Acute and Chronic Urticaria, Including New Treatment Options

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October 19, 2018
Disclosures

I have no relevant financial relationships to disclose.

I will be discussing OFF LABEL DOSING for H1 antihistamines that are already FDA approved for the treatment of Urticaria.
Acute/Chronic Urticaria: Outline

- Urticaria: Definitions
- Signs/Symptoms of Urticaria and Angioedema
- Classification/Description of Urticarial Types
- Chronic Urticaria (CIU/CSU):
  - Epidemiology, Associated Conditions
  - Laboratory Work up
  - Treatment Modalities/Options
  - When to Refer to an Allergist
Urticaria: Definitions

- **ACUTE**: < 6 weeks duration; 75% of all urticarias; typically due to allergy to food, medication, vaccines, topical agents; in children, transient viral illness

- **CHRONIC (CU): Physical or Idiopathic/Spontaneous, >6 weeks duration**
  - PHYSICAL (Inducible): No symptoms unless physical stimulus occurs; intermittent; Examples: dermatographism, cold ur., cholinergic ur. (exercise), solar ur., pressure-induced ur.

- **CHRONIC IDIOPATHIC “CIU” or SPONTANEOUS “CSU”**: Symptoms most days of week >6 weeks duration, no identifiable precipitant. 1% of population in their lifetime.

- **VASCULITIC**: Small sub-population, <1% of cases; immune complexes, complement activation, hist. release, neutrophil accum., activ./degranulate mast cells. Resistant to antihistamines. Biopsy indicated.
Urticaria: Signs/Symptoms

- Lesions ITCH!
- Central raised, white WHEAL surrounded by erythematous FLARE.
  - **WHEAL**: leakage of fluid from blood vessel extravasation and compression of vessels beneath it, making it clear.
  - **FLARE**: local neuronal reflex; dilated blood vessels in superficial layers of skin.
- Lesions rounded and circumscribed, and BLANCH w/ pressure. PHYSICAL type resolves in 1-2 hours, Others (acute, chronic) resolve in 8-24 hrs. or less, leaving no residual.
Typical Wheal/Flare Reaction
Typical Urticarial Presentations
Angioedema (AE)

- As opposed to urticaria which includes erythema and pruritis, angioedema, or AE, (previously ANGIONEUROTIC EDEMA) is characterized by swelling of DEEPER DERMAL, cutaneous and sub-mucosal tissues. 40% of CIU/CSU includes AE. In acute urticaria, same cause, when found together temporally.
- Overlying skin usually normal.
- NON-PRURITIC, “tingling/numbness/painful/burning”
- Generally occurs on hands, feet, genitalia, face (eyelids, lips commonly), tongue (occasionally), pharynx (rarely) but NEVER the larynx, (no asphyxiation), typically.
Angioedema: Lip, Eyelid
Angioedema (AE): Bradykinin-Mediated

- Bradykinin-Mediated Angioedema conditions include:
  - Hereditary (or Acquired) C1 Inhibitor Deficiency
  - Angiotensin Converting Enzyme (ACE) Inhibitor Ingestion Related AE
  - Some Idiopathic Angioedema cases resistant to antihistamine therapy.
- NOT associated with ANY Urticaria; If there are hives, no complement work up needed (C1 Inhibitor, C4)
- In CIU, pharyngeal edema can cause lump in throat, making swallowing difficult, but does NOT affect respiration. Reconsider dx of CIU if there is proven laryngeal edema. (i.e., likely bradykinin mediated)
Wheals and angioedema are not always urticaria

Table 3. Diseases related to urticaria for historical reasons and syndromes that include urticaria/angioedema

Diseases related to urticaria for historical reasons
Urticaria pigmentosa (mastocytosis)
Urticarial vasculitis
Familial cold urticaria (vasculitis)
Nonhistaminergic angioedema (e.g. HAE)

