Current Therapies for Allergies and Asthma

APP Pharmacology Conference

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3/8/2024

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Overview

- General Background
- Eczema
- Asthma
- Rhinitis (with Nasal-polyposis)
- Anaphylaxis
- Food Allergy
- Urticaria and Angioedema

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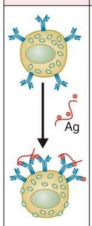
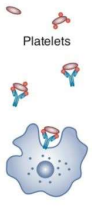
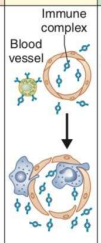
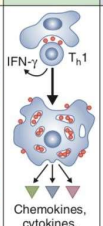
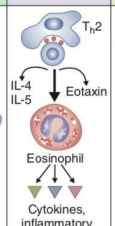
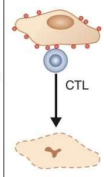
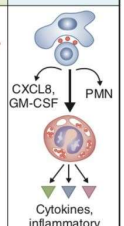
Hypersensitivity Reactions-the basics

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IFN-γ, TNF-α (T_h1 cells)	IL-5, IL-4/IL-13 (T_h2 cells)	Perforin/ granzyme B (CTL)	CXCL8, GM-CSF (T cells)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulations or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
							
Example of hypersensitivity reaction	Allergic rhinitis, sytemic anaphylaxis	Hemolytic anemia, thrombocyto-penia (e.g., penicillin)	Serum sickness, Arthus reaction	Tuberculin reaction, contact dermatitis (with IVc)	DRESS Maculopapular exanthema with eosinophilia	SJS/TEN Bullous exanthema and fixed drug eruption Hepatitis	AGEP Behçet disease

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	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
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	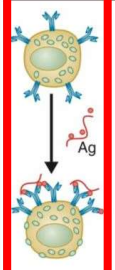	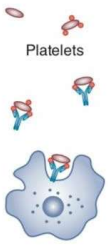	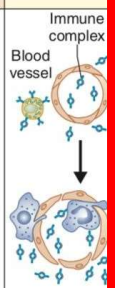	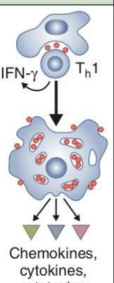	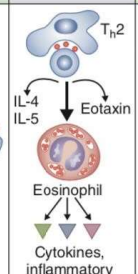	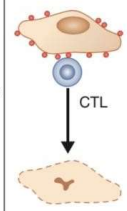	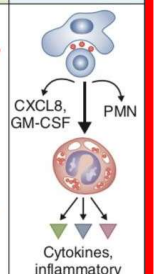
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ECZEMA

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Eczema

- Features
  - Pruritis
  - Eczematous lesions (associated with TH2 and TH22 inflammation)
  - Dry skin (related to epidermal barrier dysfunction

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Characteristic Lesions, Atopic Dermatitis top right image and middle images and Atopic dermatitis, Infraorbital Folds, left image – Reproduced with permission from Dr. P. Marazzi/Science Photo Library. Characteristic Lesions, Atopic Dermatitis bottom right image; Characteristic Lesions, Chronic Plaque. Psoriasis top left and middle left images, and Chronic Plaque Psoriasis, Inverse involvement left image – Reproduced with permission from Science Photo Library. Characteristic Lesions, Chronic Plaque Psoriasis bottom right image - Reproduced with permission from Dr. Harout Tanielian/Science Photo Library. Chronic Plaque Psoriasis, Inverse involvement right image – Reproduced with permission from Monica Schroeder/Science Photo Library. Atopic Dermatitis, Infraorbital Folds bottom-right image - Reproduced with permission from Lippincott Williams & Wilkins. Copyright © 2003. Associated Findings, Chronic Plaque Psoriasis – Top-left image – Reproduced with permission from DermNet NZ. Copyright © 2022. www.dermnetnz.org. Atopic Dermatitis, Hyperlinear Palms image reproduced with permission from DermNet NZ and Professor Raimo Suhonen. Copyright © 2022 Professor Raimo Suhonen. www.dermnetnz.org.

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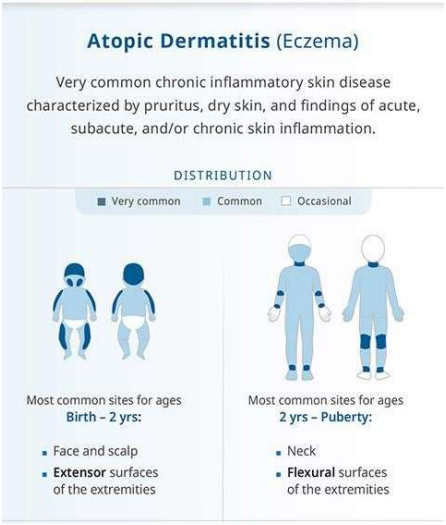
Eczema



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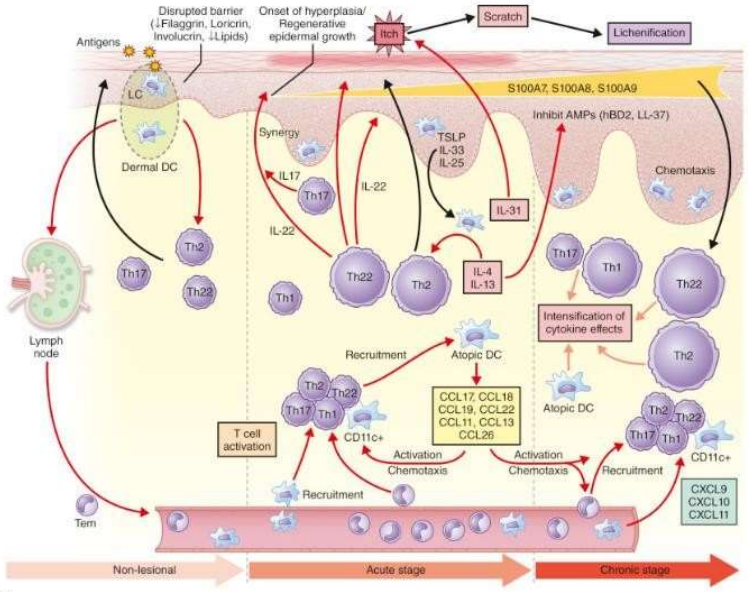

Fig. 33.5
Skin barrier and immunologic abnormalities in atopic dermatitis.
(Reproduced from Leung DY, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. J Allergy Clin Immunol 2014;134:769-79.)

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Eczema Treatment Overview

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Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape

Mark Boguniewicz, MD [*]; Luz Fonacier, MD [†]; Emma Guttman-Yassky, MD, PhD [‡]; Peck Y. Ong, MD [§]; Jonathan Silverberg, MD, PhD, MPH [‖]; Judith Rosen Farrar, PhD [¶]

	Non-lesional	Mild	Moderate	Severe
Maintenance Treatment	**BASIC MANAGEMENT** **1. Skin Care** • Moisturizer, liberal and frequent (choice per patient preference) • Warm baths or showers using non-soap cleansers, usually once daily and followed by moisturizer (even on clear areas) **2. Trigger Avoidance** • Proven allergens and common irritants (eg, soaps, wool, temperature extremes) • Consider comorbidities	**BASIC MANAGEMENT** **1. Skin Care** • Moisturizer, liberal and frequent (choice per patient preference) • Warm baths or showers using non-soap cleansers, usually once daily and followed by moisturizer (even on clear areas) **2. Antiseptic Measures** • Dilute bleach bath (or equivalent) ≤2x/week according to severity (especially with recurrent infections) • Antibiotics, if needed **3. Trigger Avoidance** • Proven allergens and common irritants (eg, soaps, wool, temperature extremes) • Consider comorbidities	**BASIC MANAGEMENT + TOPICAL ANTI-INFLAMMATORY MEDICATION** ***Apply on areas of previous or potential symptoms (aka flare)*** **Maintenance TCS** • Low potency 1x-2x daily (including face) • Medium potency 1x-2x weekly (except face) ***OR* Maintenance TCI (pimecrolimus, tacrolimus)** • 1x-2x daily • 2x-3x weekly (not an indicated dosage) **OR Crisaborole 2%[1]** • 2x daily	**BASIC MANAGEMENT +** ***REFERRAL to AD Specialist*** **Phototherapy** **Dupilumab[2]** **Systemic Immunosuppressants** • Cyclosporine A[3] • Methotrexate[3] • Mycophenolate mofetil[3] • Azathioprine[3] • Corticosteroids[4] **Consider acute tx for some patients to help gain control:** • Wet wrap therapy • Short-term hospitalization
Acute Treatment	**Apply TCS to Inflamed Skin** Low to medium potency TCS 2x daily for 3-7 days beyond clearance [Consider TCI, crisaborole]		**Apply TCS to Inflamed Skin** Medium to high potency TCS 2x daily for 3-7 days beyond clearance [Consider TCI, crisaborole] **If not Resolved in 7 Days, Consider** → • Non-adherence • Infection • Misdiagnosis • Contact allergy to medications • Referral	

Figure 2. Step-care management of atopic dermatitis (AD).[17] [1]Indicated for patients at least 2 years old with mild to moderate AD.[74] [2]Indicated for patients at least 18 years old with moderate to severe AD.[80] [3]Not approved by the Food and Drug Administration to treat AD. [4]Approved by the Food and Drug Administration to treat AD but not recommended for long-term maintenance. A short course of systemic corticosteroids can help resolve severe symptoms, but exacerbation at discontinuation is common. Systemic corticosteroids also can be used as cotreatment during the initiation and optimization of phototherapy, other systemic immunosuppressants, or dupilumab. TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Tx, treatment.

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Topical Steroids

- HCT, desonide-face
- Triamcinolone-body

eTable 1
Potency Classification of Topical Corticosteroids Used to Treat Atopic Dermatitis[1,4]

Class	Corticosteroid	Formulations	Approved for pediatric use
I. Very high potency or superpotent	Betamethasone dipropionate 0.05%	Cream, ointment	
	Clobetasol propionate 0.05%	Cream, ointment	
	Diflorasone diacetate 0.05%	Ointment	
	Halobetasol propionate 0.05%	Cream, ointment	
II. High potency	Amcinonide 0.1%	Ointment	
	Betamethasone dipropionate 0.05%	Cream, ointment	
	Desoximetasone 0.25%	Cream, gel, ointment	
	Diflorasone diacetate 0.05%	Ointment	
	Fluocinonide 0.05%	Cream, gel, ointment, solution	
	Halcinonide 0.1%	Cream	
	Mometasone furoate 0.1%	Ointment	≥2 y old
III. Medium to high potency	Amcinonide 0.1%	Cream, lotion	
	Betamethasone dipropionate 0.05%	Cream	
	Betamethasone valerate 0.1%	Ointment	
	Desoximetasone 0.05%	Cream	
	Diflorasone diacetate 0.05%	Cream	
	Fluocinonide 0.05%	Cream	
	Fluticasone propionate 0.005%	Ointment	
	Halcinonide 0.1%	Ointment, solution	
	Triamcinolone acetonide 0.1%	Ointment	
IV. Medium potency	Hydrocortisone valerate 0.2%	Ointment	
	Flurandrenolide 0.05%	Ointment	
	Fluocinolone acetonide 0.025%	Ointment	
	Mometasone furoate 0.1%	Cream	≥2 y old
	Triamcinolone acetonide 0.1%	Cream	
V. Medium to low potency	Betamethasone dipropionate 0.05%	Lotion	
	Betamethasone valerate 0.1%	Cream	
	Fluticasone acetonide 0.025%	Cream	
	Fluticasone propionate 0.05%	Cream	≥3 mo old
	Flurandrenolide 0.05%	Cream	
	Hydrocortisone valerate 0.2%	Cream	
	Prednicarbate 0.1%	Cream	≥1 y old
VI. Low potency	Alclometasone dipropionate 0.05%	Cream, ointment	
	Betamethasone valerate 0.05%	Lotion	
	Desonide 0.05%	Gel, foam	≥3 mo old
	Fluocinolone acetonide 0.01%	Cream, oil, solution	oil, ≥3 mo old
	Triamcinolone acetonide 0.1%	Cream	
VII. Lowest potency	Hydrocortisone hydrochloride 1%	Cream, ointment	≥2 y old
	Hydrocortisone hydrochloride 2.5%	Cream, lotion, ointment	
	Hydrocortisone acetate 1%	Cream, ointment	≥2 y old
	Hydrocortisone acetate 2.5%	Cream, lotion, ointment	
	Pramoxine hydrochloride 1.0%	Cream, lotion, ointment	
	Pramoxine hydrochloride 2.5%	Cream, lotion, ointment	

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Topical Glucocorticoids

- Reduce inflammation and pruritis
- Effective for both acute and chronic inflammation
- Suppressing inflammatory gene expression, reducing inflammation and pruritis
- Side effects ❼atrophic changes, skin thinning with telangiectasias, bruising, hypopigmentation, acne, striae, secondary infections, systemic absorption

