

Antibiotic Hypersensitivity: Classification, Mechanisms, Signs, and Diagnostic Approaches: A Critical Review

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Purpose: This review focuses on antibiotic hypersensitivity, a clinically relevant issue owing to potentially severe adverse reactions. This review describes the classification, mechanisms of occurrence, and clinical manifestations of antibiotic hypersensitivity, and the diagnostic approaches. The aim was to provide recommendations for effectively treating reactions to antibiotics.

Methods: Publications, meta-analyses, and clinical cases related to antibiotic hypersensitivity were reviewed. Four types of antibiotic hypersensitivity were identified according to the Gell and Coombs classification.

Results: Type I [immunoglobulin E (IgE)-mediated] antibiotic hypersensitivity manifests as anaphylaxis, urticaria, and bronchospasms. Type II (antibodies) causes cellular damage, resulting in thrombocytopenia or anemia. Type III antibiotic reactions are caused by immune complexes that induce inflammation. Type IV (T cells) is characterized by skin rashes or systemic symptoms. Pseudoallergies mimic allergic reactions without immune mechanisms and were separately considered. Accurate differential diagnosis is crucial in identifying true immune-mediated hypersensitivity reactions, which differ from pseudoallergic conditions, to avoid misdiagnosis and minimize patient risks associated with improper treatment or not administering necessary antibiotics. A detailed analysis of the mechanisms and clinical manifestations of antibiotic hypersensitivity allows the hypersensitivity type to be determined. Classical immunological reactions and reactions that mimic allergy but are not immune-mediated should be considered in diagnosis.

Conclusions: A comprehensive approach for diagnosing antibiotic hypersensitivity is required, which should include obtaining a thorough history, using modern laboratory methods (eg, skin, specific antibody, or basophil activation tests), and differentially analyzing clinical symptoms. Mimetic conditions, such as pseudoanaphylaxis or other pseudoallergic reactions that require different therapeutic approaches, must be considered as diagnoses in these cases.

Key Words: allergic reactions, immunological processes, anaphylaxis, intolerance, rashes, histamine dependence, cell-mediated reactions

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INTRODUCTION

The development of antibiotics was a major breakthrough in treating bacterial infections and has radically altered the patient outcomes for many infectious diseases. These drugs are used to treat a wide range of pathologies from minor respiratory infections to severe life-threatening conditions, such as sepsis or bacterial meningitis. However, antibiotic effectiveness is severely limited in certain cases due to hypersensitivity reactions in some patients. Such reactions range from mild clinical manifestations such as skin rashes or itching to severe systemic complications, such as anaphylaxis, a life-threatening acute reaction that affects multiple organs and systems. Antibiotic hypersensitivity is a major clinical challenge. The timely detection of antibiotic hypersensitivity and accurate differentiation from other side effects are critical for preventing possible complications and choosing alternative therapies.

Diagnosing antibiotic allergy requires a more standardized approach, as misdiagnosis can lead to the unjustified exclusion of effective drugs from a patient's treatment arsenal.¹ A comprehensive approach must be adopted for diagnosis, including a detailed history; skin tests; and, if necessary, controlled provocative tests. This approach reduces the risk of false positives and avoids unnecessary restrictions on the therapy available for patients with suspected allergies. The use of test kits must also be standardized for the diagnosis of penicillin allergy, including the introduction of specific skin tests as a key tool for verifying hypersensitivity.¹ Such approaches substantially reduce the risks associated with antibiotic use, such as the occurrence of adverse systemic reactions, and ensure patient safety, even if a patient has a history of allergies.

Zubchenko et al² studied drug hypersensitivity reactions through analyzing the anamnestic, clinical, and laboratory data of patients, emphasizing the importance of obtaining a thorough medical history to determine the likelihood of drug hypersensitivity reactions. The authors outlined the key laboratory parameters that can be used to verify the diagnosis of antibiotic hypersensitivity, as immune-mediated reactions and nonimmune mechanisms that mimic hypersensitivity must be differentiated. The study findings indicate the feasibility of using an integrated approach, including clinical analyses and laboratory tests, to effectively

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All data generated or analyzed in this study are included in the published article. In addition, the data are available to interested researchers from the corresponding author upon request.

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identify true cases of drug allergy. In addition, the authors emphasized the need to develop individualized diagnostic algorithms using combination of anamnestic, clinical, and laboratory characteristics to ensure the maximum safety and efficacy of therapy.

Antibiotic hypersensitivity is categorized into immune-mediated and nonimmune reactions. It was former classified into 4 main types according to the Gell and Coombs system. Type I includes immediate reactions mediated by immunoglobulin E (IgE) antibodies, which activate and degranulate mast cells, leading to the release of histamine, leukotrienes, and other inflammatory mediators. These processes in severe cases can cause urticaria, bronchospasm, and anaphylactic shock. Castells et al³ described this mechanism in detail, emphasizing the importance of accurately detecting IgE-mediated reactions to ensure that anaphylaxis is quickly treated, which can be life-threatening. Type II hypersensitivity, also known as antibody-dependent cytotoxicity, is caused by the binding of antibodies to antigens on the cell surface, which causes cytotoxic reactions through activating complement or effector cells. This activation can lead to thrombocytopenia, neutropenia, or hemolytic anemia.⁴ Type III hypersensitivity involves the formation of immune complexes that are deposited in blood vessels and tissues, which activate the complement system and induce inflammatory processes, such as vasculitis. Type IV reactions are mediated by T cells, with a wide range of manifestations, such as contact dermatitis, skin rashes, erythema, and serious systemic reactions. T-cell reactions can occur several days or even weeks after taking an antibiotic, which requires a comprehensive approach to diagnosis.⁵ Each type of hypersensitivity involves unique immunological mechanisms that determine the nature of the clinical manifestations, and these mechanisms must be studied for developing effective diagnostic and therapeutic strategies.

