Wheals in Motion: Urticaria Assessment and Management

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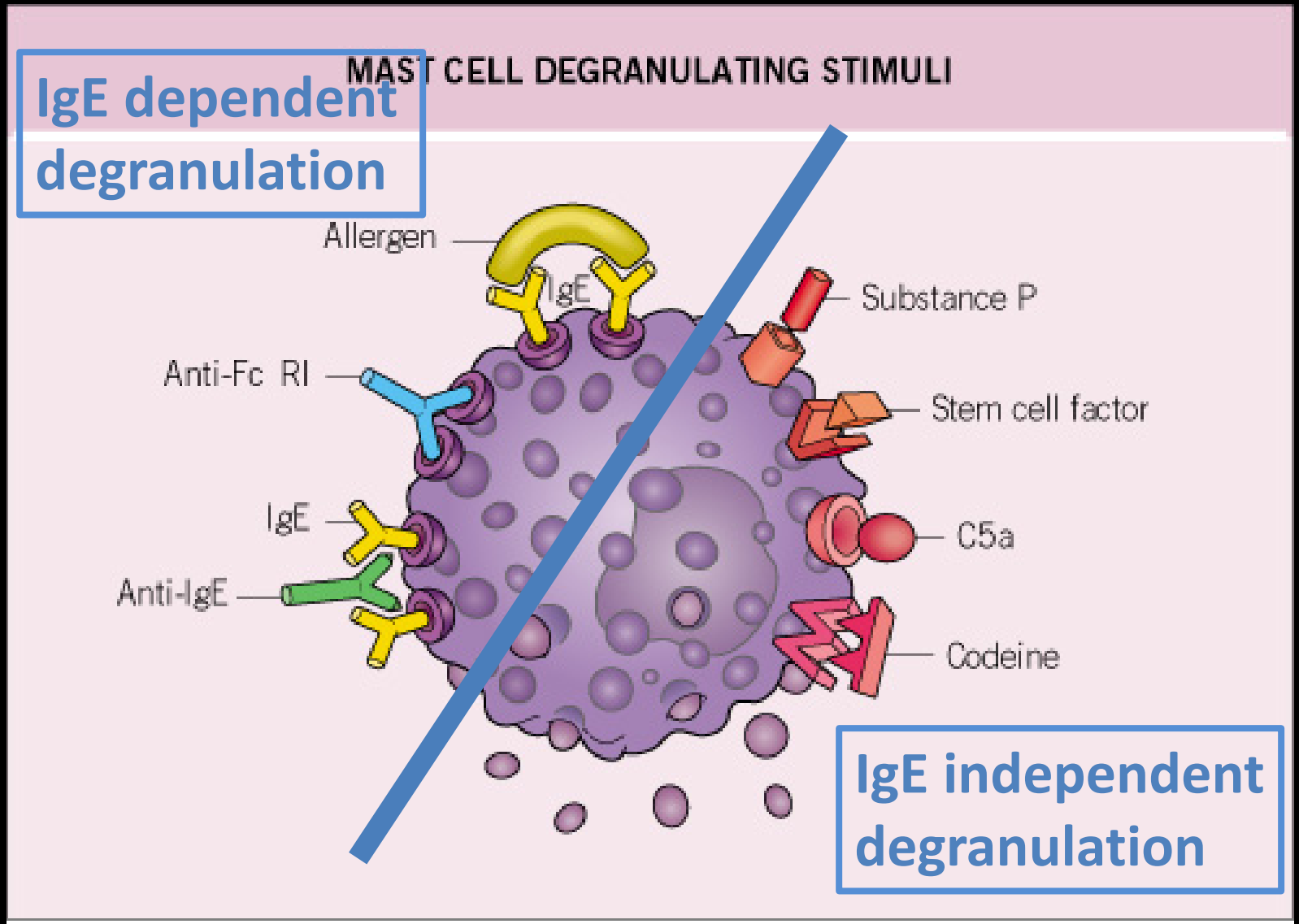
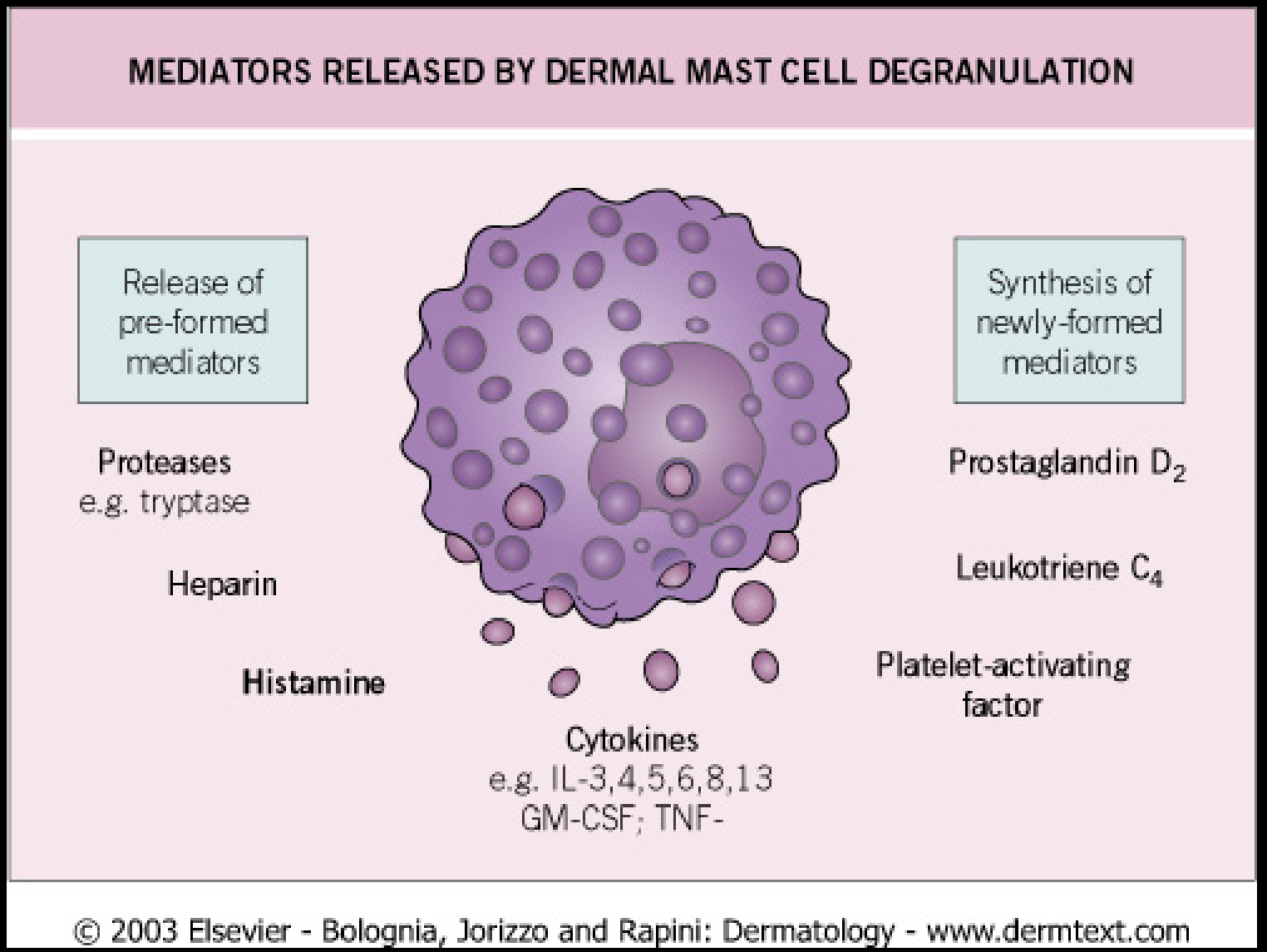
Urticaria

