PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Urticaria**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Urticaria

Developed by Dayae Jeong and Dr. Wade Watson for PedsCases.com.
February 11th, 2018

Introduction:

Hi everyone, my name is Dayae Jeong and I am a medical student at McMaster University in Ontario, Canada. This PedsCases podcast on urticaria was developed with the help of Dr. Wade Watson, a pediatric allergist, professor of pediatrics, Dalhousie University, and head of the Division of Allergy at IWK Children's Hospital. This podcast is designed to give you an overview of urticaria.

We will be addressing the following questions in our podcast:

1. What is urticaria?
2. What is the pathophysiology of urticaria, and what causes it?
3. How is urticaria classified?
4. How do you diagnose urticaria?
5. What are the management options for urticaria?

Defining Urticaria

Let's start with a case. You are a 3rd year medical student working in a general pediatrician's office, and asked to see Jimmy. Jimmy is a 6-year-old boy who is being brought in by his mother because he broke out in hives a few days ago.

Urticaria, more commonly known as hives, is a term used to describe mast cell and basophil mediated pruritic skin lesions. It presents with raised, red or pink lesions that have wheals (pale centers). These lesions are polymorphous, so they may be round or irregularly shaped. They can range in size from a few millimeters to a few centimeters. Typically, they disappear within 48 hours of appearing but may reappear[1,2].

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Pathophysiology and Etiologies of Urticaria

Urticaria is caused by degranulation of mast cells and basophils. Both types of cells are members of the innate immune system, and primarily located in the skin and mucosa. Degranulation releases many inflammatory mediators such as histamine, leukotrienes, and prostaglandins, into the surrounding space and induce vasodilation. The resulting influx of plasma into and below the skin and mucosa is what causes the swelling and redness associated with urticaria. Histamine also binds to itch receptors of the nervous system, causing pruritus. Sometimes, there is a delayed release of additional inflammatory cytokines such as tumor-necrosis-factor, interleukin 4 and interleukin 5, over the next 4-8 hours, leading to a prolonged reaction[1,3].

We can divide the factors that cause degranulation of mast cells and basophils into those which are immunologically mediated and those which are not. Among immunologically mediated factors, there is a further divide between IgE antibody mediated and non-IgE mediated urticaria[1].

IgE-mediated immunologic reactions occur on exposure to antigens that have associated IgE antibodies in the body. IgE antibodies tend to be located on mast cell surfaces, and cluster together when they are bound by their antigens, leading to degranulation. In many, cases, these antigens are allergens – including aeroallergens, contact, food, and drug allergens. Common food allergens in Canada include milk, eggs, peanuts, tree nuts, fish and shellfish. Common drug allergens are antibiotics in the beta-lactam class, particularly penicillin. Non-allergen antigens include insect venom and parasites[1,4–6]

Next, non-IgE mediated immunologic reactions result when components of the immune system other than IgE antibodies trigger degranulation. In fact, urticaria in children is most commonly caused by viral infections such as rhinovirus, rotavirus and EBV. These infections activate the complement system to trigger degranulation. Non-IgE mediated immunologic reactions may also involve auto-antibodies in the context of autoimmune diseases like lupus, vasculitides, rheumatoid arthritis, Sjogren's syndrome, celiac disease and lymphoma. Lastly, mastocytosis is a condition of an increased number of mast cells, and would also fit in this category[1,4].

Finally, non-immunologic urticaria results when the inciting agent directly causes mast cell and basophil degranulation. Medications in this category are aspirin, NSAIDs, vancomycin, and opiates. Foods in this category include those with large amounts of salicylates or histamine. Many fruits have a high concentration of salicylates, and improperly stored fish can accumulate high levels of histamine from bacterial metabolism. Finally, physical triggers for urticaria belong in this category. These include pressure on the skin (also known as dermatographism), rises in basal body temperature from exercise or heat (cholinergic urticaria), exposure to cold (cold-induced urticaria),

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exposure to ultraviolet light (solar urticaria), and exposure to water (aquagenic urticaria)[1,4].

Despite the great number of possible etiologies, a large proportion of urticaria is idiopathic[1,2,4].

Clinical Presentation and Classification

We have already discussed the physical characteristics of an urticarial rash, but let's review it one more time. You are looking for pruritic, raised, red or pink skin lesions that have a pale wheal in the center. They may come in any shape or size. In 40% of cases, urticaria is accompanied by angioedema, which is swelling beneath the skin. Angioedema frequently presents as puffiness around the eyes and swelling of the lips and tongue. If urticaria is caused by allergic triggers, it can be accompanied by edema in the airway and difficulty breathing, which should be treated as an emergency[1,4]. Please refer to the Pedscases podcast on anaphylaxis for a separate discussion on this topic.

