Review Article

Penicillin: A Comprehensive Review of its Therapeutic Profile and Adverse Drug Reactions

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Received: 11-04-2026; **Revised:** 25-06-2026; **Accepted:** 02-07-2026; **Published online:** 20-07-2026.

ABSTRACT

Penicillin remains one of the most significant discoveries in medical history, serving as a vital cornerstone for the treatment of a wide array of bacterial infections. Despite its extensive clinical success over decades, the frequent occurrence of Adverse Drug Reactions (ADRs) presents a persistent challenge for clinicians, often complicating therapeutic decisions and patient outcomes. This review provides a comprehensive evaluation of the therapeutic profile of various penicillin classes, synthesizing pharmacological insights regarding their classification and mechanism of action. By analysing clinical data, the paper explores the broad spectrum of safety concerns, ranging from common Type I hypersensitivity reactions and life-threatening anaphylaxis to less discussed non-immunological complications such as gastrointestinal distress, neutropenia, and neurotoxicity. Furthermore, the discussion emphasizes the clinical significance of the Jarisch-Herxheimer reaction and the necessity of precise allergy testing to avoid the unwarranted discontinuation of these essential antibiotics. Ultimately, this review highlights that a thorough understanding of the balance between efficacy and risk is crucial for optimized patient care. It concludes that strengthening pharmacovigilance and diagnostic protocols is essential to ensure that penicillin remains a safe and potent tool in the global fight against antimicrobial resistance.

Keywords: Adverse Drug Reactions, Beta-lactam Toxicity, Clinical Efficacy, Hypersensitivity, Penicillin, Pharmacovigilance.

INTRODUCTION

The discovery of Penicillin by Alexander Fleming in 1928 marked the commencement of the antibiotic era, unequivocally transforming the landscape of modern medicine and infectious disease management.[1] As the foundational member of the beta-lactam class, Penicillin continues to be an essential therapeutic agent due to its potent bactericidal activity and its ability to inhibit bacterial cell wall synthesis.[2] Despite the evolution of numerous synthetic alternatives, penicillin's like Amoxicillin and Piperacillin remain frontline choices for treating respiratory, skin, and systemic infections globally.

However, the clinical utility of this lifesaving drug is frequently overshadowed by the prevalence of Adverse Drug Reactions (ADRs). Research indicates that nearly 10% of patients report a penicillin allergy, although subsequent clinical assessments often reveal that many can safely tolerate the drug.[3] These reactions range from mild cutaneous eruptions to severe, life-threatening anaphylactic shock, necessitating a rigorous evaluation of the patient's pharmacological history.[4] Beyond immunological responses, non-allergic complications—including gastrointestinal disturbances, haematological toxicity, and rare neurotoxic events—pose significant risks that require careful monitoring.[5]

In the current era of antimicrobial stewardship, a precise elucidation of the risk-benefit ratio associated with penicillin therapy is imperative. Mislabelling patients with penicillin allergies often leads to the use of broader-spectrum antibiotics, which can inadvertently contribute to the rise of multi-drug resistant organisms. Therefore, this review aims to provide an updated assessment of the therapeutic profile of penicillin's while addressing the mechanisms and management of its various adverse drug reactions in contemporary clinical practice.

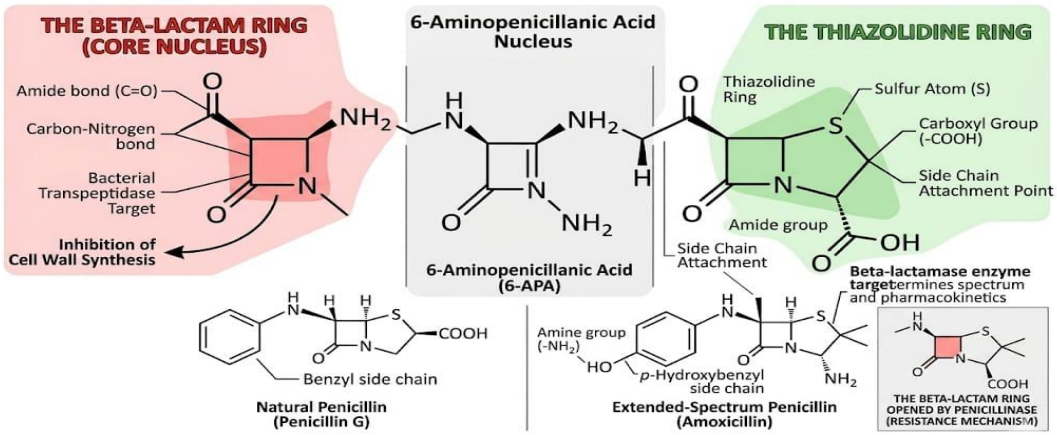

Figure 1: Basic Chemical Structure of Penicillin and Key Functional Groups.

