Danylo Halytsky Lviv National Medical University
Department of Clinical Immunology and Allergology

METHODOLOGICAL DEVELOPMENT OF TOPIC №7

practical lesson **" Drug allergy"** (2 hours) in the discipline "Clinical Immunology and Allergology" for 6-th year students of specialty "Medicine"

Theme №9: Drug allergy

1. *Relevance of the topic:* At present time it is especially important to understand by the students of the importance of participating immune mechanisms of drug allergy
2. *The goals of the class:*

- educational: students must study basic immunogical factors and clinical signs of drug allergy
- professionally oriented: students should be based on clinical and laboratory data to diagnose of drug allergy
- educational: to form a sense of responsibility for the timeliness and correctness of professional actions.

3. *Equipment* for conducting classes: Presentation for multimedia demonstration, schemes, tables, immunograms, tests, situational tasks, histological and cytological preparations, non-typical situational tasks
4. *Integrative Relations of the theme:*

4.1.Internal Integration: The topic of this practical lesson is associated with the following topics of the cycle "Clinical Immunology and Allergology" classes for students of the 6th year as "Structure and Principles of Functioning of the Immune System" and "Assessment of the Immune System", Fragment "Allergic conditions" in the topic " Allergic diseases: immunopathogenesis, immuniagnostic and treatment ».

4.2.Interdisciplinary integration: The topic of the practical lesson is connected with the topics of the same series of practical lessons "The subject and tasks of clinical immunology and allergology"

Subject	**To know**	**Be able**
1	**2**	**3**
Physiology	Know the basic parameters of external respiration	Rate normal levels of external respiration and blood indexes
Pathophysiology	Types of hypersensitivity reactions	Name the types of reactions
Pharmacology	Know the basic groups of anti-histamines, anti-serotonin, β_2-agonists, cholinolytic, mucolytic and anti-inflammatory drugs	Prescribe these drugs
Propaedeutic therapy	Features of the examination of patients with immunopathology	Perform palpation, percussion, auscultation of breath, evaluate the results of laboratory and instrumental methods of examination
Dermatology	Diagnosis of allergic skin diseases	Clinically evaluate the prevalence of skin process, the presence of secondary purulent infection
Therapy	Clinical picture, differential diagnosis of bronchial asthma, pollinosis, allergic conjunctivitis, rhinitis	Conduct clinical examination, evaluate the results of laboratory and instrumental examinations, prescribe treatment

5. Study questions:

1. Definition and triggers of drug allergy.
2. Evaluation of patients with suspected drug allergy
3. Physical examination
4. Diagnostic of drug allergy/ tests in vivo and in vitro/
5. Patients management

Practical Guidance for the Evaluation and Management of Drug Hypersensitivity

EPIDEMIOLOGY OF DRUG HYPERSENSITIVITY

Adverse drug reactions (ADRs) are estimated to account for 3% to 6% of all hospital admissions and to occur in 10% to 15%of hospitalized patients resulting in morbidity, prolongedhospitalization, and increased risk of mortality. Although most of these reactions are due to predictable and dose-dependent effects of drugs, 10% to 20% of ADRs, including allergic drug reactions, are unpredictable and dose independent.

Allergic drug reactions are also known as drug hypersensitivity reactions and account for approximately 6% to 10% of all ADRs.In children, drug allergy has also been reported with a relatively high frequency, occurring in up to 8.7% of pediatric patients in varied hospital settings and 1% to 8% of visits in outpatient pediatric offices.

From 2001 to 2012, the estimated incidence for emergency department visits for patients with allergic drug reactions rose from 0.49% to 0.94%. In a recent review from Brazil, drug allergy accounted for 40% to 60% of emergency room anaphylactic re- actions. When 806 patients presenting with drug allergy were screened, 117 (14.5%) had been diagnosed with anaphylaxis, and fewer than 34.2% of those patients had received epinephrine. The increased incidence of allergic drug reactions is consistent with an increased incidence of overall allergic sensitization in the popula tion, including reactions to foods and other allergens.

CLASSIFICATION OF DRUG HYPERSENSITIVITY

Allergic drug reactions are distinguished from other unpredictable ADRs in that they are mediated by an immunologic mechanism. No single classification scheme permits the categorization of all allergic drug reactions. They are currently categorized using the somewhat dated Gell and Coombs's classification into 4 types of hypersensitivity reactions:

Type I: Immediate reactions mediated by IgE antibodies leading to mast cell and basophil degranulation with symptoms ranging from urticaria to anaphylaxis. At this time, type I drug reactions also include those involving the activation of mast cellsand basophils through non-IgE mechanisms.

Type II: Cytotoxic IgM- or IgG-mediated reactions against a
cell surface antigen, such as drug-induced hemolytic anemia.

Type III: Immune complex deposition reactions with activation of complement, such as serum sickness-like reactions (SSLRs).

Type IV: Delayed T-lymphocyte-mediated reactions, such as contact dermatitis and delayed maculopapular rashes. Subcategorization of type IV reactions into a, b, c, and d reactions has expanded the scope of type IV delayed reactions to include thosefor which the mechanism and cellular targets are not completely understood and may involve cells other than T cells.

There are shortfalls to such a system. Some allergic drug reactions cannot be classified due to a lack of insight into the underlying mechanism, or the mechanism is known but it does not fall into the existent classification scheme. Acute reactions to taxanes can trigger mast cell/basophil activation with elevation ofserum tryptase with or without evidence of IgE, and they arecurrently considered type I reactions and amenable to desensitization. Hypersensitivity to rituximab and other monoclonal antibodies can present as mixed patterns of type I and "cytokine-storm-like" reactions with chills, fever, generalized malaise, flushing, and hypotension, and can be associated with elevations of tryptase and IL-6 in serum. Patients presenting with such reactions may have positive skin testing, demonstrating that IgE plays a role in the mixed immune mechanisms. These mixed reactions may be amenable to desensitization and, depending on the indications, will require careful evaluation of symptoms andadjusted protocols with premedications.

Severe cutaneous adverse reactions (SCARs) including Stevens- Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug hypersensitivity syndrome/drug reactions with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthema- tous pustulosis (AGEP), as well as interstitial nephritis, drug fever,vasculitis, and hepatitis are considered type IV reactions and are currently a formal contraindication for desensitization. The safety and efficacy of desensitization for these reactions is unknown at this time. Aromatic anticonvulsants can induce DRESS, which is also known as anticonvulsant hypersensitivity syndrome, and cross-reactivity among anticonvulsants sharing aromatic rings is very high and thought to be

due to specific human leukocyte antigen (HLA) phenotypes. In these cases, small amounts of medication can induce severe symptoms and desensitization is contraindicated. In contrast, reactions presenting as maculo-papular rashes without systemic involvement are considered potentially amenable to graded challenge or desensitization.