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Eczema Treatment Overview

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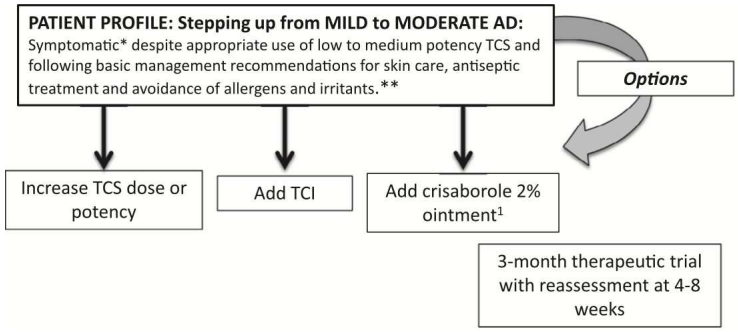

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Topical Steroids

- Escalate to mometasone or clobetasol for the body

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	Halcinonide 0.1%	Ointment, solution	
	Triamcinolone acetonide 0.1%	Ointment	
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Topical Calcineurin Inhibitors

- Can be used on face and intertriginous areas
- TACROLIMUS ointment 0.03%, 0.1%
  - Good safety profile for up to 4 years of use
  - 0.03% approved for intermittent treatment of moderate-severe AD in 2 and older
  - 0.1% approved for intermittent treatment of moderate-severe AD in adults
- PIMECROLIMUS cream 1%
  - Good safety profile for up to 2 years of use
  - Approved for intermittent treatment of mild-moderate AD in 2 and older
- Common side effects:
  - Burning sensation of the skin—typically transient but could be more persistent

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Topical Phosphodiesterase 4 Inhibitor

- Crisaborole ointment 2%
- Thin layer to affected skin twice daily, then reduce to once daily
- Reduces the release of proinflammatory cytokines
- Mild-moderate eczema
- 3 months and older
- Most common side effect application site pain

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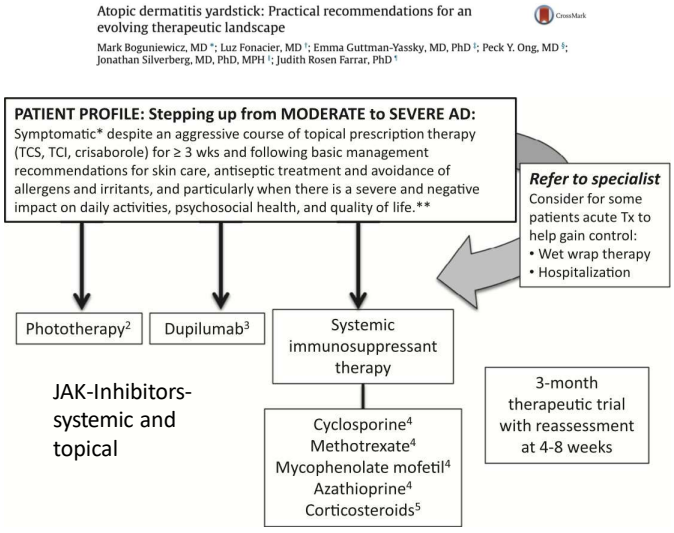
Eczema Treatment Overview



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Topical JAK inhibitors

- Ruxolitinib 1.5% cream
  - 12 and older
  - Mild-moderate AD
  - Affected areas up to 20% BSA
  - Slight advantage over TCS in controlling pruritis
  - Applied twice daily
  - JAK-I carry black box warning of serious infections, mortality, malignancy, major adverse cardiovascular events and thrombosis

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Oral JAK inhibitors

- Two options: Abrocitinib and Upatacitinib
- Adverse reactions: infections, mortality, thrombosis, malignancy, MACE
- Require lab monitoring
- CYP450 interactions
- Update immunizations prior to starting, no live vaccines while taking

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Biologics

- Dupilumab (Dupixent)
  - Approved for 6 mo and older for AD
  - More on next slide
- Tralokinumab (Adbry)
  - Monoclonal Ab vs IL-13
  - Approved for 18 and older for AD
  - Adverse reactions conjunctivitis, injection side reactions
  - No lab monitoring
  - Complete all age-appropriate immunizations before starting; avoid live vaccines during therapy

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Dupilumab

- Monoclonal Ab vs IL-4R alpha
- Approved for 6 mo and older for moderate to severe AD uncontrolled on topical CS/CI or when those meds are not advised
- Adverse reactions conjunctivitis, injection side reactions
- No lab monitoring (max increase in eosinophil count 16-20 weeks after initiating therapy)
- Complete all age-appropriate immunizations before starting; avoid live vaccines during therapy

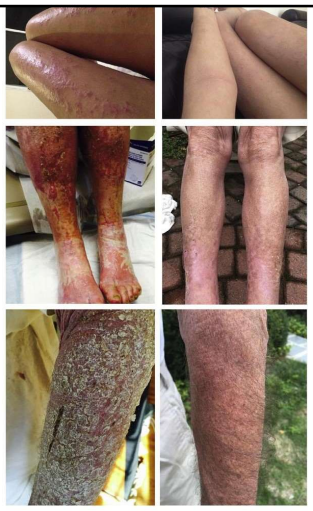

Figure 5. Images of 2 patients with severe atopic dermatitis before and after 16 weeks of treatment with dupilumab in phase 2 and 3 trials. These patients had chronic, recalcitrant disease for many years and treatment with topical and systemic agents, including cyclosporine A and oral prednisone, had failed. These patients continue to be treated with dupilumab. Photos courtesy of Emma Guttman-Yassky, MD, PhD.

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ASTHMA

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Asthma

- History of:
  - recurrent cough
  - Wheezing
  - difficulty breathing
  - chest tightness
  - Symptoms usually worsen at night or with activity
  - triggers include: exposure to allergens and irritants, changes in weather, hard laughter or crying, stress
- Reversible airway obstruction—confirm on spirometry at 5 or older

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Asthma

➡ LONG-TERM ASTHMA MANAGEMENT

GOAL: Asthma Control

Reduce Impairment

- Prevent chronic symptoms.
- Require infrequent use of short-acting beta$_2$-agonist (SABA).
- Maintain (near) normal lung function and normal activity levels.

Reduce Risk

- Prevent exacerbations.
- Minimize need for emergency care, hospitalization.
- Prevent loss of lung function (or, for children, prevent reduced lung growth).
- Minimize adverse effects of therapy.

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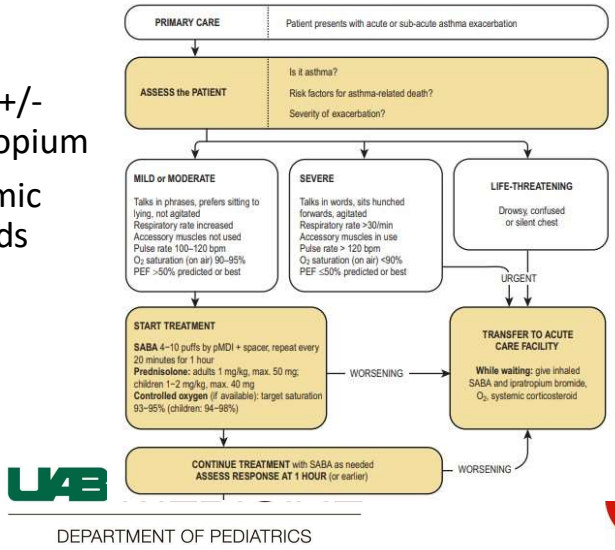
Asthma-treatment of acute exacerbations

- SABA +/- ipratropium
- Systemic steroids



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Severe Acute Asthma Exacerbation in Children: A Stepwise Approach for Escalating Therapy in a Pediatric Intensive Care Unit

I. Federico Fernandez Nievas, MD and Kanwaljeet J. S. Anand, MBBS, DPhil, FRCPCH

Step	Therapy	Comments
1	Albuterol, Ipratropium, Steroids	These medications should be ordered for all patients admitted to the PICU.
2	Continuous Albuterol	0.5-1 mg/kg/hr. If < 20 kg give 10-20 mg/hr; 20-30 kg give 10-30 mg/hr, > 30 kg give 15 -45 mg/hr
3	IV Magnesium	25 to 50 mg/kg/dose (max 2 g) infused over 20 to 30 min. Follow by continuous infusion of 15-25 mg/kg/hr. Mg level ≈ 4 mg/dL. Monitor for hypotension.
4	Heliox	Provide O_2 using non-rebreathing mask. May combine O_2 by nasal cannula if necessary to keep SaO_2 > 92%.
5	IV Terbutaline	Loading dose of 10 mcg/kg over 10 min followed by 0.4 mcg/kg/min. Increase by 0.4 mcg/kg/min every 15 min. Range 0.1 to 10 mcg/kg/min (average dose is 4 mcg/kg/min)
6	IV Theophylline	Loading dose of 5 mg/kg over 20 min followed by continuous infusion of 0.5-1 mg/kg/hr. Check serum theophylline concentration 30 min after the end of the loading dose. Target theophylline concentration is 10-20 mg/L
7	Non-Invasive Ventilation	Consider BiPAP to unload WOB. IPAP:10 EPAP:5
8	IV Ketamine	1 mg/kg/hr for sedation. Bronchodilatory properties. Increase airway secretions.
9	Intubation	Ketamine + Midazolam + Rocuronium
10	Ventilation	Try to avoid neuromuscular blockade. Permissive hypercapnia. PC/PRVC/PSV. Monitor peak to plateau pressure difference.

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Asthma

- TH2 High Asthma
  - Eosinophilic/Allergic Asthma
    - Elevated absolute eosinophil count (AEC)
    - Elevated specific IgE/Allergic sensitization
- TH2 Low Asthma
  - No evidence of eosinophilic or allergic asthma

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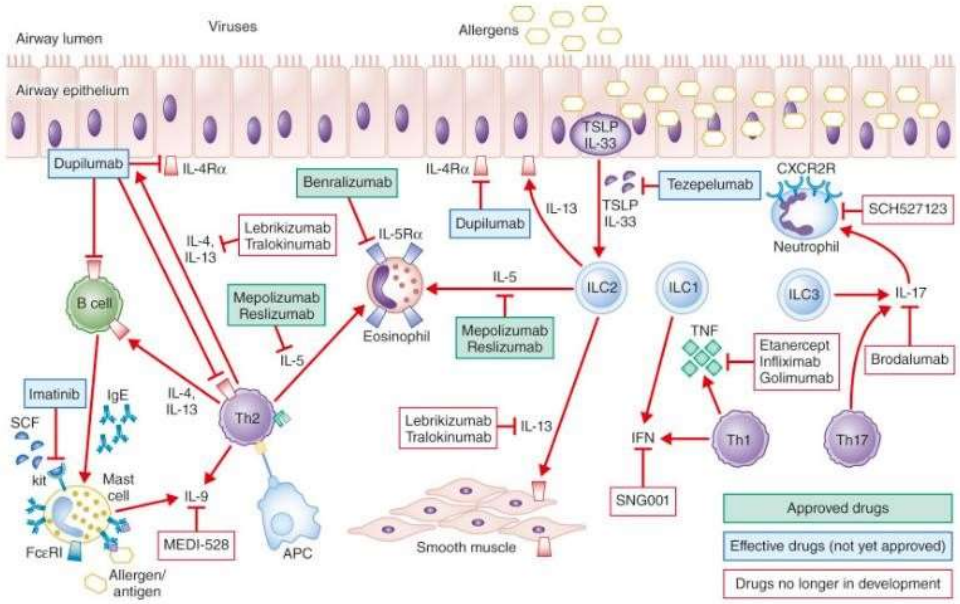

Fig. 91.1

Schematic showing the matrix of type 1, type 2, and type 17 cytokines with cells in the human airway. Highlighted are cytokines that have been therapeutic targets in human asthma.

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➞ LONG-TERM ASTHMA MANAGEMENT

GOAL:
Asthma Control

Reduce Impairment

- Prevent chronic symptoms.
- Require infrequent use of short-acting beta$_2$-agonist (SABA).
- Maintain (near) normal lung function and normal activity levels.

Reduce Risk

- Prevent exacerbations.
- Minimize need for emergency care, hospitalization.
- Prevent loss of lung function (or, for children, prevent reduced lung growth).
- Minimize adverse effects of therapy.

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Asthma Initial Assessment

INITIAL VISIT: CLASSIFYING ASTHMA SEVERITY AND INITIATING THERAPY

(in patients who are not currently taking long-term control medications)

Level of severity (Columns 2–5) is determined by events listed in Column 1 for both impairment (frequency and intensity of symptoms and functional limitations) and risk (of exacerbations). Assess impairment by patient's or caregiver's recall of events during the previous 2–4 weeks; assess risk over the last year. Recommendations for initiating therap based on level of severity are presented in the last row.