Immediate and delayed antibiotic hypersensitivity reactions is an important aspect of clinical immunology studies because these reactions can have serious clinical consequences for patients, especially when not quickly detected or are misdiagnosed.⁶ Immediate reactions usually occur within the first hour of antibiotic administration and are associated with IgE-mediated mechanisms. These reactions occur as a result of the activation of specific IgE antibodies that bind to the receptors on mast cells and basophils, leading to the degranulation of these cells and the release of inflammatory mediators such as histamine, leukotrienes, and cytokines. These mediators are responsible for the typical symptoms of anaphylaxis, including bronchospasms, tissue swelling, low blood pressure, and shock. Antibiotics belonging to the beta-lactam class are the main triggers of such immediate reactions.⁷ These immediate reactions can be life-threatening, and rapid diagnosis and treatment are essential for patient survival.

Delayed reactions can occur several days or even weeks after antibiotic administration, hindering their prompt detection. Delayed hypersensitivity reactions involve various mechanisms, such as the formation of immune complexes and T-cell activation.⁸ Immune complexes form when antibiotics or their metabolites bind to protein molecules in the

body, producing immunogenic structures that are deposited in tissues and activate the complement system, which leads to inflammatory reactions, such as vasculitis. The type III immunological mechanism is usually associated with manifestations such as swelling, skin rashes, joint pain, or fever. Type IV reactions are mediated by T cells and include a wide range of symptoms from skin rashes to serious systemic reactions such as Lyell syndrome or toxic epidermal necrolysis (TEN). Type IV reactions, especially when severe, result from the sensitization of T cells to the antigens formed via the binding of antibiotics or their metabolites to tissue protein molecules.

Beta-lactam antibiotics are generally the main agents causing immediate and delayed hypersensitivity reactions.⁹ In particular, beta-lactams often cause anaphylactic reactions associated with IgE-mediated mechanisms and later manifestations such as erythema or eosinophilia, which reflect other types of immune reactions. The type of immunological reaction must be accurately identified given the immediate or delayed effects of beta-lactam antibiotics to select the appropriate treatment strategy. Diagnosing antibiotic hypersensitivity is a complex and multifaceted process, with symptoms ranging from mild to severe.¹⁰ The key element is obtaining a thorough medical history that identifies the risk factors for allergy development, such as previous drug reactions, other allergic diseases, or genetic predispositions. Skin and laboratory tests should be performed to confirm diagnosis. Provocative tests may be used in some cases when the skin test results are insufficient for accurate diagnosis. However, these methods involve certain risks, such as severe anaphylactic reaction, and should be performed under close supervision. Brockow et al¹¹ described new algorithms that can be used to diagnose penicillin allergies, which more quickly detect hypersensitivity and are more accurate than traditional methods, such as skin tests and analyses, and specific molecular tests used to identify IgE-dependent and other immunological reactions.

Wang et al¹² retrospectively reviewed amoxicillin hypersensitivity cases over a 7-year period, with the results helping to improve diagnostic strategies, reduce the likelihood of misdiagnoses, and avoid unnecessary prescriptions of antibiotics that can cause side effects. Overall, their findings highlighted the value of using a comprehensive approach for diagnosing and treating antibiotic hypersensitivity to ensure patient safety and minimize the risk of serious complications. Elst et al¹³ examined the effectiveness of clinical decision support systems (CDSSs) in hospital emergency departments, where errors in diagnosis and treatment can lead to serious consequences when patients need immediate medical attention. Pichler et al¹⁴ analyzed how integrating CDSSs into emergency departments can help doctors make informed decisions and increase diagnostic accuracy and treatment efficiency. The system markedly reduced the time required for obtaining medical histories and diagnostic tests, especially in complex or rare cases, such as allergic reactions to antibiotics. The authors used data from previous medical records to develop a CDSS, which reduced the number of errors and incorrectly prescribed treatments compared with before its implementation. Effectively using the CDSS considerably

increased the quality of medical care in emergency situations, which is crucial in managing patients experiencing potentially dangerous drug reactions.

This literature review allowed the identification of the main challenges in the field of antibiotic hypersensitivity, including the lack of a single standardized approach for diagnosis, difficulties in identifying nonimmunological reactions, and the need for more personalized treatment approaches. The discovery of antibiotics revolutionized the treatment of bacterial infections, offering effective solutions for managing a wide range of conditions from common respiratory infections to life-threatening diseases such as sepsis and bacterial meningitis.¹⁵ However, the use of antibiotics is not without challenges. The occurrence of antibiotic hypersensitivity reactions in some patients is one of the main complications, with symptoms ranging from mild, such as skin rashes, to severe and life-threatening, such as anaphylaxis. The increasing prevalence of such reactions poses a substantial challenge for health care providers because timely and accurate diagnosis is crucial for effectively managing patients.

