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Drug Allergy and Skin: Literature Review

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ABSTRACT

This literature review explores the prevalence and impact of allergic skin reactions caused by drugs, particularly beta-lactam antibiotics and non-steroidal anti-inflammatory medications. Diagnosis of cutaneous adverse drug reactions can be challenging. The text emphasizes the importance of early recognition of these reactions to prevent severe outcomes. The review discusses the classification of drug hypersensitivity reactions, diagnostic approaches by giving diagnostic algorithms, and management strategies for allergic skin reactions. Additionally, the review raises awareness of severe cutaneous adverse reactions such as DRESS, SJS, and TEN, which can be life-threatening. The review seeks to enhance knowledge of drug-induced skin allergies and improve patient outcomes by synthesising existing research.

Keywords: Drug hypersensitivity, cutaneous adverse drug reactions, beta-lactams/adverse effects, non-steroidal-anti-inflammatory drugs/adverse effects, diagnosis

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ABBREVIATIONS

ADRs Adverse Drug Reactions

ASA Acetylsalicylic Acid (Aspirin)

AGEP Acute Generalized Exanthematous Pustulosis

CADRs Cutaneous Adverse Drug Reactions

COX cyclooxygenase

COX-1 cyclooxygenase-1

COX-2 cyclooxygenase-2

DRDs Drug-Related Deaths

DRESS Drug Reactions with Eosinophilia and Systemic Symptoms

DHRs Drug Hypersensitivity Reactions

EAACI The European Academy of Allergy and Clinical Immunology

EM Erythema Multiforme

EN Epidermal Necrolysis

FDE Fixed Drug Eruption

NECD NSAID-Exacerbated Cutaneous Disease

NERD NSAID-Exacerbated Respiratory Disease

NIUA NSAID-Induced Urticaria/Angioedema

NSAIDs Non-Steroidal Anti-Inflammatory Drugs

MPE Maculopapular Exanthema

SCARs Severe Cutaneous Reactions

SDRIFE Symmetrical Drug-Intertriginous and Flexural Exanthema

SJS Stevens-Johnson Syndrome

SNIUAA Single-NSAID-Induced Urticaria/Angioedema and Anaphylaxis

TEN Toxic Epidermal Necrolysis

1. INTRODUCTION

Skin reactions are one of the most frequently seen forms of drug allergies worldwide. These reactions are usually induced by beta-lactam antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). Identifying allergic skin reactions and their triggers can be difficult, and they can be confused with other conditions. Primary care physicians require more guidance on recognizing and diagnosing these reactions. It is vital to recognise hypersensitivity reactions early to prevent severe reactions. The exact prevalence of these reactions can vary depending on the specific drug and population. Still, estimates suggest that up to 10% of the population may experience some form of drug allergy. This literature review provides an overview and practical recommendations on all aspects of NSAIDs and beta-lactam hypersensitivity reactions from the pathophysiology to the symptoms. The goal is to develop algorithms that can accurately detect allergic skin reactions by gathering information from various sources [1,2].

Drug hypersensitivity reactions (DHRs) are classified into immediate or delayed. Immediate reactions occur within one or up to six hours of admission, and delayed reactions occur within several hours or multiple days. One way to distinguish between allergic and non-allergic intolerance reactions is by determining if the immune system is involved and if the clinical symptoms significantly impact the patient's quality of life. Factors such as increased drug use, an aging population, multimorbidity, and polypharmacy contribute to the prevalence of these reactions. The aim should be to identify patients at risk and prevent unjustified restrictions in drug therapy [2,3].

After adverse drug reactions (ADRs), allergic tests should be done within four weeks to six months. A significant number of beta-lactam allergies may be false. Less than 10 % of patients who report a beta-lactam allergy may be allergic when tested. Most commonly, the skin reactions are non-allergic, and it is safe to use the drug that causes the reaction. Drug allergies are often either underdiagnosed or overdiagnosed globally. False diagnoses are major public health problems and can lead to the use of more expensive, less effective, and more harmful alternative antibiotics [1,2,3].

The purpose of this literature review is to outline a diagnostic algorithm for drug-induced allergic skin reactions, specifically focusing on NSAIDs and beta-lactams. The review will address the mechanisms of allergic reactions, clinical symptoms, diagnostic methods, and differential diagnosis. Furthermore, it aims to raise awareness of severe cutaneous adverse reactions (SCARSs), such as drug reaction with eosinophilia (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be life-threatening, with mortality rates ranging from 10% to 50%. By synthesizing existing research, this review seeks to enhance understanding. A comprehensive medical history, detailed patient records, and photographs of skin reactions are essential in allergological

investigations. It is important to closely monitor warning signs of severe skin symptoms during the acute phase, as these are linked to an unfavourable prognosis. Further investigations are required in cases of severe reactions, denial of essential medication to the patient, or when multiple drugs are contraindicated, as this could complicate the patient's ongoing treatment [4].

The goal of this thesis is to provide a comprehensive literature review on the relationship between drug allergies and their effects on the skin. Specifically, I intend to investigate the mechanism of allergic skin reactions associated with beta-lactams and NSAIDs, clinical manifestations observed on the skin, diagnostic approaches, and management strategies. I believe that this topic is relevant not only to dermatology and allergology but also impacts the clinical skills of general practitioners, who are often the first physicians to encounter allergic skin symptoms caused by medications and to make decisions regarding the treatment and referral of patients for further tests. By synthesizing existing research, I hope to contribute to a better understanding of drug-induced skin allergies and ultimately improve patient outcomes.

2. LITERATURE REVIEW AND METHODS

This thesis takes a narrative approach to recent publications on adverse cutaneous drug reactions and how to diagnose them. The aim is to provide, through existing literature, a detailed algorithm for diagnosing cutaneous adverse drug reactions, focusing on beta-lactams and NSAIDs. It summarizes and evaluates existing literature on this topic, offering new perspectives and highlighting the need for further research. This approach allows for a comprehensive topic examination with broad research questions and extensive information collection. However, a weakness of narrative reviews is the lack of systematic data collection rules, which may lead to biases in the results. The quality of the study is also influenced by the research method and the size of the cohort.

I employed various methods to gather relevant information while compiling my literature review for my final thesis on the algorithm for diagnosing cutaneous adverse drug reactions induced by beta-lactam antibiotics and NSAIDs. My thesis aimed to guide the diagnosis of ADRs, especially in primary health care settings for general physicians who are often the first point of contact for patients experiencing such reactions.

I focused on gathering scientific articles about diagnostic methods, case reports, definitions of allergic reactions, causes, and management of cutaneous adverse drug reactions (CADRs), hypersensitivity reactions, and different reactions from mild to severe. I specifically looked for literature published within the past five years from around the world to ensure that the information was current and up to date. By employing these methods and searching for relevant literature from reputable sources, I was able to gather a comprehensive collection of information on the diagnosis of cutaneous adverse drug

reactions induced by beta-lactam antibiotics and NSAIDs. This information will be valuable in guiding general physicians in primary health care settings as they navigate the diagnosis and management of ADRs in their patients.

2.1. Inclusion and Exclusion Criteria

This narrative literature review included peer-reviewed articles, clinical guidelines, and case reports focused on CADRs, particularly those associated with beta-lactam antibiotics and NSAIDs. Studies published in English between 2019 and 2025 were prioritized to ensure the recency of clinical and diagnostic recommendations. Articles were included if they discussed:

- Mechanisms of drug hypersensitivity
- Classification and manifestations of allergic reactions
- Diagnostic algorithms for cutaneous drug reactions
- Management strategies relevant to primary care,

Excluded were:

- Animal studies
- Papers focusing exclusively on non-cutaneous manifestations
- Studies not offering original or applicable clinical insight (e.g., editorials, opinion pieces)

2.2. Study Selection and Data Synthesis

The literature search used Medline, ScienceDirect, SpringerLink, Google Scholar, and Duodecim (Finnish Evidence-Based Medicine) databases. Keywords included: *"cutaneous drug reaction," "drug allergy diagnosis," "beta-lactam hypersensitivity," "NSAID allergy,"* and *"drug reaction algorithm."* Boolean operators and filters (e.g., date range, article type) were applied to narrow the search scope.

A two-stage screening process was used:

1. Title and abstract screening to eliminate irrelevant results.
2. A full-text review will be conducted to assess content alignment with the thesis objectives.

Data from eligible studies were manually extracted and synthesized thematically based on reaction type, clinical approach, and relevance to diagnostic algorithms. Given the narrative review format, results were not pooled statistically but discussed descriptively to capture variability across studies.

2.3. Quality Assessment and Limitations

No formal risk of bias tools or scoring systems were applied, as this was not a systematic review. However, efforts were made to prioritize high-quality clinical reviews, guidelines from recognized bodies (e.g., EAACI, AAAAI), and recent peer-reviewed primary research. The lack of standardized quality assessment introduces potential **selection and reporting bias**, which is acknowledged as a limitation of the narrative review approach.

3. ADVERSE DRUG REACTIONS

3.1. Definition, Prevalence, and Mortality

Adverse drug reactions (ADRs) unfold as unexpected and potentially harmful responses to medication, occurring even when the drug is administered at doses intended for treatment. This means a patient has a harmful reaction to a medication. ADRs do not include adverse drug events related to errors in drug administration or dosing. One of the earliest definitions, given by the World Health Organization (WHO) in 1958, states that an adverse drug reaction is "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." During drug therapy, it's estimated that 5% of patients will experience adverse drug reactions, while as many as 10% may encounter these reactions within the hospital setting. Adverse drug reactions pose a challenge to public health, weaving a complex web of risks that demand urgent attention and innovative solutions [1,4,5].

ADRs impact people worldwide. In Europe, they are monitored and registered by the European Medicines Agency (EMA). ADRs are a significant issue in terms of morbidity, costs, and mortality. In Europe, approximately 5% of hospital admissions are attributed to ADRs, making them the fifth leading cause of hospital deaths. An estimated 197,000 deaths annually in Europe are linked to ADRs, based on data from a meta-analysis by Montané et al. Research indicates that drugs are a significant factor in patient deaths in European hospitals, with one out of every 1,000 hospitalized patients experiencing drug-related deaths (DRDs). Additionally, at least one in 14 deceased patients was found to have died due to drug-related issues, highlighting the importance of this healthcare concern. The number of medications and comorbidities is identified as the most common risk factors associated with DRDs. According to the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) in 2022, more than 1.25 million severe adverse events were reported in the United States, resulting in nearly 175,000 deaths. In every 1,000 hospital admissions, three patients die because of an adverse drug reaction [6,7].

3.2. Classification and Mechanism

Drug allergies refer to a range of hypersensitivity reactions mediated by the immune system, with different mechanisms and clinical symptoms. Drug hypersensitivity can manifest as either immunological (allergic) or non-immunological (non-allergic) reactions. Medications can cause immediate or delayed hypersensitivity reactions. ADRs can be classified into type A reactions and type B reactions. The most common type of reactions, A-type reactions, occur in 70-80% of cases and result from the drug's pharmacological effects. These reactions typically occur in normal patients, are dose-dependent, and can be predicted. Less common than A-type reactions, B-type reactions are dose-independent, unpredictable, and unrelated to the drug’s pharmacological effects when taken at the usual dosage. A drug allergy is a type B adverse drug reaction that is mediated by the immune system. Diagnostic tests are recommended only for hypersensitivity reactions to type B ADRs [4].

To induce an immune response, T cells must recognize antigens, which requires their presentation on major histocompatibility complex (MHC) molecules by antigen-presenting cells (APCs). However, most pharmaceutical agents are too small to bind to MHC directly. Instead, they become immunogenic by forming hapten-carrier complexes with human proteins. This process involves the small drug molecules (haptens) covalently binding to larger proteins, forming a new structure that the immune system can recognize as foreign. This mechanism is crucial for developing drug hypersensitivity reactions and highlights the importance of understanding how different medications interact with the immune system. Identifying these interactions can help clinicians recognize and manage allergic reactions more effectively [8].

The term "drug allergy" should only be used when there is evidence of an immune system response. Drug hypersensitivity reactions (DHRs) are classified according to time: immediate or delayed reactions. The reactions can be mild or severe. Other organ systems, including the liver, kidneys, blood, and lymphatic systems, can also be affected. Severe reactions can be life-threatening, require hospitalization, or cause death. Additionally, DHRs typically impact individuals with a genetic predisposition. The mechanism of drug hypersensitivity can be classified as either immunological/allergic or non-immunological/non-allergic. Immunological reactions are mediated by the immune system and occur when the body's immune system mistakenly identifies a drug as a harmful substance, triggering an immune response. An IgE-mediated mechanism primarily causes immediate reactions. In contrast, non-immediate reactions are frequently mediated by specific T cells, although other mechanisms may also be involved. These immune-mediated reactions can be further classified into four types based on the Gell and Coombs classification [4,8].

3.2.1. Drug-Induced Type I Hypersensitivity

Type I is an immediate hypersensitivity reaction characterized by a rapid and severe allergic response. This reaction occurs immediately after exposure to the drug, usually within an hour; however, symptoms can appear up to six hours later. The drug-IgE complex binds to mast cells, releasing histamine and other inflammatory mediators. This reaction can cause anaphylaxis, urticaria, angioedema, and bronchospasm [4].

3.2.2. Drug-induced Type II and Type III Hypersensitivity

Type II and Type III hypersensitivity reactions are similar. In Type II, the cytotoxic hypersensitivity reaction, IgG or IgM antibodies are directed against drug-modified cells. This leads to cell destruction and causes blood cell dyscrasia, which is seen, for example, in anemia, cytopenia, and thrombocytopenia. Type III is an immune complex-mediated hypersensitivity reaction. It involves immune complexes that deposit in tissues, leading to inflammation and conditions like serum sickness, vasculitis, fever, rash, and arthralgia. These reactions occur within one to three weeks after drug exposure [4].

