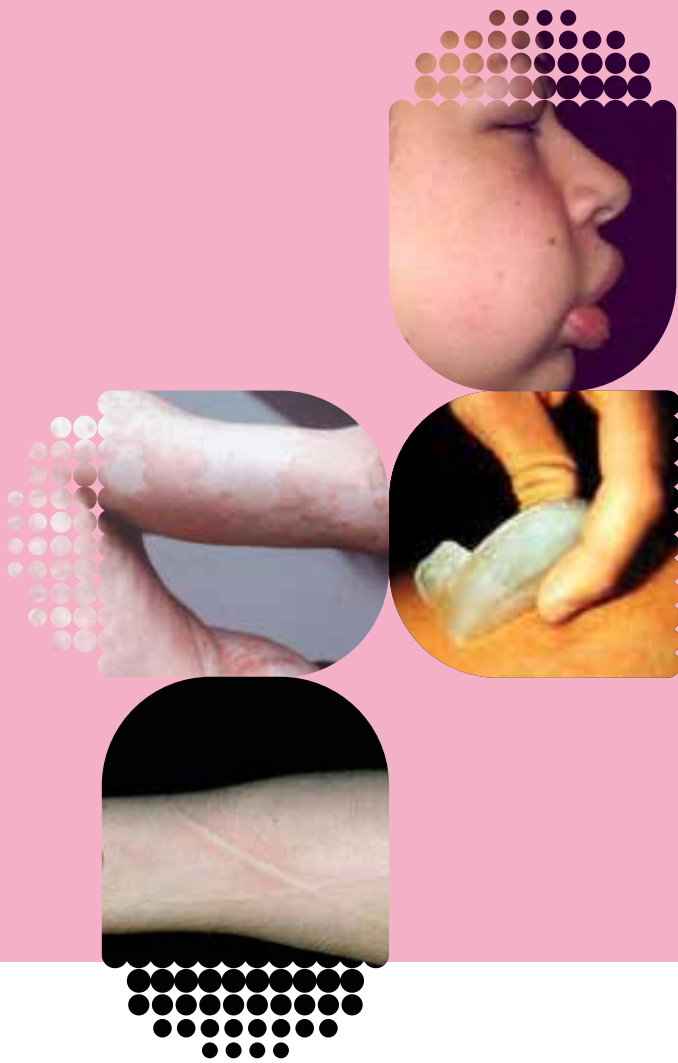
Urticaria and Angioedema

Prepared by:

Dr. Mehdi Adeli, MD, FAAAAI, FAP
Senior Consultant, Allergy and Immunology
Assistant Professor, Weill Cornell Medicine-Qatar
Allergy and Immunology Awareness Program (AIAP)
Pediatrics Department, Hamad Medical Corporation
Doha, Qatar



مؤسسة حمد الطبية
Hamad Medical Corporation
HEALTH • EDUCATION • RESEARCH صحة • تعليم • بحوث
حمد Hamad

Urticaria and Angioedema

Dr. Mehdi Adeli, MD, FAAAAI, FAP
Senior Consultant, Allergy and Immunology
Assistant Professor, Weill Cornell Medicine-Qatar
Allergy and Immunology Awareness Program (AIAP)
Pediatrics Department, Hamad Medical Corporation
Doha, Qatar

Introduction

Dr. Mehdi Adeli, MD, FAAAAI, FAP
Senior Consultant, Allergy and Immunology
Assistant Professor, Weill Cornell Medicine-Qatar
Allergy and Immunology Awareness Program (AIAP)
Pediatrics Department, Hamad Medical Corporation
Doha, Qatar

WE, the Allergy and Immunology Awareness Program (AIAP) team at Hamad Medical Corporation created this booklet guide for you and your family. We aim to provide you with beneficial information about Urticaria and Angioedema.

Our goal is to increase your awareness on these two allergic skin disorders, so you will be able to help with your condition accordingly and seek appropriate medical care.

We hope to help you effectively deal with your condition through our efforts in creating this booklet guide.

For more information and feedback, please don't hesitate to contact us at: madeli@hamad.qa or AIAP@hamad.qa

Thank you and we wish you a healthy life.

Contents

Definitions

Urticaria is commonly known as 'hives', is an itchy rash with swelling that appears on the surface of skin. The red raised bumps on the skin become white if pressed on. The hives can appear on any part of the body and vary in size. They usually disappear within hours to days,, but occasionally tend to recur many times.

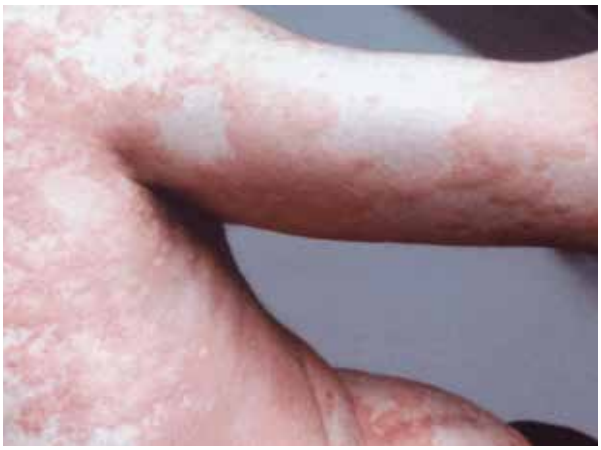


Figure illustrates urticaria. *Source: Allen P. Kaplan. Systemic Manifestations of Atopic Urticaria. 12. June 2011. http://www.worldallergy.org/UserFiles/file/WAF-Istanbul(2).pdf*

Angioedema is a swelling from the deeper layers of the skin. It often shows a big swelling on the body part(s) affected (e.g. lips, around the eyes).

The swelling in angioedema usually appears on the fingers, toes, face, head, neck, and in men, the reproductive organ. It could occur in the gut resulting in nausea and abdominal discomfort. The swelling may or may not be itchy. However, it may be painful or cause a burning feeling. The swelling is not considered dangerous, but occasionally, the tongue or throat could swell and shut down the airways. This is considered an emergency and requires urgent medical intervention.

Urticaria and Angioedema can happen together or alone.

