AN APPROACH TO URTICARIA AND ANGIOEDEMA

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Disclosures

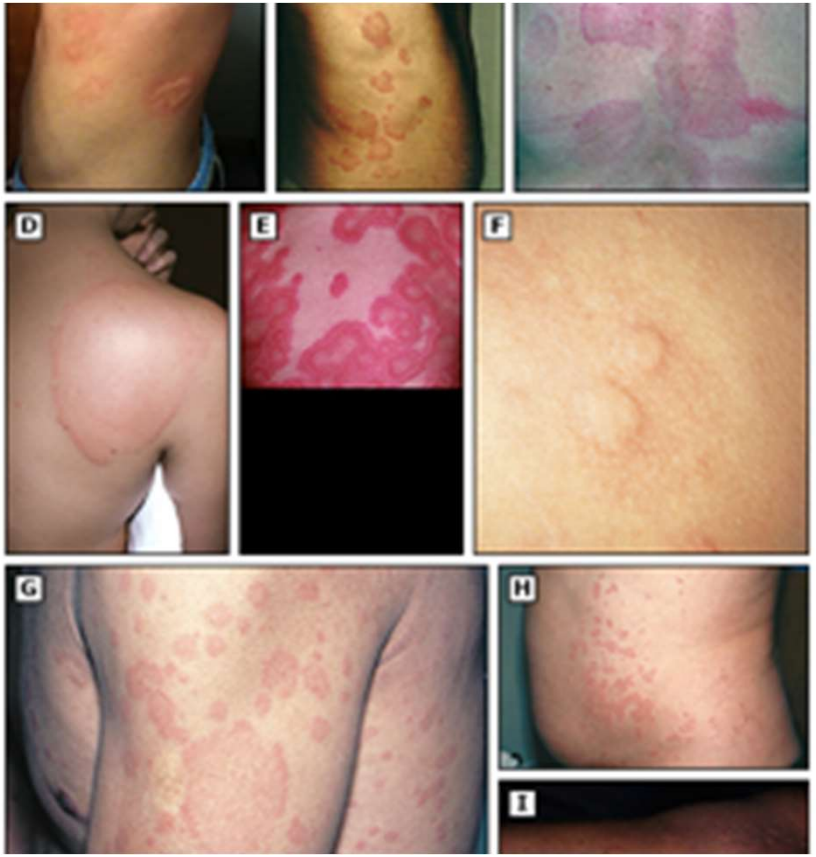
- Speaker honorarium for Medexus (Rupatadine)
- Advisory board for Sanofi Genzyme (Dupilumab)

OBJECTIVES

- Recognize acute and chronic urticaria
- Identify allergic and non-allergic etiologies of urticaria and angioedema
- Discuss recommendations for the management urticaria and angioedema

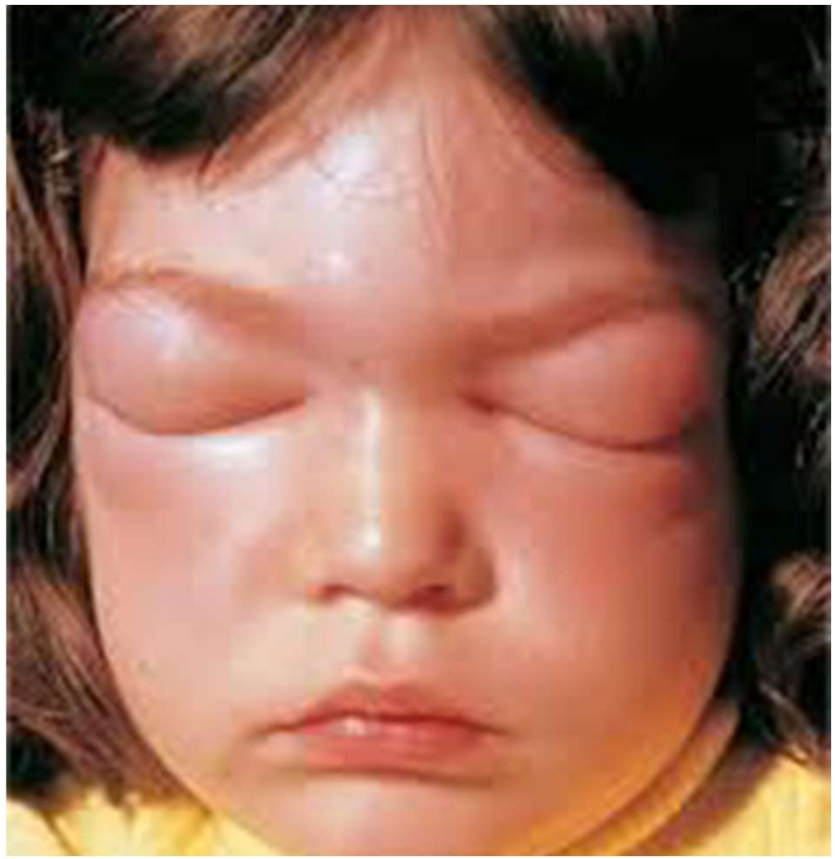
URTICARIA

- Central swelling surrounded by erythema
- Pruritic
- Lasting < 24 hours



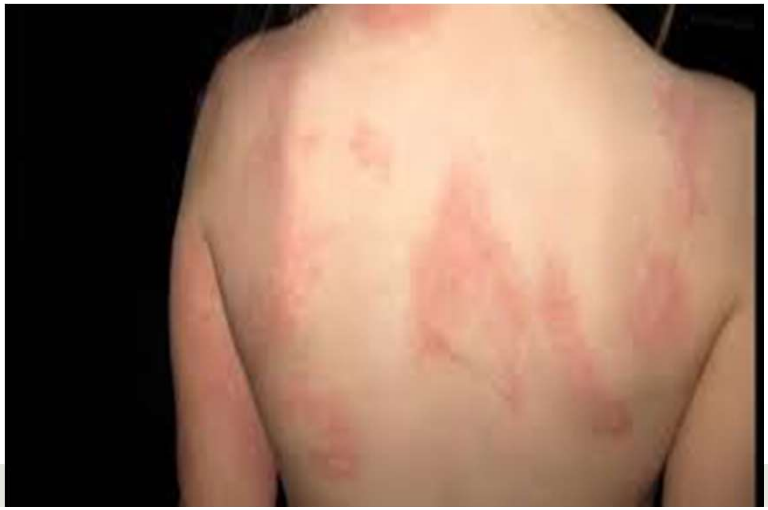
ANGIOEDEMA

- Swelling of lower dermis
- Pain or pruritus
- Commonly involves face, lips, tongue, eyelids, genitals, hands and feet



CASE #1

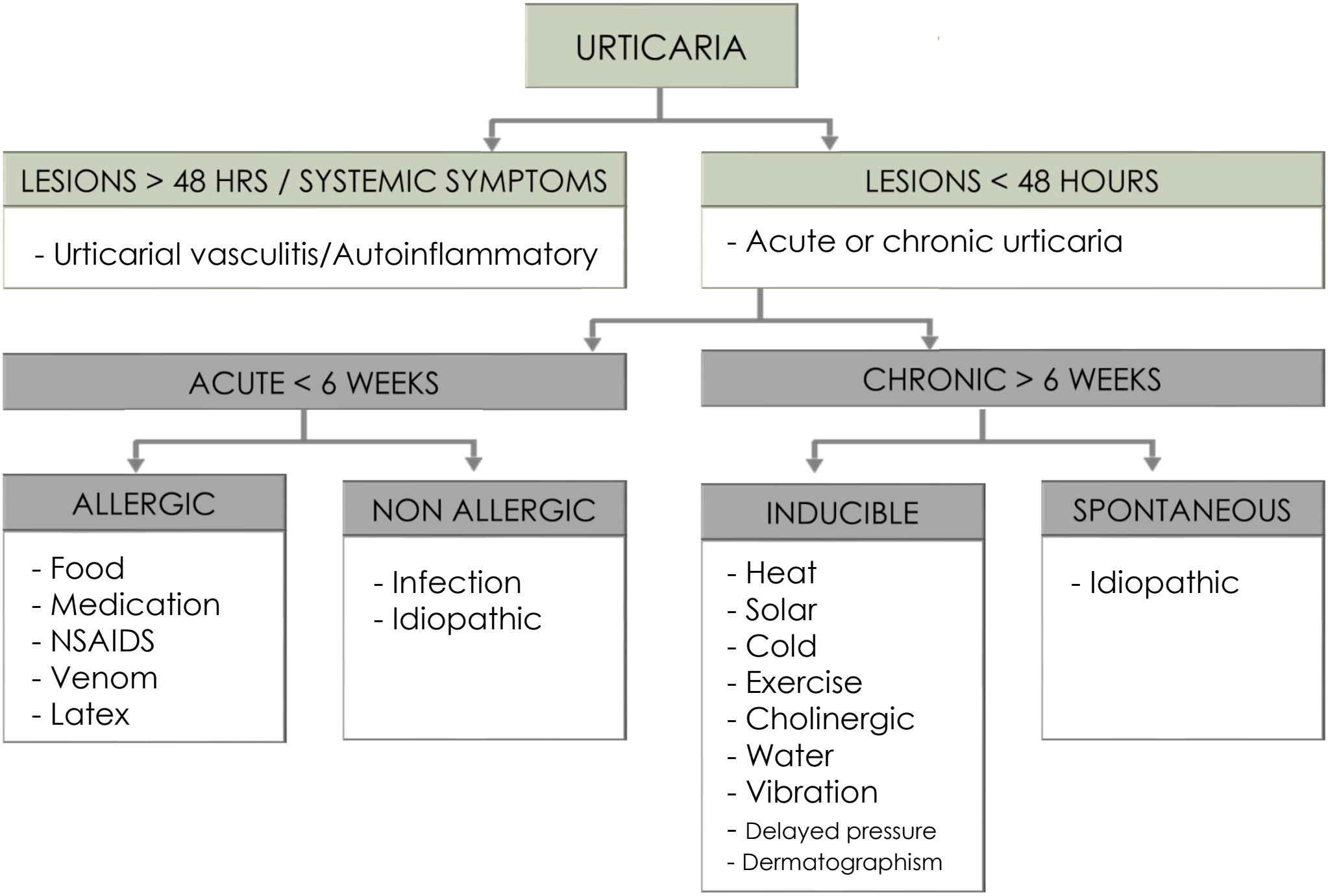
- 2 year old had his second exposure to peanut butter
- Within 10 minutes developed urticaria and wheeze
- Assessed in the emergency room



MCQ #1

- In this scenario, which is the most important first line treatment for acute management?