Components of Severity		Intermittent			Persistent								
					Mild			Moderate			Severe		
		Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years
Impairment	Symptoms	≤2 days/week			>2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤2x/month		1–2x/month	3–4x/month		3–4x/month	>1x/week but not nightly		>1x/week	Often 7x/week	
	SABA* use for symptom control (not to prevent EIB*)	≤2 days/week			>2 days/week but not daily	>2 days/week but not daily and not more than once on any day		Daily			Several times per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
	Lung function												
	→ FEV_1* (% predicted)	Not applicable	Normal FEV_1 between exacerbations >80%	Normal FEV_1 between exacerbations >80%	Not applicable	>80%	>80%	Not applicable	60–80%	60–80%	Not applicable	<60%	<60%
	→ FEV_1/FVC*		>85%	Normal†		>80%	Normal†		75–80%	Reduced 5%†		<75%	Reduced >5%†
Risk	Asthma exacerbations requiring oral systemic corticosteroids‡	0–1/year			≥2 exacerb. in 6 months, or wheezing ≥4x per year lasting >1 day AND risk factors for persistent asthma	≥2/year		Generally, more frequent and intense events indicate greater severity.			Generally, more frequent and intense events indicate greater severity.		
		*Consider severity and interval since last asthma exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.**											
Recommended Step for Initiating Therapy *(See "Stepwise Approach for Managing Asthma Long Term," page 7)*		Step 1			Step 2			Step 3	Step 3 medium-dose ICS* option	Step 3	Step 3	Step 3 medium-dose ICS* option or Step 4	Step 4 or 5
								Consider short course of oral systemic corticosteroids.					
The stepwise approach is meant to help, not replace, the clinical decisionmaking needed to meet individual patient needs.		*In 2–6 weeks, depending on severity, assess level of asthma control achieved and adjust therapy as needed. For children 0–4 years old, if no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternate diagnoses.*											

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Assessing Asthma Control

FOLLOW-UP VISITS: ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY

Level of control (Columns 2–4) is based on the most severe component of impairment (symptoms and functional limitations) or risk (exacerbations). Assess impairment by patient's or caregiver's recall of events listed in Column 1 during the previous 2–4 weeks and by spirometry and/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit. Assess risk by recall of exacerbations during the previous year and since the last visit. Recommendations for adjusting therapy based on level of control are presented in the last row.

Components of Control		Well Controlled			Not Well Controlled			Very Poorly Controlled		
		Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years
Impairment	Symptoms	≤2 days/week	≤2 days/week but not more than once on each day	≤2 days/week	>2 days/week	>2 days/week or multiple times on ≤2 days/week	>2 days/week	Throughout the day		
	Nighttime awakenings	≤1x/month		≤2x/month	>1x/month	≥2x/month	1–3x/week	>1x/week	≥2x/week	≥4x/week
	Interference with normal activity	None			Some limitation			Extremely limited		
	SABA* use for symptom control (not to prevent EIB*)	≤2 days/week			>2 days/week			Several times per day		
	Lung function → FEV,* (% *predicted*) or peak flow (% *personal best*)	Not applicable	>80%	>80%	Not applicable	60–80%	60–80%	Not applicable	<60%	<60%
	→ FEV,/FVC*		>80%	Not applicable		75–80%	Not applicable		<75%	Not applicable
	Validated questionnaires† → ATAQ* → ACQ* → ACT*	Not applicable	Not applicable	0 ≤0.75‡ ≥20	Not applicable	Not applicable	1–2 ≥1.5 16–19	Not applicable	Not applicable	3–4 Not applicable ≤15
Risk	Asthma exacerbations requiring oral systemic corticosteroids§	0–1/year			2–3/year	≥2/year		>3/year	≥2/year	
		Consider severity and interval since last asthma exacerbation.								
	Reduction in lung growth/Progressive loss of lung function	Not applicable	Evaluation requires long-term follow-up care.		Not applicable	Evaluation requires long-term follow-up care.		Not applicable	Evaluation requires long-term follow-up care.	
	Treatment-related adverse effects	*Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.*								
Recommended Action for Treatment *(See "Stepwise Approach for Managing Asthma Long Term," page 7)* *The stepwise approach is meant to help, not replace, the clinical decisionmaking needed to meet individual patient needs.*		*Maintain current step.* *Regular follow-up every 1–6 months.* *Consider step down if well controlled for at least 3 months.*			Step up 1 step	Step up at least 1 step	Step up 1 step	*Consider short course of oral systemic corticosteroids.* *Step up 1–2 steps.* *Reevaluate in 2 weeks to achieve control.*		
					Reevaluate in 2–6 weeks to achieve control. *For children 0–4 years, if no clear benefit observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.*					
					Before step up in treatment: *Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue and use preferred treatment for that step. For side effects, consider alternative treatment options.*					

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Asthma Management Overview

STEPWISE APPROACH FOR MANAGING ASTHMA LONG TERM

The stepwise approach tailors the selection of medication to the level of asthma severity (see page 5) or asthma control (see page 6).
The stepwise approach is meant to help, not replace, the clinical decisionmaking needed to meet individual patient needs.

ASSESS CONTROL:

STEP UP IF NEEDED (first, check medication adherence, inhaler technique, environmental control, and comorbidities)

STEP DOWN IF POSSIBLE (and asthma is well controlled for at least 3 months)

		STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
		At each step: Patient education, environmental control, and management of comorbidities					
0–4 years of age		**Intermittent Asthma**	**Persistent Asthma: Daily Medication** Consult with asthma specialist if step 3 care or higher is required. Consider consultation at step 2.				
	Preferred Treatment†	SABA* as needed	low-dose ICS*	medium-dose ICS*	medium-dose ICS* + either LABA* or montelukast	high-dose ICS* + either LABA* or montelukast	high-dose ICS* + either LABA* or montelukast + oral corticosteroids
	Alternative Treatment†‡		cromolyn or montelukast				
		If clear benefit is not observed in 4–6 weeks, and medication technique and adherence are satisfactory, consider adjusting therapy or alternate diagnoses.					
	Quick-Relief Medication	▪ SABA* as needed for symptoms; intensity of treatment depends on severity of symptoms. ▪ With viral respiratory symptoms: SABA every 4–6 hours up to 24 hours (longer with physician consult). Consider short course of oral systemic corticosteroids if asthma exacerbation is severe or patient has history of severe exacerbations. ▪ Caution: Frequent use of SABA may indicate the need to step up treatment.					

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Asthma Management Overview

		Intermittent Asthma	Persistent Asthma: Daily Medication Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.				
5–11 years of age	Preferred Treatment†	SABA* as needed	low-dose ICS*	low-dose ICS* + either LABA,* LTRA,* or theophylline(b) **OR** medium-dose ICS	medium-dose ICS* + LABA*	high-dose ICS* + LABA*	high-dose ICS* + LABA* + oral corticosteroids
	Alternative Treatment†,‡		cromolyn, LTRA,* or theophylline§		medium-dose ICS* + either LTRA* or theophylline§	high-dose ICS* + either LTRA* or theophylline§	high-dose ICS* + either LTRA* or theophylline§ + oral corticosteroids
			Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.**				
	Quick-Relief Medication	▪ SABA* as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments every 20 minutes as needed. Short course of oral systemic corticosteroids may be needed. ▪ Caution: Increasing use of SABA or use >2 days/week for symptom relief (not to prevent EIB*) generally indicates inadequate control and the need to step up treatment.					

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Asthma Management Overview

		Intermittent Asthma	Persistent Asthma: Daily Medication Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.				
≥12 years of age	Preferred Treatment†	SABA* as needed	low-dose ICS*	low-dose ICS* + LABA* **OR** medium-dose ICS*	medium-dose ICS* + LABA*	high-dose ICS* + LABA* **AND** consider omalizumab for patients who have allergies††	high-dose ICS* + LABA* + oral corticosteroid§§ **AND** consider omalizumab for patients who have allergies††
	Alternative Treatment†,‡		cromolyn, LTRA,* or theophylline§	low-dose ICS* + either LTRA,* theophylline,§ or zileuton‡‡	medium-dose ICS* + either LTRA,* theophylline,§ or zileuton‡‡		
			Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.**				
	Quick-Relief Medication	▪ SABA* as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments every 20 minutes as needed. Short course of oral systemic corticosteroids may be needed. ▪ Caution: Use of SABA >2 days/week for symptom relief (not to prevent EIB*) generally indicates inadequate control and the need to step up treatment.					

