PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Drug Allergy.**" 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.

Drug Allergy

Developed by Lucy Duan, Stephanie Erdle and Dr. Vy Kim for PedsCases.com.
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Introduction
Hi everyone! Our names are Dr. Lucy Duan and Dr. Stephanie Erdle, and we are both paediatric allergy fellows. Thank you to Dr. Vy Kim for supervising us for this podcast. In this podcast, we will be discussing drug allergies. This is an issue that comes up in all areas of paediatrics, so developing a clear approach to drug allergies is important.

Part 1. Objectives

After listening to this podcast, the listener should be able to:
1. Differentiate allergic drug reactions from other adverse drug reactions
2. Develop an approach to drug allergy diagnosis
3. Understand the four main categories of drug allergies and their clinical manifestations
4. Develop a differential diagnosis of other conditions to consider
5. Understand a general treatment approach to drug allergies

Part 2. Generic cases
We will begin with a few cases to start us off.

Case 1. A 10-year-old girl with acute lymphoblastic leukemia is undergoing IV chemotherapy with Cisplatin. 10 minutes after the infusion starts, she develops diffuse urticaria, swelling of the lips and eyes, and difficulty breathing. Is this an allergic reaction? If so, what type?

Case 2. A 16-year-old male hospitalized on the Neurosurgery ward developed high fever, skin blistering and sloughing, and mucosal erosions, following the 4th dose of phenytoin prescribed for new onset seizures following head trauma. Is this a drug reaction, if so, what type?

Case 3. A 5-year-old boy presents to his primary care provider with cough, runny nose and fever. His left tympanic membrane looks red on examination, so he is started on amoxicillin for a suspected acute otitis media. Three days after starting the antibiotic he wakes up with an itchy red rash. Is this an allergic reaction?

Part 3. Adverse drug reactions

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Adverse drug reactions are defined as a harmful or unintended reaction to a drug. These reactions can be classified as Type A or Type B reactions. Type A reactions are considered to be predictable events that are usually dose dependent and can occur in anyone. An example of a type A reaction is diarrhea from an antibiotic. Type B reactions are unpredictable reactions generally unrelated to the pharmacologic actions of the drug, that only occur in susceptible individuals. Examples of type B reactions include drug allergy, non-allergic drug hypersensitivity reactions, intolerance, and idiosyncratic reactions. This podcast will focus on true drug allergy.

Drug allergy is a Type B adverse drug reaction that results from a specific immunologic response to a medication with varying mechanisms and clinical presentations. Drug allergies account for about 5-10% of all adverse drug reactions and are commonly seen in all areas of medicine. Diagnosis of drug allergy relies on a careful history and physical examination. In some instances, additional testing including skin testing and oral challenges are helpful and may be required.

Risk factors for developing a drug allergy include female sex, certain genetic polymorphisms, viral infections, and drug-related factors. Susceptibility to drug allergy is also influenced by the route of administration. Topical, intramuscular, and intravenous routes are more likely to cause allergic drug reactions than oral administration.

Part 4. Drug allergies

There are four major categories of drug allergies, which are most commonly classified based on the Gell and Coombs' classification system. We will first give a brief overview of each category, then go into each category in more detail.

Type I reactions are a typical IgE-mediated allergy. This is what people typically think of when they hear the word allergy. These reactions are immediate in onset, typically in less than one hour and can develop into anaphylaxis.

Type II, III and IV are all delayed onset allergic reactions with different mechanisms.

Type II reactions are delayed in onset and caused by antibody-mediated cell destruction. Patients may present with hemolytic anemia, thrombocytopenia or neutropenia.

Type III reactions are delayed in onset and caused by IgG:drug immune complex deposition and complement activation. Patients may present with serum-sickness like reaction, which we will describe in more detail.

Type IV reactions are delayed in onset and T-cell mediated. These patients can present in many different ways – ranging from contact dermatitis, to severe reactions like SJS or TEN, DRESS syndrome, and many more.

We will now go through each type in more detail. For each type, we will briefly cover the pathophysiology, the timing of the reaction, the classic presentation, and some examples of drugs that are known to cause the reaction type.

