The Skinny of The IMMUNE SYstem

Julie Sterbank, DO
Assistant Professor
Case Western Reserve University/
Allergist & Immunologist
MetroHealth Medical Center
Cleveland, Ohio
October 13, 2017

CASE WESTERN RESERVE UNIVERSITY EST. 1826

MetroHealth

I have no disclosures to make financial or otherwise today.

I would also like to thank Dr. Robert Hostoffer who was kind enough to share his slides and thoughts regarding this presentation but was unable to join us here today.

Case Western Reserve University EST. 1826

MetroHealth

Case Western Reserve University EST. 1826

MetroHealth

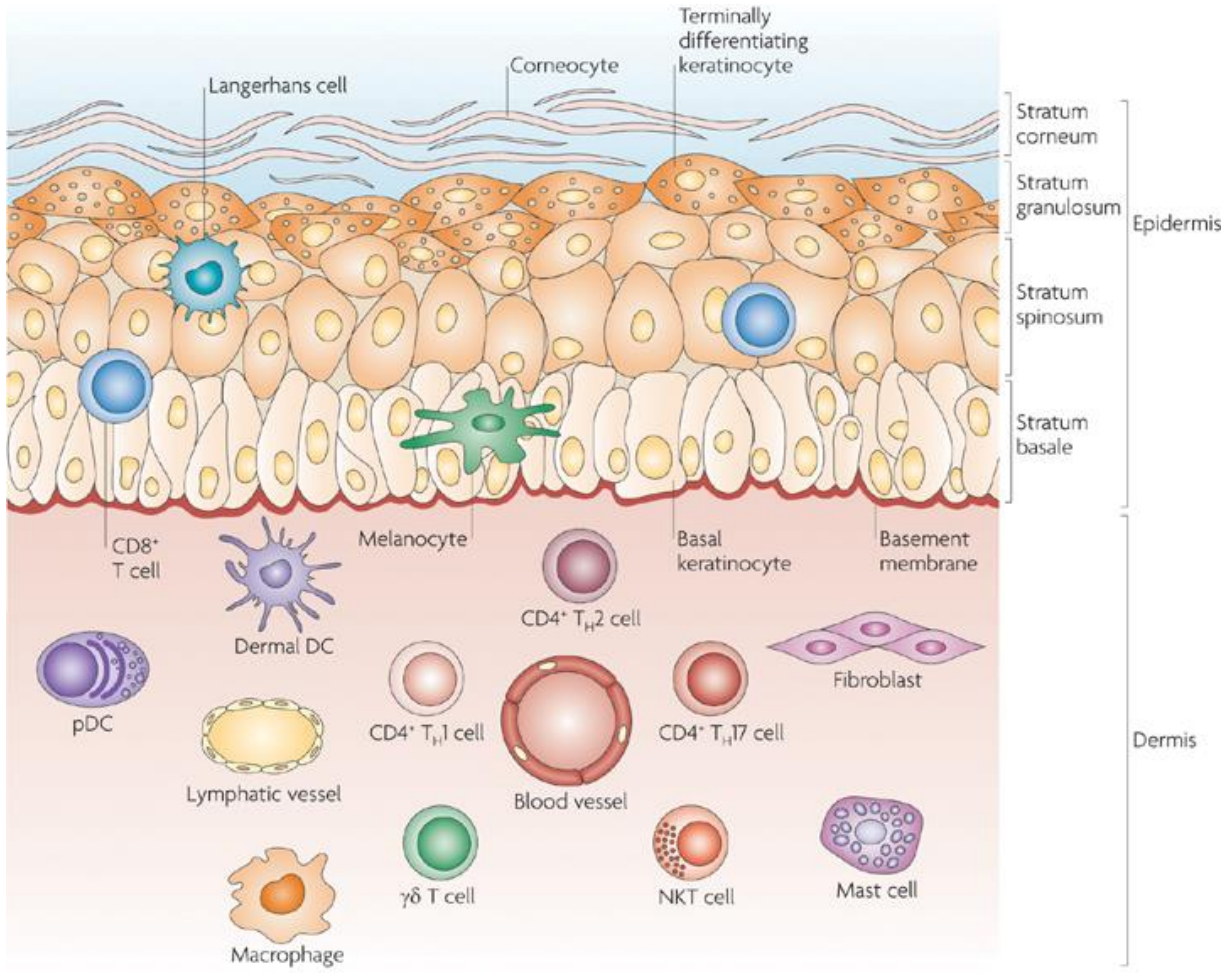
Metro Life Flight

Case Western Reserve University Est. 1826

MetroHealth

Objectives

1. Review basics of skin immunology & the similarities/differences of innate versus adaptive immunity
2. Discuss the etiologies of allergic/atopic skin disease & the inadequacies of current topical and immunosuppressive treatments.
3 Explore the current biologicals available for allergic/atopic skin disease.