Let's go back to Jimmy. His mother describes his rash as bumpy and red, much like "a bunch of mosquito bites". This rash sounds like urticaria so far, but your suspicions are confirmed when she pulls up some pictures on her phone. She also notes that he had very mild angioedema around his lips, but no stridor, cyanosis or other signs of difficulty breathing. Jimmy's urticaria can be categorized based on the timeline of his symptoms, and there are two time periods that we must distinguish.

The first is the duration of time for which the individual lesions are present. Individual lesions of urticaria last for less than 48 hours, but recur. Lesions that remain for greater than 48 hours may indicate urticarial vasculitis, which indicates an inflammation of the skin blood vessels and is a more serious condition. We will talk more about this when we review the differential diagnosis[2,4].

The second timeframe to determine is the total amount of time for which the episodes of urticaria have been occurring. If the rash has been present for most days of the week, for less than 6 weeks, we classify it as acute urticaria. If the rash has been present on most days of the week for 6 weeks or longer, we classify it as chronic urticaria. Chronic urticaria is much more common in the adult population, particularly in females[2,4].

Although acute and chronic urticaria are both frequently idiopathic in nature, their etiologies do differ. Acute urticaria is usually secondary to infection, exposure to allergens and venoms, and medications. In contrast, chronic urticaria is often due to physical triggers or an autoimmune process[2,4].

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Diagnosis

A diagnosis of urticaria is based on a thorough history and physical examination.

In your history, it is important to ask questions about the physical appearance of the rash. Describe the skin lesions in terms of size, shape, color, texture, and any associated skin changes. What is the distribution of the rash? Try to qualify the severity of the rash and its impact on the child's life. It is also necessary to clarify the two aspects of timing that we discussed earlier. How long do the skin lesions last? How long has the rash been occurring as a whole? Next, ask whether any triggers have already been identified. If not, go through the most common causes in a systematic fashion, asking about recent infections, new exposures to potential allergens, venoms, new medications, physical triggers and autoimmune symptoms[1,2].

It may also be beneficial to inquire into a personal or family history of the atopic triad, which consists of eczema, asthma and allergic rhinitis. Allergies travel in packs, and these individuals tend to have a genetic pre-disposition to develop IgE mediated responses to environmental triggers[2].

A physical examination can be helpful in diagnosing urticaria. Start with vital signs if you have any concerns that the child is unstable. As with any child, examine the cardiovascular, respiratory, gastrointestinal, and ENT systems. Next, move on to a thorough exam of the skin. If the rash is present at the time of the visit, describe the morphology, distribution, and whether it is painful or pruritic. If the rash isn't present, you can ask the parents if they have any pictures. Check for any yellow or tan pigmented lesions which can indicate urticaria pigmentosa, a form of cutaneous mastocytosis[7].

In many patients, a history and physical are enough for a diagnosis of urticaria. If the history is ambiguous and insufficient for a diagnosis, select additional investigations may be warranted.

When considering physical urticaria, it is possible to expose the patient to a physical stimulus and watch for a reaction. For example, dermatographism can be confirmed by applying light pressure on the back with a tongue depressor, then watching for hives to form in the same pattern. If you suspect that there is an allergic trigger for the urticaria, skin prick testing and serum IgE testing may be done. If you suspect an autoimmune origin, serum protein electrophoresis (SPE) can confirm the presence of auto-antibodies. An autologous serum skin test (ASST), is essentially a skin prick test with the patient's own serum, and can also reveal a reaction. Again, none of these tests are routinely done and you should refer the patient to an allergist at this stage[1,2].

Let's revisit Jimmy. You ask his mother about any possible triggers, and she mentions that Jimmy has been having some upper respiratory tract infections symptoms of runny

nose and cough for a few days. He has been afebrile so she has not given him any NSAIDs, but she did give him some kids' Claritin for the rash, which up within an hour. He is otherwise healthy, and does not take any medications or have any known allergies. You suspect that he may have a viral URTI which led to his urticaria, and decide that no investigations are warranted.

Differential Diagnoses

There are many other diagnoses that must be considered in a patient presenting with rash. The nature of the rash will narrow this list down, as a vesicular or painful rash likely points to an infectious agent like varicella or coxsackie virus. Chronic atopic dermatitis will result in dry and thickened skin around the rash. Symmetric, target lesions which progress in a distal to proximal manner are more indicative of erythema multiforme minor, a T-cell mediated type IV hypersensitivity reaction[2,8].