A major issue is the misdiagnosis of antibiotic allergies, such as penicillin allergies, which results in the unnecessary exclusion of certain antibiotics from a treatment regimen for a patient. This often leads to the use of less-effective or broad-spectrum antibiotics, increasing the risk of antibiotic resistance and complicating treatment. Allergy delabeling is the process of reassessing and possibly removing a previously diagnosed antibiotic allergy. Allergy delabeling is receiving attention as a critical strategy for optimizing treatment options. However, consensus on standardized diagnostic approaches is lacking, which prevents true allergic reactions and nonimmune system-mediated side effects from being differentiated.

These issues underscore the need to develop a comprehensive multidisciplinary approach for diagnosing antibiotic hypersensitivity. Accurate diagnosis requires not only a detailed patient history but also the use of specific diagnostic tools, such as skin, laboratory, and provocative tests. Moreover, diagnostic algorithms and technologies are key to enhancing diagnosis accuracy, particularly in cases of penicillin allergy, where the risk of misdiagnosis is high. Therefore, the aim in this study was to explore the classification, mechanisms, and clinical manifestations of antibiotic hypersensitivity, with focus on the challenges leading to allergy misdiagnosis and the potential for developing more personalized and effective therapeutic strategies.

MATERIALS AND METHODS

Data were analyzed from 2019 to 2025 from scientific sources covering antibiotic hypersensitivity, including its classification, mechanisms, clinical manifestations, and diagnostic approaches. The most relevant peer-reviewed publications, clinical protocols, and other academic sources included in this study were published from 2019 until 2025. This cutoff point ensured that the findings were based on the most current, accessible, and reviewed data available at the time.

Information was collected from peer-reviewed articles, clinical protocols, and reports of international organizations such as the World Health Organization, PubMed, Scopus, and Web of Science databases. The key queries used for the search were “antibiotic hypersensitivity,” “allergic reactions to antibiotics,” “Jell and Coombs classification of hypersensitivity,” “immune-mediated drug reactions,” and “pseudoallergy and antibiotic intolerance.” These queries were connected using Boolean operators such as AND and OR to narrow or broaden the search. For example, the search term “antibiotic hypersensitivity” AND “allergic reactions to antibiotics” was used to focus on publications simultaneously discussing both concepts, whereas “pseudoallergy and antibiotic intolerance” OR “immune-mediated drug reactions” was employed to capture studies that addressed either of these concepts. The literature search specifically focused on identifying studies on the molecular and genetic mechanisms underlying antibiotic hypersensitivity and evaluating modern diagnostic approaches.

The inclusion criteria were articles published between 2019 and 2025 containing detailed descriptions of the mechanisms underlying immunological and nonimmunological antibiotic reactions, clinical cases of antibiotic hypersensitivity, and modern diagnostic and therapeutic tools. The full criteria are shown in Figure 1. This review included studies with clear descriptions of methodology, peer-reviewed validation, and relevance to the selected topic. Publications with an insufficient methodological basis, duplicate data from previous studies, or studies based on outdated methods were excluded. A total of 412 sources met the search queries in the first stage. The inclusion and exclusion criteria were applied, with 43 studies remaining for inclusion in the analysis (Fig. 1).

The relevance of the study for this review was determined based on whether the mechanisms, clinical manifestations, or diagnostic approaches related to antibiotic hypersensitivity were directly referenced. The mechanisms through which antibiotic hypersensitivity occurs were investigated through analyzing the literature on immunological classifications adapted to the latest scientific data. The main focus was type I–IV reactions according to the Gell and Coombs classification, and the mechanisms through which pseudoallergic reactions occur, which mimic allergic conditions but are not immune-mediated. The main pathophysiological processes of each type of reaction were discussed in detail, including the involvement of IgE in type I reactions, IgG and IgM antibodies in type II reactions, formation of immune complexes in type III reactions, and the role of T cells in type IV reactions. Particular attention was paid to the relationship between immunological reactions and clinical manifestations. Publications highlighting the molecular markers of inflammation and immune activation, which help explain the complex mechanisms involved in antibiotic hypersensitivity, were also analyzed.