a) IM benadryl
b) IV fluids
c) IM epinephrine
d) IV steroids


URTICARIA
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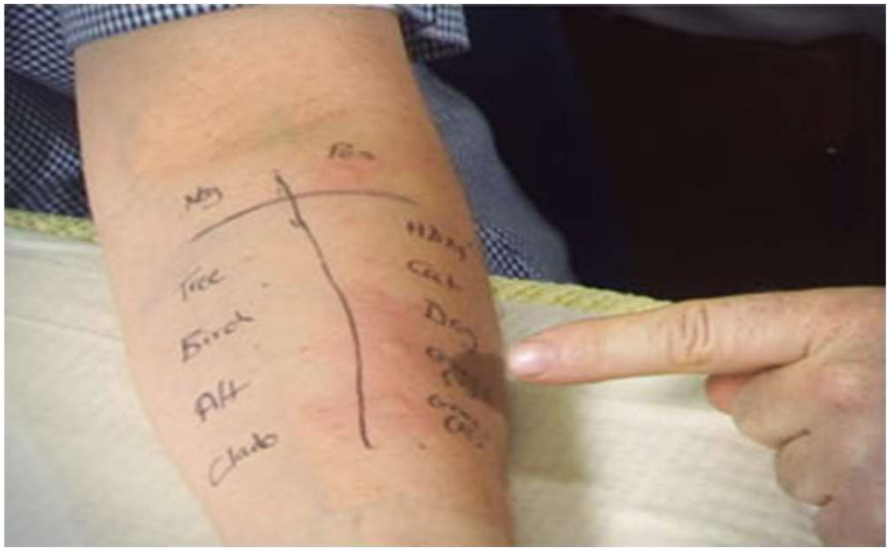
- Urticarial vasculitis/Autoinflammatory
LESIONS < 48 HOURS
- Acute or chronic urticaria
ACUTE < 6 WEEKS
CHRONIC > 6 WEEKS
ALLERGIC
- Food
- Medication
- NSAIDS
- Venom
- Latex
NON ALLERGIC
- Infection
- Idiopathic
INDUCIBLE
- Heat
- Solar
- Cold
- Exercise
- Cholinergic
- Water
- Vibration
- Delayed pressure
- Dermatographism
SPONTANEOUS
- Idiopathic

ACUTE URTICARIA

- Affects up to 20% of the general population
- More likely to have an identifiable trigger
- Skin testing considered ONLY if trigger identified on history



CASE #1

- Diagnosed with anaphylaxis
- Managed with intramuscular epinephrine

- Discharged home with epinephrine autoinjector and referral to an allergist
- Skin testing confirmed peanut allergy
  - Candidate for peanut oral immunotherapy

Epinephrine Autoinjectors

Epipen Jr 0.15mg and 0.3mg

Allerject
0.15mg and
0.3mg
*Back ordered

Emerade* – Approved in Canada Oct 2020
(0.3mg, 0.5mg)
*Voluntary recall

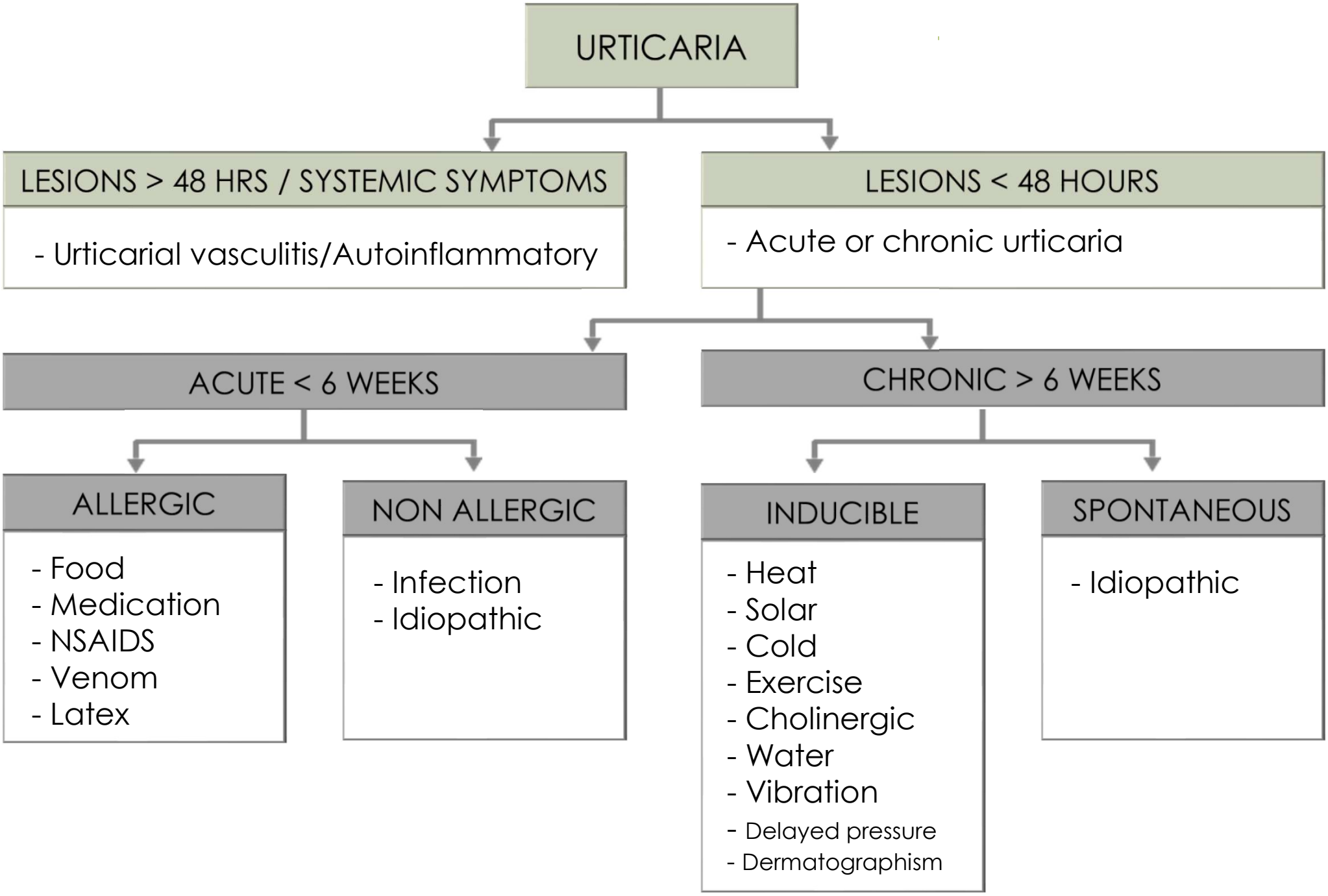
Dosing:
0.15mg for < 25kg
0.3mg for ≥ 25kg
*0.5mg for > 60kg

CASE # 2

- 5 year old presents to ER with 10 day history of urticaria
- Subsides with use of antihistamines but returns within a few hours
- No systemic involvement such as respiratory, GI, CV symptoms
- No allergic trigger identified
- 10 days ago had fever and upper respiratory symptoms

MCQ #2

- What is the most likely cause of this patient's hives?
  a) Wheat allergy
  b) Recent viral illness
  c) Penicillin allergy
  d) Bee sting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INFECTION INDUCED URTICARIA

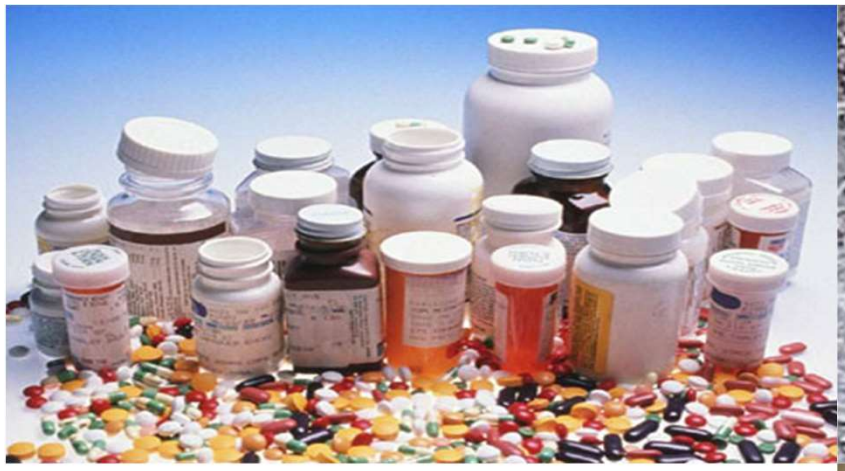
- Infections are associated with over 80% of cases of acute urticaria in some pediatric series
- Viral, bacterial, parasitic infections
- Urticaria may occur before, during or after onset of infections symptoms

INFECTION INDUCED URTICARIA

- Prospective study of 57 consecutive infants aged 1 – 36 month old hospitalized with acute urticaria
- Infectious cause for urticaria identified in 46 of 57 cases
  - 5 adenovirus, 5 Epstein Barr virus, 3 enterovirus, 3 RSV
  - 1 rotavirus, 1 varicella zoster virus, 1 E coli
  - **27 possible viral illness**

Mortureux et al. Acute urticaria in infancy and early childhood. Arch Dermatol. 1998:134;319 - 323

ACUTE URTICARIA MANAGEMENT



ACUTE URTICARIA MANAGEMENT

- 2/3 of cases are self limiting and resolve spontaneously
- Second generation antihistamines are first line
  - E.g. Cetirizine, loratadine, desloraradine, fexofenadine
  - Minimally sedating
  - Minimal anticholinergic effects
  - Few significant drug-drug interactions
  - Require less frequent dosing compared with first-generation antihistamines ie Benadryl

ACUTE URTICARIA MANAGEMENT

- Antihistamine dose increased two – four-fold for refractory cases

Table 2 Antihistamines commonly used and indicated for the treatment of urticaria

Second-generation H1-receptor antihistamines	Standard adult dose (mg daily)	4 times standard adult dose (mg daily)	Usual pediatric dose
Cetirizine (Reactine)	10–20	40	5–10 mL (1–2 teaspoons) daily (children's formulation)
Desloratadine (Aerius)	5	20	2.5–5 mL (0.5–1.0 teaspoon) daily (children's formulation)
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Rupatadine (Rupall)	10	40	5–10 mL (1–2 teaspoons) daily (children's formulation)