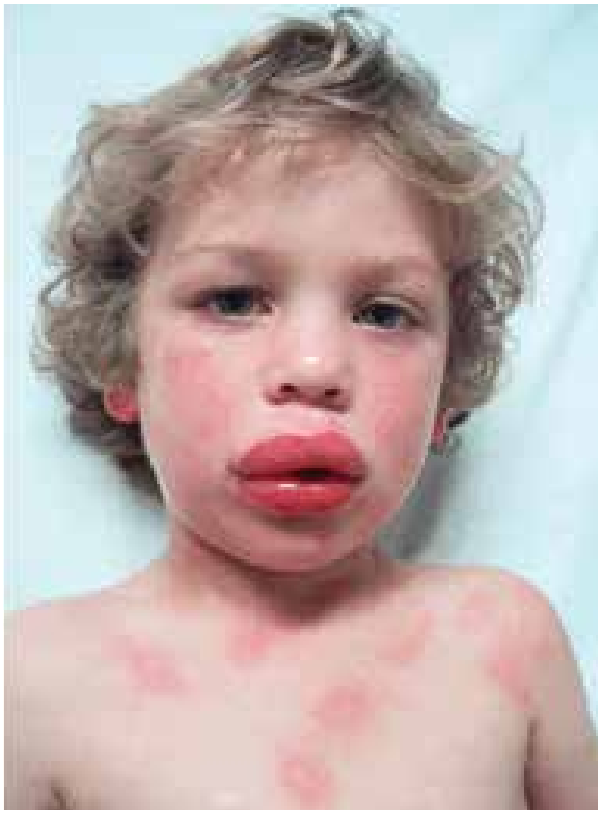
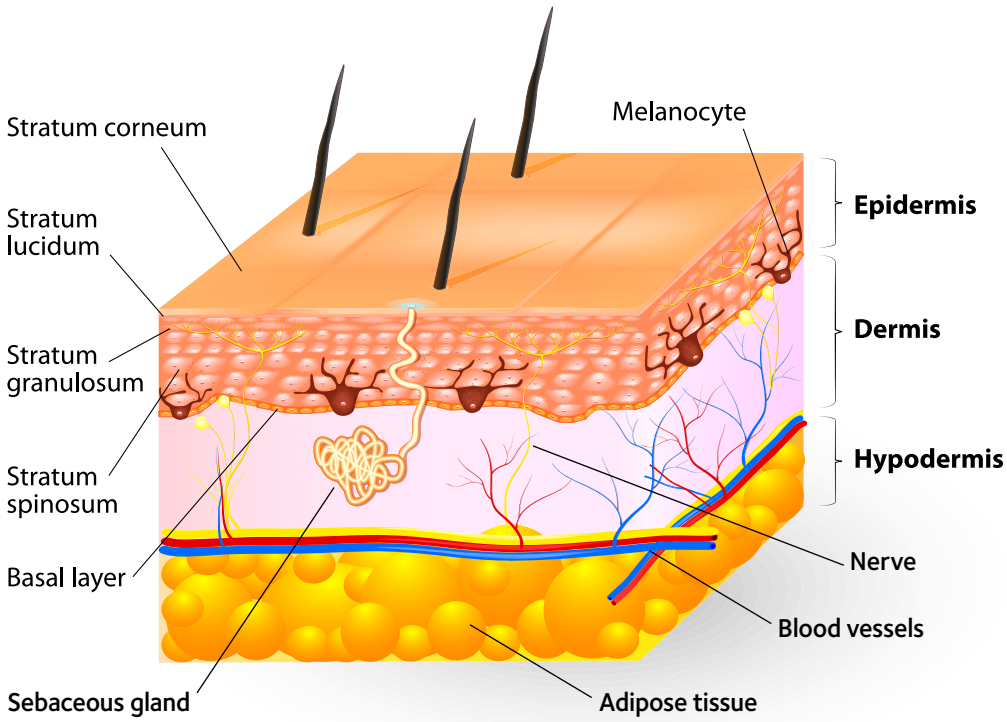


Figure illustrates angioedema, *Source: Allen P. Kaplan, Connie H. Katelaris, Paul C. Potter, Timothy J. Craig. GLORIA Module 7:Angioedema. 6. June 2011.*

They are common. 10% to 20% of the population is affected by acute urticaria at some point in their lives and only 3% will have chronic urticaria. 1 in 3 of them will have angioedema as well. It is less common to have angioedema alone.

Most of the cases are not considered dangerous, but can cause severe discomfort and alter the patient's quality of life.

THE LAYERS OF HUMAN SKIN



Urticaria happens on the first layer of the skin called the epidermis. Angioedema occurs in the deeper layers of the skin called dermis and hypodermis (subcutaneous tissue).

How do urticaria and angioedema happen?

Our body's defense system is in charge of checking the things that come into contact with us. It labels normal things as "safe" and dangerous things that can harm you (like viruses), as "unsafe". The defense system will protect us from harmful things by making antibodies to attack "unsafe" things.

The defense system may sometimes make a mistake by considering something safe, as unsafe and will attack it. For example, if the skin was stung by a honey bee, the defense system will think the venom from the honey bee is unsafe and will attack it. The chemicals the defense system releases to fight against "unsafe things" are called histamines. Histamines, along with other chemicals, cause the skin to itch, to redden, and to swell.

Mast cells are specialized cells within the immune system. They are formed in the bone marrow and when they are stimulated, they release a number of chemicals including histamine, leukotriene and others that start an allergic reaction. Histamine makes three major changes on the skin: a) redness; b) swelling; c) itchiness

Predisposing factors of urticaria or angioedema?

It is more likely that you will get urticaria or angioedema if your parents had/have it too. This is also true if your parents have allergies like allergic rhinitis, skin allergies, chest allergies or even food allergies. These cases are called hereditary, which means that they run in families. Your parents can pass it to you or you can pass it on to your children.

Urticaria alone or with angioedema is more common in women, whereas, angioedema alone is more common in men. Less than 10% of hives become chronic. A lot of times, hives attack occurs without anyone understanding why it has happened on the first attack. It is likely that it needs to happen again to give way in understanding the cause of the attacks.

Classification

Urticaria is classified according to the length of time that the swelling and itchiness stays. Less than six weeks is called acute. More than six weeks is chronic. This makes a difference in the way doctors treat these conditions.

Acute urticaria
Acute hives can develop fast and last for 1-2 hours. Sometimes, the hives can develop slower and last for 36 hours.

Chronic urticaria and Angioedema
These last for more than 6 weeks. Sometimes it can be hard to tell if one rash has been going on for 6 whole weeks, or if many small rashes that are close to each other are happening at the same time.

