ISSN: 2755-6328

Review Article

Open Access Journal of Pharmaceutical Sciences and Drugs

Pharmacological Effects of β-Lactam Antimicrobial: A Comprehensive Literature Review on Pharmacokinetics, Pharmacodynamics, and Resistance Mechanisms

Amir Emami[1*] and Abdollah Bazargani[2]

[1]*Amir-Al-Momenin Burn and Wound healing research center, Department of Microbiology, Shiraz University of Medical Sciences, Shiraz, Iran*

[2]*Medical University, Department of Microbiology, Shiraz University of Medical Sciences, Shiraz, Iran*

[*]**Corresponding author**

Amir Emami, Associate Professor of Microbiology, Burn and Wound Healing Research Center, Department of Microbiology, Shiraz University of Medical Sciences, Fars, Shiraz, Iran.

Received: October 20, 2025; **Accepted:** November 06, 2025; **Published:** November 15, 2025

ABSTRACT

β-lactam antibiotics represent one of the most extensive classes of antimicrobial agents in modern medicine, due to their broad activity, favorable safety profiles, and well-established clinical efficacy. These agents – including penicillins, cephalosporins, carbapenems, and monobactams – exert their antibacterial effects by inhibiting the synthesis of the cell wall of bacteria through binding to penicillin-binding proteins (PBPs). Despite their widespread application, the advent of resistance mechanisms such as β-lactamase production, altered PBPs, and efflux pumps have significantly compromised their therapeutic potential.

This literature review aims to provide a comprehensive analysis of the pharmacological properties of β-lactam antibiotics, with a particular focus on pharmacokinetics (PK), pharmacodynamics (PD), and resistance mechanisms. The review synthesizes findings from peer-reviewed studies published over the past two decades, highlighting the importance of PK/PD optimization in clinical decision-making. Time-dependent killing, a hallmark of β-lactam activity, underscores the need for dosing strategies that maintain drug concentrations above the minimum inhibitory concentration (MIC) for an adequate duration.

Furthermore, the review explores current challenges in β-lactam therapy, including suboptimal dosing in critically ill patients, diagnostic delays in resistance detection, and gaps in antimicrobial stewardship. Future research directions are proposed, such as the development of novel β-lactamase inhibitors, personalized dosing regimens based on PK/PD modeling, and rapid diagnostic tools for resistance profiling. By integrating pharmacological insights with clinical practice, this review seeks to inform strategies that preserve the efficacy of β-lactam antibiotics in an era of escalating antimicrobial resistance.

Keywords: Pharmacological, Pharmacokinetics, Pharmacodynamics, β-Lactamase, Antimicrobial

Introduction

Alexander Fleming's discovery of penicillin in 1928 was a revolutionary milestone in the history of medicine and laid the foundation for the development of β-lactam antibiotics – agents that have since become the cornerstone of antimicrobial treatment. Over the past century, β-lactam antibiotics have evolved into a diverse group of compounds, including penicillins, cephalosporins, carbapenems, and monobactams, each with distinct structural features and antimicrobial spectrums [1]. Their main mechanism of action consists of inhibiting the synthesis of the bacterial cell wall through irreversible binding to penicillin-binding proteins (PBPs), which leads to cell lysis and death. It has a strong antibacterial activity mechanism and has contributed to the widespread clinical use of β-lactams in the treatment of infections caused by Gram-positive and Gram-negative organisms [2,3].

Despite their therapeutic success, the clinical utility of β-lactam antibiotics is increasingly undermined by the global rise of antimicrobial resistance. Resistance mechanisms such as the production of β-lactamases (including extended-spectrum

Citation: Amir Emami, Abdollah Bazargani. Pharmacological Effects of β-Lactam Antimicrobial: A Comprehensive Literature Review on Pharmacokinetics, Pharmacodynamics, and Resistance Mechanisms. Open Access J Pharma Sci and Drug. 2025. 1(2): 1-9. DOI: doi.org/10.61440/OAJPSD.2025.v1.20

β-lactamases [ESBLs], AmpC enzymes, and carbapenemases), structural modifications of PBPs, and changes in bacterial membrane permeability have significantly reduced the efficacy of these agents. The emergence of multidrug-resistant organisms—particularly in hospital settings—has led to increased morbidity, mortality, and healthcare costs, posing a serious threat to public health [4].

In this context, a deeper understanding of the pharmacological behavior of β-lactam antibiotics is essential for optimizing their clinical use. Pharmacokinetics (PK), which involves drug absorption, distribution, metabolism, and excretion, and pharmacodynamics (PD), which describes the relationship between drug concentration and antimicrobial effect, are critical determinants of treatment success. β-lactams exhibit time-dependent killing, which means that their effectiveness is closely related to how long the drug concentration remains above the minimum inhibitory concentration (MIC). Failure to achieve appropriate PK/PD targets can result in suboptimal outcomes and promote the selection of resistant strains [5].

Moreover, the complexity of treating infections in critically ill patients—who often exhibit altered PK parameters due to organ dysfunction, fluid shifts, and other pathophysiological changes—necessitates individualized dosing strategies. The integration of PK/PD principles into clinical decision-making, along with the use of therapeutic drug monitoring and extended infusion techniques, has shown promise in improving outcomes and mitigating resistance.