- Moderate to severe impact on quality of life
  - Comparable to severe atopic dermatitis
  - Comparable to coronary artery disease
  - Higher prevalence of depression, anxiety, and sleep difficulties
  - Patients missed 14% of the prior week's work hrs
  - Health care use greatly elevated among those with chronic hives: extra 6 visits per patient in 6months - approx double the rate of controls

Pathogenesis





Vasodilation, leakage of plasma, pruritus

Urticaria Diagnosis

- Acute onset
- Wheals:
  - Swelling & erythema
  - Pruritus/burning sensation
  - Transient (1-24hrs)
- Angioedema (40%)
- Often prominent in dependent areas or in areas of pressure/constriction

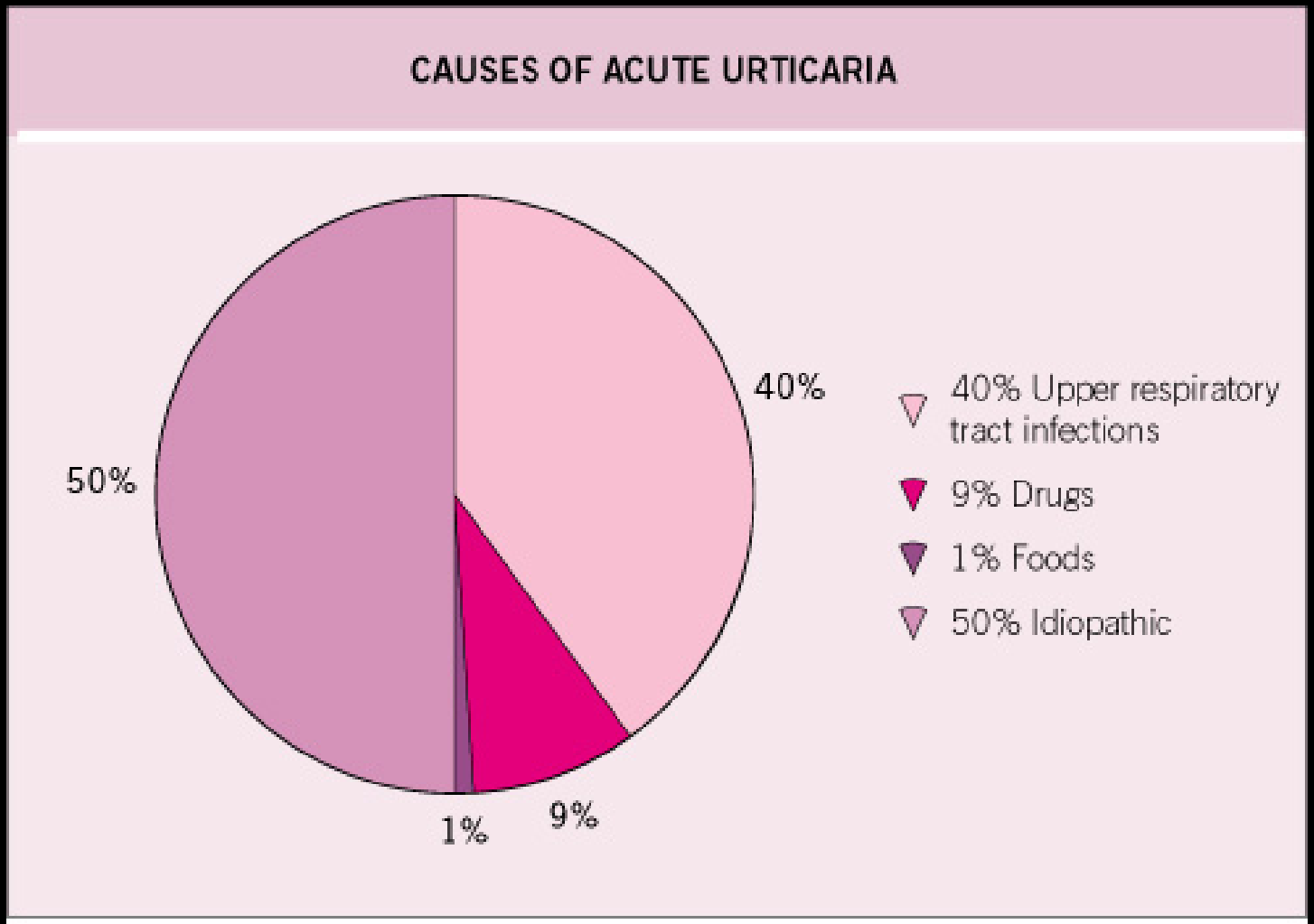
Angioedema: nonpitting edema without associated erythema, often NOT in dependent areas