3.2.3. Drug-Induced Type IV Hypersensitivity

Type IV is a delayed-type hypersensitivity reaction. This reaction is mediated by T cells and can result in contact dermatitis, drug-induced hypersensitivity syndrome, and organ damage. Additionally, eosinophils, monocytes, and neutrophils might be activated during the reaction. It occurs within two to seven days or up to two months after drug exposure. Type IV reactions can also be classified according to subtypes: IVa involves macrophages, IVb involves eosinophils, IVc involves CD4+ or CD8+ T cells, and IVd involves neutrophils [4].

Table 1. Classification of ADRs [4,6]

ADVERSE DRUG REACTIONS (ADRs): Harmful reactions to medications. ADRs can happen with any type of medication and can range in intensity and occurrence based on the individual and the drug being taken.	
TYPE A: NON-IMMUNE MEDIATED, dose-dependent and predictable/toxic	TYPE B: IMMUNE MEDIATED, dose-independent and unpredictable
- Common, 80% of ADRs, can occur to anyone - Symptoms occur because of the expected and dose-dependent effects of a medication when taken at the recommended dosage.	- Hypersensitivity reactions, 20-25% of ADRs Allergic: immunologically mediated, immediate type I hypersensitivity/IgE mediated or delayed type IV hypersensitivity/T-cell-mediated, type II hypersensitivity/cytotoxic and type III hypersensitivity/immune complex

	OR Non-allergic hypersensitivity, non-immunological
Examples: - Intoxication/drug overdose - Interactions with other drugs - Side effects, related to known pharmacological effects of the medication, e.g. hair loss due to cytostatic treatments, sedative effect of antihistamines - Toxicity e.g. bleeding from anticoagulants	Examples: - Allergic reaction: allergic mechanism is detectable e.g. Penicillin-induced anaphylaxis - Non-allergic reactions: allergic mechanism is not detectable, typical manifestation immediate-type symptoms *Drug intolerance* typical symptoms develop even at low doses when the patient is not able to tolerate the medication, and they are not caused by underlying abnormalities of metabolism or drug excretion *Drug idiosyncrasy* unexpected reaction to a medication that is not related to the drug's known pharmacological properties, usually caused by underlying abnormalities of metabolism, excretion, or bioavailability

3.3. Risk Factors

Recognising the patients who are most at risk for ADRs is essential. Identifying a subgroup of patients who are likely to experience adverse drug reactions and adjusting their treatment accordingly can reduce the risk of such reactions. The most common risk factors include age, multiple comorbidities, and polypharmacy. Geriatrics, 60 years and over, and pediatric patients have a higher risk for ADRs. Children are at a higher risk of developing ARDs due to the limited availability of clinical trial data on the safety of drugs in children. The risk of developing ARDs increased with the number of medications administered, particularly when using 10 or more medications, and the presence of comorbidities, specifically four or more diseases. Also, the most vulnerable patients who require intensive care or have cancer have a higher risk of ARDs [4].

Various factors, including patient characteristics and specific medications, can increase the likelihood of developing a drug allergy. Genetic variations like HLA and certain viral infections like HIV, EBV, and herpes viruses, can also contribute to immune reactions to drugs. While a family history of drug allergy does not necessarily increase the risk of an individual developing a drug allergy, atopic patients may be at a higher risk of experiencing severe allergic reactions. Also, the previous response to the drug increases the risk of having drug allergies [4,5,6].

4. CUTANEOUS ADVERSE REACTIONS TO DRUGS

4.1. What are They?

Drug-induced allergic reactions most commonly and prominently affect the largest human body organ, the skin. Every drug carries risks and potential side effects for users. Allergies to medications are hypersensitivity reactions mediated by the immune system, exhibiting diverse mechanisms and clinical manifestations. The classification of cutaneous adverse reactions to drugs depends on a thorough clinical examination and precise description of the skin's morphological features. While any drug has the potential to cause hypersensitivity, it is commonly seen with antimicrobials, anti-inflammatory drugs, antiepileptic drugs, and anticancer drugs. It is important to note that adverse effects related to the drug's known mechanism of action are not considered hypersensitivity reactions. For example, antibiotic treatment may disrupt the natural bacterial balance in the intestine, leading to symptoms that are not classified as drug hypersensitivity. Also, allergic reactions will always recur if the patient is exposed to the offending drug, whereas non-allergic reactions may not necessarily happen again [4,5,9].

Urticaria and angioedema are the most common immediate CADRs. In this reaction, the patient has developed a sensitivity to the drug, producing IgE-type antibodies. However, it is important to note that many acute drug reactions are non-allergic. The most severe outcome of the immediate allergic reactions is anaphylaxis. Delayed skin reactions appear as severe exanthematous eruptions that can impact specific organs like the liver, lungs, kidneys, and blood systems. Recognizing that exanthematous eruptions may be attributed to various viral infections is essential. Both reactions can stem from multiple mechanisms, including immediate IgE-mediated or T cell-mediated delayed hypersensitivity responses. Additionally, idiosyncratic reactions and those triggered by toxic metabolites may play a role, with some of these mechanisms potentially influenced by genetic factors. Understanding these pathways is crucial for effectively identifying and managing adverse drug reactions [9,10].

The CADRs are clinically classified by their severity. Mild reactions include maculopapular exanthema, urticaria, symmetrical drug-induced skin fold exanthema (SDRIFE), and fixed drug eruption (FDE). Severe reactions include Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP). Other common disorders that can be caused by drug allergy include vasculitis, which may occur one to three weeks after exposure. Other disorders are eczema, hepatitis, nephritis, and photosensitivity, which can develop from days to years. These conditions lead to noticeable purpura, particularly in the lower limbs, and may involve internal organ manifestations as well as hemorrhagic or necrotic skin changes [9,10,11].

Table 2. Drug-Induced Cutaneous Hypersensitivity Reactions [4,5,6,9]

Reactions:	**Onset of reaction:**	**Symptoms and general features:**	**Typical drugs that induce the reactions:**
Immediate - Anaphylaxis - Urticaria/angioedema - Exacerbation of asthma	Typically, within 1h, rarely up to 6h	- Erythema, urticaria, angioedema, hypotension, bronchospasm -Wheals, angioedema - Dyspnea, cough, wheezing	Penicillin, Cephalosporins, NSAIDs
Delayed without systemic symptoms - FDE < 8h - MPE < 4-14 days - SDRIFE up to 7 days	6–10 days after the first exposure or within 3 days of the second exposure	FDE: Widespread red macules or papules MPE: Single/multiple erythematous plaques, arise at the same site after the intake of the same drug, resolve leaving hyperpigmentation SDRIFE: Erythematous rash involving the skin folds and genital area	FDE: Sulphonamides NSAIDs, barbiturates, tetracyclines, carbamates, metamizole MPE: Antibiotics, antiepileptics SDRIFE: Allopurinol, NSAIDs, beta-lactams
Delayed with systemic symptoms - AGEP 1-12 days - SJS/TEN 4-28 days - DRESS 2-8 weeks	2-6 weeks after first drug exposure, within 3 days of second exposure.	AGEP: Skin folds erythema, widespread pustules, fever, neutrophilia SJS/TEN: Painful rash, vesicles/blistering, mucosal/cutaneous erosions, epidermal detachment, red purpuric macules/erythema multiforme, fever DRESS: Widespread maculopapular rash, erythroderma, facial and limb edema, fever, lymphadenopathy, liver dysfunction, eosinophilia	AGEP: Beta-lactams, macrolides, diltiazem, terbinafine, dapsone, chloroquine SJS/TEN: Allopurinol, antiepileptics, nevirapine, NSAIDs DRESS: Antiepileptics, allopurinol, dapsone, sulphonamides

Abbreviations: FDE=Fixed Drug Eruptions, MPE=Maculopapular Exanthem, SDRIFE= Symmetrical Drug-Intertriginous and Flexural Exanthema, AGEP= Acute Generalized Exanthematous Pustulosis, SJS=Stevens-Johnson Syndrome, TEN=Toxic Epidermal Necrolysis, DRESS= Drug Reactions with Eosinophilia and Systemic Symptoms, NSAIDs=Non-Steroidal Anti-Inflammatory Drugs

4.2. Drug Induced Urticaria and Angioedema

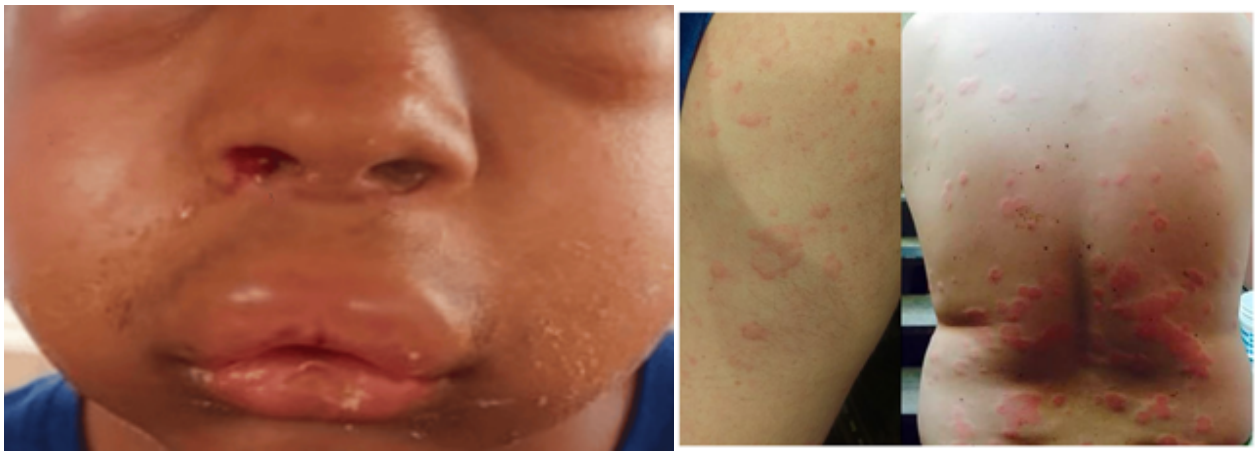
Urticaria, also known as hives, is a common skin disorder that affects 15-25% of individuals at some point in their lives. This skin condition is characterized by itchy, raised welts with pale centers and redness around the edges that can appear anywhere on the body. The size of the urticarial welts can vary from a few millimeters to several centimeters in diameter and typically resolves within 24 hours without leaving scars. However, some hives may last up to 48 hours. Common medications that can cause urticaria with or without angioedema include antibiotics, especially beta-lactams and sulfonamides, NSAIDs, acetylsalicylic acid (ASA), opioids, and narcotics. Urticaria can be categorized as either acute or chronic, based on the duration of symptoms and the presence of triggering factors. Acute urticaria lasts less than six weeks and may include angioedema. Chronic urticaria, on the other hand, persists for at least six weeks, with or without angioedema, occurring either continuously or intermittently [9,10,11].

Approximately 40% of individuals with hives also experience swelling known as angioedema. This condition is characterized by localized swelling of the skin and mucous membranes that is erythematous and non-pitting. Angioedema often affects the face, lips, tongue, throat, extremities, and genitals. In contrast to urticaria, individuals with angioedema typically experience a sensation of burning and pain on the skin rather than itching. Although usually self-limiting, it can present a risk of life-threatening respiratory obstruction. Common drugs that induce angioedema include ACE inhibitors and ARBs, but antibiotics (beta-lactams, sulphonamides, fluoroquinolones) and NSAIDs can also induce the reaction [9,10,11,12].

Mast cells play a key role in causing urticaria and angioedema. These cells, found throughout the body, including in the skin and mucous membranes, contain high-affinity IgE receptors. When mast cells are activated, they release inflammatory substances like histamine, leukotrienes, and prostaglandins, leading to vasodilation and plasma leakage in the skin and surrounding tissues [9,10].

Urticaria and angioedema should be differentiated from anaphylaxis, which requires immediate medical attention and treatment with epinephrine. In contrast, urticaria and angioedema may be less severe and can often be managed with antihistamines or steroids [9,10,11].

Figure 1. On the right, angioedema of the lips and eyelids, hypersensitivity reaction to diclofenac [13]. On the left, drug-induced urticaria of the arm and the back [11].



4.3. Drug-induced anaphylaxis

If a patient presents with urticaria, angioedema, and obstruction of the airways or gastrointestinal symptoms, it is crucial to consider the possibility of anaphylaxis. Anaphylaxis continues to be a significant issue in the field of medicine. The worldwide occurrence ranges from 50 to 112 cases per 100,000 person-years, with a lifetime prevalence of 0.3% to 5.1%. Hospitalizations due to anaphylaxis have doubled in the past decade, while the mortality rate has decreased from 0.12 to 0.16 deaths per million person-years [14,15].

The initial symptoms of anaphylaxis may include erythema, burning sensations on the skin, and stinging or itching, often accompanied by tachycardia. It is essential to recognize the signs and symptoms promptly, as the condition can progress rapidly and result in serious complications if not addressed on time. Initiating appropriate medical care is, therefore, critical. Individuals may also experience a sensation of thickness in the pharynx and chest, leading to coughing. As the condition progresses, secondary symptoms can develop, such as angioedema and urticaria. Gastrointestinal symptoms like abdominal pain, nausea, vomiting, and diarrhea are common, along with systemic signs such as hypotension, sweating, and paleness. In severe cases, the reaction can escalate to laryngeal spasm, shock, and even respiratory or cardiac arrest, and death. The early and accurate identification, followed by the removal of the offending medication, is crucial for safeguarding the patient's life [14,15].