A 2017 Practical Allergy Report (PRACTALL) document from a consensus precision medicine initiative between the American Academy of Asthma Allergy and Immunology (AAAAI) and the European Academy of Allergy and Clinical Immunology (EAACI) has provided an inclusive definition of drug allergy to encompass phenotypes, endotypes, and molecular markers. This broader categorization, bridging clinical presentations and symptoms, provides useful tools for a better understanding of underlying mechanisms of allergy and helps personalized recommendations. Drug allergy phenotypes are classified as immediate onset or delayed onset. Immediate-onset drug allergy includes symptoms within 1 to 6 hours of expo- sure that are not limited to IgE-mediated reactions or direct mast cell/basophil activation and can occur with or without previous drug exposure. Delayed-onset drug allergy can occur days to weeks after allergen exposure and can present with heterogeneous symptoms due to isolated single-organ involvement or systemic multiorgan involvement. Endotypes responsible for immediate and delayed drug reactions include IgE and direct mast cell activation, cytokine release, T-cell mediation, and genetic predisposition associated with specific HLA phenotypes, among additional mechanisms. Biomarkers of drug allergy include specific IgE and tryptase levels and can be identified using skin testing, basophil activation test (BAT), and other approaches.

RISK FACTORS FOR DRUG HYPERSENSITIVITY

Females have a higher risk for drug hypersensitivity reactions, and the mechanisms underlying this propensity are not fully understood. Cyclical hormonal changes are thought to be the basis for progestogen hypersensitivity syndromes (formerly pro gesterone autoimmune dermatitis), in which either progesterone- like hormones that are endogenous or exogenous during *in vitro* fertilization treatments or estrogens serve as sensitizing allergens that can induce reactions ranging from dermatitis to anaphylaxis. Environmental chemicals containing quaternary ammonium compounds found in products such as cosmetics and detergents are thought to be cross-reactive with neuromuscular blocking agents and opioids and therefore may increase the risk of reactions during general anesthesia.

Patients with cancer or cystic fibrosis (CF) are likely at higher
risk of drug hypersensitivity as well. Atopy has been shown to be a risk factor for the development of drug hypersensitivity in patients with cancer exposed to taxanes. Increased IgE sensitization to drug allergens has been observed in patients with multiple drug allergies. In women with ovarian cancer, IgE-mediated hypersensitivity reactions to carboplatin occur in up to 27% of the patients after 6 or more treatments and earlier in patients with *BRCA* mutations. The risk of a patient reacting to multiple drugs with unrelated allergenic epitopes is infrequent for IgE-mediated reaction but has been described for type IV re- actions. T-cell clones isolated from drug allergic patients with CF were found to proliferate and release cytokines after stimulation with piperacillin, meropenem, or aztreonam, and cross-reactivity with the different drugs was not observed, indicating specific T- cell responses to 3 different antigenic determinants.

The drugs most commonly implicated in type I reactions in patients with CF are penicillins and cephalosporins. Overall, allergic reactions to antibiotics are more common in patients with CF than in the general population. This is due in part to the improving survival of these patients as well as the increased use of high-dose intravenous antibiotics. Although some are immediate-type (IgE-mediated) re-actions, including anaphylaxis, the majority are late onset and may have nonspecific features such as rash and fever.

Heterologous responses to viral infections in the context of specific HLA alleles have been implicated as novel mechanisms associated with SCARs. Pathogen-directed T effector memory cells induce heterologous immune responses that can modify T-cell-mediated immunity. Human herpesvirus, cytomegalovirus, and some other viruses can establish lifelong subclinical infections and cellular latency, with periodic transcriptional reactivation of the virus resulting in viral proteins that stimulate virus-specific T-cell memory. In that context, the induction of drug hypersensitivity requires an HLA risk allele, a primary infection with human herpesvirus or another virus, and a polyclonal expansion of CD8 T memory cells. On drug exposure, the interaction with specific HLAs induces the generation of neoantigens recognized by the CD8 T memory cells. These reactions can occur at first exposure and do not require sensitization.

HLA risk alleles are key to the viral responses, and the antiretroviral drug abacavir has exemplified their importance, as it induces severe hypersensitivity reactions in individuals expressing HLA-B*5701. Patch testing with abacavir is positive before systemic abacavir exposure in HLA-B*5701-positive individuals (approximately 5% of those of European ancestry, 1% of those of Asian ancestry, and <1% of those of African ancestry)
due to the local skin T-cell activation that results from abacavir binding to HLA-B*5701. Other risk alleles have been identified and associated with susceptibility to aromatic anticonvulsants and reactions to allopurinol and sulfonamides. Genotyping for drug susceptibility can identify potential reactors and aid in protecting at-risk populations, but this recommendation is currently limited to a few drugs.

EVALUATION OF PATIENTS WITH SUSPECTEDDRUG HYPERSENSITIVITY

History

A thorough history is essential for the evaluation of patients with suspected drug allergy. Whenever possible, the medical records should be carefully reviewed. Some important questions to address when obtaining the history are listed below:

(1) What were the names of each of the suspected medicationsand how long ago did the reaction occur?

Patients often may not remember the medications they received, and this is especially the case if multiple medications were given simultaneously, for example, in an intensive care unit or operating room. In these cases, reviewing the medical records becomes critical. It is important to consider that patients may experience reduced drug sensitivity over time.

(2) Was this the patient's first exposure to the medication?

An IgE-mediated reaction typically does not occur with the first exposure although the possibility of exposure *in vitro* or while breastfeeding should be considered, particularly with younger children. As mentioned earlier, quaternary ammonium com- pounds present in cosmetics are thought to be cross-reactive with neuromuscular blocking agents and increase the risk of reactions during general anesthesia. Cross-reactivity between paclitaxel, with hazelnut and tree pollen, has been suggested as the cause of re-actions at first or second exposure in patients with cancer.

(3) What was the underlying condition for which themedication(s) were prescribed?

The underlying condition, such as a viral syndrome, may be the cause of skin rash or possibly other symptoms. For example, patients with *Mycoplasma pneumoniae* infection can develop acute urticaria or SJS. In addition, patients with infectious mononucleosis are more likely to react to ampicillin, andpatients with HIV infection are more likely to react totrimethoprim-sulfamethoxazole.