Nature Reviews | Immunology

MetroHealth

Innate Immune System

- Non-specific
- Fast-acting
- Like a “hand-grenade”

Adaptive Immune System

- Specific response to antigen
- Typically slow response for an initial exposure
- Repeat exposures will respond more quickly
- Thought of a “smart bomb”

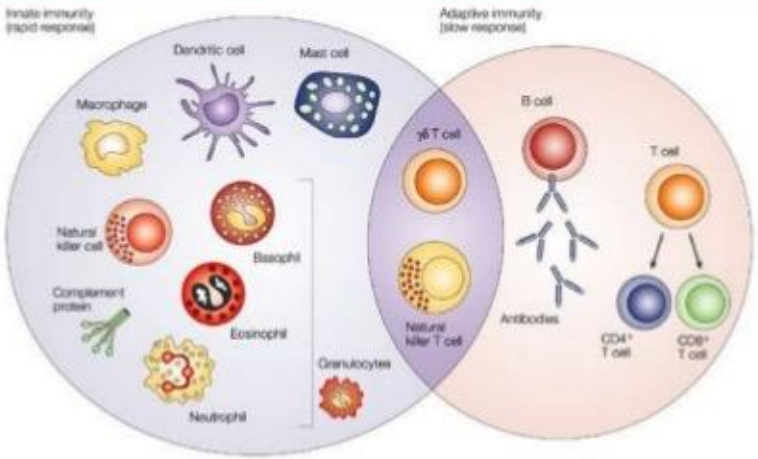
Comparison

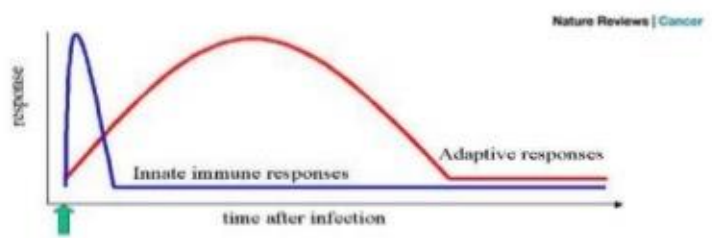
Innate *vs* adaptive immunity

	innate	adaptive
self / non-self discrimination	present, reaction is against foreign	present, reaction is against foreign
lag phase	absent, reponse is immediate	present, response takes at least a few days
specificity	limited, the same response is mounted to a wide variety of agents	high, the response is directed only to the agents that initiated it.
diversity	limited, hence limited specificity	extensive, and resulting in a wide range of antigen receptors.
memory	absent, subsequent exposures to agent generate the same response	present, subsequent exposures to the same agent induce amplified reponses

Immune System – Innate vs Adaptive

Innate:
- Nonspecific
- Responds quickly





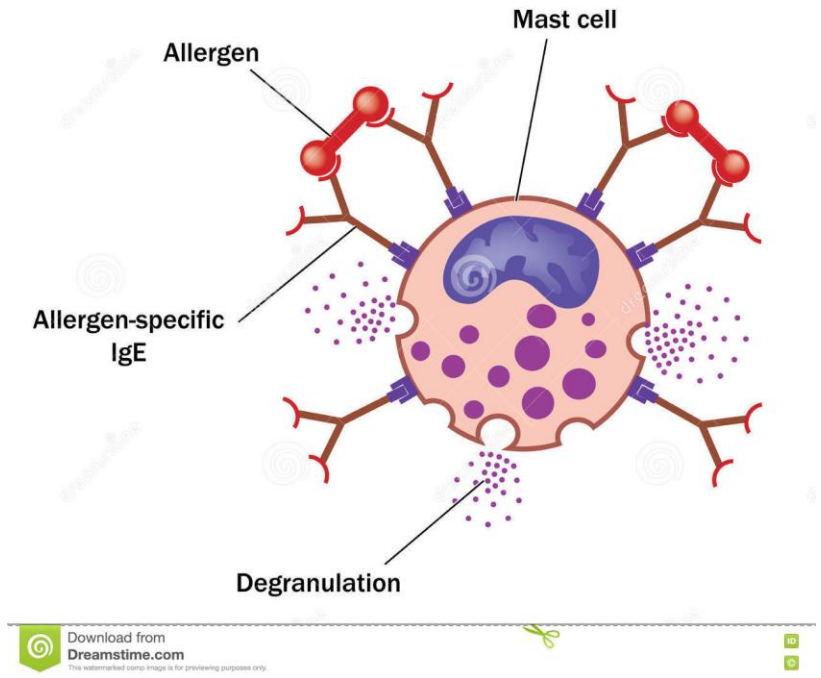
Adaptive:
- Specific
- Responds Slowly the 1st time