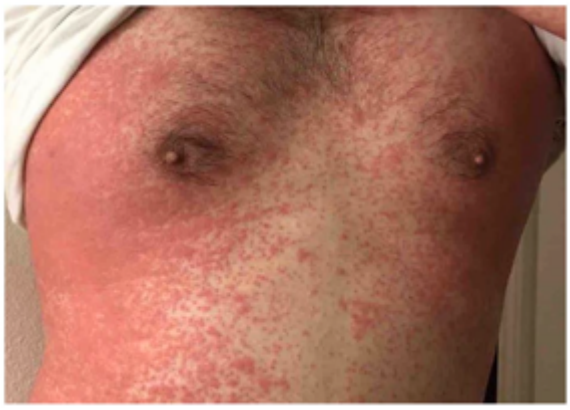
4.4. Mild Cutaneous Adverse Drug Reactions

4.4.1. Maculopapular exanthema

Maculopapular exanthema is the most common form of drug-induced eruption. 95% of drug-induced skin reactions are maculopapular exanthema. This condition is also known as morbilliform drug

eruption and exanthematous drug eruption. In these reactions, symmetrical reddish patches and papules typically emerge on the trunk and proximal extremities, potentially spreading to widespread erythroderma. A maculopapular exanthem is marked by red, flat macules that develop into bumpy papules ranging from one to five millimeters in diameter, which may merge to form plaques. This drug eruption generally presents itself in areas such as the face, neck, or upper trunk, with a tendency to spread symmetrically and bilaterally to the limbs over time. Patients may experience accompanying symptoms, including itching, ranging from mild to moderate, and a mild fever. The symmetrical distribution and potential for bilateral involvement are noteworthy characteristics, indicating that both sides of the body may be affected equally. The rash is self-limiting, usually resolving within seven to 14 days after discontinuing the offending drug. As it heals, the lesions may turn brownish, and peeling of the skin might occur. While isolated small blisters or pustules may appear, there is no extensive epidermal detachment, and mucosal symptoms are absent. Skin peeling may occur during the healing process. The diagnosis is confirmed with no skin blistering or severe systemic symptoms [11,16].

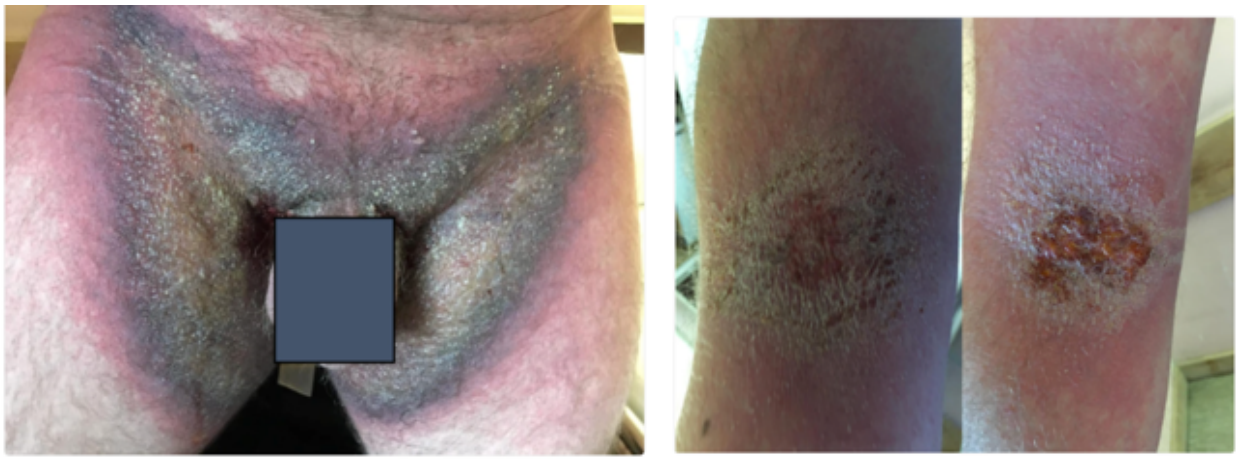
Figure 2. Maculopapular rash. Delayed allergic reaction to ibuprofen [17].



4.4.2. Symmetrical Drug-Intertriginous and Flexural Exanthema

Symmetrical Drug-Intertriginous and Flexural Exanthema (SDRIFE) is a subtype of maculopapular exanthema that typically presents with well-defined redness and isolated pustules in fold areas like the armpits, groin, and around the genital and anal regions. This condition develops five to 14 days after the administration of the drug. SDRIFE typically develops within hours to days after exposure to the medication. The rash manifests as a well-defined redness on the buttocks, natal cleft, and/or upper inner thighs, resembling the red bottom of baboons. This redness is generally symmetrical and often takes on a V-shape. The neck, armpits, and other large skin folds (flexures) may also be affected. Skin peeling may occur during the healing process. Patients with SDRIFE are in good overall health and have no systemic symptoms. Beta-lactam antibiotics cause 50% of the cases [16, 18].

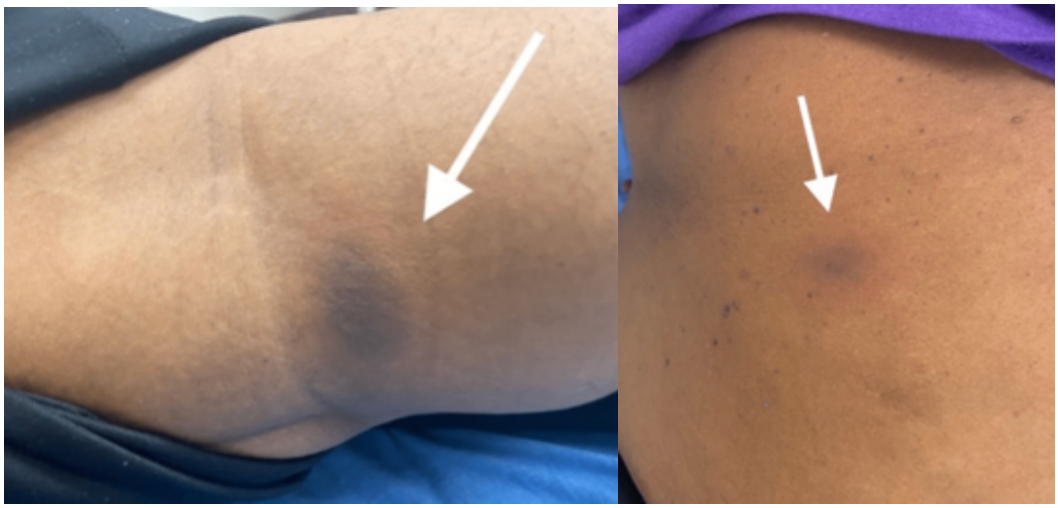
Figure 3. SDRIFE in the inguinal fossa and in the cubital fossa. Allergic reaction to amoxicillin [18].



4.4.3. Fixed Drug Eruption

Fixed drug eruptions (FDEs) are frequently underdiagnosed or misidentified as insect bites, urticaria, or erythema multiforme. They can appear anywhere from 30 minutes to eight hours, and in some cases, up to two months after taking a medication. These lesions are typically well-defined and can present as solitary or multiple papules or plaques. Their color ranges from dusky red to violet. While FDEs can often be asymptomatic, some patients may experience pain and itching. The lesions typically resolve within seven to ten days, but hyperpigmentation may linger for years. Common sites for these lesions include the lips, trunk, legs, arms, and genitals. Usually, there are one or a few lesions, but the erythema can be widespread in rare cases. Upon re-exposure to the triggering drug, the spots reappear on the same skin area within a short period, sometimes as quickly as 30 minutes. After healing, the lesion often leaves a long-lasting brownish hyperpigmented mark [1,19].

Figure 4. FDEs. On the left, FDE on the popliteal fossa. On the right, FDE on the upper abdomen. Allergic reaction to ibuprofen [19].



4.5. Severe Cutaneous Adverse Reactions

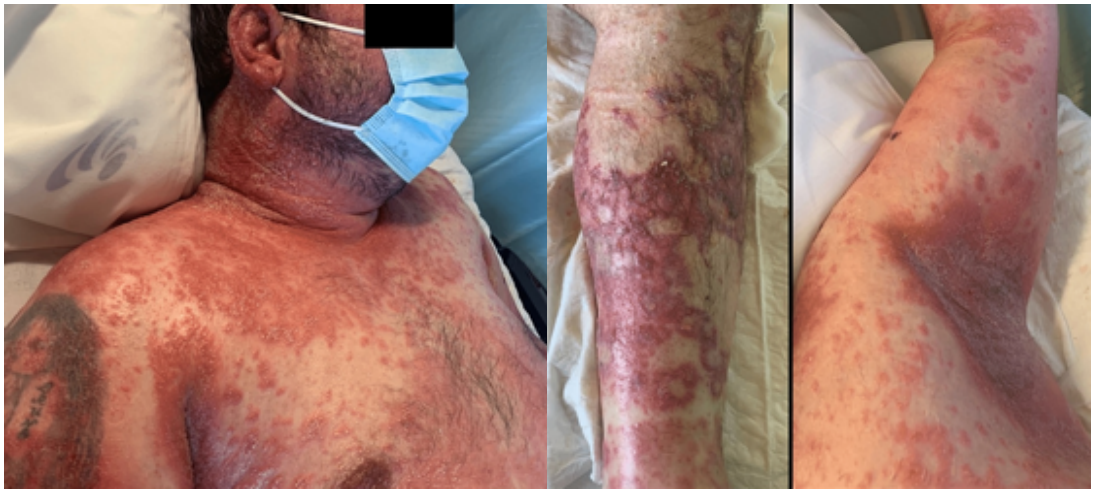
Severe cutaneous adverse reactions (SCARs) are the most serious drug reactions, encompassing three major syndromes: Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). SCARs often affect multiple organs, including mucosal, hepatic, hematologic, and renal systems. Symptoms indicating internal organ involvement include high fever, malaise, muscle and joint pain, and disseminated lymphadenopathy. Survivors of SCARs may experience long-term complications such as scarring, dermatologic issues, and psychological effects [10,16,20].

The pathophysiology of SCARs is not fully understood. The immunopathogenesis of SCARs involves T cell-mediated drug hypersensitivity and potential molecular mimicry between prior viral infections and current drug exposure in susceptible individuals. SCARs caused by drugs are rare but should be identified early, as they can be life-threatening. They can negatively impact quality of life and may become chronic. Treatment often necessitates hospitalization in intensive care or a burn unit to monitor vital signs and internal organ functions. Stopping the triggering medication is crucial for improving patient outcomes [20].

4.5.1. Acute Generalized Exanthematous Pustulosis

Acute Generalized Exanthematous Pustulosis (AGEP) is a rare and severe skin condition. Systemic involvement occurs in approximately 20% of cases. It typically presents on the trunk and flexures with a sudden outbreak of numerous small pustules on a widespread rash. Skin lesions usually begin on the face, underarms, and groin before spreading more widely. Patients often have fever, and laboratory tests show elevated white blood cell and neutrophil levels. As the reaction resolves, the skin may peel off aggressively. Symptoms generally resolve a few days after discontinuing the offending drug or following treatment with corticosteroids. AGEP can affect individuals of any age, but it is more frequent in older adults with significant comorbidities. Pustular psoriasis is an important condition to consider in the differential diagnosis. The typical manifestation is a generalized morbilliform drug eruption, characterized by raised, red lesions that appear within days to 3 weeks after exposure to the drug. These lesions usually start on the trunk and then spread to the limbs [10,16,20].

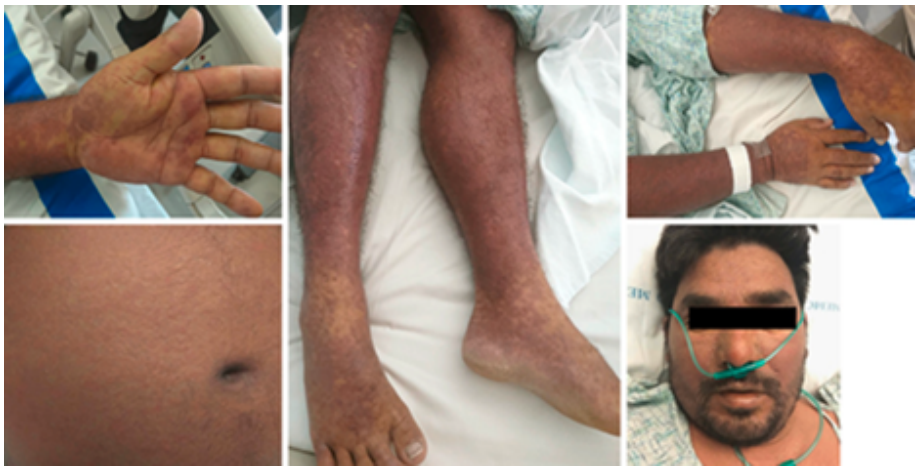
Figure 5. AGEP on the face, neck, thorax, leg, and armpit. Allergic reaction to ceftriaxone [21].



4.5.2. Drug Reaction with Eosinophilia and Systemic Symptoms

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a type of generalized drug reaction that typically presents with a widespread dark red or purplish maculopapular rash on the skin. Symptoms usually begin with fever, malaise, lymphadenopathy, and pruritus. Then it progresses into a morbilliform rash and diffuse scaling. Swelling of the face and extremities can also be observed. A rash indicative of DRESS is considered when it covers more than 50% of the body's surface area. Vesicles or bullae, atypical target lesions, purpuric spots, and small sterile follicular pustules may appear. Blood tests show an elevated white blood cell count, increased eosinophils, and atypical lymphocytes. The most common reaction affects the liver, although other internal organs can be affected. The symptoms of this reaction persist even after stopping the drug that caused it, and it is linked to the reactivation of herpes viruses. The mortality rate of DRESS is around 4% [10,16,22,23].