(4) What were the symptoms and signs of the reaction, and whatwas the timing relative to when the patient received the medication?

Certain symptoms and signs such as urticaria and pruritus, particularly if they occur less than an hour after receiving a medication, would be more suggestive of an IgE-mediated or non-IgE-mediated immediate reaction. This is in contrast to a T-cell-mediated reaction, which presents with different
symptoms and is often delayed in nature. Patients with cancer who are premedicated with antihistamines may not describe symptoms of pruritus during an IgE-mediated reaction and may present with delayed symptoms due to the premedication regi- men's masking of the side effects.

(5) If other drugs were concomitantly administered, what was the timing of each symptom and/or sign in relation to the administration of each medication?

This may help determine which drug or drugs were more likelyto have been associated with the reaction. In the example of perioperative anaphylaxis, the record of the exact time of intro- duction of each medication should be reviewed at the time of allergy evaluation. It is similarly important to check whether narcotics and nonsteroidal anti-inflammatory drugs (NSAIDs) were administered, as these drugs can trigger pruritus and potentially rash as a result of scratching and/or dermatographism. These could otherwise be mistaken as symptoms of IgE-mediated allergy.

(6) Has the patient received any of the medications or a related combination medication since the initial reaction, and were there any reactions associated with the most recent exposure?

If there was no reaction with the repeat administration of the drug or a related combination drug, it is unlikely that the drug being considered was the cause of the initial reaction (eg, apatient who has tolerated amoxicillin/clavulanate after a history of amoxicillin allergy is unlikely to be allergic to either amoxicillin or clavulanate).

(7) Has the patient experienced similar symptoms/signs in the absence of the culprit medication(s)?

In these cases the patient's primary condition could be the trigger for the symptoms/signs rather than drug exposure, such asurticaria in a patient with chronic urticaria.

(8) How long after the drug was discontinued did the reaction resolve, and did the reaction seem to respond to factors other than discontinuing the drug? Did some of the interventions fail?

A faster resolution suggests IgE or mast cell involvement. An immediate response to antihistamines and/or epinephrine might also suggest an IgE-mediated or mast cell reaction, and a lack of response makes such mechanisms less likely. Benign rashes that persist for months or years are unlikely to be attributable to a drug-related allergic response.

PHYSICAL EXAMINATION

If the allergist/immunologist is consulted during the reaction, performing a physical examination is critically important. This is particularly relevant if there is a rash present, and attention to the pattern and appearance of the rash as well as other concomitant signs will provide important information about the potential nature of the reaction. It is important to consider the presence of Nikolsky's sign (blisters and erosions appear when normal or erythematous skin in between lesions is rubbed gently) in SCARs. Also, the percent detachment of the skin is typically less than 10% of body surface in SJS, from 10% to 30% in overlap SJS-TEN, and greater than 30% in TEN. In addition to the location, geography, and phenotype of the skin involvement, findings such as fever, mucosal involvement, photophobia, conjunctival erythema, respiratory distress, lymphadenopathy, liver or spleen enlargement, or joint involvement should always be investigated.

More commonly, however, the allergist/immunologist is consulted in the later stages of a reaction or after it has resolved. In this scenario, reviewing images of the reaction, potentially obtained with the current plethora of cell phone cameras, would be invaluable. Examples of these include pictures of rash and/or angioedema, mucosal involvement, and joint swelling versus angioedema of the skin overlying the joint area. Physicians should remember to ask patients about objective documentation (ie, photos), as patients may not always think to volunteer this information. Such documentation can be incorporated into the medical record with consent and protection of identity. In addition, using a camera to obtain such documents in case of future reactions should be discussed with all patients with drug allergy.

LABORATORY TESTS: *IN VIVO* AND *IN VITRO*

General tests may include a complete blood count with the differential focusing on eosinophil count, liver enzymes, and tryptase level. Elevated serum tryptase levels indicate both IgE- mediated and non-IgE-mediated mast cell/basophil activation. Levels above 11.4 ng/mL are considered abnormal. There is a linear association between tryptase levels and measures of reaction severity including the presence of hypotension. Clinical symptoms of mast cell and/or basophil activation may be masked in patients premedicated with antihistamines and/or steroids. In these cases, an elevated tryptase level is an invaluable tool in identifying reaction-eliciting drugs, predicting future reactions, protecting patients from re-exposure, and providing a basis for desensitizations. Another tryptase level should be obtained after resolution of the reaction (baseline), as anaphylaxis can occur with normal acute tryptase, and comparing changes in a patient's tryptase levels with baseline is important, using the formula of a tryptase change >1.2 baseline 2. This will also help identify patients with systemic mastocytosis (elevated baseline tryptase levels) who are at risk for reactions when exposed to nonsteroidal anti-inflammatory medications and opioids. If tryptase re-mains elevated 4 to 6 weeks after an initial drug reaction including anaphylaxis, genotyping for the KITD816V mutation and a bone marrow biopsy are recommended to rule out a clonal mast cell disorder including systemic mastocytosis.

The signs and symptoms of the reaction will dictate more specific tests such as direct and indirect Coombs test for type II reactions and investigation of circulating immune complexes and complement levels for type III reactions. Other laboratory values including erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and urinalysis may be abnormal, suggesting a type III reaction. Although they are nonspecific tests, elevations in ESR and CRP may be seen in reactions with systemic features. In complex cases in which multiple drugs are involved without a clear-cut temporal relationship, or in cases with atypical skin lesions, obtaining a skin biopsy could prove useful. However, there are no absolute histologic criteria for the diagnosis of drug-induced eruptions, and a skin biopsy might not definitively exclude alternative causes. Liver biopsy is rarely indicated if the etiology of hepatitis in a patient taking 1 or more medications cannot be determined, as drug-induced hepatitis can have a distinct histologic pattern.

