URTICARIA

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Urticaria is characterized by evanescent short-lived circumscribed areas of raised erythema and edema of the skin due to transient leakage of plasma from small blood vessels into the surrounding connective tissue. The superficial swelling of the dermis is called wheal. The wheals are itchy and become pale in the center because of the edema. The wheal is surrounded by a flare, which is due to local axon reflex. The wheals resolve within hours leaving no marks unless the skin is excoriated by scratching.

In angioedema (AO) the swelling is deeper and affect the dermis and subcutaneous or submucosal tissue. The angioedema is rather painful than pruritic and takes longer time than the wheal to clear.

Urticarial wheals are often associated with angioedema but each may occur alone.

AO may appear after trauma particularly dental trauma. 20% may die from suffocation due to laryngeal edema. Hereditary AO is treated with:

Androgens
Danazol 200-600mg / day
Stanazolal 0.5 – 2mg daily
Epsilon Aminocaproic acid 12-18 grams daily
Replacement therapy with fresh frozen plasma especially given prophylactic before tooth extraction

AO may be acquired - acquired C-1 esterase inhibitor deficiency is seen in

- B.Cell lymphoma
- SLE
- Autoantibodies against inhibitors

It is estimated that 40% of patients get urticaria alone and 11% get angioedema alone and 49% get both urticarial wheals and angioedema (AO). The Commonest sites affected by AO are lips, eyelids, genitalia, tongue and larynx.

Angioedema alone may be due to C-1 esterase inhibitors deficiency in hereditary AO, which is autosomal dominant with onset in early childhood but may be delayed to adulthood.

Hereditary AO represents 1% of all cases of AO and 5% of cases of AO not associated with urticarial wheals.

Acute forms of urticaria last less than 6 weeks while chronic forms of urticaria last more than 6 weeks (1). Urticaria and angioedema affect about 15% of general population during their life time (2) and only 5% of those who report to dermatologists. In acute urticaria history may display a cause and usually no diagnostic work up is needed. However the aetiology of many cases of both acute and chronic urticaria cannot be identified.

Basic Mechanism

The basic mechanism in acute urticaria is an immediate hypersensitivity reaction involving binding of the allergen to specific IgE on mast cells and its consequent degranulation with release of preformed mediators of inflammation.

The preformed mediators include:

- Histamine
- Heparin
- Cytokines – IL 3, IL4, IL5, IL6
  IL8, IL13
  G.MCSF
  TNF α
  Eosinophil chemotactic factor
  Neutrophil chemotactic factor
- Proteases (Tryptase, chymase)

The degranulation of mast cells gives usually generated archidonic acid metabolites, which include prostaglandin D2 and leukotriene C4. These mediators lead to dilatation of capillaries and small venules with increased permeability. Other potential mediators produced by cells other than mast cells include:

1- Endothelial cells	Prostaglandin I2
2- Platelets	Platelet activating factor
	Platelet Factor 4
3- Eosinophils	major basic protein
	Eosinophil cationic protein
4- Neutrophil	leukotriene B4
	Tryptase
	Chymase
5- Basophil	histamine
	leukotriene C4 and D4
	Eosinophil chemotactic factor
	Neutrophil chemotactic factor

6- Nerves	acetyl choline Neutropeptide (Substance P)	
7- Epidermal cells	IL-1	
8- Mononuclear phagocytes	IL-1	
9- Plasma products	C3a, C5a, serum factor, kinin, fibrin degradation	

Urticaria / angioedema are clinically classified into [1]:

I- Acute IgE mediated urticaria

II- Physical urticaria, which is defined by the triggering factor
   1- Adrenergic urticaria
   2- aquagenic urticaria
   3- cholinergic urticaria
   4- cold urticaria
   5- delayed pressure urticaria
   6- dermographism
   7- exercise induced anaphylaxis
   8- localized heat urticaria
   9- solar urticaria
   10- vibratory angioedema

III- Contact urticaria induced by biologic or chemical skin contactants for example
   1- From polyethylene gloves [3]
   2- From hops [4]
   3- From benzophenone [5]
   4- From Geranial [6]

IV- Uritcaria Vasculitis

V- Angioedema

- Urticaria is also broadly classified into acute or chronic
- It is also classified into allergic and non-allergic
- The allergic urticaria is due to type I reaction and represent 3-5% of patients attending skin outpatient
- It was also found that chronic urticaria is more common among first-degree relatives of affected individuals than in general population and this may suggest that there is a genetic background for chronic urticaria and provide a clinical support to the reported association between chronic urticaria and HLA DR4 [7].