Syndromes that can be associated with urticaria/angioedema
Muckle-Wells syndrome (Urticaria-deafness-amyloidosis), sensorineural deafness, recurrent urticaria (hives), fevers, arthritis
Schnitzler’s syndrome monoclonal gammopathy, recurrent fever, arthritis
Gleich’s syndrome (episodic angioedema with eosinophilia), IgM gammopathy, eosinophilia
Well’s syndrome (Eosinophilic cellulitis), granulomatous dermatitis with eosinophilia

Zuberbier et al. EAACI/GA2LEN/EDF/WAO urticaria guideline 2009.
Acute Urticaria: Specific Stimulus

- Allergic, IgE mediated reaction to specific allergen, common in both children and adults, self-limited.
- Physiology: Allergen arrives via bloodstream to MAST cells in skin, binds to IgE, and activates the MAST cell to degranulate. Release of histamine, leukotrienes, PAF, tryptase, chymase, cytokines and interleukins.
- Allergens that cause hives generally INGESTED (food or drug, esp. abx i.e., penicillin, sulfa) or INJECTED (drugs, venom from stings, i.e., honeybee, wasp, hornet, yellow jacket, fire ant).
- Local Penetration= Local Hives, i.e., contact urticaria from latex gloves.
Acute Urticaria: Non-Specific Stimuli

- Mast cells degranulate in absence of an allergen
  - RADIOCONTRAST Dye: due to density of the media (not related to shellfish allergy). Common to progress to systemic anaphylactoid rxn: wheeze, laryngeal edema, cramps, diarrhea, hypotension.

- VIRAL illnesses: I.e., Rhinovirus, hives last a few weeks and subside, often attributed erroneously to an antibiotic if given at same time. Other viral triggers include Hepatitis B or EB virus (mono).

- Also helminthic PARASITES may trigger acute hives; generally have a high peripheral eosinophil count.
Acute Urticaria: Non-Specific Stimuli

- CODEINE/OPIATES cause degranulation of mast cells by stimulating opiate receptors.
- ASPIRIN and NSAIDs: Alter arachidonic acid metabolism, and urticaria and angioedema result.
- ACE INHIBITORS: Recurrent angioedema, urticaria less likely;
  - ACE inactivates bradykinin, so bradykinin levels rise with ACE Inhibitors. (Similar to acquired or C1 inhibitor deficiency)
  - Most common cause of angioedema in the ER.
  - Tongue, throat and laryngeal edema can be severe, intubation often necessary.
Physical/Inducible Urticarias

- Induced by environmental factors: temperature change, direct stimulation by pressure, stroking, vibration, light.
- Types include: Dermatographism, Cold, Cholinergic, Solar, Delayed Pressure, and Aquagenic.
- Respond to antihistamines, sometimes high dose needed. Does NOT respond to use of corticosteroids.
Dermatographism: Examples
Physical/Inducible Urticarias

- **COLD**: Pruritis, erythema, swelling after exposure to cold stimulus.
  - Limited to those localized parts of the body exposed.
  - 4-5 minute Ice Cube Test. Hive in 10 min or less. Hive occurs when the skin temperature rewarms.
- Localized vs. Systemic Cold Urticaria; Difference is that Systemic has a negative ice cube test, and hives are generalized from systemic cold, such as jumping into a cold lake.
Cold Urticaria: Wheal and Flare Reaction upon Rewarming.
Cold-Induced Angioedema in a Patient with Cold Urticaria
Physical/Inducible Urticarias

- **CHOLINERGIC:** heat trigger, i.e., from exercise, hot showers, sweating, anxiety.
  - Small, punctate lesions (1mm), spread from neck upper chest to trunk/extremities.
  - Rarely, symptoms of lacrimation, salivation, diarrhea may occur. Mediated by cholinergic nerve fibers.

- Exercise-induced anaphylaxis: Large hives, 1-2 cm. Spectrum of pruritis, urticaria, angioedema, wheeze, hypotension. Food related subtypes: 1. Within 5 hours of eating a specific food allergen, and 2. Within 5 hours of having eaten, no matter which food.
Rare Physical/Inducible Urticarias

- **DELAYED PRESSURE-INDUCED** Urticaria/angioedema: Rare, 4-6 hrs. post exposure. Angioedema more common. Examples of triggers incl. hammering (hands), standing on ladder (feet), sitting for long periods (buttocks).

