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Variety of allergic symptoms in the therapy of selected respiratory and autoimmune diseases

Różnorodność objawów alergicznych w terapii wybranych chorób układu oddechowego i chorób autoimmunologicznych

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Abstract

Introduction and Objective. Drug hypersensitivity reactions are common in the therapy of various diseases. The Gell and Coombs classification divides immunologic drug hypersensitivity reactions into four major pathophysiologic categories based on immunologic mechanism (I, II, III, IV). The reactions may occur during the treatment of cystic fibrosis and autoimmune diseases, such as diabetes and inflammatory bowel diseases. Allergy symptoms can vary from mild, local reactions to severe anaphylaxis requiring hospitalization. The aim of this review is to systematize the latest knowledge on the diversity of allergic reactions to various types of treatment of common autoimmune and respiratory diseases and show the need for future research in this field.

Brief description of the state of knowledge. Allergic reactions may include fever, nausea, vomiting, hypotension, haemolytic anaemia, joint swelling, itching, rash with eosinophilia, urticaria and many more. To confirm hypersensitivity, it is important to conduct an extensive interview, confirm the proper use of the preparation, and conduct allergy tests. The study presents allergic reactions in the treatment of the following diseases: cystic fibrosis, inflammatory bowel diseases and diabetes mellitus.

Summary. Allergic reactions may vary depending on the type of treatment and patient›s predispositions. Undeniably, the occurrence of side-effects in the form of allergic reactions negatively affects the results of therapy and the patient's quality of life. Further research is needed on how to avoid allergic side-effects and treatment options for those already developed without the need to prematurely terminate therapy.

Key words

diabetes mellitus, cystic fibrosis, anaphylaxis, drug hypersensitivity, inflammatory bowel diseases, allergic reactions

Streszczenie

Wprowadzenie i cel pracy. Reakcje nadwrażliwości na leki są powszechne w terapii różnych chorób. Klasyfikacja Gella i Coombsa dzieli immunologiczne reakcje nadwrażliwości na leki na 4 główne kategorie patofizjologiczne na podstawie mechanizmu immunologicznego (I, II, III, IV). Reakcje te mogą wystąpić podczas leczenia mukowiscydozy oraz chorób autoimmunologicznych, takich jak cukrzyca i choroby zapalne jelit. Objawy alergii mogą wahać się od łagodnych, miejscowych reakcji do ciężkiej anafilaksji wymagającej hospitalizacji. Celem niniejszej pracy jest usystematyzowanie najnowszej wiedzy na temat różnorodności reakcji alergicznych na różne rodzaje leczenia powszechnych chorób autoimmunologicznych i chorób układu oddechowego oraz wskazanie potrzeby przyszłych badań w tej dziedzinie.

Opis stanu wiedzy. Reakcje alergiczne mogą obejmować gorączkę, nudności, wymioty, niedociśnienie, niedokrwistość hemolityczną, obrzęk stawów, świąd, wysypkę z eozynofilią, pokrzywkę i wiele innych objawów. W celu potwierdzenia nadwrażliwości ważne jest zebranie obszernego wywiadu, potwierdzenie prawidłowego stosowania preparatu oraz przeprowadzenie testów alergicznych. W artykule przedstawiono reakcje alergiczne w leczeniu następujących chorób: mukowiscydozy, nieswoistych zapaleń jelit i cukrzycy.

Podsumowanie. Reakcje alergiczne mogą być różne w zależności od rodzaju leczenia i predyspozycji pacjenta. Niewątpliwie występowanie skutków ubocznych w postaci reakcji alergicznych negatywnie wpływa na wyniki terapii i jakość życia pacjenta. Potrzebne są dalsze badania nad sposobami unikania alergicznych skutków ubocznych i opcjami leczenia tych, które już wystąpiły, bez konieczności przedwczesnego kończenia terapii.

Słowa kluczowe

cukrzyca, choroby zapalne jelit, anafilaksja, nadwrażliwość na leki, mukowiscydoza, reakcje alergiczne

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INTRODUCTION

Autoimmune and respiratory diseases are an increasing global health problem, and the incidence is constantly increasing. Unfortunately, their therapy may be associated with side-effects, including immediate (urticaria, anaphylaxis, rash, nausea, swelling, itching) and delayed allergic reactions (contact eczema, angioedema). Drug hypersensitivity reactions (DHRs) are a frequent reason for consultation in allergy departments. It has been estimated that DHRs are responsible for 3% – 6% of all hospital admissions and that they occur in 10% – 15% of hospitalized patients. Some studies have suggested that there is lower prevalence of DHRs, because not all patients were confirmed by allergy testing or drug challenge. A correct diagnosis of drug hypersensitivity reactions is very important and challenging due to lack of standardized tests for many drugs. The diagnostic process is time consuming, requires trained personnel and involves risky procedures. Moreover, false positive results lead to avoidance, unnecessary drugs substitutions and incorrect diagnosis.