In the diagnosis of urticaria:

- The timing of onset, morphology of lesion and duration of individual wheals may clinically help in inducing an initial diagnosis as shown in the following table:

Type of urticaria	Time of appearance	Morphology	Duration of wheal	
Ordinary urticaria	Within 30 minutes to an hour	Evanescent wheals	2 - 24 hours	
Physical urticaria	Within 10-minutes of exposure to the physical agent	* Linear in Dermographism * Papular wheal in cholinergic urticaria and aquagenic urticaria * Restricted to light exposed area in solar urticaria Wheal lasts one hour		
Delayed Pressure Urticaria 40% of patients with chronic ordinary urticaria have delayed pressure urticaria	Several hours after sustained pressure	Affect palms soles and lower back	24 hours	

Type of urticaria	Time of appearance	Morphology	Duration of wheal
Contact urticaria. **common contactants are foods, food additives, drugs animal saliva, dander grass Pollens Caterpillars, rubber gloves, algae, lichen, ammonium persulfate in hair dressers**	Within 10 to 30 minutes of exposure to contactant	Wheals at site of contact usually on hands and mouth	2 hours
Urticarial vasculitis and drug reaction		Wheals tend to bruise and give burning sensation rather than itch	1 – 7 days.

Provoking causes of urticaria may be:

1] Drugs

1- NSAID (Salicylates, indomethacin, and other related drugs) can aggravate urticaria and asthma in 30-50% of cases.
This may be due to releasing histamine similar to other non-immunologic histamine releasing drugs as (codeine, curare, dextrin, morphine, polymixin, and compound 48/80).
Or may be due to true allergic reaction
Or may be due to effect on cycloxygenase.

2- Penicillin may cause urticaria, anaphylaxis or serum sickness like reaction
Atopics are particularly susceptible to penicillin reaction
Penicillin may have a role in some patients with chronic urticaria.

3- Angio-tensin converting enzyme inhibitors may have a direct effect on kinin system and provoke angioedema

4- Foods

- reaction to food is acute or recurrent acute attacks
- it occurs within minutes to hours from ingestion
- the reaction may be allergic or non-allergic
- some foods contain natural salicylates as almonds, apples, apricots, bananas, black berries, blue berries, cherries, cucumber, grapefruits, grapes, green peas, green pepper, lemon, melons, nectarine, oranges. peaches, pickles, plums, prunes, tomatoes
- fish may cause:
  - direct histamine release
  - allergic reaction
  - old stored fish is more potent allergenic than fresh fish
  - foods that are main offenders in urticaria include – eggs, nuts, chocolate, fish, shell fish, tomatoes, pork, strawberries, milk, cheese, spices, and yeast
- food allergy is seldom found in chronic urticaria

5- Food additives:

- Tartrazine and other azodyes
- Benzoates and salicylates
- Hydroxybenzoate
- All coloring or flavoring material
- Beer and bakery foods
- Candy, cider, canned fish
- Ketchup
- Fruit juice
- Jelly, jam

- Luncheon
- Ice cream
- Mint, mayonnaise and macaroni
- Salad dressing
- Wine
- Sulphites: they are preservatives and antioxidants added to keep vegetables and fruits fresh colored.
- The sulfites used are sodium, bisulfite, potassium bisulfite, sodium metabisulfite, potassium metabisulfite and sulphurdioxide. The sulfite reaction is characterized by:
  - Sudden onset within 2-15 minutes (Food allergy occur 30-60 minutes after food)
  - Flushing
  - Urticaria
  - Angioedema
  - Pruritus
  - Asthma

It may simulate anaphylaxis and was reported fatal in one case.