Chronic Idiopathic Hives and Idiopathic Angioedema
Most of these chronic cases happen without a known cause. When nothing seems to be causing the hives or angioedema, it is called idiopathic. It may be mild or severe. It also may come and go for some time. The lab tests usually show that everything is alright. Chronic urticaria and idiopathic angioedema do not need a contact with an allergen for them to happen – they just do

Causes

Allergens

An allergen is something that the body overly reacts to, when it gets in contact with it. Over reaction of the body's defense system will cause allergic urticaria, which is a common condition. Allergic reaction can happen when the allergen enters the body either by swallowing, breathing or touching it. The body's defense system releases histamine to fight against the allergen. The release of histamine ends up giving the hives.

Common allergens include foods (e.g. peanuts), drugs (particularly antibiotics such as penicillin), dust, and venoms from the stings of insects (e.g. bee, wasp, yellow jacket, hornet, fire ant). Generally, any kinds of allergen have the potential to cause hives. Even latex can be an allergen to some people.

If an allergen causes hives or swelling, it usually enters the body through the mouth (e.g. food, pills) or through injection (e.g. medicine, insect stings). Other kinds of allergen that you breathe in commonly cause asthma or rhinitis.

Non-specific Causes

Hives can be a part of a bigger reaction like anaphylaxis. Anaphylaxis is a life-threatening allergic reaction. It is very serious and can cause the blood pressure to drop to a very low level. This can be a total body allergic reaction to any number of things.

Some infections can also cause the defense system to react a certain way, thus giving urticaria if medications were taken for these infections, It can be hard to tell whether the urticaria was caused by the infection or whether it was caused by the medicine. Antibiotics like penicillin can be the cause of hives in some people. The doctor will likely order some tests to find out.

Some studies have shown the possible involvement of Helicobacter pylori (H. pylori) infection in chronic urticaria, but the relationship remains controversial. Research meta-analysis showed H. pylori infection is significantly, though weakly, associated with an increased risk of chronic urticarial.

Drugs that may cause hives are:

- Some types of pain killers: Aspirin, Nonsteroidal anti-inflammatory drugs (NSAIDs)
  E.g. Ibuprofen
- Some types of high blood pressure medicines: ACE inhibitors
  E.g. Enalapril
- Contrast dye used for imaging like computed tomography (CT) scan and X-ray.

A lot of the time, the case is idiopathic. About 35-45% of those may be related to autoimmunity. That means the body's defense system is attacking itself by mistake. These are usually less serious and can go away with anti-histamines.

Physical urticaia

urticaria and/or angioedema can be caused by things around us, like a change in temperature, something pressing on the skin, or even vibration. Two rare causes of hives are being exposed to sunlight and touching water.

Cold-dependent Disorders

Cold urticaria is caused by being in cold weathers (e.g. rainy, snowy, windy), cold environment (e.g. swimming) and while holding cold objects (e.g. cold glass of juice). It usually only affects the skin that was exposed to the cold. A small test can be done by placing an ice-cube on the arm for 4-5 minutes. If it is cold urticaria, the rash will appear there in the shape of the ice-cube a few minutes later.

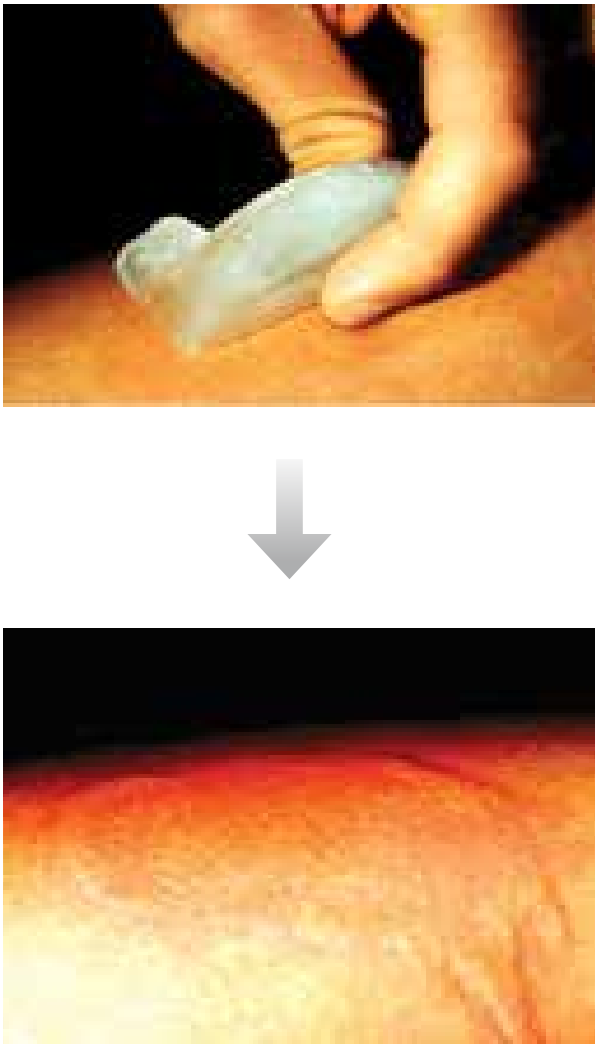


Figure illustrates cold urticaria, *by permission of world allergy organization (WAO) http://www.worldallergy.org/UserFiles/file/Atopic%20urticaria%20Maurer(2).pdf*

Cold-dependent dermatographism is a condition where hives form when the skin is scratched and then chilled. It affects 4-5% of the population. It's usually less pruritic than other causes of urticaria.

Figure illustrates dermatographism. *Source: Allen P. Kaplan. Systemic Manifestations of Atopic Urticaria. 9. June 2011. http://www.worldallergy.org/UserFiles/file/WAF-Istanbul(2).pdf*

Cholinergic or generalized heat urticaria
Cholinergic or generalized heat urticaria is the presence of small wheals surrounded by a large area of redness that appears after or during exercise, hot showers, sweating, and anxiety.

The rash starts on the neck and chest along with severe itching. It spreads slowly to the face, back, arms and legs. The wheals get bigger. Sometimes, they come together and look like angioedema. it could be associated with watery eyes, drooling and diarrhea all together. This is the only type of hives that can be caused by change in emotions.