Moreover, the constant interplay between beta-lactamases and the development of new inhibitors has necessitated a re-evaluation of penicillin's role in modern therapy.[6] In clinical settings, particularly for inpatients, the management of penicillin allergy has become a critical aspect of patient safety protocols.[7] Recent clinical updates also emphasize the importance of 'de-labelling' patients who have been incorrectly diagnosed with penicillin allergies to improve treatment outcomes.[8]

The diagram illustrates the core nucleus of penicillin, emphasizing the four-membered beta-lactam ring fused to a five-membered thiazolidine ring. The elucidation of these structural components is crucial, as the beta-lactam ring serves as the primary pharmacodynamic site for inhibiting bacterial cell wall synthesis. Furthermore, the assessment of various side chain attachments, as seen in Penicillin G and Amoxicillin, highlights their role in determining the drug's antimicrobial spectrum and resistance to beta-lactamase enzymes.

Classification of Penicillin's

The structural diversity of penicillin's allows for a broad clinical application, ranging from simple infections to complex systemic diseases. Based on their antibacterial spectrum and chemical modifications, penicillin's are primarily categorized into distinct generations. Understanding this classification is vital for an accurate assessment of their therapeutic efficacy and potential resistance patterns.[9]

Natural Penicillin's:

These are the original forms of the drug, primarily effective against Gram-positive organisms. Penicillin G (parenteral) and Penicillin V (oral) remain the commencement point for treating infections like syphilis and streptococcal pharyngitis.[10]

Penicillinase-Resistant Penicillin's (Antistaphylococcal):

Developed to combat bacteria that produce the penicillinase enzyme, these drugs—including Oxacillin, Dicloxacillin, and Nafcillin—are specifically designed to maintain their structural integrity against enzymatic degradation.[11]

Aminopenicillins:

This class, featuring Amoxicillin and Ampicillin, offers an extended spectrum of activity that unequivocally covers several Gram-negative bacteria. They are frequently utilized in paediatric and respiratory medicine due to their superior oral absorption.[12]

Antipseudomonal Penicillin's:

Advanced agents like Piperacillin and Ticarcillin are reserved for severe systemic infections. They provide an elucidation of the drug's evolution, offering high potency against Pseudomonas aeruginosa and other resilient pathogens.[13]

Beta-lactamase Inhibitor Combinations:

To overcome bacterial resistance, penicillin's are often combined with inhibitors like Clavulanic acid or Tazobactam. These combinations broaden the therapeutic reach and safeguard the beta-lactam ring from destruction .[14,15]

Table 1: Classification and Clinical Spectrum of Penicillin's

Category	Representative Drugs	Primary Spectrum
Natural Penicillins	Penicillin G, Penicillin V	Gram-positive cocci, Spirochetes
Penicillinase-Resistant	Nafcillin, Dicloxacillin	*Staphylococcus aureus* (MSSA)
Aminopenicillins	Amoxicillin, Ampicillin	Gram-positive & some Gram-negative
Antipseudomonal	Piperacillin, Ticarcillin	*Pseudomonas*, *Proteus* species
Combinations	Amoxicillin-Clavulanate	Beta-lactamase producing strains

The table provides a detailed elucidation of various penicillin categories, their representative drugs, and the primary bacterial spectrum they cover. This assessment is crucial for understanding the commencement of targeted antibiotic therapy.