The drugs most associated with allergic reactions are: beta-lactam antibiotics, sulfonamides, macrolide antibiotics, quinolones, non-steroidal anti-inflammatories, corticosteroids and other cytostatics, angiotensin converting enzyme inhibitors, general and local anaesthetics (such as propofol, sevoflurane, isoflurane, midazolam, nitrous oxide etc.), biological drugs, antiepileptic drugs (phenytoin, carbamazepine), vaccines and more [1]. Treating cystic fibrosis with elexacaftor/tezacaftor/ivacaftor may result in malaise, progressive rash, facial swelling, pruritus, liver damage and toxic epidermal necrolysis. Inflammatory bowel diseases are treated with 5-ASA (mesalazine, sulfalazine) and due to hypersensitivity the patient may develop Stevens-Johnson syndrome, Sweet syndrome, PIE syndrome, rash, diarrhea, dry cough. Moreover, infusions of anti-TNF antibodies such as infliximab are used in therapy and erythematous rash, swelling of the hands and face, fever, joint pain, urticarial spots, extensive rash, psoriatic lesions, drug-induced lupus, erythema multiforme and vasculitis; anaphylaxis may also occur. In diabetic patients, allergy may occur both in the case of standardly used insulins and modern substitutes; moreover, additional substances in insulin preparations can cause allergic reactions.

OBJECTIVE

The aim of the review is to summarize and highlight the latest knowledge on the diversity of allergic symptoms in response to drugs used in autoimmune and respiratory diseases, their pathogenesis, development and course.

MATERIALS AND METHOD

The review presents currently available literature on the topic of allergic symptoms arising in the treatment of cystic fibrosis, inflammatory bowel diseases and diabetes mellitus. Online database PubMed was searched using different combinations of specific key words: 'cystic fibrosis', 'inflammatory bowel diseases', 'diabetes mellitus', 'drug hypersensitivity', 'drug allergic reactions', 'anaphylaxis' and 'insulin treatment'. Only papers published since 2016 and in the English language have been used. To avoid excluding important studies, the research was not restricted by the type of publication or study design. The total number of works searched was 1,407, of which 50 the most closely related to the topic of the review and contributing current and relevant information were used.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Cystic fibrosis. Cystic fibrosis is a genetic disease in which there is a mutation in the gene encoding the CFTR protein and, consequently, the transport of anions through protein channels in the epithelia of the entire body is impaired. Pathological changes also occur in smooth muscles, myeloid cells, endothelial cells, and during cartilage development [2]. The main organs affected by the disease are the lungs, pancreas, sweat glands, intestines, liver, nasal mucosa, salivary glands and the reproductive system, while the most common clinical manifestation is obstructive pulmonary disease. The treatment of cystic fibrosis has three basic goals: reducing the amount of secretions in the respiratory tract, ensuring the absence of infections in the respiratory system,and maintaining optimal nutritional status [3]. In the treatment of pulmonary symptoms of cystic fibrosis, the following are used: antibiotics – prevention and control of infection; NSAIDs, inhaled or systemic steroids and cromoglycanic acid – anti-inflammatory effect; β agonists – bronchodilation; dornase alfa and 3–6% hypertonic saline solution are also recommended.

A new group of drugs used in the treatment of cystic fibrosis are CFTR modulators [4]. In patients with cystic fibrosis, new infections or exacerbations of pulmonary symptoms may require longer antibiotic therapy than in the general population (lasting up to 2–3 weeks), which causes the antibiotic to accumulate in the body [5]. It was shown that in patients who received more courses of antibiotic therapy, hypersensitivity reactions occurred much more often than in patients who received less antibacterial therapy (median 124 vs. 46). It was also observed that the occurrence of antibiotic hypersensitivity reactions increased with the age of the patient [6]. Antibiotics administered to cystic fibrosis patients to reduce pulmonary symptoms and prevent loss of function are administered by inhalation, orally, or a combination of both routes, and in the case of acute exacerbation, they are administered intravenously [7].