The clinical manifestations of antibiotic hypersensitivity were examined through analyzing reviews and retrospective studies describing the systematization of skin symptoms and systemic reactions. Particular attention was paid to stratifying patients according to condition severity and

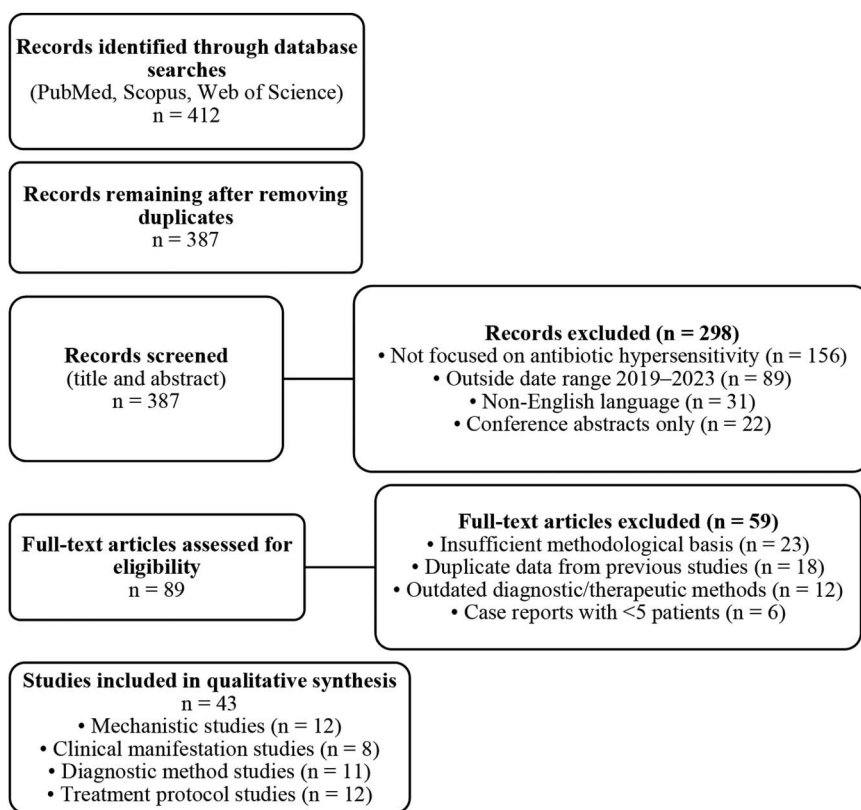


FIGURE 1. Flowchart of selecting antibiotic hypersensitivity studies for literature review (2019–2023).

reaction mechanisms, which allowed a more accurate capture of the clinical manifestations of antibiotic hypersensitivity.

RESULTS AND DISCUSSION

Development and Clinical Aspects of Antibiotic Hypersensitivity

The main theoretical aspects of antibiotic hypersensitivity were summarized in detail, including its classification, mechanisms of development, clinical manifestations, and diagnostic approaches. Antibiotic hypersensitivity is divided into 2 broad groups, immediate and delayed reactions, according to the time of symptom onset after antibiotic administration. Immediate hypersensitivity usually develops within the first few minutes or hours after drug administration, resulting from IgE-mediated reactions. This type of antibiotic hypersensitivity includes serious clinical conditions, such as anaphylaxis, urticaria, bronchospasm, and angioedema. Anaphylaxis is the most serious manifestation of immediate hypersensitivity and can lead to death without proper medical intervention. The release of histamine and other inflammatory mediators from mast cells and basophils leads to itching, rash, shortness of breath, and swelling, which are characteristic of urticaria, bronchospasm, and angioedema. These reactions are the result of immune mechanisms, in particular, through IgE-mediated reactions that activate mast cells and basophils, which release inflammatory mediators such as histamine, cytokines, and leukotrienes, leading to the development of anaphylactic symptoms.¹⁴

Delayed hypersensitivity develops several days or weeks after the exposure to an antibiotic and involves more severe clinical forms, such as Stevens–Johnson syndrome (SJS), TEN, and drug reactions with eosinophilia and systemic manifestation (DRESS) syndrome. SJS and TEN involve severe skin and mucous membrane damage, leading to ulcers and erosion of the epidermis and epithelial linings, including those of the eyes, oral cavity, and respiratory and gastrointestinal tracts. The pathological process can extend to internal organs, markedly increasing the mortality rate. Amoxicillin can cause a variety of reactions that manifest with different timelines, from immediate to delayed symptoms, which greatly complicates diagnosis and requires the use of special tests to determine sensitivity to antibiotics.¹⁵ DRESS syndrome is accompanied by serious damage to internal organs such as the liver, kidneys, and heart and requires long-term monitoring and immunosuppressive therapy.¹⁶

Automatic medication error prevention systems, even if reviewed by physicians, considerably reduce medication errors, underscoring the value of accurate diagnostic approaches when prescribing antibiotics for patients with hypersensitivity.¹⁷ The mechanisms of antibiotic hypersensitivity are classified into immunological and nonimmunological mechanisms. Immunological reactions are classified into 4 main types according to the Gell and Coombs system. Type I includes IgE-mediated reactions, which are most often observed in immediate allergic reactions. These reactions involve the activation of mast cells and basophils, which release inflammatory mediators, such as histamine, cytokines, and leukotrienes. Anaphylaxis is a common indication of type

I reactions, which results in a rapid decline in blood pressure, respiratory distress, and laryngeal edema. Other type I clinical manifestations include urticaria and bronchospasm; Baines et al also discussed the mechanisms through which skin irritation and contact dermatitis occur. The incorrect diagnosis of penicillin allergy in patients' medical records can lead to using expensive alternative antibiotics, which increases treatment costs and delays patient recovery.¹⁸ Addressing incorrect diagnoses is critical for improving clinical and economic outcomes.