Case Western Reserve University EST. 1826

MetroHealth

Innate Immune Skin Cells

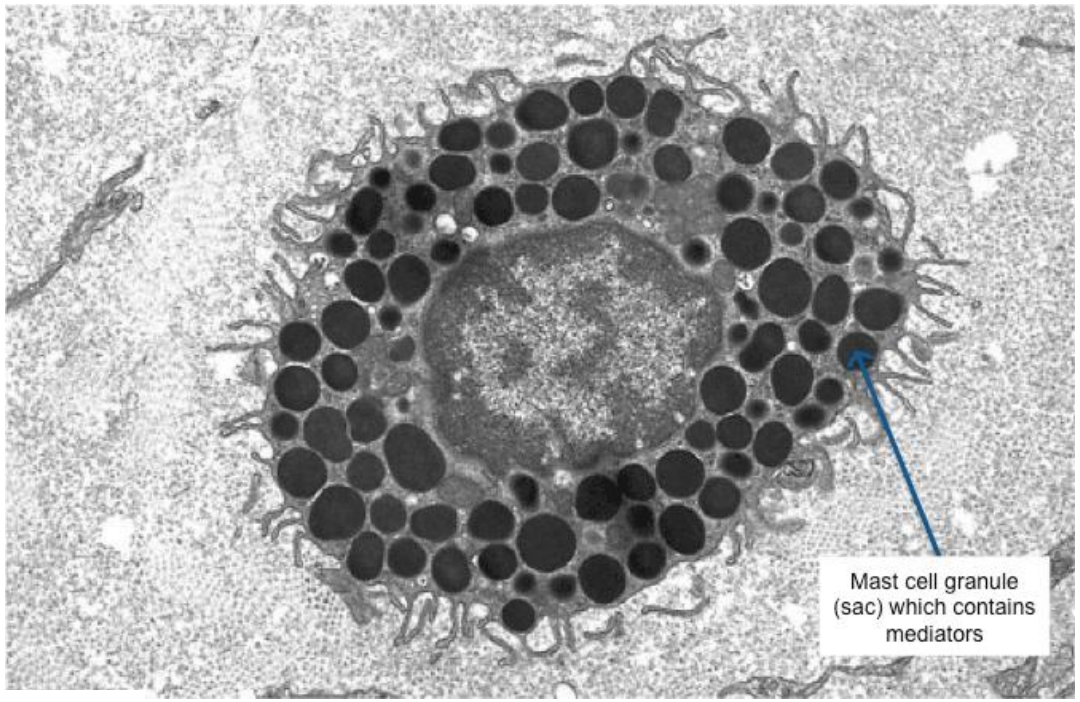
- Dendritic cells
  - Langerhans cells
  - Dermal dendritic cells
- Mast cells
- Macrophages
- Granulocytes
- Complement Proteins



Tay et al. The skin-Resident Immune Network. (2014) Curr Derm Rep 3:12-22.

