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ISSN: 2167-1052
Advances in Pharmacoepidemiology and Drug Safety

Opinion Article

# Mechanisms, Diagnosis, and Management of Non-IgE-Mediated Immediate Drug-Induced Hypersensitivity Reactions

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## DESCRIPTION

Non-IgE-mediated immediate Drug-Induced Hypersensitivity Reactions (DIHRs) are a complex and clinically significant group of adverse reactions that occur rapidly after drug administration, yet do not involve Immunoglobulin E (IgE) antibodies. Unlike IgE-mediated reactions, which are driven by allergen-specific antibodies and involve sensitization upon initial exposure followed by a rapid response upon re-exposure, non-IgE-mediated immediate reactions follow alternative immunological pathways. These reactions can present similarly to IgE-mediated responses, such as anaphylaxis, making their identification and management critical for patient safety.

One of the primary mechanisms through which non-IgE-mediated immediate DIHRs occur is direct mast cell activation. Certain medications can directly stimulate mast cells and basophils, leading to the release of histamine and other inflammatory mediators. This pathway does not require prior sensitization, meaning the reaction can occur upon first exposure to the drug. Opioids, for instance, are well-known for their ability to induce histamine release from mast cells, causing symptoms such as urticaria, angioedema, and even anaphylaxis-like presentations. Vancomycin, an antibiotic, can cause the "Red Man Syndrome," characterized by widespread flushing, pruritus, and hypotension, due to non-IgE-mediated histamine release.

Another pathway involves the activation of the complement system. Some drugs can trigger this system, leading to the production of anaphylatoxins such as C3a and C5a, which can induce mast cell degranulation. Radiocontrast agents used in imaging studies are common culprits.

These agents can cause severe reactions, including urticaria, angioedema, bronchospasm, and cardiovascular collapse, through complement activation. Unlike IgE-mediated anaphylaxis, these reactions are not dependent on prior exposure and sensitization, which makes them unpredictable and particularly hazardous.

Bradykinin pathway activation is yet another mechanism implicated in non-IgE-mediated immediate DIHRs. Bradykinin is a potent vasodilator, and its increased levels can lead to angioedema. Angiotensin-Converting Enzyme (ACE) inhibitors, commonly used to treat hypertension and heart failure, can elevate bradykinin levels by inhibiting its degradation. This can result in potentially life-threatening angioedema, typically involving the face, lips, tongue, and throat, leading to respiratory distress.

Clinically, non-IgE-mediated immediate DIHRs can present with a range of symptoms that overlap with those seen in IgE-mediated reactions. These include urticaria (hives), angioedema (swelling, often involving the face, lips, and throat), bronchospasm (constriction of the airways), gastrointestinal symptoms (such as nausea and vomiting), and cardiovascular symptoms (such as hypotension and shock). The similarity in clinical presentation can make it challenging to distinguish between IgE-mediated and non-IgE-mediated reactions based solely on symptoms.

Diagnosing non-IgE-mediated immediate DIHRs involves a combination of clinical evaluation and, where appropriate, diagnostic testing. A detailed patient history is essential to identify the temporal relationship between drug administration and symptom onset. Unlike IgE-mediated reactions, skin testing is typically less useful for non-IgE-mediated reactions because these do not involve specific allergen-antibody interactions. However, laboratory tests can sometimes aid in diagnosis. Elevated levels of histamine or tryptase shortly after the onset of symptoms can support a diagnosis of mast cell activation. Measuring complement levels, specifically C3a, C4a, and C5a, can help identify complement activation. Drug challenge tests, which involve the controlled re-administration of the suspected drug under medical supervision, can sometimes be used to confirm the diagnosis, but these tests carry significant risks and must be conducted with extreme caution.

Management of non-IgE-mediated immediate DIHRs focuses on both acute treatment and prevention of future reactions. Acute

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**Received:** 03-Jun-2024, Manuscript No. PDS-24-26450; **Editor assigned:** 06-Jun-2024, PreQC No. PDS-24-26450 (PQ); **Reviewed:** 20-Jun-2024, QC No. PDS-24-26450; **Revised:** 27-Jun-2024, Manuscript No. PDS-24-26450 (R); **Published:** 04-Jul-2024, DOI: 10.35250/2167-1052.24.13.359

**Citation:** Liu P (2024) Mechanisms, Diagnosis, and Management of Non-IgE-Mediated Immediate Drug-Induced Hypersensitivity Reactions. Adv Pharmacoepidemiol Drug Saf.13:359.

management mirrors that of IgE-mediated reactions in many respects. Epinephrine is the cornerstone of treatment for severe reactions, particularly those with anaphylaxis-like symptoms. It acts rapidly to reverse airway constriction, hypotension, and other severe symptoms. Antihistamines can help alleviate symptoms caused by histamine release, such as urticaria and pruritus, while corticosteroids may be used to reduce inflammation and prevent late-phase reactions. For patients experiencing hypotension and shock, intravenous fluids and vasopressors may be necessary to stabilize blood pressure.

Preventing future reactions involves several strategies. Avoidance of the offending drug is paramount. In cases where the drug is essential, premedication protocols may be employed. These protocols often include the use of antihistamines and corticosteroids administered prior to the drug to mitigate potential reactions. For some drugs, especially those for which alternatives are not available or are less effective, desensitization protocols can be considered. Desensitization involves the gradual administration of increasing doses of the drug, aiming to induce a temporary state of tolerance. This process is complex and must be carried out in a controlled medical environment due to the risk of inducing a severe reaction during the procedure. Examples of drugs commonly associated with non-IgE-mediated immediate DIHRs include opioids, vancomycin, radiocontrast media, and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Opioids can cause direct mast cell activation, leading to histamine release. Vancomycin, particularly when infused rapidly, can cause Red Man Syndrome through a similar mechanism. Radiocontrast media can activate the complement system, resulting in severe reactions. NSAIDs can provoke pseudo-allergic reactions, possibly through inhibition of cyclooxygenase enzymes, leading to an imbalance in prostaglandins and leukotrienes.

## CONCLUSION

In conclusion, non-IgE-mediated immediate drug-induced hypersensitivity reactions are a critical aspect of drug safety and patient management. Their rapid onset and potential severity necessitate prompt recognition and treatment. Understanding the underlying mechanisms, such as direct mast cell activation, complement activation, and bradykinin pathway activation, helps in differentiating these reactions from IgE-mediated responses. Clinicians must be vigilant in diagnosing these reactions through clinical evaluation and appropriate testing, and they must implement effective management strategies to treat acute reactions and prevent future occurrences. As our understanding of these reactions continues to evolve, so too will our ability to ensure safer medication use and better patient outcomes.