mcg/spray)	One spray once daily	12 years	≥12 years: One spray once daily	Pressurized aerosol spray (3.4% alcohol)
Fluticasone furoate	Flonase Sensimist (OTC) (27.5 mcg/spray)	Two sprays once daily	2 years	One or two sprays once daily; in children 2 to 11 years, start with one spray once daily	Aqueous suspension pump spray
Fluticasone propionate	Flonase Allergy Relief (OTC) (50 mcg/spray)	Two sprays once daily or one spray twice daily	4 years	4 to 11 years: One spray once daily ≥12 years: Two sprays once daily or one spray twice daily	Aqueous suspension pump spray (0.25% alcohol)
Mometasone	Nasonex 24HR Allergy (OTC) (50 mcg/spray)	Two sprays once daily	2 years	2 to 11 years: One spray once daily ≥12 years: Two sprays once daily	Aqueous suspension pump spray

Glucocorticoids: Mechanism of Action

- Inhaled glucocorticoids are non-specific suppressors of inflammation:
  - GCs inhibit arachidonic acid metabolism, resulting in the decreased production of leukotrienes (LT) and prostaglandins (PG).
  - GCs reduce the migration and activation of inflammatory cells by inhibiting cytokine production.
  - GCs also increase the responsiveness of $beta_2$ receptors in airway smooth muscle (bronchioles)--> promote bronchodilation in asthma/COPD.



Glucocorticoid Nasal Sprays: General Considerations

(1) GC nasal sprays are effective for nasal congestion in patients who don't respond to oral or nasal antihistamines.

(2) Some GC nasal spray products (brand and generic) are available OTC: fluticasone (Flonase), mometasone (Nasonex), and budensonide (Rhinocort).

(3) GC nasal sprays are the most effective single maintenance therapy for allergic rhinitis and cause few side effects at the recommended doses.

(4) There is no evidence to suggest that doses greater than the max recommended doses offer additional benefit. High doses are associated with systemic absorption and systemic adverse effects (HPA-axis suppression, etc…)

(5) Initially, clinicians may start treatment at maximum recommended doses to control symptoms, then decrease doses in a "stepped down" approach at 1-week intervals to the lowest effective dose.

(6) All GCs products are equally efficacious at the recommended doses; therefore, once daily preparations may be preferred since they are more convenient and may improve compliance.

(7) Flunisolide (Nasalide): 2 sprays BID-TID --> less convenient dosing schedule than once daily dosing of other agents.

(8) Most GCs have an onset of action of a few hours (3-12 hours) and may take several days for max effect in patients with chronic symptoms.

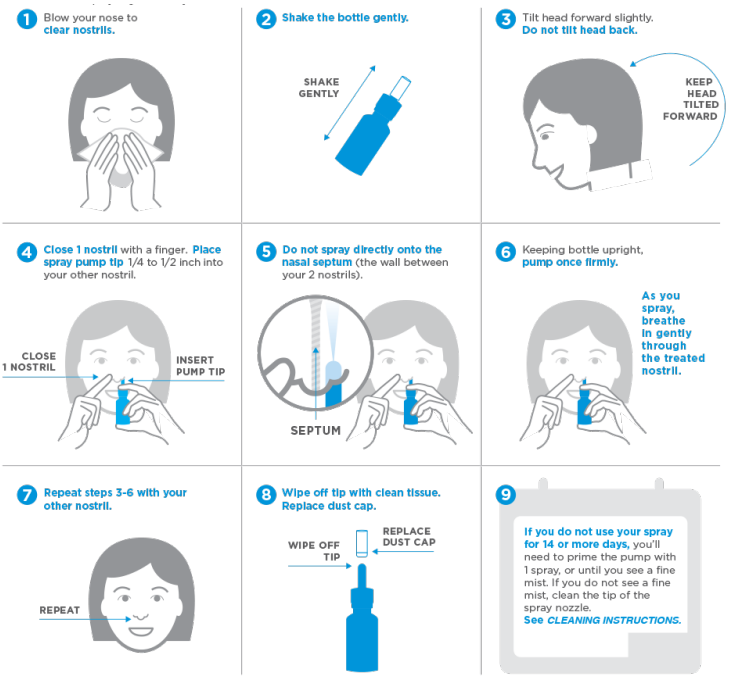
(9) If mucus crusting is present, rinse nose with a saline nasal spray or irrigation to prevent treatment failure. GC must coat the nasal mucosa for efficacy.

Glucocorticoid Nasal Spray: General Considerations (cont.)

(10) For patients who are nasally obstructed, a decongestant spray 10 mins prior to using a nasal GC may helpful; but this should only be used for 5 days to avoid rhinitis medicamentosa. If the nasal decongestant spray is not effective in relieving the obstruction, a very short course of oral GC may be used.