Mechanism of Action

The bactericidal efficacy of penicillin's is fundamentally rooted in their ability to disrupt the structural integrity of the bacterial cell wall, a process that represents a sophisticated biochemical elucidation of drug-receptor interaction. As illustrated in Figure 2, penicillin's specifically exert their bactericidal effect by targeting the inhibition of cell wall synthesis, as highlighted in Point 1 of Figure 2. To appreciate the commencement of this antibacterial action, one must understand that the bacterial cell wall is a dynamic structure, constantly undergoing synthesis and remodelling to maintain osmotic stability against high internal pressure. Penicillin's, as members of the beta-lactam family, target this vital process with high specificity, unequivocally leading to the cessation of bacterial growth and eventual cell death.[16]

Targeted Binding to Penicillin-Binding Proteins (PBPs):

The primary molecular targets for penicillin's are a group of enzymes known as Penicillin-Binding Proteins (PBPs), located on the inner surface of the bacterial cell membrane. These enzymes, particularly transpeptidases, are responsible for the final cross-linking of the peptidoglycan layer. Penicillin's possess a structural similarity to the D-alanyl-D-alanine terminal of the nascent peptidoglycan chain. This assessment of molecular mimicry allows the drug to covalently bind to the active site of PBPs, effectively neutralizing their enzymatic activity.[17,18] Once these proteins are inhibited, the bacteria lose their ability to form a rigid and functional cell wall, leaving the organism vulnerable to environmental stressors.

Inhibition of Peptidoglycan Cross-linking:

In a healthy bacterial cell, peptidoglycan strands are cross-linked to form a mesh-like scaffold that provides mechanical

strength. By binding to PBPs, penicillin's block the formation of these cross-links. This inhibition does not immediately destroy the bacteria but prevents the commencement of new cell wall assembly during the division phase.[19] Consequently, as the bacteria attempt to grow and divide, they produce weakened, structurally deficient cell walls that cannot sustain the internal turgor pressure of the cytoplasm.

Activation of the Autolytic System:

Beyond the mere blockade of synthesis, the presence of penicillin triggers a more aggressive physiological response within the microorganism. Recent pharmacological studies provide an elucidation of how penicillin exposure leads to the deregulation of bacterial autolysins—enzymes that are normally involved in controlled cell wall remodeling.[20] Under the influence of beta-lactams, these autolytic enzymes become hyperactive, actively degrading the existing peptidoglycan scaffold from within.[21]

Osmotic Lysis and Bactericidal Conclusion:

The culmination of inhibited synthesis and accelerated degradation leads to the formation of spheroplasts or protoplasts, which are extremely fragile. Without the protection of a rigid wall, the bacteria undergo rapid osmotic rupture or lysis. This lethal outcome is most pronounced during the logarithmic phase of growth, as the drug requires active cell wall synthesis for its bactericidal effects to be fully realized.[22] This comprehensive mechanism ensures that penicillin remains a potent agent against susceptible pathogens while maintaining a high degree of safety for human cells, which lack a peptidoglycan-based cell wall

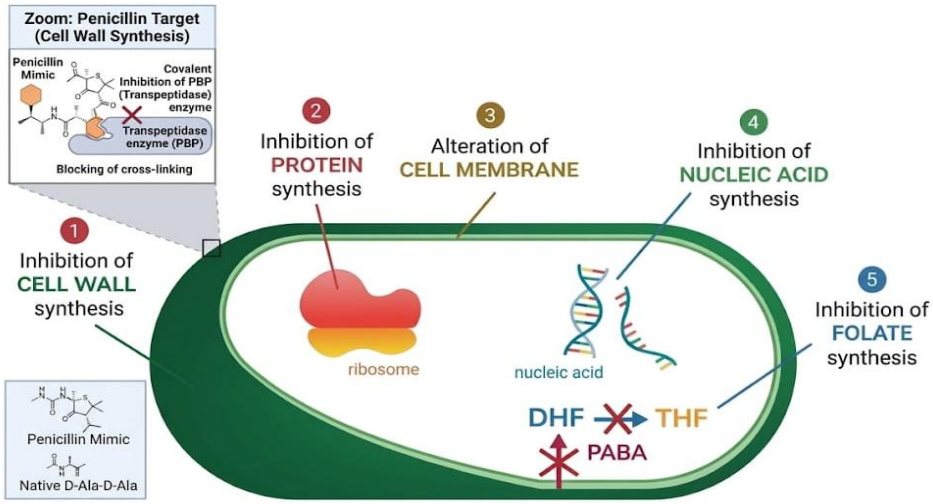

Figure 2: General Mechanism of Antibiotic Action with Primary Focus on Bacterial Cell Wall Inhibition.