- Asthmatic patients are prone to sulfite reaction (10%)
- Mechanism is possibly neural affecting vagus with parasympathetic stimulation causing pruritus, urticaria, angioedema and asthma and the antidote is atropine.
- Sulfite reaction affects persons who have deficiency of Sulfite oxidase. Vitamin B12 act as a catalyst for oxidation of sulfites and offer good protection for such patients
- Foods that contain sulfites include .
  - Dried fruits
  - Potato ships
  - French fries
  - Vegetables unwrapped in cellophane
  - Some fruit drinks
  - Shrimps
  - Sausages
  - Baked products
  - Vinegar
- Treatment is with:
  - Atropine, Doxepin, Cromolyn, B12

6- In halants – grass pollens, house dust, animal dander, mould spores

7- Infections are uncommon causes for e.g. Bacterial infection, focal sepsis, urinary infection and virus infection

8- Psychological factors may have a contributory role

9- General medical disorders as
  - SLE, Lymphoma, polycythemia, macroglobulinemia, carcinoma
  - Pregnancy (Persistent Urticarial plaques of pregnancy PUPP)
  - Premenstrual aggravation of urticaria is attributed to progesterone sensitivity
  - Metal pins of femer, metal dental prosthesis and dental amalgam.

Simple acute urticaria can be treated with:

1] H1 antihistamine agents with avoidance of the allergen.

They relieve pruritus and the rash. Some of the commonly used of these agents are:

1- Hydroxyzine hydrochloride (Atarax) adult dose 50-100mg PO qid
Children < 6 years 50mg in divided doses
Children >6 years 50-100 mg in divided doses

2- Diphenhydramine (Benadyrl, Benylin)
Dose PO 25-50 mg 3-4 times/day do not exceed 400mg/day
children give 5mg / kg / day
may exacerbate glaucoma, hyperthyroidism

3- Cyproheptadine (Periactin) dose 4mg tid dose ranges between 12 - 16 mg/day – do not exceed 0.5 mg/kg/day
Children total daily dose 0.25mg/kg
  - contraindicated in glaucoma, symptomatic prostatic hypertrophy, bladder neck obstruction.
  - it is usually safe in pregnancy
  - it inhibits expectoration and bronchial secretion becomes thick

4- Loratidine (Claritin) - selectively inhibits peripheral H1 receptors
Adult dose 10mg on empty stomach
Children 2-6 years dose is 5mg
Children > 6 years are given adult dose
Can be given in pregnancy but benefits must out weight the risk
  - interaction – ketoconazole, erythrosin, alcohol and procarbazine may increase loratidine level

5- Desloratidine (Aerius) – it is a major metabolites of loratidine. Dose for adult is 5mg/day and children > 12 years
   - drug interaction with erythrosin and ketoconazole
   - precaution – decrease dose in hepatic impairment
6- Zyrtec (Cetrizine dihydrochloride) dose 10mg / day
7- Xyzal a new generation of cetrizine
8- Phenothiazine
9- Telfast (Fexofenadine hydrochloride 120 and 180 mg – not given to children below 12 years old – not given in pregnancy or lactation – its level increases 2-3 times if given with erythrosin or ketoconazole. Given 2 hours after anti acid containing aluminum or magnesium hydroxide since absorption of Telfast is reduced.
10- Tavegyl = Clemastine
   Dose for adults and children over 12 years is 1-tablet 1mg up to 6 tablets per day
   Amp 2ml 2mg I.M.
   Interacts with sedatives, hypnotics, MAO & alcohol
   Side effects fatigue, sedation, dry mouth, headache, dizziness
11- Fenistil – Dimethidene maleate 1mg tablet
   Dose 1-2 tablets 1 – 3 times / day
12- Ketotifen – mast cell stabilizer dose 1mg twice daily

II] Tricyclic antidepressants – they have central and peripheral anticholinergic effect, sedative effect, block reuptake of nor epinephrine and serotonin

1- Doxepin (Sinequan, Adapin, adult Dose 10-150 mg/day bid or tid, for 12 years old 25-50mg / day and increase gradually to 100 its in contraindicated in:
   - recovery period of myocardial infarction
   - glaucoma
   - MAO within past 7-10days, co-administration with MAO, can cause, seizures, hyperexcitability, sweating, coma, hyperthermia, tachycardia, tachypnea, headache, hypotension, Barbiturate coagulopathy disseminated intravascular (DIV) and death
   - Barbiturate may decrease serum level
   - Charcoal prevent absorption
   - Cimetidine cause higher levels

