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This is a text version of a podcast from Pedscases.com on “Anaphylaxis in Children.” 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.

Anaphylaxis in Children

Developed by Alex McNulty and Dr. Jessica Foulds for PedsCases.com.
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Hello listeners, my name is Alex McNulty, and I am a medical student at the University of Alberta in Edmonton, Alberta, Canada. This podcast was developed with the help of Dr. Jessica Foulds, a pediatrician at the Stollery Children’s Hospital in Edmonton, Alberta Canada. The purpose of this podcast is to give you a basic understanding of, and an approach to, anaphylactic reactions in children.

In this podcast we will address the following objectives:

1. Define anaphylaxis
2. Describe the pathogenesis of anaphylactic reactions
3. Discuss triggers of anaphylaxis
4. Describe anaphylactic symptoms and signs
5. Determine how to diagnose anaphylaxis
6. Provide an approach for managing anaphylaxis
7. Discuss the types of medications used in treatment

Case

Let’s start with a clinical case. Imagine you are a third-year medical student working in the pediatric emergency room on a steady evening shift. You have been asked to see a 14-year-old boy who presented with hives, shortness of breath, wheeze, nausea, diarrhea, and abdominal cramping after taking penicillin for strep throat. He has taken penicillin in the past with no concerns. Anaphylaxis comes to mind. But, you wonder is this true anaphylaxis?

So, let’s start first by explaining what we mean when we say a patient has had an anaphylactic reaction.

Pathophysiology

Anaphylaxis is defined as “a serious allergic reaction that is rapid in onset and may cause death.”(1) Anaphylaxis occurs when there is a massive, IgE-mediated, systemic release of mast cell and basophil contents. In the presence of allergens, allergen-

specific IgE molecules on the surface of mast cells and basophils will bind to these allergens. When more than one IgE molecule on the surface of a mast cell or basophil binds the same allergen, the IgE molecules become cross-linked. This cross-linkage initiates a protein cascade within the cell that culminates in degranulation. Inflammatory mediators that are released include histamine, leukotrienes, and platelet activating factor. Importantly, a previous exposure is required in order for a patient to become sensitized to an allergen. This means anaphylaxis cannot occur with the first exposure to an allergen, but may occur with any subsequent exposure.

There are two types of histamine receptors. Activation of H1 histamine receptors leads to smooth muscle constriction and increased permeability of endothelial cells. These effects are responsible for bronchoconstriction, increased bowel peristalsis, vasodilation, and increased vascular permeability. This helps explain anaphylactic symptoms including shortness of breath, wheeze, nausea, abdominal pain, diarrhea, urticaria, and angioedema. Stimulation of H2 histamine receptors also increases permeability of endothelial cells, increases gastric acid secretion from stomach parietal cells, and stimulates airway mucus production. These effects contribute to swelling, gastro-intestinal, and respiratory symptoms of anaphylaxis.

In our case our patient had recently taken penicillin. Is this an important part of the history? Let's review anaphylactic triggers to find out!

Unfortunately, the trigger for an anaphylactic reaction is often never found, as only 1/3 of cases will present with an identifiable cause. When there is an identifiable trigger, food allergens are the most common. Of these, peanuts, tree nuts, fish, milk, eggs, and shellfish are most frequently involved in serious reactions. Reactions to these allergens can even lead to death. Drugs can also trigger anaphylaxis. These include penicillins, cephalosporins, sulfonamides, and NSAIDs. Reactions to hymenoptera venom are also common. This category includes stings or bites from bees, wasps, yellow jackets, hornets, and fire ants. Anaphylaxis can also occur with exposure to latex, allergen immunotherapy, food dependent exercise, vaccinations, radio contrast dyes, blood products, and idiopathic causes.

Clinical Presentation

In our case, our patient's symptoms included shortness of breath, nausea, diarrhea, and abdominal cramping. Some signs he presented with include hives and wheeze. Are all of these consistent with anaphylaxis?

The Canadian Paediatric Society has organized the signs and symptoms of anaphylaxis based on the organ system involved, which includes the central nervous system, the skin, the upper and lower airways, the cardiovascular system, and the gastrointestinal system. Let's review them now.

If the patient has been difficult to settle, has been more sluggish or apathetic, or has an altered level of consciousness, think about central nervous system involvement.

The skin is often involved and the patient may present with urticaria, pruritis, angioedema, and flushing. Let's review the differences between urticaria and angioedema quickly. Urticaria, or hives, involves swelling of the dermis and can be described as pruritic lesions with raised pale centers and surrounding erythema that can occur anywhere on the body. They manifest quickly after exposure to an allergen and may last from 1-24hrs. Angioedema, however, involves swelling of the deeper dermis or subcutaneous tissue and typically occurs in the peri-oral and peri-orbital regions, as well as the tongue and in the hands. It is typically not pruritic and lasts longer than 24hrs.

Urgent intervention may be required if swelling causes obstruction of the upper airway. Edema of the oropharynx, larynx, uvula, lips, or tongue can manifest with stridor and hoarseness. Other upper airway symptoms of anaphylaxis include sneezing, and rhinorrhea.