β-lactams are the most common cause of hypersensitivity, with piperacillin being the main hypersensitivity factor [6, 8]. Different classes of β-lactams often cause cross-reactions [8]. Allergies are also common in the case of co-trimoxazole [5, 9]. In the studies conducted by Kowalik et al, the reactions that occurred were mostly mild to moderate and were mainly limited to the skin, while anaphylactic reactions were rare. The most common symptoms were pruritus, skin rash, urticaria and angioedema. A symptom reported less frequently was tingling caused by treatment with colistimethate, meropenem and piperacillin. Symptoms reported from other systems include the digestive system (nausea, vomiting, diarrhea), respiratory system (shortness of breath, cough), and cardiovascular system (tachycardia, dizziness, hypotension). Hypersensitivity reactions to intravenous antibiotics usually (48%) had a late onset (>24 hours) [6]. In the study by Abuzgai et el, five patients experienced only skin lesions (maculopapular

or morbilliform rash, urticaria), but in as many as 15 patients, drug allergy also manifested itself with systemic symptoms (fever, swelling of the hands and feet, nausea and vomiting, oral pain, hypotension, haemolytic anaemia, joint swelling, drug rash with eosinophilia and systemic symptoms [DRESS]) [9]. When treating an exacerbation of cystic fibrosis with antibiotics, a drug reaction with eosinophilia and general symptoms may occur. It usually appears two to six weeks after starting the drug. Symptoms are usually fever, extensive skin lesions and eosinophilia [10]. This reaction has been demonstrated in patients with cystic fibrosis during intravenous piperacillin-tazobactam therapy, oral rimfapicin and trimethoprim-sulfamethaxazole [10–12]. In the case of children with cystic fibrosis, allergic reactions occur with a similar frequency to the general population [13, 14]. In a study conducted by Tugcu et el, two children developed an allergy to trimethoprim-sulfamethaxazole, confirmed by a provocation test [13]. In the case of the study by Süleyman et al, B-lactams were responsible for the majority of allergic reactions, with ceftazidime and piperacillin-tazobactam being the most common causes of hypersensitivity. The most frequently reported symptom was urticaria or urticaria with angioedema. It has been shown that an immediate allergic reaction can be a predictive factor for a confirmed allergic reaction [15]. During the phase 3 elexacaftor/tezacaftor/ivacaftor clinical trial, as many as 10.9% of patients experienced a delayed-onset rash [16]. A non-immediate allergic reaction was documented two weeks after starting lumacaftor treatment, manifesting as malaise and a severe generalized skin reaction with progressive rash, facial swelling and pruritus [17]. Type IV hypersensitivity may also occur, i.e. liver damage induced by elexacaftor/ivacaftor/tezacaftor–treatment [18, 19]. Five months after starting the treatment, the patient experienced an increase in liver enzymes (ALT, ASP), and after discontinuing the drug, a liver biopsy showed necrolysis. In the case of ivacaftor therapy, hepatotoxicity was demonstrated with elevated ALT and AST levels more than eight times above the upper limits of normal, leading to discontinuation of therapy in one to two percent of subjects [18]. In the case of CFTR modulator therapy, the cause of elevated liver enzymes should be precisely assessed. In a study conducted by Daniel Tewkesbury et al., among 337 patients taking elexacaftor/tezacaftor/ivacaftor, 19 had an increase in transaminases, but in as many as 12 patients it was due to alternative causes [19]. Combination therapy with elexacaftor/tezacaftor/ivacaftor may also result in toxic epidermal necrolysis (TEN). It has not been established whether hypersensitivity reactions to CFTR modulators are related to a genetic factor [20]. A significant problem in the assessment of hypersensitivity reactions in patients with cystic fibrosis is the lack of allergy tests that would confirm the occurrence of allergy. This is caused by the need to quickly apply treatment and the inability to perform allergy tests before therapy [6].