Glucocorticoids Nasal Spray: Adverse Effects

- Local irritation of the nasal mucosa (drying, burning, discomfort) --> 2-10% of patients.
  - Formulations with alcohol or propylene glycol are more irritating than aqueous formulations.
  - Reducing doses to lowest effective dose is recommended.
  - Proper administration technique is helpful. Proper positioning of head can prevent the spray from draining down the throat --> keep head pointed slightly downward and avoid tilting the head back. Avoid pointing the spray at the septum, which can become irritated.
  - Long-term studies have not found evidence of damage to the nasal mucosa with nasal GC, despite years of use in the majority of patients.



- Epistaxis, observed as scant blood found in the nasal mucus, is usually due to mucosal irritation. This is often remedied by stopping treatment on the side of the nose where bloody mucus has been noted for a few days and then restarted therapy.
- Systemic absorption of GC in nasal sprays at recommended doses with 2nd-generation agents has demonstrated little to no effects with HPA-axis suppression, bone-mineral density, intraocular pressure, or cataract formation.

Systemic Glucocorticoids

- A short course of oral glucocorticoids (5-7 days) in "severe" allergic rhinitis may be indicated to alleviate intolerable symptoms in patients who are unable to sleep or work productively.

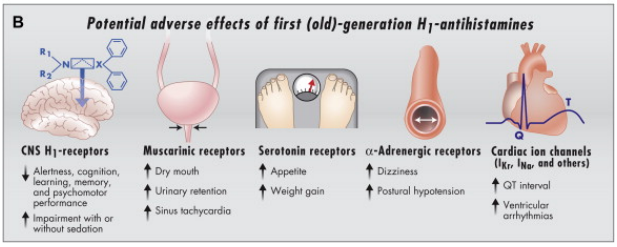
Major Adverse Effects Associated with Systemic (PO/IV) Glucocorticoid Therapy

Metabolic & Endocrine Hyperglycemia Adrenal Insufficiency (i.e., HPA-Axis Suppression) Immune System Immunosuppression (risk of infection) Hematologic Leukocytosis Cardiovascular Fluid Retention Hypertension	Neuropsychiatric Dysphoria/Depression Mania/Psychosis Euphoria Insomnia Ophthalmologic Elevated Intraocular Pressure Cataract Formation Exophthalmos Gastrointestinal Gastritis Peptic Ulcer Disease (PUD)	Bone & Muscle Osteoporosis Myopathy Dermatologic & Appearance Cushingoid Appearance Facial Erythema Skin thinning Weight Gain Hirsutism Acne Striae

TREATMENT OPTIONS IN PEDIATRICS

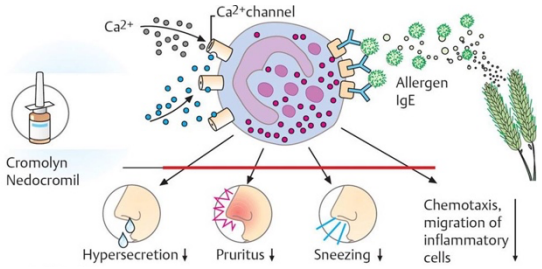
Antihistamines (Mild-Moderate Rhinitis)

- **Minimally Sedating Antihistamines**
  - Cetirizine (Zyrtec), Loratadine (Claritin), and Fexofenadine (Allegra)
    - Cetirizine is approved for children ≥ 6 months.
    - Loratadine and fexofenadine are approved for children ≥ 2 years.
    - These antihistamines may be taken routinely or as needed (PRN), preferably 2-5 hours before exposure with cetirizine and fexofenadine; whereas loratadine peaks 8 hours after administration.
- **Sedating Antihistamines**
  - Diphenhydramine (Benadryl), Chlorpheniramine (Chlor-Trimeton), and other 1st generation antihistamines should be avoided in young children since these agents may cause paradoxical agitation and anticholinergic side effects.



Cromolyn Nasal Spray (Mild to Moderate Rhinitis)

- Cromolyn nasal spray (Nasalcrom) is available OTC and is very safe in pediatrics because it is not systemically absorbed. (SE: mild nasal mucosa irritation)
- Cromolyn is less effective than glucocorticoid nasal sprays and more difficult to administer than oral antihistamines in pediatrics.
- Cromolyn may be taken "PRN" (30 min before exposure) for brief exposure to allergen(s); but for prolonged exposures, it's best to begin 4-7 days in advance.