This literature review aims to provide a comprehensive analysis of the pharmacological effects of β-lactam antibiotics, with a particular focus on their PK and PD characteristics, mechanisms of resistance, and clinical implications. By synthesizing findings from recent research, the review seeks to inform evidence-based strategies for preserving the efficacy of β-lactam therapy and guiding future investigations in the field of antimicrobial pharmacology [3,6].

Methodology of Literature

This literature review was conducted using a structured and systematic approach to identify, evaluate, and synthesize relevant scientific publications concerning the pharmacological effects of β-lactam antibiotics. The primary objective was to gather comprehensive insights into their pharmacokinetics (PK), pharmacodynamics (PD), and mechanisms of resistance, with a particular emphasis on clinical implications and future research directions.

Search Strategy

A comprehensive search was performed across multiple academic databases including PubMed, ScienceDirect, Scopus, and Google Scholar. The search covered publications from January 2000 to July 2025, ensuring both historical context and inclusion of the most recent advancements.

Additional filters were applied to include only peer-reviewed articles, clinical trials, systematic reviews, and meta-analyses. Reference lists of selected articles were manually screened to identify further relevant studies not captured by the initial search.

Inclusion and Exclusion Criteria

To ensure relevance and scientific rigor, the following inclusion criteria were applied:

- Articles published in English
- Studies involving human subjects or clinically relevant bacterial strains
- Publications providing original data or systematic reviews on β-lactam PK/PD or resistance mechanisms
- Research addressing clinical applications, dosing strategies, or therapeutic outcomes.

Exclusion criteria

- Non-peer-reviewed sources (e.g., editorials, opinion pieces, blogs)
- Studies focused solely on veterinary or agricultural applications
- Articles lacking methodological transparency or sufficient data for analysis
- Publications before 2000 unless historically significant.

Data Extraction and Thematic Analysis

Selected articles were reviewed independently and systematically. Key data points extracted included:

- Classification and spectrum of β-lactam antibiotics
- PK parameters: absorption, distribution, metabolism, elimination
- PD metrics: MIC values, time above MIC (%fT>MIC), dosage regimens
- Resistance mechanisms: β-lactamase types, altered PBPs, efflux pumps, porin channel modifications
- Clinical outcomes: therapeutic success, failure rates, adverse effects
- Recommendations for dosing optimization and stewardship practices.

Thematic analysis was employed to identify recurring patterns, emerging trends, and gaps in the literature. Studies were grouped based on their focus (e.g., pharmacokinetics, resistance, clinical trials) and critically appraised for methodological quality, sample size, and relevance to the review's objectives.

Quality Assessment

To ensure the reliability of findings, selected studies were assessed using standardized tools such as the PRISMA checklist for systematic reviews and the GRADE framework for evaluating evidence quality. Studies with high methodological rigor and clinical applicability were prioritized in the synthesis.

Classification and Mechanism of Action of β-Lactam Antibiotics

β-lactam antibiotics constitute a large and diverse class of antimicrobial agents characterized by the presence of a β-lactam ring in their chemical structure. This four-membered cyclic amide is essential for their antibacterial activity, as it enables the inhibition of bacterial cell wall synthesis. The β-lactam ring mimics the D-Ala-D-Ala moiety of peptidoglycan precursors, allowing the drug to bind irreversibly to penicillin-binding proteins (PBPs), which are enzymes involved in the final stages of peptidoglycan cross-linking. This disruption leads to cell wall instability, osmotic imbalance, and ultimately bacterial cell lysis [6].

Structural Overview

All β-lactam antibiotics share the core β-lactam ring, but differ in their side chains and fused ring systems, which influence their spectrum of activity, resistance to β-lactamases, and pharmacokinetic properties.

Major Subclasses of β-Lactam Antibiotics

Penicillins

- Structure: β-lactam ring fused to a thiazolidine ring
- Examples: Penicillin G, ampicillin, amoxicillin, piperacillin
- Spectrum: Primarily Gram-positive; extended-spectrum agents cover some Gram-negatives
- Limitations: Susceptible to β-lactamases; often combined with inhibitors (e.g., clavulanic acid).

Cephalosporins

Structure: β-lactam ring fused to a dihydrothiazine ring

Generations:

- 1st Gen: Cefazolin – Gram-positive coverage
- 2nd Gen: Cefuroxime – added Gram-negative activity
- 3rd Gen: Ceftriaxone – enhanced Gram-negative and CNS penetration
- 4th Gen: Cefepime – broad-spectrum, including Pseudomonas
- 5th Gen: Ceftaroline – active against MRSA.

Advantages: Increased resistance to β-lactamases compared to penicillins.

Carbapenems

- Structure: β-lactam ring with a modified side chain that confers high stability
- Examples: Imipenem, meropenem, doripenem
- Spectrum: Broadest among β-lactams; active against ESBL-producing organisms and anaerobes
- Clinical Use: Reserved for severe or multidrug-resistant infections
- Resistance Concern: Carbapenemase-producing organisms (e.g., KPC, NDM).

Monobactams

- Structure: Monocyclic β-lactam ring (no fused ring)
- Example: Aztreonam
- Spectrum: Selective activity against Gram-negative aerobes
- Advantage: Safe in patients with penicillin allergy; no cross-reactivity.