MetroHealth

Human Mast Cell

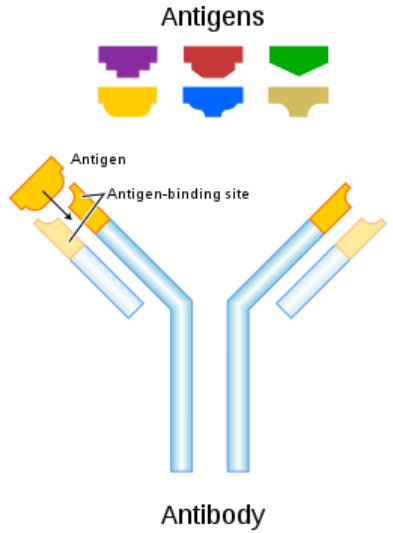


Case Western Reserve University Est. 1826

MetroHealth

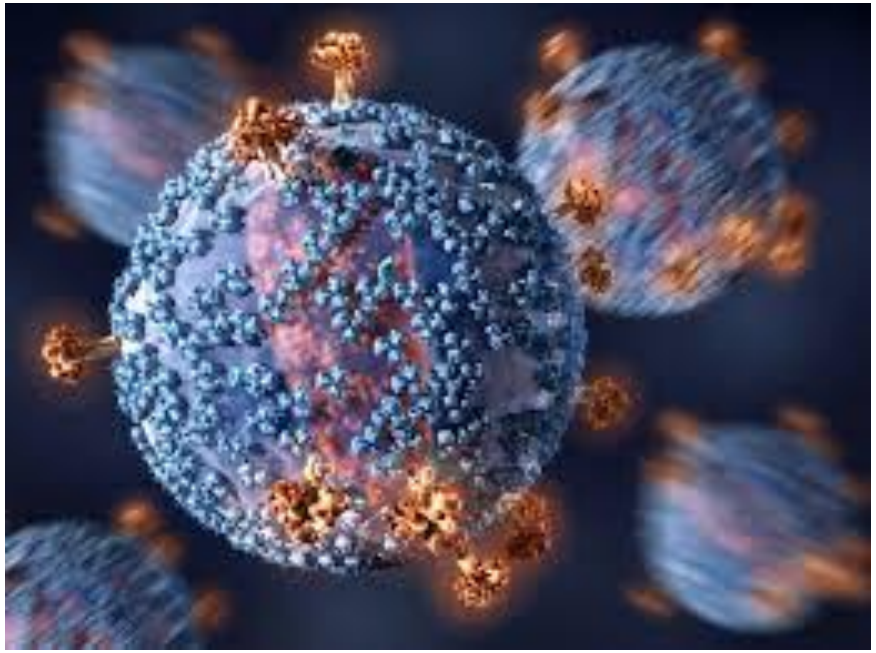
Adaptive Immune Skin Cells

- B cells
  - antibodies
- T cells
  - CD4
  - CD8



By Fvasconcellos 19:03, 6 May 2007 (UTC)