   Other tricyclic antidepressants (TCAs) may cause dangerous hypertensive crisis
   - Increase half life of anticoagulants
   - Antagonize guanethidine

III] Glucocorticoids:
   Adult dose is 1mg / kg / day
   Children dose 1-2 mg/kg/day
   Taper over 2 weeks
   Drug interaction
   - eostrogen decrease clearance
   - phenobarb, phenytoin and rifampicin increase metabolism so consider increasing maintenance dose of prednisolone

   Precautions:
   - caution with hyperthyroidism
   - nonspecific ulcerative colitis
   - osteoporosis
   - D.M.
   - Myasthenia gravis
   - Cirrhoses

IV] H2 receptor antagonists
   - combination H1 and H2 antagonist may be helpful in chronic idiopathic urticaria.
   - Some H2 receptor antagonists:

1- famotidin (pepcid)
   adult dose 20-40 mg bid Po
   20 mg I.V. bid
   children 1-2 mg/kg/day
   it may decrease effect of ketoconazole and itraconazole and if renal function is affected discontinue drug.
2- Ranitidine (Zantac)
   - Dose 150mg Bid do not exceed 600 mg/day.
   - > 12 years 1.25 – 2.5 mg/kg/day
   do not exceed 300 mg
   - it decreases effect of ketoconazole and itraconazole
   - if changes in liver or kidney function occurs discontinue treatment
3- Cimetidine (Tagamet)
   - dose 300-800 mg PO q 6-8 hours

300 mg I.V./IM q 6-8 hours
- may cause confusion in elderly
- may cause gynecomastia because of its weak antiandrogen effects
- if changes in renal function occurs, discontinue the drug

Chronic Urticaria

* In contrast with acute urticaria chronic urticaria is a frostrating problem and is a diagnostic challenge.
* Frequently detailed history, investigations and selected allergy tests often fail to disclose the cause or help in treatment
* In chronic urticaria and recurrent angioedema many triggering factors are considered and symptoms persist for years
* Chronic urticaria is a heterogenous group that include:
  - Physical urticaria 35%
  - Idiopathic urticaria about 30%
  - Autoimmune urticaria about 24%
  - Urticarial vasculitis 5%
  - Pseudoallergic urticaria 3%
* The points that should be always asked about and looked for in chronic urticaria are symbolized [8] in the letters of the word METAPHYSICAL where each letter stands for the following:

M= Medication and chemical as
- Penicillin, angiotension converting enzyme inhibitors which provide angioedema
- NSAID [9] may aggravate urticaria and asthma in 30-50% of cases
- Histamine releasing drugs
- All patients with acute or chronic urticaria should be carefully asked about drug intake particularly antibiotics, analgesics and contrast media [10].
- Some of the drugs reported in the literature to produce urticaria are deflazacort [11], Atrovastatin [12], Roxithromycin [13] and Cox-2 inhibitors [14]
- The urticaria and angioedema induced by drugs is quite high. In a retrospective study of 2287 patients observed over 10 years period (1988 – 1997) the urticaria angioedema was found in 86.2%. The most frequently involved drugs were NSAID especially Aspirin and antimicrobial mainly betalactams [15].

E = Endocrinapathy
- Antithyroid antibodies
- Autoimmune progesterone urticaria
- Primary parathyroidism can be a rare cause of chronic urticaria [16].

T = Thymic (Psychologic, neurologic, effective)

A = Allergic foods
Urticaria can be produced also by airborne allergens [17].

P = Paraneoplastic – leukemia – lymphoma, myeloma, lymphoproliferative disease and small cell carcinoma of lung [18].

H = Hereditary angioedema and Muckle Well Syndrome [19].