Mechanism of Action

β-lactam antibiotics exert their bactericidal effect by targeting PBPs, which are essential for the synthesis and maintenance of bacterial cell walls. By binding to these enzymes, β-lactams inhibit the transpeptidation reaction that cross-links peptidoglycan strands. This leads to:

- Cell wall weakening
- Loss of osmotic integrity
- Autolysin activation
- Cell lysis and death.

The efficacy of β-lactams depends on their ability to reach and bind PBPs, which varies among bacterial species and is influenced by drug permeability, efflux mechanisms, and the presence of β-lactamases.

Pharmacological Considerations

- Time-dependent killing: β-lactams require sustained concentrations above MIC for optimal efficacy
- Low post-antibiotic effect (PAE): Reinforces the need for frequent or continuous dosing
- Synergistic potential: Often used in combination with aminoglycosides or β-lactamase inhibitors [7, 8].

Pharmacokinetics of β-Lactam Antibiotics

Pharmacokinetics (PK) refers to the study of how a drug is absorbed, distributed, metabolized, and eliminated by the body. For β-lactam antibiotics, understanding PK parameters is essential for optimizing dosing regimens, achieving therapeutic efficacy, and minimizing the development of resistance. β-lactams are characterized by time-dependent killing, meaning their bactericidal activity is most effective when drug concentrations remain above the minimum inhibitory concentration (MIC) for a sufficient duration.

Absorption

Most β-lactam antibiotics are administered intravenously due to poor oral bioavailability and instability in gastric acid. However, some agents such as amoxicillin and cephalexin are available in oral formulations with acceptable absorption profiles.

Oral bioavailability varies by subclass and compound:

- Amoxicillin: ~75%
- Cephalexin: ~90%
- Penicillin V: ~60%
- Food interactions: Certain β-lactams may have reduced absorption when taken with food, although amoxicillin is relatively unaffected.

Distribution

β-lactams are hydrophilic compounds with limited tissue penetration. They distribute primarily in extracellular fluid and exhibit low protein binding, which facilitates free drug availability.

- Volume of distribution (Vd): Typically low (0.1–0.3 L/kg)
- CNS penetration: Limited under normal conditions; improves during meningeal inflammation (e.g., ceftriaxone, meropenem)
- Special populations: In critically ill patients, altered capillary permeability and fluid shifts may increase Vd, necessitating dose adjustments.

Metabolism

Most β-lactam antibiotics undergo minimal hepatic metabolism and are excreted largely unchanged.

Exceptions:

- Nafcillin and oxacillin are metabolized hepatically
- Imipenem is hydrolyzed by renal dehydropeptidase I and requires co-administration with cilastatin.

Elimination

Renal excretion is the primary route of elimination for most β-lactams.

- Half-life: Generally short (0.5–2 hours), requiring frequent dosing
- Renal clearance: Via glomerular filtration and tubular secretion

- Dose adjustment: Essential in patients with renal impairment to avoid accumulation and toxicity
- Prolonged infusion: Used to maintain plasma concentrations above MIC for time-dependent efficacy.

Pharmacokinetic Variability in Special Populations
- Critically ill patients: Altered PK due to sepsis, organ dysfunction, and fluid resuscitation
- Obese patients: Increased Vd may reduce plasma concentrations
- Pediatric and geriatric populations: Require individualized dosing due to developmental or age-related changes in renal function.

Clinical Implications

Optimizing PK parameters is crucial for maximizing the efficacy of β-lactam antibiotics. Strategies include:
- Extended or continuous infusion: Improves %fT>MIC, especially in severe infections
- Therapeutic drug monitoring (TDM): Emerging tool for individualized dosing
- Loading doses: May be necessary in critically ill patients to rapidly achieve target concentrations.

Failure to consider PK variability can lead to subtherapeutic exposure, treatment failure, and the selection of resistant organisms. Therefore, integrating PK principles into clinical practice is essential for effective β-lactam therapy [9].

Pharmacokinetics of β-Lactam Antibiotics

Pharmacokinetics (PK) refers to the study of the absorption, distribution, metabolism, and excretion (ADME) of drugs within the body. For β-lactam antibiotics, PK parameters are critical in determining therapeutic efficacy, especially given their time-dependent bactericidal activity. Unlike concentration-dependent antibiotics, β-lactams require sustained plasma concentrations above the minimum inhibitory concentration (MIC) for optimal bacterial killing. Therefore, understanding and applying PK principles is essential for effective dosing, particularly in vulnerable populations such as critically ill patients.

Absorption

Most β-lactam antibiotics are administered parenterally due to poor oral bioavailability and acid instability. However, select agents such as amoxicillin, cephalexin, and cefuroxime axetil are available in oral formulations with acceptable absorption profiles.

Oral bioavailability varies significantly:
- Amoxicillin: ~75–90%
- Cephalexin: ~90%
- Penicillin V: ~60% .

Factors influencing absorption:
- Gastric pH and motility
- Food intake (may delay or reduce absorption for some agents)
- Formulation type (e.g., extended-release vs. immediate-release).