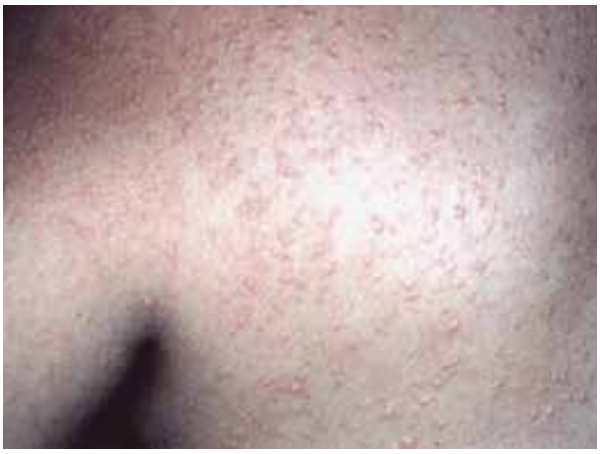
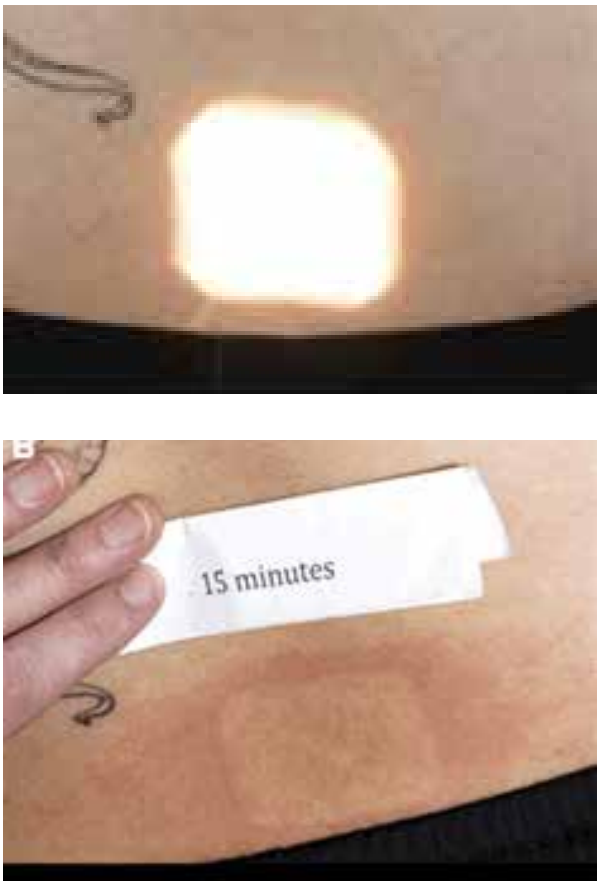


Figure illustrates heat urticaria, *source: Allen P. Kaplan. Systemic Manifestations of Atopic Urticaria. 8. June 2011. http://www.worldallergy.org/UserFiles/file/WAF-Istanbul(2).pdf*

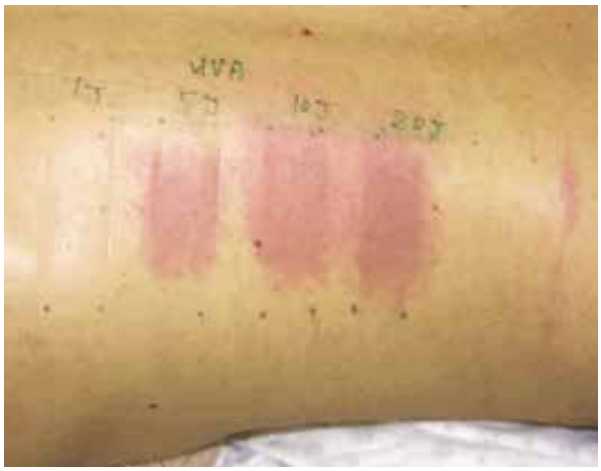
Exercise-induced anaphylaxis is when itching, skin rash, swelling, wheezing, and low blood pressure occur after or during exercise. The hives seen with exercise-induced anaphylaxis are large in size. Exercising should be stopped at the start of any symptoms.

Pressure-induced urticaria/Angioedema
Pressure-induced urticaria/angioedema happens 4-6 hours after constant pressing on the skin. There may be either a rash or swelling, or both on skin areas covered by tight clothing, on feet and hands after using them for a long time (e.g. hammering, walking), and on buttocks after sitting for long hours. Pressure-induced urticaria is commonly seen in patients with chronic urticaria.

Solar Urticaria
This is a rare disorder. Itching and redness occur in the first few minutes (1-3 minutes) after being out on sunlight. Redness and swelling can happen on the parts of your body not covered by clothes. It usually goes away within 3 hours.



Solar urticaria challenge testing. *A, Visible light exposure (380-700 nm) directed to the lower back with(B) development of raised, erythematous wheals 15 min postexposure. Source: Hirsh D. Komarow, A. Robin Eisch, et al. Images In Allergy. J ALLERGY CLIN IMMUNOL PRACT.789, September/October 2015.*



Urticarial reaction to 5-20 J of UVA light with the dose effect. Source: : Hirsh D. Komarow, A. Robin Eisch, et al. Images In Allergy. J ALLERGY CLIN IMMUNOL PRACT.790, September/October 2015.

Aquagenic Urticaria
This is a rare kind of urticaria that some people can get after contact with water.

Urticaria and systemic diseases
Urticaria could be a feature of systemic disorder: e.g. systemic lupus erythromatosis, Rheumatoid arthritis, vasculitis or malignancies. this type of urticaria usually persists for more than 24 hours and may cause staining of the skin after the rash disappears. The uricaria is more painful than itchy.

Urticaria and Autoimmune Thyroid Disease
Autoimmune disease means that the body produces antibodies that attack his own cells and organs.

Chronic urticaria can be associated with thyroid problems. The doctor can run tests to see whether or not your thyroid is affected. It may be the cause of your urticaria.

How do you know what is the cause of your symptoms?

Knowing the cause is important since the first step in treatment is to avoid the trigger.

The doctor will ask few questions and do a physical examination to try to identify the specific cause that triggers the symptoms. Some blood tests may be needed if the cause couldn't be identified and the symptoms persist for a long period of time to exclude any systemic disease.

Skin testing can be done if allergy is suspected to be the cause.

Treatment

- Even without treatment, most cases of acute urticaria and angioedema will resolve spontaneously within hours.
- Avoiding the allergens, if any, is the number one step.
- A special preservative-free diet has been suggested. It is also helpful to avoid stress, and fatigue.
- Try to keep the air around you cool and comfortable. Avoid tight or restricting clothes, long sitting, and long walking.
- There are also certain medications that may worsen chronic urticaria rather than help. Hence, it is best to avoid medicines such as angiotensin converting enzyme (ACE) inhibitors, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs).
- If the hives or angioedema are in fact part of an anaphylactic reaction, then you may be in urgent need of an **epinephrine injection**.
- **H1 antihistamines:** This will block the effect of histamine in your body.