SKIN TESTING FOR EVALUATION OF IgE-MEDIATED HYPERSENSITIVITY

When the history suggests a potential IgE-mediated mechanism, skin testing (skin prick and intradermal testing read at 15 to 20 minutes) to the drug(s) should be considered. Histamine should be used as positive control and saline as negative control. In the evaluation of intradermal testing results, comparing the wheal size with the measurement obtained immediately after injecting the drug should be considered as the saline control wheal may fade and result in false diagnosis. In many cases, however, skin testing may not be feasible, not only because of the patient's general condition but also because of current administration of antihistamines or other medications that may interfere. In addition, it is best not to perform skin testing within the first 4 to 6 weeks after anaphylaxis due to the potential for mast cell mediator depletion that may temporarily lead to false-negative reactions. A refractory period for skin testing has been demonstrated in patients with perioperative anaphylaxis. *In vitro* desensitization of human skin mast cells has demonstrated that at least 4 to 7 days are needed to restore full activating responses. In a limited study of 25 cases of perioperative anaphylaxis, skin testing was

performed at 2 time intervals, within 0 to 4 days and 4 to 8 weeks later. Twelve patients were positive in both periods; however, 3 patients were only detected in the early time point, and 10 were detected in the late period. Hence in patients with severe conditions such as cancer, CF, or other disorders in which delaying treatment would adversely affect survival, skin testing may be performed 2 to 3 weeks after the initial hyper- sensitivity reaction, bearing in mind that a false-negative result is possible.

A validated skin test protocol is currently only available for penicillin and beta-lactams. Nonirritating concentrations are available for other antibiotics as well. Skin test protocols have also been reported for a variety of other drugs. If the nonirritating concentration is not described in the literature or if the medication is new, skin testing starts with the standard (undiluted) concentration for prick (in non vesicant medications and typically not exceeding 100 mg/mL) and 1/100 and 1/10 of that con- centration for intradermal testing in conjunction with skin testing control subjects. In cases of anaphylaxis, the additional dilution of 1/1000 may be considered. Although this is a non- standardized approach with unknown specificity and sensitivity, if the concentrations prove to be nonirritating in control subjects, they may be of use in patients to help with diagnosing IgE sensitization.

DELAYED SKIN TEST READINGS AND PATCH TESTING FOR EVALUATION OF DELAYED-TYPE HYPERSENSITIVITY

Delayed skin test reading after intradermal drug injection, which can induce local inflammation and erythema at the site of injection at 24 hours later and up to 96 hours later, can be used to determine type IV sensitization and help predict reactions such as maculopapular exanthem (MPE). The sensitivity and specificity of delayed intradermal skin test readings have not been established, but the test has been helpful in the diagnosis of non severe delayed reactions induced by beta-lactam antibiotics, radiocontrast media, heparins, and biological agents.

Patch testing with application of the drug allergens to the skin can be used to uncover drugs responsible for contact dermatitis and other type IV reactions. Petrolatum is the recommended base for the dilution of the drugs (typically at 10% dilution), and the back is the best test location to avoid accidental removal during daily activities. Commercial reagents are available containing common contact allergens and provide high specificity for metal allergies. Commercial patch tests are not available for systemic drugs in the United States. Patch testing has been used for MPE and severe cutaneous ADRs with systemic symptoms (SCARs), although its sensitivity is undetermined. Because there is potential concern about SCAR reactivation and/or significant localized reaction with patch testing, such testing should only be considered if multiple drugs are involved and/or the drug is the first-line treatment option or there are no alternate medications available. In a study of 134 patients with delayed drug-induced reactions, patch testing identified the culprit drug in 64% of DRESS cases, 58% of AGEP cases, but only 24% of SJS/TEN cases. It most frequently implicated carbamazepine and beta- lactams.

SPECIFIC *IN VITRO* ASSAYS

A number of drug specific IgE tests are available including but not limited to ImmunoCAP assays for penicillin G and penicillin V. However, these assays have a low sensitivity, rarely play a critical role in patient evaluation, and are not useful in diagnosing penicillin allergy in patients with remote histories of penicillin allergy. Measuring specific IgE to platins including carboplatin, cisplatin, and oxaliplatin is a research tool with potential application in identifying reactors but requires further study. In our expert opinion and review of published data, commercially available assays for drug reactions rarely play a critical role in the evaluation and management of patients.

The usefulness of other *in vitro* diagnostic tests, such as the BAT, has been reported. It should be noted that the BAT is currently not commercially available. This test detects specific activation markers that are expressed on the surface of peripheral blood basophils after their incubation with the potentially responsible drug. At present, the most commonly used markers are CD63 and CD203c, and although their expression may help identify platin-sensitive patients, additional research is required. This said, the BAT can identify patients with cancer with carboplatin allergy without the need for skin testing. It can be performed shortly after a patient's reaction and does not involve the risk of skin testing in those with severe anaphylactic reactions, and it holds potential as a diagnostic tool. Specificity and sensitivity are under investigation, and further validation will require studies in larger sample populations.

The lymphocyte transformation test relies on the activation and proliferation of T cells cultured in the presence of drug allergens. These tests can be of value in type IV reactions but have not been standardized in such a manner to be useful in the field of drug allergy or to be commercially available.

Genotyping is available for the screening of patients at risk for SCARs including SJS/TEN, such as HLA B-5701 for patients starting abacavir treatment and HLA-B*1502 for patients exposed to carbamazepine. Metabolic pathway analysis for cytochrome isoforms of the P450 pathway can help identify patients with opioid intolerance, due to CYP2D6 deficiencies and other metabolic defects, that may place them at risk during surgery and anesthesia. It should be noted that although many enzyme pharmacogenomic assays are available, their clinical utility is at this time debatable.

DRUG CHALLENGE

Understanding the clinical history and the potential risks ofre-exposure is an important part of managing patients with drug hypersensitivity. Risk stratification is a process by which the physician reviews these risks and can then advise patients on optimal next steps. For example, a patient reporting a fine papular nonpruritic rash and no other clinical symptoms whilebeing treated with amoxicillin in the setting of a viral infection isvery unlikely to be allergic to amoxicillin. Instead, it is likely thatthe viral infection induced the exanthem, and if re-exposed toamoxicillin, the patient is unlikely to experience a rash. In contrast, a patient who reports recent symptoms of anaphylaxis requiring treatment with epinephrine during a carboplatininfusion is likely to be allergic to carboplatin. The Brownanaphylaxis criteria are useful in risk stratification and contain3 grades, with grade 3 associated with changes in vital signs,syncope, or seizures and being of greatest severity.

The process of obtaining an informed consent is key to patient safety and is critically important to delivering quality patient care. The risks, benefits, and potential alternatives of all procedures should be discussed in detail with the patient and/or a pediatric patient's parents, and approval along with a signed consent formis recommended before proceeding.