Figure 6. DRESS. A diffuse maculopapular rash was observed in the patient due to an allergic reaction to naproxen [23].



4.5.3. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are the most severe skin-related adverse reactions, commonly triggered by medications. Both conditions are associated with high rates of morbidity and mortality, which can be as high as 90%. SJS and TEN are different levels of severity of the same condition known as Epidermal Necrolysis (EN). SJS affects less than 10% of the skin, and TEN affects more than 30% of the skin. The mixed form of SJS and TEN affects 10-30% of the skin. The risk of SJS/TEN is higher in individuals with specific HLA haplotypes, HIV, cancer, or systemic lupus erythematosus. Managing patients with SJS/TEN presents significant clinical challenges for physicians due to its rarity and the rapid progression of its systemic nature, which includes severe skin, mucosal, and systemic symptoms [24,25,26].

The skin lesions are typically large patches or unusual targetoid lesions that quickly form blisters, usually within 12 hours, due to detachment related to epidermal necrosis. The skin may be painful even before the blisters appear. Patients often experience significant pain and may have a fever. The lesions are most commonly widespread over the body. Additionally, blistering can occur on all mucosal surfaces, including the mouth, genitals, and conjunctiva [24,25,26].

It is important to distinguish between lesions caused by EN and erythema multiforme (EM). EM lesions are characterized by prominent target lesions with three layers, typically on the extremities. Infections often cause these lesions and they tend to resolve on their own. In contrast, EN lesions typically have two layers, with the outer layer appearing red and the inner layer turning purple as the skin begins to die. EN lesions are more amorphous in shape compared to the circular target lesions seen in EM. Additionally, while small areas of epidermal peeling may occur in EM lesions, EN lesions typically affect larger areas of the skin. If the symptoms are unclear, it is better to keep the patient monitored in the hospital until the condition improves. SJS/TEN often heals, leaving hyperpigmentation on the area of the lesions [27].

Figure 7. On the left, TEN. Epithelial detachment on the lips and face due to an allergic reaction to carbamazepine [24]. On the right, SJS/TEN reaction on oral mucosa [25].

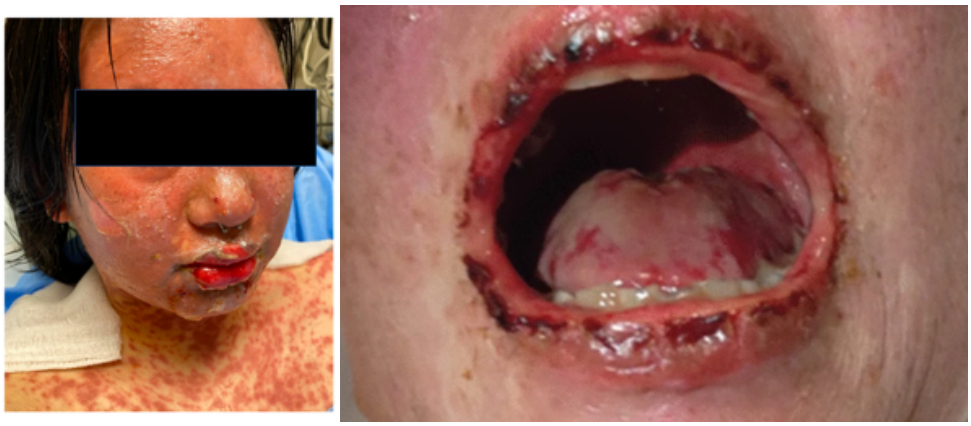


Table 3. Red flags of severe adverse reactions [2,5,16]

IMMEDIATE REACTIONS:	**DELAYED REACTIONS:**
Sudden widespread itching (pruritus) and/or redness, especially in the palmoplantar and scalp	More than 50% of the skin is affected
Angioedema of the oral mucosa	Small blisters and/or scabs
Severe urticaria (hives): rashes spread rapidly throughout the body	Atypical target and hemorrhagic necrotising lesions: the colour of the rash is grey-purple or dark
Shortness of breath, dyspnea	Painful or burning skin
Nausea, sudden intestinal symptoms	Bloody mucosal changes (mucositis)
Hypotension	Detachment of the epidermis
Unconsciousness	Facial and skin lesions swelling and infiltration

5. DIAGNOSIS OF CUTANEOUS ADVERSE REACTIONS TO DRUGS

5.1. Diagnosis

Diagnosing drug hypersensitivity reactions (DHRs) is a complicated process. The initial step involves accurately determining if the patient is experiencing DHRs. Patients often describe any symptoms that occur while taking a drug as an allergy to that specific medication. To make a correct diagnosis, it is essential to gather a detailed drug history, which should include information such as the dates when the medication was taken, the type of drug formulation, the dosage, and the method of administration. Additionally, it is important to note any clinical symptoms experienced, along with the timing and duration of these symptoms related to the drug exposure [2, 28].

When there is uncertainty surrounding DHRs' diagnosis, various decision aids and algorithms can be utilized. These tools include the Naranjo algorithm, the Begaud algorithm, the Yale algorithm, the Jones algorithm, the Karch algorithm, ADRAC, WHO-UMC16, and the quantitative approach algorithm. While these algorithms can assist in determining the causality of DHRs, they are not definitive in proving or disproving such a connection. The most used tool is the Naranjo scale, which consists of ten questions, with each response given a score. The total score indicates the likelihood of a drug-related adverse drug reaction. A score of nine or higher is considered definite, five to eight is probable, one to four is possible, and zero is doubtful. Um et al. compared in a retrospective cohort study one of the newest tools, the Liverpool Causality Assessment Tool, to the Naranjo Scale. The Liverpool Causality Assessment Tool is more sensitive than the Naranjo Scale for assessing potential ADRs, although both tools have low specificity. All these tools are useful as additional support for clinical reasoning in diagnosing ADRs or deciding whether further investigations are needed. Additional diagnostic tests are necessary to determine the mechanism of ADRs or establish a direct link between a drug and symptoms [28,29].

Primary care physicians are typically the first point of contact for patients and are responsible for determining whether a patient may have DHRs. As such, they play a crucial role in deciding whether a patient should be referred to an allergist. Additionally, the primary care physicians are tasked with prescribing a safe alternative if needed. Recognizing the drugs that frequently cause hypersensitivity reactions is essential for diagnosing and evaluating whether a drug has initiated a reaction [2,28].

There is currently no definitive test considered the gold standard for diagnosing adverse drug reactions or severe cutaneous adverse reactions. Various tests, including history, skin tests, in vitro tests, and provocation tests, can help identify the culprit medication. It is important to accurately describe and classify the suspected clinical reaction for proper evaluation. Gathering comprehensive information about when the medication was started and how long it was used, when the reaction began, any previous similar reactions, and how the patient responded to stopping the medication and then taking it again can aid in early diagnosis and lower the risk of complications and death [2,28,30].

It is strongly recommended that allergy diagnostics be conducted between four weeks and six months after the reaction. The classification of a drug reaction and subsequent planning of allergy diagnostics should be determined based on the clinical presentation, timing of symptoms, and the suspected causative drug. Diagnosis begins with identifying skin symptoms. It is essential to establish and document the timeline between the drug’s start and the last dose taken, as this is typically the most accurate information. Additionally, the patient's response to stopping the drug, any other medications being taken, and any other medical conditions should also be documented [2,28,30].

It is important to document the rash and other symptoms for further investigation. The type of condition should be carefully documented, categorizing it as generalized, widespread, or localized. Additionally, it is essential to note its specific appearance, such as whether it presents as a spot, wheal, or blister. Taking good photographs can be beneficial for later reference, and it is recommended to ask the patient to document the progress of their reaction. Such detailed documentation is essential for accurate assessment and effective communication. For mild reactions, discontinuing the medication is typically sufficient. In severe reactions, a thorough clinical examination should be conducted along with laboratory tests, including complete blood count, liver and kidney function tests, and inflammatory markers. In cases of suspected vasculitis, a urine sample should also be taken. If anaphylaxis is suspected, tryptase levels should be tested within three hours of the reaction onset [28,30].

Validated skin and laboratory tests are only available for a limited number of drug groups, such as beta-lactam antibiotics, heparins, radio-contrast media, muscle relaxants, and platinum compounds. In practice, specific IgE tests are primarily used to investigate suspected hypersensitivity to beta-lactam antibiotics. However, for many drugs, either no valid tests exist, or their sensitivity is low. It is essential to assess skin and laboratory tests in conjunction with all relevant data to ensure a comprehensive evaluation. In cases where there is a history of severe reactions or if skin tests are not feasible or declined, validated in vitro tests are recommended prior to skin tests. These tests can confirm hypersensitivity when combined with a convincing history and/or other tests [2,30].

A skin biopsy can be a helpful diagnostic tool, especially in severe reactions. Nikolsky's sign is a clinical dermatological indicator of severe delayed reactions, signifying detachment of the epidermis. It is performed by gently pressing the skin. The sign is considered positive if the epidermis detaches from the dermis with this maneuver. Controlled provocation testing is often necessary to confirm or rule out a diagnosis. If severe symptoms develop, it is advisable to seek specialized medical care from a dermatology or allergology unit. Patients with extensive skin detachment may require treatment in a burn unit. If the suspected drug is unlikely to be needed for future treatment purposes, such as sulfa-antibiotics, a diagnostic work-up may not be necessary [28,30,31].

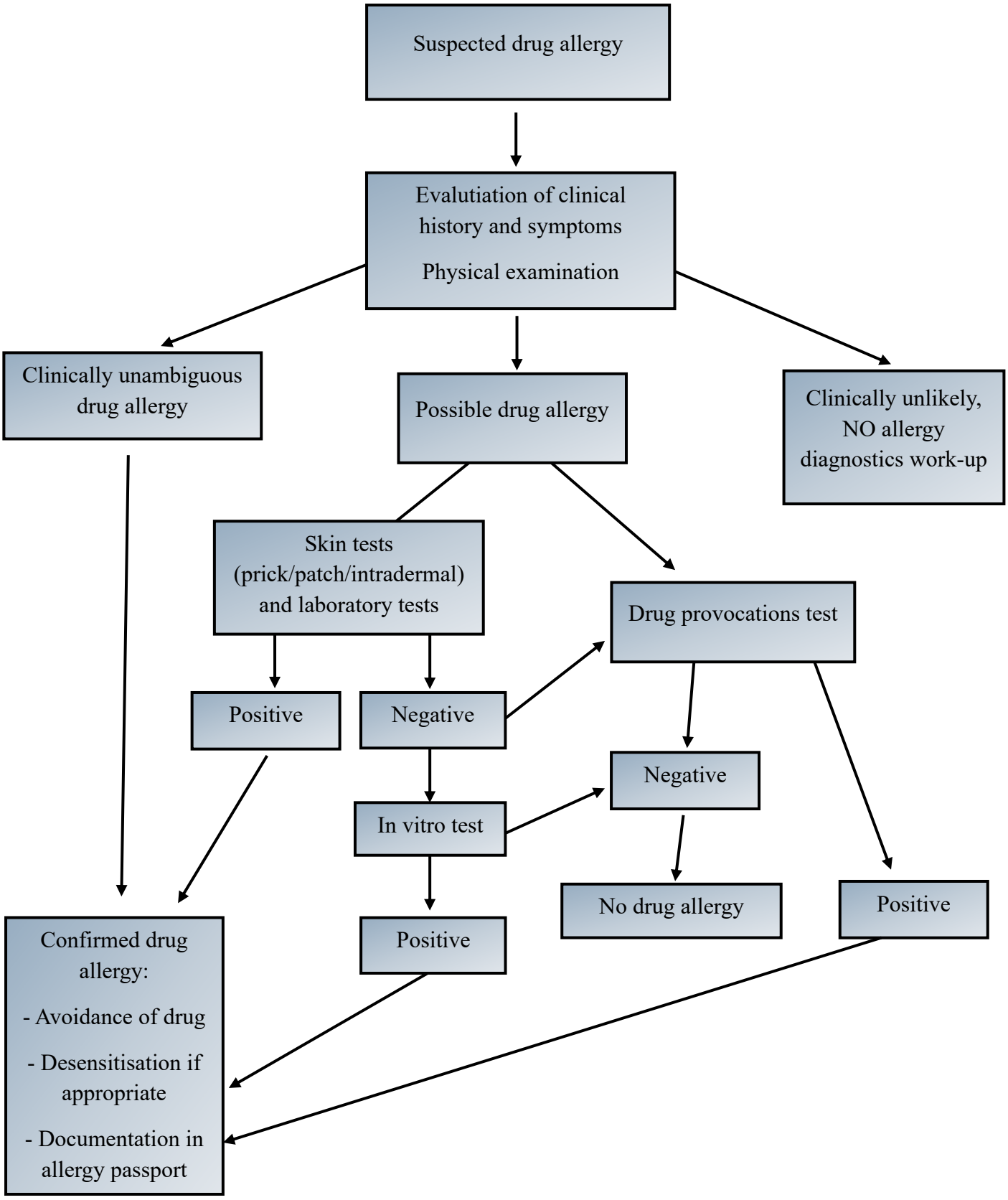
5.2. Differential diagnosis

Due to the diverse range of clinical symptoms associated with drug allergies, it is important to rule out other potential conditions that can present similarly. In an IgE-mediated immediate allergic reaction, urticaria and angioedema are typical skin reactions. When it progresses, anaphylaxis may occur. Similar symptoms can be caused by infections, insect bites or stings, carcinoid syndrome, food and latex allergies, mastocytosis, asthma exacerbation, and flares of chronic spontaneous

urticaria/angioedema. For example, it can be challenging to differentiate between urticaria and exanthema. Urticaria is characterized by elevated lesions that persist for up to 24 hours. To confirm the type of rash, it is recommended to use a marker to outline its boundaries and check if the markings remain visible the following day [4,5,28].