Type II hypersensitivity reactions are antibody-mediated, where IgG or IgM antibodies bind to antigens on cells surface, causing the complement system to activate and damage the cells.¹⁹ This process leads to pathologies such as hemolytic anemia, in which antibodies attack red blood cells, or thrombocytopenia, which decreases the platelet count and increases the risk of bleeding. Contact dermatitis is an example of an antibody-mediated reaction in which an antigen, such as a drug, interacts with skin cells to cause inflammation and rash.²⁰ Type III mechanisms involve immunocomplex reactions in which the immune complexes formed in the body are deposited in tissues and cause inflammatory reactions, leading to vasculitis or glomerulonephritis. Immune complexes can accumulate in various tissues, such as the kidneys and joints, causing severe inflammatory processes.²¹ The type IV reaction is T-cell hypersensitivity, which often manifests in delayed reactions such as SJS or TEN because of T-cell activation. Various methods are used to diagnose antibiotic hypersensitivity, including clinical examinations, medical history reviews, laboratory tests, and skin tests. Obtaining a thorough medical history is essential for assessing the relationship between symptoms and antibiotic use. Skin tests (intradermal and prick tests) are performed for detecting IgE-mediated reactions. The laboratory methods for diagnosing antibiotic hypersensitivity include determining the levels of specific IgE antibodies, using ELISA and ImmunoCAP, and basophil activation testing, which is used for diagnosing immediate allergic reactions. Basophil activation testing is a method for assessing IgE-mediated reactions to antibiotics.²² The lymphocyte transformation test is the main method used for detecting T-cell activation for diagnosing delayed-onset antibiotic hypersensitivity.

Genetic and Nonimmunological Aspects of Antibiotic Hypersensitivity

A number of genetic studies have been conducted to identify the associations of antibiotic hypersensitivity with certain human leukocyte antigen (HLA) alleles, such as HLA-B57:01 for abacavir and HLA-B15:02 for carbamazepine, which help with predicting the risk of developing allergic reactions to certain antibiotics.²³ These associations aid in diagnostics, allowing allergy development to be predicted, especially in cases where standard methods do not provide definitive results. Genetic testing is an additional tool for determining predisposition to drug hypersensitivity.²⁴ Provocative tests are performed in a hospital setting to confirm the diagnosis in complicated cases where other methods do not provide definitive results.²⁵ This deposition induces inflammatory processes, as the accumulation of immune

complexes activates white blood cells and the complement system. This process can lead to serious clinical manifestations such as vasculitis and glomerulonephritis.²⁶ Immune complexes can also induce systemic inflammatory processes that affect various organs and tissues, increasing the risk of serious complications such as acute renal failure.

The nonimmunological mechanisms of antibiotic hypersensitivity can be divided into 2 main processes: the direct toxic effects of antibiotics on tissues and the activation of immune cells without the participation of specific antibodies. These mechanisms are often observed in situations where antibiotics accumulate in the body, having toxic effects, or when antibiotics nonspecifically activate immune cells owing to their chemical properties. These nonimmunological reactions differ from immunological reactions as antibodies or immune complexes do not form. An antibiotic can directly affect the cells of organs, such as the liver or kidneys, in toxic reactions, leading to organ damage and dysfunction. Amoxicillin can cause crystal nephropathy when residual amounts accumulate in the body, having toxic effects on the kidneys.²⁷

Immune cells are usually activated without antibodies via the activation of macrophages, neutrophils, or other immune cells that cause inflammation even if the antibiotic is not an allergen. The cross-reactivity among antibiotics of the same class is particularly important in nonimmunological reactions. For example, the chemical structures of beta-lactam antibiotics, such as penicillin, cephalosporins, and carbapenems, are similar. Using multiple antibiotics in this class increases the likelihood of developing allergic reactions, even if the patient was previously allergic to a particular drug. This cross-reactivity in antibiotic hypersensitivity must be understood to help health care professionals choose alternative drugs in cases of allergic reactions. Caruso et al²⁸ described the problem created by the cross-reactivity between cephalosporins and other beta-lactam antibiotics in detail, with the results guiding the selection of safe alternatives. In addition, antimicrobial stewardship programs in hospitals can substantially reduce the likelihood of antibiotic-related adverse events by controlling antibiotic use.²⁸ Table 1 summarizes the types of antibiotic resistance, their mechanisms of development, and the most commonly used diagnostic methods.

The clinical manifestations of antibiotic hypersensitivity widely vary depending on the type of reaction. Dermatological reactions are the most common clinical manifestations of antibiotic hypersensitivity, accounting for a large proportion (38.8%) of all antibiotic allergy cases.²⁹ These reactions include maculopapular rashes (red patches with elevation), urticaria, exanthema (a rash covering a large part of the skin), and itching. Although these symptoms are not usually life-threatening but cause considerable discomfort and require drug adjustment. Gastrointestinal symptoms such as diarrhea, nausea, and vomiting are also common, occurring in 28.4% of patients who are allergic to antibiotics.³⁰ These symptoms indicate a toxic effect of the antibiotics on the gastrointestinal mucosa or the immune response. These symptoms do not usually pose a serious threat; however, the treatment may need to be adjusted or the antibiotic may need to be temporarily discontinued in cases of severe disorders. More