PROTOCOLS

Drug challenge is considered the gold standard for thediagnostic evaluation of ADRs. This procedure is defined as there-administration of a drug, usually with progressively increasingdoses, to verify that a patient does not experience an ADR. It isideal to perform skin testing first whenever possible, particularly in cases where immediate reactions are being assessed and/orwhen the maximum nonirritating concentration for skin testingof the drug is known. Generally, a drug challenge is subsequentlyperformed in patients with negative skin testing. It can also,however, be used in the absence of prior skin testing based on thepatient's history, especially if skin testing is not feasible orvalidated. Drug challenges should only be performed whereimmediate clinical support is available.

TABLE I.Severity grading system of immediate hypersensitivity reactions

Grade	Severity	Description
1	Mil	Symptoms are limited to the skin (eg,flushing) or involve a single organ/system and are mild
2	Moderate	Symptoms involve at least 2 organs/systems (eg,flushing and dyspnea), but there is no significant decrease in blood pressure or oxygen saturation
3	Sever	Symptoms typically involve at least 2 organs/systems, and there is a significant decrease inblood pressure (systolic<90 mm Hg and/or syncope) and/or oxygen

Graded challenges can usually exclude immediate hypersensitivity in patients with a low-risk history and allow for the evaluation of cross-reactivity of structurally related compounds among different drug classes. This approach is not recommended for patients with a history consistent with a severe non-IgE-mediated reaction, or SCARs such as SJS, TEN, interstitial nephritis, hepatitis, or hemolytic anemia.If the history, skin test, and/or laboratory data suggest a mild non-IgE-mediated reaction or a reaction that was possibly unrelated, re- administration of the drug using a graded challenge procedure

may be considered. Unlike desensitization procedures, graded challenge does not modify a patient's immunologic reactivity. After a successful graded challenge and therapeutic course of thedrug, future courses of the drug can be started without the need to perform another challenge. In contrast to desensitization,wherein patients receive incremental doses of a drug who have confirmed or highly likely allergy, drug challenge is a diagnostic procedure that is performed in cases of low suspicion that a reaction is due to drug hypersensitivity. Graded challenge may beconsidered with caution for patients with SSLRs, and it shouldbe on an individual case basis that balances risks, benefits, and alternative approaches.

Drug challenges should be performed in a monitored clinical setting with rescue medications available in the event of a reaction. The decision to perform a drug challenge and location of the challenge, that is, in an outpatient clinic or in a more monitored setting, may be determined based on the patient's history, age, developmental maturity, current clinical condition, and skin testing.

Despite the widespread use of drug challenges, at present there is no evidence-based guidance delineating the optimal number ofsteps. In a recent publication, Iammatteo et al sought to determine the safety of test doses, or graded challenge, among patients with a history of ADRs. A test dose could be considered either as synonymous with a typical, multistep graded challenge or as a subset that consisted of 1 or 2 steps. A 1-step test dose wasdefined as the administration of the full dose of a medication followed by a specific time period (ie, 60 minutes) of observation. A 2-step test dose was defined as one-tenth of the full dose for a parenteral medication or one-fourth of a pill for an oral medication followed by

administration of the full dose after a specific period of observation. The authors compared the out- comes of 1- or 2-step test doses with multistep graded challenges comprising 3 or 4 steps performed during the same time period. They found that 1- or 2-step test doses were safe in appropriately selected, low-risk patients for the evaluation of ADRs. The overwhelming majority of test doses did not result in ADRs. Furthermore, when reactions did occur, they were mild and often did not require treatment. Multistep challenges do not seem to confer additional safety, but they may be performed depending on patient history or when caution is required, such as in those with anxiety or multiple comorbid conditions. The starting dose for graded challenge is generally higher than for desensitization procedures, and subsequent doses are usually administered in 10-fold dose increments in contrast to the 2-fold increments used in desensitization.

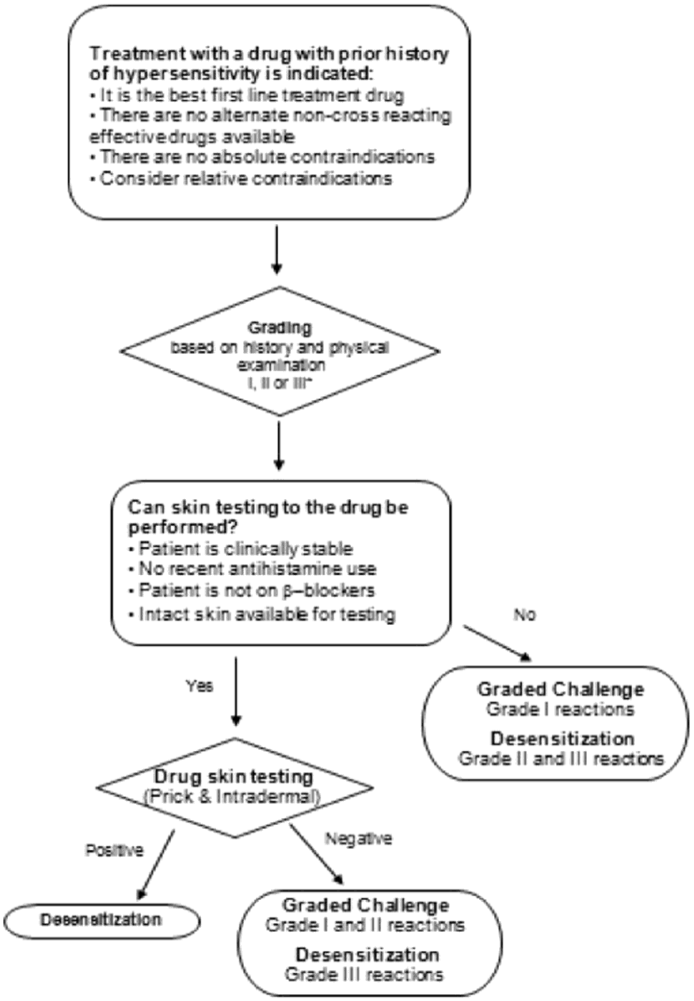
Time intervals between doses vary based on the type of potential reaction (ie, immediate vs delayed), and they typically range from 30 to 60 minutes. A typical starting dose for graded challenge to a drug is one-tenth of the target treatment dose, followed by nine-tenths. The protocols for local anesthetics and NSAID challenge generally involve more steps.[67] Other approaches should be considered to assess delayed reactions, which may require longer observation periods and/or updosing intervals anywhere from 24 to 48 hours to 7 to 14 days, as described in the literature. The route of administration may be oral, intravenous, subcutaneous, or intramuscular.