The schematic representation elucidates the diverse pathways of antibiotic action, specifically highlighting the inhibition of peptidoglycan synthesis in the bacterial cell wall. It unequivocally demonstrates how penicillin mimics the D-Ala-D-Ala substrate to block transpeptidation, leading to bacterial lysis.

Therapeutic Profile

The therapeutic landscape of penicillin's represents a cornerstone of infectious disease management, following the historic commencement of the antibiotic era. An elucidation of their clinical utility reveals an expansive repertoire, effectively addressing a diverse array of bacterial pathogens. From primary care settings to intensive clinical environments, the clinical assessment of penicillin's remains vital, as they are unequivocally recognized as frontline agents for numerous life-threatening and common infections.[23]

Respiratory Tract Infections (RTIs):

Penicillin's, particularly the aminopenicillin class, are widely regarded as the gold standard for treating upper and lower respiratory tract infections. Amoxicillin remains the primary choice for acute otitis media, bacterial sinusitis, and streptococcal pharyngitis. In the management of community-acquired pneumonia (CAP), the commencement of therapy often involves penicillin's due to their excellent penetration into lung tissue and potency against Streptococcus pneumoniae. An assessment of clinical outcomes confirms that despite rising resistance, penicillin's remain the most effective and least toxic option for paediatric respiratory medicine.[24]

Sexually Transmitted Infections (STIs):

One of the most remarkable and enduring therapeutic profiles of penicillin is its role in treating syphilis, caused by Treponema pallidum. Benzathine penicillin G remains the only agent that is unequivocally effective for all stages of syphilis, including neurosyphilis and congenital cases. The drug's unique pharmacokinetic profile allows for sustained treponemicidal concentrations, ensuring the complete eradication of the pathogen. This remains a critical area of pharmacotherapy where no synthetic alternative has been able to surpass the efficacy of the original natural penicillin.[25]

Skin and Soft Tissue Infections (SSTIs):

The development of penicillinase-resistant penicillin's, such as Nafcillin and Oxacillin, has significantly enhanced the therapeutic reach against Staphylococcus aureus. These agents are vital in treating cellulitis, impetigo, and more severe infections like osteomyelitis. The elucidation of their specialized side chains explains their stability against staphylococcal enzymes, making them indispensable in surgical and dermatological settings.[26]

Severe Systemic and Hospital-Acquired Infections:

Advanced antipseudomonal penicillin's, specifically Piperacillin when combined with Tazobactam, provide a broad-spectrum assessment for critically ill patients. They are frontline defences against Pseudomonas aeruginosa and are frequently utilized in the treatment of intra-abdominal infections, febrile neutropenia, and hospital-acquired pneumonia. The commencement of such broad-spectrum therapy is essential in intensive care units to prevent systemic sepsis and improve survival rates.[27]

Prophylactic Applications:

Beyond active treatment, penicillin's play a prophylactic role in preventing the recurrence of rheumatic fever and endocarditis. Long-acting injectable formulations provide consistent protection for high-risk patients undergoing dental or surgical procedures. This preventive assessment highlights the drug's versatility in not only curing infections but also safeguarding long-term cardiovascular health.[28]

The flowchart illustrates a systematic approach for clinicians to identify the appropriate penicillin class based on pathogen susceptibility and patient allergy assessment. This decision-making tool is essential for the commencement of safe antimicrobial stewardship and the prevention of adverse drug reactions.