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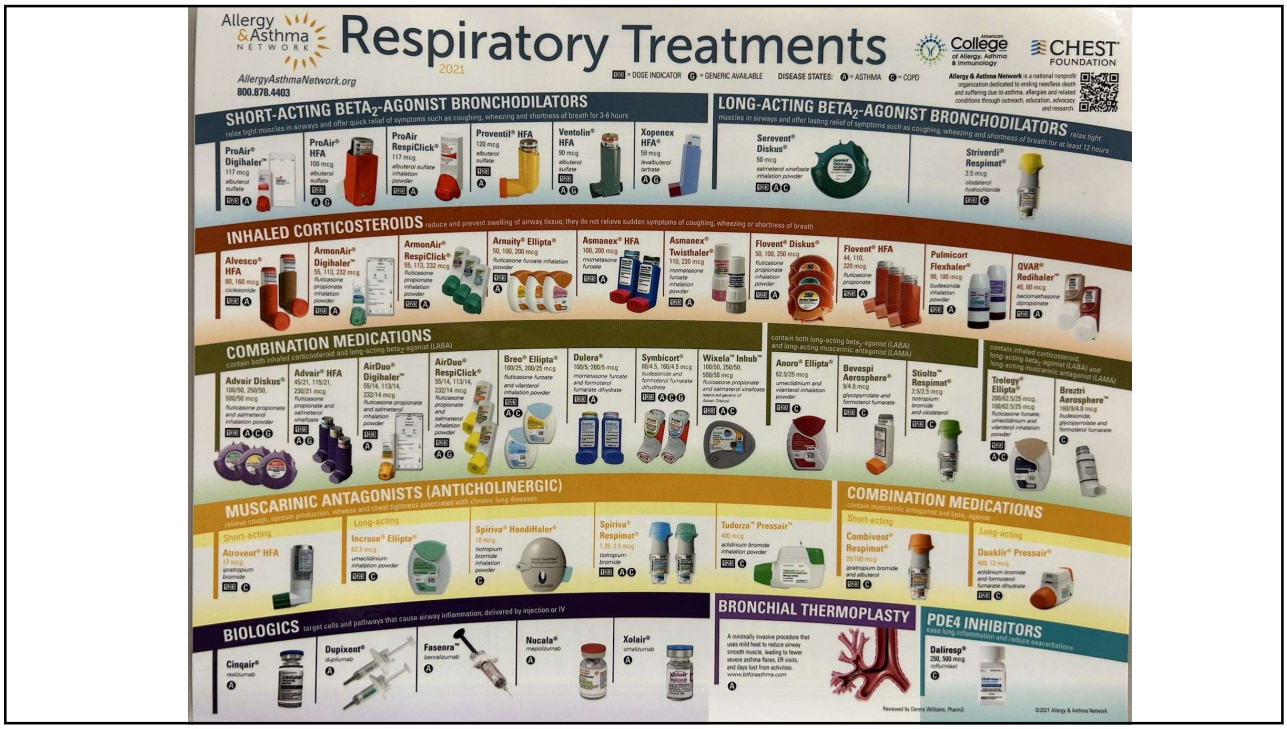
Allergy & Asthma Network
Respiratory Treatments
2021
AllergyAsthmaNetwork.org
800.878.4403
College of Allergy, Asthma & Immunology
CHEST FOUNDATION
DOSE INDICATOR
GENERIC AVAILABLE
DISEASE STATES: ASTHMA COPD
SHORT-ACTING BETA2-AGONIST BRONCHODILATORS
relax tight muscles in airways and offer quick relief of symptoms such as coughing, wheezing and shortness of breath for 3-6 hours
ProAir® Digihaler™
ProAir® HFA
ProAir RespiClick®
Proventil® HFA
Ventolin® HFA
Xopenex HFA®
LONG-ACTING BETA2-AGONIST BRONCHODILATORS
muscles in airways and offer lasting relief of symptoms such as coughing, wheezing and shortness of breath for at least 12 hours
Serevent® Diskus®
Striverdi® Respimat®
INHALED CORTICOSTEROIDS
reduce and prevent swelling of airway tissue; they do not relieve sudden symptoms of coughing, wheezing or shortness of breath
Alvesco® HFA
ArmonAir® Digihaler™
ArmonAir® RespiClick®
Arnuity® Ellipta®
Asmanex® HFA
Asmanex® Twisthaler®
Flovent® Diskus®
Flovent® HFA
Pulmicort Flexhaler®
QVAR® Redihaler™
COMBINATION MEDICATIONS
contain both inhaled corticosteroid and long-acting beta2-agonist (LABA)
Advair Diskus®
Advair® HFA
AirDuo® Digihaler™
AirDuo® RespiClick®
Breo® Ellipta®
Dulera®
Symbicort®
Wixela™ Inhub™
contain both long-acting beta2-agonist (LABA) and long-acting muscarinic antagonist (LAMA)
Anoro® Ellipta®
Bevespi Aerosphere®
Stiolto™ Respimat®
contain inhaled corticosteroid, long-acting beta2-agonist (LABA) and long-acting muscarinic antagonist (LAMA)
Trelegy® Ellipta®
Breztri Aerosphere™
MUSCARINIC ANTAGONISTS (ANTICHOLINERGIC)
relieve cough, sputum production, wheeze and chest tightness associated with chronic lung diseases
Short-acting
Atrovent® HFA
Long-acting
Incruse® Ellipta®
Spiriva® HandiHaler®
Spiriva® Respimat®
Tudorza™ Pressair™
COMBINATION MEDICATIONS
contain muscarinic antagonist and beta2-agonist
Short-acting
Combivent® Respimat®
Long-acting
Duaklir® Pressair®
BIOLOGICS
target cells and pathways that cause airway inflammation; delivered by injection or IV
Cinqair®
Dupixent®
Fasenra™
Nucala®
Xolair®
BRONCHIAL THERMOPLASTY
A minimally invasive procedure that uses mild heat to reduce airway smooth muscle, leading to fewer severe asthma flares, ER visits, and days lost from activities.
www.btrasthma.com
PDE4 INHIBITORS
ease lung inflammation and reduce exacerbations
Daliresp®
Reviewed by Dennis Williams, PharmD
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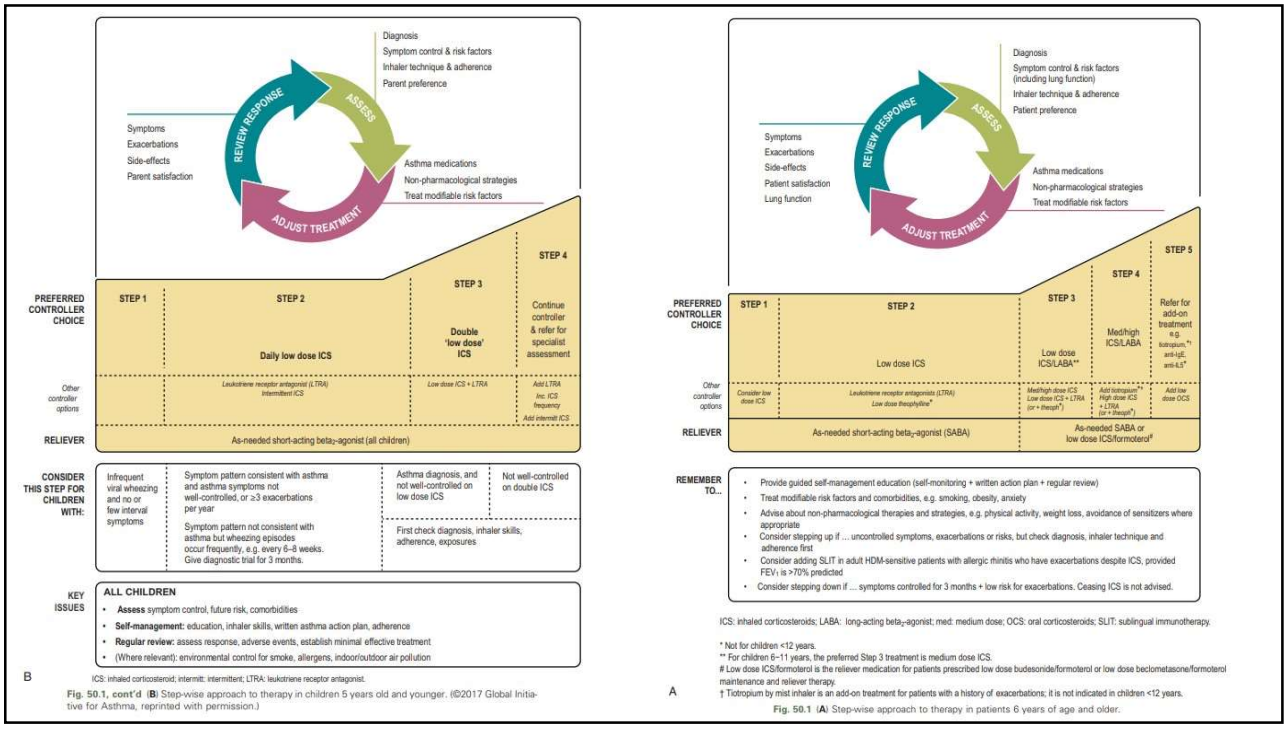
Diagnosis
Symptom control & risk factors
Inhaler technique & adherence
Parent preference
Symptoms
Exacerbations
Side-effects
Parent satisfaction
REVIEW RESPONSE
ASSESS
ADJUST TREATMENT
Asthma medications
Non-pharmacological strategies
Treat modifiable risk factors
PREFERRED CONTROLLER CHOICE
STEP 1
STEP 2
Daily low dose ICS
STEP 3
Double 'low dose' ICS
STEP 4
Continue controller & refer for specialist assessment
Other controller options
Leukotriene receptor antagonist (LTRA) intermittent ICS
Low dose ICS + LTRA
Add LTRA
Inc. ICS frequency
Add intermit ICS
RELIEVER
As-needed short-acting beta2-agonist (all children)
CONSIDER THIS STEP FOR CHILDREN WITH:
Infrequent viral wheezing and no or few interval symptoms
Symptom pattern consistent with asthma and asthma symptoms not well-controlled, or ≥3 exacerbations per year
Symptom pattern not consistent with asthma but wheezing episodes occur frequently, e.g. every 6–8 weeks. Give diagnostic trial for 3 months.
Asthma diagnosis, and not well-controlled on low dose ICS
Not well-controlled on double ICS
First check diagnosis, inhaler skills, adherence, exposures
KEY ISSUES
ALL CHILDREN
Assess symptom control, future risk, comorbidities
Self-management: education, inhaler skills, written asthma action plan, adherence
Regular review: assess response, adverse events, establish minimal effective treatment
(Where relevant): environmental control for smoke, allergens, indoor/outdoor air pollution
B
ICS: inhaled corticosteroid; intermit: intermittent; LTRA: leukotriene receptor antagonist.
Fig. 50.1, cont'd (B) Step-wise approach to therapy in children 5 years old and younger. (©2017 Global Initiative for Asthma, reprinted with permission.)
Diagnosis
Symptom control & risk factors (including lung function)
Inhaler technique & adherence
Patient preference
Symptoms
Exacerbations
Side-effects
Patient satisfaction
Lung function
REVIEW RESPONSE
ASSESS
ADJUST TREATMENT
Asthma medications
Non-pharmacological strategies
Treat modifiable risk factors
PREFERRED CONTROLLER CHOICE
STEP 1
STEP 2
Low dose ICS
STEP 3
Low dose ICS/LABA**
STEP 4
Med/high ICS/LABA
STEP 5
Refer for add-on treatment e.g. tiotropium, *† anti-IgE, anti-IL5*
Other controller options
Consider low dose ICS
Leukotriene receptor antagonists (LTRA) Low dose theophylline*
Med/high dose ICS Low dose ICS + LTRA (or + theoph†)
Add tiotropium*† High dose ICS + LTRA (or + theoph*†)
Add low dose OCS
RELIEVER
As-needed short-acting beta2-agonist (SABA)
As-needed SABA or low dose ICS/formoterol#
REMEMBER TO...
Provide guided self-management education (self-monitoring + written action plan + regular review)
Treat modifiable risk factors and comorbidities, e.g. smoking, obesity, anxiety
Advise about non-pharmacological therapies and strategies, e.g. physical activity, weight loss, avoidance of sensitizers where appropriate
Consider stepping up if ... uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS, provided FEV1 is >70% predicted
Consider stepping down if ... symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.
ICS: inhaled corticosteroids; LABA: long-acting beta2-agonist; med: medium dose; OCS: oral corticosteroids; SLIT: sublingual immunotherapy.
* Not for children <12 years.
** For children 6–11 years, the preferred Step 3 treatment is medium dose ICS.
# Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy.
† Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years.
A
Fig. 50.1 (A) Step-wise approach to therapy in patients 6 years of age and older.

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Inhaled Short Acting Beta 2 Agonist (SABA)

- B2 agonist➐GPCR➐smooth muscle relaxation
- Examples: albuterol, salbutamol, and terbultaline
- Rapidly reverse bronchoconstriction
- Rapid onset within 5-10 mins
- Duration of action 3-4 hours
- Drugs lose potency and efficacy over time

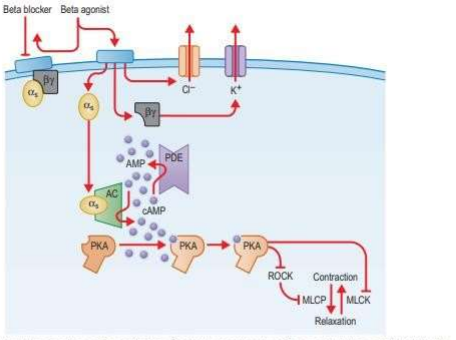

Fig. 93.1 Intracellular signaling after activation of the β_2-receptor by a β_2-agonist. When activated by β_2-agonists, the receptor's G protein trimer, called Gs, disassociates into a Gα subunit and a $\beta\gamma$ dimer. Gα binds to and activates adenylyl cyclase, causing increased cyclic adenosine monophosphate (*cAMP*), which in turn activates protein kinase A (*PKA*). PKA phosphorylates myosin light-chain kinase (*MLCP*), which is ineffective in sustaining active tone in airway smooth muscle, and therefore, the tissue relaxes. Rho kinases (ROCK), which are needed for contraction, are also targeted. The β_2-receptor also activates some transduction pathways, such as the sodium–hydrogen exchanger regulatory protein, without involving Gs protein, and also couples directly to potassium channels linked to relaxation of airway smooth muscle.

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Inhaled Long Acting Beta 2 Agonist (LABA)

- Not used a monotherapy in the US—3 fold risk of mortality of salmeterol monotherapy in the UK
- Fast onset in within 5-10 mins (formoterol) vs. slower onset (salmeterol and others)
- LABAs duration of action 12-14 hours
  - Examples: formoterol and salmeterol
- Ultra-LABAs duration of action ≥24 hours
  - Examples: indacaterol and olodaterol➐only approved for COPD

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Effects of glucocorticoids on inflammation in asthma. Glucocorticoids have effects on many inflammatory aspects of infiltrating and resident inflammatory cells to suppress inflammation. The activity (T lymphocytes and macrophages) and/or number of infiltrating cells (eosinophils, T-lymphocytes, macrophages, basophils, mast cells, and dendritic cells) are decreased by glucocorticoids. Glucocorticoids also have a suppressive effect on resident tissue cells and can reduce mediator release and adhesion molecule expression on epithelial and endothelial cells, microvascular leak from blood vessels, angiogenesis, and both the numbers of mucus glands and release of mucus from these glands.

Effects of Corticosteroids on the Airway

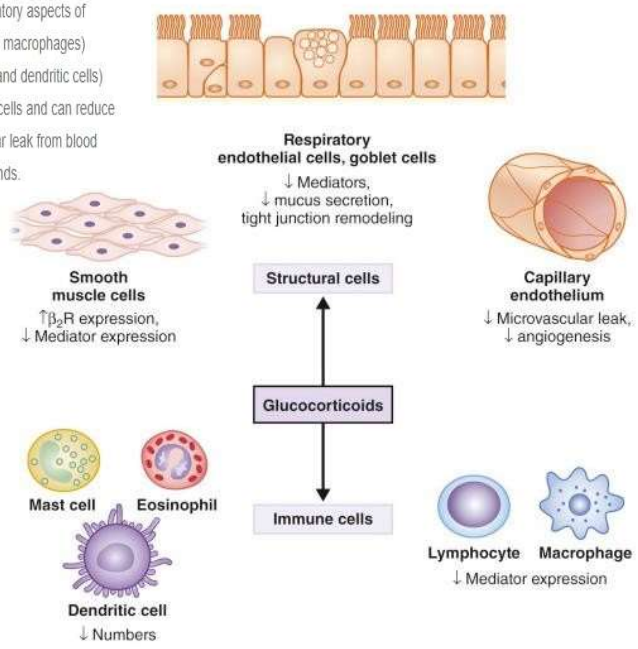

Fig. 96.3

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Systemic glucocorticoids

- Lots of side effects associated with u s e ❼
  - skin and muscle atrophy
  - delayed wound healing
  - osteoporosis and bone necrosis
  - glaucoma and cataracts
  - behavioral changes
  - HTN
  - peptic ulceration, GI bleeding
  - increased risk of infection (decrease lymphocyte counts)
  - obesity and redistribution of body fat
  - type 2 diabetes
  - striae

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Inhaled Corticosteroids (ICS)

- Beneficial clinical effects start 4-6 hours and last 18-36 hours
- ICS ➖ a/w glaucoma, cataracts, tissue atrophy and reduced wound healing, increase risk of infection, adrenal suppression and osteoporosis at high doses… perhaps some growth retardation in children that is made of up during adolescence

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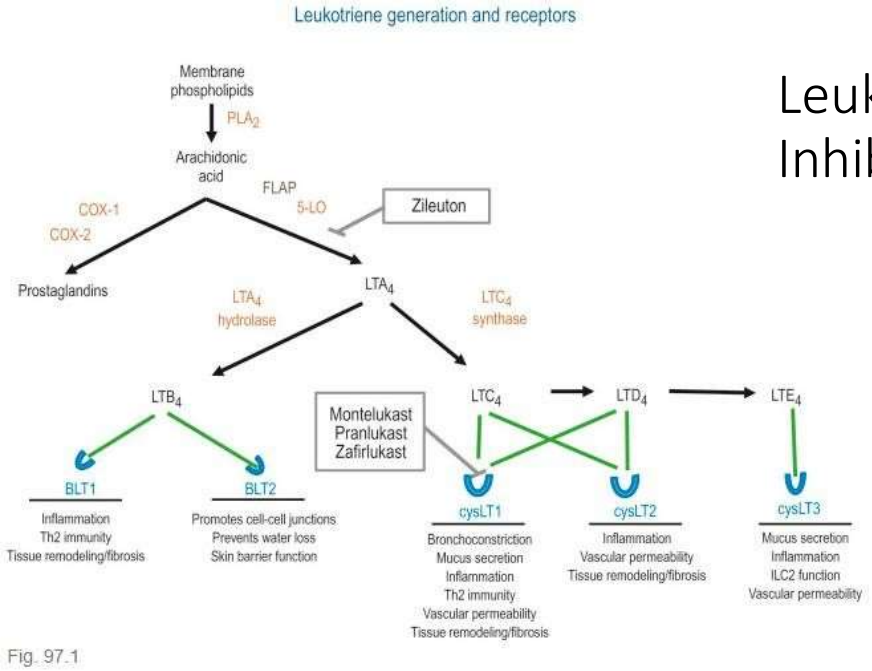