If the patient is presenting with a rash characteristic of urticaria, but it is painful and lasts more than 48 hours, consider urticarial vasculitis. Urticarial vasculitis is an autoimmune inflammatory condition of small blood vessels. You should also consider urticaria pigmentosa if you see pruritic lesions that are yellow to brown, or localized hives form after rubbing the skin (also known as Darier's sign). Urticaria pigmentosa is a common manifestation of both cutaneous and systemic mastocytosis[4,7].

Management of Urticaria

Management of acute and chronic urticaria relies on avoidance of triggers and anti-histamines. In some cases, avoidance of triggers is not sufficient to control the urticaria, or there are no known triggers to avoid. At this point, regular use of second generation, non-sedating H1 receptor antihistamines is the first-line management. These include fexofenadine, desloratadine, loratadine, levocetirizine, cetirizine, bilastine and rupatidine. Try to avoid first generation H1 receptor antihistamines as they are sedating. If a patient is not responsive to the initially prescribed antihistamine, it is worth trying another in the same class or increasing the dose by up to 4 times the usual. If that still does not provide relief, adjunct therapies can be added in the form of H2 receptor antihistamines like cimetidine, ranitidine, and nizatidine, or leukotriene receptor antagonists such as montelukast[1,2,4].

Patients with severe chronic urticaria that is refractory to treatment should be referred to an allergist or dermatologist, who may titrate them on immunosuppressive and immunomodulatory therapies. The treatment of choice is omalizumab (an anti-IgE monoclonal antibody), but cyclosporine, sulfasalazine, IVIG, and dapsone are also possible options. In the short term, severe and unresponsive symptoms may be treated with a 3-10 day course of oral corticosteroids. This is uncommon and not treated as the

standard because of the serious side effects of steroids, and a risk of relapse once they are stopped[1,2].

Approximately a third of patients with chronic urticaria will have spontaneous resolution of symptoms within a year, and another third will experience improvement in their symptoms. Patients with chronic idiopathic urticaria do better in terms of symptom resolution than those with chronic physical urticaria[1,4].

Let's re-visit Jimmy one last time. His mother wants to know how to stop this from happening again. You tell her that although there is no way to prevent the urticaria from returning, she can provide symptomatic relief. You tell her she can continue to use loratadine as needed, and reinforce that she should avoid Benadryl as it is sedating.

Summary

We've reached the end of this PedsCases podcast, so it's time for a quick recap. Here are some take-home points to remember:

1. Urticaria, commonly known as hives, is characterized by a pruritic rash. The rash consists of red, raised lesions with pale centers. The shape and size of the lesions may vary.
2. Urticaria results from degranulation of mast cells and basophils.
3. Urticaria that has been present for fewer than 6 weeks is classified as acute, whereas urticaria that has been present for greater than 6 weeks is classified as chronic.
4. Half of acute urticaria cases are idiopathic. Other common etiologies include viral infections, allergens, medications, and bacterial and parasitic infections.
5. Most chronic urticaria is also idiopathic. Other common etiologies incude autoimmune processes and physical stimuli.
6. The first line management for urticaria is avoidance of triggers and regular use of second-generation, non-sedating, H1 antihistamines.

Thank you for listening to this PedsCases podcast. Stay tuned for more!

References

1. Schaefer P. Acute and Chronic Urticaria: Evaluation and Treatment. 2017;95(11).
2. Kanani A, Schellenberg R, Warrington R. Urticaria and angioedema. *Allergy, Asthma Clin Immunol*. 2011;7(Suppl 1):S9. doi:10.1186/1710-1492-7-S1-S9.
3. Barbara A. Muller. Urticaria and Angioedema: A Practical Approach. *Am Fam Physician*. 2004;69(5):1123-1128.
4. Deacock SJ. An approach to the patient with urticaria. *Clin Exp Immunol*. 153(2).

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5. Swain AR, Dutton SP, Truswell AS. Salicylates in foods. *J Am Diatetic Assoc*. 1985;85(8):950-960.
6. Kurowski K, Boxer RW. Food Allergies: Detection and Management. 2008;77(12).
7. William A. Alto. Cutaneous and Systemic Manifestations of Mastocytosis. *Am Fam Physician*. 1999;59(11):3047.
8. Michele R., Sternbach MR, Hsu WT. Erythema Multiforme. *Am Fam Physician*. 2006;74(11):1883-1888.

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