1st generation H1 antihistamines:
- Diphenhydramine
- Chlorpheniramine
- Hydroxyzine

2nd generation H1 antihistamines:
- Cetirizine
- Loratadine

3rd generation H1 antihistamines:
- Levocetirizine
- Desloratadine
- Fexofenadine

The 2nd generation drugs are preferred as 1st line therapy due to less side effects (sedation, dry mouth, blurred vision, constipation, urine retention), and longer half-life which allows for less daily dosing. Continuous use on a daily basis is found to be superior to as needed use as they prevent the development of the swelling rather than treat already existing one.

The newer 2nd generation H1 antihistamines or what are known as The "3rd generation H1 antihistamines". They are safer and do not cause heart problems.

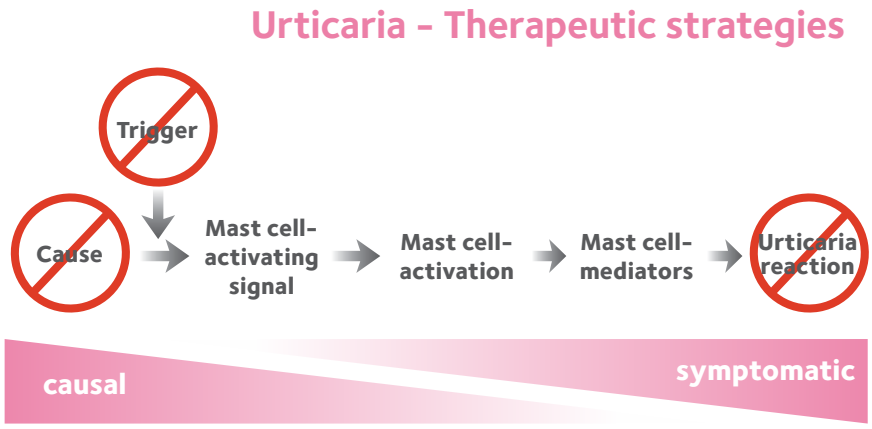


Figure illustrates therapeutic strategies for urticaria. *Source: Marcus Maurer. Atopic urticaria: Different phenotypes and diverse treatment. 14. June 2011. http://www.worldallergy.org/UserFiles/file/Atopic%20urticaria%20Maurer(2).pdf*

If there is no improvement of the symptoms after 2 weeks of initiation of 2nd generation antihistamine, the doctor may increase the dose of the drug.
The dose can be increased up to fourfold of the recommended dose to achieve symptomatic control.
Another option is adding a second 2nd generation antihistamine or adding an H2 antihistamine.

H2 antihistamines:
- Cimetidine
- Ranitidine

The doctor could also add another type of medications known as leukotriene receptor blockers: e.g. montelukast, zafirlukast. or zileuton, which blocks the production of leukotriene.

One of the chemicals produced by the immune system involved in urticaria formation is a substance known as leukotriene, so by inhibiting the action of this substance, urticaria formation decreases.

While taking these drugs, the patient needs to follow with his doctor and monitor his liver enzymes regularly.

The doctor can add a 1st generation antihistamine at bed time.

- Doxepin is an antidepressant that has both H1 and H2 antihistamines properties. It can be use, but it causes sedation.
  If the symptoms are still not controlled, the case is said to be refractory; the doctor will consider using an anti-inflammatory or immunosuppressive drug:
- Corticosteroids: can be used for a short time (few weeks) in severe or persistent cases, but because of their side effects, it is preferred not to use them for a long period of time.
- Cyclosporine is an immunosuppressive drug that can be used in persistent cases with no response to steroids especially autoimmune urticaria or as a steroid sparing agent in patient who had a response, but it has many side effects (e.g. it can damage the kidney and icrease the blood pressure)

Other immunosuppressive drugs that can be used: E.g. dapsone, sulfasalazine, hydroxychloroquine colchicine, Mycophenolate

These are highly effective, but require frequent monitoring with different laboratory testing to check for any side effects.

Intravenous immunoglobulins are also effective in refractory cases.

Omalizumab is an IgE antibody that was found to be effective in the treatment of chronic urticaria in patients with symptoms not controlled by H1 antihistamines. It prevents the IgE mediated activation of mast cells and the release of histamine which prevent urticaria formation. No monitoring is required.

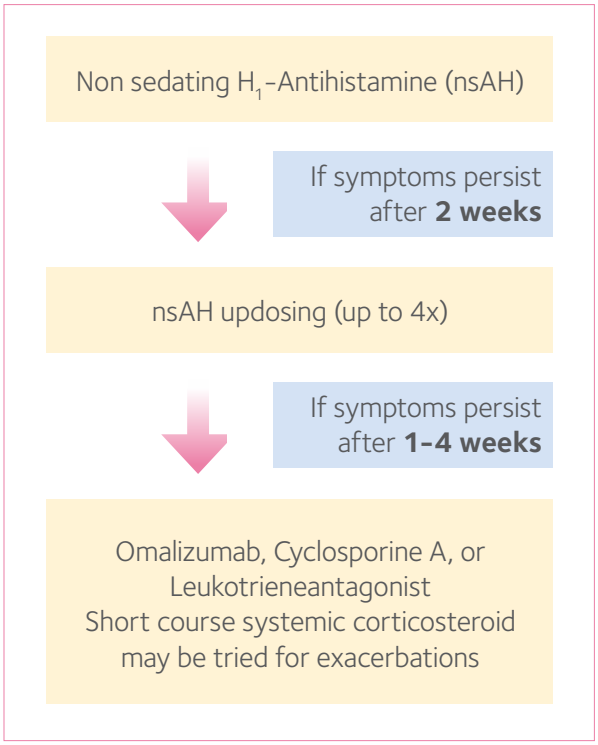


Figure illustrates urticaria/angioedema treatment, *Source: Zuberbier et al., The EAACI/GA²LEN/EDF/WAO Guideline for the definition, classification, diagnosis and management of Urticaria. The 2013 revision and update. Allergy 2014: 69; 868-887.*

Less preferred therapies due to side effects and frequent monitoring:

- Androgens
- Methotrexate
- Phototherapy
- Anticoagulants
- Cyclophosphamide
- Nifedipine
- Gold salts

After the symptoms become fully controlled, the patient will have to continue on the same treatment for 2 to 3 months before the dose can be reduced gradually or the medications stopped. This should be done after a physician consult.

Chronic urticaria is a disabling disease

Treat it until it is gone!