Additional education about test doses and drug challenge in patients who are unlikely to be allergic will expand the scope of practice, as many of these can be performed safely in an outpatient allergy clinic by trained staff.

DRUG DESENSITIZATION

Mechanisms

The term "drug desensitization" is defined as a procedure that modifies a patient's immune response to a drug, allowing temporary tolerance that can be maintained as long as serum drug levels are maintained. This state is lost as soon as the drug is eliminated (2 to 3 half-lives). Desensitization protocols are specific for each drug and each patient and typically include more than 3 steps. The starting dose is approximately 1/10,000th of the final dose, with doses doubling at each increment until the target dose is attained. Desensitization results in transiently reduced skin sensitivity to drug allergens in most patients with IgE-mediated reactions, and some become skin test negative by the end of the protocol. The mechanisms by which temporary mast cell/basophil tolerance is induced during drug desensitization are not entirely clear. They are thought to be due to subthreshold doses of antigen that are not internalized and rearranged at the membrane and thus uncouple specific calcium responses. Activation of inhibitory molecules preventing signal transduction and protecting against cell activation and the release of mediators involved in anaphylaxis has also been demonstrated in mast cells *in vitro*. The possibility that IgG antibodies may neutralize drug epitopes and serve a "blocking" function for IgE-dependent reactions has not been conclusively demonstrated, and maintaining the drug desensitization state is dependent on continuous exposure to the drug.



Algorithm for evaluation of drug hypersensitivity reactions.

Absolute contraindications: severe cutaneous adverse reactions including Stevens-Johnson syndrome and other bullous dermatitis, toxic epidermal necrolysis, drug reactions with eosin- ophilia and systemic symptom syndrome, and acute generalizedexanthematous pustulosis.*Grading*: based on the Brown anaphylaxis criteria.

Patients with an IgE-mediated drug allergy often respond well to desensitization procedures. However, similar desensitization procedures have been increasingly used with success in patients for whom evidence of IgE sensitization is lacking and who may have experienced direct mast cell/basophil activation through immune-related and non-immune-related receptors.

Delayed reactions usually begin a few hours after exposure to the culprit drug and are typically classified as type IV reactions. The symptoms of delayed reactions are usually limited to the skin with maculopapular rashes. It should be noted that chemotherapy and monoclonal antibodies can also induce delayed reactions. These have features of type I classification thatoccur hours to days after the infusion and are due to the prolonged systemic effects of premedications.

Desensitizations for type IV reactions have been performed with increasing frequency and success, although no standardized protocols are available. In many instances, a patient's clinical history suggests allergy, but there are limited objective data

proving allergy before desensitization is performed with success, and this presents a caveat to this scenario. Reactions that involve mucosal membranes and/or are associated with systemic symptoms are not amenable to desensitization due to the risk of inducing a severe systemic reaction similar to the initial reaction with even minuscule amounts of drug antigen.

The mechanism of delayed reactions is not fully understood. T-cell activation has been evaluated *in vitro* after exposure to drugs inducing maculopapular rashes. CD4 and CD8 T-cell sulfamethoxazole-specific clones secreting IFN, IL-10, and IL-6 have been derived from patients with CF presenting delayed rashes. Further study into these and other underlying mechanisms is required.

PRINCIPLES AND PROCEDURES

Desensitization to a drug with validated skin testing should be considered if the patient has a positive skin test reaction and when no alternate treatment option is available, or when the drug is first-line treatment and desensitization is not otherwise contraindicated. In the case of drugs for which no validated skin tests are available, desensitization may be considered regardless of the skin test result depending on the pattern of their initial drug-associated reaction.

Although desensitization is most successful if the history is strongly suggestive of an IgE-mediated reaction, as mentioned earlier, it is also possible to perform desensitization for non-IgE-mediated immediate drug reactions including some type IV reactions.

Desensitization is not recommended for type II and type III SSLRs and should NEVER be attempted in patients with histories of reactions including SCARs that involve significant skin desquamation such as erythema multiforme, SJS, or TEN. Even small doses of the drug may induce irreversible and potentially fatal recurrent desquamative reactions.

Immediate reactions begin suddenly, usually within minutes of initiation of the infusion in the case of intravenous or injected medication or within an hour of the intake of oral medications. Because chemotherapy drugs and monoclonal antibodies may be administered with antihistamine and steroid premedication per national guidelines, acute reactions may occur later than 1 hour after the exposure. The signs and symptoms most typical for immediate-type allergic reactions include pruritus, flushing, urticaria, angioedema, throat tightening, wheezing, nausea, diarrhea, hypotension, syncope, and cardiorespiratory arrest that can lead to death. Atypical symptoms include back, chest, or abdominal pain, chills, and fever (such as seen with taxanes, oxaliplatin, monoclonals such as rituximab, and intravenous iron preparations). These reactions result from the sudden activation of mast cells and/or basophils through IgE and non-IgE mechanisms, both of which respond to desensitization protocols. Drugs implicated in IgE-mediated allergic reactions include but are not limited to antibiotics such as penicillins and cephalosporins, platinum-based chemotherapy agents (eg, carboplatin, cisplatin, and oxaliplatin), taxanes including paclitaxel and docetaxel, and monoclonal antibodies such as rituximab, cetuximab, trastuzumab, and infliximab.

If desensitization is being considered, appropriate specialists including those in infectious disease, rheumatology, oncology, and pulmonology should be consulted to help determine reasonable alternatives to the drug in question and/or that in fact the drug is first-line treatment for the patient's condition. For example, if a patient has penicillin allergy with positive skin testing, is penicillin treatment requiring desensitization the optimal next step or are there reasonable alternative treatment options?

Similar to graded challenge, signed informed consent must be obtained and patients and/or a patient's parents or guardian should be informed that desensitization involves administration of a drug to which the patient is known or highly suspected to be allergic. Accordingly, there is substantial risk of at least a mild allergic reaction. Anaphylaxis is always a risk and is more common in highly sensitized patients or with aggressive dose escalations.