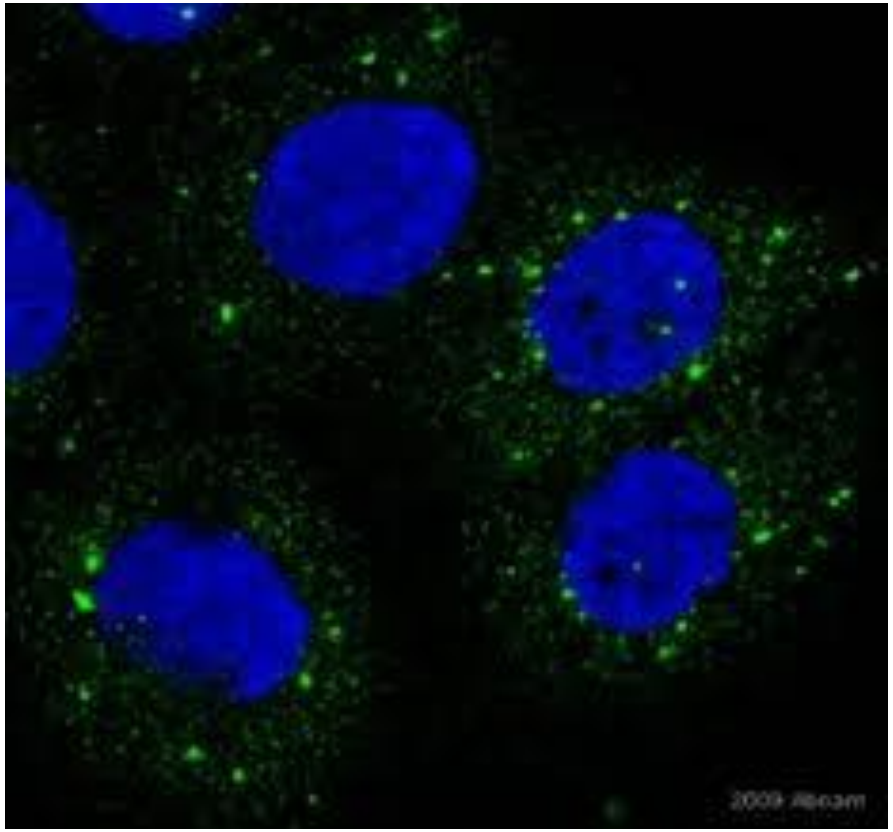
Virus and Antibody Bound to Virus



Case Western Reserve University Est. 1826

MetroHealth

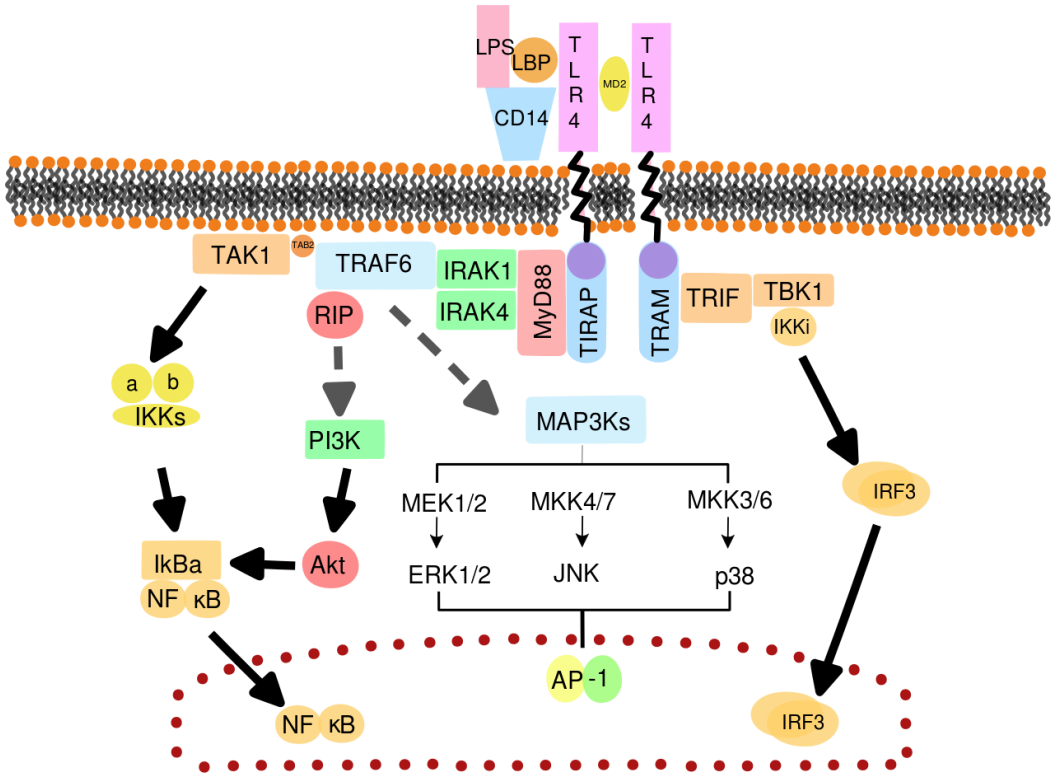
S



Toll Receptors

- Protein receptors of the innate immune system
- Recognize the structure of microbes
- Signal the response of the immune system once skin or mucosa breached

Suffice to Say, It's Complicated



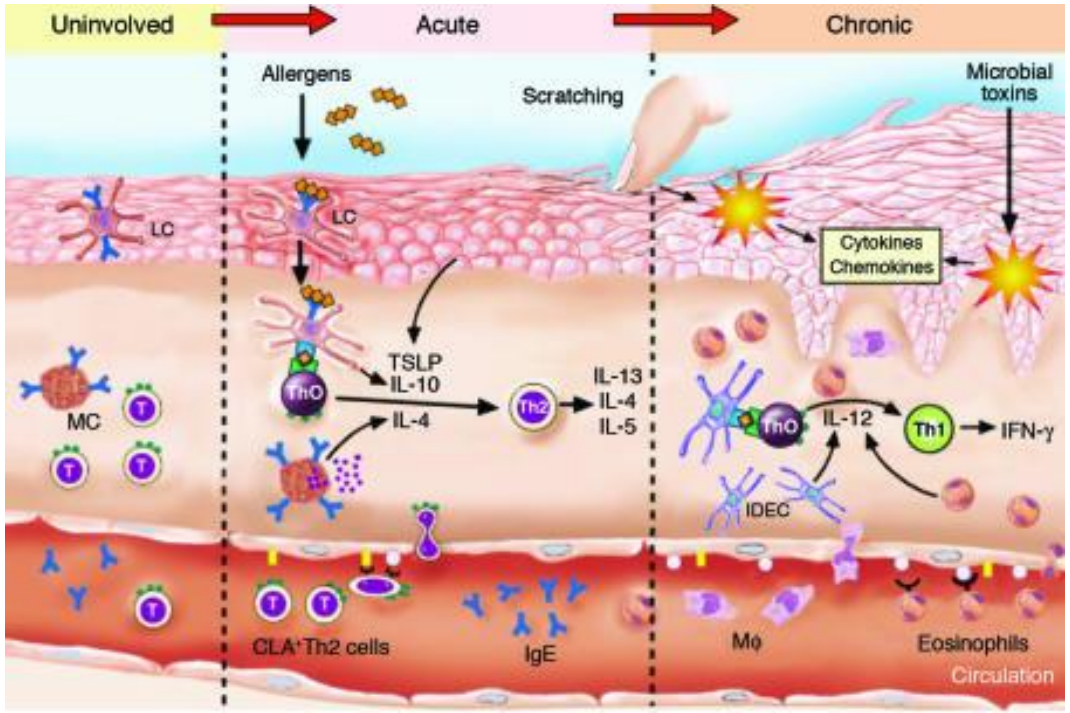
MetroHealth

Etiology of Atopic Dermatitis

- Defect in protein structure of skin (filaggrin)
- Complex interaction of the innate and adaptive &immune system
- Thought to involve interleukin pathways IL13 and IL4 and IgE