Inflammatory bowel diseases. Inflammatory bowel diseases (IBD) are disorders of the digestive tract, manifested by chronic, recurrent intestinal inflammation with phases of active disease or its remission. The two main conditions classified as IBD are Crohn›s disease (CD) and ulcerative colitis (UC). The etiology of the development of inflammatory bowel disease is still unclear; the process is complex and related to many factors. However, it is known that the immunological component plays an important role in the pathogenesis. Treatment of inflammatory bowel diseases is adjusted depending on the degree of disease activity. During periods of exacerbation, intensive treatment is used, supportive treatment is mainly used to prevent disease recurrence. Even after successful initial treatment, patients with ulcerative colitis (UC) or Crohn›s disease (CD) typically require long-term maintenance therapy [21]. Drugs from the aminosalicylate group (5-ASA – mesalazine, sulfasalazine)) are a fundamental element of conventional pharmacological therapy of uncomplicated ulcerative colorectal disease. Many patients can successfully use them for a long period of time. 5-aminosalicylic acid preparations are used primarily in the treatment of mild and medium flares of this disease. If the response to 5-ASA induction therapy is inadequate, steroid therapy is indicated [22]. Unlike ulcerative colitis (UC), mesalazine has no proven efficacy in Crohn's disease (CD). Local or systemic glucocorticosteroids and sulfasalazine are used as anti-inflammatory treatment [21]. In cases of resistance to glucocorticosteroids or in case of their severe complications, immunosuppressive drugs, such as thiopurines or methotrexate, may also be used in anti-inflammatory treatment. The choice of therapy depends mainly on the severity of the disease [21, 23]. Hypersensitivity reactions can be divided into immediate and delayed. They may occur during treatment, e.g. as a result of infliximab infusion. Delayed hypersensitivity reactions occur approximately one to two weeks after the infusion. They result in an erythematous rash, swelling of the hands and face, fever and joint pain. An immediate reaction occurs within two hours of starting the infusion. In this case, the appearance of urticarial spots, an extensive rash, and anaphylaxis may be observed [24]. Several drugs used to treat IBD may cause hypersensitivity reactions manifesting as lesions of the skin or mucous membranes. TNF-α antagonist drugs may cause a variety of skin reactions, both local and systemic [25]. There is evidence of a relationship between anti-TNF drugs and the development of immunogenicity and autoimmune reactions. As a result of such therapy, e.g. psoriatic lesions, drug-induced lupus, as well as erythema multiforme or vasculitis may develop [23]. A clinically interesting phenomenon is the so-called a paradoxical reaction that results from the use of anti-tumour necrosis factor alpha (TNF-α) [23].

Psoriatic skin lesions caused by therapy may develop on the entire body, including the scalp and genital areas. Unfortunately, the mechanism of psoriasis induced by anti-TNFα drugs is not fully understood. However, there are several hypotheses, of which the most common is that it is the result of a reduction in TNF-α levels combined with an increase in interferon (IFN)-α produced by plasma dendritic cells [23]. One of the commonly used anti-TNF antibodies is Infliximab (IFX), which is effective not only in induction, but also in maintaining remission in moderately to severe Crohn's disease (CD) and ulcerative colitis (UC) [26]. IFX is a chimeric monoclonal antibody which is mostly well tolerated, but side-effects may occur. Skin symptoms may include psoriasis, skin eczema and dry skin; other symptoms include opportunistic infections and infusion reactions (IR) [27]. The most common side-effects are acute and delayed infusion reactions. The mechanisms governing infusion response are not fully understood. They may involve specific antibodies directed against IFX. Infusion reactions occur with a frequency of five to ten percent, depending on specific

tests. The former are also called immediate hypersensitivity reactions, and include reactions occurring within 24 hours of drug infusion. The symptoms observed can be very diverse and their severity may vary from mild to severe anaphylactic reactions [26]. Classically, these symptoms include fever, rash or hives, chest pain, and hypotension [27]. If immediate hypersensitivity occurs, re-administration of the drug may be undertaken using slower infusion rates and enhanced premedication with steroids and antihistamines. However, the use of premedication with antihistamines may be a factor increasing the occurrence of IHR [26]. Other options are desensitization and tolerance induction. Unfortunately, research on inducing tolerance to Infliximab is very limited [26]. Delayed infusion reactions include symptoms appearing 24 hours after taking the drug and up to 14 days. These are mainly type III hypersensitivity reactions which are less common than acute reactions. Symptoms are also diverse and include muscle pain, rash, fever, polyarthralgia, itching, swelling, shortness of breath and headaches. They only appear during repeated IFX therapy [27]. 5-Aminosalicylate drugs (i.e., mesalazine and sulfasalazine) are oral and topical drugs used in the induction and maintenance therapy of mild to moderate ulcerative colitis [28]. Mesalazine, on the other hand, is a commonly used treatment for UC [29]. Despite the effectiveness of mesalazine in the treatment of ulcerative colitis (UC), it may unfortunately cause hypersensitivity reactions. Symptoms may present as a worsening of the underlying disease, with fever, diarrhea and bloody stools. The endoscopic image then shows swollen mucosa, purulent ulcers and erosions. The deterioration caused by the drug reverses after discontinuation of therapy [30]. Mesalazine intolerance is very similar to an exacerbation of UC, therefore it is often difficult to differentiate between them. Adverse reactions to this drug are observed in approximately 15% of patients, in which case the use of immunomodulatory or biological drugs should be considered. Mesalazine allergy appears to be a type IV reaction, where inflammation results from interactions between antigens and T cells. The process of developing type IV allergy occurs in two stages: the sensitization stage and the induction stage [31]. Mesalazine may also cause eosinophilic pneumonia in isolated cases. The time it takes for the disease to develop from the start of treatment may vary from two days to even several years. The clinical picture includes shortness of breath, dry cough and fever [32].