Drug desensitization should always be performed in settings in which resuscitation personnel and resources are readily available. One-to-one nursing is required with a nurse who has been specifically trained to monitor desensitization protocols and recognize and treat allergic reactions, including the prompt administration of intramuscular epinephrine for anaphylaxis. Depending on the patient's history and whether this is the first desensitization or a repeat desensitization after the one that was previously successful, the physical location may be an intensive care unit, in patient floor, or outpatient infusion center. Patients with mild-moderate reactions can be desensitized in the outpatient setting under close observation by experienced and appropriately trained staff with readily available resuscitation medications, equipment, and resources. Patients with more severe reactions including grade 3 reactions should be desensitized in an intensive care unit. For patients with cardiac disease, those with restrictive or obstructive pulmonary diseases, and those for whom beta-blocker therapy cannot be easily discontinued for the procedure, desensitization should be performed in an intensive care setting. Desensitization in an intensive care setting is also most often preferable for the younger pediatric population, particularly in the case of first-time de- sensitizations. Young children have more limited and potentially less reliable communication skills than adults. This would also apply to older children with developmental issues and adults with the same. After an initial successful desensitization, repeat procedures may be performed in a carefully monitored outpatient center in the presence of appropriately trained staff. The supervising physician should be available throughout the procedure and located within a few minutes of the desensitization site.

Drug desensitization can be performed in patients of any age and in pregnant women when alternative therapies are not possible (eg, for penicillin treatment in a penicillin-allergic woman with syphilis).

PREMEDICATIONS, TYPES, AND USE

Pretreatment with H1 blockers, H2 blockers, antileukotrienes or leukotriene receptor antagonists, prostaglandin antagonists, and/or corticosteroids may be considered in selected cases, particularly in more difficult cases and those that are more likely to be non-IgE-mediated. Although clinical experience supports the use of premedication regimens to decrease the incidence, frequency, and severity of reactions, formal clinical trials comparing premedication protocols are lacking. Premedications may not prevent IgE-dependent anaphylaxis, but they may help prevent and treat breakthrough reactions in cases of desensitization for suspected IgE-mediated drug allergy.

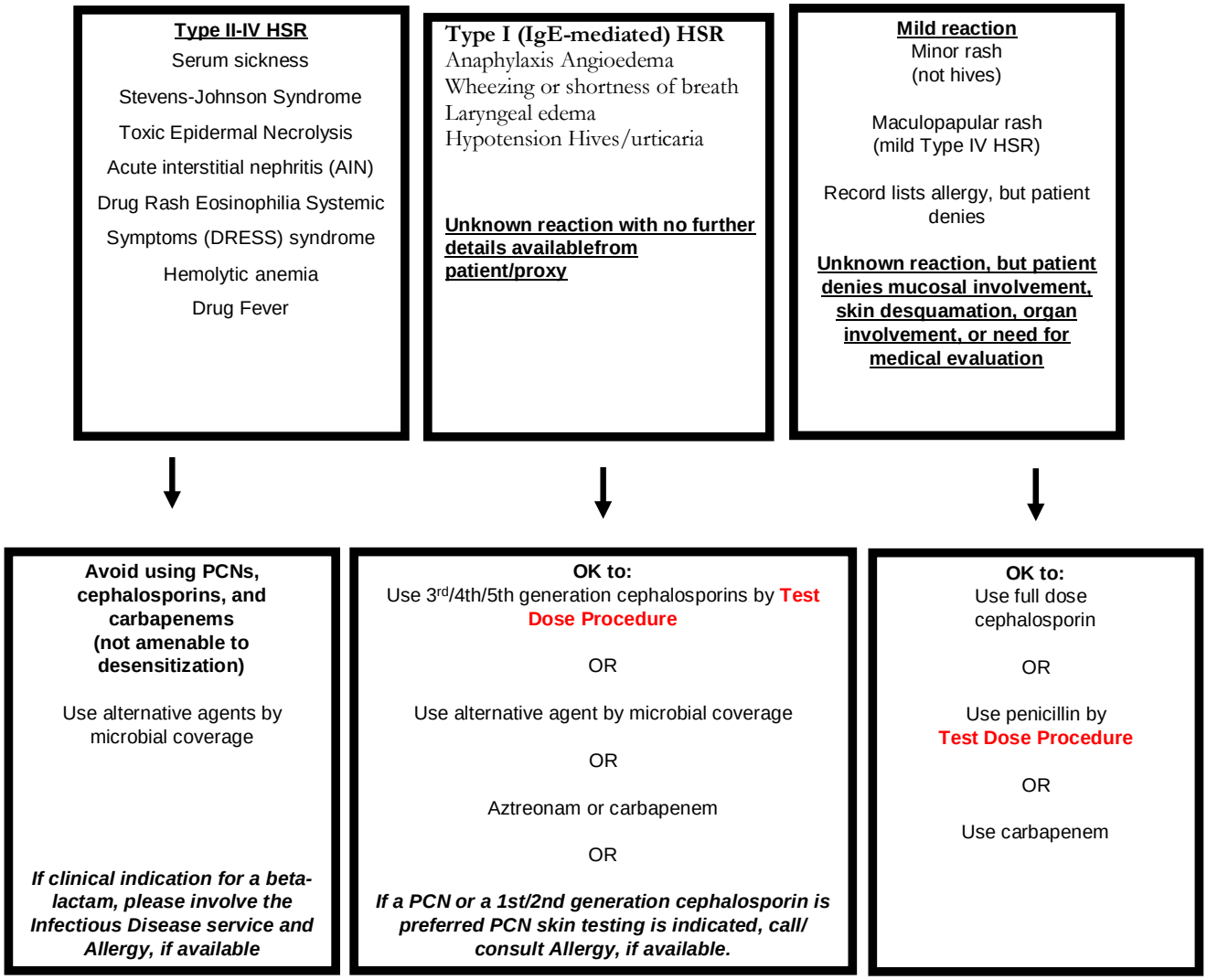
PROTOCOLS FOR IMMEDIATE REACTIONS

Protocols for drug desensitization have been successfully used for antibiotics, chemotherapy drugs, and monoclonal antibodies among other drugs in patients with IgE- and non-IgE-mediated hypersensitivity reactions. The most commonly used intravenous desensitization protocols are standardized 12- to 16-step protocols. The 12-step protocol is used for patients with initial reactions of grades I and II per the Brown anaphylaxis criteria and assumed mild-to-moderate risk of adverse events during desensitization. The 16-step protocol is employed for patients with grade III reactions including anaphylaxis who are at higher risk during desensitization. Protocols shown have been used successfully in adult patients with immediate hypersensitivity reactions to a variety of drugs including antibiotics, chemotherapy, monoclonal antibodies, and other drugs. These protocols comprise 3 or 4 intravenous bags of a drug concentration that approximately doubles at each step up to a full concentration bag (1:1). The protocols have also been successfully used in the pediatric population, although in cases of desensitization to monoclonal antibodies, younger patients seem to require more prolonged procedures with slower last step infusion rates. In addition, desensitization to coagulation factors requires more prolonged protocols, likely due to the presence of inhibitor antibodies in these patients. A variety of other protocols have been described not only for intravenous desensitization but also for oral, subcutaneous, and intraperitoneal routes in both outpatient and inpatient contexts.