Kanani et al. Allergy Asthma Clin Immunol 2018, 14(Suppl 2):59

ACUTE URTICARIA MANAGEMENT

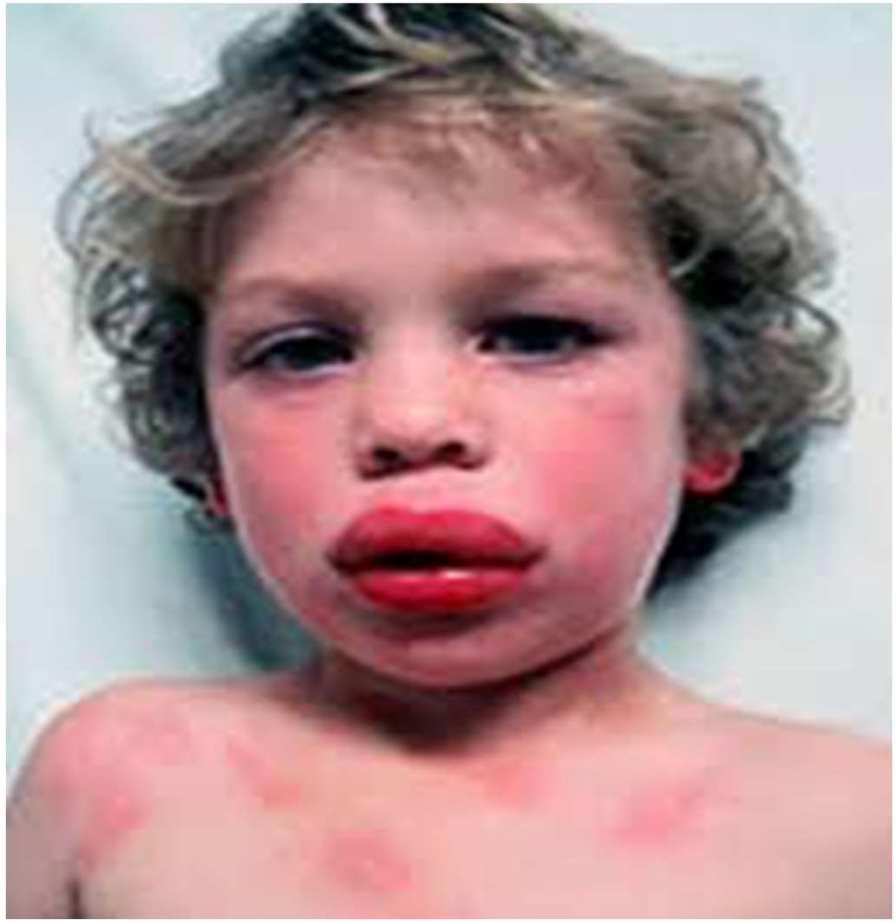
- Oral steroids
  - Severe and refractory cases
  - Ex prednisolone 0.5 – 1mg/kg/day maximum 60mg for 5 – 7 days

CASE # 2

- Diagnosed acute urticaria likely secondary to viral illness
- Managed with daily cetirizine 5mg twice daily until the urticaria resolved
- Urticaria returned 6 months later with another viral infection
- Family managed at home with cetirizine

CASE #3

- 5 year old male developed urticaria at daycare
- Lip angioedema
- No respiratory, GI or CV symptoms
- Called ambulance
- Assessed in the ER



CASE #3

- Managed with epinephrine, diphenhydramine, ranitidine and corticosteroids
- Urticaria resolved approximately 3 hour after assessment
- Discharged home with epinephrine autoinjector
- Continued to have daily urticaria for 8 weeks
- Using diphenhydramine daily plus topical corticosteroid

MCQ #3

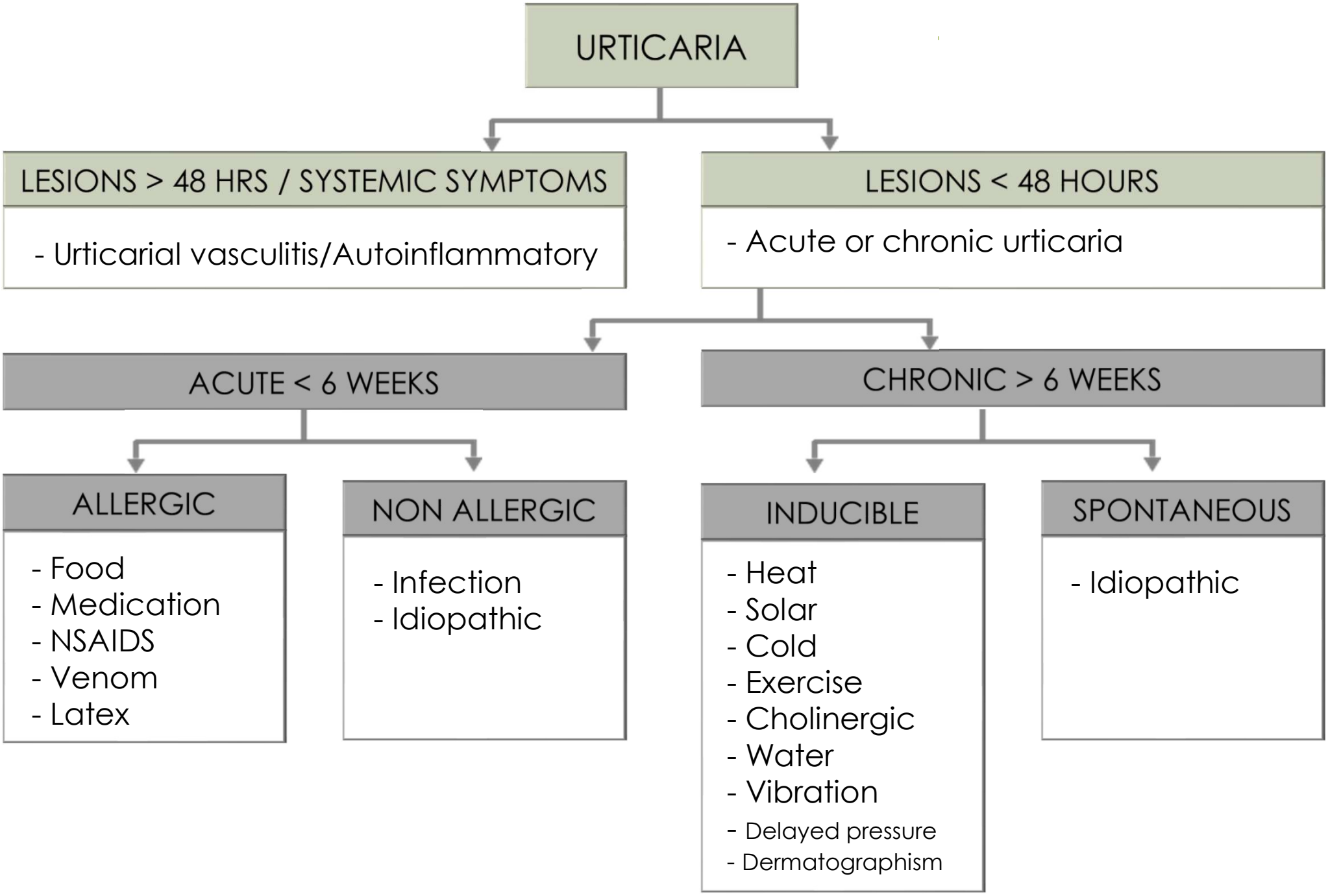
- If a patient is having daily hives despite once daily anti-histamine (ie Reactine 10mg), what would be the next best step in management?

a) Add Benadryl once daily

b) Course of oral prednisone for 7 days

c) Cut out all milk and wheat from their diet

d) Increase Reactine to 10mg twice daily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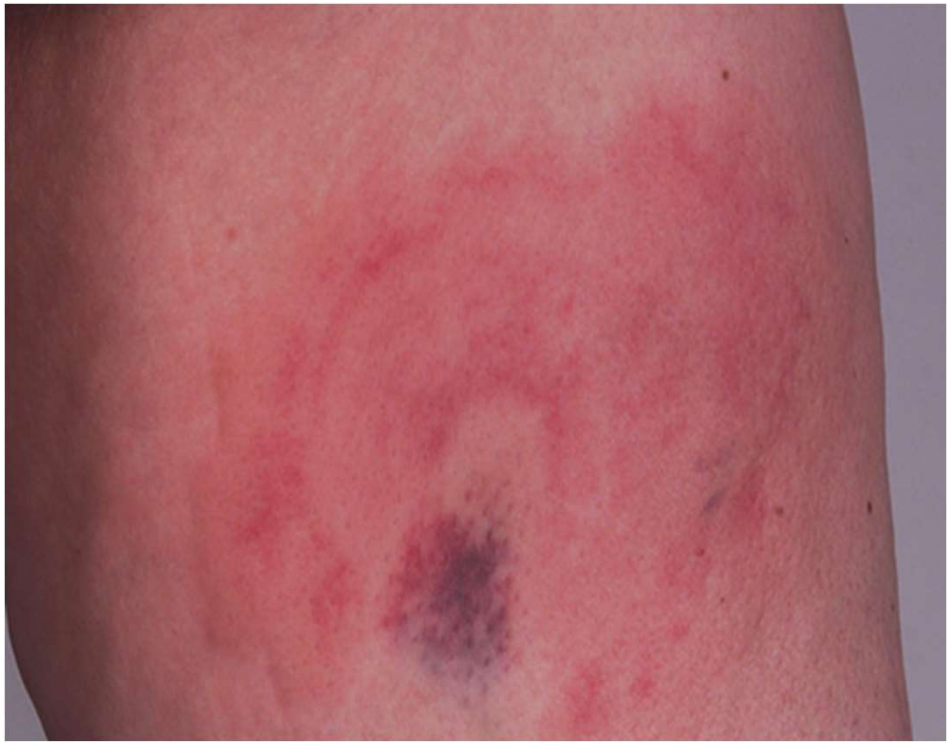
CHRONIC URTICARIA

- Affects 0.5 – 1% of the general population
- Identifiable trigger in < 2% of patients with chronic urticaria
- Angioedema with urticaria in up to 2/3 of patients

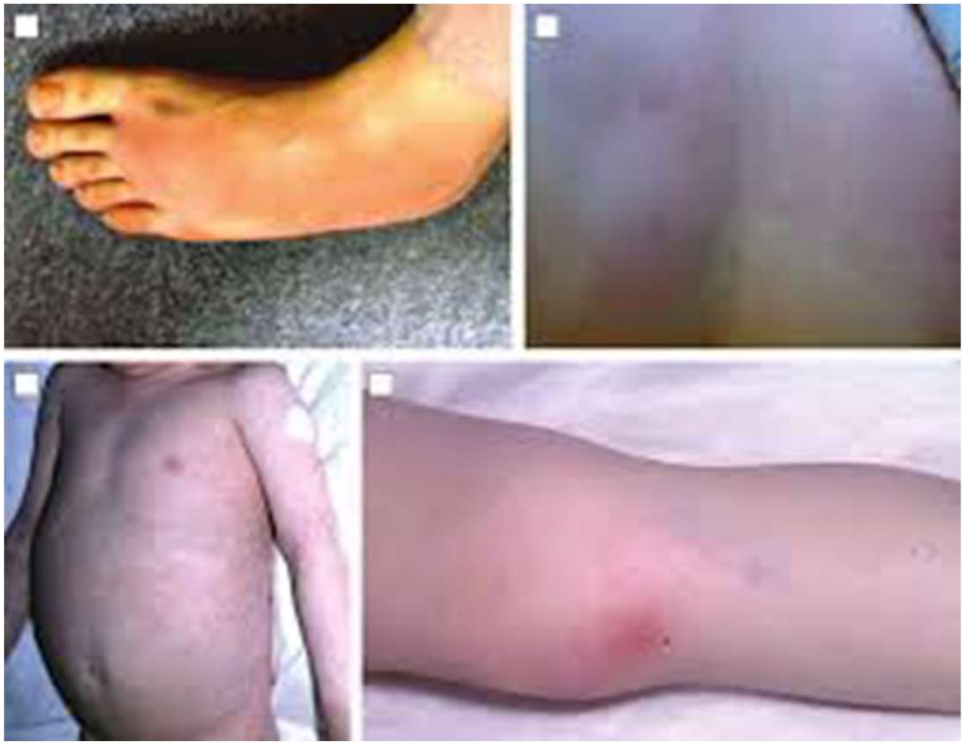
Zuberbier et al. Methods report on the development of the 2013 revision and update of the EAACI/ GA2LEN/ EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy* 2014;69:e1-29.