Another possible, although rare, complication of mesalazine therapy may be myocarditis and pericarditis. Although this is a rare adverse reaction, it is extremely dangerous. The mechanism of pathology development is still poorly understood. Inflammation mainly begins within two to four weeks of mesalazine administration, and disappears after discontinuation of the drug [29]. Cases of lupus or lupus-like syndromes resulting from the use of mesalazine have also been described in the literature [33]. Biological drugs in the treatment of both ulcerative colitis and Crohn's disease include vedolizumab. Vedolizumab is a gut-selective monoclonal antibody that reduces intestinal inflammation by inhibiting the migration of lymphocytes into the intestine. Among patients treated with this drug, joint problems occurred more often in patients previously treated with TNF antagonists [34]. The main adverse effects observed in patients treated with vedolizumab included skin rash and angioedema, arthralgia and abdominal pain [35]. It seems important that treatment-induced allergic reactions may appear for the first time even after the administration of several doses [36]. Vedolizumab is also suspected of causing acute renal failure, possibly as a result of delayed-type hypersensitivity. Therefore, patients undergoing such drug therapy should be monitored for deterioration of renal function [35].

Diabetes mellitus. Type 1 diabetes is an autoimmune disease with a multifactorial cause. Genetic, epigenetic and environmental factors are known, among others. In type 1 diabetes, there is a T-cell-dependent destruction of insulin-producing β-cells in the pancreas [37]. Insulin is a polypeptide produced by the β-cells of the pancreatic islets. This hormone is secreted in response to hyperglycaemia and plays a fundamental role in regulating serum glucose levels [38]. Insulin therapy is the basic form of therapy in type 1 diabetes and uncontrolled or difficult to control type 2 diabetes [39]. The most commonly used insulins are human insulin analogues (HIA) and human insulin (NPH, regular insulin) [40]. Immune reactions are relatively rare and their frequency has further decreased since the introduction of human recombinant insulins [38]. Allergic reactions may occur both in the case of standardly used insulins and modern substitutes, for example, Insulin Aspart Biosimilar SAR341402 [41]. Also, additional substances in insulin preparations, such as protamine, zinc, glycerol, myristic acid, phenol mannitol and metacresol, may cause an allergic reaction [42, 43]. Allergic reactions after using insulins may range from mild in the form of subtle skin lesions to life-threatening anaphylaxis [38].

Hypersensitivity is classified into four groups, in the case of reactions after using insulin, there are three. These are most often reactions from the first group (Ig E mediated, rapid onset, typically within one hour of administration) [44–46]. The third type of reaction (IgG/IgM antigen–antibody immune complexes mediated, occur after hours after exposure) and the fourth (T-cell mediated, typically occur within eight to twelve hours of insulin use, peak at 24 h and last up to seven days) [38, 44, 45]. Possible allergic manifestations after insulin administration are summarized in Figure 1.

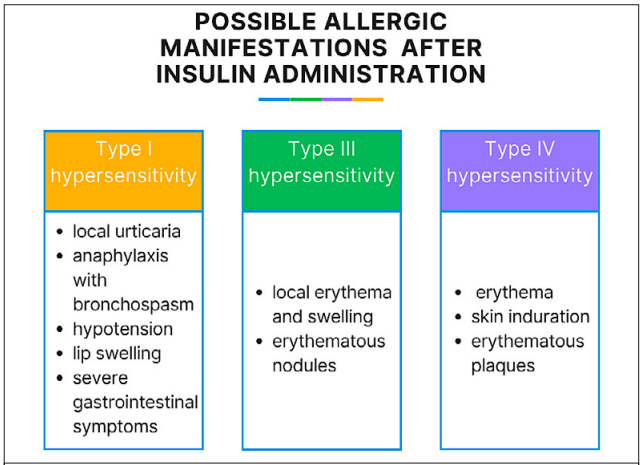

Figure 1. Possible allergic manifestations after insulin administration

In the case of gestational diabetes mellitus (GDM), allergic reactions related to the use of insulin, occur with

a significantly lower frequency. Itchy, painful, erythematous nodules resulting from the injection of insulin detemir have been described. These changes disappeared completely after switching to insulin glargine [42].