- **SOLAR**: Rare, Brief light exposure induces urticaria within 1-3 minutes. Pruritis in 30 seconds, then edema (only in light exposed area), then erythema. Lesions disappear in 1-3 hrs.

- **AQUAGENIC**: Rare. Development of small wheals after water contact, regardless of temperature. Resolve in minutes to an hour or more.
CIU/CSU Features

- Common disorder (1% of population); NO KNOWN CAUSE, >6 weeks duration. Ratio is 70/30, W/M.
- Work up unremarkable: NL CBC, ESR, BMP; no systemic disease
- Subjects do NOT have increased incidence of atopy, i.e, allergic rhinitis, asthma or eczema. There is no exogenous etiologic agent; manipulations of diet, lifestyle, and medication has little effect.
- Dermatographism may be a feature (<30%). However friction, heat and pressure all serve to stimulate outbreaks. Angioedema present in up to 50% of cases.
CIU/CSU Features

- IgE is not a factor, no allergen triggers attacks.
- Can be mild to severe, may wax and wane, and intermittently subside, only to return months/years later. 50% last <12 mon.; 20% 12-36 mon., 20% 36-60 mon., some many years.
- Impacts quality of life with economic costs due to absenteeism, and medication.
  - One study: Impairment of quality of life was equal in magnitude to that experienced by patients with 3 vessel CAD waiting for bypass surgery.
- Histologically: Perivascular cellular infiltrate, increased mast cells, non-specific. Cannot diagnose any Urticaria on biopsy alone!!
Skin Biopsy of CIU

- Infiltration around small, intact blood vessels
- Endothelial cells
CIU Associations: H. Pylori

- Etiologic factors occ. attributed to CU throughout history: H. Pylori infection, pseudo-allergens (food, food additives), thyroid disease, autoimmunity, hepatitis B and C, and other infections/infestations.

- H. Pylori: 50% of CIU pts. have evidence of past/present H. Pylori infection; Antibiotic treatment of H. Pylori does not influence the course of CU. Therefore, No consensus that investigation of H. Pylori should be performed as a routine. Proper double-blind studies have never been done.
CIU Associations: Pseudo-Food Allergy

- In recurring CIU: Histamine intolerance caused by excessive histamine in diet, or in pts. with abnormal histamine metabolism by way of diamine oxidase (DAO) deficiency. DAO is the main enzyme involved in degradation of histamine in small intestine.
- Alcohol/some meds (commonly verapamil, clav. acid., chloroquine, metoclopramide and cefuroxime) decrease activity of DAO.
- Histamine rich foods include tuna, sardines, anchovies, cheeses, salami, sausage, fruits and tomatoes wine and beer.
- Food additives causing pseudo-food allergy (1-3% of pts) include tartrazine, monosodium benzoate, metabisulfite and MSG. Much literature in the 1950s-70s, but studies not well controlled and much was anecdotal.
Recent article by Rajan, et. Al. : 100 patients with CIU were challenged with array of additives present in foods or medications. Results: 2 had equivocal positive challenges and 98 were negative.

A pseudo-allergic diet that purports to positively affect symptoms has a success rate minimally above the placebo rate, and a long time interval to response (months).

Skin testing for foods or for aeroallergens for that matter, is not recommended, and not expected to reveal a cause.

In addition, diet manipulations are not routinely recommended, and by themselves will not induce remission.
Both Hashimoto’s thyroiditis and Grave’s disease are associated with CIU.

Anti thyroid antibodies are found in 15-27% of CIU, and 19% have abnormal thyroid function, generally hypo-function.