DIFFERENTIAL DIAGNOSIS

- Urticarial vasculitis

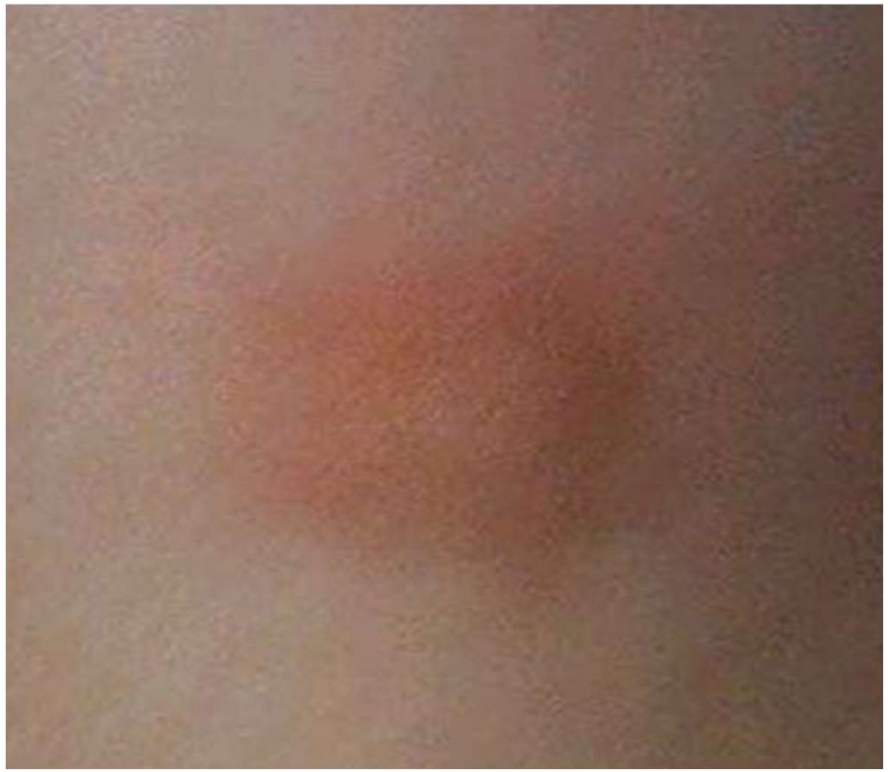


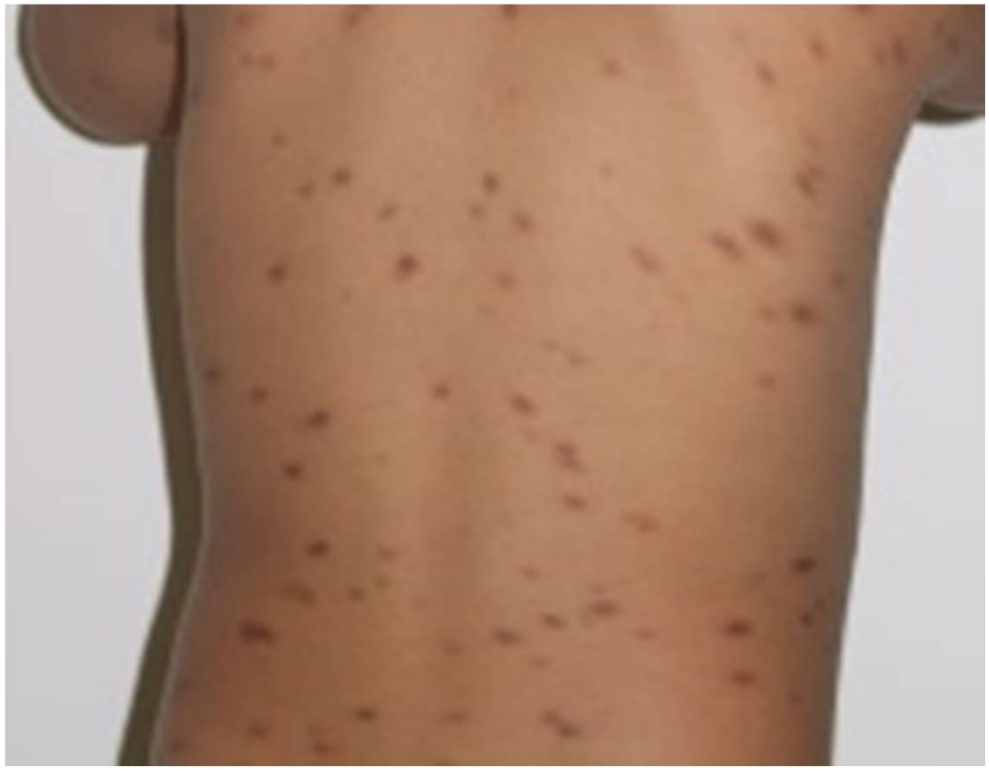
- Autoinflammatory syndromes



DIFFERENTIAL DIAGNOSIS

- Cutaneous or systemic mastocytosis



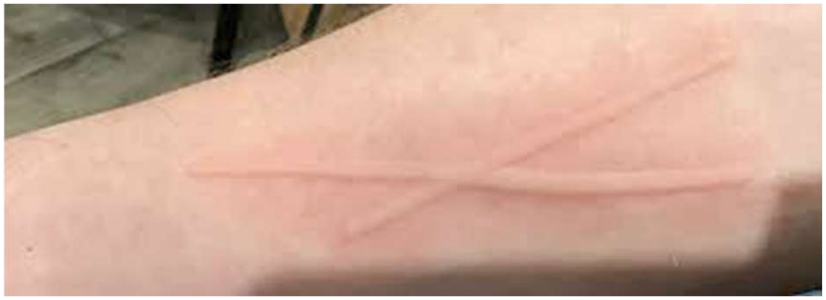


EVALUATION

- Clinical diagnosis

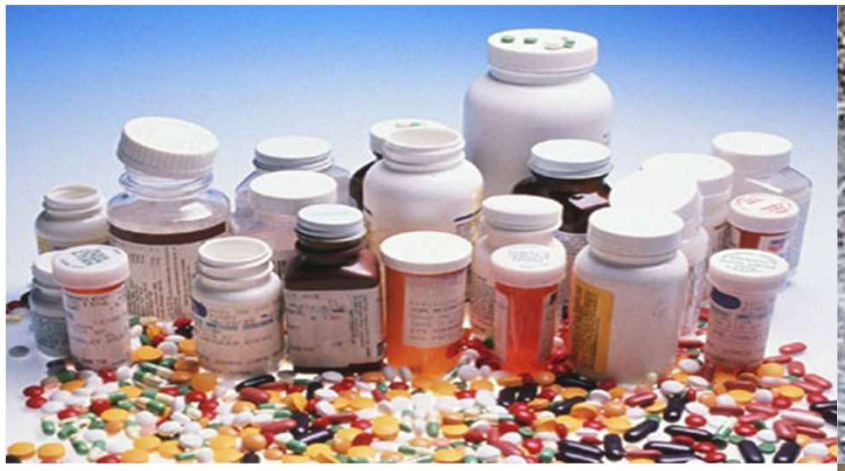
EVALUATION

- Skin testing
  - Skin testing for possible allergen ONLY if obvious trigger
- Rule out systemic disorders
  - CBC, CRP, TSH, T4
  - GI symptoms: Celiac screen
- Inducible urticaria
  - Provocation testing
- Urticarial vasculitis
  - Skin biopsy

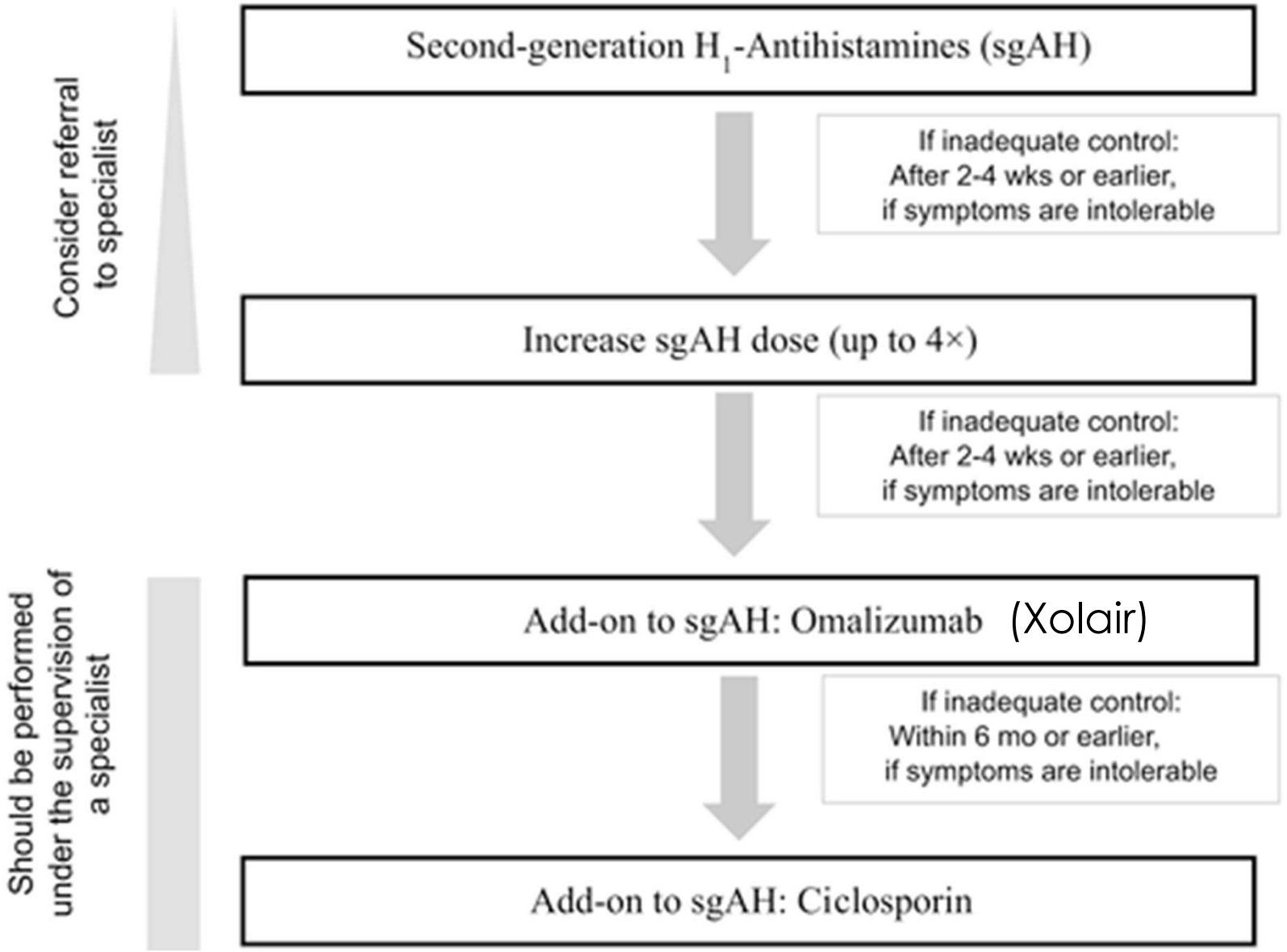


Dermatographism

CHRONIC URTICARIA MANAGEMENT



Chronic urticaria guidelines



The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73:1393–1414.