TABLE 1. Classification of Types of Antibiotic Hypersensitivity, Mechanisms of Their Development, and Diagnostic Methods

Type of Hypersensitivity	Mechanism of Reaction Development	Clinical Manifestations	Diagnostic Methods
Type I (IgE-mediated)	Activation of IgE antibodies, leading to degranulation of basophils and mast cells	Anaphylaxis, urticaria, oedema, pruritus	Skin tests (intradermal, prick tests), IgE level determination
Type II (cytotoxic)	Interaction of antibiotic antigens with cell membranes, complement activation	Hemolytic anemia, thrombocytopenia, nephritis	Antibody and biochemical tests (eg, creatinine level)
Type III (immunocomplex)	Formation of immune complexes (antigen–antibody), their deposition in tissues	Vasculitis, glomerulonephritis, joint pain, rash	Laboratory tests (complement level, basophil activation test)
Type IV (T-cell–mediated)	Activation of T lymphocytes, leading to inflammation and tissue damage	Contact dermatitis, maculopapular rashes	Provocation and skin tests, tissue biopsy
Nonimmunological mechanisms	Toxic effect of antibiotic or activation of immune cells without participation of antibodies	Toxic hepatitis, renal failure, gastrointestinal symptoms	Laboratory tests (elevated enzyme levels, ultrasound)

serious reactions include anaphylaxis and hypovolemic shock, which can be life-threatening. Anaphylaxis can quickly develop after antibiotic administration and is accompanied by severe breathing difficulties, laryngeal edema, low blood pressure, tachycardia, and loss of consciousness. The hypovolemic shock resulting from anaphylaxis requires urgent medical intervention, such as the administration of epinephrine, antihistamines, and oxygen inhalation. Although these reactions are rare, they can be fatal without timely medical intervention.

Methods for Diagnosing Antibiotic Hypersensitivity: Approaches and Limitations

Various methods have been used to diagnose antibiotic hypersensitivity, each with specific characteristics and limitations. The primary step is thoroughly analyzing the history of the patient, which allows an identification of the relationship between antibiotic use and the development of allergic symptoms. The medical history taking should include questions about previous reactions to antibiotics and factors that contribute to the development of hypersensitivity, such as genetic predisposition or comorbidities. This medical history allows doctors to detect possible allergic reaction to a particular antibiotic before conducting other tests. One of the most common diagnostic methods is skin testing, which is used to detect immediate allergic reactions, such as IgE-mediated reactions. Skin tests include intradermal, prick, and skin tests using small amounts of antibiotics applied to the skin. This test allows physicians to assess whether an antibiotic causes a local allergic reaction, which indicates hypersensitivity.

Skin tests are effective in detecting allergies to certain drugs, such as penicillin; however, their sensitivity may not be sufficient. Test results need to be carefully interpreted as false-positive or false-negative results are possible, which can lead to an erroneous determination of the presence or absence of an allergy. de Vicente et al³¹ reported that patients with a penicillin allergy tolerate cephalosporins and carbapenems, although additional tests (eg, drug provocation tests) are needed to confirm the safety of these drugs. The researchers stated that the chemical structure of antigenic determinants such as cephalosporins should be understood to determine the mechanisms through which IgE-mediated allergy to certain antibiotics occur. Cephalosporin is an antibiotic, specifically a second-generation cephalosporin, and is not an antigenic determinant. However, the chemical structure of cefaclor

and other cephalosporins can be used to predict cross-reactivity with other beta-lactam antibiotics such as penicillin. Cephalosporins contain a beta-lactam ring, which is a structural feature shared with penicillin. This structural similarity can lead to cross-reactivity in individuals allergic to penicillin. Shenoy et al³² highlighted the importance of accurately diagnosing penicillin allergy and the role of a comprehensive approach to managing penicillin allergy to improve patient outcomes.

Specific IgE tests are used to detect antibodies produced by the body in response to antibiotics, confirming the presence of an immune response.³³ Basophil activation tests measure changes in basophil function after exposure to antibiotics, which indicate allergic reactions.³⁴ However, these laboratory methods have limitations such as low sensitivity and specificity, which reduce their effectiveness in everyday clinical practice. Therefore, these tests are used in combination with other diagnostic methods to increase diagnostic accuracy. Broad-spectrum antibiotics increase the risk of various adverse reactions, including hypersensitivity, owing to their wide range of activities against various bacteria, highlighting the need for the careful monitoring during the use of these antibiotics in hospital settings.³⁵ This broader activity may disrupt the normal microbiota, influencing immune responses and increasing the risk of hypersensitivity reactions. Asim et al³⁶ highlighted the necessity of considering the toxic effects of antibiotics, such as amoxicillin–clavulanate. Acute tubulointerstitial nephritis should also be considered during diagnosis.