Leukotriene Inhibitors

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Leukotriene Inhibitors

- Inhibitors of 5-lipoxygenase pathway
  - Zileuton
    - ≥12 yo; can cause hepatotoxicity (avoid in patients with liver disease)
- Leukotriene receptor antagonists
  - Montelukast
    - ≥6 mo; NEUROPSYCH effects, eosinophilia and vasculitis, some elevations in ALT/AST (rare <2!%)
  - Zafirlukast
    - ≥5 yo; can cause hepatotoxicity, eosinophilia and vasculitis, increased infections, neuropsych events, interact with warfarin

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ICS/LABA

- Significant reduction in severe asthma exacerbations (with ICS/LABA compared to ICS alone in pts with mod-severe asthma)
- No increase in risk of asthma deaths, intubations or hospitalizations
- Can use as controller and rescue (if using one containing a fast-acting LABA)

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Anti-cholinergic Inhalers

- Anticholinergic agents = Competitive inhibitors of muscarinic receptors
  - Cholinergic nervous system hyper-reactivity in the lung promote bronchospasm, mucous hypersecretion, inflammatio
- Short acting ❼pratropium
  - Acute exacerbations ❼w/ B2 agonists can improve lung function and decrease rates of hospitalization
- Long acting ❼Tiotropium (≥6yo add on tx), Aclindinium, Glycopyrrolate, Umeclididum
  - Add on therapy for moderate-severe persistent asthma uncontrolled on ICS-LABA—increases FEV1
  - Helpful in patients with higher cholinergic tone

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Xanthines

- Theophylline, bamifylline and doxophylline (similar structure to caffeine)
- Approved for ≥6 months of age
- Bronchodilator, decreased eosinophil recruitment and activation in the airways, improves nighttime symptoms
- Peds studies—effect comparison to low dose ICS
- Narrow therapeutic window—monitoring levels is necessary
  - If over therapeutic threshold ➡ Nausea, vomiting, diarrhea ➡ insomnia, irritability, headache ➡ cardiac arrythmia, hypotension, hypokalemia, hyperglycemia ➡ seizures, brain damage, death
- Metabolized in the liver via cytochrome P450

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Biologics-Overview

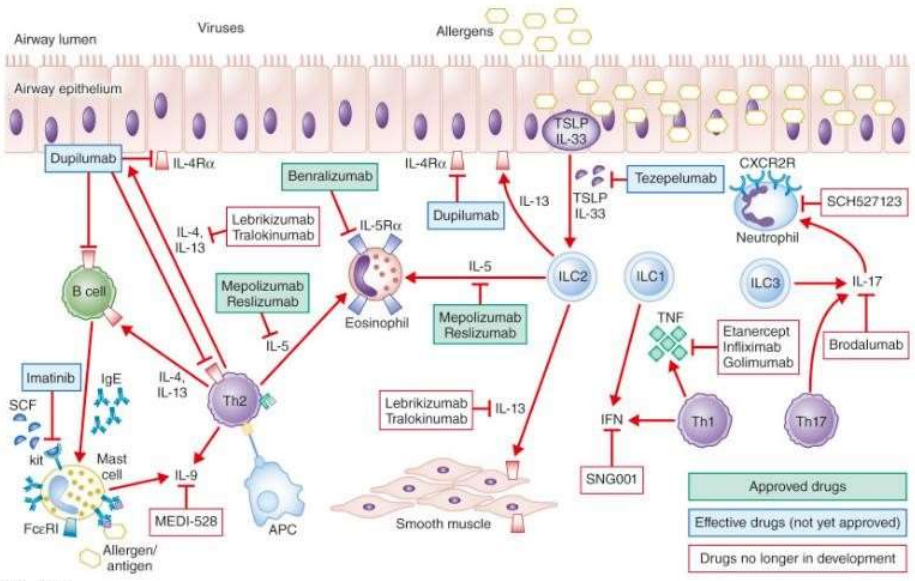

Fig. 91.1
Schematic showing the matrix of type 1, type 2, and type 17 cytokines with cells in the human airway. Highlighted are cytokines that have been therapeutic targets in human asthma.

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Remember-IgE mediated hypersensitivity

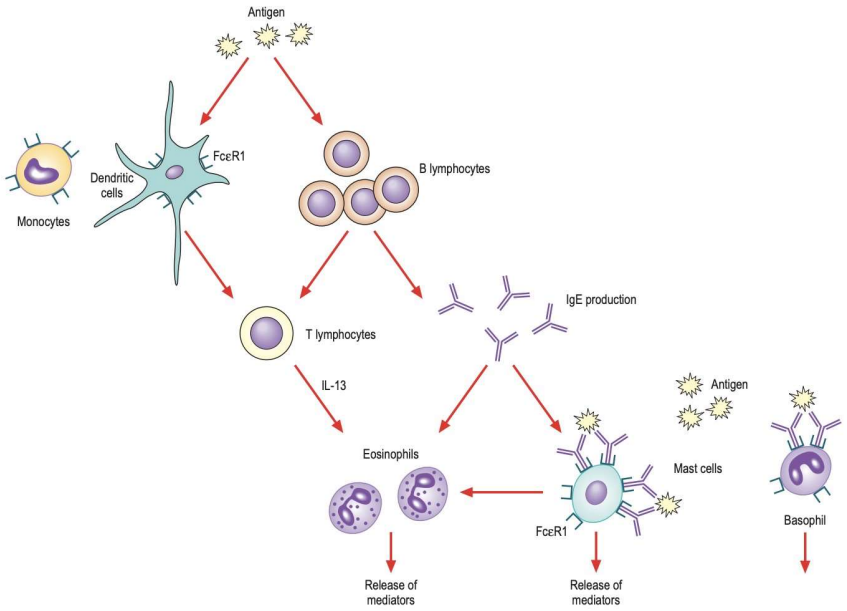

Fig. 90.1 Type 1 hypersensitivity reaction. *FcεRI*, High-affinity IgE receptor; *IgE*, immunoglobulin E; *IL*, interleukin.

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Omalizumab-for Asthma

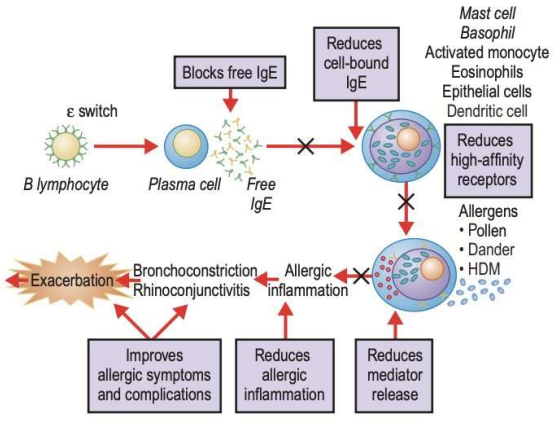

Fig. 90.4 Omalizumab's mechanisms of action. *HDM*, House-dust mite; *IgE*, immunoglobulin E.

- Approved for ≥6 yo
- w/ allergic sensitization (skin or serum testing) to perennial aeroallergen
- Uncontrolled on ICS
- Dosing every 2-4 weeks, based on weight and total IgE levels
- Benefits: decreased exacerbations, ICS doses, asthma symptoms, rescue medication use, QOL, ER visits, hospitalizations, improved pulmonary function
- Risk: anaphylaxis

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Biologics-Overview

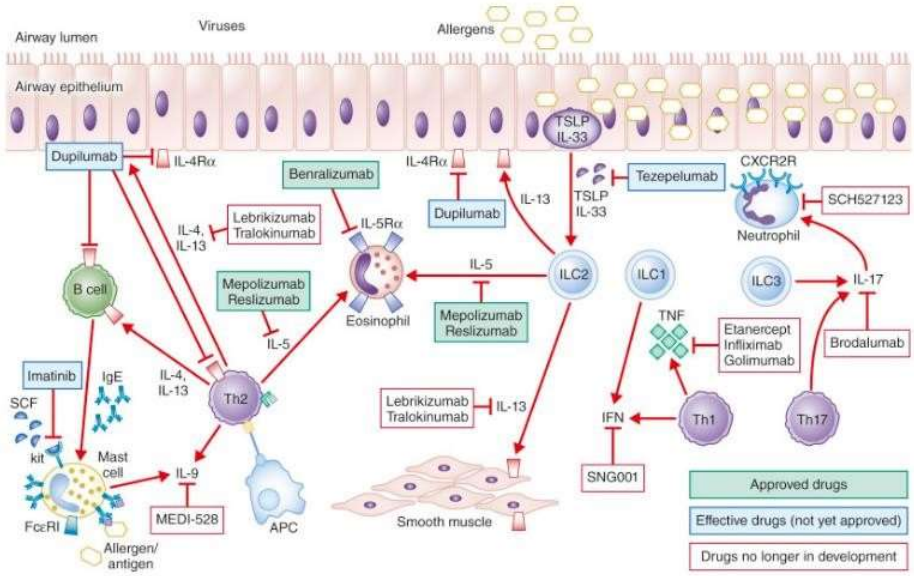

Fig. 91.1

Schematic showing the matrix of type 1, type 2, and type 17 cytokines with cells in the human airway. Highlighted are cytokines that have been therapeutic targets in human asthma.

DEPAI

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Dupilumab

- Anti IL-4Rα (inhibiting IL-4 and IL-13 signaling)
- ≥6 yo
- Moderate-severe persistent asthma w/ and eosinophilic phenotype or OCS dependent asthma
- Age and weight-based dosing
- Decreased asthma exacerbations, FENO, B-agonist use
- Increase in FEV1
- Side effects:
  - Conjunctivitis with keratosis (4%)
  - Eosinophilia (expect the AEC to peak 16-20 weeks after initiation of therapy)
  - Arthralgias
  - Parasitic/helminthic infections

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Biologics-Overview

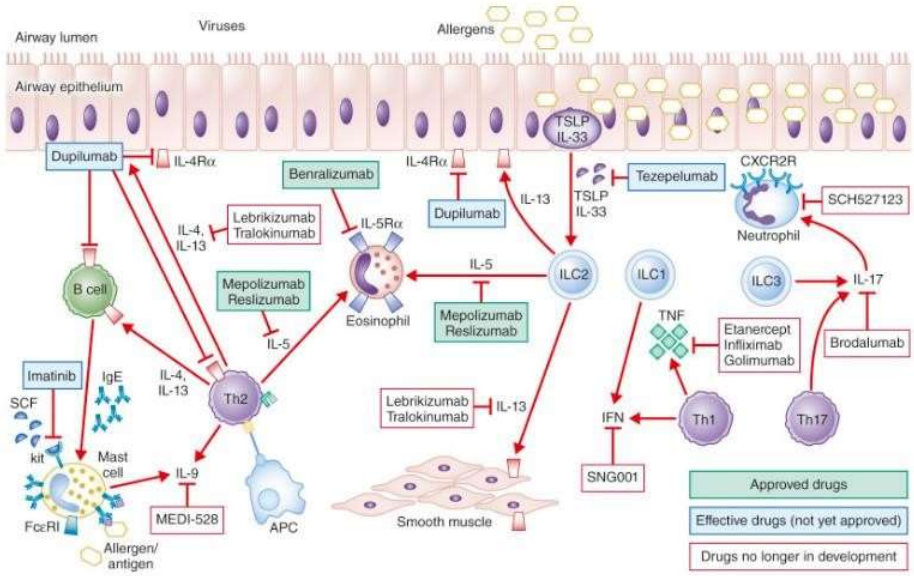

Fig. 91.1

Schematic showing the matrix of type 1, type 2, and type 17 cytokines with cells in the human airway. Highlighted are cytokines that have been therapeutic targets in human asthma.

DEPAI

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Mepolizumab

- Anti-IL5
- ≥12 yo
- 40 or 100 mg SC every 4 weeks (based on weight)
- Severe asthma with eosinophilic phenotype
- Decreased asthma exacerbations, eosinophils in sputum + blood, systemic steroid use
- Increased control and quality of life, improved lung function

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Biologics-Overview

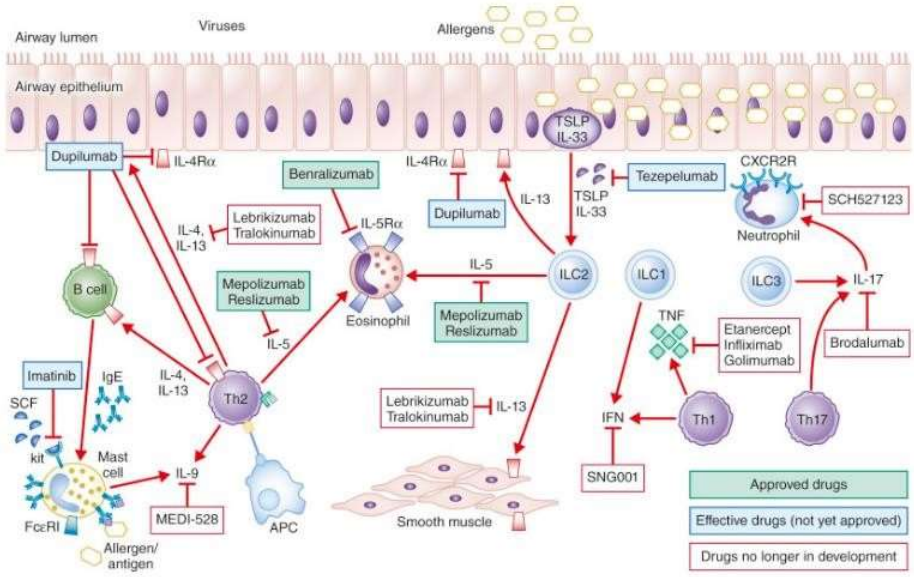

Fig. 91.1

Schematic showing the matrix of type 1, type 2, and type 17 cytokines with cells in the human airway. Highlighted are cytokines that have been therapeutic targets in human asthma.