Type I

Of the four types, type I reactions are the most common. As we mentioned, type I reactions are what we think of as classic allergic reactions. These reactions require the presence of a drug-specific IgE. Once formed, these IgE bind to mast cells and basophils throughout the body. If the drug or its metabolite is encountered again, it can bind to the IgE, forming drug-IgE complexes that then cause degranulation, with release of histamine and other inflammatory mediators, causing an allergic reaction.

These reactions are rapid in onset, typically within one hour of drug administration. The timing can vary depending on how the drug is given - for example, a drug given intravenously may lead to a more rapid reaction than the same drug given orally. The reaction may be even later if the oral medication is given with food, causing delayed absorption.

These patients classically present with symptoms caused from the histamine release. These reactions can include urticaria, angioedema, respiratory symptoms, GI symptoms or hypotension and may develop into anaphylaxis.

Diagnosis is guided by detailed history, physical examination, and in some cases, skin-prick testing and oral challenge. Skin-prick testing is only useful in type 1 drug allergy reactions, and not the other types of reactions.

Patients with type I reaction need to be treated in the same way you would treat any other IgE-mediated allergic reaction. If the patient presents with anaphylaxis, they need to be given IM epinephrine immediately. You can listen to the PedCases podcast on anaphylaxis for more detail on the management of anaphylaxis.

The drugs that most commonly cause these reactions include beta-lactams, such as penicillins or cephalosporins, chemotherapeutic agents, and foreign proteins such as monoclonal antibodies.

Type II

Type II reactions are much less common than type I reactions. Type II reactions are caused by antibody-mediated cell destruction. In these cases, the drug binds to the surface of certain cell types, and acts as an antigen. Specific IgG or IgM antibodies that match these drug antigens then bind to them, causing them to be destroyed.

These reactions are delayed, with patients presenting at least 5-8 days after drug exposure, however, then can occur much more quickly if the causative drug is stopped then restarted.

The cell types that are most commonly affected are RBCs, platelets and neutrophils. Patients therefore classically present with either hemolytic anemia, thrombocytopenia or neutropenia.

There are many drugs that can cause a type II hypersensitivity reaction, some commonly seen drugs include cephalosporins, penicillins, anti-convulsants, NSAIDs, heparin, and sulfonamides.

Type III

Type III reactions are caused by IgG-drug immune complex deposition. In this type of reaction, the drug can bind IgG and form immune complexes. Immune complexes can activate complement and an inflammatory cascade, and precipitate in different tissues including blood

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vessels, joints, and renal glomeruli. Re-exposure to the same drug can lead to more rapid and severe effects.

These reactions are delayed and typically manifest 1-3 weeks following drug exposure.

Patients with type III reactions can present in several different ways including serum sickness and vasculitis. Serum sickness is an immune-complex reaction where patients present with fever, arthralgia, lymphadenopathy, cutaneous lesions, and in some cases acute glomerulonephritis.

Commonly encountered agents that can cause a type III hypersensitivity reaction include heterologous antibodies, antibiotics, thiazides, allopurinol.

Type IV
Type IV reactions are T-cell mediated hypersensitivity reactions, and in contrast to the other 3 types, are not caused by antibodies. These reactions are also known as delayed-type hypersensitivity reactions, and can be further subdivided, however that is beyond the scope of this podcast. These reactions are caused by drug-specific T cells that recognize drugs through their T-cell receptors in an MHC-dependent way. This leads to subsequent cytokine and inflammatory mediator release, and can be associated with the recruitment of eosinophils, monocytes, and neutrophils.

Type IV reactions are typically delayed by at least 1-3 days, and can occur days to weeks following exposure to the offending drug. If following a repeat exposure to a drug, symptoms may appear within 24 hours.

Clinically, this group of reactions is highly variable and range from mild skin reactions, to life-threatening conditions.

An example of a common type IV hypersensitivity reaction is allergic contact dermatitis, which is characterized by erythema and edema with/without vesicles and bullae. It is caused by a wide variety of topical medications, and is the most frequent occupational skin disease. Patch testing can be used to aid in the diagnosis of contact dermatitis.