Distribution

β-lactams are hydrophilic molecules with limited lipid solubility, resulting in preferential distribution within extracellular fluid compartments.
- Volume of distribution (Vd): Typically low (0.1–0.3 L/kg), indicating limited tissue penetration
- Protein binding: Generally low to moderate (e.g., ceftriaxone ~85%, penicillin G ~60%)
- CNS penetration: Poor under normal conditions; enhanced during meningeal inflammation (e.g., ceftriaxone, meropenem)
- Special considerations:
- In critically ill patients, increased capillary permeability and fluid shifts may expand Vd, leading to reduced plasma concentrations
- In obese patients, altered body composition may affect distribution kinetics.

Metabolism

Most β-lactam antibiotics undergo minimal hepatic metabolism and are excreted largely unchanged in the urine.

Exceptions:
- Nafcillin and oxacillin are metabolized hepatically and excreted via bile
- Imipenem is hydrolyzed by renal dehydropeptidase I and requires co-administration with cilastatin to prevent degradation
- Clinical relevance: Hepatic metabolism may influence dosing in patients with liver dysfunction, although this is rare for most β-lactams.

Elimination

Renal excretion is the predominant route of elimination for β-lactam antibiotics.
- Mechanism: Glomerular filtration and active tubular secretion
- Half-life: Generally short (0.5–2 hours), necessitating frequent dosing or continuous infusion
- Renal impairment: Requires dose adjustment to prevent accumulation and toxicity
- Prolonged infusion strategies: Used to maintain plasma concentrations above MIC for extended periods, especially in severe infections.

Pharmacokinetic Alterations in Special Populations
- Critically ill patients:
- Altered renal clearance due to augmented renal clearance (ARC) or acute kidney injury (AKI)
- Expanded Vd due to fluid resuscitation and capillary leak syndrome
- May require higher loading doses and individualized maintenance dosing.

Pediatric Patients
- Immature renal and hepatic function affects drug clearance
- Dosing must be weight-based and age-adjusted
- Geriatric patients:
- Reduced renal function and changes in body composition necessitate careful monitoring

Obese patients
Increased Vd may dilute plasma concentrations; dosing based on adjusted body weight may be necessary

Clinical Implications
Failure to achieve appropriate PK targets can result in subtherapeutic exposure, treatment failure, and the emergence of resistant organisms. Therefore, integrating PK principles into clinical practice is essential. However, the following should be considered: 1.) Extended or continuous infusion: Enhances %fT>MIC and improves outcomes in severe infections. 2.) Therapeutic drug monitoring (TDM): Emerging as a tool for personalized β-lactam dosing, especially in ICU settings. 3) Loading doses: Recommended in critically ill patients to rapidly achieve therapeutic concentrations. 4.) PK/PD modeling: Supports individualized therapy and stewardship efforts [10-12].

Pharmacodynamics of β-Lactam Antibiotics
Pharmacodynamics (PD) refers to the relationship between drug concentration and its biological effect, particularly the antimicrobial activity in the context of antibiotics. For β-lactam antibiotics, PD principles are crucial in guiding dosing strategies, optimizing therapeutic outcomes, and minimizing the emergence of resistance. Unlike concentration-dependent antibiotics (e.g., aminoglycosides, fluoroquinolones), β-lactams exhibit time-dependent killing, meaning their efficacy is primarily determined by the duration that free drug concentrations remain above the minimum inhibitory concentration (MIC) of the target pathogen.

Time-Dependent Killing
The bactericidal activity of β-lactams is best described by the %fT>MIC parameter, which represents the percentage of the dosing interval during which the free (unbound) drug concentration exceeds the MIC.

- Penicillins: Optimal efficacy at ~50% fT>MIC
- Cephalosporins: Optimal efficacy at ~60–70% fT>MIC
- Carbapenems: Optimal efficacy at ~40% fT>MIC.

These thresholds vary slightly depending on the pathogen and infection site, but maintaining drug levels above MIC for the majority of the dosing interval is essential for bacterial eradication.

Post-Antibiotic Effect (PAE)
β-lactams generally exhibit a short or negligible PAE, especially against Gram-negative organisms. This means that bacterial regrowth resumes quickly once drug concentrations fall below MIC, reinforcing the need for frequent or continuous dosing to sustain antimicrobial pressure.

Dosing Strategies Based on PD
To optimize %fT>MIC, several dosing strategies have been developed:
- Standard intermittent dosing: Traditional approach, may be insufficient in critically ill patients
- Extended infusion: Administering the dose over 3–4 hours to prolong time above MIC
- Continuous infusion: Maintaining steady plasma concentrations, especially useful for pathogens with high MICs or in patients with altered pharmacokinetics
- Loading doses: Used to rapidly achieve therapeutic concentrations, particularly in sepsis or ICU settings.

Clinical studies have demonstrated that extended or continuous infusion of β-lactams improves microbiological and clinical outcomes, especially in severe infections such as ventilator-associated pneumonia, bloodstream infections, and intra-abdominal sepsis.