Source: Marcus Maurer. Atopic urticaria: Different phenotypes and diverse treatment. 6. June 2011. http://www.worldallergy.org/UserFiles/file/Atopic%20urticaria%20Maurer(2).pdf

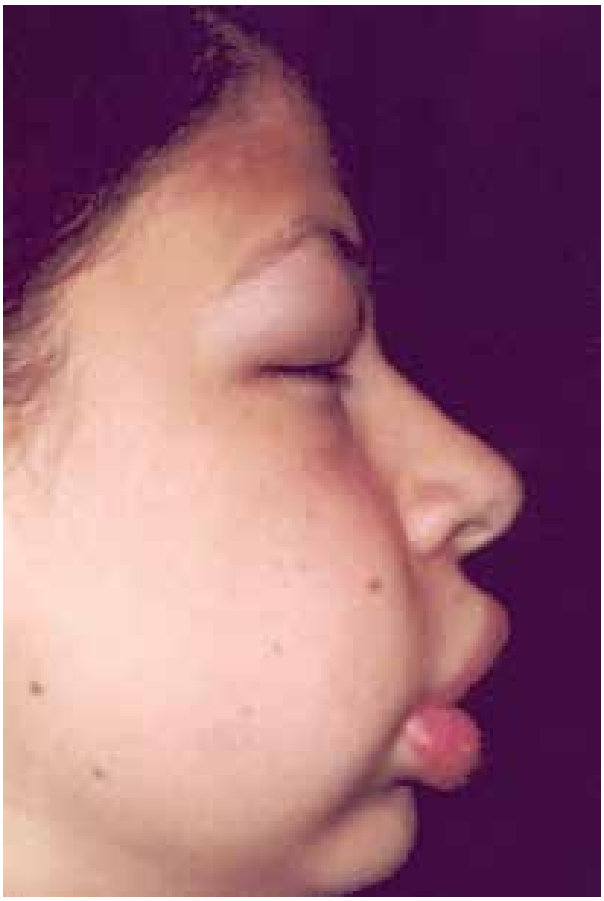
Hereditary Angioedema

Defining Hereditary Angioedema (HAE)?
HAE is a very rare but serious condition. It affects somewhere between 1 in 10,000 and 1 in 50,000 people. It causes attacks of swelling on different parts of the body, usually associated with abdominal problems. When the swelling occurs in the throat (larynx), it can stop a person's breathing and should be taken seriously. Years ago, 20-30% of people with HAE died before proper treatment was developed. That is why it's important for people to have increase awareness about HAE.

Symptoms of HAE

HAE presents with swellings of the skin on the face, arms & legs, and some cases would include swelling in the genitals. Rarely, it can cause swelling of the skin on the tummy, chest or neck. HAE can start affecting people at ages 7 - 13 and have been known to get worse during puberty. The swelling could be preceded by warning symptoms like fatigue, tingling sensation, flu-like symptoms or non-urticarial rash. It usually enlarges over the first 24 hours and may last for 3-4 days.

Figure illustrates hereditary angioedema, Source: Allen P. Kaplan, Connie H. Katelaris, Paul C. Potter, Timothy J. Craig. GLORIA Module 7:Angioedema. 14. June 2011.



Signs of HAE: big swelling on the face (lips or around the eyes), on the arms and legs, some cases genitals. *Source: Allen P. Kaplan, Connie H. Katelaris, Paul C. Potter, Timothy J. Craig. GLORIA Module 7:Angioedema. 8. June 2011.*

Angioedema becomes dangerous when swelling reach the throat and/or the tongue. It is uncommon but should be taken seriously because it can block your breathing. It starts as a tight feeling in the throat or a change in voice and can advance to a full block. Full block of your breathing doesn't happen often, but when it does, it can cause death. If you think you have HAE and feel tightness in your throat, have difficulty breathing or hear a change in your voice, please seek emergency medical help immediately.

HAE can also cause swelling of the internal organs. Swelling of the intestines can be painful. Some people experience vomiting and diarrhea. These, plus the swelling itself, can cause the person's blood pressure to drop dangerously. It sometimes results in unnecessary surgical operations or excessive use of pain medication.

Less common signs that can happen with HAE are: swelling of the tongue and the inner parts of the mouth, pain when swallowing, problems with eyesight, standing/walking straight, and problems with breathing. Other less common symptoms are urination problem, joints issue, and muscle pain.

How does HAE happen?

There are three main types of HAE. They are mostly due to a problem with a protein that prevents the leakage of fluids to the tissue. This protein in the body is called C1-esterase inhibitor (C1-INH). This problem is usually a result of something genetic. It causes the protein to not be made in enough amounts or makes the protein not work well. Also, parents with HAE should know that their children may have a 50% chance of having HAE.

Saying that HAE seems to come from a genetic problem doesn't mean it has to run in the family. Sometimes, the problem with the gene happens only to the person affected by HAE. This is called a spontaneous mutation of the gene.

Although C1-INH (C1 inhibitor) has other functions related to the immune system and blood clotting, these don't seem to be affected in HAE.

What triggers HAE attacks?

Sometimes these random attacks of swelling happen due to cold, heat, small injuries or even change in emotions. A lot of the time they seem to happen for no known reason at all! This is why people with HAE should always carry their medicines, wear some sort of HAE identifying tag with them and participate in raising awareness about this rare disease.

Attacks can be set off by small trauma to the area such as dental work, accidents, minor surgery, or tubes going down the throat, like for example during general anesthesia or camera scopes (endoscopies) for people who have stomach ulcers. Repeated activities like typing, gardening or construction work can trigger swellings. For some, standing for a long time can cause swelling on the bottom of the feet. The same goes for sitting for hours, where it can cause swelling of the buttocks. In women, menstruation and pregnancy seem to affect their attacks. In some, they have more attacks during their periods. Some have said that their attacks lessened during pregnancy. On the other hand, oral contraceptives and hormone replacement therapy is associated with an increase in the number of attacks and their severity.

Medicines normally used to treat high blood pressure called ACE Inhibitors have been known to increase the frequency and intensity of HAE attacks. Hence, ACE inhibitors are to be avoided.

Types of HAE

C1 inhibitor (C1-INH) mainly controls inflammation. When there's a problem with the C1 inhibitor, the body can't control inflammation very well and sometimes leads to HAE.

- Type I HAE: The body doesn't make enough C1 inhibitor. This type is the most common.
- Type II HAE: There are sufficient amounts of C1 inhibitor, but it doesn't work as well as it should.
- Type III HAE: More common in women and can become worse with pregnancy or birth control medicines. The C1 inhibitor is normal. The cause is unknown.

Diagnosing HAE

The doctor will ask you questions about the attack. The doctor will note if the HAE attack happened without itching. Usually, this helps to tell whether the swelling was due to HAE or part of an allergic reaction.