The main risk during a desensitization procedure is that of a recurrent immediate reaction and anaphylaxis when the patient is re-exposed to the culprit drug, but current data suggest that most breakthrough reactions are mild and less severe than the patient's initial hypersensitivity reaction. The authors are unaware of any published fatalities resulting from failed desensitization procedures, and they are considered to be safe procedures when no alternate treatment is available or the drug is first line treatment for the patient's condition.

Milder reactions can be treated with the same medications described above as premedications and the desensitization may be resumed, usually at a slower rate, after such mild break-through reactions. Rare delayed reactions have been reported after desensitization in patients who required high-dose or extended-duration therapy, including serum sickness, hemolytic anemia, thrombocytopenia, and nephritis.

Once the patient has received at least 1 full dose after desensitization without further reactions, subsequent dosing may be administered with outpatient status, assuming proper patient education and the availability of epinephrine autoinjectors. If changes in dosing schedule are indicated for the patient's convenience, the medication can be administered earlier than a scheduled dose. This will maintain the temporary induction of tolerance state, as long as the new interval is not interfering with the steady state of the drug or potentially leading to drug toxicity. It is advised that these changes are made during inpatient status and that the patient is discharged on a strict dosing schedule. Subsequent dosing should be administered on schedule, and if there is a delay in administration and/or 1 or more doses are missed, then the patient may have to undergo desensitization again, particularly if the delay comprises more than 2 half-lives of the medication.



Penicillin hypersensitivity pathway. *PCN*, Penicillin.

PROTOCOLS FOR DELAYED REACTIONS

Protocols for desensitization after mild delayed reactions include starting doses at 1/100,000 to 1/100 the target dose. Each subsequent step doubles the dose at time intervals ranging from 30 minutes to 6 to 12 hours. These protocols span several days, and recent data suggest that some mild delayed reactions may be amenable to using protocols with shorter time intervals. Rapid graded challenge protocols similar to desensitization protocols (more than 3 doses at fixed time intervals) for trimethoprim sulfamethoxazole have been successful for delayed reactions. Patients with delayed reactions without features of SJS/TEN can lose sensitivity over time, similar to those with IgE-mediated reactions, and it is possible that some of these patients may have had reduced sensitivity before desensitization. Itis also possible that a rapid desensitization protocol targets T-cellsignal transduction as it targets mast cells and basophils.

DECISION MAKING AND BEST PRACTICES FOR DRUG ALLERGY: THE PENICILLIN PATHWAY

Evidence suggests that patients lose allergic sensitivity to drugs over time, and because reactions attributed to drug allergy maynot be truly allergic, depriving patients of their first-line therapy at the critical time of need is not optimal. Patients labeled aspenicillin allergic when entering a hospital may suffer fromunnecessary increased hospitalization days and infectious com- plications, and they may incur increased health care costs due to the use of a more expensive

antibiotic.[99] Over the past few years,clinical practices and pathways have been developed to guide

clinicians in addressing patients with a label of penicillin allergywho are in need of beta-lactam antibiotics. With the goal of avoiding morbidity and mortality and providing safe first-line antibiotic coverage, a penicillin pathway has been developed at Partners institutions in Boston and other institutions nationwide. When time constraints do not allow for skin testing or alternative tests, the clinical history directs the decision-making process according to type I reactions, type II-IV reactions, and mild re- actions including delayed rashes. Alternative antibiotics, test dose procedure, and challenge and desensitization are recommendedbased on the presence of differentiating symptoms in the historyand on risk stratification. It is mandatory that an allergist/immunologist be involved in cases with high index of suspicion for type I reactions to provide recommendations and to perform appropriate measures including skin tests. It should also be noted that such an algorithmic approach, in avoiding penicillin and prescribing beta-lactams that may not be ideal alter- natives, does not substitute for future penicillin allergy testing. This testing should still be performed at a nonemergent time in either the inpatient or an outpatient setting. Preliminary out- comes indicate that there have been no cases of SJS/TEN or anaphylaxis in the first 12 months of applying this clinical standard at one of the Partners hospitals based on its use in several hundred patients. The pathway has also been translated into an application that can be viewed on a hand-held device, and newer pathways for cephalosporin use have also beendeveloped.

Study questions.

1. Reasons for the development, triggers and genetic basis of allergy
2. Immunological mechanisms and types of injury biostructures
3. Non-allergic conditions, causes and mechanisms of formation
4. Basic principles of diagnosis of allergic diseases
5. Principles of treatment of allergic diseases
6. The main types of allergic diseases: clinical features, diagnosis, treatment approaches

Control questions

1. Role of triggers in the formation of allergic diseases.
2. Mechanisms of atopy.
3. Differential diagnosis of allergic and non-allergic reactions.
4. The sequence of pathoallergic diagnosis.
5. Approaches to the treatment of allergic diseases.
6. Specific immunotherapy mechanism of action, indications and contraindications for its implementation.
7. Allergic rhinitis, conjunctivitis, polinosis: symptoms, diagnosis and treatment.
8. Bronchial asthma: etiology, clinical features, stepwise approach to treatment.
9. Diagnosis and treatment of insect and food allergy.
10. Diagnosis and treatment of dryg alleegy.

Practical skills:

1. Be able to collect allergic anamnesis and diagnose allergic rhinitis, atopic and allergic dermatitis.
2. Know instrumental and laboratory methods for diagnosis of allergic diseases.
3. Master the modern principles of diagnosis and treatment of bronchial asthma.
4. To be able to evaluate the specific skin tests.
5. Know and be able to carry out specific immunotherapy.

The conclusions.

1. To be able to clarify modern knowledge about the mechanisms of immunological reactions of biostructures damage, genetic and environmental bases of allergic diseases.

2. To form the basic principles of clinical and laboratory and instrumental diagnostics of allergic diseases.
3. To determine the basic methods of laboratory diagnosis of allergic diseases (the role of specific IgE and its connection with specific immunotherapy)
4. To determine the basic group of antihistamines and approaches to the treatment of allergic diseases.
5. To know new moecular-based allergy diagnostics, that is allowed for improved management of allergic diseases.

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