PD Variability Among Subclasses
Although all β-lactams share time-dependent killing, subtle differences exist:
- Carbapenems: Exhibit the most potent activity and lowest MICs against resistant Gram-negatives
- Cephalosporins: Vary in PBP affinity and spectrum across generations
- Penicillins: Often require combination with β-lactamase inhibitors to restore PD efficacy
- Monobactams (e.g., aztreonam): Limited to Gram-negative aerobes; PD principles remain similar

Impact on Resistance Development
Suboptimal PD exposure—such as insufficient %fT>MIC—can promote the selection of resistant subpopulations. This is particularly concerning in nosocomial pathogens like Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacter baumannii.
- Low drug concentrations allow survival of partially resistant strains
- Inadequate dosing intervals contribute to adaptive resistance mechanisms
- PD-guided therapy is essential to suppress resistance and improve outcomes.

Integration into Clinical Practice
Modern antimicrobial stewardship emphasizes PD-informed prescribing. This includes:
- PK/PD modeling to simulate optimal regimens
- Therapeutic drug monitoring (TDM) for high-risk patients
- Individualized therapy based on infection site, pathogen MIC, and patient physiology
- By aligning dosing strategies with PD principles, clinicians can enhance the efficacy of β-lactam antibiotics while minimizing toxicity and resistance [13,14].

Pharmacodynamics of β-Lactam Antibiotics
Pharmacodynamics (PD) describes the relationship between drug concentration and its antimicrobial effect, encompassing the mechanisms by which antibiotics exert their bactericidal activity and the parameters that predict clinical efficacy. For β-lactam antibiotics, PD principles are particularly critical due to their time-dependent killing behavior, which distinguishes them from concentration-dependent agents such as aminoglycosides and fluoroquinolones.

Time-Dependent Killing and %fT>MIC
The primary PD parameter for β-lactams is the percentage of time that free drug concentrations remain above the minimum inhibitory concentration (MIC) during the dosing interval,

denoted as %fT>MIC. This metric correlates strongly with bacterial eradication and clinical success.

- Penicillins: Require ~50% fT>MIC
- Cephalosporins: Optimal require at ~60–70% fT>MIC
- Carbapenems: Effective require at ~40% fT>MIC due to higher PBP affinity and lower MICs.

Failure to maintain adequate %fT>MIC can result in subtherapeutic exposure, treatment failure, and the selection of resistant subpopulations.

Post-Antibiotic Effect (PAE)

β-lactam antibiotics generally exhibit minimal or absent PAE, especially against Gram-negative organisms. This means that bacterial regrowth resumes rapidly once drug concentrations fall below MIC, necessitating frequent dosing or continuous infusion to maintain antimicrobial pressure.

- Gram-positive organisms may show modest PAE with β-lactams
- Gram-negative organisms typically require sustained exposure for suppression.

Penicillin-Binding Proteins (PBPs) and Target Affinity

The bactericidal activity of β-lactams is mediated through irreversible binding to PBPs, which are essential enzymes involved in peptidoglycan cross-linking during bacterial cell wall synthesis.

- Different β-lactams exhibit variable affinity for distinct PBPs, influencing their spectrum of activity and potency
- For example, ceftaroline binds PBP2a in MRSA, conferring activity against resistant Gram-positive strains.

Dosing Strategies Based on PD Principles

To optimize %fT>MIC and enhance clinical outcomes, several advanced dosing strategies have been developed:

- Extended infusion: Administering β-lactams over 3–4 hours prolongs time above MIC
- Continuous infusion: Maintains steady-state concentrations, particularly beneficial in critically ill patients
- Loading doses: Used to rapidly achieve therapeutic levels, especially in sepsis or high-volume distribution states
- Therapeutic drug monitoring (TDM): Emerging tool for individualized dosing in complex cases
- Clinical trials have demonstrated that PD-optimized regimens improve microbiological clearance, reduce mortality, and minimize resistance development in severe infections such as ventilator-associated pneumonia, bloodstream infections, and intra-abdominal sepsis.

PD Variability Among β-Lactam Subclasses

Although all β-lactams share time-dependent killing, subclass-specific differences exist:

- Carbapenems: Exhibit potent activity and low MICs; effective even with shorter %fT>MIC
- Cephalosporins: Vary in PBP affinity and resistance profiles across generations
- Penicillins: Often require β-lactamase inhibitors to restore PD efficacy
- Monobactams (e.g., aztreonam): Limited to Gram-negative aerobes; PD principles remain consistent.

Role of PD in Resistance Suppression

Suboptimal PD exposure is a key driver of antimicrobial resistance. Inadequate %fT>MIC allows survival of partially resistant bacterial populations and promotes adaptive resistance mechanisms such as:

- Upregulation of β-lactamase enzymes
- Alteration of PBPs
- Activation of efflux pumps and porin channel modifications.

PD-guided therapy is essential to suppress resistance, particularly in high-risk settings such as intensive care units and oncology wards.

Integration into Clinical Practice

Modern antimicrobial stewardship programs emphasize the integration of PD principles into prescribing practices. This includes:

- PK/PD modeling to simulate optimal regimens
- Rapid susceptibility testing to guide empirical therapy
- Individualized dosing based on infection site, pathogen MIC, and patient physiology

By aligning dosing strategies with PD targets, clinicians can maximize the efficacy of β-lactam antibiotics while minimizing toxicity and resistance [12,15,16].