The pathogenesis of hypersensitivity reactions to insulin is not well understood. One hypothesis assumes that insulin molecules combine to form larger conglomerates, which increases the likelihood of producing antibodies against them in the subcutaneous tissue. The role of genetic factors is also suspected, the HLA DR4 gene has been associated with a high level of insulin antibody production. Additionally, the route of administration is important, as hypersensitivity reactions are more common with subcutaneous injection compared to intravenous administration [38].

Allergic reactions may also occur in connection with the use of diabetic devices [47, 48]. These include irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD), unspecified skin eruptions, oedema and urticaria [48]. The risk of an allergic reaction when using diabetic devices is related to strong external cutaneous adhesives and long skin contact time [49]. The compounds most frequently associated with the occurrence of allergic reactions when using insulin delivery devices are acrylate chemicals (including isobornyl acrylate – IBOA), 2,2′-methylenebis monoacrylate or cyanoacrylates [48].

In confirming insulin hypersensitivity, it is important to collect an extensive history, confirm the proper use of the preparation, and perform confirmatory allergic/immunological tests [44].

Desensitization is used as a possible form of hypersensitivity therapy with the use of the least reactive insulin for a given patient. It can be performed using regular, aspart, glargine and lispro subcutaneous injections or continuous subcutaneous insulin infusion (CSII) [44]. Other possibilities include using steroids, antihistamines in high doses to control symptoms, immunosuppressive drugs (methotrexate, cyclosporine), and as a last resort therapy – pancreas transplantation [44, 45].

As effective in alleviating allergies in the case of type 4 hypersensitivity reactions to various insulin (including insulin actrapid, insulin aspart, insulin glargine, insulin detemir, and biphasic insulin aspart 30) that do not respond to desensitization, a combination of biphasic insulin aspart 30 and dexamethasone used in subcutaneous injections for a period of eight months has been described [50]. More and more clinical trials include biological drugs as a form of therapy, for example omalizumab – anti-IgE recombinant humanized monoclonal antibody and rituximab [45]. In summary, insulin and other medications used to treat diabetes can cause various types of allergic reactions. These range from minor erythematous lesions to life-threatening anaphylaxis with respiratory disorders. Appropriate diagnosis to exclude other possible causes of the reaction and the use of an effective form of prevention and therapy are important.

CONCLUSIONS:

Allergic reactions to drugs are common immune-mediated public-health problem with highly diverse, sometimes dangerous and life-threatening symptoms which may involve further organs, such as liver, kidneys or bone marrow.

DHRs are a significant diagnostic issue due to the high rate of false-positive results.

Hypersensitivity reactions may be caused by well-known drugs, such as antibiotics administered in respiratory infections in patients with cystic fibrosis, and modern drugs such as monoclonal antibodies used in IBD therapy.

Among antibiotics, the group most frequently associated with allergic reactions are β-lactams, especially piperacillin, which is commonly administered in cystic fibrosis.

In patients with IBD, DHRs are divided into immediate (within two hours) and delayed (one to two weeks after) reactions as a result of infliximab infusion. They may result in rash, swelling of the hands and face, fever, joint pain, urticarial spots, and anaphylaxis. Another biological drug associated with allergic side effects is vedolizumab.

Mesalazine is effective in the treatment of ulcerative colitis; however, it may induce allergic reactions such as fever, diarrhea and bloody stools. The symptoms are very similar to an exacerbation of UC, and is therefore difficult to differentiate.

Commonly used insulin may be the reason of allergic side-effects in diabetic patients. The pathogenesis is not fully understood, it is suspected that insulin molecules combine to conglomerates and antibodies against them are produced in the subcutaneous tissue. There are also genetic factors such as the HLA DR4 gene. Moreover, the route of administration is important, DHRs are more common with subcutaneous injection.

Medical professions, especially emergency physicians, should be aware of their possible manifestations because reactions are not directly related to dose, range from minor cutaneous lesions to anaphylaxis with respiratory disorder, and can occur within minutes to hours or days of exposure.

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