Leung, D. Y. M., Boguniewicz, M., Howell, M. D., Nomura, I., & Hamid, Q. A. (2004). New insights into atopic dermatitis. *Journal of Clinical Investigation*, *113*(5), 651–657. http://doi.org/10.1172/JCI200421060

Acute versus Chronic Skin Changes



MetroHealth

Initial Treatments for Atopic Dermatitis

- Attempt to restore the barrier - emollients, ceramides
- Attempt to decrease the inflammatory process
    - Topical steroids
    - Topical anti-inflammatories (calcinuerin Inhibitors)

Initial systemic treatments for Atopic Dermatitis

Oral steroids***

Oral antibiotics

T-cell targets

Methotrexate

Cyclosporin

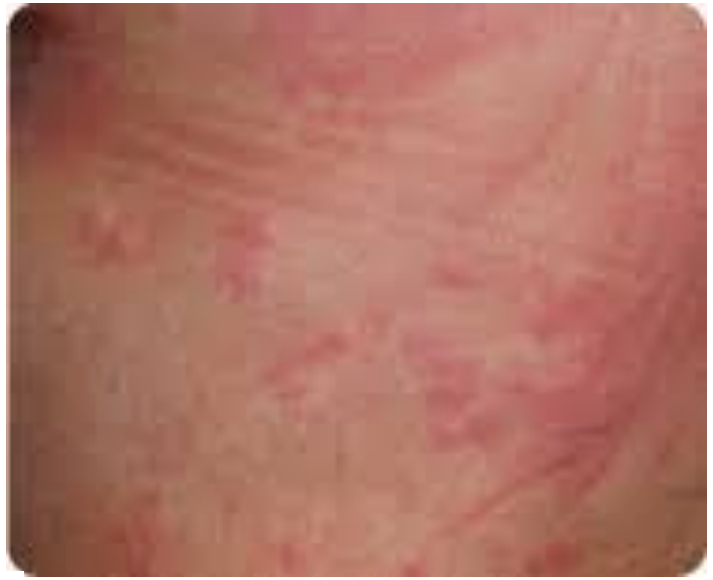
.

HALFTIME

Case Western Reserve University Est. 1826

MetroHealth

Chronic Urticaria



Case Western Reserve University Est. 1826

MetroHealth

Chronic Urticaria (continued)

- Estimated 1.5 million people in US affected
- Women 2x more likely than men to suffer
- Typically benign, but occasionally can be sign of a serious underlying condition
- Typically age where urticaria first seen -
    - ages 20 to 40 years

Chronic Urticaria (continued)

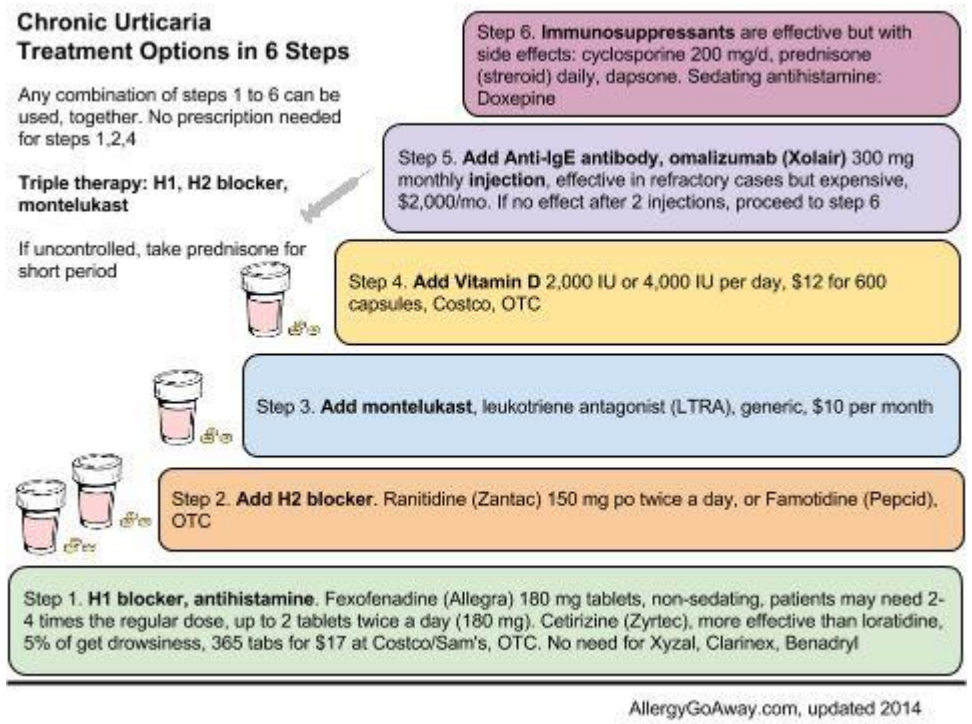
- Etiology is thought to be degranulation of mast cells in the skin as a result of autoantibodies to the IgE receptor to basophils and mast cells
- Closer to skin surface: Hives
- Deeper in skin tissue: Angioedema