Resistance Mechanisms to β-Lactam Antibiotics

The widespread use of β-lactam antibiotics has led to the emergence of diverse bacterial resistance mechanisms that compromise their clinical efficacy. These mechanisms vary across bacterial species and are influenced by genetic, environmental, and therapeutic factors. Understanding the molecular basis of resistance is essential for guiding empirical therapy, developing novel agents, and implementing effective antimicrobial stewardship.

β-Lactamase Production

The most prevalent resistance mechanism among Gram-negative bacteria is the enzymatic hydrolysis of the β-lactam ring by β-lactamases, rendering the antimicrobial inactive.

a. In general narrow-Spectrum β-Lactamases, inactive hydrolyze penicillins and early-generation cephalosporins. These inactivators are common in Escherichia coli and Klebsiella pneumoniae.
b. Extended-Spectrum β-Lactamases (ESBLs), also inhibits the following parts among the bacteria: Hydrolyze penicillins, third-generation cephalosporins, and aztreonam. They either, inhibited by clavulanic acid, tazobactam, and newer agents like avibactam, and genes often located on plasmids, facilitating horizontal transfer.
c. AmpC β-Lactamases, are inducible enzymes found in Enterobacter spp., Citrobacter spp., and Serratia spp. , which they confer resistance to cephamycins and are poorly inhibited by classical β-lactamase inhibitors.
d. Carbapenemases are another enzyme which hydrolyzes carbapenems and other β-lactams. They include KPC (Klebsiella pneumoniae carbapenemase), NDM (New Delhi metallo-β-lactamase), VIM, IMP, and OXA-type enzymes. In this condition, it is often associated with multidrug resistance and high mortality rates.

Alteration of Penicillin-Binding Proteins (PBPs)
Resistance in Gram-positive organisms, particularly Staphylococcus aureus and Streptococcus pneumoniae, is often mediated by structural modifications in PBPs. For example, MRSA: Acquires the mecA gene encoding PBP2a, which has low affinity for β-lactams, and Penicillin-resistant S. pneumoniae: Exhibits mosaic PBPs with reduced β-lactam binding. These changes prevent effective inhibition of cell wall synthesis despite adequate drug concentrations

Efflux Pumps
Efflux systems actively transport β-lactam molecules out of bacterial cells, reducing intracellular concentrations below therapeutic thresholds. These Efflux Pumps are common in Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacteriaceae. This efflux pump often works synergistically with other resistance mechanisms. These pumps may be constitutive or inducible, and encoded chromosomally or plasmid-borne.

Reduced Membrane Permeability
In Gram-negative bacteria, the outer membrane acts as a barrier to β-lactam entry. Resistance can arise from: Loss or modification of porin channels (e.g., OmpK35, OmpK36 in K. pneumoniae), OR downregulation of porin expression, limiting drug influx. These often co-occurs with β-lactamase production, enhancing resistance.

Biofilm Formation
Biofilms provide a physical and metabolic shield against antimicrobials, including β-lactams. In the form of biofilm, bacteria exhibit reduced growth rates and altered gene expression [5, 17].

These bacteria with biofilm, are common in chronic infections (e.g., prosthetic joint infections, cystic fibrosis lung infections). In this case, β-lactams may penetrate poorly and fail to reach effective concentrations.

Horizontal Gene Transfer and Genetic Mobility
Resistance genes are frequently carried on mobile genetic elements such as plasmids, transposons, and integrons. This frequently facilitates rapid dissemination across species and environments. This promotes co-resistance to multiple antimicrobial classes.

Sadly for these points, something like environmental reservoirs (e.g., wastewater, livestock) contribute to global spread of resistance.

Clinical Implications
In some cases, patients receive treatment failure or ineffective treatment due to undiagnosed resistance. In this case of the study, limited options take their place, particularly in carbapenem-resistant Enterobacteriaceae (CRE). There is also an increase in morbidity and mortality, especially in immunocompromised patients and ICUs.

Accordingly, considering the presence of resistance in bacteria, the length of hospitalization of patients can be reduced.

Strategies to Overcome Resistance
For these strategies, the following methods are used: 1.) Use of β-lactamase inhibitors: clavulanic acid, tazobactam, avibactam, relebactam, vaborbactam, 2.) Combination therapy: synergistic effects with aminoglycosides, fluoroquinolones or polymyxins, 3.) PK/PD Optimization: Extensive or continuous injection to maximize %fT >MIC, 4.) Rapid diagnosis: Molecular assay for resistance gene detection, 5.) Antimicrobial Monitoring: Rational Prescribing to Minimize Selection Pressure [9,16-19].

Clinical Implications and Challenges of β-Lactam Antimicrobial Use
The clinical application of β-lactam antimicrobials in the treatment of bacterial infections is fundamental in a wide range of healthcare settings. Their broad-spectrum activity, favorable safety profiles, and pharmacological properties have made them first-line agents for community-acquired infections and nosocomial infections. However, the increasing prevalence of antimicrobial resistance, combined with evolving patient-specific agents and limitations of the healthcare system, pose significant challenges to their effective use.

In general, one of the most pressing clinical concerns is the failure of β-lactam therapy in the presence of resistant pathogens. Infections caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, AmpC-expressing organisms, and carbapenemase-producing strains often exhibit high MICs, rendering standard β-lactam regimens ineffective.