H1 ANTIHISTAMINES

- Daily second generation non sedating antihistamines preferred for treatment of urticaria
- Standard doses fail to control symptoms in ~50%

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Kanani et al. Allergy Asthma Clin Immunol 2018, 14(Suppl 2):59

THIRD LINE THERAPIES

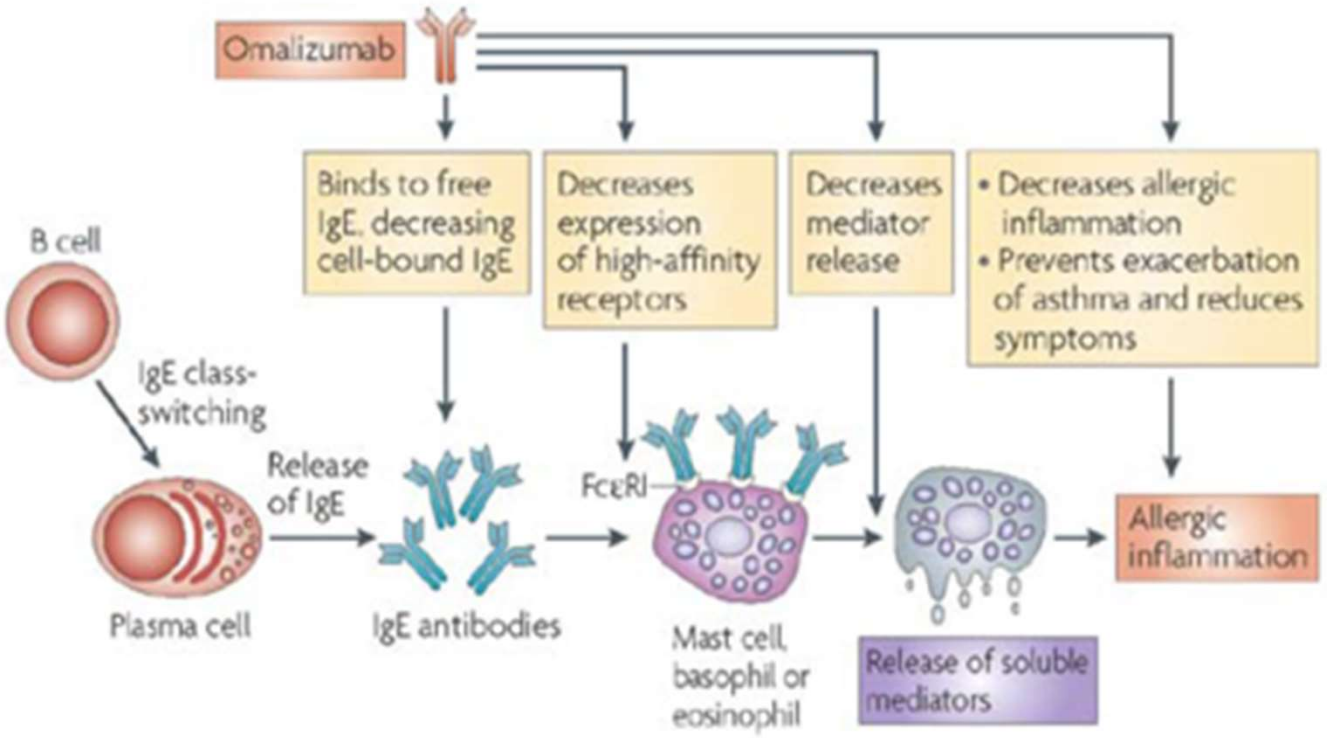
- Up to 1/3 remain symptomatic with four fold second generation non-sedating antihistamines
  - Ie Reactine 20mg BID, Aerius 10mg BID
- H2 antihistamines
  - No evidence to support the use of ranitidine for the management of urticaria
- Leukotriene receptor antagonist
  - Trial of montelukast as add on therapy to second generation H1-antihistamines
  - Low level of evidence

THIRD LINE THERAPIES

- Anti-inflammatory medications
  - Includes dapsone, sulfasalazine or hydroxychloroquine
  - Low side effect profile but often not effective
- Immunosuppressive therapies
  - Cyclosporine can be tried as add on therapy to second generation H1-antihistamines
  - Oral corticosteroids maximum 10 days (topical not effective)
  - High side effect profile
- IVIG (Limited evidence)

THIRD LINE THERAPIES

- Omalizumab (Xolair)
  - Anti-IgE monoclonal antibody subcutaneous injection



PROGNOSIS

- **Chronic Spontaneous Urticaria (CSU)**
  - Previously called "Chronic Idiopathic Urticaria"
  - 50% spontaneous remission within 1 year
  - 10 – 25% recurrent urticaria > 5 years
  - 30% may have angioedema
  - 10% may present as only angioedema (responds to anti-histamine)

PROGNOSIS

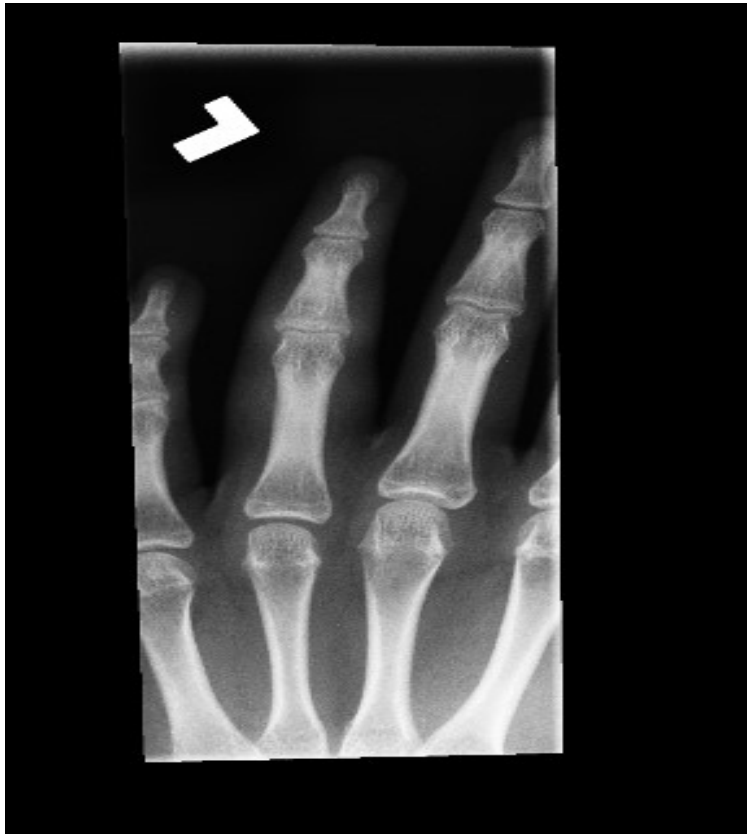
- **Refractory chronic urticaria**
  - More severe symptoms
  - Concurrent angioedema
  - Concurrent inducible urticaria

CASE #3

- Referred to allergy clinic for chronic urticaria
- No trigger identified
- CBC, TSH, T4, CRP normal
- Managed with cetirizine 10mg BID for 3 months then tapered
- Does not need epinephrine autoinjector or topical corticosteroids