DEPAI

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Benralizumab

- Anti-IL5Rα
- ≥12 yo
- 30 mg SC every 4 weeks x3 doses then every 8 weeks
- Severe asthma with an eosinophilic phenotype
- Decreased asthma exacerbations
- Precautions in parasitic/helminthic infections

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Biologics-Overview

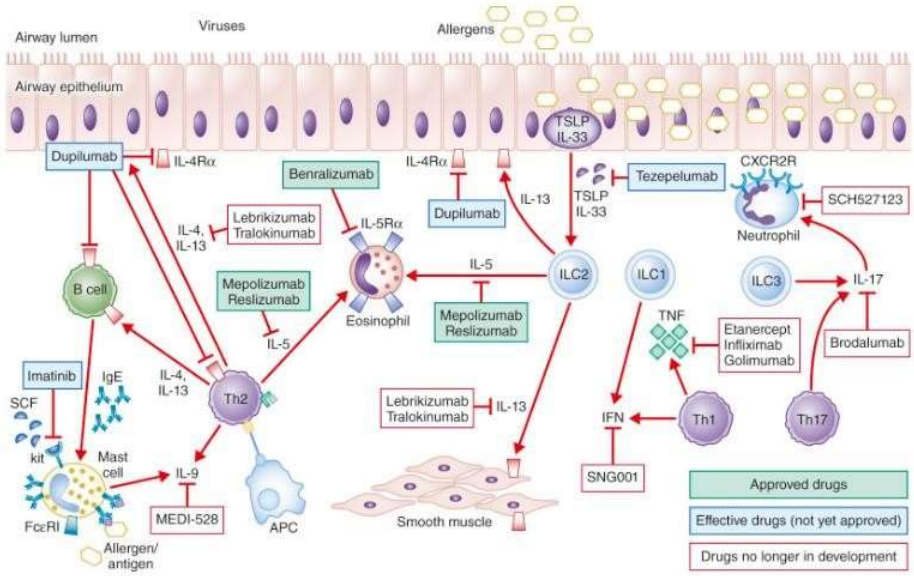

Fig. 91.1

Schematic showing the matrix of type 1, type 2, and type 17 cytokines with cells in the human airway. Highlighted are cytokines that have been therapeutic targets in human asthma.

DEPAI

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Tezspire

- Anti-TSLP
- ≥12 yo
- 210 mg SC every 4 weeks
- Severe asthma
- Precaution in parasitic/helminthic infections, avoid live attenuated vaccines

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RHINITIS

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Rhinitis

Non-allergic rhinitis

- No evidence of allergies on testing
- Multiple types: exercise induced, cold air induced, gustatory, atrophic, medication-induced, hormonal, aging, systemic diseases
- Symptoms: congestion, rhinorrhea, sneezing

Allergic rhinitis

- Caused by hypersensitivity to aeroallergens (dust mite, cat, dog, cockroach, mold, pollen)***
- 50% of rhinitis
- Symptoms: congestion, discharge (typically clear and watery), sneezing, and mucosal pruritis

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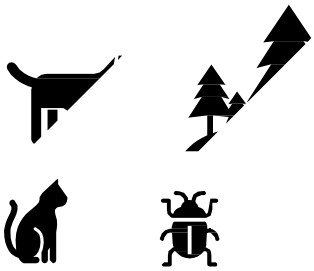
Allergic rhinitis



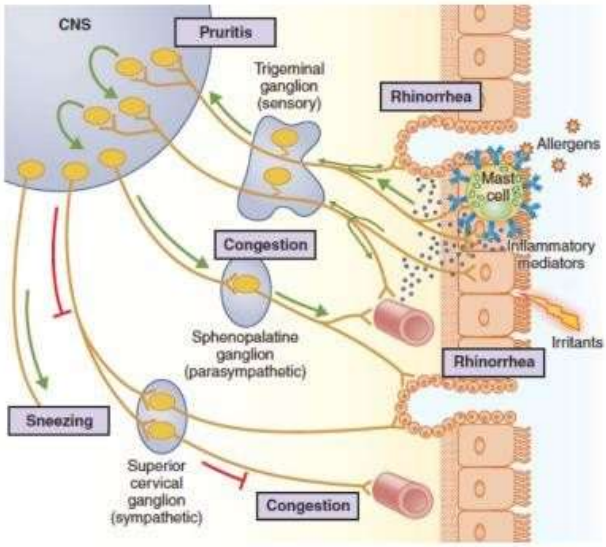


Fig. 40.2
Pathogenesis of allergic rhinitis.

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Allergic Rhinitis Treatment

- Allergen avoidance measures (for those aeroallergens that are pertinent for that patient)
- ***Intranasal corticosteroids—most effective medication***
- Oral antihistamines and intranasal antihistamines
- Leukotriene inhibitors
- Cromolyn sodium
- Anticholinergic nasal sprays
- Sublingual immunotherapy

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Intranasal steroids

- Most potent, best medications to treat AR (and non-allergic rhinitis)
  - Decrease in early and late inflammatory mediators
  - Also treats conjunctivitis symptoms as well
- Side effects:
  - Nasal irritation (10%); epistaxis (4-8%)
  - Perhaps can lead to decreased growth short-term—but long term effects on growth unclear
- Examples: fluticasone, mometasone, budesonide, ciclesonide, beclomethasone, flunisolide, triamcinolone,

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Oral and Intranasal antihistamines

- Antagonizing the histamine receptor
- H1 ❼reduce histamine mediated symptoms (itching, sneezing, rhinorrhea and conjunctivitis) but not good at relieving congestion
- Oral antihistamines
  - Side effects:
    - 1st generation ❼sedation
      - Examples: diphenhydramine
    - 2nd generation ❼much less sedating
      - Examples: loratadine, cetirizine, desloratadine, fexofenadine, levocetirizine

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Oral and Intranasal antihistamines

- Intranasal antihistamines
  - Azelastine, olopatadine
    - Similar effects but likely superior to the systemic antihistamines
    - Sginificantly reduces itching, sneezing, rhinorrhea + nasal congestion
    - BITTER

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Leukotriene inhibitors

- Leukotrienes are generated in AR
  - Inhibitors of 5-lipoxygenase pathway
    - Zileuton
      - ≥12 yo; can cause hepatotoxicity (avoid in patients with liver disease)
  - Leukotriene receptor antagonists
    - Montelukast
      - ≥6 mo; NEUROPSYCH effects, eosinophilia and vasculitis, some elevations in ALT/AST (rare <2!%)
    - Zafirlukast
      - ≥5 yo; can cause hepatotoxicity, eosinophilia and vasculitis, increased infections, neuropsych events, interact with warfarin
- Better than placebo at treating congestion, rhinorrhea and sneezing but not better than INS, anti-histamines
- Not recommended as monotherapy for AR (maybe real benefit is in in patients with AR + asthma)

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Cromolyn sodium

- Unclear mode of action
- Most effective when started before onset of symptoms
- Intranasal cromolyn sodium 4% used 4-6 times daily (issues with compliance)
- Helpful for sneezing, itching, rhinorrhea
- Not effective for congestion
- Safe; approved ≥2 yo

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Anticholinergic nasal spray

- Acts on muscarinic receptors, decreasing mucous production
- Most useful in combating rhinorrhea
- No effect on sneezing, itching or nasal congestion
- Allergic rhinitis, non-allergic rhinitis (gustatory rhinitis and others)
- Ipratropium bromide 0.03% or 0.06% with 2 sprays 2-4 times daily depending on indication or age
- Avoid in patients with narrow angle glaucoma

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Immunotherapy

- Subcutaneous
- Sublingual

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Subcutaneous immunotherapy

- Indications: severe uncontrolled AR, new or worsening allergic asthma, adverse effects of medications or wanting to reduce medications
- Risk: anaphylaxis
- Important considerations: uncontrolled asthma, age

BOX 85.3 Conventional Allergen Extract Treatment Schedule

The following schedule should be used, with modification if necessary as outlined in the accompanying "Instructions for the Injection of Allergenic Extracts." Begin with Vial # **4** and progress to Vial #1 which is the most concentrated or "maintenance" solution. The injections should be given every **week**. Once maintenance is reached, the injection should be given every **3 to 4** weeks with the following exceptions: **give weekly for first injections and every 2 weeks for the third and fourth injections.**

Vial #5	Vial #4	Vial #3	Vial #2	Vial #1
0.05 mL	0.05 mL	0.05 mL	0.05 mL	0.05 mL
0.10 mL	0.10 mL	0.10 mL	0.07 mL	0.07 mL
0.20 mL	0.20 mL	0.20 mL	0.10 mL	0.10 mL
0.40 mL	0.40 mL	0.40 mL	0.15 mL	0.15 mL
			0.25 mL	0.20 mL
			0.35 mL	0.30 mL
			0.50 mL	0.40 mL
				0.50 mL

The bold, underlined entries are representative instructions that would be placed in the blank spaces in the schedule.

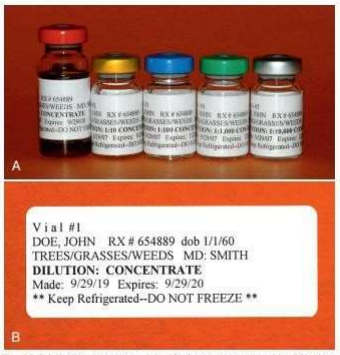

Fig. 85.2 Labeling treatment vials. (**A**) A treatment set with vials color-coded according to the recommendations of the Immunotherapy Practice Parameters 3rd Update.[154] The vials are capped from red (the concentrate) through progressive tenfold dilutions marked yellow, blue, green, and silver, respectively. (**B**) A representative treatment set label with all the information recommended by the Immunotherapy Practice Parameters 3rd Update.

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Sublingual immunotherapy (FDA approved tablets)

- Local irritation most common
- Risk of anaphylaxis, need to carry IM EPI
- Special considerations: Asthma, EOE, Hold if oral wounds are present
- 1st dose in MD office
- Limited variety, typically want mono-sensitized patients
  - ODACTRA (dust mites)
    - 12-65 years, contraindicated in EOE
  - ORALAIR (sweet vernal, orchard, perennial rye, timothy, Kentucky blue grass pollen)
    - 5-65 years, 4 months before allergy season and for duration of season, contraindicated in EOE
  - RAGWITEK (short ragweed)
    - 5-65 years, start 12 weeks before allergy season and for duration of season

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Nasal polyposis

- 1st assess for CF in children and young adults
- Surgery
- Biologics
  - Dupilumab
    - ≥18 yo; 300 mg every 2 weeks
  - Mepolizumab
    - ≥18 yo; 100 mg every 4 weeks
  - Omalizumab
    - ≥18 yo; weight and IgE based dosing given every 2-4 weeks

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ANAPHYLAXIS

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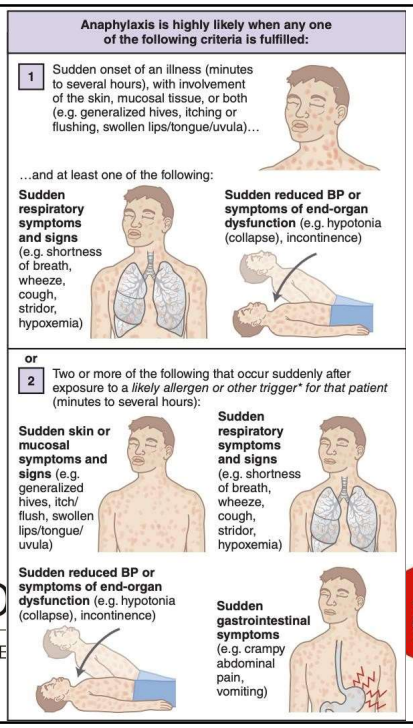
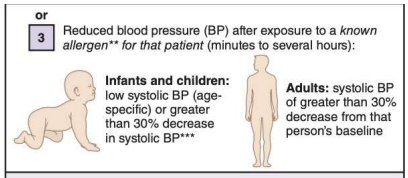
BOX 75.1 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized urticaria, itching or flushing, swollen lips-tongue-uvula)
   And at least one of the following:
   A. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
   B. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
   OR
2. Two or more of the following that occur rapidly after exposure to a likely allergen (or other trigger) for that patient (minutes to several hours)
   A. Involvement of the skin/mucosal tissue (e.g., generalized urticaria, itch-flush, swollen lips-tongue-uvula).
   B. Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
   C. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   D. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
   OR
3. Reduced blood pressure after exposure to a known allergen or other trigger for that patient (minutes to hours).
   A. Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
   B. Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline





* For example, immunologic but IgE-independent, or non-immunologic (direct mast cell activation).