Another case is the high infection of the patient due to bacterial infections. Patients admitted to intensive care units (ICUs) often experience pharmacokinetic changes due to sepsis-induced changes in organ function, fluid changes, and renal clearance (ARC). These factors complicate β-lactam dosage, and increase the risk of low antimicrobial exposure [18-20].

Diagnostic Limitations
Timely identification of resistant organisms is critical for guiding β-lactam use. However, conventional culture-based methods are slow and may delay effective therapy. Turnaround time for susceptibility testing often exceeds 48–72 hours.

Although molecular methods for detecting emerging resistance mechanisms are promising, this method is not universally available or cost-effective, so phenotypic methods should be used, but it should be noted that these phenotypic methods may fail to detect emerging resistance mechanisms.

It should be noted, however, that the lack of MIC-guided doses in many establishments limits the optimization of PD.

Stewardship and Prescribing Practices
Inappropriate prescribing of β-lactams contributes to resistance development and therapeutic inefficacy. Overuse of β-lactams in outpatients, causes settings for viral or self-limiting infections.

Economic and Logistical Burdens
The clinical challenges associated with β-lactam resistance and dosage complexity translate into significant healthcare costs. In these cases, we can mention the following: 1.) Prolonged hospital

stays due to delayed effective therapy, 2.) Need for combination regimens involving costly agents, 3.) Increased laboratory and monitoring requirements, 4.) Resource limitations in low- and middle-income countries hinder optimal use.

Therefore, for all of the above, it is necessary to do the following answers: 1.) Implementation of antimicrobial stewardship programs (ASPs) to guide rational β-lactam use, 2.) Integration of PK/PD modeling and TDM into clinical workflows, 3.) Investment in rapid diagnostic technologies for resistance detection, 4.) Education of prescribers on individualized dosing and resistance mechanisms, and 5.) Development of novel β-lactamase inhibitors and combination therapies.

Future Research Directions in β-Lactam Antimicrobial Therapy
The escalating threat of antimicrobial resistance and the pharmacological complexity of β-lactam Antimicrobials necessitate a strategic and multidisciplinary research agenda. Future investigations must address both molecular and clinical dimensions to preserve the efficacy of β-lactams and optimize their therapeutic application in diverse patient populations.

Accordingly, the following should be implemented:

1. Development of Novel β-Lactamase Inhibitors. The emergence of carbapenemase-producing organisms and ESBLs has rendered many β-lactams ineffective. Research should focus on designing next-generation β-lactamase inhibitors with broader activity and enhanced stability.
2. Targeting metallo-β-lactamases (e.g., NDM, VIM), which are currently resistant to most inhibitors.
3. Dual-action inhibitors that combine enzymatic blockade with membrane penetration enhancement
4. Structure-guided drug design using crystallography and molecular docking to optimize binding affinity.

While the use of antibiotics, especially beta-lactams, is widely used in Iran, especially for people who are not hospitalized, we are currently planning a research center for the prevention and use of beta-lactam drugs locally. If this plan is successful, we will be able to increase the effectiveness of antibiotics in the country and use them for people in need if necessary.

Conclusion

β-lactam Antimicrobials continue to serve as a cornerstone of antimicrobial therapy due to their broad-spectrum activity, favorable safety profile, and well-established pharmacological properties. However, the increasing prevalence of resistance mechanisms—including β-lactamase production, altered penicillin-binding proteins, efflux pumps, and reduced membrane permeability—has significantly compromised their clinical utility. These challenges are further exacerbated by pharmacokinetic variability in special populations, diagnostic delays, and suboptimal prescribing practices.

A comprehensive understanding of the pharmacokinetics and pharmacodynamics of β-lactam Antimicrobials is essential for optimizing therapeutic outcomes. Time-dependent killing, minimal post-Antimicrobial effect, and the critical importance of maintaining drug concentrations above the minimum inhibitory concentration (%fT>MIC) underscore the need for individualized dosing strategies. Extended and continuous infusion regimens, therapeutic drug monitoring, and PK/PD modeling have emerged as valuable tools in enhancing efficacy and suppressing resistance.

Clinically, the implications of β-lactam resistance are profound, leading to increased morbidity, mortality, and healthcare costs. In critically ill patients, altered drug distribution and clearance necessitate dynamic and patient-specific dosing approaches. Moreover, the lack of rapid diagnostic tools and limited access to advanced stewardship programs hinder timely and effective therapy.

Future research must prioritize the development of novel β-lactamase inhibitors, rapid molecular diagnostics, and personalized dosing algorithms. Investigations into host-pathogen-drug interactions, combination therapies, and innovative delivery systems will be pivotal in preserving the effectiveness of β-lactam Antimicrobials. Integration of pharmacological insights into clinical practice, supported by stewardship-driven policies and real-world implementation science, will be essential to combat the evolving threat of antimicrobial resistance.

In conclusion, the sustained utility of β-lactam antimicrobials in modern medicine hinges on a multidisciplinary approach that bridges molecular pharmacology, clinical pharmacokinetics, and evidence-based therapeutic strategies. Only through continued innovation, vigilance, and collaboration can we ensure the longevity of these vital agents in the global fight against infectious diseases. In conclusion the pharmacokinetic profile of β-lactam antibiotics is a key determinant of their clinical success. Tailoring dosing strategies based on patient-specific PK parameters can optimize efficacy, reduce toxicity, and help combat antimicrobial resistance.