Cough, wheeze, shortness of breath, and tachypnea suggest the lower airway has been affected. Respiratory arrest can occur in severe cases.

Symptoms suggesting the cardiovascular system is involved include dizziness, lightheadedness, and if the patient has had any syncopal episodes. Cardiovascular signs include tachycardia, hypotension, pallor, and cyanosis. More infrequently, arrhythmias and even cardiac arrest can occur.

Gastrointestinal symptoms that occur in anaphylaxis include nausea, vomiting, diarrhea, and abdominal pain.

Anaphylaxis can occur in biphasic reactions with a second phase of symptoms occurring 1-72 hours after the initial phase. However, this second phase most often occurs in the first 4-6 hours. The second phase usually involves the same organ system. Importantly, the severity of the second phase cannot be predicted based on the severity of the first phase.

Diagnosis

According to the Canadian Paediatric Society, anaphylaxis is highly likely if any of the following 3 criteria are met:

1. An acute onset of illness, occurring within minutes to several hours, involving the skin, mucosa, or both. Manifestations can include generalized hives, pruritis, flushing, or swollen lips, tongue, or uvula. In addition, there must be at least one of the following:
    a. Respiratory involvement, which can include shortness of breath, bronchospasm causing wheeze, stridor, reduced peak expiratory flow, or hypoxemia

    OR

   b. A reduction in blood pressure or symptoms consistent with end organ dysfunction. This can include hypotonia, syncope, or incontinence

To recap, criterion 1 requires an acute onset of skin and/or mucosal involvement with either respiratory compromise or a drop in blood pressure or evidence of end-organ dysfunction.

2. Criterion 2 requires an acute onset, within minutes to several hours, of any two or more of the following criteria after exposure to a likely allergen:
   a. Skin and/or mucosa involvement, which can include generalized hives, pruritis, flushing, and angioedema
   b. Respiratory involvement, such as shortness of breath, wheeze, stridor, reduced peak expiratory flow, or hypoxemia
   c. A reduced blood pressure or symptoms consistent with end organ dysfunction, such as hypotonia, syncope or incontinence
   d. Persistent gastrointestinal complaints, which can include crampy abdominal pains and vomiting.

To repeat, criterion 2 requires an acute onset of any two of the following after exposure to a likely allergen: skin and/or mucosal involvement, respiratory compromise, hypotension, or end organ dysfunction, or GI symptoms.

3. Finally, criterion 3 is a drop in blood pressure that occurs within minutes to hours after a patient is exposed to a known allergen. For infants and children, this includes a finding of age-specific systolic hypotension or a greater than 30% decrease in systolic blood pressure.

Can we diagnose our patient based on these criteria? Our patient had hives, shortness of breath, wheeze, nausea, diarrhea, and abdominal cramping, all of which are consistent with anaphylaxis. In addition, these occurred after an exposure to penicillin, which is a common anaphylactic trigger. Therefore, our patient meets criterion 2 with skin, respiratory, and GI involvement after exposure to a likely allergen. Also, we know from the history that he has previously taken penicillin in the past, after which he likely became sensitized.

Management

Ideally, any child suspected of being in anaphylaxis should be treated with self-injectable epinephrine intramuscularly in the community before arriving to hospital. Education is key to teach both patients and families on the proper use of their injectable epinephrine and the importance of erring on the side of caution. Often, patients or families will be unsure when to administer epinephrine. They should be taught to give epinephrine at the first instant they become suspicious of anaphylaxis, especially after exposure to a known allergen. The patient should then go to hospital for assessment.

Self- injectable epinephrine currently comes in two doses: 0.15mg and 0.3mg. These are available as EpiPen. and EpiPen Jr. EpiPen contains the 0.3mg dose, whereas EpiPen Jr. contains the 0.15mg dose.

The indicated dose of epinephrine is 0.01mg/kg of epinephrine 1:1000 concentration. As a result, it is currently recommended that patients weighing 10-25kg should be prescribed a 0.15mg dose, while patients over 25kg should be given a 0.30mg dose. For patients under 10kg, epinephrine would have to be drawn by syringe by a responsible adult, presenting many opportunities for errors in technique and delayed administration.

The first thing to do is assess the patient's airway, breathing, and circulation, and to remember anaphylaxis in your differential diagnosis. To clarify, if you suspect anaphylaxis, immediately give IM epinephrine while doing your ABC's. Epinephrine 1:1000 IM should be given immediately, and can be repeated every 5-15min as required. Again, the pediatric dosing is 0.01mg/kg with a maximum total dose of 0.5mg. The preferred site for IM injection is the anterior lateral thigh.

Special attention is warranted for the patient's airway. Carefully assess whether the upper airway is involved. Signs to look for include stridor, respiratory distress, and swollen lips and tongue. If you suspect the patient may need intubation, call for help early from a respiratory therapist and anaesthesiologist. The intubation will likely be very difficult and rapid sequence intubation may be required. Always be ready for an emergent surgical airway.

A sick patient should have continual cardiorespiratory monitoring and supplemental O2 as needed.