URTICARIA DIAGNOSIS

Individual wheals last ≤ 24 hours

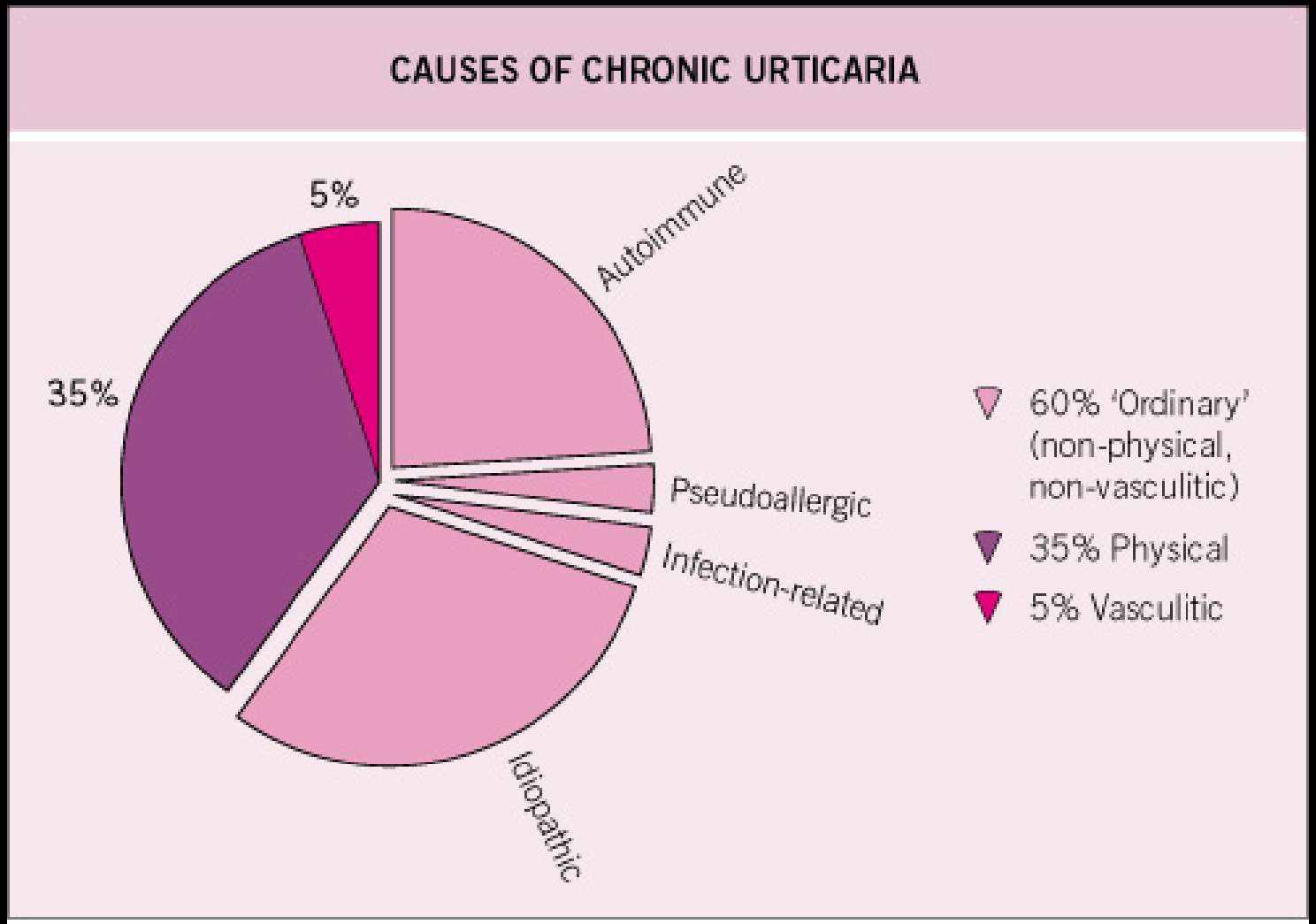
Acute Urticaria

- **<6 weeks -** Incidence: 15-25 %



Chronic Urticaria

- **Chronic > 6 weeks -** ~30% become chronic



Chronic Urticaria - Prognosis

- Spontaneous resolution in ~20-50% within 1 yr
- Divided into inducible/physical urticarias and spontaneous chronic urticaria
  - Inducible/Physical urticaria and autoimmune urticaria have a more prolonged course

Inducbile/Physical Urticarias ~ 20-35%

- Dermatographism: wheal arises moments after scratching skin
  - 2-5% general population, usually asymptomatic

Inducible/Physical Urticarias

- Cholinergic: follows exercise/increased temp, hot water, stress
  - 30% of physical urticarias
  - Distinct morphology – small 2-5 mm macules
  - Teens young adults

Inducible/Physical Urticarias

- Cold - 5-30% of physical urticarias
  - Rare reports of hypotension, death after swimming in cold water reported

Apply ice cube for 5 min – hives develop upon rewarming

Inducible/Physical Urticarias

- Delayed Pressure – angioedema 4-6 hrs post pressure, may last up to 48hrs
- Solar (immediate with UV exposure)
- Vibratory urticaria
- Aquagenic

Spontaneous Chronic Urticaria – Idiopathic/Autoimmune ~75%

- Many have IgG antibodies that crosslink FcЄR1
- Rare patients have anti-IgE antibodies

Presence of antibodies has no predictive effect on response to treatment

Spontaneous Chronic Urticaria - Others ~ ≤ 5%

- Ingestants
- Contactants
- Infections
- Hormonal changes
- Systemic illness
- Occult malignancy

Food allergy testing not indicated

Age-appropriate malignancy screening only

Diagnostic Evaluation of Chronic Urticaria

- Thorough history and physical