Since HAE is rare, diagnosing it may be difficult. This disorder may be hereditary but about a quarter of people with HAE have no family history of the condition. Sometimes, whether or not other family members have had history of this condition does not help that much with diagnosing HAE.

Patients will have a history of swelling for unknown reasons or unexplained belly aches with or without vomiting and diarrhea. Some may suggest of exploratory abdominal surgeries, however no exact solution was reached.

Screening by laboratory testing should be done if the physician suspects the condition from the history or physical examination, or in case of a positive family history of HAE.

Measuring the C4 complement level is used as a screening test. A normal level makes HAE unlikely.

If the C4 complement level is low, Laboratory analysis of blood samples or genetic testing is required to establish the diagnosis of HAE. There are two specific blood tests that confirm HAE:

- C1-inhibitor quantitative (antigenic): available at Hamad Medical Corporation (HMC).
- C1-inhibitor functional: not available (now) at HMC.

The tests can be done more than once to be sure. Levels may be normal when a person isn't having an attack at the time the test was taken. They should also be done at a trusted facility.

Treatment of HAE

As HAE is not an allergic condition, it won't respond to the medications used for treatment of urticaria/angioedema. Antihistamine, epinephrine and corticosteroids are not effective.

There is no cure for HAE; Management is divided into controlling the symptoms of acute attack, short

term prophylaxis to prevent the attack in conditions associated with increase risk and long term prophylaxis to decrease the frequency and severity of the attacks.

Treatment of acute attack

Available options for treatment of acute attack are:

- C1 inhibitor concentrate (plasma derived C1INH)
- Recombinant human C1 inhibitor.
- Ecallantide, a drug that prevents the production of bradykynin.
- Icatibant, which blocks bradykinin's receptor. This will not allow the swelling to happen.
- Human plasma, either solvent/detergent-treated plasma or fresh frozen plasma.

Laryngeal attack: this is the most serious type and requires early recognition and treatment to prevent the progression to full airway obstruction and death.

Early intubation to maintain the patency of airways is very important and should be done immediately when any sign of laryngeal swelling is detected. This includes any change in voice or noisy breathing.

After intubation, the first line drugs are C1 inhibitor concentrate, Ecallantide or Icatibant.

Human plasma is not considered a first line therapy because it is associated with increased risk of transmission of infections. It also can cause exacerbation of the attack.

Gastrointestinal attack: in addition to treatment with C1INH concentrate, Ecallantide and Icatibant, fluid replacement and control of pain and nausea is required.

Personal emergency plan: to ensure appropriate care and to make sure you are prepared in case of emergency:

- The patient should wear a medical information bracelet that identifies his condition.
- The patient should carry a form or ID card that gives some information about his condition and treatment options in case of acute attack.
- The patient should communicate with the health care providers to discuss the condition and ensure the availability of needed therapy.
- Share the emergency plan with family, friends and colleagues.
- Some of the drugs can be self- administered at home. The patient should discuss this with his physician as the decision to prescribe therapies for acute treatment at home must be individualized. The clinician must consider each patient's situation, history of attacks, proximity to care, ability to self-administer medications, and preferences

Hereditary Angioedema Identification Card:

Patient's name: .....

Diagnosis: Hereditary angioedema

Treating clinician's name and contact information:

.....

.....

.....

.....

Hereditary angioedema (HAE) is a disorder of C1 inhibitor, in which there are recurrent episodes of angioedema (deep tissue swelling). These most commonly affect the skin and small bowel. Swelling can also affect the pharynx and larynx. Swelling in HAE is caused by bradykinin. This type of swelling does NOT respond to intramuscular epinephrine, glucocorticoids, or antihistamines. It is not an allergic reaction.

ACUTE SWELLING SHOULD BE MANAGED AS FOLLOWS:

- Any swelling involving the throat or structures near the throat should be immediately evaluated to determine the status of the airway and then regularly monitored. **LARYNGEAL EDEMA CAN PROGRESS RAPIDLY TO ASPHYXIATION AND CAN BE FATAL!** The patient should be in a setting in which endotracheal intubation or tracheostomy can be performed immediately if necessary, although most attacks resolve without requiring this intervention.

Pharmacologic treatments to reduce swelling include:

- Infusion of C1 inhibitor concentrate (available products are Cinryze [United States only], Berinert [United States], Berinert P [Europe], or Ruconest).
- Ecallantide (Kalbitor) (available in the United States only). This medication blocks production of bradykinin.
- Icatibant (Firazyr). This medication is an antagonist of the bradykinin B2 receptor.
- If none of these therapies is available, then plasma may be used. Solvent/detergent-treated plasma is preferred over fresh frozen plasma is preferred over fresh frozen plasma. The initial dose is 2 units.

By permission of www.uptodate.com, http://www.uptodate.com/contents/hereditary-angioedema-treatment-of-acute-attacks?source=search_result&search=hereditary+angioedema&selectedTitle=2%7E141

Short term prophylaxis

This means giving drugs for a short period of time before a surgery or other procedure that could cause an acute attack in a patient with HAE.

Oral and dental procedures are known triggers of swelling and can cause throat swelling that usually develops within 48 hours after the procedure, so C1INH concentrate is given 1 to 2 hours before and should be available for 2 days after.

An alternative is administration of androgens such as danazol for 5 days before and 3 days after the procedure.

Long term prophylaxis

These are drugs given to decrease the frequency of attacks and improve the quality of life.

- Anabolic steroids (also known as androgens) such as Danazol, Oxandrolone and Stanozolol have, historically, been the most commonly used medicines to help prevent HAE attacks. While anabolic steroids have been shown to be useful, they are not well-tolerated by many women and are contraindicated in pregnancy. They can harm the liver and cause problems with cholesterol. Also, they can't be used on children. Anabolic steroids can cause a person to get attacks of belly or throat swelling when stopping the medicine; as a result this may require hospitalization.

  Due to their side effects, androgens are only used in patients with severe or frequent attacks.

- antifibrinolytic drugs such as tranexamic acid or aminocaproic acid are sometimes used as alternative to androgens.

On 2014, the US FDA has approved manufactured C1 inhibitor injections, among others, for the treatment of acute attacks of HAE in adults and adolescents. The health provider should teach the patient how to inject this medication by himself. Other injections have also been approved to be taken 2-3 times weekly like purified C1-INH (Cinryze) to help prevent swelling attacks.