T cell-mediated late allergic reactions cause severe skin eruptions in AGEP, DRESS, and SJS/TEN. The following conditions should be considered when diagnosing late allergic reactions: viral infections with exanthema and Streptococcal infection, insect bites and stings, psoriasis, vasculitis, cutaneous manifestations of connective tissue diseases, acute graft-versus-host disease, Kawasaki disease, and Still's disease [4,5,28].

Figure 8. Algorithm for diagnosing drug allergy [2,4,5,19].



6. BETA-LACTAM ANTIBIOTICS

Beta-lactam antibiotics are often prescribed as the first-line treatment for various infections. This group of antibiotics includes penicillins, cephalosporins, carbapenems, and monobactams. In 1929, Alexander Fleming made a groundbreaking discovery by identifying that the mold Penicillium notatum inhibits the proliferation of staphylococci on a bacterial plate. This discovery ultimately facilitated the development of the first beta-lactam antibiotic, penicillin, which is regarded as one of the most significant inventions in human history. These medications have significantly contributed to saving countless lives; however, their overuse and misuse have increased antibacterial resistance [32,33,34,35].

Generally, beta-lactams are well tolerated and considered safe for administration. The most common side effects are allergic reactions. In Western countries, approximately 10% of adults and a higher percentage of hospital patients claim to have a beta-lactam allergy. However, true IgE or T-cell-mediated allergy is uncommon. Up to 98% of patients who reported an allergy can tolerate beta-lactams in allergy testing. These antibiotics are contraindicated in previous cases of anaphylaxis and in severe skin reactions like SJS and TEN. Overall, anaphylactic reactions are rare, occurring in only 0.001% of cases with parenteral administration and 0.0005% with tablet administration. The patient's medical history and the balance of risks and benefits influence the diagnostic process. It is advisable to conduct allergy testing for suspected beta-lactam allergies to ensure the best medical care for the patient [32,33].

6.1. Classification and Mechanism of Action

Penicillins, cephalosporins, carbapenems, and monobactams have different side chains attached to the core four-membered beta-lactam ring structure. The side chains determine the specific properties and activities of each antibiotic. Penicillin has a five-membered thiazolidine ring attached to the beta-lactam ring, with the R1 side chain distinguishing it from the others. Cephalosporins, on the other hand, have a six-membered sulfur-containing dihydrothiazine ring and two side chains, R1 and R2. Carbapenems have a carbon double bond instead of sulfur in the five-membered thiazolidine ring, with the R side chain. Monobactam contains only the beta-lactam ring [35,36,37].

Beta-lactams work by binding to and inactivating enzymes necessary for bacterial cell wall synthesis, disrupting cell wall integrity and leading to bacterial lysis and death. They achieve this by binding to and inhibiting enzymes called penicillin-binding proteins, which are involved in the cross-linking of peptidoglycan, a major component of the bacterial cell wall. This disruption of cell wall synthesis weakens the cell wall, resulting in cell lysis and, ultimately, bacterial death. Beta-lactam antibiotics are effective against a wide range of bacteria, including both Gram-positive and Gram-negative

species. Allergic reactions to beta-lactams can be categorized as either immediate, IgE-mediated responses or delayed, typically T-cell-mediated reactions. Identifying the specific allergy mechanism to effectively manage future antibiotic treatments is important [35,36,37].

Figure 9. Chemical structures of beta-lactams. R-side chains distinguish beta-lactams from other members of the same class [38].

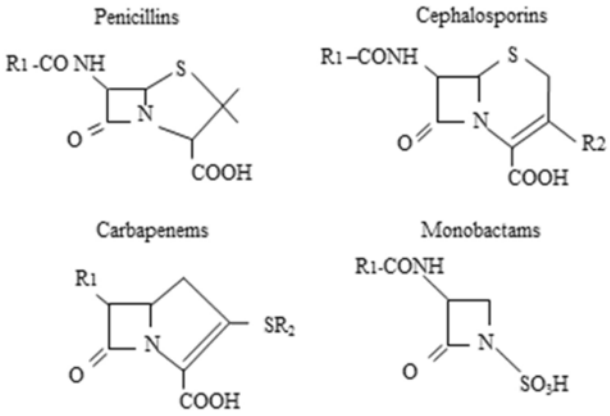


Table 4. Most used beta-lactam antibiotics and examples of indications [5,35].

ANTIBIOTICS	EXAMPLES OF INDICATION
Basic penicillins:	
Phenoxymethylpenicillin (penicillin V)	Tonsillitis
Benzylpenicillin	Erysipelas, pneumonia
Benzathine benzylpenicillin	Prevention of erysipelas
Procaine benzylpenicillin (penicillin G)	Erysipelas
Aminopenicillins:	Sinusitis, acute otitis media
Amoxicillin (/clavulanic acid)	Severe infections caused by enterococci
Ampicillin	
Antistaphylococcal penicillins:	Skin and soft tissue infections
Flucloxacillin	Severe infections caused by S. aureus
Cloxacillin	
Other penicillins:	Complicated abdominal surgical infections
Piperacillin-tazobactam	Urinary tract infections
Pivmecillinam	

Cephalosporins: 1st generation: cephalexin 1st generation: cefazolin 2nd generation: cefuroxime 3rd generation: ceftriaxone 3rd generation: ceftazidime 5th generation: ceftaroline	 Skin and soft tissue infections Severe infections caused by S. aureus Skin and soft tissue infections, pneumonia Nosocomial infections Severe infections caused by Pseudomonas Infections caused by methicillin-resistant S. aureus (MRSA)
Carbapenems: Ertapenem Meropenem	 Complicated hospital-acquired infections, also effective against bacteria producing extended-spectrum beta-lactamase (ESBL) Complicated hospital-acquired infections, also effective against ESBL-producing bacteria
Monobactams: Aztreonam	 Complicated hospital-acquired infections (Gram-negative bacteria)

6.2. Does Your Patient Have a Beta-Lactam Allergy?

True beta-lactam allergies are less common than believed. It is important to evaluate the authenticity of the allergy critically. In clinical practice, physicians come across patients who claim to have a beta-lactam allergy. This challenges physicians in selecting the most suitable antibacterials for treatment. Overall, the suspicion of a drug allergy affects the quality of life for patients, leading to increased anxiety about their treatment options. When an allergy is suspected, broad-spectrum and less effective treatments are often used. These alternatives cause more side effects than narrow-spectrum antibiotics, are linked to antibiotic resistance, and are more expensive for the patient. Treating infections with broad-spectrum antibiotics is almost ten times more costly than testing for beta-lactam allergy. By ruling out allergies through allergy tests, healthcare costs can be reduced using targeted antibiotic treatments, ultimately benefiting society. Additionally, patients with a suspected history of beta-lactam allergy have a higher incidence of colonization or infection with methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococci (VRE), and the prevalence of Clostridium difficile is also increased in this group [5,35,39].

All suspected allergic reactions to beta-lactams should be investigated, regardless of the patient's age. Identifying triggers and preventing unnecessary avoidance of these antibacterials is important for accurately ruling out an allergy. When evaluating risk factors, the physician should determine whether the patient is at high or low risk for experiencing severe adverse effects from the drug. The risk is increased if the patient has previously visited the emergency department or been hospitalized due to an allergic reaction, especially if mucosal tissues or organs were involved. Conversely, the risk is lower if the reaction occurred more than 10 years ago, involved only cutaneous symptoms, and was successfully treated with antihistamines. Additionally, the likelihood of experiencing an allergic reaction is minimal if the patient has avoided the drug due to a family history of allergies or based on the screening test results. If the patient experienced nausea, diarrhea, and headache after taking beta-lactams, these are likely non-allergic symptoms, as they are expected side effects of the medication. It is essential to calm the patient's mind and clarify the difference between genuine allergic reactions caused by the medication and common side effects associated with its use [5,35,39].

Diagnostic procedures for beta-lactam allergy typically consist of four primary components: patient history, laboratory tests, skin tests, and drug provocation tests. The diagnostic process begins with gathering the patient's history regarding the suspected allergy. The physician must classify the allergic reaction based on its timing – whether it is immediate (occurring within one to six hours) or delayed (spanning from over an hour to several weeks). To identify the drug allergy accurately, the physician requires specific details about the reaction, including symptoms, severity, and resolution methods. Additionally, information about the medication that triggered the reaction, any past drug allergies or sensitivities, previous adverse drug reactions (ADRs), underlying medical conditions, and any other allergies that could increase the risk of drug allergies is essential. Current medications and a family history of drug allergies or adverse reactions are also critical for the physician. This comprehensive information facilitates a precise diagnosis and enables effective management of the patient's drug allergy [39,40,41].

The patient's medical history plays a crucial role in informing the choices for subsequent diagnostic procedures. In cases where there is a risk of severe, life-threatening reactions, in vitro testing proves to be beneficial, as it enables allergy testing without exposing the patient to the allergen. Tests for immediate reactions include tryptase, IgE antibodies, and various cellular in vitro tests. Specifically, the cellular in vitro tests for immediate allergic reactions consist of basophil activation, cellular antigen stimulation, and histamine release assays. These tests can be conducted prior to skin testing for immediate reactions, and they should be performed within two weeks to six months after the reaction. For delayed allergic reactions, the T-cell/cellular in vitro tests include the lymphocyte transformation test, enzyme-linked immunosorbent spot assay, flow cytometric test, and enzyme-

linked immunosorbent assay. These methods can serve as complementary tests when diagnosing delayed reactions, MPE, FDE, AGEP, and DRESS, especially when other tests yield negative results. T-cell in vitro tests are ideally conducted two weeks post-reaction, though results may still be valid after many years. Additionally, in vitro testing is advantageous for high-risk patients who are unable to undergo in vivo testing, as well as in situations where skin testing is impractical due to existing skin conditions [39,40,41].

Skin tests are particularly useful for diagnosing beta-lactam allergies. The methods consist of the patch test, skin prick test, and intradermal test. It is advisable to conduct these tests at least one month after the reactions occur or within one year. For immediate allergic responses, skin prick and intradermal tests are preferred, while patch tests are suitable for delayed allergic reactions. It's essential to acknowledge that skin tests may lead to systemic, severe, or life-threatening reactions; therefore, patient monitoring during and after the procedure is critical. A study involving 290 patients with immediate penicillin allergies revealed that 11% of skin tests resulted in systemic reactions [39,40,41].

Drug provocation testing (DPT) is typically the final diagnostic procedure for assessing beta-lactam allergy. It involves the careful administration of a medication to confirm or rule out a drug hypersensitivity reaction. DPT is advised only after all other allergy diagnostic tests have been concluded, accompanied by an individual risk-benefit analysis. If the patient's history and positive skin tests suggest beta-lactam allergy, DPT is not conducted. Recently, direct DPT has been utilized without preceding skin tests for mild, isolated cutaneous beta-lactam reactions. This test must be carried out in a hospital under controlled conditions and with specialist supervision, as it can provoke severe reactions. Ideally, patients should be exposed to the suspected drug in its original formulation. The drug challenge can be executed as one or multiple steps based on the patient's risk level. A graded drug challenge involves giving a small initial dose of the medication, monitoring the patient, and then administering the full dose if the initial dose is well-tolerated. The choice to perform a drug challenge is determined by the patient's medical history and any underlying conditions that could heighten the risk of a severe allergic reaction [1,35,39,40].

Desensitization refers to the development of a temporary tolerance to the medication that causes an allergic reaction. The attending physician can consider desensitization if a patient has a confirmed or highly suspected immediate allergy requiring a specific drug, and alternative treatments are either unavailable or ineffective [1,35,39,40].