Y = Yeasts and parasites

S = Systemic illness, SLE

I = Infection – bacterial – viral

C = Contactants

A = Additives, dyes, preservatives

L = Lack of proper care of physician (lack of diligence)
- Autologous serum skin test can cause wheal and flare response in some cases of chronic Idiopathic Urticaria (CIU) but this skin test cannot be used alone to predict the severity of urticaria or define it as autoimmune [20].
- It is estimated that 60% of patients with CIU have a positive skin test response to autologous serum [21] and this led to identification of autoantibodies to IgE and alpha chain of the high affinity IgE receptor, Fc epsilon R1 alpha.
- It is estimated that 33% of patients with chronic urticaria have an autoimmune basis of their problem and have circulating auto antibodies to alpha chain of the high affinity IgE receptor [22], but not all autoanitbodies initiate histamine release [21, 22] from mast cells and basophils.
- The positive intradermal autologous serum skin test in some patients of CIU show evidence of immunologic inflammatory

findings as evidenced by increased production of TNF α , IL-10 and RANTES while IL-2 and INF gamma were reduced [23].

- skin biopsies from CIU showed significant increase in CD3+ve and CD 25+ve T cells as well as eosinophils, neutrophils, basophils and macrophages with lower number of tryptase positive mast cells and epidermis showed CD3+ve Tcells. This inflammatory cell profile in CIU is similar to allergen induced late phase reaction. The cytokine pattern was that of THO profile with significant increase in IL-4, IL-5 and INF gamma [24].
- Sera from patients with CIU contain anti Fc epsilon R1 alpha antibody which act on mast cells and release histamine, Leukotreine D4 and TNF α , which activate endothelial cells and induce expression of endothelial cell adhesion molecules [25]. At least 30% of patients with CIU have histamine-releasing autoantibodies against Fc epsilon R1 alpha or less commonly against IgE itself and recently complement activation is found in most cases.
- Functioning histamine releasing autoantibodies are specific for CIU.
- Non-functioning and non-histamine releasing autoantibodies were found in patients with physical urticaria, autoimmune connective tissue disease and bullous diseases [26].
- The reason why some individuals get these autoantibodies may be explained that these persons who are genetically predisposed to CIU develop autoantibodies by mimicry perhaps against lipopolysacharides of H-pylori, which frequently infect upper Gastro Intestinal tract of chronic urticaria patients [26]. An association between H.Pylori and chronic urticaria has been previously suspected [27].
- Histamine release in CIU is initiated by IgG antibodies against alpha subunit of Fc epsilon R1 followed by complement C5a activation[28].
- There is an aberrant signaling of P 21 Ras pathway in lymphocytes of patients with CIU and this finding supports the autoimmune bases of CIU [29].
- Pseudoallergic reactions could be produced in CIU by natural foods and food additives [30] and natural dietary salicylates. The underlying mechanism for psuedoallergic reaction may involve diversion of arachidonic acid metabolism from prostaglandin to leukotrienes.

Pathogenesis [1]

1- Degranulation of mast cells with release of histamine
2- In chronic urticaria mediators are easily released from mast cells
3- A range of immunologic and non-immunologic mast cells degranulating stimuli include:
   - opiates
   - neuropeptide
   - stem cell factor (c kit ligand)
   - C3a and C5a anaphylatoxins
   - Antigen that bind to IgE globulin
   - Autoantibodies that cross link cell bound IgE
   - Auto antibodies that cross link high affinity IgE receptor
4- Immediate hypersensitivity reaction involves the binding of the allergen (antigen) to IgE on mast cell and occur in acute urticaria but seems to be not important in chronic urticaria.
5- Local factors like heat and pressure cause vasodilatation with extra vascular leakage of autoantibody proteins in the dermis in concentration sufficient to induce degranulation of mast cells
6- Peripheral basophils migrate to the dermis from circulation and sustain Urticarial lesion by late phase reaction.
7- C5a augment autoantibody release of histamine from mast cells
8- Release of preformed mediators of inflammation from mast cells (histamine, proteases, heparin, IL3, Il4, Il5, Il6, IL8, IL13 – GMCSF and TNF α)
9- Release of newly synthesized mediators (LTC4, D4, E4 – platelet activating factor, prostaglandin D2).
10- TNF α promote inflammatory reaction by up regulating endothelial vascular adhesion molecules

11- Autoantibody releasing histamine occur in up to 50% of patients and many cases (30%) remain idiopathic and unexplained
12- Mast cell degranulation in physical urticaria, which comprises 35% of chronic urticaria, is not known but an immunoglobulin serum factor was detected in some cases. Histamine releasing autoantibodies were not found in physical urticaria.
13- Urticarial vasculitis which comprise 5% of cases of chronic urticaria is differentiated from CIU clinically because most cases of Urticarial vasculitis are secondary to an underlying disease and the Urticarial wheal are sore and last more than 48 hours (1-7 days) and skin biopsy shows leukocytoclastic vasculitis [21].