Godse, K. V. (2009). CHRONIC URTICARIA AND TREATMENT OPTIONS. *Indian Journal of Dermatology*, *54*(4), 310–312. http://doi.org/10.4103/0019-5154.57603

Systemic Treatments for Chronic Urticaria

- H1/H2 Blockade
- Leukotriene Inhibitors
- Immunosuppressants -
  - Methotrexate
  - Cyclosporin

Chronic Urticaria - Stepwise Treatment



Case Western Reserve University Est. 1826

MetroHealth

Recap

- Atopic Dermatitis
    - emollients
    - oral antihistamine for itching
    - topical steroids
    - oral immunosuppressants
- Chronic Urticaria:
- Oral antihistamines
- Oral immunosuppressants

Treatment Failure

What defines treatment failure?

There is no standard classification for either skin disease but you can find different scoring scales in the literature especially in atopic dermatitis (www.fda.gov)

We do know that patients that chronically itch have decreased QOL data similar to those in chronic disease (Erturk, I. E., Arican, O., Omurlu, I. K., & Sut, N. (2012). Effect of the Pruritus on the Quality of Life: A Preliminary Study. *Annals of Dermatology*, *24*(4), 406–412.)

Case Western Reserve University EST. 1826

MetroHealth

Biologics in the Treatment

TABLE I. Biologics either approved or in clinical trials for psoriasis and currently tested for AD

	Agent	Trade name	Target	Drug	Phase	Manufacturer	ClinicalTrials.gov
Psoriasis (on the market)	Infliximab	Remicade	TNF	Anti-TNF mAb	Approved	Janssen	
	Adalimumab	Humira	TNF	Anti-TNF mAb	Approved	Abbott	
	Etanercept	Enbrel	TNF	TNFR-Ig FP	Approved	Amgen/Pfizer	
	Ustekinumab	Stelara	IL-12/IL-23p40	Anti-p40 mAb	Approved	Janssen	
	Apremilast	Otezla	PDE4	Oral small molecule	Approved	Celgene	
Psoriasis (close to the market)	Secukinumab		IL-17A	Anti–IL-17A mAb	Phase III completed	Novartis	NCT01358578
	Ixekizumab		IL-17A	Anti–IL-17A mAb	In phase III	Eli Lilly	NCT01646177
	Brodalumab		IL-17RA	Anti–IL-17RA mAb	In phase III	Amgen	NCT01708629
	Guselkumab		IL-23p19	Anti-p19 mAb	Phase II completed	Janssen	NCT01483599
	Tildrakizumab		IL-23p19	Anti-p19 mAb	In phase III	Merck	NCT01722331
	BI 655066		IL-23p19	Anti-p19 mAb	In phase II	Boehringer Ingelheim	NCT02054481
	Tofacitinib	Xeljanz	JAK1 and JAK3	Oral small molecule	Phase III completed	Pfizer	NCT01241591
AD (currently tested)	Dupilumab		IL-4Rα	Anti-IL-4Rα mAb	In phase III	Regeneron	NCT01949311
	Ustekinumab	Stelara	IL-12/23p40	Anti–p40 mAb	In phase II	Janssen	NCT01806662
	ILV-094		IL-22	Anti–IL-22 mAb	In phase II	Pfizer	NCT01941537
	CIM331		IL-31R	Anti–IL-31R mAb	In phase II	Chugai	NCT01986933
	BMS-981164		IL-31	Anti–IL-31 mAb	In phase I	BMS	NCT01614756
	Apremilast	Otezla	PDE4	Oral small molecule	In phase II	Celgene	NCT02087943
	QGE031		IgE	Anti-IgE mAb	Phase II completed	Novartis	NCT01552629
	OC000459		CRTH2	Oral CRTH2 antagonist	In phase II	Atopix	NCT02002208
	AMG 157		TSLP	Anti-TSLP mAb	Phase I completed	Amgen	NCT00757042
	MK-8226		TSLPR	Anti-TSLP receptor mAb	In phase I	Merck	NCT01732510

CRTH2, Chemoattractant receptor-homologous molecule expressed on T_H2 cells; *FP*, fusion protein; *JAK*, Janus kinase; *TSLP*, thymic stromal lymphopoietin; *TSLPR*, thymic stromal lymphopoietin receptor.