6.3. Cross-Reactivity

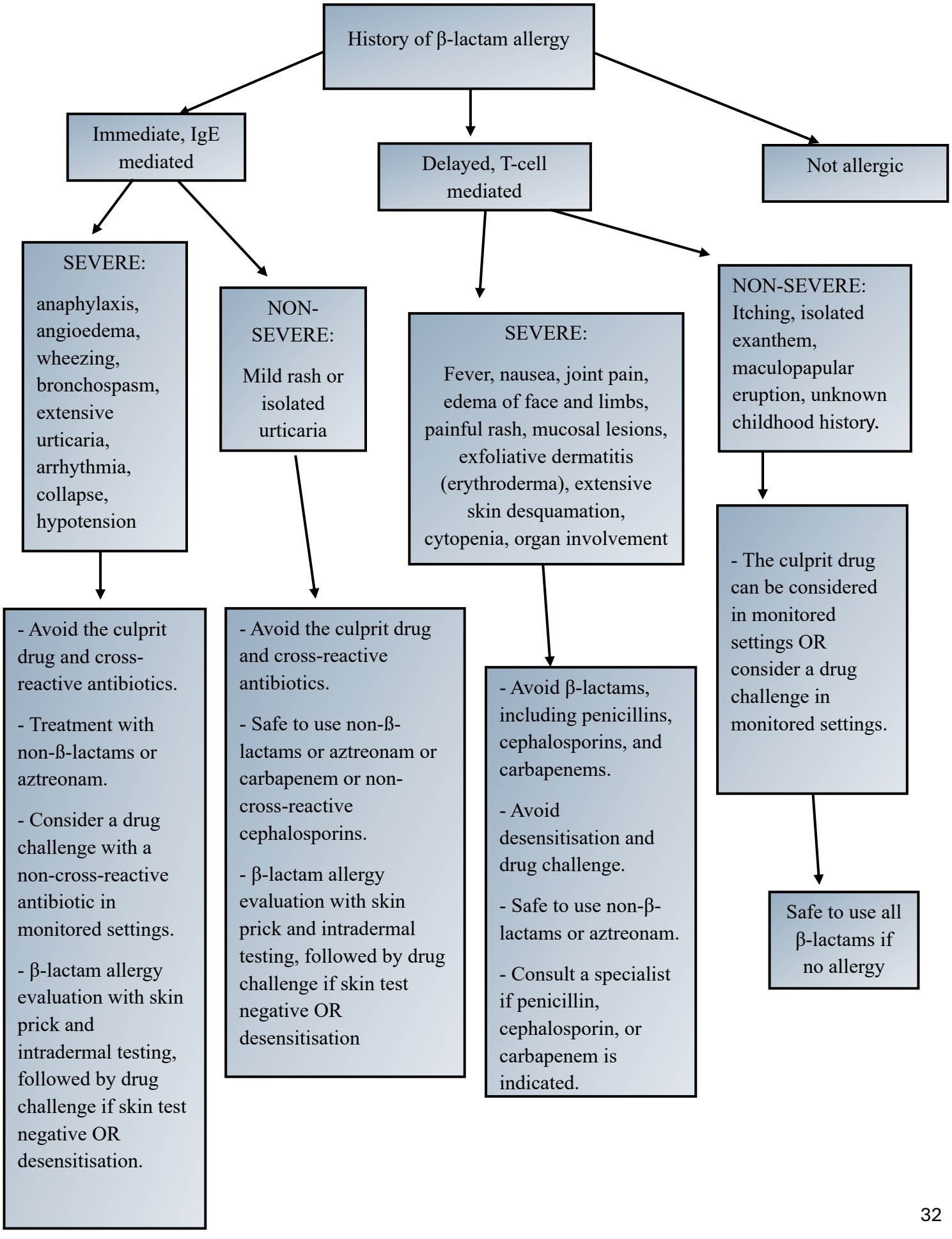
Cross-reactivity refers to the phenomenon where a patient allergic to one type of beta-lactam antibiotic may also be allergic to other antibiotics in the same group. Understanding potential cross-reactivity is extremely important in a clinical setting. Previously, it was thought that an allergy to one substance in beta-lactam antibiotics implied a cross-allergy to all other antibacterials of the same class. Today, it is known that only a small percentage of patients allergic to beta-lactam antibiotics are specifically allergic to the beta-lactam ring; cross-reactivity is more prevalent due to similarities in side chains. In cases where the side chains are identical, the risk of cross-reactivity is higher; when the side chains differ, the risk decreases [39,40,41].

Cross-reactivity is present across all beta-lactam classes, leading to the development of several cross-reaction tables that aid physicians in selecting alternative antibiotics. Aztreonam, a monobactam, has a distinct structure and is not known to cross-react with other beta-lactams, except for ceftazidime. For patients allergic to penicillin, it is advisable to avoid aminopenicillins, aminocephalosporins, and first-generation cephalosporins due to their comparable side chains. The side chains in second- and third-generation cephalosporins, such as cefuroxime and ceftriaxone, show considerable similarity, resulting in a high rate of cross-reactivity. Carbapenems exhibit minimal to no risk of cross-reactivity with other beta-lactams. In instances of anaphylaxis linked to penicillin, avoiding all beta-lactams is recommended [39,40,41].

6.4. Summary

Beta-lactam antibiotics work by inhibiting the synthesis of the bacterial cell wall through binding to and inhibiting enzymes known as penicillin-binding proteins (PBPs). This disruption weakens the cell wall, leading to cell lysis and bacterial death. Beta-lactam antibiotics are effective against a broad spectrum of bacteria, including both Gram-positive and Gram-negative bacteria. Diagnosing beta-lactam allergies involves carefully reviewing all available information, including patient history, in vitro diagnostics, skin testing, and DPT. The physician making the diagnosis should understand common allergic reactions and know that cross-reactivity can occur between different beta-lactam antibiotics. It is essential to provide appropriate treatment and consider referring the patient to an allergist for further evaluation. Allergic reactions to beta-lactams are common, with about 10% of adults in Western countries reporting a penicillin allergy. The overuse and misuse of these drugs have led to an increase in antibacterial resistance. Accurate diagnosis of these allergies is essential for effective treatment in the future. Assessing risk factors and conducting proper tests can help determine if a patient truly has a beta-lactam allergy. It is crucial to distinguish between allergic reactions and expected side effects to provide the best care for patients [5,35,39,41,42].

Figure 10. The Algorithm for Diagnosing Beta-Lactam Allergy [5,35,39,41].



7. NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used analgesics worldwide and are thought to be involved in 20-25% of all ADRs. NSAIDs comprise a broad range of medications that block the enzyme cyclooxygenase (COX), preventing the production of prostaglandins from arachidonic acid. These drugs are divided into two groups: COX-1 NSAIDs and COX-2 NSAIDs. Reported drug allergies to NSAIDs in adults are approximately 1.9%. COX-2 inhibitors pose a lower risk of side effects because of their selectivity. NSAIDs hypersensitivity can manifest in various clinical syndromes, and they are believed to cause more ADRs than beta-lactams [43].

7.1. Classification and Mechanism of Action

Common COX-1 NSAIDs include acetylsalicylic acid (ASA), ibuprofen, naproxen, diclofenac and indomethacin. Their mechanism of action is to block the enzyme COX-1, which produces prostaglandins in the body. Prostaglandins are chemicals that contribute to inflammation, pain, and fever. By inhibiting COX-1, these NSAIDs reduce the production of prostaglandins, decreasing inflammation, pain, and fever. However, blocking COX-1 can also cause side effects such as gastrointestinal ulcers and bleeding, as this enzyme maintains the protective lining of the stomach and intestines. These medications are classified as non-selective inhibitors, primarily targeting COX-1, while also possessing the capability to inhibit cyclooxygenase-2 (COX-2). The effect of COX-1 NSAIDs on the COX-2 enzyme is generally weaker than that of COX-2 NSAIDs [43,44].

Common COX-2 NSAIDs include celecoxib, meloxicam, etoricoxib and parecoxib. COX-2 NSAIDs work by selectively inhibiting the enzyme COX-2. By inhibiting COX-2, these medications reduce inflammation, pain, and fever without affecting the enzyme COX-1. This selective inhibition helps to minimize the risk of gastrointestinal side effects commonly associated with non-selective NSAIDs [43,44].

It is important to differentiate between multiple nonspecific NSAIDs hypersensitivities and single NSAIDs hypersensitivities, as the management of each syndrome varies significantly. Immediate-type NSAID hypersensitivity can manifest in four clinical phenotypes: NSAID-Exacerbated Respiratory Disease (NERD), NSAID-Exacerbated Cutaneous Disease (NECD), NSAID-Induced Urticaria/Angioedema (NIUA), or Single-NSAID-Induced Urticaria/Angioedema and Anaphylaxis (SNIUAA). These reactions are categorized into predictable type A and unpredictable type B reactions. Type A reactions are more common and are due to the drug's pharmacological properties, while type B reactions are independent of the dose and properties of the drug. Examples of type A reactions to NSAIDs include gastritis, while type B reactions include various conditions such as respiratory disease, cutaneous disease, and anaphylaxis. There are various mechanisms through which

NSAIDs can trigger hypersensitivity reactions, resulting in similar symptoms that can make it challenging to pinpoint the exact cause in a specific patient [43,44].

7.2. Does your patient have an allergy to NSAIDs?

Hypersensitivity reactions to NSAIDs are often observed; however, diagnosing and accurately classifying them can be challenging. A comprehensive diagnostic algorithm is necessary to categorize the various clinical manifestations of NSAID hypersensitivity reactions. This will help determine the most effective treatment plan and prognosis for each patient and identify safe alternative medications. The diagnostic algorithm should include a detailed clinical history, physical examination, and specific provocation tests [45].

Patients experiencing a reaction to an NSAID should be counseled to avoid using any NSAIDs until more information is available regarding potential cross-reactivity. The European Academy of Allergy and Clinical Immunology (EAACI) position paper states that standard allergological diagnostic procedures are unsuitable for NSAID hypersensitivity. The diagnostic value of cutaneous tests for NSAIDs is not clearly defined. Skin tests are not recommended, and, for example, specific IgE and basophil activation tests are not reliable for this condition. Serum tryptase levels are also not associated with NSAID hypersensitivity. Some NSAID reactors have elevated levels of prostaglandin D2 and leukotriene E4, which may help identify individuals at risk. Still, these levels cannot be used for a definitive diagnosis [45,46,47,48].

The gold standard for testing NSAID allergy is the drug provocation test (DPT). This test serves two purposes: confirming a diagnosis and finding a safe alternative to NSAIDs. ASA is a potent COX-1 inhibitor and is often used to test for general NSAID hypersensitivity based on the patient's history and potential risks. It is advisable to effectively manage asthma prior to undergoing any drug challenge. Contraindications for the DPT include severe asthma, active urticaria/angioedema, pregnancy, recent infection, or vaccination. Relative contraindications encompass the use of beta-blockers or ACE inhibitors. To ensure accurate results, histamine and leukotriene antagonists should be discontinued three days before the challenge, while asthma inhalers should be continued for safety. Utilizing a standardized scoring system and a double-blind, placebo-controlled format can improve the reliability of the drug challenge. These challenges must be monitored by experienced specialists because DPTs can potentially trigger severe allergic reactions that require immediate medical intervention. Therefore, it is important to oversee these tests and ensure quick access to emergency medical services in case of any adverse reactions [48,49].

Beta-blockers and ACE inhibitors can potentially mask or exacerbate symptoms of an allergic reaction to NSAIDs during a provocation challenge. Beta-blockers interfere with the body's normal

response to an allergic reaction, making it harder to detect the signs and symptoms. Similarly, ACE inhibitors can affect the body's response to an allergic reaction and may increase the risk of severe reactions during a provocation challenge. Therefore, these medications are considered relative contraindications for testing NSAID allergies via provocation challenge, as they can complicate the interpretation of results and increase the risk of adverse reactions [49].

Patients with a history of multiple NSAID reactions and/or allergic responses such as urticaria, angioedema, or chronic respiratory diseases are likely to experience multiple NSAID hypersensitivities. In such cases, challenges with ASA can lead to severe symptoms or even life-threatening asthma exacerbations. It is recommended to perform a challenge with an alternative medication, such as a specific COX-2 inhibitor, in these patients [48,49].

Patients who experience isolated urticaria after NSAID ingestion without a clear history are particularly challenging to diagnose. An ASA challenge can help differentiate between NIUA and SNIUAA. If the history is unclear, the primary goal is to establish a causal link between NSAID ingestion and the reaction. Depending on the severity of the reaction, a challenge with the culprit drug may be conducted first. A negative result would exclude any NSAID hypersensitivity, while a positive result may prompt further testing with ASA to determine single or multiple NSAID hypersensitivities. In cases where SNIUAA is suspected, challenging the patient with the suspected drug may be risky. Instead, it is recommended to conduct a challenge with ASA to rule out potential multiple NSAID hypersensitivity syndrome. If the patient tolerates ASA well, they can avoid the culprit NSAID and safely use other classes of NSAIDs [48,51,52].

Table 5. NSAID Hypersensitivity Syndromes [46,47,48]