CDSSs show promise as a tool for increasing the diagnosis accuracy and prevention of allergic reactions to antibiotics. CDSSs provide physicians with access to up-to-date and detailed information on the possible risks of antibiotic use, such as allergies, enabling informed and individualized treatment decisions.³⁷ CDSSs analyze large amounts of clinical data, including the medical history and previously identified allergies of the patient, cross-reactivity between different antibiotics, and other factors that reduce the risk of allergic reactions. CDSSs play a valuable role in detecting and preventing cross-reactivity between antibiotics, which is relevant when using drugs with a similar chemical structure, such as beta-lactam antibiotics. Doctors can quickly obtain information about possible allergic reactions to new antibiotics using CDSSs, which substantially increases the safety of treatment and reduces the likelihood of serious

complications.³⁸ Clinical pharmacists play a crucial role in optimizing the use of CDSSs in this context and ensuring that the information provided is accurately interpreted and applied. Clinical pharmacists closely collaborate with physicians to interpret the data from the CDSS, ensuring that the recommendations align with the overall treatment plan and medical history of the patient.³⁹ Clinical pharmacists monitor patients for signs of allergic reactions and accordingly manage medication, adjusting treatments as necessary based on real-time patient data. In addition, clinical pharmacists educate other health care providers on effectively using the CDSS, such as understanding the nuances of the cross-reactivity between antibiotics, particularly among those with similar chemical structures such as beta-lactams. Clinical pharmacists leverage their expertise in pharmacotherapy to help prevent medication administration and prescription errors and adverse drug reactions, enhancing patient safety and treatment outcomes. Clinical pharmacists can counsel patients on the need to adhere to prescribed therapies and inform them about the potential side effects and signs of allergic reactions. The role of clinical pharmacists in the context of a CDSS shows that a multidisciplinary approach to patient care is required, in which the expertise of pharmacists complements the technological capabilities of decision support systems to improve patient outcomes.

A CDSS can be used in clinical practice to reduce the risk of allergic reactions in patients and optimize treatment strategies.⁴⁰ CDSSs can be used to ensure a timely response to changes in patient condition, allowing doctors to promptly adjust therapy and choose the most effective and safest drugs. In particular, these systems can warn doctors of the need to change antibiotics if a patient was previously allergic to drugs or is at risk of severe allergic reactions such as anaphylaxis or SJS. Thus, using a CDSS in combination with traditional diagnosis and treatment methods can considerably increase the quality of medical care, reduce the number of allergic reactions, increase diagnostic accuracy, and provide more effective and safe treatment for patients. Integrating such technologies into clinical practice is a step toward creating safer and more personalized treatment approaches that meet modern health care requirements.

The discourse on antibiotic hypersensitivity as a clinical problem requires the careful analysis of the wide range of possible reactions, which range from mild rashes to serious, life-threatening anaphylactic reactions or severe skin syndromes, such as SJS and TEN. These reactions support the need to rapidly detect such reactions to ensure patient safety, as an allergy to antibiotics can complicate the treatment of infectious diseases and have serious clinical consequences. The consideration of antibiotic hypersensitivity is complicated by allergic symptoms having a wide range of manifestations, which can appear immediately to several days after drug administration. A delay in diagnosis can lead to patients receiving the wrong treatment, which can complicate the course of recovery. Severe allergic reactions such as anaphylaxis are dangerous and can lead to shock and death if not quickly detected and treated.

Older adult patients are among the most vulnerable because they often have chronic diseases and simultaneously

use several medications, which increases the likelihood of allergic reactions.⁴¹ In addition, the immune system of older adults is often unable to respond effectively to new allergens, increasing the risk of severe side effects of antibiotics. Therefore, special attention should be paid to the early detection of allergies in these patients and the prevention of possible complications. Antibiotic hypersensitivity should be properly diagnosed and treated to ensure patient safety.⁴² The early detection of allergic reactions helps with promptly changing treatment and reduces the risk of severe complications. Therefore, modern methods, such as skin, specific IgE antibody, and other laboratory tests, should be used for quickly identifying the type of allergy and selecting the optimal treatment approach. Particular attention should be paid to the cross-sensitivity between antibiotics because patients who are allergic to 1 antibiotic may react to other drugs in the same group. This cross-sensitivity increases the complexity treatment and requires a more cautious approach to antibiotic selection.

The rapid diagnosis and prevention of allergic reactions to antibiotics are essential, particularly in inpatient settings, where the risk of developing such reactions is much higher, especially among older adult patients, in whom even mild allergic reactions can lead to serious life-threatening complications. The use of a CDSS, which integrates global standards for identifying drugs and their potentially dangerous effects, could considerably reduce the risk of repeated allergic reactions to antibiotics. Using CDSSs allows for quickly detecting and preventing severe allergic reactions such as anaphylaxis, sudden and potentially fatal reactions, and syndromes related to skin reactions such as SJS. CDSSs are especially useful in inpatient settings, where patients are often simultaneously administered many drugs, which increases the likelihood of allergic reactions.

An allergic reaction typically occurs when the immune system inappropriately responds to a harmless substance such as an antibiotic and recognizes this substance as a threat. This process leads to reactions ranging from mild skin rashes to severe conditions such as anaphylaxis or SJS.¹⁶ Using a CDSS helps manage this risk by providing timely information about potential drug interactions and allergies, thus preventing severe allergic reactions. Conversely, the lack of an immune response, particularly in older or immunocompromised patients, can lead to increased susceptibility to infections and severe drug side effects because the immune system may not effectively neutralize pathogens or properly metabolize drugs, leading to toxicity or adverse drug reactions.