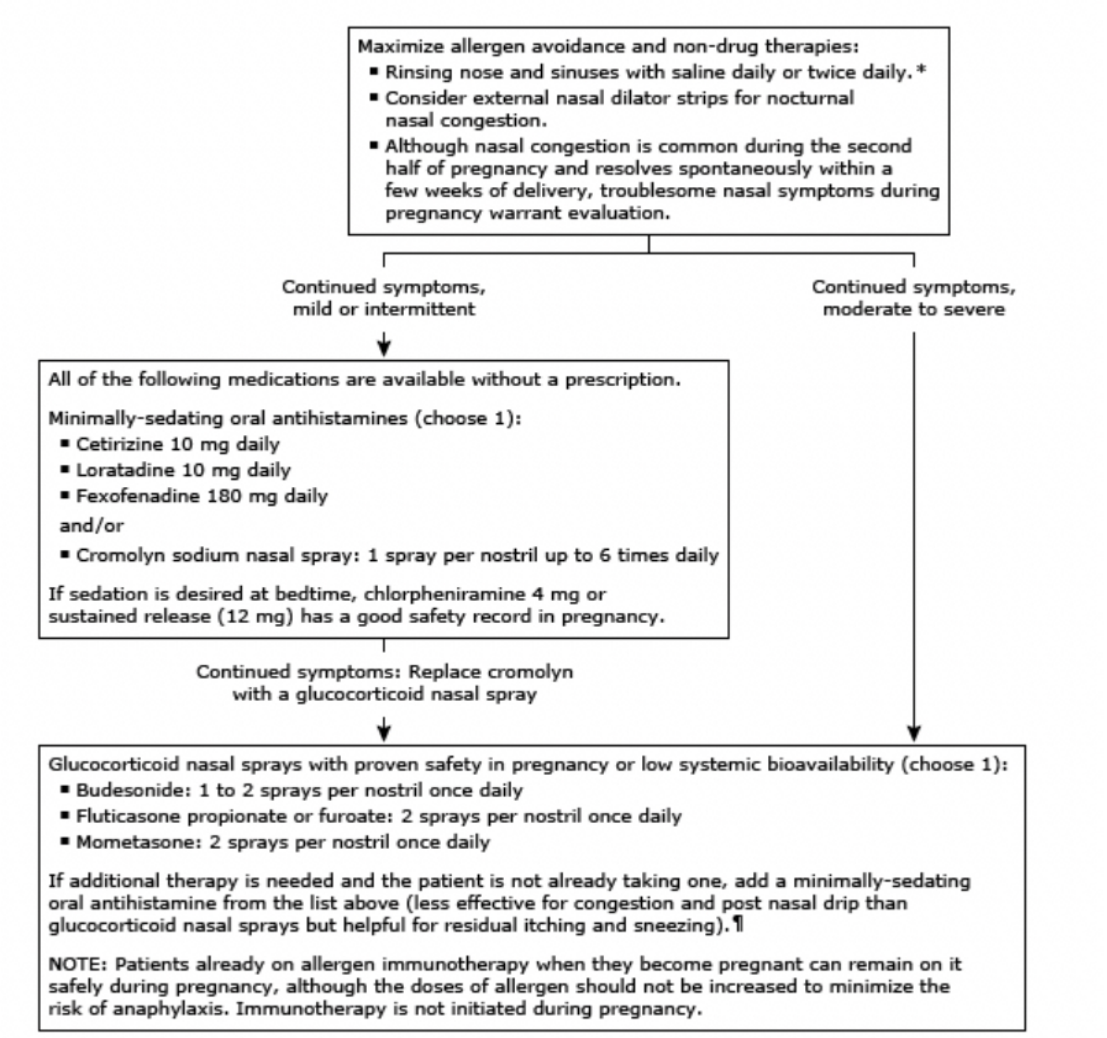
Antihistamine Nasal Sprays (Mild to Moderate Rhinitis)

- Antihistamine nasal spray is useful for mild to moderate symptoms of allergic rhinitis.
- Azelastine nasal spray (Astelin, Astepro) is FDA-approved in children > 6 years-old.
- Olopatadine nasal spray (Patanase) is approved in children > 12 years-old, since its safety and efficacy have not been evaluated in younger children.

Glucocorticoid Nasal Sprays (Moderate to Severe Rhinitis)

- Glucocorticoid nasal sprays are recommended for moderate to severe symptoms of allergic rhinitis since they are more effective than oral and intranasal antihistamines and cromolyn nasal spray in pediatric patients.
- Mometasone (Nasonex), fluticasone furoate (Flonase), and triamcinolone (Nasacort) are approved by the FDA for peds ≥ 2 years. Fluticasone "propionate" is approved for peds ≥ 4 yrs.
  - Dose: 1 spray in each nostril once daily.
    - GC doses may be increased to 2 sprays in each nostril in acute episodes of severe symptoms for up to 2 weeks, since high doses are associated with systemic absorption and systemic adverse effects (e.g., HPA-axis suppression).
    - If taken "PRN" for episodic allergic rhinitis, give 2 days before exposure and continue through for 2 days after the end of exposure.

Allergic Rhinitis: Treatment Options in Pregnancy



* The nasal passages can be rinsed with a saline spray or the lower sinuses can be rinsed with larger volumes using a neti pot or squeeze bottle. Refer to UpToDate content on pharmacotherapy for allergic rhinitis, discussion of nasal saline.

¶ Medications that are generally avoided in pregnancy include oral decongestants (especially in the first trimester), antihistamine nasal sprays (due to lack of human data), and herbal therapies (not regulated and thus could contain contaminants).

Non-Pharmacologic Options: Nasal Dilator Strips / Saline Rinse

Nasal saline sprays rinse allergens from the nasal passages. Saline sprays and irrigations are also useful when removing crusted nasal secretions prior to GC sprays (to improve penetration and application on the nasal mucosa).