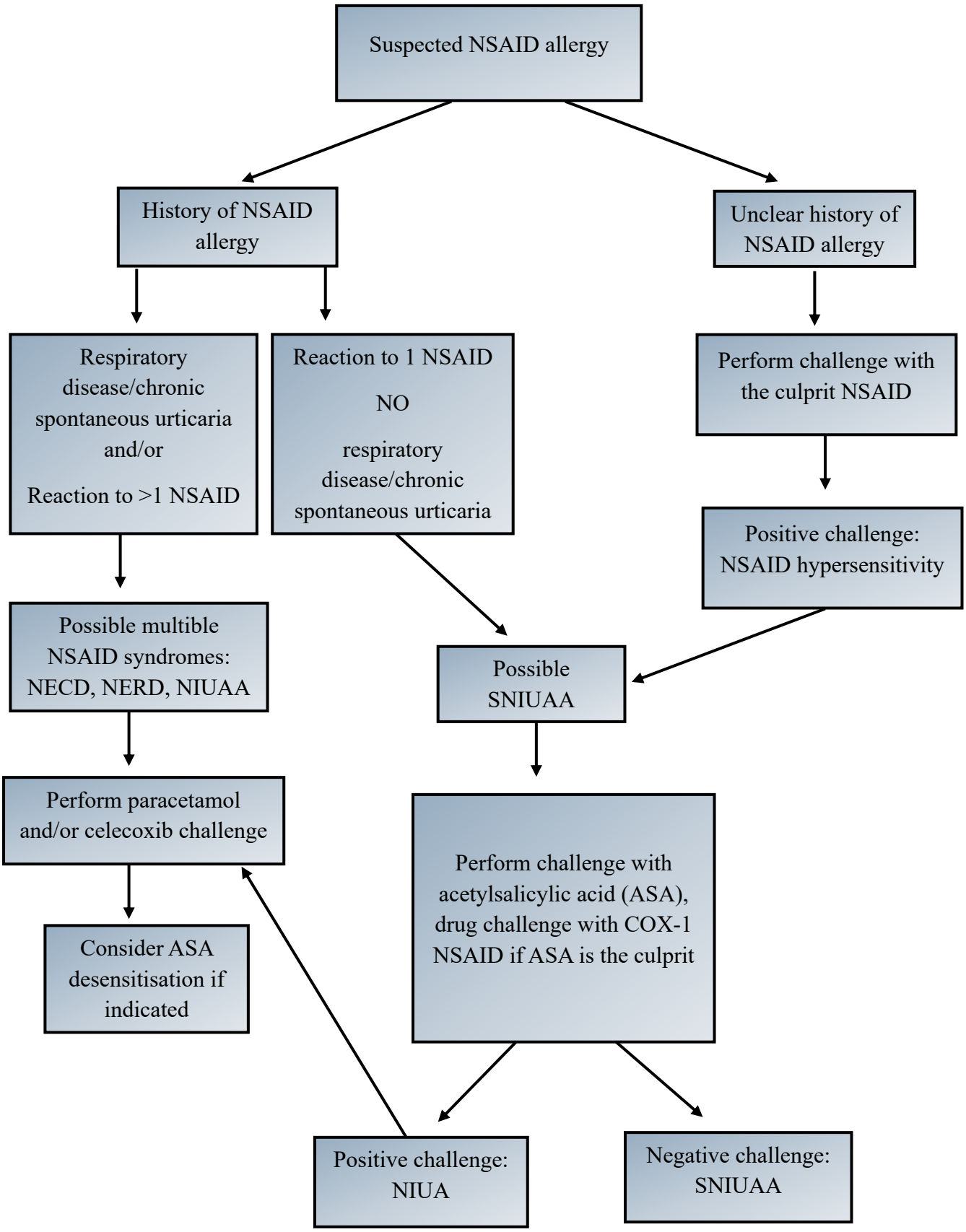
SYNDROMES	NIUA	NECD	NERD	SNIUAA
Onset of reaction:	< 24h	< 24h	< 24h	< 2h
Reactions to multiple NSAIDs	Yes	Yes	Yes	No
Symptoms	Urticaria and/or angioedema	Urticaria and/or angioedema	Nasal congestion, rhinorrhoea, bronchospasm	Anaphylaxis, also only urticaria possible
Underlying disease	No or 60% of cases have atopic disease	Chronic spontaneous urticaria and/or angioedema	Asthma with polyposis nasi, and/or chronic sinusitis	No
Risk of reaction to COX-2 inhibitor	6-25%	17%	0-9%	No
Risk of reaction to paracetamol	13%	44%	33%	No

Abbreviations: NIUA= NSAID-Induced Urticaria/Angioedema, NECD= NSAID-Exacerbated Cutaneous Disease, NERD= NSAID-Exacerbated Respiratory Disease, SNIUAA= Single-NSAID-Induced Urticaria/Angioedema and Anaphylaxis, NSAIDs=Non-Steroidal Anti-Inflammatory Drugs, COX-2=Cyclooxygenase 2

7.4. Summary

NSAIDs block the enzymes COX-1 and COX-2, reducing inflammation, pain, and fever by inhibiting prostaglandin production. There are two types of NSAIDs: COX-1 inhibitors, which may cause gastrointestinal side effects, and COX-2 inhibitors, which have a reduced risk of these side effects due to their selectivity. NSAID hypersensitivity reactions can manifest in various clinical syndromes, and it is essential to differentiate between multiple nonspecific NSAID hypersensitivities and single NSAID hypersensitivities. Skin tests and specific IgE tests are not reliable for diagnosing NSAID hypersensitivity, and a provocation challenge is often used to confirm a diagnosis or find a safe alternative medication. In cases where single NSAID-induced urticaria and angioedema are suspected, a challenge with ASA may help differentiate between single and multiple NSAID hypersensitivity. Properly diagnosing and managing NSAID hypersensitivity requires careful evaluation and testing by skilled allergists [46,48].

Figure 11. Algorithm for Diagnosing NSAIDs Allergy [46,47,48]



8. CLINICAL CASES

8.1. Case 1. NSAIDs Allergy

A 56-year-old man was referred to the allergy outpatient clinic due to an adverse reaction to diclofenac. He had been prescribed diclofenac 50 mg three times daily for bruised ribs from a cycling accident. On the third day of use, he developed rapidly progressive urticaria, abdominal cramps, and heavy sweating 30 minutes after ingestion. Although he did not have respiratory symptoms, he exhibited hypotension upon arrival at the emergency department. It is important to note that he had previously tolerated ibuprofen, diclofenac, and acetaminophen without issues; however, this reaction was severe and immediate [48].

The patient's presentation of generalized urticaria accompanied by hypotension following the ingestion of diclofenac aligns with the diagnostic criteria for severe anaphylaxis. In the absence of respiratory symptoms and chronic spontaneous urticaria, a specific diclofenac allergy, SNIUAA, is hypothesized. A challenge test with diclofenac is unnecessary for diagnostic purposes. It is advisable to avoid conducting a challenge test when there is uncertainty about the patient's history, as this may pose a risk of triggering a severe allergic reaction [48].

In this patient, a challenge test with ASA is recommended to determine whether alternative NSAIDs can be tolerated. This approach will help identify safe pain management options for the patient in the future [48].

8.2. Case 2. Beta-Lactam Allergy

A 39-year-old man with a history of cerebrospinal fistula of the ethmoidal bone following trauma was admitted to the internal medicine ward for Streptococcus pneumoniae meningitis. After 48 hours of treatment with ceftriaxone, the patient showed improvement with no fever and reduced inflammation markers. On the fourth day of treatment, he developed a skin rash with pustular lesions on his upper limbs, armpits, neck, and face. He also had a fever and increased inflammatory markers. This was determined to be a reaction to ceftriaxone, so the antibiotic was stopped and switched to vancomycin. The patient was started on topical therapy with betamethasone and zinc oxide after consultation with a specialist [21].

The skin lesions worsened, leading to a diagnostic hypothesis of AGEP. A skin biopsy was conducted, and treatment with oral corticosteroids was initiated. The skin biopsy revealed a spongiotic epidermis with the presence of neutrophils, edema, and inflammatory cells in the papillary dermis, consistent with subcorneal pustular dermatosis. The patient's diagnosis of an AGEP was confirmed [21].

9. MANAGEMENT

The most effective approach to managing drug allergies is to avoid or stop taking the offending drug. Alternative medications with different chemical structures should be used instead. When selecting alternatives, it is important to consider cross-reactivity among drugs. In cases where a specific drug is medically necessary, suitable alternatives are unavailable, and the patient has a history of IgE-mediated reactions, temporary drug tolerance induction (drug desensitization) may be an option. Treatment for DHRs is mainly supportive and symptomatic. Topical corticosteroids and oral antihistamines can help alleviate skin symptoms. In cases of anaphylaxis, epinephrine is the preferred treatment, administered via an intramuscular injection in the thigh and intravenously in more severe reactions. Systemic corticosteroids and immunomodulators may be used to treat severe systemic reactions but should never replace, or precede, epinephrine in cases of anaphylaxis. Severe reactions like SJS/TEN and DRESS are best managed in intensive care or burn unit settings [10,16,38,43].

10. DISCUSSION

Despite advancements in our understanding of drug hypersensitivity, several key challenges remain in the diagnosis and classification of allergic cutaneous reactions, particularly those caused by beta-lactams and NSAIDs.

1. Overdiagnosis vs. Underdiagnosis: A Persistent Dilemma

One of the most significant controversies in the field is the overdiagnosis of beta-lactam allergies, particularly penicillin, based solely on patient history. Studies consistently show that over 90% of patients with a penicillin allergy label test negative during formal allergy testing. This results in the unnecessary use of broad-spectrum antibiotics, leading to increased healthcare costs and antibiotic resistance. Conversely, underdiagnosis of SCARs such as DRESS or SJS/TEN remains a risk due to nonspecific early symptoms and lack of awareness among primary care physicians.

More studies are needed to validate point-of-care risk stratification tools and develop low-cost allergy testing protocols suitable for primary care.

2. Diagnostic Algorithms: Inconsistent Implementation

While diagnostic flowcharts exist for beta-lactam and NSAID hypersensitivities, they are not uniformly applied or validated across clinical settings. For NSAID hypersensitivity, relying on clinical history without reliable in vitro or skin tests complicates the classification of syndromes like NERD, NECD, or SNIUAA. The gold-standard drug provocation test is time-consuming, potentially risky, and resource-intensive, limiting its use in general practice.

There is a controversy in medical literature: should we adopt simplified oral challenges as routine tools in primary care, or reserve them for specialist units?

3. Lack of Biomarkers and Standardization

No universal biomarker or laboratory test can definitively confirm most drug-induced cutaneous reactions, especially in delayed hypersensitivity. The sensitivity and specificity of skin prick, patch, or intradermal tests vary widely between drugs and populations. Moreover, interpretation often relies on clinical experience rather than quantifiable metrics.

A research priority is developing validated, standardized diagnostic kits with higher predictive value.

4. Genetic and Immunologic Predictors: Promise but Inaccessibility

Pharmacogenetic screening, such as HLA allele typing, has shown promise in predicting severe reactions (e.g., HLA-B*1502 for carbamazepine-induced SJS/TEN), but these tests are not yet routine. Their availability, cost, and integration into clinical practice remain limited outside specialized centers.

Large-scale, ethnically diverse genomic studies are needed to build robust predictive models for drug reactions.

5. Patient Factors and Reporting Bias

The reliance on patient-reported symptoms and retrospective diagnosis introduces recall bias, especially for reactions that occurred years prior. Furthermore, clinical studies often exclude pediatric, elderly, or multi-morbid patients, limiting generalizability.

Recommendation: Design real-world, prospective registries and encourage more structured patient education and documentation tools (e.g., allergy passports).

11. CONCLUSIONS

Investigations into drug-induced skin reactions are essential in cases where the reaction has been severe, the drug is crucial for the patient's treatment, or multiple suspected allergies have complicated treatment. An outpatient exposure protocol has recently been developed for milder suspected allergies, particularly for common antibiotics like penicillin. Patients who have had severe immediate and delayed skin hypersensitivity reactions are advised to avoid drugs that may potentially cross-react.

NSAIDs and beta-lactam allergies are common. These allergies can lead to various negative outcomes, such as the use of less effective alternative antibiotics, prolonged hospital stays, higher

rates of antibiotic-resistant infections, and increased medical expenses. Interestingly, among patients who claim to have a penicillin allergy, as many as 98% test negative and can safely receive this antibiotic. Many patients who claim to have a penicillin allergy can tolerate the medication without any problems. Unfortunately, there is often a lack of questioning or reassessment of documented penicillin allergies in the healthcare field.

Primary healthcare physicians should courageously reevaluate a patient's reported drug allergy. It is important to discuss with the patient the significance of investigating this issue. If there are valid reasons to remove the penicillin allergy label, they should be clearly explained to the patient. It is recommended to consider direct exposure to amoxicillin for appropriate candidates, as this can assist in making future antibiotic choices.

Drug allergies are a common issue in clinical practice, and patients should be assessed by an allergist for proper diagnosis and management. Diagnosis can be challenging but should involve a thorough history and physical examination, along with possible skin and/or laboratory tests and graded challenges. Direct oral challenges may be appropriate to rule out or confirm allergies.

Treatment for drug allergies usually involves avoiding the offending drug and using alternative medications with different chemical structures when possible. When selecting alternatives, it is important to consider cross-reactivity among drugs. In cases where the allergic drug is necessary and no suitable alternative is available, induction of drug tolerance procedures may be an option.

REFERENCES:

[1] Kommu, S., Carter, C., & Whitfield, P. Adverse Drug Reactions. StatPearls publishing. 2024, Jan 10. Available from https://www.ncbi.nlm.nih.gov/books/NBK599521/

[2] Doña, I., Caubet, J. C., Brockow, K., Doyle, M., Moreno, E., Terreehorst, I., & Torres, M. J. (2018). An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity. Clinical and Translational Allergy, 8, 16. https://doi.org/10.1186/s13601-018-0206-8

[3] Doña, I., Torres, M. J., Celik, G., Phillips, E., Tanno, L. K., & Castells, M. (2023). Changing patterns in the epidemiology of drug allergy. Allergy, 79(3), 613-628. https://doi.org/10.1111/all.15970

[4] Jeimy, S., Wong, T., Ben-Shoshan, M., Copaescu, A. M., Isabwe, G. A. C., & Ellis, A. K. (2024). Drug allergy. Allergy, Asthma & Clinical Immunology, 20(78). https://doi.org/10.1186/s13223-024-00936-1

[5] Brockow K, Wurpts G, Trautmann A, Pfützner W, Treudler R, Bircher AJ, Brehler R, Buhl T, Dickel H, Fuchs T, et al. Guideline for allergological diagnosis of drug hypersensitivity reactions: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI) in cooperation with multiple professional societies. Allergol Select. 2023 Aug 9;7:122–139. doi: 10.5414/ALX02422E. Available from: https://doi.org/10.5414/ALX02422E

[6] Hausmann OV, Schnyder B, Pichler WJ. Etiology and Pathogenesis of Adverse Drug Reactions. Progress in Allergy. 2012 May; 97:32-46. DOI: 10.1159/000335614.