** For example, after an insect sting, reduced blood pressure might be the only manifestation of anaphylaxis; or, after allergen immunotherapy, generalized hives might be the only initial manifestation of anaphylaxis.

*** Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70mm Hg + [2 × age]) from 1 to 10 yrs, and less than 90 mm Hg from 11 to 17 yrs. Normal heart rate ranges from 80–140 beats/minute at age 1–2 yrs; from 80–120 beats/minute at age 3 yrs; and from 70–115 beats/minute after age 3 yrs. In infants and children, respiratory compromise is more likely than hypotension or shock, and shock is more likely to be manifest initially by tachycardia than by hypotension.

Fig. 75.1 Criteria for diagnosing anaphylaxis. From Simons et al.[118]

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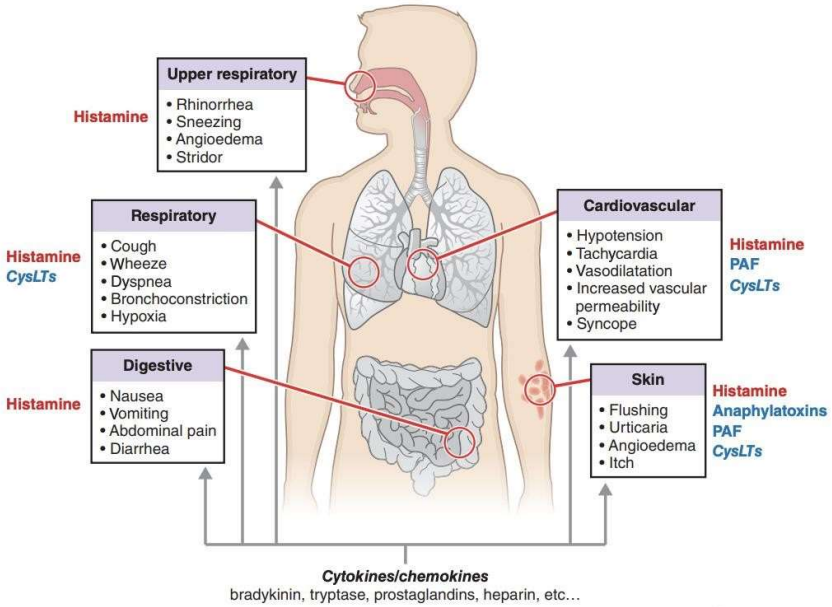

Fig. 75.3 Mediators of anaphylaxis and their effects in anaphylaxis. From Reber et al.[29]

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TABLE 75.3 Summary of Incidence for Common Triggers of Anaphylaxis

Agent	Comment/Findings
Drugs	Antibiotics are arguably the most common cause of drug-induced anaphylaxis. Anesthetic drugs (particularly neuromuscular blocking agents), NSAIDs, and most recently biologics are increasing in importance.
Foods	As many as 4% of children and 1% of adults have food allergy. In addition to natural exposures, anaphylaxis can occur during diagnostic oral food challenges.
Venoms	Potentially life-threatening systemic reactions to insect stings occur in an estimated 0.4%-0.8% of children and 3% of adults.
Latex	Although the incidence of sensitization to latex had dropped because of decreased use of latex in the health care setting, many latex-allergic patients must be managed carefully, particularly in regard to medical interventions.
Radiocontrast media	Adverse reactions to ionic contrast media (hyperosmolar agents) occur with a frequency of 4%-12% and to nonionic (lower osmolar) agents at a frequency of 1%-3%.
Allergen-specific immunotherapy	Subcutaneous allergen-specific immunotherapy has a small risk of anaphylaxis (approximately 0.2% per injection). Although reactions are typically mild, severe reactions are possible, and guidelines should be followed carefully.
Physical triggers	Exercise–induced anaphylaxis is not uncommon but is most likely related to the prior (0-4 hours) ingestion of an allergenic food.
Idiopathic anaphylaxis	Cause remains unidentified in as many as two-thirds of adults presenting to an allergist/immunologist for evaluation of anaphylaxis.

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Anaphylaxis

- Treatment—IM epinephrine!
- Supportive care—IVF, albuterol, steroids, glucagon (if on beta blocker)
- Check a serum tryptase—
  - best obtained 1-4 hours after onset of symptoms
  - Can be normal in food-triggered anaphylaxis

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Treatment of anaphylaxis

- Epinephrine IM
  - 0.01 mg/kg of 1:1000 (1mg/mL) to lateral thigh
  - <14 kg give 0.1 mg
    - Auvi-Q (only goes to ASPN mail order pharmacy)
  - > or = to 14-25 kg give 0.15 ~~
    - Auvi-Q
    - Epi Pen Jr
    - Generic epinephrine autoinjector
  - > or = to 25 kg give 0.3 mg
    - Auvi-Q
    - Epi Pen
    - Generic epinephrine autoinjector

https://www.nationaljewish.org/conditions/anaphylaxis/using-an-auvi-q

https://www.attentivesafety.com/anaphylaxis-and-epinephrine-auto-injector.html

https://www.researchgate.net/figure/Proposed-child-restraint-options-for-the-administration-of-an-epinephrine-auto-injector_fig3_315508117

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URTICARIA & ANGIOEDEMA

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Urticaria and Angioedema- histaminergic

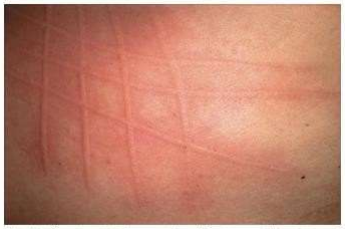
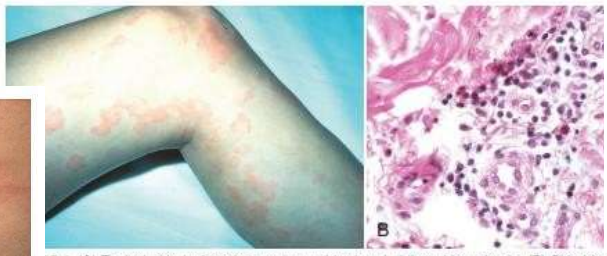


Fig. 35.3 Symptomatic dermographism. Onset was within minutes of scratching. (From Bolognia JL, Jorizzo JL, Schaffeer JV, editors. Dermatology. 3rd ed. London: Saunders; 2012. Courtesy Jean L. Bolognia, MD.)



35.4 (A) Typical skin lesions in a patient with chronic idiopathic urticaria. (B) Skin bio ient with chronic idiopathic urticaria (hematoxylin-eosin stain).

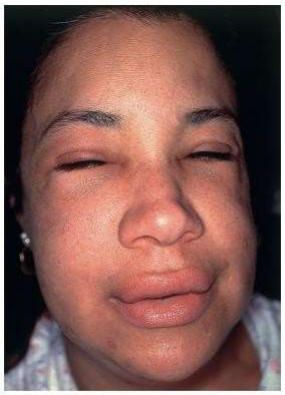


Fig. 35.5 The swelling is deeper than that with typical wheals and may affect mucosal surfaces. Note the swelling of the lips and periorbital region and the lack of erythema. (From Bolognia JL, Jorizzo JL, Schaffeer JV, editors. Dermatology. 3rd ed. London: Saunders; 2012.)

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Acute Urticaria

- Review timeline/history to identify if there are any food or medication triggers
- If no obvious trigger, then likely is viral mediated

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Chronic Idiopathic Urticaria +/- Angioedema

- Symptoms occurring most days for at least 6 weeks
- Insanely itchy--not harmful but symptoms are very distressing for patients
- Stepwise approach to therapy:
  - **<u>Use H2 antihistamines—up to 4 times the standard daily dose***</u>**
  - Consider leukotriene pathway inhibitor
  - Consider adding H1 and H2 blocker
  - Omalizumab (for patients 12 or older, that have failed 4 weeks of high dose H2 antihistamines)
  - REFRACTORY cases: sulfasalazine, dapsone, hydroxychloroquine, calcineurin inhibitors, mycophenolate

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Hereditary Angioedema

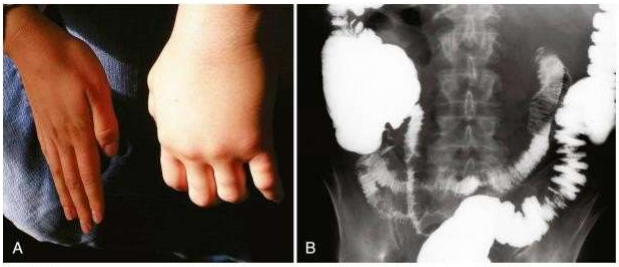

Fig. 36.1

Swelling in patients with hereditary angioedema. (**A**) Example of asymmetric swelling of the hands. (**B**) A barium study performed during an abdominal attack with evidence of submucosal swelling of the distal wall of the small intestine manifested as spiculation and thickening of intestinal folds.

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Hereditary Angioedema

TABLE 36.1 Bradykinin-Mediated Angioedema Syndromes

Syndrome	Pathophysiology	Affected	Prevalence	C4 Level	C1INH Antigen	C1INH Function	C1q Level
Type 1 HAE	Mutation in *SERPING1* gene causing C1 inhibitor deficiency	All	~1:50,000	Low	Low	Low	Normal
Type 2 HAE	Mutation in *SERPING1* gene causing functional C1 inhibitor deficiency	All	~1:250,000	Low	Normal	Low	Normal
HAE with normal C1INH	Mutations in FXII, PLG, and ANGPT1 as well as unknown	All, but many more women	Unknown	Normal	Normal	Normal	Normal
Acquired C1INH deficiency	Excessive consumption of C1 inhibitor leading to deficiency	Older patients	~1:250,000	Low	Low	Low	Low
ACE-I–associated	Inhibition of bradykinin catabolism	All, but increased in African-Americans	~1:250	Normal	Normal	Normal	Normal
Nonhistaminergic idiopathic	Unknown	Unknown	Unknown	Normal	Normal	Normal	Normal

ACE-I, Angiotensin-converting enzyme inhibitor; *HAE*, hereditary angioedema.

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Hereditary Angioedema

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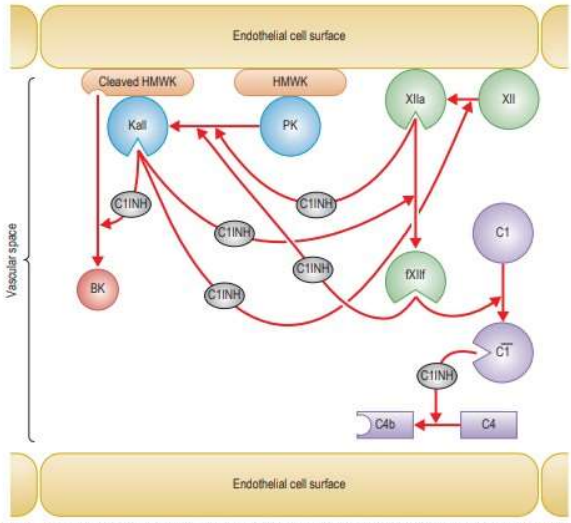

Fig. 36.3 Contact system activation generates bradykinin. Contact system activation is initiated by assembly of the contact system components high molecular weight kininogen (*HMWK*), the zymogen plasma prekallikrein (*PK*), and the zymogen coagulation factor XII (*fXII*) on an appropriate surface. Activation is initiated by either autoactivation of factor XII to active factor XIIa or prolylcarboxypeptidase-mediated activation of plasma prekallikrein to active plasma kallikrein (*Kall*). Zymogen proteases are shown as *circles* and active proteases as *circles with a small pie-shaped section deleted*. Factor XIIa and plasma kallikrein can reciprocally activate each other, thereby rapidly amplifying contact system activation. Plasma kallikrein has two additional effects on the contact system: It cleaves factor fXIIa to active fXIIf, and it cleaves high molecular weight kininogen to release the mediator bradykinin (*BK*). Factor XIIf can cleave plasma prekallikrein to plasma kallikrein, as well as activate the complement C1 zymogen proteases, which can then cleave C4. Proteolytic activity inhibited by C1INH is shown by *grey ovals*.

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Hereditary Angioedema

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TABLE 36.2 Approved Drugs Used to Treat Hereditary Angioedema Attacks

Drug (Trade Name, Manufacturer)	Regulatory Status	Self-Administer?	Dosage	Mechanism	Anticipated Potential Side Effects
Plasma-derived nanofiltered C1INH (Berinert, CSL Behring)	Approved in United States and Europe for children and adults	Yes	20 U/kg IV	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	*Rare*: risk of anaphylaxis *Theoretical*: transmission of infectious agent
Plasma-derived nanofiltered C1INH (Cinryze, Takeda)	Approved in Europe for children and adults	Yes	Pediatric: 10-25 kg, 500 U IV with possibility of second 1000-U dose after 60 min; All >25 kg: 1000 U IV, with possibility of second 1000-U dose after 60 min	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	*Rare*: risk of anaphylaxis *Theoretical*: transmission of infectious agent
Ecallantide (Kalbitor, Takeda)	Approved in United States for patients ≥12 years of age	No	30 mg SC	Inhibits plasma kallikrein	*Uncommon*: antidrug antibodies, risk of anaphylaxis
Icatibant (Firazyr, Takeda)	Approved in United States for patients ≥18 years of age; Approved in Europe for patients ≥2 years of age	Yes	Pediatric: 12-25 kg, 10 mg SC; 26-40 kg, 15 mg SC; 41-50 kg, 20 mg SC; 51-65 kg, 25 mg SC; >65 kg, 30 mg SC Adults: 30 mg SC	Bradykinin B2 receptor antagonist	*Common*: discomfort at injection site
Recombinant human C1INH (Ruconest, Pharming)	Approved in United States and Europe for adolescents and adults	Yes	50 U/kg *or* 4200 U (whichever is lower) IV	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	*Uncommon*: risk of anaphylaxis in rabbit-sensitized individuals

IV, Intravenously; *MASP-1, -2*, Mannose-binding lectin–associated serine proteases 1, 2; *SC*, subcutaneously.