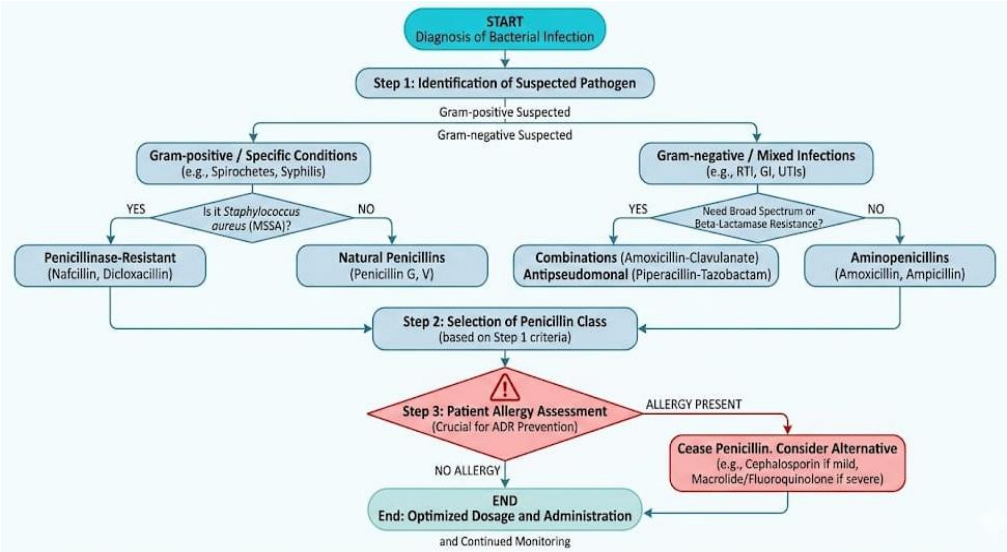

Figure 3: Clinical Decision Flowchart for Penicillin Therapy Selection.

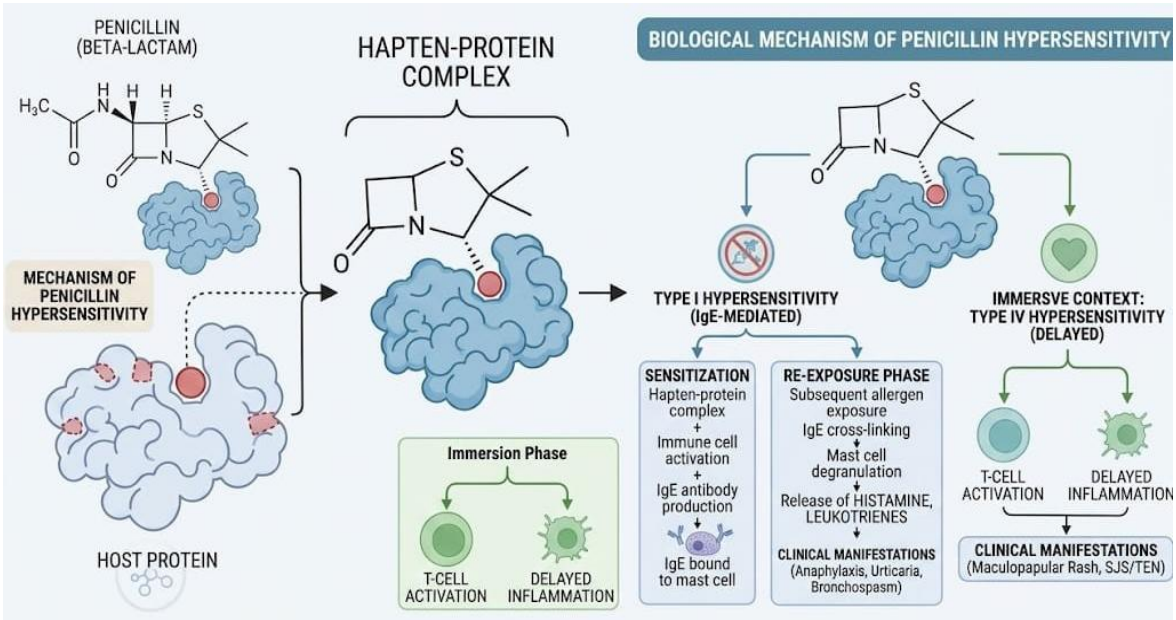

Figure 4: The Hapten-Protein Complex Formation.

Adverse Drug Reactions (ADRs)

The pharmacological assessment of penicillin's, while unequivocally highlighting their life-saving potential, also necessitates a meticulous elucidation of their adverse drug reaction (ADR) profile. Clinical commencement of penicillin therapy requires a high degree of vigilance, as the spectrum of reactions ranges from mild cutaneous eruptions to life-threatening systemic emergencies. An assessment of global pharmacovigilance data reveals that penicillin's are among the most frequent causes of drug-induced hypersensitivity, making the understanding of these reactions a fundamental requirement for clinical safety.[29,30]

Hypersensitivity Reactions (The Primary Concern):

Penicillin-induced hypersensitivity is the most documented ADR, often categorized using the Gell and Coombs classification system. The commencement of an allergic response is typically due to the drug's ability to act as a hapten, binding to host proteins to elicit an immune response.