Itch as a symptom in CIU has been analyzed in 100 patients with the following characteristics [31]

1- Pruritus on daily basis was found in 68
2- Pruritus more at night 83
3- Pruritus causing difficulty in sleeping 62
4- Pruritus involving arms 86 / Back 78 / Legs75
5- accompanying sensation of heat 45
6- accompanying sweating 15
7- accompanying stinging 27
8- accompanying tickling 25
9- accompanying burning 23
10- accompanying depression 14

Rare syndromes associated with urticaria and or angioedema

1- Muckle- Well Syndrome is characterized by sensorineural deafness and is associated with amyloidosis and is sometimes associated with Familial Cold Urticaria (FCU), which is triggered by exposure to cold. Both conditions Muckle-Well Syndrome and Familial cold urticaria are autosomal dominant and both are characterized by recurrent inflammatory crisis that start in childhood and are often associated with fever, arthralgia and urticaria [19].
2- Familial Mediterranean Fever autosomal recessive and affect Sephardic Jews, Armenians and Arabs characterized by:
   - febrile attacks of 1-2 days
   - tendency for peritonitis and pleurisy
   - synusitis
   - skin shows erysipelas like lesions on lower limbs, urticaria, Henck Schoenlein purpura and vasculitis nodules
   - 25% of cases get renal amyloidosis which is often fatal
   - some of the symptoms may be controlled by colchicine
3- Urticaria, fever and Eosinophilia syndrome
4- Urticaria with preceding vomiting
5- Cyclic oedema (periodic oedema) characterized by edema of skin with striking periodicity and is described with autoimmune progesterone urticaria, Mediterranean fever and idiopathic edema
6- Exercise induced anaphylaxes may resemble cholinergic urticaria and is characterized by pruritus, whealing, angioedema, asthma and cardiovascular collapse. It is cholinergic and has been linked with heavy food before exercise.

References:

1- Grattan CEH, Sabroe RA and Greaves MW: Chronic Urticaria.
J. Am. Acad. Dermatol 2002; 46:645-57

2- Charlesworth EM: Chronic Urticaria: back ground, evaluation and treatment.
Curr-Allergy –Asthma-Rep 2001; 1(4): 342-7.

3- Sugiura K; Sugiura M; Shiraki R; et al: Contact Urticaria due to polyethylene gloves.
Contact Dermatitis 2002; 46(5) 262-6

4- Estrada JL; Gozalo F; Cecchini C; et al: Contact Urticaria from hops (Humulus lupulus) in a patient with previous urticaria angioedema from Reanut chest nut and banana.
Contact Dermatitis 2002; 46(2) 127.

5- Yesudian PD; King CM: Severe contact urticaria and anaphylaxi's from benzophenone-3 (2-hydroxy 4-methoxy benzophenone)
Contact Dermatitis 2002; 46(1): 55-6.

6- Yamamota A; Mouta A; Tsuji T; et al: Contact urticaria from geroniol.
Contact Dermatitis 2002; 46(1): 52

7- Asero R: Chronic idiopathic urticaria: a family study.
Ann- Allergy-Asthma-Immunal 2002; 89(2): 195-6

8- Torrelo, A; Allegue F; Harto A: Meta physical urticaria. Arch dermatol 1992; 128 (7): 992-3

9- Biedermann-T; Hartmann K; Sing A; et al: Hypersensitivity to non-steroidal anti-steroidal anti-inflammatory drugs and chronic urticaria cured by treatment of Blaslocystis hominis infection
Br. J. Dermatol 2002; 146(6): 1113-4

10- Greaves MW; Hussein SH: Drug induced urticaria and angioedema: Pathomechanisms and frequencies in developing country and in developed countries.
Int- Arch-Allergy –Immunaol 2002; 128(1): 1-7.