There are 3 other type IV hypersensitivity reactions which are much more severe: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms, known as DRESS.

SJS/TEN is characterized by detachment and necrosis of the epidermis. Patients present with fever, mucous membrane involvement, and epidermal skin sloughing. Symptoms appear 1-4 weeks following drug exposure, but re-exposure can lead to symptom onset in 2-3 days. SJS is when skin detachment is less than 10% of the body surface, and TEN is when skin detachment affects greater than 30% of the body surface area. SJS/TEN overlap describes patients with skin detachment of 10-30%. Common offending drugs include allopurinol, sulfonamides, NSAIDs, and anticonvulsants including lamotrigine, carbamazepine, phenytoin, and phenobarbital. Patients with SJS/TEM can become very sick and often require intensive care admission or burn unit admission, for initiation of supportive treatment. Management includes prompt discontinuation of the drug, wound care, fluid and electrolyte management, nutritional support, pain control, and treatment of any superinfections.

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DRESS is a rare but potentially life-threatening type IV hypersensitivity reaction. Clinically, patients present with fever, skin rash, malaise, hematologic abnormalities including eosinophilia and atypical lymphocytosis, increased lymphadenopathy, and multi-organ involvement. In most patients, symptoms begin 2-6 weeks following the initiation of the offending drug. The most common category of medications that cause DRESS are antiepileptics including carbamazepine, lamotrigine, phenytoin, and phenobarbital. Other medications include allopurinol and sulfonamides. Management is similar to that of SJS/TEN and involves removal of the offending drug and supportive care.

Part 5. Differential Diagnosis

Since the clinical manifestations of drug allergy are variable, it is important to consider and exclude other medical conditions in the differential diagnosis. This list is broad, but we have included some important diagnoses to think about. For immediate onset allergic reactions consider other allergies such as food allergy or latex allergy, asthma, infectious causes such as EBV or hepatitis, insect bites, and mastocytosis. For delayed onset reactions consider viral infections, bacterial infections such as streptococcal infection, autoimmune conditions such as psoriasis, Kawasaki Disease, or Still's disease, and insect bites.

Part 6. Approach to Diagnosis

On history, information should be obtained about what medication was taken, the dose and duration, the route of administration, if this was the first time this medication was being used, and any concurrent prescription and non-prescription medications (in particular, NSAIDs). It is important to obtain a detailed timeline of the reaction, description of clinical symptoms, any treatment that was given, and any previous or subsequent exposures to the medication. A detailed review of systems including looking for intercurrent illnesses such as viral infections, as well as past medical history of other allergic reactions also important.

In addition to a detailed history, a careful physical examination should be conducted including examination of the cardiovascular, respiratory, gastrointestinal, and cutaneous symptoms. More detailed description of clinical findings of drug reactions will be discussed in the subsequent sections.

Useful investigations depend on the type of adverse reaction. For immediate IgE-mediated hypersensitivity reactions, skin testing procedures such as skin prick testing (SPT) and intradermal testing (IDT) are useful and performed by allergists. Serum specific IgE tests are available for a limited number of medications, however in most clinical settings, serum specific IgE tests for medications are not used for the diagnosis of drug allergy and should not be ordered without consultation with allergists. For delayed hypersensitivity, patch testing by specialists can also be used.

Part 7. Treatment

Management of drug allergy varies depending on the type of reaction. In most cases, the most effective strategy is to avoid or discontinue the offending drug. Cross-reactivity amongst drugs should be considered when choosing alternative agents. In the event of anaphylaxis, the patient must be treated with epinephrine by intramuscular injection. Additional therapies involve

symptomatic and supportive care. The specific treatment for each type is outside the scope of this podcast.