Type I (Immediate Hypersensitivity): This is the most severe form, characterized by IgE-mediated responses such as urticaria, angioedema, and bronchospasm. An assessment of clinical cases confirms that anaphylaxis, though rare, can occur within minutes of administration. This unequivocally requires immediate intervention with epinephrine to prevent fatal outcomes.[31,32]

The diagram elucidates the biochemical commencement of penicillin-induced allergy. The highly reactive beta-lactam ring of penicillin acts as a hapten, covalently binding to endogenous host proteins. This assessment shows how the immune system subsequently recognizes this complex as a foreign antigen, unequivocally leading to the sensitization of IgE antibodies and the eventual manifestation of hypersensitivity reactions.

Type II (Cytotoxic Reactions): Although less frequent, penicillin's can lead to immune-mediated haemolytic anaemia or thrombocytopenia. This occurs when the drug binds to the surface of blood cells, leading to their premature destruction by the immune system.[33]

Type III (Immune Complex-Mediated): Serum sickness-like reactions can occur, typically manifesting as fever, joint pain, and rashes approximately 7 to 21 days after the commencement of therapy.[34]

Type IV (Delayed Hypersensitivity): These are T-cell mediated reactions, including maculopapular rashes. In extreme cases, severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) may occur, necessitating an immediate cessation of all beta-lactam therapy.[35]

The clinical differentiation of penicillin-induced hypersensitivity is categorized into four distinct types based on the Gell and Coombs classification. This assessment highlights the variations in immune mechanisms, ranging from IgE-mediated immediate responses to T-cell-mediated delayed reactions, along with their respective clinical manifestations and typical timings of onset.

Table 2: Classification of Penicillin Hypersensitivity Reactions.

Type of Reaction	Immune Mechanism	Clinical Manifestations	Timing of Onset
Type I (Immediate)	IgE-mediated	Anaphylaxis, Urticaria, Bronchospasm	Within minutes to 1 hour
Type II (Cytotoxic)	IgG/IgM-mediated	Hemolytic Anemia, Thrombocytopenia	72 hours to weeks
Type III (Immune Complex)	Immune complexes	Serum Sickness, Drug Fever	1 to 3 weeks
Type IV (Delayed)	T-cell mediated	Maculopapular rash, SJS/TEN	Days to weeks

Gastrointestinal and Microbiome Disruptions:

The oral administration of penicillin's frequently leads to gastrointestinal disturbances. Since penicillin's unequivocally affect the gut flora, patients may experience nausea, vomiting, or diarrhoea. A significant clinical assessment in this domain is the risk of Clostridioides difficile-associated diarrhoea (CDAD). The elucidation of this condition reveals that the suppression of normal intestinal microbiota allows for the overgrowth of toxicogenic bacteria, which can lead to severe pseudomembranous colitis.[36,37]

Neurological and Renal Toxicity:

At exceptionally high doses, particularly in patients with pre-existing renal impairment, penicillin's can exert neurotoxic effects. These may manifest as neuromuscular irritability, confusion, or even seizures. Furthermore, certain penicillin's, like Methicillin (historically) and occasionally others, have been linked to interstitial nephritis. Regular renal function assessment is crucial during the commencement of long-term or high-dose parenteral therapy to prevent acute kidney injury.[38]

Haematological and Electrolyte Imbalances:

Extended use of penicillin's has been associated with transient leukopenia or neutropenia. Additionally, certain formulations, such as Carbenicillin or high-dose Penicillin G potassium, can lead to electrolyte imbalances like hyperkalaemia or fluid overload, particularly in patients with cardiovascular or renal vulnerabilities. An assessment of these metabolic shifts is essential for maintaining patient stability during intensive treatment protocols.[39]

The Jarisch-Herxheimer Reaction:

Specifically, during the treatment of syphilis, the commencement of penicillin therapy can trigger a Jarisch-Herxheimer reaction. This is not a true allergy but a systemic inflammatory response to the sudden release of endotoxins from dying spirochetes. Symptoms include fever, chills, and exacerbation of skin lesions, unequivocally requiring supportive care and patient reassurance.[40]

Clinical Pharmacology, Toxicity, and Therapeutic Management

Mechanisms of Penicillin Toxicity:

The pharmacological elucidation of penicillin toxicity involves a sophisticated understanding of how the drug interacts with the host's molecular pathways. While penicillin's are unequivocally recognized for their high therapeutic index, toxicity can manifest through specific biochemical mechanisms when systemic commencement exceeds the body's threshold. One primary mechanism is the formation of "hapten-protein complexes," where the reactive beta-lactam ring binds covalently to endogenous proteins. This assessment reveals that these complexes trigger an immune-mediated cascade, leading to the diverse ADRs observed in clinical practice. Additionally, neurotoxicity occurs through GABA antagonism; at high concentrations, penicillin's structurally compete with gamma-aminobutyric acid (GABA) receptors in the central nervous system, which can unequivocally lead to neuronal hyperexcitability and seizures, particularly in patients with compromised renal clearance.[41,42]

Management and Prevention of Adverse Drug Reactions (ADRs):

Effective management and prevention strategies are fundamental to optimizing the safety profile of penicillin therapy. The commencement of any treatment must be preceded by a rigorous clinical assessment of the patient's allergic history. The elucidation of "allergy de-labelling" through skin prick testing and intradermal challenges is a crucial prevention tool, as it helps identify patients who are not truly allergic, thereby avoiding the unnecessary use of broader-spectrum alternatives. For those with a confirmed hypersensitivity where penicillin is indispensable, a structured desensitization protocol may be initiated. Furthermore, prevention of non-allergic toxicity unequivocally depends on precise dose adjustments. An assessment of renal function is mandatory, as titrating the dosage in accordance with the glomerular filtration rate (GFR) significantly reduces the risk of nephrotoxicity and neurotoxic events.[43,44]

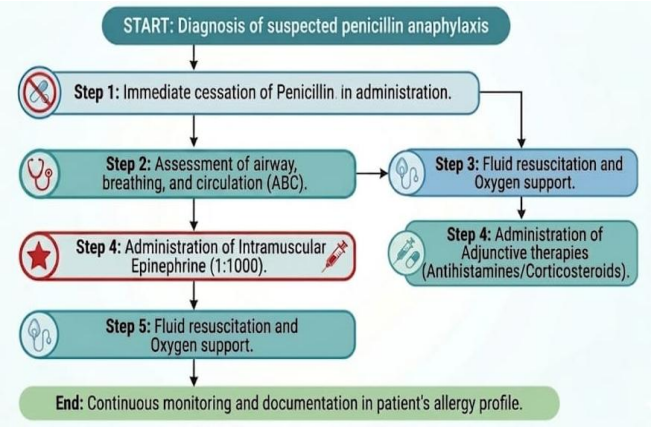

Figure 5: Management Protocol for Suspected Penicillin Anaphylaxis.

The flowchart delineates the systematic clinical commencement for managing acute anaphylactic reactions. It emphasizes the immediate cessation of the offending agent, followed by the rapid assessment of ABC (Airway, Breathing, and Circulation) and the unequivocal administration of intramuscular epinephrine. This assessment of the protocol ensures standardized care during a medical emergency.

DISCUSSION

The clinical utility of penicillin remains a subject of intense deliberation within modern antimicrobial stewardship. The assessment of its therapeutic efficacy unequivocally supports its role as a first-line agent for various infections; however, the persistent challenge of ADRs necessitates a balanced discussion on risk-benefit ratios. A significant point of elucidation in recent literature is the socio-economic impact of penicillin "allergy labels," which often lead to the commencement of more expensive and toxic second-line treatments. This practice not only increases healthcare expenditure but also contributes to the global surge in antimicrobial resistance. Therefore, integrating advanced diagnostic tools and pharmacovigilance into routine practice is essential. The discussion highlights that while penicillin's are indispensable, their future utility depends on our ability to refine safety protocols and enhance clinician awareness regarding the nuances of drug hypersensitivity.[45]

CONCLUSION

In conclusion, penicillin continues to be a cornerstone of infectious disease management, nearly a century after its commencement in clinical medicine. The elucidation of its complex ADR profile and the underlying mechanisms of toxicity provides a roadmap for safer prescribing practices. An assessment of current trends indicates that the future of penicillin therapy lies in personalized medicine, where genetic screening and rapid bedside testing will unequivocally minimize the risk of severe reactions. As we move forward, the role of robust pharmacovigilance cannot be overstated; it is the primary mechanism through which we can track emerging toxicity patterns and ensure patient safety. Ultimately, maintaining the delicate balance between the drug's unparalleled bactericidal power and its potential for adverse effects is the hallmark of modern clinical pharmacology.[46,47]

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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