Consensus: Tests for antithyroid antibodies (antithyroglobulin and anti-peroxidase) and for thyroid function should be performed in ALL CIU cases, and then treated accordingly. Hive control and even remission can occur when thyroid supplementation pushes the TSH toward 1.0 level, especially if pt. is clinically hypothyroid and TSH is borderline elevated.
Thyroid autoimmunity

- In 1983, Leznoff et al. first reported on the association between CU and autoimmune thyroid disease
  - 15% prevalence of autoimmune thyroid antibodies in patients suffering from CSU but with a normal thyroid function

- In 1989, Leznoff et al. report that patients with CIU have an increased frequency of Hashimoto thyroiditis

- Thyroid antibody determination can be a useful tool as an indirect marker for autoimmunity

CIU: Autoimmunity/Autoreactivity

- 50% of CIU are considered autoimmune diseases, as patients have circulating histamine releasing autoantibodies directed against IgE high affinity receptors (FceRIa) found on mast cells and basophils.

- There is a connection between CU and a positive Autologous Serum Skin Test (ASST) and autoimmune disease such as autoimmune thyroiditis, celiac dis., RA, Grave’s dis. and Type 1 D.M.

- Females with CIU and the above autoantibodies had a greater incidence of RA, Sjogren’s, celiac dis., type 1 DM, and SLE during their lifetime and especially in the ten years following diagnosis of CIU.
A strong association was found between CU and major autoimmune diseases.
ASST: Autologous Serum Skin Test

- Significance of a negative ASST: rules out autoimmune urticaria
- Significance of a positive ASST: indicates the presence of autoreactivity in the serum, but in vitro confirmation is required before this can be attributed to functional autoantibodies
- Test reading depends on induction of histamine release from cutaneous mast cells
Autoantibody-dependent Activation of Mast Cells

FceRI high-affinity IgE receptor

IgG

Anti-FceRI antibodies

Histamine release causes hives (urticaria)

H1 and H2 receptors

Treatment with H1 and H2 blocker (Fexofenadine and Ranitidine)
CIU: Hepatitis B and C

- Already established that Hepatitis B can be cause of wheals/hives, esp. acute urticaria or in pts. with established CU.

- Widely debated that Hep C can cause hives.

- Therefore, patients with risk factors or abnormal LFT’s should be screened for Hepatitis B and C.
CIU: Parasites/Infestations

- Association of CU/AE long postulated with parasites, protozoa and helminths i.e., Giardia lamblia, Toxocara canis, Echinococcus, Strongloides, Ascaris lumbricoides, and others; more importantly, Blastocystis hominis and Anisakis simplex, nematodes found in raw/undercooked seafood.
  - Anisakiasis: acute disease in humans; RAST blood test.
  - Blastocystis hominis: 50% in undeveloped countries. Check in stool, in endemic areas, and treat with metronidazole.
- Parasitic infections can induce chronic or recurrent urticaria, but uncommon in the U.S.
- If Eo count or clinical suspicion is high, (i.e., dysentery travel history), only then should studies be done.
CIU: Work Up

- Diagnosis is clinical, and **does not require biopsy except in suspected vasculitis**, a minimal work up should be done to look for possible associated conditions.

- Many differing tests have been proposed over the years: CBC, ESR/CRP, BMP, TSH, anti thyroid antibodies, ANA, C3, C4, C1q, Chest XR, stool for O an P, Hepatitis B/C.

- At a minimum: CBC, ESR/CRP, BMP, TSH and autoantibodies should be done.
  - Elevated Eosinophil count: Stool for O and P.
  - Elevated ESR/CRP: autoimmunity, infections, malignancy
  - Elevated LFTs: check hepatitis profiles.
CIU: Work Up

- If patient has hives lasting several days in same spot, or resistant to antihistamine therapy, with associated purpura, consider VASCULITIS and do C3, C4, C1q, and a skin biopsy.
- Patients with CIU are over-investigated. Study: 356 patients, 1,872 lab tests done. Only 1 patient had an abnormality that affected the therapy.
- Bottom Line: only order further testing over the minimum above discussed, if clinically indicated.
According to Dr. Allen P. Kaplan CIU/CSU expert, Annals of Allergy May-June 2018, Vol. 39, no. 3, a new guideline for therapy will appear in next few months and is below.

Therapy Goal: Complete remission, then drug w/d. Eliminate drug/physical triggers, i.e., NSAIDs, heat, tight clothing.