Such technologies should be integrated into clinical practice for ensuring the safety of antibiotic treatment by warning doctors about potentially dangerous drugs before they are prescribed to patients. This approach is particularly relevant in cases of multipharmacological treatments, where the risk of cross-allergic reactions is considerably higher than that with monotherapies. In addition, using a CDSS can reduce the workload of medical staff through automating the risk identification process and supporting clinical decision making by considering evidence-based standards.

Wang et al¹² reported that anaphylaxis is one of the most common reactions to antibiotics among patients,

indicating the high risk of anaphylaxis in clinical practice, which must be rapidly detected and appropriately treated to reduce fatalities. The risk of anaphylaxis emphasizes that patients should be continuously monitored, especially those who are prone to allergies or who regularly take antibiotics.

Severe skin reactions are more complex allergic reactions, involving toxic skin reactions such as exfoliative dermatitis and SJS. Kim et al²⁶ reported that antibiotics, in particular beta-lactams, are the main triggers of severe skin reactions, which require high-sensitivity diagnosis to ensure timely treatment. These reactions usually develop more slowly than anaphylaxis, but their treatment is more complex, requiring specialized approaches. Severe skin reactions must be detected early given their potential severity, and appropriate therapeutic strategies must be developed to minimize complications. The clinical classification of antibiotic hypersensitivity helps with understanding the mechanisms through which each allergic reaction occurs in more detail. This information can be used to guide the selection of the most suitable approach to treatment. For example, type I allergy, which is commonly associated with anaphylaxis, is different from type IV allergy, which is mediated by T cells and leads to chronic skin reactions, such as severe skin reactions. The different types of reactions require appropriate diagnostic approaches, as their manifestations may be nonspecific and similar to those of other diseases.

Diagnosing antibiotic hypersensitivity remains challenging because of the diversity of clinical manifestations. The main diagnostic methods include a thorough clinical interview and history-taking to identify symptoms and risk factors. Skin and specific IgE tests are widely used to confirm type I allergies; however, these tests are not always sufficiently accurate.⁴³ Molecular tests, particularly genetic testing, are being used to identify predispositions to certain types of allergic reactions, allowing for more individualized treatment approaches. This testing is especially indicated for patients at high risk of developing allergies, such as older adults or those who regularly take antibiotics. Elst et al¹³ found that using a decision support system such as a CDSS integrated with a health care facility database facilitated diagnosis by providing quick access to information about previous allergic reactions.

Technologies such as cloud-based clinical decision support systems should be used to provide information on cross-allergies and other relationships between different antibiotics. Doctors can receive information from these systems on potentially dangerous drug combinations, which increases patient safety. In particular, a CDSS can consider individual patient characteristics, patient history of previous allergic reactions, and cross-sensitivity between antibiotic groups, which minimizes the risk of serious allergic reactions to prescribed antibiotics such as anaphylaxis or antibiotic-related skin reactions.

CDSSs should be optimized to facilitate interactions between health care professionals and the system. This process includes minimizing the excessive provision of alerts by adjusting the algorithms such that the alerts are relevant and necessary for a particular patient. In addition, integrating a CDSS into daily clinical practice requires the training of

doctors and medical staff to ensure confidence and competence in using the system and that the information provided is correctly interpreted.

CONCLUSIONS

Hypersensitivity to antibiotics is a serious medical issue that requires in-depth theoretical research to thoroughly understand the mechanisms through which these allergic reactions occur to guide the selection of effective diagnostic and treatment methods. A theoretical analysis of the literature showed that antibiotic hypersensitivity manifests in various forms from mild rashes to serious conditions such as anaphylaxis or SJS. The immunological and nonimmunological mechanisms of the development of these reactions must be considered in practice as the mechanism affects the treatment decisions. The immunological reactions include IgE-mediated reactions (type I), which lead to anaphylaxis, and cell-mediated reactions (type IV), which manifest as chronic skin syndromes. Nonimmunological mechanisms result in antibiotics having direct toxic effects on tissues and the activation of immune cells without the involvement of specific antibodies. These processes can produce toxic effects such as liver or kidney damage or induce inflammatory reactions through the activation of macrophages and neutrophils.

A theoretical analysis of selected studies showed that cross-susceptibility to antibiotics, particularly beta-lactam drugs, is a problem in clinical practice that can lead to allergy development, even in the absence of a previous reaction to a particular antibiotic. The most commonly used methods for diagnosis antibiotic hypersensitivity are thorough history-taking, skin tests, and tests for specific IgE antibodies. Molecular and genetic testing can complement diagnosis in cases in whom the results of initial testing are not definitive. In particular, molecular and genetic testing can help in identifying predispositions to certain allergic reactions and increase diagnostic accuracy. Attention was paid to the latest technologies such as cloud-based clinical decision support systems. These systems can substantially increase diagnostic accuracy and prevent allergic reactions by rapidly analyzing large amounts of clinical information. However, lack of trust in technologies can reduce the effectiveness of their use. Future research prospects in this field include implementing personalized approaches for diagnosing reactions to antibiotics using molecular tests and selecting the appropriate treatments using cloud-based decision support systems.

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