11- Gomez CM; Hignero NC; Moral-de-Gregorio; et al: Urticaria-angioedema by deflazacort.
Allergy 2002; 57(4): 370-1

12- Anliker MD; Wathrick B: Chronic urticaria to atrovastatin.
Allergy 2002; 57(4): 366

13- Curvinder SK; Tham P; Kanwar AJ: Roxithromycin induced acute urticaria
Allergy 2002; 57(3): 262

14- Grimm V; Rakoski J; Ring J: Urticaria and angioedema induced by Cox-2 inhibitors .
J-Allergy-Clin-Immunol 2002; 109(2): 370.

15- Nettis E; Marcandrea M; Maggio GD; et al: Retrospective analysis of drug induced urticaria and angioedema: a survey of 2287 patients.
Immunopharmacol-Immunotoxicol 2001; 23(4): 585-95.

16- Dagher HN; Aboujaoude ZC; Jabbour SA: Chronic Urticaria: an unusual initial manifestation of primary hyperparathyroidism.
Endocr. Pract. 2002; 8(1): 47-9.

17- Bourrain JL: Airborne allergen induced urticaria.
Ann-Dermatol-Venereol 2001; 128(1-pt2): 1139-41.

18- Greiner D; Schofer H; Boehncke WH: Urticaria associated with a small cell carcinoma of the lung.
Cutis 2002; 89(1): 49-50

19- Dode-C; Le-Du-N; Cuisset L; et al: New mutations of SIAS1 that are responsible for Muckle-Wells Syndrome and familial cold urticaria: a novel mutation underlies both syndrome.
Am. J. Hum. Genet 2002; 70(6): 1498-506.

20- Nettis E; Dambra P; D'Oronzio L; et al: Reactivity to autologous serum skin test and clinical features in chronic idiopathic urticaria.
Clic. Exp- Dermatol 2002; 27(1): 29-31.

21- Napoli DC; Freeman TM: autoimmunity in chronic urticaria and urticarial vasculitis.
Curr-Allergy-Asthma. Rep 2001; 14: 329-36.

22- Sabroe-RA; Fiebiger E; Francis DM; et al: Classification of anti-Fc epsilon R1 and anti-IgE autoantibodies in chronic idiopathic urticaria and correlation with disease severity.
J-Allergy-Clin-Immunol 2002; 110(3): 492-9.

23- Piconi S; Trabattoni D; Temoli E; et al: Immune profiles of patients with chronic idiopathic urticaria.
Int-Arch-Allergy Immunol 2002; 128(1): 59-66.

24- Ying-S; Kikishi-Y; Meng-Q; et al: TH-1/TH-2 cytokines and inflammatory cells in skin biopsy specimens from patients with chronic idiopathic urticaria: comparison with the allergen –induced late-phase Cutaneous reaction.
J-Allergy-Clin-Immunol 2002; 109(4): 694-700

25- Lee-KH; Kim JY; Kang DS; et al: Increased expression of endothelial cell adhesion molecule due to mediator release from human foreskin mast cell stimulated by autoantibodies in chronic urticaria sera.
J-Invest-Dermatol 2002; 118(4): 658-63.

26- Greaves MW: Pathophysiology of chronic urticaria.
Int-Arch-Allergy-Immunol 2002; 127(1): 3-9.

27- Liutu M; Kalimo K; Uksila J; et al: Extraction of IgE-binding components of Helicobacter pylori by immunoblotting analysis in chronic urticaria patients.
Int-Arch-Allergy-Immunol 2001; 126(3): 213-7.

28- Kikuchi-Y; Kaplan-AP: A role for C5a in augmenting IgG=dependent histamine release from basophils in chronic urticaria.
J-Allergy-Clin-Immunol 2002; 109(1): 114-8

29- Confino-Cohen-R; Aharoni-D; Goldberg-A; et al: Evidence for aberrant regulation of the p21 Ras pathway in PBMCS of patients with chronic idiopathic urticaria.
J-Allergy-Clin-Immunol 2002; 109(2): 349-56.

30- Zuberbier-T; Pfrommer-C; Specht-K; et al: Aromatic components of foods as novel eliciting factors of pseudoallergic reactions in chronic urticaria.
J-Allergy-Clin-Immunol 2002; 109(2): 343-8.

31- Yosipovitch-G; Ansari-M; Goon-A; et al: Clinical characteristics of pruritus in chronic idiopathic urticaria.
Br. J. Dermatol 2002; 147(1): 32-6.