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Hereditary Angioedema

TABLE 36.3 Drugs Used for Hereditary Angioedema Prophylaxis

Drug (Trade Name, Manufacturer)	HAE Regulatory Status	Dosage	Mechanism	Anticipated Potential Side Effects
Plasma-derived nanofiltered C1 INH (Cinryze, Takeda)	Approved in United States for adolescents and adults; Approved in Europe for patients ≥6 years of age	*Pediatric (6-11 years):* 500 IU every 3-4 days IV *Adults:* 1000 U IV every 3-4 days Dosage may need to be adjusted according to individual response	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	*Rare:* risk of anaphylaxis *Theoretical:* transmission of infectious agent
Plasma-derived nanofiltered C1INH (Berinert, CSL Behring)	Approved in Europe for preprocedural short-term prophylaxis	*2-11 years and 10-25 kg:* 500 IU IV; *2-11 years and >25 kg:* 1000 IU IV *Adolescent and adult:* 1000 IU IV	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	*Rare:* risk of anaphylaxis *Theoretical:* transmission of infectious agent

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Hereditary Angioedema

TABLE 36.3 Drugs Used for Hereditary Angioedema Prophylaxis—cont'd

Drug (Trade Name, Manufacturer)	HAE Regulatory Status	Dosage	Mechanism	Anticipated Potential Side Effects
Plasma-derived nanofiltered C1INH (HAEGARDA, CSL Behring)	Approved in United States for adolescents and adults	60 IU/kg every 3-4 days SC	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	*Rare:* risk of anaphylaxis *Theoretical:* transmission of infectious agent
Lanadelumab (Takhzyro, Takeda)	Approved in United States for age 12 years and older	300 mg q2 weeks with possibility of lowering dose to q4 weeks after 6 months	Inhibits plasma kallikrein	*Theoretical:* risk of immunogenicity
Danazol (Danocrine, Sanofi-Synthelabo)	Approved in United States for adults	*Adult:* 200 mg/day PO (100 mg every 3 days to 600 mg/day) *Pediatric:* 50 mg/day PO (50 mg/week to 200 mg/day)	17α-Alkylated androgen; mechanism unknown	*Common:* weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities, increase in liver enzymes, hypertension, and alterations in lipid profile *Uncommon:* decreased growth rate in children, masculinization of the female fetus, cholestatic jaundice, peliosis hepatis, and hepatocellular adenoma
Stanozolol (Winstrol, Winthrop)	Approved in United States for adults and children	*Adult:* 2 mg/day PO (1 mg every 3 days to 6 mg/day) *Pediatric:* 0.5 mg/day PO (0.5 mg/week to 2 mg/day)	17α-Alkylated androgen; mechanism unknown	
Oxandralone (Oxandrin)	Not approved for HAE indication	*Adult:* 10 mg/day PO (2.5 mg every 3 days to 20 mg/day) *Pediatric:* 0.1 mg/kg/day PO (2.5 mg/week to 7.5 mg/day)	17α-Alkylated androgen; mechanism unknown	
Methyltestosterone (Android)	Not approved for HAE indication	*Adult men:* 10 mg/day PO (5 mg every 3 days to 30 mg/day) *Women and pediatric:* not recommended	17α-Alkylated androgen; mechanism unknown	
Epsilon aminocaproic acid (Amicar, Xanodyne Pharmaceuticals)	Not approved for HAE indication	*Adult:* 2 g PO tid (1 g bid to 4 g tid) *Pediatric:* 0.05 g/kg PO bid (0.025 g/kg bid to 0.1 g/kg bid)	Antifibrinolytic; mechanism unknown	*Common:* nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with increased muscle enzymes *Uncommon:* thrombosis
Tranexamic acid (Cyklokapron, Pfizer; Lystada, Ferring)	Not approved for HAE indication	*Adult:* 1 g PO bid (0.25 g bid to 1.5 g tid) *Pediatric:* 20 mg/kg PO bid (10 mg/kg bid to 25 mg/kg tid)	Antifibrinolytic; mechanism unknown	

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FOOD ALLERGY

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Food Allergy-diagnosis

- HISTORY
  - Symptoms should occur within seconds up to 2 hours after ingestion and resolve quickly—within hours
  - Symptoms include: hives, swelling, rhinorrhea/sneezing, cough/wheezing/difficulty breathing, vomiting/diarrhea, change in mentation, hypotension
- Confirm the food trigger with allergy testing—skin followed by blood
- Common food allergens: **egg, milk**, wheat, soy, peanut, tree nuts, shellfish, tree nuts, sesame seed
- NEVER EVER send blood food allergy testing if you are not an allergist—**you can do real, irreversible and significant harm**
- If you suspect a food allergy, prescribe IM Epi autoinjectors and tell the family to only avoid the food trigger

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Food Allergy-prevention

- YOU have the power to prevent food allergy
- Encourage parents to introduce developmentally appropriate foods early and keep them in diet often
- The strongest evidence is for children with eczema—super important to introduce peanut powder between 4-6 months of age or as soon as the patient is ready
  - https://www.niaid.nih.gov/sites/default/files/addendum_guidelines_peanut_appx_d.pdf

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APPENDIX D. INSTRUCTIONS FOR HOME FEEDING OF PEANUT PROTEIN FOR INFANTS AT LOW RISK OF AN ALLERGIC REACTION TO PEANUT

These instructions for home feeding of peanut protein are provided by your doctor. You should discuss any questions that you have with your doctor before starting. These instructions are meant for feeding infants who have severe eczema or egg allergy and were allergy tested (blood test, skin test, or both) with results that your doctor considers safe for you to introduce peanut protein at home (low risk of allergy).

General Instructions

1. Feed your infant only when he or she is healthy; do not do the feeding if he or she has a cold, vomiting, diarrhea, or other illness.
2. Give the first peanut feeding at home and not at a day care facility or restaurant.
3. Make sure at least 1 adult will be able to focus all of his or her attention on the infant, without distractions from other children or household activities.
4. Make sure that you will be able to spend at least 2 hours with your infant after the feeding to watch for any signs of an allergic reaction.

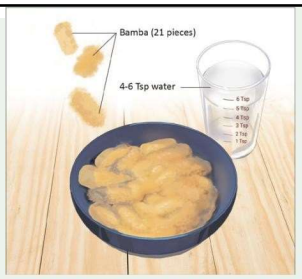
Feeding Your Infant

1. Prepare a full portion of one of the peanut-containing foods from the recipe options below.
2. Offer your infant a small part of the peanut serving on the tip of a spoon.
3. Wait 10 minutes.
4. If there is no allergic reaction after this small taste, then slowly give the remainder of the peanut-containing food at the infant's usual eating speed.

What are symptoms of an allergic reaction? What should I look for?

- Mild symptoms can include:
  - a new rash
    or
  - a few hives around the mouth or face
- More severe symptoms can include any of the following alone or in combination:
  - lip swelling
  - vomiting
  - widespread hives (welts) over the body
  - face or tongue swelling
  - any difficulty breathing
  - wheeze
  - repetitive coughing
  - change in skin color (pale, blue)
  - sudden tiredness/lethargy/seeming limp

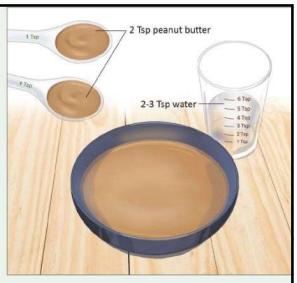
If you have any concerns about your infant's response to peanut, seek immediate medical attention/call 911.



Option 1: Bamba (Osem, Israel), 21 pieces (approximately 2 g of peanut protein)

Note: Bamba is named because it was the product used in the LEAP trial and therefore has proven efficacy and safety. Other peanut puff products with similar peanut protein content can be substituted.

a. For infants less than 7 months of age, soften the Bamba with 4 to 6 teaspoons of water.

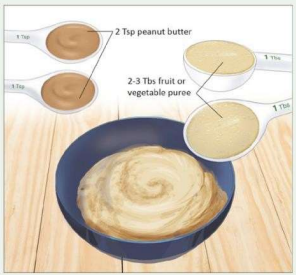


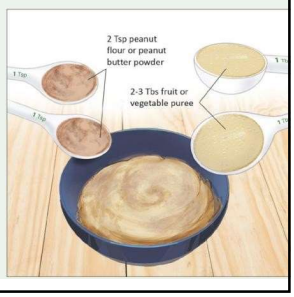
Option 2: Thinned smooth peanut butter, 2 teaspoons (9-10 g of peanut butter; approximately 2 g of peanut protein)

a. Measure 2 teaspoons of peanut butter and slowly add 2 to 3 teaspoons of hot water.

b. Stir until peanut butter is dissolved, thinned, and well blended.

c. Let cool.





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Food allergy-treatment

- Avoidance
- (IM Epinephrine)
- Oral immunotherapy (Palforzia)
- Omalizumab

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Palforzia

Palforzia®
Peanut (*Arachis hypogaea*) Allergen Powder-dnfp

- 4-17 years of age
- Contraindications: uncontrolled asthma, EOE/EGID
- Essentially eating small amounts of peanut
- Reduce the severity of allergic reactions that may occur with accidental exposure to peanut
- Not a cure! Just raising a threshold!
- Patients WILL have anaphylaxis on treatment!

Up-Dosing

Total Daily Dose	Daily Dose Configuration
3 mg	Three 1 mg capsules
6 mg	Six 1 mg capsules
12 mg	Two 1 mg capsules; One 10 mg capsule
20 mg	One 20 mg capsule
40 mg	Two 20 mg capsules
80 mg	Four 20 mg capsules
120 mg	One 20 mg capsule; One 100 mg capsule
160 mg	Three 20 mg capsules; One 100 mg capsule
200 mg	Two 100 mg capsules
240 mg	Two 20 mg capsules; Two 100 mg capsules
300 mg	One 300 mg sachet

Maintenance

Total Daily Dose	Daily Dose Configuration
300 mg	One 300 mg sachet

300 mg is about 1 peanut

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Omalizumab

Omalizumab for the Treatment of Multiple Food Allergies

Robert A. Wood, M.D., Alkis Togias, M.D., Scott H. Sicherer, M.D., Wayne G. Shreffler, M.D., Ph.D., Edwin H. Kim, M.D., Stacie M. Jones, M.D., Donald Y.M. Leung, M.D., Ph.D., Brian P. Vickery, M.D., J. Andrew Bird, M.D., Jonathan M. Spergel, M.D., Ph.D., Ahmar Iqbal, M.D., M.B.A., Julie Olsson, M.D., et al.

- FDA approval 2/2024
- 1-55 years of age
- Allergic to peanut and at least 2 other foods (cashew, milk, egg, walnut, wheat and hazelnut)
- Increased threshold for reaction after 16 weeks of therapy (given every 2-4 weeks with dose based on IgE level and weight)

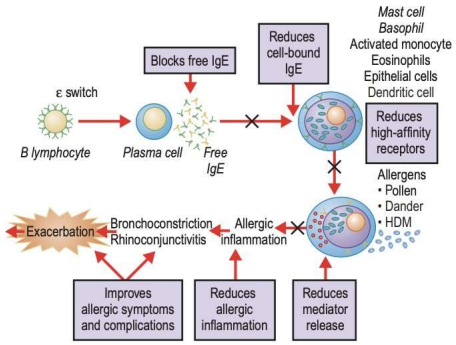

Fig. 90.4 Omalizumab's mechanisms of action. *HDM*, House-dust mite; *IgE*, immunoglobulin E.

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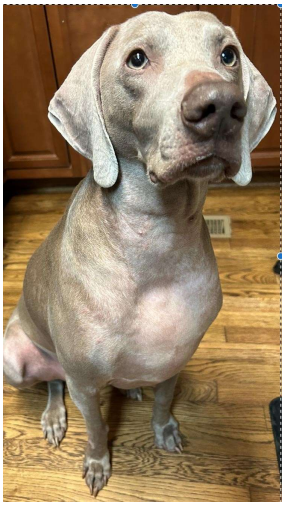
Questions?



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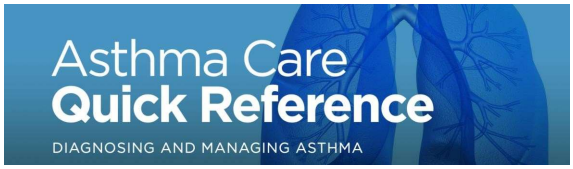
Sources



Special Article

Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape

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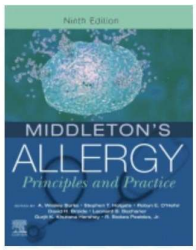

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