Action Plan for HAE

Step 1: Identify Symptoms

Step 2: Start Action

Symptoms	Action
MILD : • Peripheral Swelling • Mild Abdominal Pain	**Pain Relief:** Observe progress!
MODERATE TO SEVERE (Peripheral Swelling) • Severe facial, genital, or peripheral swelling • Significant discomfort or disability	**For Adult:** Administer Icatibant (Firazyr) SQ or C1 INH (Berinert = 20 u/kg IVI or Cinryze = 1,000U IVI) **For Children:** Administer or C1 INH (Berinert = 20 u/kg IVI or Cinryze = 1,000U IVI)
MODERATE TO SEVERE (Abdominal Symptoms) • Moderate – Severe Abdominal Pain • Vomiting • Distension • Dehydration (dry mouth, thirst, confusion)	**For Adult:** Administer Icatibant (Firazyr) SQ or C1 INH (Berinert = 20 u/kg IVI or Cinryze = 1,000U IVI) **For Children:** Administer or C1 INH (Berinert = 20 u/kg IVI or Cinryze = 1,000U IVI) **URGENT hospital treatment is needed if symptoms last longer than 2 hours!** **Additional Hospital Treatment:** • Opiate Analgesia • IV fluid rehydration • Give 2nd dose of specific treatment
MODERATE TO SEVERE (Airway Swelling) • Tongue swelling • Throat swelling • Difficulty breathing, swallowing, talking	**For Adult:** Administer Icatibant (Firazyr) SQ or C1 INH (Berinert = 20 u/kg IVI or Cinryze = 1,000U IVI) **For Children:** Administer or C1 INH (Berinert = 20 u/kg IVI or Cinryze = 1,000U IVI) **Call Ambulance 999 Seek URGENT hospital treatment** **Additional Hospital Treatment:** • Prepare for emergency intubation or cricothyrotomy • Give 2nd dose of specific treatment if inadequate response after 1 hour

(This action plan was taken from Ascia (www.allergy.org.au)

***ADRENALINE, ANTIHISTAMINES, AND CORTICOSTEROIDS are NOT EFFECTIVE for HAE attacks

Patient Education Checklist

- I have received urticaria/angioedema education.
- I understand what is Urticaria and angioedema.
- I understand how they develop.
- I have a clear idea what the causes of my condition are.
- I have reviewed the medicines and know how and when they are taken.
- I understand what HAE is.
- I know what the triggers of HAE are.
- I have a clear explanation of how to manage an acute attack.
- I understand the short term and long term prophylaxis.
- I understand the importance of having a personal emergency plan.
- I will follow my HAE action plan.

Epilogue

We would like to thank you for giving us the opportunity to serve you. We hope, through this booklet we have accomplished the goal of increasing your awareness about urticaria, angioedema and hereditary angioedema.

In our endeavor to improve our services, we would really appreciate to hear your feedback and opinion.

We look forward to your continuous support and cooperation in achieving our goal which is helping you live a healthy life.

For any questions, please contact us on email:

madeli@hamad.qa or AIAP@ hamad.qa

Dr. Mehdi Adeli, MD, FAAAAI, FAP
Senior Consultant, Allergy and Immunology
Assistant Professor, Weill Cornell Medicine-Qatar
Allergy and Immunology Awareness Program (AIAP)
Pediatrics Department, Hamad Medical Corporation
Doha, Qatar

References

1. Daniel C. Adelman, Thomas B. Casale, Jonathan Corren. Urticaria and Angioedema. Manual of Allergy and Immunology. Page (243-258), 2012.
2. Carsten Bindslev-Jensen. Urticaria. Global Atlas of Allergy. Page (2014 ,(208-206.
3. M Ferrer, J Bartra, A Giménez-Arnau, I Jauregui, M Labrador-Horrillo, J Ortiz de Frutos, J F Silvestre, J Sastre, M Velasco, A Valero,Management of urticaria: not too complicated, not too simple.Clin Exp Allergy. 2015 April; 743–731 :(4)45.
4. Sun Hee Choi, Hey Sung Baek,Approaches to the diagnosis and management of chronic urticaria in children.Korean J Pediatr. 2015 May; 164–159 :(5)58.
5. Giuliana Ferrante, Valeria Scavone, Maria Concetta Muscia, Emilia Adrignola, Giovanni Corsello, Giovanni Passalacqua, Stefania La Grutta.The care pathway for children with urticaria, angioedema, mastocytosis,World Allergy Organ J. 5 :(1)8 ;2015. Published online 2015 February 2. doi: 10.1186/s-0052-014-40413x
6. Paulo Ricardo Criado, Roberta Facchini Jardim Criado, Celina Wakisaka Maruta, and Vitor Manoel Silva dos Reis,Chronic urticaria in adults: state-of-the-art in the new millennium. An Bras Dermatol. 2015 Jan-Feb; 89–74 :(1)90.
7. Morgan M, Khan DA.Therapeutic alternatives for chronic urticaria: an evidence-based review, part 1. Ann Allergy Asthma Immunol. 2008 May;-403:(5)100 11
8. Morgan M, Khan DA,Therapeutic alternatives for chronic urticaria: an evidence-based review, Part 2. Ann Allergy Asthma Immunol. 2008 Jun;26-517:(6)100.
9. Kaplan AP, Greaves M. Pathogenesis of chronic urticaria.Clin Exp Allergy. 2009 Jun;87-777:(6)39. Epub 2009 Apr 22. Review.
10. I Jáuregui,M Ferrer, J Montoro, I Dávila, J Bartra, A del Cuvillo, J Mullol, J Sastre, A Valero . Antihistamines in the treatment of chronic urticaria . J Investig Allergol Clin Immunol 2007; Vol. 17, Suppl. 52-41 :2
11. Kaplan AP et al. Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol, 18774392 .2008.
12. Huiyuan Gu, Lin Li, Min Gu, and Guoxin Zhang,Association between Helicobacter pylori Infection and Chronic Urticaria: A Meta-Analysis, Gastroenterology Research and Practice Volume 2015, Article ID 9 ,486974 pages http://dx.doi.org/486974/2015/10.1155
13. Hirsh D. Komarow, A. Robin Eisch, et al. Images In Allergy. J ALLERGY CLIN IMMUNOL PRACT.790-789, September/October 2015.
14. Allen P. Kaplan. Systemic Manifestations of Atopic Urticaria. 8,9,12. June 2011.
15. Allen P Kaplan, Malcolm W Greaves. GLORIA Module 12: Urticaria. 97 pages. June 2011.
16. Marcus Maurer. Atopic urticaria: Different phenotypes and diverse treatment. 51 pages. June 2011.