Part 8. Penicillin allergy

One of the most common referrals we get in our allergy clinic is for concerns of penicillin, or amoxicillin, allergy. This most often presents with a vague history of rash sometime during the course of antibiotics. Over 95% of the time, the patients do not actually have a penicillin allergy, and this can largely be determined by history alone. The first thing to determine is whether the patient has received penicillin before. In order to have an IgE-mediated reaction, the patient needs to be sensitized to the antibiotic, which requires previous exposure to the antibiotics. If they have not had a previous course of the antibiotics, it is unlikely to be an IgE-mediated reaction. The next step is to determine the timing of the reaction. IgE-mediated reactions typically occur with an hour of the first dose on re-exposure. If the reaction occurs several hours after a dose, or after a few days into the course of antibiotic, it is unlikely to be an IgE-mediated reaction. Rashes while on antibiotics are extremely common, and are most often secondary to the infection itself such as a viral urticaria or other viral exanthem.

If the reaction sounds like an IgE-mediated reaction, it is important to refer to an allergist for testing. This involves epicutaneous and intradermal testing, and if negative, an oral challenge. If the reaction is a rash that occurs several days into the course of antibiotics, it is unlikely to be IgE-mediated. In these cases, the families can be reassured that this is not a drug allergy. If the family is anxious to try the antibiotic again, we will often give them an age-appropriate dose of the antibiotic in clinic, and observe them for an hour, for reassurance. If no reaction develops, they can be reassured that they are not allergic to the drug.

In a small subset of patients, they will have isolated rashes several days into the course of antibiotics on each re-exposure. As long as the child is well and only have a rash, this is not dangerous, and the families do not need to stop the antibiotics.

Part 9. Returning to the cases

Let's now return to the cases.

As you recall, in the first case we had a 10-year-old girl undergoing IV chemotherapy with Cisplatin. 10 minutes after starting the drug infusion she developed diffuse urticaria, facial swelling and had difficulty breathing. Do you think this is an allergic reaction? If so, what type? If you guessed a type I IgE-mediated reaction, you are right! Remember, type I reactions are immediate, IgE-mediated reactions, causing histamine release, causing reactions ranging from urticaria development to anaphylaxis. This patient has developed an anaphylactic reaction from her chemotherapy, and requires immediate IM epinephrine.

In our second case, a 16- year- old male developed fever, skin sloughing, and mucosal erosions following the 5th dose of phenytoin prescribed for new onset seizures following head trauma. Is this a drug reaction, if so, what type? This is an example SJS/TEN, a severe type IV hypersensitivity reaction that is a T-cell mediated reaction. Phenytoin and other aromatic antiepileptic medications are known offending agents for SJS/TEN and should been on your differential diagnosis if you see a patient with a similar clinical presentation. Remember that it is

important to obtain a detailed medication history in patients! This patient needs immediate removal of the offending drug, and active supportive care.

In our third case, a 5 year old boy developed an itchy red rash after being treated with amoxicillin for three days for a suspected acute otitis media. Is this an allergic reaction? Does this reaction fit with any of our above reaction types? Some people might think that this is a type I IgE-mediated reaction, but this reaction developed after 3 days of an antibiotic, and not immediately after receiving it. This patient most likely had a viral infection, and this is likely a viral exanthem, or a viral rash. Viral rashes are commonly mistaken for allergic reactions, and amoxicillin is the most commonly implicated antibiotic. Usually with a good history and timeline of the reaction, you can figure out if there is actually a concern for a true allergic reaction.

Part 10. Summary

In this podcast, we reviewed what adverse drug reactions are, and that drug allergy is an example of a type B adverse drug reaction. We discussed an approach to diagnosing drug allergy which includes the importance of obtaining a detailed history and careful physical examination. The Gell and Coombs' classification system is commonly used to describe the 4 types of hypersensitivity reactions. We also discussed a broad differential diagnosis and general treatment approach. Here are few key take-home points:

1. A drug allergy is a Type B adverse drug reaction that results from a specific immunologic response to a medication with varying mechanisms and clinical presentations.
2. A detailed drug history including dates and route of administration, drug formulation, and timing and duration of clinical symptoms is the most important aspect in the diagnosis of drug allergy.
3. There are four major categories of drug allergies, which are most commonly classified based on the Gell and Coombs' classification system.
4. The mainstay of treatment is avoidance of the offending drug.
5. Penicillin allergy is the most common labeled drug allergy in children, however most children do not have a true IgE mediate hypersensitivity reaction to penicillin.

Thanks for listening!

References

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