Dupilumab

- For the treatment of atopic dermatitis
- Approved in Feb 2017
- MOA: binds to the alpha subunit of the IL-4 receptor blocking IL4 and IL13 pathway
- Side effects include allergic reactions, cold sores and inflammation of the cornea
- Reported 75% improvement or greater in 12 weeks

SOLO1 & SOLO2 Trials

Omaluzimab

- For the treatment of IgE mediated asthma
- Has only shown occasional improvement in atopic dermatitis patients
- MOA: monoclonal antibody which binds to free IgE
- Approved in 2003 for asthma
- More recently received approval for chronic urticaria
- Has box warning for late anaphylaxis

Drawbacks to the biologics

- Cost - these drugs literally cost thousands of dollars per injection and require insurance prior authorization
- They require in office injection
- In the case of omaluzimab - there is a risk of late anaphylaxis and long-term risk of cancer is still questionable

What to do when biologics fail?

Unfortunately we still revert to immunosuppressives because we don’t have other options……

Question 1

Atopic Dermatitis is a disease that:

A. Is directly caused by allergic disease

B. Always requires a referral to an allergist

C. First line therapy involves restoring the skin barrier

D. Requires aggressive symptom control

E. Both C & D

Question 1

Atopic Dermatitis is a disease that:

A. Is directly caused by allergic disease

B. Always requires a referral to an allergist

C. First line therapy involves restoring the skin barrier

D. Requires aggressive symptom control

E. Both C & D

Question 2

Omaluzimab is a humanized monoclonal antibody that was previously allowed to be self-administered. Currently, the FDA requires that patients receiving omaluzimab to:

A. Have a current epinephrine auto-injector and be familiar with its use

B. Be observed in the office for a 2 hour wait period for the first three injections

C. Be observed in the office for every injection for 4 to 6 hours

D. A & B

E. A & C

Question 2

Omaluzimab is a humanized monoclonal antibody that was previously allowed to be self-administered. Currently, the FDA requires that patients receiving omaluzimab to:

A. Have a current epinephrine auto-injector and be familiar with its use

B. Be observed in the office for a 2 hour wait period for the first three injections

C. Be observed in the office for every injection for 4 to 6 hours

D. A & B

E. A & C

Question 3

.The reason we are talking about atopic dermatitis and chronic urticaria today is:

A. Treatment failures can be easily managed with biologic therapies

B. Most providers are comfortable with using systemic therapies involving biologics and immunosuppressants for refractory cases of both

C. There are typically effective treatments for both conditions primary care providers should be familiar with

D. A & C

E. B & C

Question 3

.The reason we are talking about atopic dermatitis and chronic urticaria today is:

A. Treatment failures can be easily managed with biologic therapies

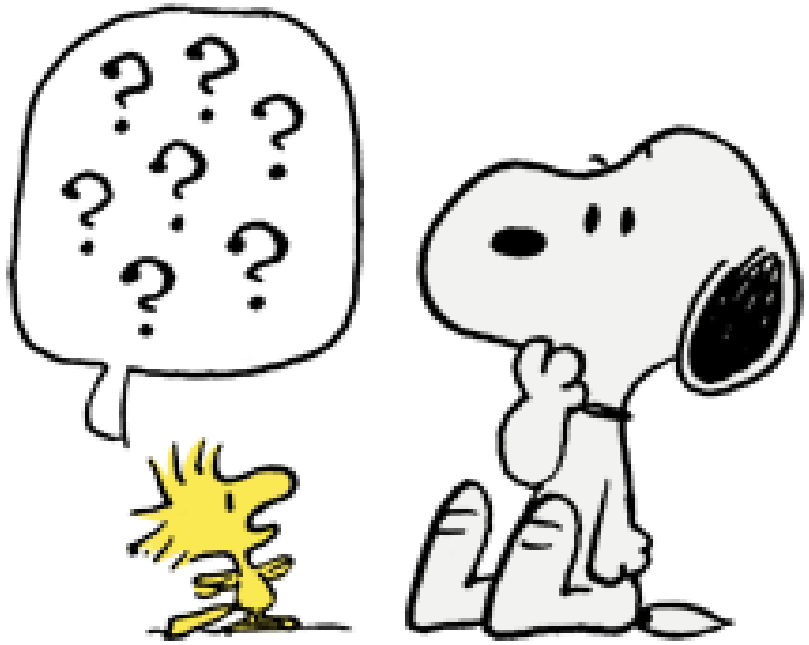
B. Most providers are comfortable with using systemic therapies involving biologics and immunosuppressants for refractory cases of both

C. There are typically effective treatments for both conditions primary care providers should be familiar with

D. A & C

E. B & C

Questions? AND Thank You!



CASE WESTERN RESERVE UNIVERSITY EST. 1826

MetroHealth