- Targeted laboratory testing based upon findings
  - Routine lab screening is controversial but generally not recommended. If performed, limit to
    - CBC with differential
    - Basic metabolic panel
    - CRP, ESR

Treatment

- EDUCATION
- Prevention
  - Avoidance of physical triggers (tight clothing, heat)
  - Avoidance of drugs capable of exacerbating urticaria (NSAIDS, opiate analgesics, etc) when possible
  - Emollients

Treatment - 1st Line

- H1 Antihistamines (large placebo-ctrl'd RCTs)
  - **2nd+ generation (cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine, etc)**
    - **Daily or bid for two weeks, then increase to 4 times standard dose if no response**
    - **May be combined with 1st generation antihistamines**
  - 1st generation (diphenhydramine, hydroxizine)
    - Must be taken 3-4 times daily
    - Sedating, hangover effect

Treatment – 1st line

- Doxepin (tricyclic antidepressant)
  - H1 and H2 antihistamine activity
  - Sedation, anticholinergic effects, increased appetite, QT prolongation
  - Start at 10 mg QHS and slowly increase to max of 75-125 mg QHS

Treatment – 1st line

- H2 antihistamines (cimetidine, ranitidine, famotidine)
  - 15% of histamine receptors in skin are H2 type
  - Inhibits cytochrome p450 enzymes that metabolize 1st generation antihistamines and consequently increase their plasma concentration
  - Not recommended as monotherapy, may provide modest benefit when added to H1-blockers

Treatment – 1st Line

- Systemic corticosteroids
  - Brief use for severe symptoms only
  - Highly effective but no long-term remittive effect
- Epinephrine (0.3mL of 1:1000 IM)
  - Rapidly reverses urticaria and angioedema
  - Patients at risk for life-threatening angioedema or anaphylaxis should have an Epipen