Two large bore IVs should be obtained because the patient may need extensive fluid resuscitation to maintain hemodynamic stability, especially in severe anaphylaxis. Tachycardia, hypotension, dizziness, and poor capillary refill all indicate cardiovascular compromise and the patient should receive normal saline boluses of 20mL/kg. You may need to consider re-positioning the patient in order to decrease blood pooling in the legs and maximize return to the heart. Consider trying the supine or Trendelenburg positions. Err on the side of caution; up to 35% of circulating blood volume can be lost in the first 10 min due to third-spacing from increased endothelial permeability. Re-evaluate perfusion, blood pressure, and signs of fluid overload after every bolus.

Transfer to ICU should be considered if the patient is believed to need further support.

Epinephrine is an adrenergic hormone that affects both alpha and beta receptors. When it acts on alpha1 receptors, it works to constrict blood vessels, counteracting the increased vascular permeability mediated by histamine. This helps improve symptoms of urticaria and angioedema. When epinephrine acts on Beta-1 receptors in the heart, it increases the heart rate and acts as an inotrope, increasing stroke volume, which helps

to raise blood pressure. Epinephrine also acts on B2 receptors to help with bronchodilation and relieve respiratory symptoms.

We will cover several adjunct medications but want to emphasize that epinephrine is the only lifesaving treatment. Oral antihistamines are used for cutaneous manifestations such as urticaria, but have no effect on GI, lung, or cardiovascular involvement. H1 antagonists that can be used include cetirizine and diphenhydramine. H2 antagonists, like ranitidine, can be given in combination with H1 antagonists if you need an extra kick.

Corticosteroids are also used in the management of anaphylaxis. You do not have to give these right away because they won't start working for 4-6h. They are important for their anti-inflammatory effects and in preventing the second phase of bi-phasic anaphylaxis.

Inhaled bronchodilators can be important medications if the patient has significant respiratory involvement. 5-10 puffs of salbutamol every 20 min via an MDI is preferred, but nebulized salbutamol may be needed for severe respiratory distress.

So how did we manage our patient? You assess his airway, breathing and circulation AND ask for a nurse to administer IM epinephrine at the same time. He weighs 50kg. So based on our dosing of 0.01mg/kg, he gets 0.5mg of epinephrine IM. You determine he is able to protect his airway, but notice he is still wheezing and feels short of breath. You ask for salbutamol via MDI. He is mildly tachycardic but normotensive and you ask for two large bore IV's, keeping in mind that he may decompensate quickly from third-spacing. Fortunately, after you give him a fluid bolus his tachycardia resolves. You continue to monitor his fluid balance with no concerns. 10 minutes later, your patient is still a little short of breath, but you decide he does not need another dose of epinephrine. 20 minutes from his last salbutamol, he gets another 5 puffs, after which you feel he can get more q4-6h PRN. You're confident he's stable so, you give him some oral diphenhydramine for his hives and corticosteroids to prevent a biphasic reaction.

Discharge and Admission Criteria

So I've treated my patient and he is stable, when is it safe to let him/her go home? Since most biphasic reactions occur within the first 4-6hrs of the initial presentation, patients should be observed for at least 4-6hrs. Patients should be informed however that the second phase could occur at any time in the first 72hrs.

You decide to watch our patient for another 6hrs.

The patient should be admitted to hospital if they have had a biphasic reaction, required 2 or more doses of epinephrine, or if the reaction was severe, for example with significant hypotension or respiratory distress. Other considerations include peanut-allergy, asthma, or use of beta-blockers. ICU care may be required in severe cases.

All right, now my patient is ready for discharge, anything else? Every patient should be prescribed an epinephrine injector when they are sent home. It is key that both the patient and family be taught how to use it properly. It is especially important to teach them to administer the epinephrine with first onset of symptoms and avoid delays in treatment. A three-day course of oral H1 and H2 antihistamines and corticosteroids may also be prescribed. A MedicAlert bracelet for known triggers or referral to an allergist if there are questions of diagnosis/triggers should also be recommended.

Back to our patient, you prescribe him an EpiPen, educate him and his parents how to use it, and give him a 3-day course of oral H1 and H2 antihistamines and corticosteroids. You tell them to watch out for a late biphasic reaction and suggest he get a MedicAlert bracelet for penicillin allergy. You also arrange for follow-up with an allergist at the parent's request.

Conclusion

Finally, here are a few key points to remember about anaphylaxis:

1. Anaphylaxis is a serious, rapidly occurring allergic reaction that involves a systemic release of inflammatory mediators like histamine from mast cells and basophils, affecting multiple organ systems including skin, CNS, respiratory, CVS and GI systems.
2. Food allergens are the most common identifiable triggers and peanuts, tree nuts, fish, milk, eggs, and shellfish are most commonly involved in fatal or near-fatal reactions.
3. Initial management involves both stabilizing ABCs AND rapid administration of IM epinephrine. Don't delay epinephrine!
4. Watch out for biphasic reactions! Observe the patient for at least 4-6h and warn the patient that a biphasic reaction can occur at any time in the first 72hrs.
5. All patients should get a prescription for injectable epinephrine when discharged and patients and family members should be educated about their proper use.

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