High dose, second generation (H1) antihistamines are the drugs of choice for initial daily treatment, up to 4 X (off label) that normally recommended. Monotherapy or even 2 or 3 drugs in combination is acceptable. ~50% response.

Second generation levocetirizine, cetirizine, fexofenadine, desloratadine, or loratadine preferred over first generation, (hydroxyzine HCl, Diphenhydramine, Chlorpheniramine) due to less sedation and mucosal dryness. (If necessary, use first generation at HS only.)
CIU/CSU: Omalizumab

- For those still not in remission, next add the biologic Omalizumab, (Xolair, Novartis Ph., East Hanover NJ) approved on March 21, 2014 for treatment of CIU in 12 y.o.+. Antihistamines + Xolair = 85%- 90% remission.

- Omalizumab is most effective agent with the best adverse effect profile.

- Phase III trials (DBPC) demonstrated 60-70% response rate in >900 patients, and complete remission of 40%, with effective doses of 150mg and 300mg (300mg q 4 weeks injected s.q. was superior.)

- Anaphylaxis not observed in urticaria trials: DOC.
Omalizumab

- Recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody
- Binding IgE --> inhibits binding of IgE to the high-affinity IgE receptor (FcεRI) on mast cell & basophil surface
- Down-regulating the FcεRI receptor
- Decrease the release of circulating interleukin-6 and TNF-α
- Decrease the recruitment of T cells, eosinophils, and macrophages in the inflammatory response
Bound free IgE

- Rapid onset due to
  1) binding to free IgE antibodies, within a few hours of administration, that reduces the binding of IgE to the high affinity receptor FcεRI on basophils and mast cells
  2) downregulation of the expression of FcεRI
     - basophils (within 2 weeks)
     - mast cells (within 8 weeks)
Assessing CIU/CSU Severity: UAS7
Urticaria Activity Score, Weekly

Itch (intensity)
0 = none
1 = mild
2 = moderate
3 = intense
Once daily

Hives (number)
0 = none
1 = <20 hives
2 = 20–50 hives
3 = >50 hives
Once daily

Sum for 7 days

Daily UAS (0–6)

UAS7 (0–42)
**Omalizumab: Glacial Study**

**Omalizumab Increased the Proportion of Patients Well Controlled or Free of Itch and Hives**

<table>
<thead>
<tr>
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<th>Proportion of Patients With UAS7 ≤ 6 at Week 12, %*</th>
<th>Proportion of Patients With UAS7 = 0 at Week 12, %*</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Omalizumab 300 mg</td>
<td>52.4</td>
<td>33.7</td>
</tr>
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</table>

*P Value*< .001

*Secondary end point.*
For those 15% that do not respond to both antihistamines and omalizumab, next most effective drug is Cyclosporine, a calcineurin inhibitor, borne out by DBPC studies, and latter reports. Dose: 200mg/day.

Potential for toxicity: Monitor BP, BUN, Creat. Q6 weeks

Combination of high dose antihistamines, Omalizumab (Xolair), and cyclosporine can achieve 93% + remission.

Other drugs used with variable success (30-40% response) are dapsone, sulfasalazine, methotrexate, and hydroxychloroquine, plaquenil (very effective for urticarial vasculitis syndrome.)
CIU/CSU: Corticosteroids

- Corticosteroids are 95% effective for CIU/CSU
- Use should be limited to a short course for acute episodes of U/A, not for chronic use, as adverse effects far outweigh its efficacy.
  - Isolated Angioedema: 40 mg/D for 2 consecutive days, then D/C.
  - Severe Urticaria: 40mg QD in am for three days, then decrease by 5mg daily, total 10 days.
## Response Rates for Drug Treatment of CIU/CSU

<table>
<thead>
<tr>
<th>Agent</th>
<th>Response Rate, %</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Antihistamines</td>
<td>40-65</td>
<td>Requires high dose: up to 4 times the dose recommended for allergic rhinitis</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>95</td>
<td>May require high doses; probably 60%-70% response for prednisone ≤ 15 mg</td>
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<tr>
<td>Cyclosporine</td>
<td>70</td>
<td></td>
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<tr>
<td>Omalizumab</td>
<td>65-75</td>
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This is an off-label recommendation. Aplan AP. *Ann Allergy Asthma Immunol.* 2014;112:419-425.
CIU/CSU: What NOT to Use

- **H2-antagonists**: (famotidine, ranitidine, etc): Have never been shown to improve urticaria beyond that achievable with H1-antagonists.