[7] Montané E, Castells X. Epidemiology of drug-related deaths in European hospitals: A systematic review and meta-analysis of observational studies. Brit Jnl Clinical Pharma. 2021;87(10):3659–3671. https://doi.org/10.1111/bcp.14799

[8] Pallardy, M., Bechara, R., Whritenour, J., Mitchell-Ryan, S., Herzyk, D., Lebrec, H., Merk, H., Gourley, I., Komocsar, W. J., Piccotti, J. R., Balazs, M., Sharma, A., Walker, D.B., Weinstock, D. (2024). Drug hypersensitivity reactions: review of the state of the science for prediction and diagnosis. Toxicological Sciences, 200(1), 11–30. https://doi.org/10.1093/toxsci/kfae046

[9] Brockow, K., Ardern-Jones, M. R., Mockenhaupt, M., Aberer, W., Barbaud, A., Caubet, J. C., Spiewak, R., Torres, M. J., & Mortz, C. G. (2018). EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. Allergy, 73(8), 1599-1614. https://doi.org/10.1111/all.13562

[10] Liippo, J. Hypersensitivity to drugs. EBM Guidelines. 2021 Oct 5. https://www.ebm-guidelines.com/apps/dtk/ebmg/article/ebm00296

[11] Kanani A, Betschel SD, Warrington R. Urticaria and angioedema. Allergy Asthma Clin Immunol. 2018;14(Suppl 2):59. https://doi.org/10.1186/s13223-018-0288-z

[12] Crisafulli, G., Franceschini, F., Caimmi, S., Bottau, P., Liotti, L., Saretta, F., Bernardini, R., Cardinale, F., Mori, F., & Caffarelli, C. (2019). Mild cutaneous reactions to drugs. Acta Biomedica, 90(Suppl 3), 36–43. doi: 10.23750/abm.v90i3-S.8159

[13] Raikar SR, G S, Sneha S, et al. (July 13, 2024) Drug-Induced Angioedema Without Urticaria: A Case Report. Cureus 16(7): e64452. doi:10.7759/cureus.64452

[14] Muraro, A., Lemanske Jr., R. F., Castells, M., Torres, M. J., Khan, D., Simon, H.-U., Bindslev-Jensen, C., Burks, W., Poulsen, L. K., Sampson, H. A., Worm, M., & Nadeau, K. C. (2017). Precision medicine in allergic disease—food allergy, drug allergy, and anaphylaxis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology. Allergy, 72(7), 1006-1021. https://doi.org/10.1111/all.13132

[15] Cardona et al. World Allergy Organization Journal (2020) 13:100472 World Allergy Organization Anaphylaxis Guidance 2020. 2020 Oct 30. http://doi.org/10.1016/j.waojou.2020.100472

[16] Mandelin, J., Alakoskela, J-M. Lääkkeiden aiheuttamat ihoreaktiot. Lääkärilehti. HUS-tulehduskeskus, Iho- ja allergiasairaala. 2022 March 2. Suom Lääkäril 2022;77:e30749, www.laakarilehti.fi/e30749 https://www.laakarilehti.fi/tieteessa/katsausartikkeli/laakkeiden-aiheuttamat-ihoreaktiot/

[17] Wong J, Sandoval A, Jean T, Gharib Naderi A. A case of delayed maculopapular eruption to ibuprofen and acute urticaria to acetaminophen. SAGE Open Med Case Rep. 2021 Oct 28;9:2050313X211056409. doi: 10.1177/2050313X211056409. PMID: 34733518

[18] Miranda OL, Martins J, Almeida A, Formigo M, Pereira O, Rocha M, et al. Symmetrical Drug-related Intertriginous and Flexural Exanthema (Baboon Syndrome). Eur J Case Rep Intern Med. 2021 Dec 2;8(12):003029. doi: 10.12890/2021_003029

[19] Shaker G, Mehendale T, De La Rosa C. Fixed Drug Eruption: An Underrecognized Cutaneous Manifestation of a Drug Reaction in the Primary Care Setting. Cureus. 2022 Aug 23;14(8):e28299. doi: 10.7759/cureus.28299. PMCID: PMC9397151. PMID: 36034061

[20] Castro CF, Teixeira CA, Fernandes NC, et al. Severe cutaneous adverse reactions to drugs: a case series study. Rev Bras Farm Hosp Serv Saude. 2020;11(3):0471. DOI: 10.30968/rbfhss.2020.113.0471

[21] Santos MI, Sousa M, Cerqueira P, Ambrioso I, Moniz Ramos M. A case of acute generalized exanthematous pustulosis induced by ceftriaxone. Cureus. 2023 Mar 17;15(3):e36281. doi: 10.7759/cureus.36281

[22] Calle AM, Aguirre N, Ardila JC, Cardona Villa R. DRESS syndrome: A literature review and treatment algorithm. World Allergy Organ J. 2023 Mar;16(3):100673.

[23] Sasi S, Altarawneh H, Petkar MA, Nair AP. Drug reaction with eosinophilia and systemic symptoms secondary to naproxen: a case report and literature review. Case Rep Acute Med. 2020;3(2):63-72. doi:10.1159/000509712

[24] Frantz R, Huang S, Are A, Motaparthi K. Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: A Review of Diagnosis and Management. Medicina. 2021;57(9):895. doi:10.3390/medicina57090895

[25] Shah H, Parisi R, Mukherjee E, Phillips EJ, Dodiuk-Gad RP. Update on Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: Diagnosis and Management. Am J Clin Dermatol. 2024;25:891-908. doi: 10.1007/s40257-024-00889-6

[26] Weiqiang Fei, Jun Shen & Hui Cai (2023) Causes of Drug-Induced Severe Cutaneous Adverse Reaction Epidermal Necrolysis (EN): An Analysis Using FDA Adverse Event Reporting System (FAERS) Database, Clinical, Cosmetic and Investigational Dermatology, 2023 Aug 16. 2249-2257, DOI: 10.2147/CCID.S422928

[27] Newkirk RE, Fomin DA, Braden MM. Erythema Multiforme Versus Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis: Subtle Difference in Presentation, Major Difference in Management. Military Medicine. 2020;185(9-10):e1713-e1717. doi:10.1093/milmed/usaa029

[28] Rodríguez-Pérez, R., de las Vecillas, L., Cabañas, R., & Bellón, T. (2023). Tools for Etiologic Diagnosis of Drug-Induced Allergic Conditions. International Journal of Molecular Sciences, 24(16), 12577. https://doi.org/10.3390/ijms241612577

[29] Um, S. H., Abuzgaia, A., & Rieder, M. (2023). Comparison of the Liverpool Causality Assessment Tool vs. the Naranjo Scale for predicting the likelihood of an adverse drug reaction: A retrospective cohort study. Basic & Clinical Pharmacology & Toxicology. https://doi.org/10.1111/bcp.15704

[30] Barbaud A, Castagna J, Soria A. Skin tests in the work-up of cutaneous adverse drug reactions: A review and update. Contact Dermatitis. 2022 May;86(5):344-356. doi: 10.1111/cod.14063. Epub 2022 Mar 9. PMID: 35122269

[31] Mockenhaupt M. Bullous Drug Reactions. Acta Dermato-Venereology. 2020 Febr 6. doi:10.2340/00015555-3408.

[32] Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. Lancet. 2019 Jan 12;393(10167):183-198. doi: 10.1016/S0140-6736(18)32218-9

[33] Jeimy S, Ben-Shoshan M, Abrams EM, Ellis AK, Connors L, Wong T. Practical guide for evaluation and management of beta-lactam allergy: position statement from the Canadian Society of Allergy and Clinical Immunology. Allergy Asthma Clin Immunol. 2020;16:95. https://doi.org/10.1186/s13223-020-00494-2.

[34] Sirkeoja, S., Huttunen, R., Korhonen, L., Syrjänen, J. Onko potilaallasi penisilliiniallergia? Lääkärilehti. 2020 Feb 28. https://www.laakarilehti.fi/tieteessa/katsausartikkeli/onko-potilaallasi-penisilliiniallergia

[35] Felix, M.M.R., Aun, M.V., de Menezes, U.P., de Queiroz, G.R.S., Rodrigues, A.T., D'Onofrio-Silva, A.C., Perelló, M.I., Camelo-Nunes, I.C., & Malaman, M.F. (2021). Allergy to penicillin and betalactam antibiotics. Einstein (Sao Paulo), 19, eMD5703. https://doi.org/10.31744/einstein_journal/2021MD5703

[36] Romano, A., Atanaskovic-Markovic, M., Barbaud, A., Bircher, A. J., Brockow, K., Caubet, J. C., Celik, G., Cernadas, J., Chiriac, A. M., ... and the European Academy of Allergy and Clinical Immunology Drug Allergy Interest Group (2019). Towards a more precise diagnosis of hypersensitivity to beta-lactams — an EAACI position paper. Allergy, 218. https://doi.org/10.1111/all.14122

[38] Broyles, A. D., Banerji, A., & Castells, M. (Eds.). Practical Guidance for the Evaluation and Management of Drug Hypersensitivity: Specific Drugs. pp. 16-24, 78. J Allergy Clin Immunol Pract, 8(9S), October 2020. https://doi.org/10.1016/j.jaip.2020.08.006

[39] Iuliano S, Senn L, Moi L, Muller YD, Ribi C, Buss G, & Comte D. (2022). Management of Beta-Lactam Antibiotics Allergy: A Real-Life Study. Frontiers in Allergy, 3:853587. 2022 Apr 8. https://doi.org/10.3389/falgy.2022.853587

[40] Stingeni L, Bianchi L, Tramontana M, Pigatto PD, Patruno C, Corazza M, Foti C, Fabbrocini G, Micali G, Romita P, Napolitano M, Hansel K. Skin tests in the diagnosis of adverse drug reactions: a

systematic review. Giornale Italiano di Dermatologia e Venereologia. 2020 Sep 17. DOI: 10.23736/S0392-0488.20.06698-5

[41] Wurpts, G., Aberer, W., Dickel, H., et al. Guideline on diagnostic procedures for suspected hypersensitivity to beta-lactam antibiotics. Allergologie select, 4, 11-43. 2020 May 28. DOI: 10.5414/ALX02104E

[42] Molina-Molina, G.-J., Velandia, D. R. G., Andrés-López, B., Perales, C., Marin-Asensio, L., Jurgens, Y., Esteso, O., Escobar, C., Vidal, X., Vendrell, L., Gómez-Ganda, L., Agustí, D. R., Montané, E., Cardona, V. (2024). Delabelling beta-lactam allergy. Frontiers in Pharmacology. June 2024 Jun 27. DOI: 10.3389/fphar.2024.1423719

[43] Blanca-Lopez, N., Soriano, V., Garcia-Martin, E., Canto, G., & Blanca, M. (2019). NSAID-induced reactions: classification, prevalence, impact, and management strategies. Journal of Asthma and Allergy, 217-233. DOI: 10.2147/JAA.S164806. https://doi.org/10.2147/JAA.S164806

[44] David A. Khan, David B. K. Golden, Marcus Shaker, MSc, and David R. Stukus. Drug allergy: A 2022 practice parameter update. American Academy of Allergy, Asthma & Immunology. Elsevier Inc. https://doi.org/10.1016/j.jaci.2022.08.028

[45] Brockow, N., Wurpts, G., & Trautmann, A. (2022). Patients with questionable penicillin (beta-lactam) allergy: Causes and solutions. Allergologie select, 6, 33-41. 2022 Feb 1. DOI: 10.5414/ALX02310E.

[46] Doña, I., Pérez-Sánchez, N., Eguiluz-Gracia, I., Muñoz-Cano, R., Bartra, J., & Cornejo-García, J. A. (2019). Progress in understanding hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. Wiley, European Academy of Allergy, Asthma and Clinical Immunology. 2019 Aug 27. doi:10.1111/all.14032.

[47] Doña, I., Sáenz de Santa María, R., Moreno, E. M., Bartra, J., & Torres, M. J. (2024). An algorithm for the diagnosis and treatment of nonsteroidal anti-inflammatory drugs hypersensitivity, 2024 update. Allergy, 1-15. https://doi.org/10.1111/all.16349

[48] Hermans MAW, Otten R, Karim AF, van Maaren MS. Nonsteroidal anti-inflammatory drug hypersensitivity: not always an allergy! Neth J Med. 2018;76(2):52-59

[49] Barbaud, A., Arcolaci, A., Chiriac, A. M., Brockow, K., Garvey, L. H., Torres, M., Laguna, J. J., Bonadonna, P., Hofmeier, K. S., Cernadas, J., Caubet, J. C. EAACI/ENDA position paper on drug provocation testing. European Journal of Allergy and Clinical Immunology. 2023 Dec 13. DOI: 10.1111/all.15996

[50] Yeung, W. Y. W., & Park, H. S. (2019). Update on the Management of Nonsteroidal Anti-Inflammatory Drug Hypersensitivity. Yonsei Medical Journal, 61(1), 4–14. https://doi.org/10.3349/ymj.2020.61.1.4

[51] Trinh HKT, Pham LD, Le KM and Park H-S (2021) Pharmacogenomics of Hypersensitivity to Non-steroidal Anti-inflammatory Drugs. Front. Genet. 12:647257. 2021 June 25. doi: 10.3389/fgene.2021.647257

[52] Sonsupap C, Pokhakul P, Kariya T, Suzuki Y, Hamajima N, Yamamoto E. Characteristics of adverse drug reactions due to nonsteroidal anti-inflammatory drugs: a cross-sectional study. Nagoya J Med Sci. 2023;85:668-681. doi:10.18999/nagjms.85.4.668

[53] Faraji, N., Goli, R., Mohsennezhad, P., Mohammadpour, Y., Parizad, N., Salamat, E., Pourbahram, R., & Bazbandi, S. NSAID (nonsteroidal anti-inflammatory drugs) Induced Stevens Johnson Syndrome in a 50-year-old woman: A case study. Toxicology Reports, 11, 1001-1005. 2020 Feb 28. https://doi.org/10.1016/j.toxrep.2024.02.006