Treatment – 2nd Line

- Leukotriene inhibitors (small placebo-ctrld RCTs)
  - Block leukotriene receptors (which are potent inflammatory mediators)
  - (montelukast, zafirlukast, etc)
  - Not as effective as H1 blockers alone
  - May enhance response when combined with H1 blockers

Treatment – 2nd Line

- Omalizumab (large placebo-ctrld RCTs)
  - Humanized IgG anti-IgE antibody (binds IgE and inhibits its binding to FcЄR-I)
  - 150-300 mg subq Q4weeks
  - Complete/almost complete resolution of symptoms ~66-70%
  - High cost

Treatment – 2nd Line

- Cyclosporine A (small placebo-ctrld RCTs)
  - Inhibits clacineurin --> reduced transcription of inflammatory cytokines
  - 150-300 mg subq Q4weeks
  - Complete/almost complete resolution of symptoms ≥53-70%
  - Toxicities: close hematologic, renal.hepatic monitoring

3nd Line Treatments

DRUG	LEVEL OF EVIDENCE
H2 Blockers (with H1 antihistamine)*	III
Hydroxychloroquine	Ib
Dapsone	Ib
Sulfasalazine	III
Colchicine	III
Mycophenolate mofetil	IIb
IVIG	III
Rituximab	IV
Chronic/frequent corticosteroids	IV

* Pharmacokinetic effect of H2 blocker + 1st generation antihistamines

Urticaria Treatment Approach

1st

- Prevention via elimination of known triggers
- 2nd+ generation antihistamine

2nd

- 4X dose of 2nd generation histamine divided bid
- Add Bedtime 1st generation antihistamine or doxepin

3rd

- If ≥6weeks, perform thorough H&P with ROS, targeted studies, and CBC, ESR, CRP
- If urticaria have atypical appearance/symptoms, consider skin biopsy/alternative Dx
- Add leukotriene inhibitor vs. omalizumab vs. cyclosporine

4th

- Consider 3rd line agent based on severity of symptoms & comorbidities

Chronic Urticaria Differential Dx

- Generalized pruritus – excoriations, but no primary skin lesions
- Flushing – macular erythema, no wheals
- Urticarial vasculitis
  - Lesions typically last >24 hr and resolve with purpura or hyperpigmentation, often tender/painful
  - Biopsy demonstrates leukocytoclastic vasculitis

Urticarial vasculitis

Chronic Urticaria Differential Dx

- Urticarial phase of autoimmune bullous disease

Chronic Urticaria Differential Dx

- Urticaria pigmentosa

Chronic Urticaria Differential Dx

- Hereditary or acquired angioedema – angioedema without urticaria

Chronic Urticaria Differential Dx

- Autoinflammatory/periodic fever syndromes – atypical urticaria, systemic symptoms, family history
  - Familial Mediterranean fever
  - Hyper-IgD syndrome
  - Blau syndrome
  - Familial cold autoinflammatory syndrome
  - Muckle-Wells syndrome
  - Neonatal onset multisystem inflammatory disorder

Urticaria – KEY POINTS

- Major impact on quality of life
- Wheals that last ≤ 24 hours
- Acute urticaria < 6 weeks, Chronic > 6 weeks
- Antihistamines are first line treatment
- Thorough H&P with ROS is most critical diagnostic step
- Exhaustive lab testing is typically unnecessary
- Chronic urticaria typically lasts for years

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Level	Therapy/Prevention, Aetiology/Harm
1a	Systematic review (with homogeneity) of RCTs
1b	Individual RCT (with narrow Confidence Interval)
1c	All or none (ie all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it)
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
2c	"Outcomes" Research or ecologic studies (studies of group ch[ics])
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion or based on physiology, bench research or "first principles"

Oxford Centre for Evidence Based Medicine

Herbs associated with urticaria

- Cranberry
- Echinacea
- Hypericum
- Willow
- Garlic
- Ginger
- Glucosamine
- Horseradish
- Phytoestrogen
- Propolis
- Royal jelly
- Valerian