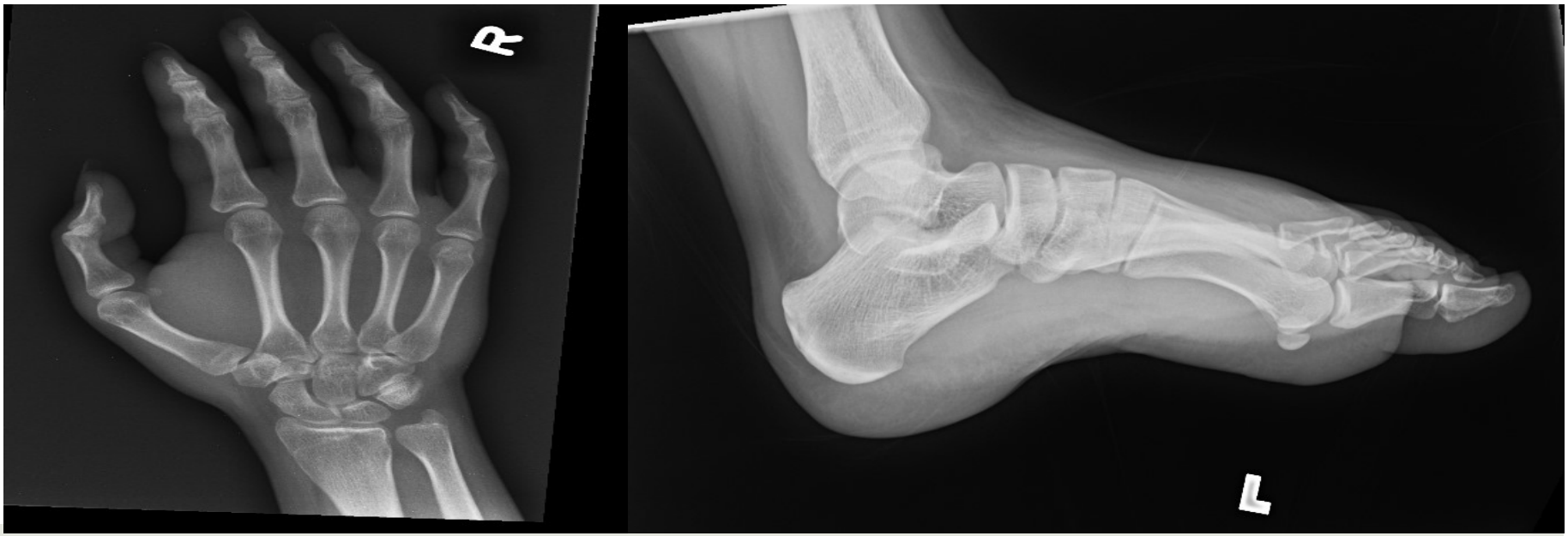
CASE # 4

- 17 year old female
- First episode of hand swelling age 12 while in karate



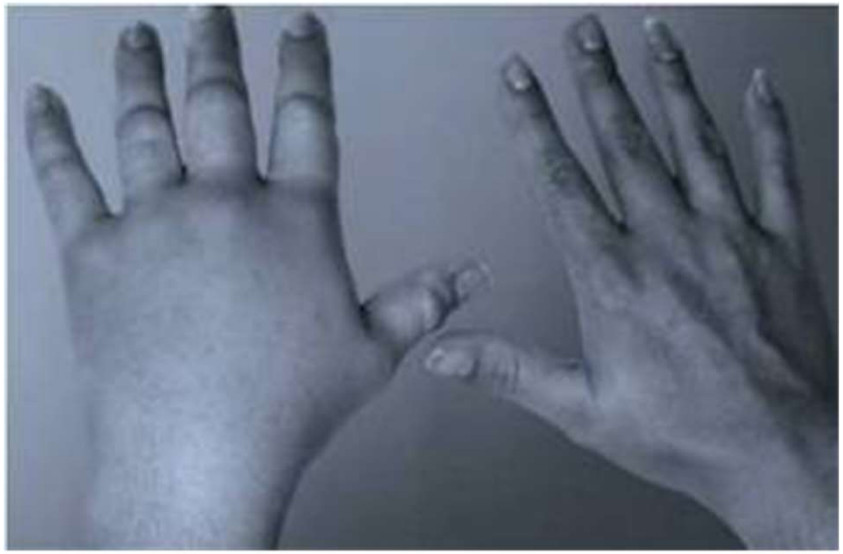
CASE # 4

- 4 subsequent visits to ER during adolescence for significant swelling provoked with minimal trauma
- Swelling last approximately 4 days, resolve



CASE # 4

- Significant upper extremity swelling following bloodwork
- Referred to ER for US to rule out neurovascular compromise
- Labeled “allergic” to estrogen containing OCP



MCQ #4

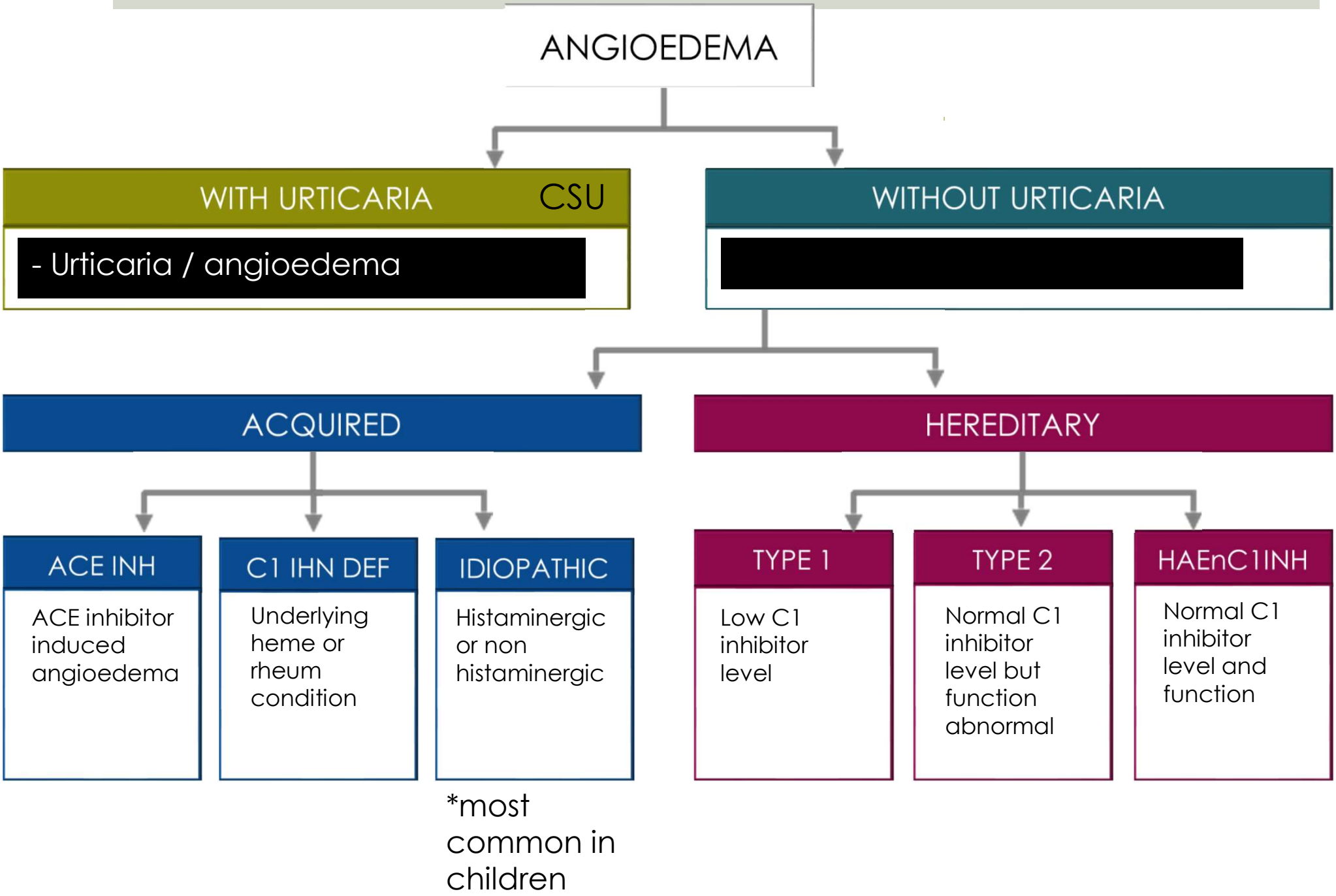
- What is the most common cause of angioedema in children?

a) Medications

b) Hereditary angioedema

c) Viral trigger

d) Autoimmune disease

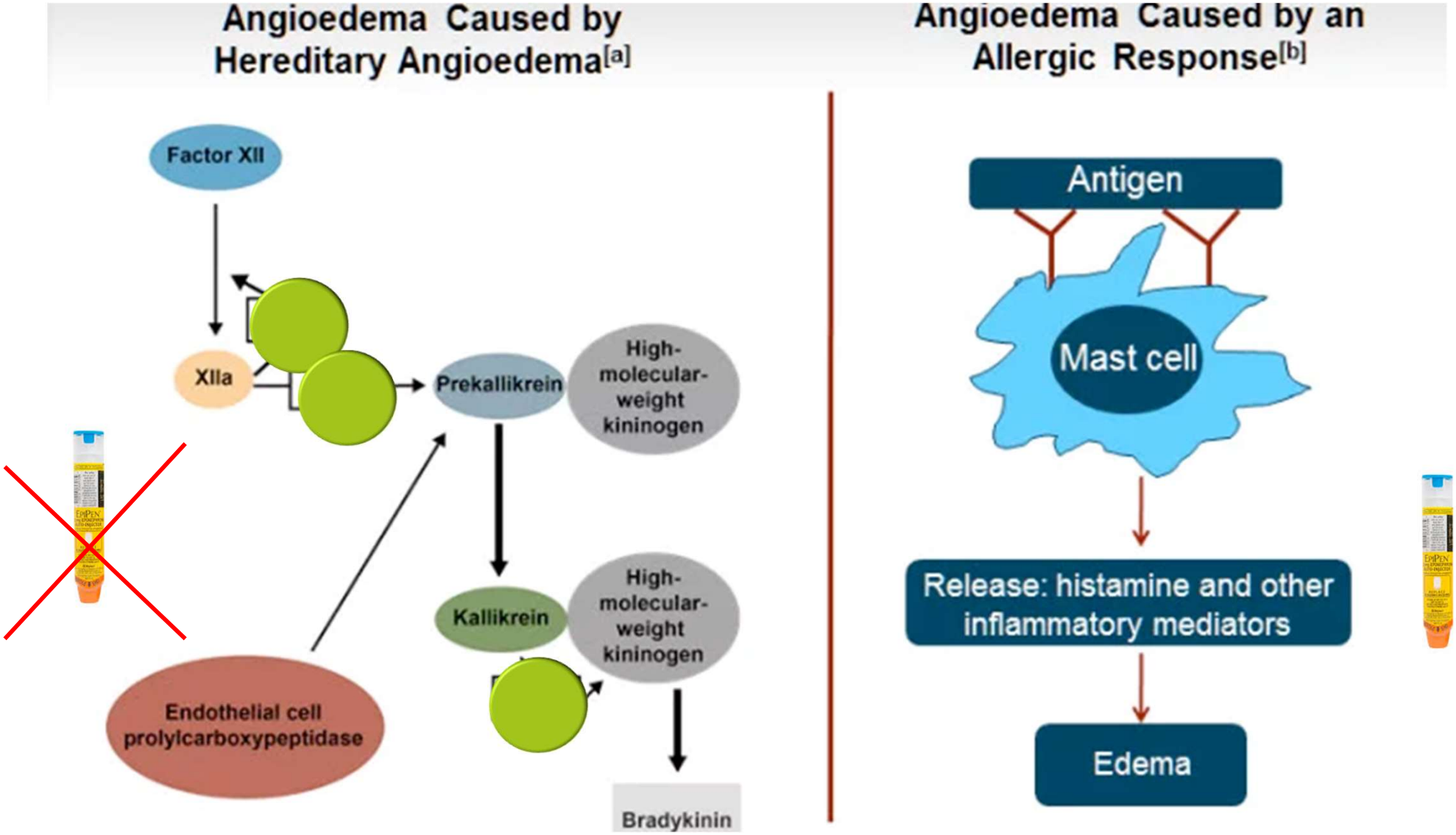

ANGIOEDEMA
WITH URTICARIA
CSU
- Urticaria / angioedema
WITHOUT URTICARIA
ACQUIRED
HEREDITARY
ACE INH
ACE inhibitor induced angioedema
C1 IHN DEF
Underlying heme or rheum condition
IDIOPATHIC
Histaminergic or non histaminergic
*most common in children
TYPE 1
Low C1 inhibitor level
TYPE 2
Normal C1 inhibitor level but function abnormal
HAEnC1INH
Normal C1 inhibitor level and function

HEREDITARY ANGIOEDEMA

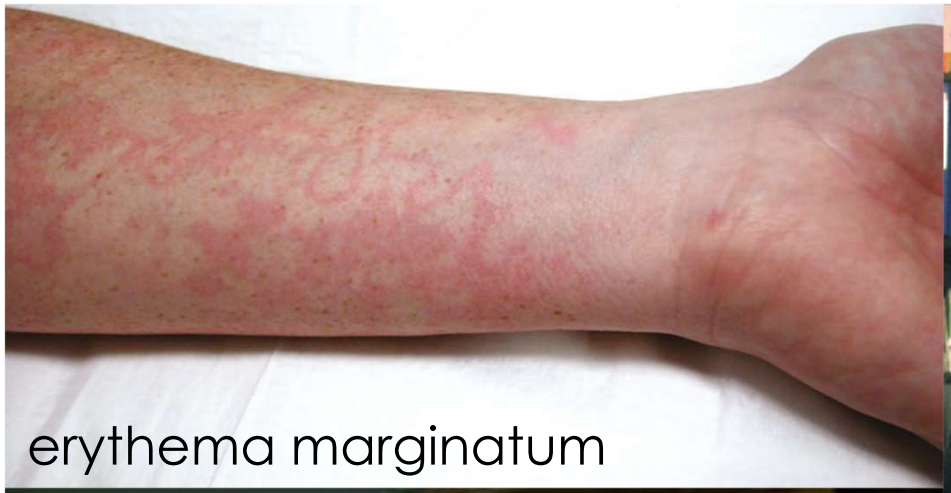
- Autosomal dominant disorder caused by C1 inhibitor deficiency / dysfunction
- Resulting from a mutation in the C1inhibitor gene
- 25% of cases arise from spontaneous mutations
- Prevalence 1 : 50,000

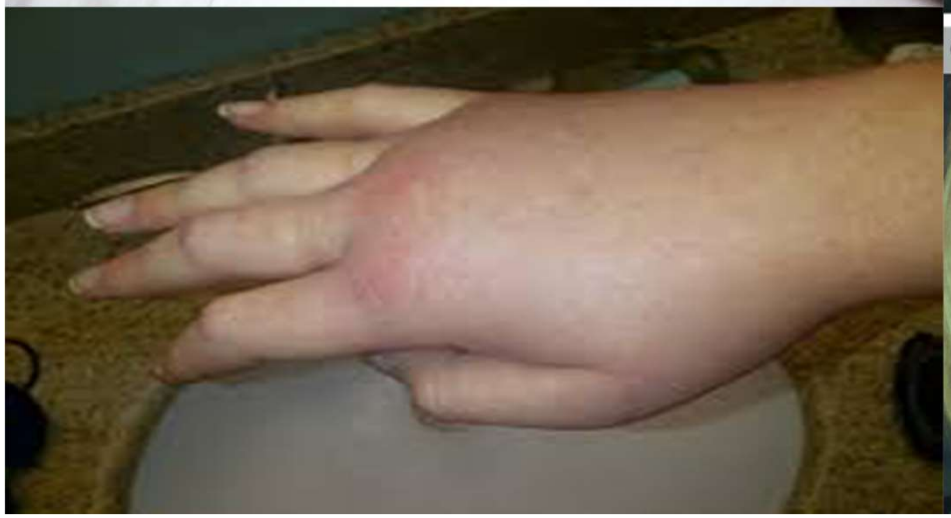
Bowen T et al. Ann Allergy Asthma Immunol. 2008;100 (suppl 2):S30-S40

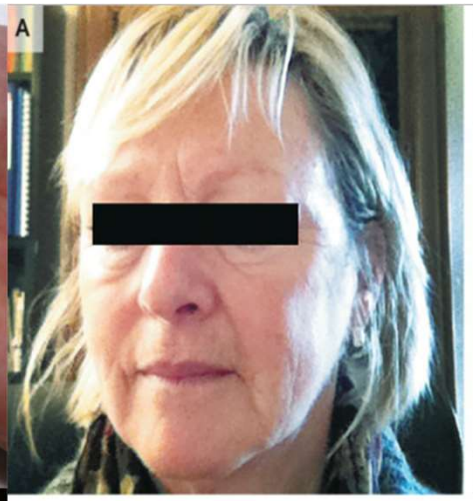
Bradykinin pathway

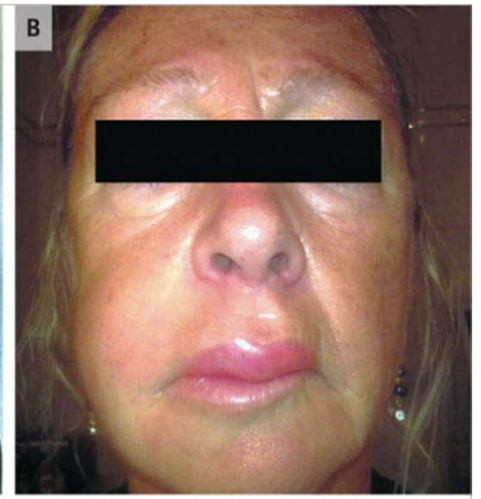


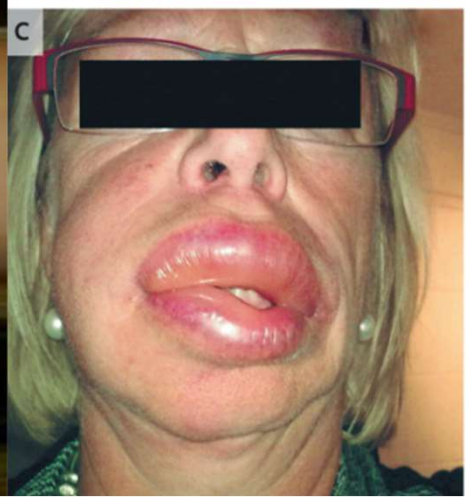
CLINICAL PRESENTATION

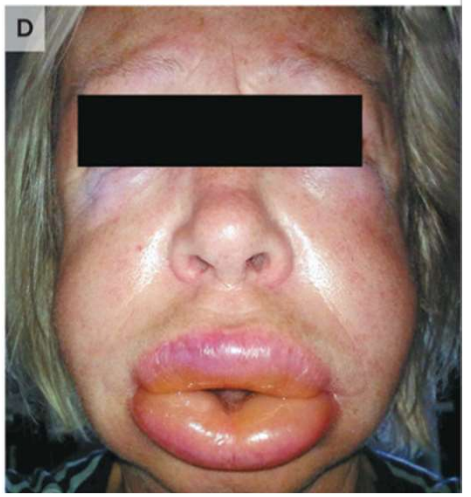












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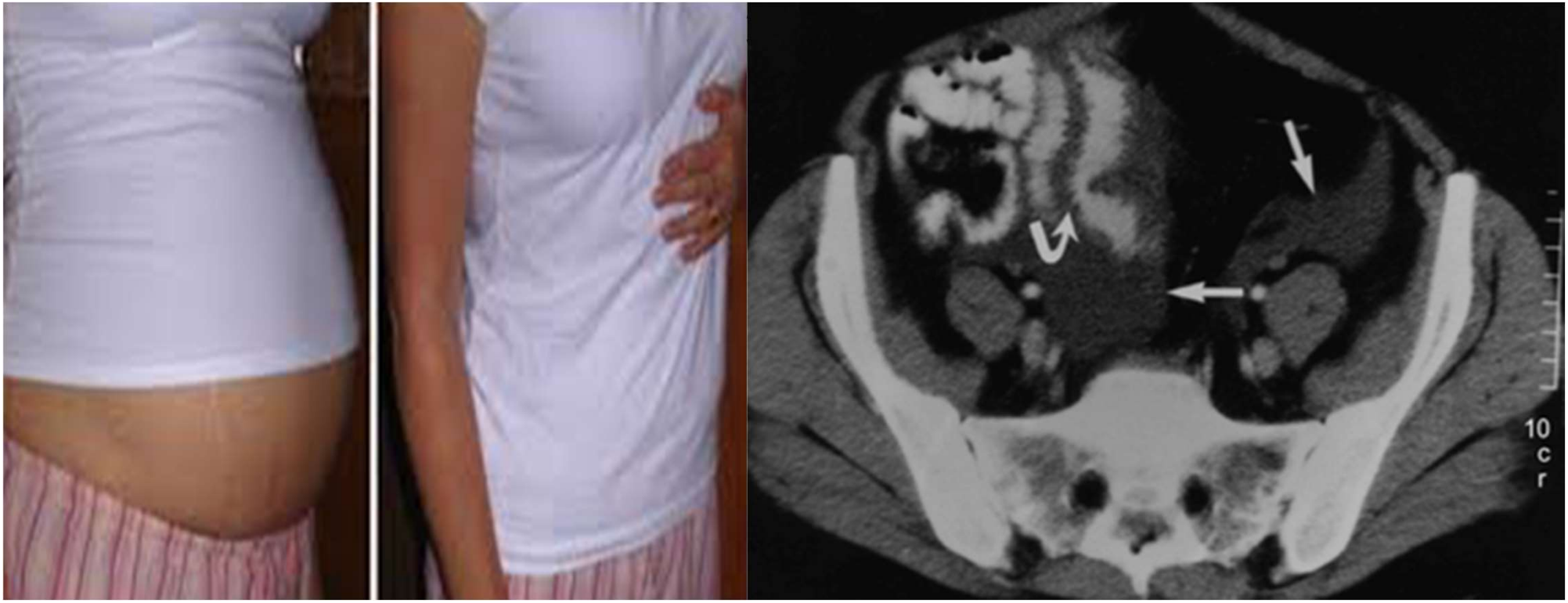
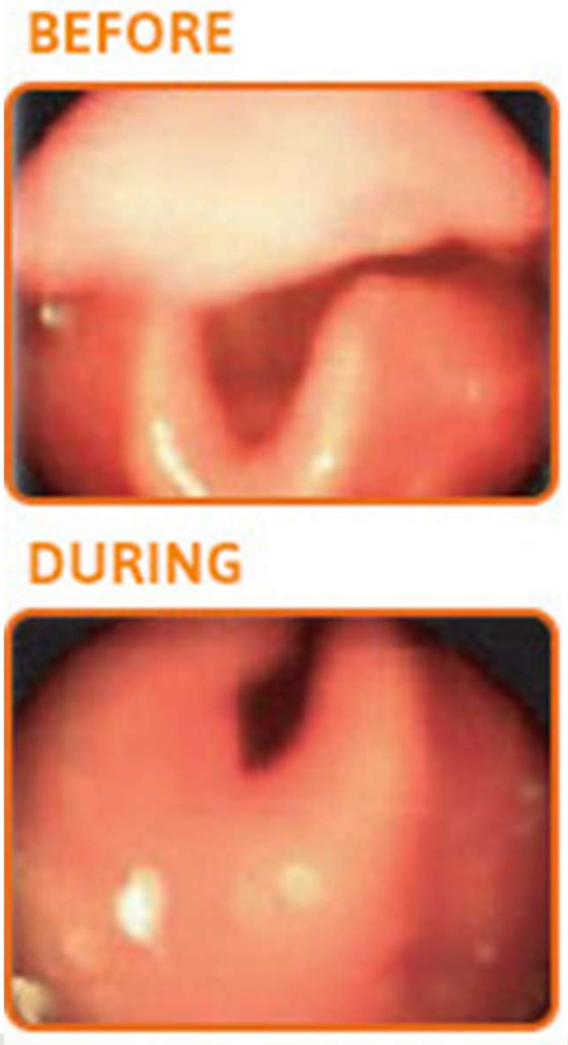


CLINICAL PRESENTATION

- Sites of involvement: upper airway
- 50% of patients will have at least 1 laryngeal attack in their lifetime



CLINICAL PRESENTATION

- Episodic non pruritic angioedema without urticaria
- 75% have first attack by age 15 years old
- Triggered by trauma, stress, infection, ACE inhibitors, estrogen, puberty, dental work/surgery, vaccines
- Develops over 12 – 36 hours, last 1 – 3 days
- Frequency varies from weekly to once per year

SCREENING

- Indications for screening
  - Recurrent angioedema without urticaria
  - Unexplained recurrent episodes of self-limited abdominal pain
  - Unexplained laryngeal angioedema (even a single episode)
  - Family history of angioedema

INVESTIGATIONS

- C4 level
- C1 inhibitor antigenic level (C1-INH)
- C1 inhibitor functional assay
- C1q if acquired angioedema considered
- Genetics for mutations in SERPING1 or factor X11

INVESTIGATIONS

	C4	C1 INH Level	C1INH Function	C1 q
HAE Type 1 (85%)	↓	↓	↓	Normal
HAE Type 2 (15%)	↓	Normal	↓	Normal
HAE normal C1 INH - FX11 mutation - Unknown	Normal	Normal	Normal	Normal
Acquired angioedema	↓	↓	↓	↓
ACE inhibitor	Normal	Normal	Normal	Normal
Histamine / idiopathic	Normal	Normal	Normal	Normal

** C4 is reduced in 98% of cases for HAE 1 and HAE 2 and nearly 100% of the time during an attack

TREATMENT

The International/Canadian Hereditary Angioedema Guideline
Betschel et al. Allergy Asthma Clin Immunol (2019) 15:72

HAE-specific treatment	Product name and company	Mechanism of action	Approved indications	Dose and route of administration	County licensed and age indications
pdC1-INH	Berinert®[a] (CSL)	Replaces C1-INH	Acute treatment	20 U/kg intravenous	Australia, Canada, EU, USA (adult and pediatric)
			Pre-procedural	Adults: 1000 U Pediatrics: 15 to 30 U/kg body weight	EU (adult and pediatric)
	Cinryze® (Shire—now part of Takeda)	Replaces C1-INH	Acute treatment	≥ 12 years: 1000 U intravenous 2–11 years: 1000 U (> 25 kg body weight) 500 U (< 25 kg body weight)	Australia (≥ 12 years) EU (≥ 2 years)
			Pre-procedural	≥ 12 years: 1000 U intravenous 2–11 years: 1000 U (> 25 kg body weight) 500 U (< 25 kg body weight)	Australia (≥ 12 years) EU (≥ 2 years)
			Long-term prophylaxis	1000 U intravenous q 3–4 days (6–11 years 500 U q 3–4 days)[b]	Australia, Canada (≥ 12 years) EU, USA (≥ 6 years)
	Haegarda® (CSL)	Replaces C1-INH	Long-term prophylaxis	60 U/kg body weight twice weekly (every 3–4 days)	Australia[c], Canada, EU[d], USA (≥ 12 years)
rhC1-INH	Ruconest® (Ruconest)	Replaces C1-INH	Acute treatment	50 U/kg intravenous (< 84 kg); 4200 U intravenous (≥ 84 kg)	EU (adults), USA (adults and adolescents)
Ecallantide	Kalbitor® (Shire—now part of Takeda)	Selective, reversible inhibitor of plasma kallikrein	Acute treatment	30 mg (3 × 10 mg/1 ml) subcutaneous injections	USA (≥ 12 years)
Icatibant	Firazyr® (Shire—now part of Takeda)	Synthetic selective and specific antagonist of bradykinin 2 receptor	Acute treatment	30 mg subcutaneous injection; dose-adjusted for adolescents < 65 kg and children ≥ 2 years[e]	USA (≥ 18 years) Australia, Canada, EU (≥ 2 years)
Lanadelumab	Takhzyro® (Shire—now part of Takeda)	Fully human monoclonal antibody that binds plasma kallikrein and inhibits its proteolytic activity	Long-term prophylaxis	300 mg subcutaneous injection every 2 weeks a dosing interval of 300 mg every 4 weeks may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months	Australia, Canada, EU, USA (≥ 12 years)

***New Canadian guidelines coming out Sept 2024*

ACUTE ATTACKS

- **pdC1 inhibitor (Berinert®)**
  - MOA: Plasma derived C-INH replacement
  - Dose: 20 units/kg IV
- **Icatibant (Firazyr®)**
  - MOA: Synthetic selective and specific antagonist of bradykinin 2 receptor
  - Dose: 30 mg SQ injection
    - dose-adjusted for adolescents < 65 kg and children ≥ 2 years

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ACUTE ATTACKS

	Laryngeal Attack	**Abdominal Attack**	**Cutaneous Face/Neck**	**Cutaneous Extremity/Trunk**
Observation	X	X	X	✓
Acute treatment - C1-INH - Icatibant - Ecallantide	✓	✓	✓	✓
ICU - Intubation - Tracheotomy	✓ If indicated	X	X	X

**** All laryngeal attacks must be assessed in the ER**

Bowen et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy, Asthma & Clinical Immunology. 2010;6:24

SHORT TERM PROPHYLAXIS

Short Term Prophylaxis

Minor Manipulations

If plasma-derived C1 inhibitor (pdC1INH) immediately available:
- No prophylaxis needed

If pdC1INH not available:
Prophylaxis for five days before and two to 5 days post event
- Danazol (avoid during first two trimesters of pregnancy; 2.5-10 mg/kg/day, maximum 600 mg daily)
- Stanozolol 4-6 mg/day

Major Procedures or Intubation:

Plasma-derived C1 inhibitor (pdC1INH)
Give one to six hours before procedure*
(optimum dose not yet established – see text)
Second dose of pdC1INH should be immediately available

If pdC1INH not available:
Danazol prophylaxis as per minor and
Solvent/detergent treated plasma (SDP; if not available, then fresh frozen/frozen plasma but less safe than SDP) one to six hours before procedure*
10 ml/kg; 2-4 units (400-800 ml) for an adult
***as close to procedure as feasible**

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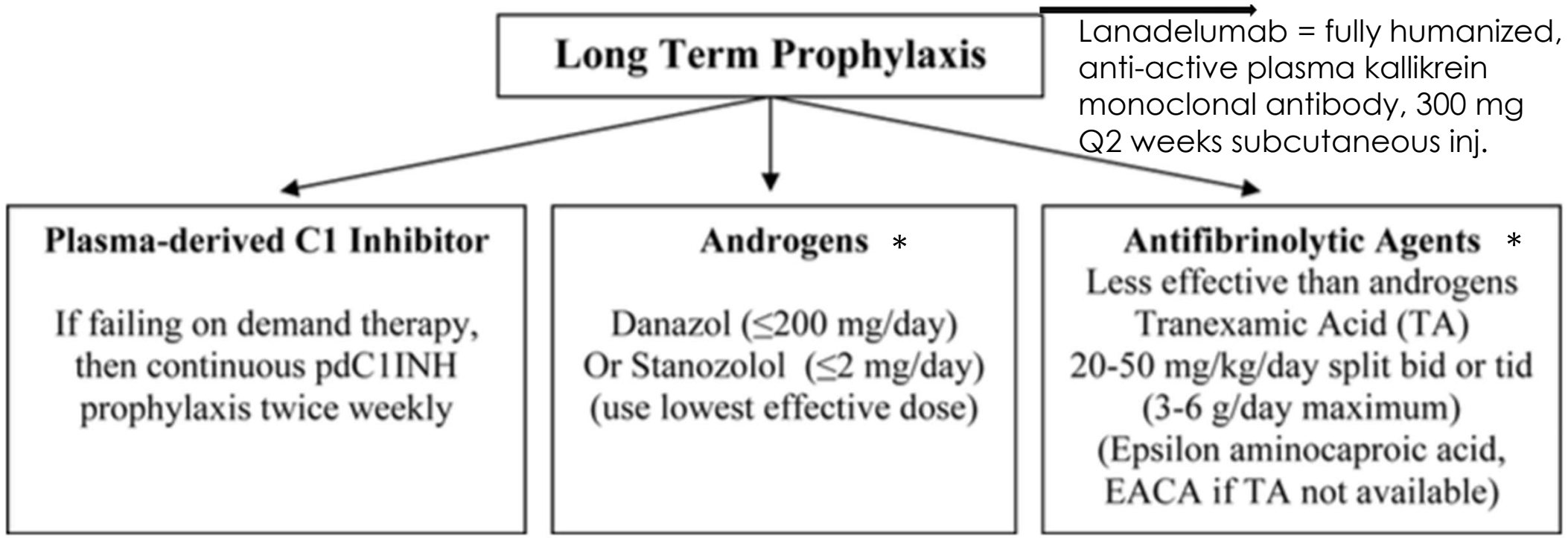
LONG TERM PROPHYLAXIS



First line: pd-C1 INH or Landelumab

*2nd line (Lower level evidence)

*Orladeyo is also a new oral prophylaxis option approved in Canada now

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PROGNOSIS - HAE

- Prognosis is variable
- Attacks generally continue throughout the patient's life, although the frequency of attacks can be dramatically reduced by therapy
- Prior to the introduction of effective therapies for HAE, up to 1/3 patients died of asphyxiation
- Important that all patients have an acute management plan (ie ER letter from specialist re: treatment, notify local bloodbank)

CASE #4

- Referred to Allergy / Immunology 10 years after the onset of symptoms

	Patient	**Reference Range**
C4	**0.04**	0.15 – 0.57 g/L
C1 inhibitor level	**< 0.048**	0.15 – 0.35 g/L

Dx: HEREDITARY ANGIOEDEMA

SUMMARY -1

- Acute urticaria more likely to have an allergic trigger such as food, medications, latex, venom
- Chronic urticaria has an identifiable trigger in < 2%
- Initial management of urticaria involves up to 4-fold dosing of non-sedating oral antihistamines

SUMMARY - 2

- Indications to screen for hereditary angioedema
  - Recurrent angioedema without urticaria
  - Unexplained recurrent episodic abdominal pain in patients
  - Any episode of unexplained laryngeal angioedema
  - Family history of angioedema

THANK YOU!

QUESTIONS?

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