Limitations of the Review

While every effort was made to ensure comprehensive coverage, certain limitations must be acknowledged. The exclusion of non-English literature may have omitted relevant findings from non-English-speaking regions. Publication bias may have influenced the availability of negative or inconclusive results. Additionally, variability in study designs, definitions of resistance, and PK/PD metrics may affect the comparability of findings across studies.

Despite these limitations, the methodology employed provides a robust foundation for analyzing the pharmacological landscape of β-lactam antibiotics and informing evidence-based clinical practice.

Refrences

1. Landmarks ACSIHC. The Discovery and Development of Penicillin. 1928-1945: Discovery and Development of Penicillin.
2. Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA. Carbapenems: past, present, and future. Antimicrobial agents and chemotherapy. 2011. 55: 4943-4960.
3. Allison MG, Heil EL, Hayes BD. Appropriate antibiotic therapy. Emergency Medicine Clinics. 2017. 35: 25-42.

4. Zhao C, Xin L, Xu X, Qin Y, Wu W. Dynamics of antibiotics and antibiotic resistance genes in four types of kitchen waste composting processes. Journal of Hazardous Materials. 2022. 424: 127526.
5. Märtson AG, Barber KE, Crass RL, Hites M, Kloft C, et al. The pharmacokinetics of antibiotics in patients with obesity: a systematic review and consensus guidelines for dose adjustments. The Lancet Infectious Diseases. 2025.
6. Bradley JS, Garonzik SM, Forrest A, Bhavnani SM. Pharmacokinetics, pharmacodynamics, and Monte Carlo simulation: selecting the best antimicrobial dose to treat an infection. The Pediatric infectious disease journal. 2010. 29: 1043-1046.
7. Bush K, Bradford PA. β-Lactams and β-lactamase inhibitors: an overview. Cold Spring Harbor perspectives in medicine. 2016. 6: a025247.
8. Eliopoulos GM, Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. Clinical infectious diseases. 2003. 36: 1433-1437.
9. Karaba SM, Cosgrove SE, Lee JH, Fiawoo S, Heil EL, et al. Extended-infusion β-lactam therapy, mortality, and subsequent antibiotic resistance among hospitalized adults with gram-negative bloodstream infections. JAMA Network Open. 2024. 7: e2418234-.
10. Spellberg B, Bartlett JG, Gilbert DN. The future of antibiotics and resistance. New England Journal of Medicine. 2013. 368: 299-302.
11. Namikawa H, Imoto W, Yamada K, Tochino Y, Kaneko Y, Kakeya H, Shuto T. Predictors of mortality from extended-spectrum beta-lactamase-producing Enterobacteriaceae bacteremia. Emerging Microbes & Infections. 2023. 12: 2217951.
12. Nowak MA, Nelson RE, Breidenbach JL, Thompson PA, Carson PJ. Clinical and economic outcomes of a prospective antimicrobial stewardship program. American Journal of Health-System Pharmacy. 2012. 69: 1500-1508.
13. Emami A, Bazargani A, Mohammadi AA, Zardosht M, Jafari SM. Detection of blaPER-1 & blaOxa10 among imipenem resistant isolates of Pseudomonas aeruginosa isolated from burn patients hospitalized in Shiraz Burn Hospital. Iranian journal of microbiology. 2015. 7: 7.
14. Lepe JA, Martínez-Martínez L. Resistance mechanisms in Gram-negative bacteria. Medicina Intensiva (English Edition). 2022. 46: 392-402.
15. Bakdach D, Elajez R, Bakdach AR, Awaisu A, De Pascale G, et al. Pharmacokinetics, pharmacodynamics, and dosing considerations of novel β-lactams and β-lactam/β-lactamase inhibitors in critically ill adult patients: focus on obesity, augmented renal clearance, renal replacement therapies, and extracorporeal membrane oxygenation. Journal of Clinical Medicine. 2022. 11: 6898.
16. Javanmardi F, Emami A, Pirbonyeh N, Rajaee M, Hatam G, Keshavarzi A. Study of multidrug resistance in prevalent Gram-negative bacteria in burn patients in Iran: a systematic review and meta-analysis. Journal of global antimicrobial resistance. 2019. 19: 64-72.
17. Tängdén T. Combination antibiotic therapy for multidrug-resistant Gram-negative bacteria. Upsala journal of medical sciences. 2014. 119: 149-53.
18. Roger C, Louart B. Beta-lactams toxicity in the intensive care unit: an underestimated collateral damage?. Microorganisms. 2021. 9: 1505.
19. Williams DJ, Edwards KM, Self WH, Zhu Y, Arnold SR, McCullers JA, Ampofo K, Pavia AT, Anderson EJ, Hicks LA, Bramley AM. Effectiveness of β-lactam monotherapy vs macrolide combination therapy for children hospitalized with pneumonia. JAMA pediatrics. 2017. 171: 1184-1191.
20. Craig W. Pharmacodynamics of antimicrobial agents as a basis for determining dosage regimens. European Journal of Clinical Microbiology and Infectious Diseases. 1993. 12: S6-8.