- Their use was based on observations that a histamine W/F reaction in skin can be further blocked by H2-antagonist once H1-antagonist was achieved. But this does not translate into clinical efficacy for CIU/CSU.

- H2-antagonists were eliminated in the last European Academy of Allergy and Clinical Immunology (EAACI) guideline.
CIU/CSU: What NOT to Use

- Leukotriene antagonists (LTRAs): montelukast, zafirlukast.
- There is PRO/CON literature, but no large scale, DBPC studies done.
- Dr Kaplan’s personal experience: Patients refractory to antihistamines will not respond to LTRAs so he is opposed to their general use.
- LTRAs may play a role in patients whose CIU is exacerbated by aspirin/NSAIDs, but avoidance is better approach. Substitute acetaminophen.
Approaches to Consider When Antihistamines Fail

<table>
<thead>
<tr>
<th>Recommended</th>
<th>For Consideration</th>
<th>Not Recommended</th>
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<tbody>
<tr>
<td>Omalizumab</td>
<td>Dapsone</td>
<td>Corticosteroids*</td>
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<tr>
<td></td>
<td>Hydroxychloroquine</td>
<td>H₂ receptor antagonists</td>
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<td></td>
<td>Sulfasalazine</td>
<td>Leukotriene antagonists</td>
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<td>IV gamma globulin</td>
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<td>Plasmapheresis</td>
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Failure of antihistamines, omalizumab, and cyclosporine may leave no option other than those listed in the middle column or use of a low-dose chronic corticosteroid with provisos.

Prognostic Indicators

4 factors that seem to be associated with a long duration:

1. Disease Severity
2. Angioedema
3. Combination of CSU and Physical Urticaria
4. ASST Positive
CIU/CSU: When to Refer

- Referral to an allergist is recommended when:
  - Diagnosis is in question, i.e., lesions/presentation is not classic, Differential Diagnosis still exists.
  - Treatment with high dose second generation antihistamines, up to 4 times daily dose, does not achieve remission, and omalizumab is the next likely step.
  - Patient has required more than 1 short course of steroids for control.
Two weeks ago, you prescribed a second generation antihistamine for your 23 y.o. female patient with chronic idiopathic urticaria (CIU). On her follow up visit with you today she still has hives and itching. She mentions she has been taking ibuprofen for the past week for pain related to a hamstring injury. Which of the following would you NOT consider as a next step?

A. Tell her to stop taking ibuprofen.
B. Increase the dose of the antihistamine she is taking
C. Add an anti-inflammatory agent
D. Add another second generation, non sedating antihistamine
Post-Test

Which of the following drugs has among the highest response rate to CIU, but the least desirable adverse event profile?

A. Antihistamines
B. Corticosteroids
C. Omalizumab
D. Cyclosporine
A 56 year old man with giant hives and type 2 diabetes returns for his third visit after treatment with high doses of a potent antihistamine, Hydroxyzine HCl, was unsuccessful. Which of the following is not recommended as a next step in treatment?

A. Dapsone
B. Corticosteroids
C. Omalizumab
D. Cyclosporine
A 50 year old female with no previous atopic history, is seen in your office for initial evaluation of spontaneous episodes of angioedema of lips and eyelid, AND concurrent classic hives of 9 weeks duration. What prudent testing would be indicated in the initial work up?

A. CBC and differential, BMP
B. C4 level and/or C1 inhibitor, functional and total
C. TSH, anti-thyroid antibodies (anti peroxidase, antithyroglobulin)
D. Food allergy (IgE) RAST testing
E. A and C
F. B and D
Thank You !!!

References: