VANCOMYCIN HYDROCHLORIDE: INTEGRATING BIOSYNTHESIS, PHARMACOKINETICS, RESISTANCE, AND PRECISION DOSING FOR CONTEMPORARY THERAPY

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ABSTRACT

Vancomycin hydrochloride is a cornerstone glycopeptide antibiotic used worldwide for the management of serious infections caused by multidrug-resistant Gram-positive bacteria, particularly methicillin-resistant Staphylococcus aureus, Clostridioides difficile, and Vancomycin-susceptible enterococci. Despite decades of clinical experience, its therapeutic use is increasingly challenged by emerging resistance phenotypes (VISA, VRSA, VRE), a narrow therapeutic index, and exposure-related toxicities such as nephrotoxicity and infusion reactions. This review synthesises contemporary evidence on the historical development, chemistry, biosynthesis, mechanism of action, pharmacokinetics and pharmacodynamics, clinical applications, and toxicological profile of vancomycin hydrochloride, with particular emphasis on AUC/MIC-guided dosing, population-specific considerations, and combination strategies that restore activity against resistant pathogens. Advances in fermentation optimization, downstream purification, and analytical technologies are highlighted alongside regulatory and manufacturing perspectives that underpin consistent product quality. Finally, the review discusses second-generation l ipoglycopeptides, semisynthetic analogues, biomarker-guided precision dosing, and resistance-mitigation strategies that will shape the future role of vancomycin-based therapies in an era of escalating antimicrobial resistance.

KEYWORDS

Vancomycin hydrochloride; glycopeptide antibiotic; MRSA; pharmacokinetics; AUC/MIC; therapeutic drug monitoring; nephrotoxicity; biosynthesis; lipoglycopeptides; antimicrobial resistance.

1. INTRODUCTION

1.1. Background and Clinical Relevance

Vancomycin hydrochlorideis one of the most enduring antibiotics in clinical use, originally discovered in 1952 following the isolation of Streptomyces orientalis from a soil sample sent from Borneo by a missionary to Dr E.C. Kornfield at Eli Lilly & Co.(1) This soil-dwelling actinomycete produced a compound designated 05865, which demonstrated potent bactericidal activity against penicillin-resistant Staphylococcus aureus and other Gram-positive pathogens.(2)

Initial preparations of vancomycin were crude and impure, often containing up to 70% contaminants, and had a distinctive brown colour that earned it the nickname “Mississippi Mud”.(1) However, its effectiveness, especially in the treatment of resistant infections, prompted fast-track FDA approval in 1958, even before methicillin, the first semisynthetic penicillin, became available.(2) The drug was named “vancomycin” from the word “vanquish,” reflecting its anticipated role in combating difficult infections.(3)

Despite initial enthusiasm, the clinical use of vancomycin declined in the 1960s and 70s due to its side effects, particularly nephrotoxicity and ototoxicity, as well as the availability of newer, better-tolerated β-lactam antibiotics.(1) However, the emergence of methicillin-resistant S. aureus (MRSA) in the 1980s triggered a renewed interest in vancomycin as a last-resort therapy.(4) Importantly, earlier reports of toxicity were later found to be largely related to impurities in the original formulation. With improved purification techniques, vancomycin regained clinical acceptance.(1)

Vancomycin’s mechanism of action involves binding to the D-Ala-D-Ala terminus of peptidog lycan precursors, thereby inhibiting bacterial cell wall synthesis at the transglycosylation and transpeptidation stages. This interaction is stabilised by multiple hydrogen bonds, making vancom ycin a highly effective agent against Gram-positive bacteria.(3)

Vancomycin resistance first emerged in enterococci (VRE) in 1988, about 30 years after its clinical introduction.(5) This resistance was followed by the appearance of vancomycin-intermediate S. aureus (VISA) and later vancomycin-resistant S. aureus (VRSA), primarily due to genetic exchange involving vanA and vanB resistance operons. Additionally, historical use data showed a marked rise in vancomycin use in the United States during the 1980s–1990s, correlating with the increasing prevalence of resistance in healthcare settings.(4)

Structurally, vancomycin is a tricyclic glycopeptide with a molecular weight of 1,485 Da. It shares key structural and mechanistic features with other natural glycopeptides such as teicoplanin, but is distinguished by its earlier discovery and broader historical significance in clinical practice.(1, 3) Interestingly, the complete structural elucidation of vancomycin was not accomplished until 1982, nearly three decades after its clinical debut.(3)

In recent years, the rise of multidrug-resistant Gram-positive infections has spurred the development of semisynthetic derivatives such as telavancin, dalbavancin, and oritavancin, each engineered to overcome specific limitations of vancomycin, including reduced tissue penetration, nephrotoxicity, and declining efficacy against resistant strains.(3, 5)

Vancomycin hydrochloride remains a vital therapeutic agent in the management of serious infections caused by multidrug-resistant Gram-positive bacteria. Its enduring clinical relevance stems from its potent activity against pathogens such as methicillin-resistant Staphylococcus aureus (MRSA), Clostridioides difficile, and vancomycin-susceptible Enterococci species. As resistance to β-lactam antibiotics escalates globally, vancomycin has become indispensable in both hospital and community-acquired infection settings.(6)

The accurate determination of vancomycin susceptibility is a cornerstone of its clinical use. Minimum inhibitory concentration (MIC) testing enables clinicians to categorise pathogens as susceptible, intermediate, or resistant, guiding effective treatment selection. New methodologies, including testing in physiologic media like human serum or urine, have improved the relevance of MIC data, helping to bridge the gap between in vitro results and in vivo therapeutic outcomes.(7)

In specific clinical contexts such as hemodialysis, therapeutic drug monitoring (TDM) of vancomycin is crucial due to altered pharmacokinetics and an increased risk of nephrotoxicity. A study comparing the fluorescence polarisation immunoassay (FPIA) and high-performance liquid chromatography (HPLC) methods demonstrated that the FPIA method frequently overestimates serum vancomycin concentrations in hemodialysis patients. While convenient, FPIA may not reliably reflect actual drug levels, potentially leading to misinformed dosing unless corrected for such biases.(8)

Despite its broad-spectrum efficacy, vancomycin is not immune to challenges. The intrinsic and acquired resistance among enterococcal species, especially those harbouring vanA, vanB, or vanC genotypes, continues to compromise its effectiveness. Enterococci with intrinsic vanC-type resistance exhibit low-level, constitutive resistance to vancomycin, though they generally remain susceptible to teicoplanin. While these organisms are not often linked to hospital outbreaks, they underscore the need for vigilant surveillance and resistance profiling.(9)

Another area highlighting vancomycin’s clinical relevance is its local use in surgical applications, such as the management of periprosthetic joint infections (PJI). In a clinically representative mous e model, vancomycin-loaded polymethylmethacrylate (PMMA) spacers demonstrated partial succ ess in limiting infection localized to the joint space. However, the study revealed that these spacers failed to eliminate periprosthetic tissue infections, underscoring the necessity of adjunctive systemic antibiotic therapy in surgical infection control.(10)

Adverse reactions remain a concern. Immediate hypersensitivity reactions (HSRs), such as Red Man Syndrome, are frequently encountered in clinical settings. While these are often IgE-

independent and manageable through infusion rate adjustment or antihistamines, differentiating them from true allergic reactions is critical for continued therapy. Recent studies have shown that traditional skin testing protocols may use irritant diluents like sterile water, leading to misleading results. Human serum albumin-based diluents have been proposed as a better alternative, allowing for more accurate intradermal testing and minimizing misclassification of vancomycin allergies.(6)

Vancomycin hydrochloride continues to play an essential role in modern clinical practice. From systemic therapy in life-threatening infections to localized applications in surgical infections, and from careful pharmacokinetic monitoring to allergenic safety profiling, its clinical value is both diverse and enduring. However, emerging resistance, variability in drug exposure among patient populations, and potential adverse reactions necessitate a multidisciplinary approach to ensure safe and effective use.

1.2. Objectives and Scope of the Review

Vancomycin hydrochloride remains a cornerstone antimicrobial agent for the treatment of severe Gram-positive infections, particularly those caused by methicillin-resistant Staphylococcus aureus (MRSA) and other resistant pathogens. Despite its long-standing clinical use, the therapeutic landscape of vancomycin has evolved significantly due to advances in pharmacokinetic understa nding, emerging resistance patterns, and the shift toward precision medicine approaches. The primary objective of this review is to critically evaluate the contemporary scientific and clinical evidence surrounding.

2. HISTORICAL CONTEXT AND DEVELOPMENT

2.1. Discovery and Isolation

Vancomycin hydrochloride is a glycopeptide anti-biotic originally isolated from Amycolatopsis orientalis. It is widely used to treat serious Gram-positive bacterial infections, particularly those caused by methicillin-resistant Staphylococcus aureus (MRSA).

2.1.1. Isolation and Chemical Characterization Approaches

The spectrophotometric method developed by Hadi (2023) offers a simple, reliable approach for analysing vancomycin hydrochloride using diazotisation and azo coupling reactions. This method indirectly confirms the presence of vancomycin by forming a measurable azo dye with diazotised procaine and sulfacetamide sodium. The resulting chromophores showed maximal absorbance at 447 nm and 439 nm, respectively, with a strong linear response between 1–45 µg/mL.(11)

For high-purity isolation in injectable formulations, Ramesh et al. (2022) designed and validated a dual-detection system based on HPLC and UV spectroscopy using a Quality by Design (QbD) framework. Their approach allows for robust method optimisation, ensuring accurate separation and detection of vancomycin hydrochloride from complex pharmaceutical matrices.(12)

2.1.2. Formulation Innovations and Implications for Isolation

The encapsulation of vancomycin hydrochloride in niosomal vesicles, as reported by Patel et al. (2025), represents a breakthrough in formulation science. The study highlights how nanoencapsulation not only preserves the structural integrity of vancomycin but also allows its controlled release through fast-dissolving oral films. This approach enhances stability and transport across mucosal barriers, critical for developing oral versions of the typically IV-ad ministered drug.(13)

2.1.3. Molecular and Subcellular Detection Techniques

Recent advances in nano-chemical imaging have enhanced the ability to observe antibiotic interactions at the cellular level. Zhang et al. (2025) employed mid-infrared photothermal microscopy to visualise vancomycin's precise binding to peptidoglycan in Bacillus subtilis. This study provides critical information about drug-target interactions without requiring fluorescent labelling or staining, indirectly supporting compound verification and localisation at the site of action.(14)

2.1.4. Real-Time Response and Resistance Profiling

Real-Time Response and Resistance Profiling Liu et al. (2024) introduced a label-free SERS-based diagnostic tool for monitoring purine metabolites as early markers of antibiotic action. While the method is not vancomycin-specific, it allows rapid detection of antibiotic-induced m etabolic disruption. The technique offers indirect confirmation of drug bioactivity in real time and may assist in isolating effective dosages or assessing resistance levels.(15)

2.1.5. Mechanistic Insights into Binding and Action

Lang et al. (2008) pioneered the nanomechanical detection of antibiotic target interactions using cantilever sensors. Their work directly measured the binding force between vancomycin and D-Ala-D-Ala moieties in bacterial cell wall precursors, confirming vancomycin's specificity at a molecular level. This foundational study is crucial for understanding how vancomycin recognizes and binds to its target, information that guides both isolation methods and the development of resistance-mitigating analogs.(16)

2.2. Early Clinical Use and Formulation

Vancomycin hydrochloride (VHCL) is a glycopeptide antibiotic primarily used in the treatment of severe Gram-positive bacterial infections, including those caused by methicillin-resistant

Staphylococcus aureus (MRSA). While its intravenous administration remains the gold standard, recent advancements have significantly diversified its clinical applications and delivery systems.

2.2.1. Early Clinical Use and Pediatric Dosing

Initial clinical use of vancomycin emphasised critical care settings, especially for neonates and pediatric populations. Studies have shown that individualised dose optimisation in neonates, guided by population pharmacokinetics, significantly improves therapeutic outcomes while minimising nephrotoxicity.(17) Implementation of such model-informed dosing approaches is particularly crucial in critically ill patients, where pharmacokinetic variability is high.(18)

Furthermore, machine learning-assisted strategies, such as the OPTIVAN model, have emerged as powerful tools to predict optimal vancomycin dosing in diverse patient populations, including those in the ICU. These approaches improve both accuracy and safety in early treatment protocols.(19)

2.2.2. Advancements in Drug Formulation

Traditional vancomycin formulations have limitations, particularly due to poor oral bioavailability and instability in certain compounded forms. However, several innovative drug delivery strategi es have been developed to overcome these barriers. One of the most notable advancements is the nanoformulation of VHCL. In a recent 2025 study, vancomycin was successfully encapsulated into fast-dissolving oral film formulations using niosomal vesicles, improving both bioavailability and patient compliance.(20) Similarly, PEGylated niosomes produced via a supercritical CO_2-assisted process have demonstrated enhanced drug stability and prolonged release profiles.(21)

In ophthalmology, an extemporaneously compounded vancomycin eye drop formulation has shown promise as a safe and effective treatment for ocular infections, with studies confirming its chemical and microbiological stability.(22) These developments represent crucial steps toward expanding VHCL's applicability across multiple routes of administration.

A major clinical challenge is vancomycin’s limited efficacy against bacterial biofilms. Addressing this, recent research has explored vancomycin-eluting niosomes, which demonstrate enhanced inhibition of staphylococcal biofilm formation on abiotic surfaces.(23) Another study using a niosomal drug delivery system specifically designed to target MRSA revealed significant a ntibacterial and antibiofilm activity, underlining the potential of nanocarriers in managing resistant infections. To further elucidate the mechanism of action and distribution of vancomycin at the cellular level, researchers employed mid-infrared photothermal imaging techniques. These allowed visualisation of the drug’s interaction with bacterial cell walls in real time, offering new insights into its antibacterial activity and resistance mechanisms. Beyond research laboratories, these innovations are finding their way into clinical practice. Model-informed precision dosing protocols are now being evaluated and implemented in hospital settings, facilitating safer and more

effective vancomycin use.(18) The integration of AI and pharmacokinetic modelling not only enh ances early clinical decision-making but also supports individualized therapy.(19)

2.3. Comparison with Other Glycopeptides

Vancomycin hydrochloride, a cornerstone in the treatment of Gram-positive bacterial infections, has long been compared with other glycopeptides and lipoglycopeptides for efficacy, pharmacokinetics, and resistance management. Its clinical application has evolved, particularly as new agents such as teicoplanin, telavancin, dalbavancin, and oritavancin have emerged, each with unique properties that offer potential advantages over traditional vancomycin therapy.

A comprehensive review by Butler et al. highlights the structural evolution of glycopeptides, showcasing how newer derivatives like dalbavancin and oritavancin possess longer half-lives, allowing for reduced dosing frequency while maintaining robust antimicrobial activity against resistant strains.(5) Similarly, telavancin's dual mechanism of action, disruption of cell wall synthesis and membrane depolarisation, has demonstrated superior bactericidal activity in vitro compared to vancomycin, although its toxicity profile requires careful consideration.(24)

While vancomycin remains a frontline agent, clinical comparisons reveal notable differences in safety and tolerability. For example, teicoplanin has been shown to offer comparable efficacy in treating Gram-positive infections but with lower nephrotoxicity, making it a preferred option in patients with renal impairment.(25) This was echoed in a study assessing MRSA pneumonia treatment, where teicoplanin performed similarly to vancomycin in clinical outcomes, but showed a reduced risk of kidney damage. Furthermore, newer glycopeptides like dalbavancin and telavancin provide therapeutic convenience through weekly dosing and increased potency, as noted in earlier pharmacokinetic investigations.(26) This prolonged half-life significantly enhances patient compliance and reduces the need for prolonged hospital stays.

In real-world clinical settings, vancomycin's performance has also been challenged by alternativ es such as daptomycin, particularly in the management of MRSA bacteraemia. A meta-analysis revealed comparable cure rates, though some studies suggest vancomycin may offer slightly lower 30-day mortality in haemodialysis patients, depending on infection site and comorbidities.(27) Moreover, resistance mitigation strategies involving β-lactam combinations with vancomycin have shown promise, enhancing bactericidal action and potentially preventing treatment failure in MRSA infections.(28)

Despite these advancements, limitations remain. A 2020 review emphasised the narrow therapeutic window and toxicity risks of vancomycin, advocating for close monitoring and consideration of alternatives in high-risk populations.(29) These findings reinforce the importance of personalised therapy, balancing pharmacodynamic efficacy with patient-specific risk profiles.

while vancomycin hydrochloride continues to be a vital antibiotic, emerging glycopeptides offer compelling clinical advantages, especially in terms of safety, dosing convenience, and resistance management. Comparative studies affirm that vancomycin, although effective, may no longer be the optimal first-line agent in all clinical scenarios, particularly when newer agents offer improv ed outcomes with fewer side effects.

Table-1: Comparative tabular column for vancomycin v/s other glycopeptides

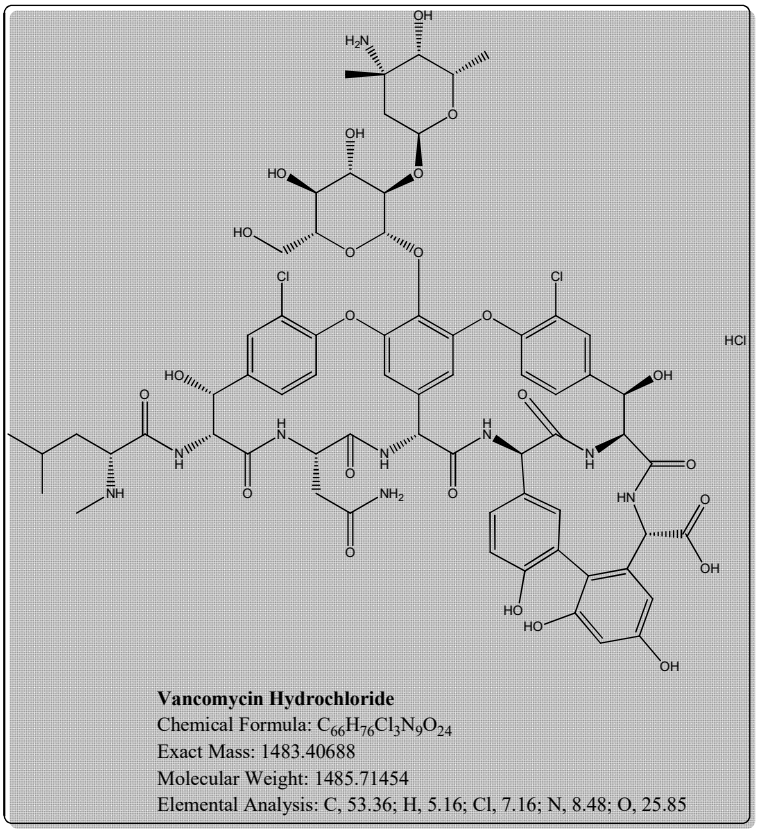
Parameter	Vancomycin	Telavancin	Dalbavancin	Oritavancin	Teicoplanin
Clinical efficacy	Reference standard for Gram-positive infections	Non-inferior to vancomycin in HAP(30)	Comparable or superior in SSTIs and bone infections (31, 32)	Comparable efficacy across SSTIs and bacteraemia (31, 33)	Comparable to vancomycin (34, 35)
Nephrotoxicity risk	Moderate–high, exposure-dependent	Higher creatinine elevation reported (30)	Lower than vancomycin (31, 32)	Low–moderate (31, 33)	Lower than vancomycin (34, 35)
Infusion reactions	Common (e.g., red man syndrome)	Less frequent	Rare	Rare	Rare
Dosing frequency	Multiple daily IV doses	Once daily IV	Weekly or bi-weekly IV	Single or weekly IV	Once daily IV
Half-life	~6–12 h	~8 h	~8–14 days	~10 days	~70–100 h
Therapeutic drug monitoring	Required	Not routinely required	Not required	Not required	Rarely required
In vitro potency (MICs)	Baseline comparator	Lower MICs than vancomycin	Lower MICs than vancomycin	Lower MICs than vancomycin	Similar to vancomycin (36)
Key clinical advantage	Broad experience, low cost	Enhanced bactericidal activity	Long-acting, OPAT-friendly	Single-dose convenience	Improved tolerability
Primary limitation	Nephrotoxicity, monitoring burden	Renal safety concerns	Higher acquisition cost	Limited long-term data	Availability varies by region

3. CHEMICAL AND PHYSICOCHEMICAL CHARACTERISTICS OF VANCOMYCIN HYDROCHLORIDE

3.1. Molecular Structure and Functional Groups

Vancomycin hydrochloride is a complex tricyclic glycopeptide antibiotic characterized by a rigid heptapeptide backbone extensively cross-linked through aromatic residues and decorated with sugar moieties, including vancosamine and glucose derivatives (37). High-resolution NMR and mass spectrometric analyses have conclusively established the molecular architecture, confirming the presence of multiple phenolic hydroxyl groups, secondary and tertiary amines, amide linkages, ether bonds, and chlorine-substituted aromatic rings that collectively define its structural rigidity and biological activity.(37)

The abundance of hydrogen-bond donors and acceptors within the vancomycin structure underpins its high affinity for the D-Ala-D-Ala terminus of bacterial peptidoglycan precursors, which is central to its mechanism of action. However, this same structural complexity also contributes to poor membrane permeability and limited oral bioavailability, necessitating parenteral administration for systemic infections.(37, 38) The hydrochloride salt form improves aqueous compatibility and handling during formulation and clinical use without altering the core molecular framework.



Structure-1: Vancomycin Hydrochloride

3.2. Solubility, Stability, and Degradation

Vancomycin hydrochloride exhibits moderate aqueous solubility that is strongly influenced by pH, ionic strength, and temperature. Physicochemical profiling studies report solubility values of approximately 0.2–0.25 mg/mL in neutral aqueous media, with enhanced solubility under mildly

acidic conditions due to protonation of amine functionalities.(38) These properties are critical in determining formulation strategies for injectable, oral, and localized delivery systems.

Stability investigations across multiple dosage forms demonstrate that vancomycin hydrochloride is chemically stable within a defined pH window but undergoes degradation under extreme acidic, alkaline, oxidative, or thermal stress conditions.(39, 40) Long-term and accelerated stability studies of compounded oral solutions and infusion preparations reveal that elevated temperatures and prolonged storage can lead to measurable potency loss, emphasising the importance of controlled storage conditions.(39, 41) Similar stability trends have been observed in antimicrobial catheter seal solutions, where temperature and excipient compatibility significantly influence drug integrity.(42)

Advanced UHPLC-MS/MS analyses have identified specific degradation pathways involving hydrolysis, oxidative cleavage of phenolic groups, and breakdown of glycosidic linkages, particula rly under environmental and simulated physiological conditions.(43) These degradation products may lack antibacterial activity and, in some contexts, contribute to formulation instability or reduced therapeutic effectiveness.

3.3. Physicochemical Characteristics

The physicochemical behaviour of vancomycin hydrochloride is governed by its high molecular weight, amphoteric nature, and extensive hydrogen-bonding capacity. The compound exhibits multiple pKa values associated with its phenolic and amine groups, resulting in pH-dependent ionisation behaviour that directly affects solubility, stability, and drug excipient interactions (38). Its low lipophilicity (low log P) limits passive membrane diffusion, reinforcing the reliance on parenteral delivery for systemic therapy.

Studies evaluating vancomycin at high concentrations in polypropylene syringes and polymeric delivery systems have demonstrated acceptable physicochemical stability when appropriately formulated, although adsorption and light sensitivity can occur under suboptimal conditions .(40, 44) Incorporation into gels, microparticles, and electrospun scaffolds further highlights how formu lation matrices can modulate stability and release kinetics while preserving chemical integrity.(44, 45)

Stability-indicating analytical methods, including fluorimetric and chromatographic techniques, have been validated to monitor degradation kinetics and ensure quality control during ma nufacturing and storage.(46) Collectively, these physicochemical characteristics dictate formulation design, shelf-life determination, and regulatory specifications for vancomycin hydrochloride products.

Table-2: Physicochemical Characteristics of Vancomycin Hydrochloride

Parameter	Description / Reported Value	Relevance to Formulation & Stability	Reference
Chemical Class	Glycopeptide antibiotic (tricyclic heptapeptide)	Determines complex molecular interactions and formulation challenges	(37)
Molecular Formula	$C_{66}H_{75}Cl_2N_9O_{24}\cdot HCl$	Reflects high molecular complexity and salt form	(37)
Molecular Weight	~1485 Da (hydrochloride salt)	High MW limits membrane permeability and oral absorption	(37, 38)
Physical Appearance	White to off-white hygroscopic powder	Hygroscopicity affects storage and packaging	(38)
Ionization (pKa)	Multiple pKa values (phenolic and amine groups)	pH-dependent solubility and stability behavior	(38)
Solubility in Water	~0.2–0.25 mg/mL at neutral pH; higher in acidic media	Influences injectable concentration limits and oral formulations	(38, 47)
Log P (Lipophilicity)	Very low (highly hydrophilic)	Explains poor oral bioavailability and limited tissue penetration	(38)
pH Stability Range	Most stable between pH 3–6	Guides formulation buffer selection	(47)
Thermal Stability	Stable at refrigerated conditions; degradation increases at ≥25–37°C	Determines storage and transport conditions	(47)
Photostability	Sensitive to prolonged light exposure	Requires light-protective packaging	(44)
Chemical Degradation	Hydrolysis, oxidation, glycosidic bond cleavage	Impacts shelf life and potency	(43, 46)
Oxidative Sensitivity	Degrades under oxidative stress (e.g., peroxide exposure)	Antioxidant-free formulations require strict control	(43, 46)
Adsorption Potential	Possible adsorption to plastics at high concentration	Relevant for infusion systems and syringes	(40)

Stability in Infusion Solutions	Stable for defined periods depending on concentration and temperature	Supports extended infusion protocols	(41)
Compatibility with Polymers	Stable in gels, microparticles, and electrospun matrices	Enables controlled-release and local delivery systems	(44, 45)
Analytical Stability Monitoring	HPLC, UHPLC-MS/MS, and fluorimetry validated	Ensures regulatory-compliant quality control	(37, 46)

4. BIOSYNTHESIS AND SEMISYNTHETIC DERIVATIVES

4.1. Natural Biosynthetic Pathway (Actinoplanes teichomyceticus)

Vancomycin hydrochloride belongs to the glycopeptide antibiotic (GPA) class, whose biosynthesis is among the most structurally and enzymatically sophisticated pathways described in actinomycetes. The natural biosynthetic paradigm was first elucidated in Actinoplanes teichomyceticus (producer of teicoplanin) and subsequently validated and expanded in Amycolat opsis orientalis, the industrial producer of vancomycin and norvancomycin.(48, 49)

At the core of vancomycin biosynthesis lies a non-ribosomal peptide synthetase (NRPS) assembly line, encoded within a large, tightly regulated biosynthetic gene cluster (BGC). This NRPS machi nery catalyses the stepwise condensation of seven amino acid residues, including several non-proteinogenic aromatic precursors, into a linear heptapeptide scaffold.(50, 51) Genome sequencing of A. orientalis has confirmed that the NRPS modules, tailoring enzymes, transporters, and resistance genes are physically clustered, ensuring coordinated expression during secondary metabolism.(49)

Comparative genomics and transcriptomics analyses have demonstrated that transcriptional regulation of this BGC is a major determinant of yield, with specific pathway-specific regulators modulating flux through the NRPS and downstream tailoring steps.(48) These findings underscore that vancomycin biosynthesis is not limited by enzyme availability alone, but by global regulatory networks and precursor supply, particularly aromatic amino acids derived from the shikimate pathway.(48, 50)

Following peptide backbone assembly, the nascent heptapeptide undergoes a sequence of post-NRPS tailoring reactions, which are essential for biological activity. These include regio- and stereospecific oxidative phenolic cross-linking catalysed by cytochrome P450 monooxygenases, forming the rigid cup-shaped aglycone that enables high-affinity binding to the D-Ala-D-Ala terminus of bacterial peptidoglycan.(51, 52) Subsequent glycosylation reactions, mediated by

dedicated glycosyltransferases, attach sugar moieties that enhance solubility, stability, and antibacterial potency.(51)

Insights from Actinoplanes teichomyceticus have been particularly influential in defining the architectural logic of GPA biosynthetic clusters, as early cloning and functional characterisation of the teicoplanin BGC established a template for understanding vancomycin biosynthesis.(53)

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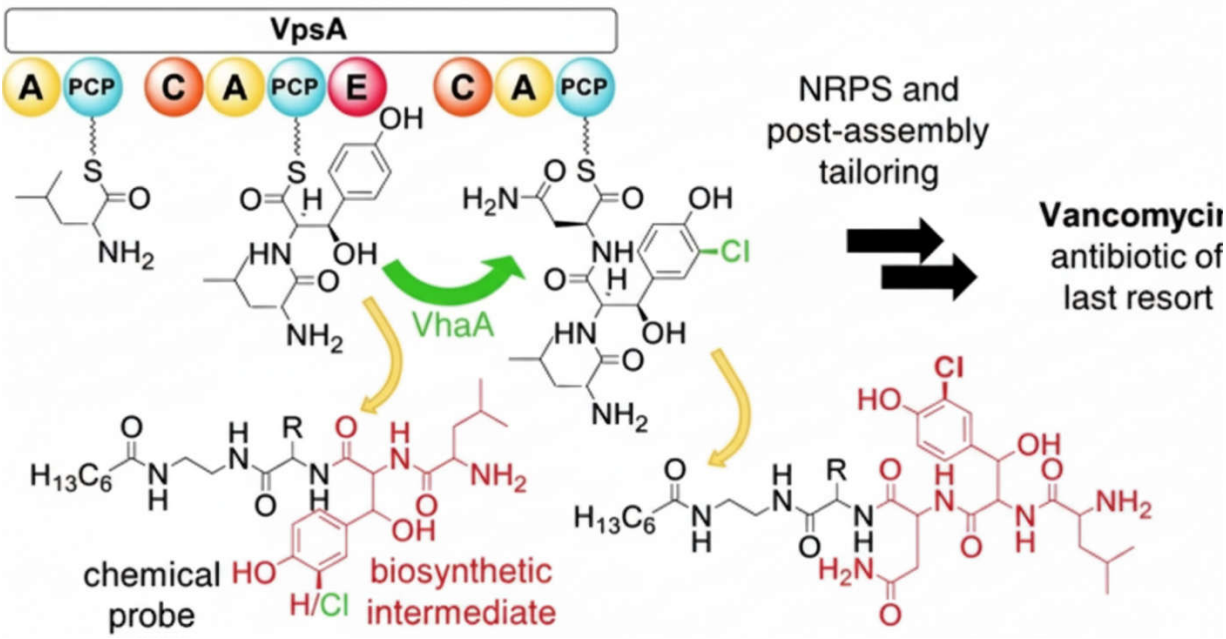
Recent studies highlight that biosynthetic gene clusters often co-localise self-resistance determinants, such as vanHAX-like operons, ensuring producer survival during antibiotic syn thesis.(54) This genomic organisation reflects evolutionary pressure to balance antibiotic production with cellular protection and has important implications for resistance mitigation strategies.

Advances in metabolic engineering and genome editing have further expanded understanding of the natural pathway. CRISPR/Cas9-mediated manipulation of GPA producers has enabled precise interrogation of regulatory genes, boundary elements of BGCs, and competing metabolic nodes, revealing opportunities to enhance vancomycin yield or generate novel derivatives.(55) Parallel metabolic engineering of precursor pathways, particularly the shikimate and aromatic amino acid pathways, has demonstrated that precursor availability is a critical bottleneck in glycopeptide b iosynthesis.(50)

Beyond native biosynthesis, enzymatic flexibility within the NRPS and tailoring systems allows peripheral modifications that form the biochemical foundation for semisynthetic vancomycin derivatives. Enzymatic oxidation, halogenation, and glycosylation steps create chemically add ressable positions that can be exploited for derivative development, as demonstrated in mechanistic studies of GPA tailoring enzymes.(52)

The natural biosynthetic pathway of vancomycin hydrochloride, exemplified by Actinoplanes teichomyceticus and refined through Amycolatopsis genomics, represents a highly regulated, mo dular, and evolutionarily optimised system. Contemporary genomic, transcriptomic, and metabo lic engineering studies have transformed this pathway from a descriptive model into a platform for rational yield improvement, resistance management, and derivative innovation.(48, 49, 55, 56)



Structure-2: Vancomycin Biosynthesis Pathway

Glycopeptides such as vancomycin are antibiotics of last resort whose biosynthetic pathways still hold undefined details. Chemical probes were used to capture biosynthetic intermediates generated in the nonribosomal peptide formation of vancomycin in vivo. The putative intercepted intermediates were characterised via HR-LC-MS^2. These species provided insights into the timing of the first chlorination of the peptide backbone by the halogenase VhaA: this holds significant in terest for enzyme engineering towards the making of novel glycopeptides.(57)

Table-3: Natural Biosynthetic Pathway of Vancomycin Hydrochloride (Actinoplanes teichomyceticus Model)

Biosynthetic Stage	**Key Enzymes / Genetic Elements**	**Biochemical Role**	**Impact on Yield, Structure, or Activity**	**Key References**
Biosynthetic Gene Cluster (BGC) Organization	NRPS genes, tailoring enzymes, transporters, regulatory and resistance genes	Coordinates vancomycin biosynthesis through clustered gene expression	Tight gene clustering ensures synchronized production and self-resistance	(49, 53, 56)
Precursor Supply Pathways	Shikimate pathway enzymes (aromatic amino acid biosynthesis)	Supplies non-proteinogenic amino acids for NRPS assembly	Precursor limitation is a major bottleneck; pathway engineering increases yield	(48, 50)

NRPS-Mediated Heptapeptide Assembly	Multi-modular NRPS complexes	Sequential condensation of seven amino acids into a linear peptide	Determines core scaffold; accuracy critical for biological activity	(51),(49)
Oxidative Phenolic Cross-Linking	Cytochrome P450 monooxygenases	Forms rigid, cup-shaped aglycone via aromatic cross-links	Essential for high-affinity D-Ala-D-Ala binding and antibacterial potency	(51, 52)
Glycosylation Reactions	Glycosyltransferases	Attachment of sugar moieties to aglycone	Enhances solubility, stability, and pharmacokinetic properties	(51, 53)
Pathway-Specific Regulation	Transcriptional regulators within BGC	Modulates expression of biosynthetic enzymes	Strongly influences final vancomycin yield and productivity	(48, 55)
Self-Resistance Mechanisms	*vanHAX*-like resistance genes	Protects producer organism from antibiotic toxicity	Enables high-level intracellular accumulation during biosynthesis	(54)
Comparative Pathway Conservation	Homologous NRPS and tailoring genes in *A. teichomyceticus* and *Amycolatopsis* spp.	Establishes conserved GPA biosynthetic logic	Supports pathway engineering using cross-species insights	(53, 56)
Genome Editing & Pathway Engineering	CRISPR/Cas9 systems	Targeted modification of regulatory and biosynthetic genes	Enables rational yield improvement and pathway optimization	(55)
Basis for Semisynthetic Derivatives	Flexible tailoring enzymes and modifiable aglycone positions	Enables post-biosynthetic chemical modifications	Foundation for developing improved vancomycin derivatives	(51, 52)

4.2. Genetic and enzymatic mechanisms of production

The genetic and enzymatic mechanisms of vancomycin hydrochloride production are intricately coordinated processes involving a suite of biosynthetic gene clusters (BGCs), regulatory systems, resistance genes, and enzymatic steps that ensure structural fidelity and high-yield synthesis in ac tinomycetes such as *Actinoplanes teichomyceticus*.

The biosynthetic gene cluster responsible for vancomycin production encodes both core biosynthetic enzymes and accessory proteins involved in regulation, transport, and resistance. A pivotal study by Xu et al. (2020) elucidated the role of vanHAX, vanRS, and vanY genes within

these BGCs, highlighting how they co-evolve to provide self-resistance and feedback regulation in producer organisms, safeguarding against autotoxicity during vancomycin synthesis.(54)

Advancing this understanding, a 2021 publication in ACS Central Science employed a phylogeny-informed genome mining approach (GPAHex) to identify novel Type V glycopeptide BGCs from Actinoplanes species. The study revealed how certain cross-linking enzymes and transcriptional regulators govern the complex oxidative cyclisation processes critical to vancomycin scaffold formation.(58) These discoveries contribute to a deeper understanding of domain-specific enzymology, including the unique activities of P450 monooxygenases and halogenases involved in tailoring the final glycopeptide product.

From a genetic engineering perspective, CRISPR/Cas9-mediated genome editing has emerged as a transformative strategy for modifying antibiotic-producing actinomycetes. Notably, a 2023 st udy demonstrated successful deletion and activation of silent BGCs in Amycolatopsis keratiniphila, a related vancomycin producer, resulting in enhanced yields. These findings are translatable to *A. teichomyceticus*, offering new methods to optimize genetic circuits that control antibiotic output.(55)

At the enzymatic level, the formation of vancomycin's distinctive three-ring structure is catalyzed by a multi-enzyme oxidative cascade. A study in Organic Letters described how this cascade drives tricyclization of linear heptapeptide precursors, establishing the rigid aromatic framework responsible for binding bacterial cell wall precursors.(59) These reactions are catalyzed by oxidative enzymes that perform regioselective phenolic couplings, which are crucial for antibiot ic activity.

Finally, an expansive 2024 review in Microbial Cell Factories underscored how metabolic engineering and synthetic biology tools such as promoter refactoring and regulator overexpression (e.g., kasO* and ermE* insertions) can significantly boost biosynthetic efficiency. These interventions activate cryptic genes and redirect metabolic flux toward vancomycin production, offering a blueprint for future industrial-scale synthesis of glycopeptides in *A. teichomyceticus*.(60)

4.3. Analytical and Characterisation Techniques

The analytical and characterisation techniques for vancomycin hydrochloride (VHCl) have advanced considerably, enabling higher sensitivity, specificity, and versatility in diverse biological and pharmaceutical matrices. Recent studies showcase an array of modern analytical tools that are pivotal for therapeutic monitoring, pharmacokinetics, impurity profiling, and quality control of this critical glycopeptide antibiotic.

One of the most innovative developments involves the use of surface molecularly imprinted solid-phase extraction (SMI-SPE) combined with HPLC–MS/MS for plasma sample analysis. This tech

nique offers exceptional selectivity by mimicking vancomycin's molecular structure in the extraction phase, achieving ultra-low detection limits (LOD: 0.5 ng/mL), and is highly effective for clinical sample cleanup and quantification.(61)

In pursuit of greener analytical solutions, silver nanoparticle-enhanced nano-fluorimetric methods have been successfully applied to the quantification of VHCl in both pharmaceutical and biological matrices. This environmentally friendly approach not only improves the sensitivity and detection efficiency but also eliminates the need for toxic solvents and lengthy sample preparation procedures, representing a significant stride toward sustainable pharmaceutical analysis.(62)

Another high-throughput strategy utilizes ultra-high-performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS) coupled with micro-SPE for therapeutic drug monitoring in plasma. This method demonstrates outstanding linearity (0.5–100 μg/mL) and is especially suited for real-time therapeutic assessments, allowing clinicians to tailor dosing strategies for cri tically ill patients receiving vancomycin.(63)

In the realm of impurity profiling, a groundbreaking study has employed two-dimensional preparative liquid chromatography (2D Prep LC) followed by LC–MS and NMR to isolate and str ucturally characterise a previously unidentified impurity in VHCl. The combination of these techniques allowed for the elucidation of a novel N-methylmethionine analogue, highlighting the importance of multidimensional separation and spectroscopic analysis in pharmaceutical quality control.(64)

Additionally, HPLC–UV remains a robust and widely adopted method for pharmacokinetic and biodistribution studies. A validated protocol has been used to detect VHCl in rat plasma, skin, and lymph nodes with a limit of detection as low as 0.05 μg/mL, complying with both FDA and EMA regulatory standards. This method has proven essential for pre-clinical drug disposition studies.(65)

Collectively, these cutting-edge methods underscore the critical role of advanced analytical technologies in improving the clinical efficacy, safety, and quality assurance of vancomycin hydrochloride. Each technique offers unique strengths tailored to specific research or clinical needs, from therapeutic monitoring to environmental sustainability and structural characterisation.

5. MECHANISM OF ACTION AND PHARMACODYNAMICS

5.1. Target Binding and Inhibition of Peptidoglycan Synthesis

Target Binding and Inhibition of Peptidoglycan Synthesis by Vancomycin Hydrochloride Vancomycin hydrochloride (VH), a clinically vital glycopeptide antibiotic, exerts its bactericidal activity by specifically targeting the D-Ala-D-Ala dipeptide terminus of peptidoglycan precursors in Gram-positive bacteria, thereby obstructing cell wall biosynthesis. Its mechanism hinges on a

sophisticated hydrogen bonding network, which tightly anchors the antibiotic to its target, preventi ng transpeptidation and transglycosylation reactions essential for peptidoglycan polymerisatio n.(66) Recent crystallographic studies have elucidated the structural basis for both target rec ognition and resistance mechanisms. Notably, the VanA ligase, expressed in resistant Enterococci, catalyses the substitution of D-Ala-D-Ala with D-Ala-D-Lac, causing the loss of a crucial hydrogen bond and a significant decrease in vancomycin binding affinity.(67) This biochemical alteration reduces binding efficiency by ~1,000-fold, thereby rendering VH largely ineffective in resistant strains. Further investigations revealed that VH forms dimers and even higher-order supercomplexes via hydrophobic and hydrogen bond-mediated interactions, which enhance its a ffinity for lipid II intermediates embedded in the bacterial membrane.(68) This supramolecular b inding is critical to its inhibitory function, reinforcing its interaction with the growing pepti doglycan chain. In response to the challenge of resistance, re-engineered vancomycin analogues have emerged, incorporating modifications that allow dual recognition of both D-Ala-D-Ala and D-Ala-D-Lac termini.(69) These compounds restore potent activity against vancomycin-resistant enterococci (VRE), confirming the flexibility and tunability of VH's glycopeptide core scaffold.

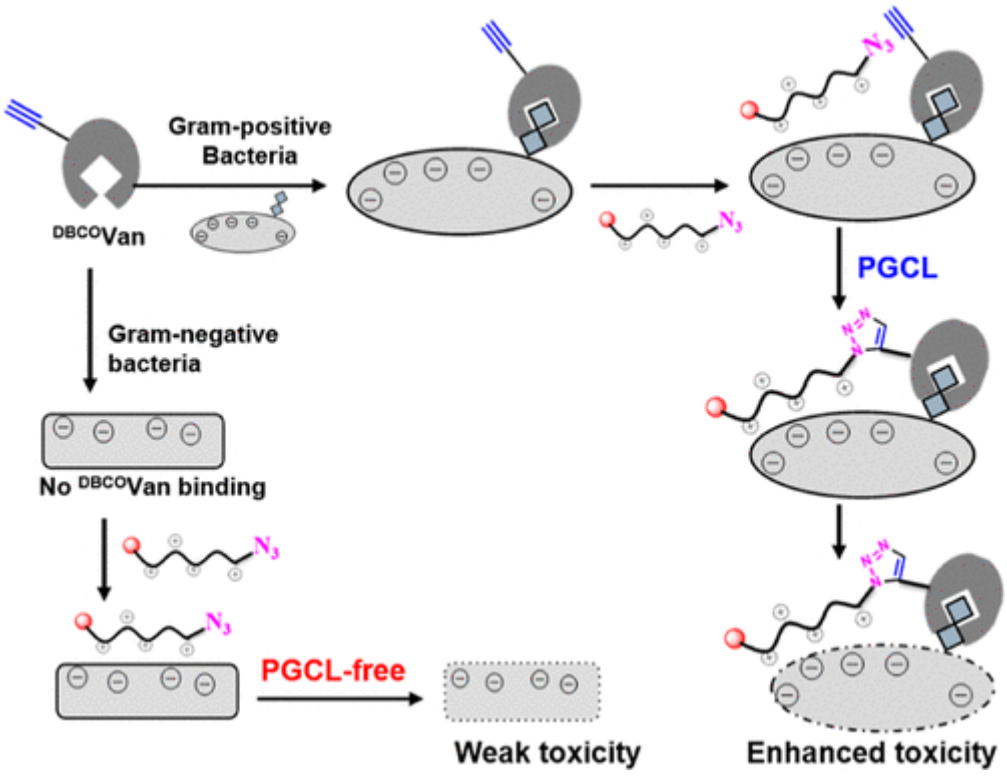


Figure-1: Schematic for PGCL synergistic antibacterial activity on Gram-positive bacteria over Gram-negative bacteria(69)

Interestingly, VH analogues can also inhibit peptidoglycan biosynthesis independently of the canonical D-Ala-D-Ala binding. Studies have demonstrated that aromatic side-chain modificati ons allow some derivatives to disrupt transglycosylation, a vital step in cell wall elongation, even

without high-affinity dipeptide binding.(70) This uncovers an auxiliary mechanism by which VH can compromise bacterial cell wall integrity. Advanced chemical ligation strategies have also been developed to selectively tether vancomycin to the bacterial cell wall through covalent interactions with peptidoglycan motifs, significantly increasing local antibiotic concentration and sp ecificity.(71) These tools enhance efficacy and reduce off-target toxicity, offering novel delivery methods. Quantitative characterisation via mass spectrometry has provided precise mapping of peptidoglycan structural variants in susceptible vs. resistant strains, correlating these modificatio ns to variations in VH binding. (72) Additionally, glycopeptide analogues like desleucyl-oritava ncin have been shown to bind multiple sites within the bacterial wall, inhibiting crosslinking enzymes and further confirming the versatility of VH's mechanism.(71) Comprehensive reviews have outlined the hydrogen bond-driven recognition mechanisms at the atomic level and described how these interactions are influenced by changes in peptidoglycan architecture.(73)

Moreover, efforts to redesign vancomycin molecules with expanded antibacterial capabilities have demonstrated their potential not only to bind modified targets but also to induce membrane disruption, a dual mode of action that significantly reduces the likelihood of resistance emergence.(74)

In the realm of real-time imaging, nanoscale photothermal spectroscopic studies have visualised VH interactions with bacterial peptidoglycan in live cells, offering unprecedented insight into the spatiotemporal dynamics of antibiotic binding.(14)

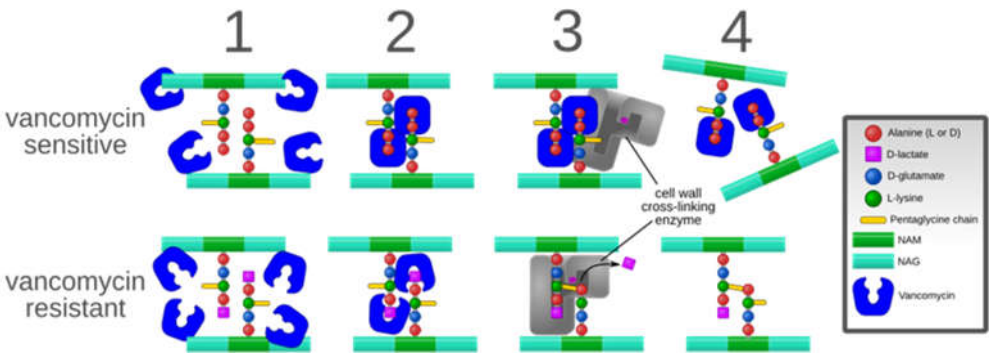


Figure-2: Mechanism of vancomycin

Mechanism of vancomycin action and resistance: This diagram shows only one of two ways vancomycin acts against bacteria (inhibition of cell wall cross-linking) and only one of many ways that bacteria can become resistant to it.

1. Vancomycin is added to the bacterial environment while it is trying to synthesise a new cell wall. Here, the cell wall strands have been synthesised, but not yet cross-linked.

2. Vancomycin recognizes and binds to the two D-ala residues on the end of the peptide chains. However, in resistant bacteria, the last D-ala residue has been replaced by a D-lactate, so vancomycin cannot bind.
3. In the resistant bacteria, cross-links are successfully formed; still, in the nonresistant (sensitive) bacteria, the vancomycin bound to the peptide chains prevents them from interacting properly with the cell wall cross-linking enzyme.
4. In the resistant bacteria, stable cross-links are formed. In the sensitive bacteria, cross-links cannot be formed, and the cell wall falls apart.

MECHANISM OF ACTION: Vancomycin targets bacterial cell wall synthesis by binding to the basic building block of the bacterial cell wall of Gram-positive bacteria, whether it is of aerobic o r anaerobic type. Specifically, vancomycin forms hydrogen bonds with the D-alanyl-D-alanine (D-Ala-D-Ala) peptide motif of the peptidoglycan precursor, a component of the bacterial cell wall. Peptidoglycan is a polymer that provides structural support to the bacterial cell wall. The peptidoglycan precursor is synthesised in the cytoplasm and then transported across the cytoplasmic membrane to the periplasmic space, where it is assembled into the cell wall. The assembly process involves two enzymatic activities: transglycosylation and transpeptidation. Transglycosylation involves the polymerisation of the peptidoglycan precursor into long chains, while transpeptidation involves the cross-linking of these chains to form a three-dimensional mesh-like structure.(75)

Vancomycin inhibits bacterial cell wall synthesis by binding to the D-Ala-D-Ala peptide motif of the peptidoglycan precursor, thereby preventing its processing by the transglycosylase; as such, vancomycin disrupts the transglycosylation activity of the cell wall synthesis process. The disruption leads to an incomplete and corrupted cell wall, which makes the replicating bacteria vulnerable to external forces such as osmotic pressure, so that the bacteria cannot survive and are eliminated by the immune system.(75)

Gram-negative bacteria are insensitive to vancomycin due to their different cell wall morphology. The outer membrane of Gram-negative bacteria contains lipopolysaccharide, which acts as a barrier to vancomycin penetration. That is why vancomycin is mainly used to treat infections caused by Gram-positive bacteria. (75)

5.2. Synergistic Effects with Other Antibiotics

Vancomycin hydrochloride (VH), a potent glycopeptide antibiotic, remains a frontline treatment against Gram-positive pathogens, particularly Staphylococcus aureus. However, the emergence of vancomycin-intermediate (VISA) and heterogeneous VISA (hVISA) strains has prompted the strategic use of antibiotic combinations to restore and enhance their efficacy. Recent high-impact

studies have shed light on the synergistic interactions between VH and various antibiotic classes, offering promising clinical implications. One notable approach is the combination of vancomycin with β-lactam antibiotics, such as oxacillin, cefazolin, and cefoxitin. This synergy enhances cell wall permeability, facilitating increased VH penetration and bactericidal activity, especially against MRSA strains with reduced vancomycin susceptibility.(76) The mechanistic rationale behind this synergy lies in β-lactams' ability to disrupt peptidoglycan synthesis, weakening the bacterial envelope and improving VH access to its target. Similarly, nafcillin, a β-lactam agent, has demonstrated significant synergy with vancomycin in hVISA strains. When used in an in vitro pharmacokinetic/pharmacodynamic (PK/PD) model, this combination significantly improved bacterial kill rates compared to monotherapy, suggesting its therapeutic potential in persistent MRSA infections.(77)

Beyond β-lactams, gentamicin, an aminoglycoside, has shown synergistic effects with VH in eradicating S. aureus biofilms on biomaterials. Biofilm-associated infections are notoriously difficult to treat due to reduced antibiotic penetration and metabolic dormancy of embedded cells. This combination effectively disrupts biofilm integrity and enhances bacterial clearance on polyu rethane surfaces, which is particularly relevant in orthopaedic and catheter-associated infect ions.(78)

Interestingly, vancomycin has also shown synergistic action with trimethoprim and nitrofurantoin, two antibiotics traditionally used against Gram-negative organisms. In wild-type Escherichia coli, these combinations enhanced outer membrane permeability, allowing vancomycin normally ineffective against Gram-negative bacteria, to exhibit antibacterial activity. This breakthrough opens the door for using VH in expanded bacterial spectra when paired with membrane-perturbing agents.(79)

Furthermore, recent research has emphasized that synergy between β-lactams and glyco/li poglycopeptides like vancomycin and dalbavancin is maintained even in the absence of the seesa w effect. The seesaw effect describes the inverse susceptibility of MRSA to β-lactams and glycopeptides; however, the study found that synergy persists despite this inverse relationship, underscoring a robust combinatorial effect independent of susceptibility shifts.(80)

5.3. Strategies to Achieve Higher Yield and Product Recovery of Vancomycin Hydrochloride

5.3.1. Fermentation Optimisation

Efficient production of vancomycin hydrochloride fundamentally depends on optimising the fermentation stage, as this step determines the initial antibiotic titer produced by *Amycolatopsis orientalis*.

a) Carbon–Nitrogen Balance

Optimising the carbon–nitrogen (C/N) ratio is critical for redirecting metabolic flux from biomass growth to secondary metabolite synthesis. Studies demonstrate that slowly metabolised carbon sources, such as maltodextrin, combined with complex nitrogen sources like soybean meal, sign ificantly enhance vancomycin yield by sustaining antibiotic biosynthesis during the stationary phase(81). Excessively rapid carbon utilisation, in contrast, suppresses glycopeptide production.

b) Phosphate Regulation

Phosphate Regulation Phosphate acts as a global regulator of secondary metabolism. Controlled phosphate limitation has been shown to relieve repression of vancomycin biosynthetic gene clusters, resulting in higher antibiotic titers.(81, 82) Excess phosphate suppresses vancomycin formation despite adequate biomass accumulation.

c) Sustainable Feedstocks and Inoculum Control

The substitution of refined substrates with industrial residues (e.g., crude glycerol) maintains vancomycin yields while reducing production costs and improving sustainability.(83) Precise inoculum control further ensures reproducibility by preventing excessive biomass formation that competes with antibiotic synthesis .(83)

d) Process Parameter Control

Critical parameters such as pH, dissolved oxygen, aeration, agitation, and temperature must be tig htly regulated. Pilot- and plant-scale studies confirm that maintaining optimal dissolved oxygen levels prevents metabolic stress and ensures consistent vancomycin titers during scale-up.(84) Response surface optimisation has demonstrated that small deviations in these parameters can significantly reduce yield.(85)

e) Medium Supplementation and Culture Mode

Supplementation with amino acids (e.g., glycine, phenylalanine, tyrosine) enhances precursor availability for glycopeptide assembly, improving specific productivity.(82) Continuous or semi-continuous fermentation strategies further stabilise nutrient availability, leading to improved volumetric productivity compared with batch systems.(82)

Outcome: Fermentation optimisation can substantially increase crude vancomycin concentration, forming a strong foundation for high final product yield.(81, 85)

5.3.2. Downstream Purification and Recovery

Even with high fermentation titers, inefficient downstream processing can drastically reduce overall yield. Therefore, purification optimisation is essential.

a) Crystallisation Enhancement

Improved crystallisation techniques, including controlled feeding, optimised mixing, and temperature regulation, enable near-quantitative recovery of vancomycin hydrochloride. Ion-e

xchange-assisted crystallisation has been shown to achieve ~99% recovery while significantly reducing processing time.(86)

b) Adsorption and Resin-Based Purification

Modern purification strategies employ selective resins to adsorb vancomycin from fermentation broth, minimising product loss during washing and elution steps. Patent-based processes demonstrate that resin optimisation improves purity (>99%) and increases overall recovery efficiency.(86)

c) Reduction of Yield Loss During Multi-Step Processing

Traditional purification methods involving repeated pH shifts and recrystallisation steps are associated with cumulative yield losses. Process redesign, such as minimising unnecessary pH cycling and integrating purification steps, addresses these limitations and improves net product yield .

d) Stability-Driven Process Optimisation

Life-cycle and stability studies highlight fermentation and purification as the most resource-intensive steps. Optimising solvent use, sterilisation cycles, and storage conditions reduces degradation risks and enhances effective yield.(87)

Outcome: Advanced crystallisation and streamlined purification significantly increase re coverable vancomycin hydrochloride from high-titer broths.(86)

5.3.3. Statistical and Design-Based Optimisation Approaches

To systematically maximise yield and ensure reproducibility, statistical optimisation tools play a critical role.

a) Design of Experiments (DOE)

Design of Experiments (DOE), including Box–Behnken and response surface methodologies, enables simultaneous evaluation of multiple variables while minimising experimental runs. These approaches identify optimal parameter interactions that are not apparent through one-factor-at-a-time experiments.(85, 88)

b) Process Robustness and Scalability

DOE-guided optimisation enhances process robustness, ensuring that optimised conditions remain effective during scale-up. This is particularly important for fermentation parameters and formulation steps that influence vancomycin recovery.(85)

c) Yield Maximisation Beyond Fermentation

Statistical design principles extend to formulation and microsphere development, where entrapment efficiency and recovery yield are maximised through controlled parameter optimisation.(88)

Outcome: Statistical design approaches ensure consistently high yield, reduced variability, and efficient scale-up of vancomycin hydrochloride production.(85, 88)

Table-4: Strategies for Maximising Yield and Product Recovery of Vancomycin Hydrochloride

Process Stage	Key Parameter / Method	Optimized Approach	Impact on Yield and Product Recovery	Reference No.
Fermentation Optimization	Carbon source selection	Use of slowly metabolized carbon sources (e.g., maltodextrin)	Sustains secondary metabolism and increases vancomycin biosynthesis	(81)
	Nitrogen source optimization	Complex nitrogen sources such as soybean meal	Enhances precursor availability and improves antibiotic titer	(81, 82)
	Carbon–nitrogen synergy	Balanced C/N ratio	Redirects metabolic flux from biomass growth to vancomycin production	(81)
	Phosphate regulation	Controlled phosphate limitation	Relieves repression of van gene clusters, increasing yield	(81, 82)
	Sustainable substrates	Use of crude glycerol and industrial residues	Maintains yield while reducing cost and improving reproducibility	(83)
	Inoculum control	Optimized inoculum size and age	Prevents excessive biomass and ensures consistent production	(83, 85)
	Process parameters	Tight control of pH, dissolved oxygen, aeration, agitation	Maintains metabolic stability and high titers during scale-up	(84, 85)
	Culture mode	Continuous or semi-continuous fermentation	Improves volumetric productivity compared to batch systems	(82)
Downstream Purification	Crystallization strategy	Controlled feeding, temperature, and mixing	Achieves near-quantitative recovery (~99%) of vancomycin HCl	(86)
	Ion-exchange assistance	Resin-based adsorption and elution	Improves purity and minimizes product loss	(86)
	Process integration	Reduction of repeated pH shifts and recrystallization steps	Minimizes cumulative yield loss during purification	(88)

	Stability management	Optimized solvent use and storage conditions	Prevents degradation and improves effective yield	(87)
Statistical & Design Approaches	Design of Experiments (DOE)	Box–Behnken and response surface methodology	Identifies optimal parameter interactions with fewer experiments	(85, 88)
	Multivariate optimization	Simultaneous optimization of multiple variables	Enhances robustness and reproducibility of yield	(85)
	Scale-up validation	DOE-guided pilot- and plant-scale translation	Maintains high yield and process consistency at industrial scale	(84, 85)
	Formulation optimization	Statistical optimization of encapsulation/formulation variables	Maximizes recovery and entrapment efficiency	(88)

5.4. Pharmacodynamic Targets (e.g., AUC/MIC)

The pharmacodynamic evaluation of vancomycin hydrochloride has increasingly focused on the area under the concentration-time curve to minimum inhibitory concentration ratio (AUC/MIC) as a more accurate predictor of therapeutic efficacy and safety than traditional trough-based monitoring. This paradigm shift is supported by a growing body of clinical evidence emphasising the critical value of reaching optimal AUC thresholds while minimising nephrotoxicity risk. A multicenter study examining enterococcal bacteremia revealed that an $AUC_{48}/MIC \geq 400$ was strongly correlated with favourable clinical outcomes, validating guideline recommendations for AUC-based dosing strategies. Similarly, research conducted on methicillin-resistant coagulase-negative staphylococci (MRCoNS) infections found that achieving an $AUC_{24}/MIC \geq 373$ was significantly associated with treatment success and microbiological eradication, reinforcing the relevance of this pharmacodynamic marker in difficult-to-treat Gram-positive infections.(89)

Real-world clinical implementation, however, presents challenges. A prospective observational study involving 114 patients demonstrated that reaching the recommended AUC range of 400–650 mg·h/L is often difficult under routine conditions. Moreover, approximately 16% of patients developed acute kidney injury (AKI), emphasising the delicate balance between efficacy and renal safety.(90) In contrast, a multicenter analysis on the timing of AUC attainment indicated that achieving pharmacodynamic targets during the early phase of therapy enhanced therapeutic outcomes without significantly increasing nephrotoxicity.(91)

In terms of healthcare system practices, a pharmacy-driven AUC/MIC dosing protocol was assessed across a 12-hospital network. Results showed no increase in nephrotoxicity compared to traditional trough-based monitoring while significantly improving adherence to blood sampling

schedules and protocol feasibility, showcasing a scalable model for therapeutic drug monitoring (TDM).(92)

these studies collectively demonstrate that AUC/MIC is a clinically validated and operationally feasible pharmacodynamic target for optimising vancomycin hydrochloride therapy. Incorporating AUC-guided dosing can lead to better clinical outcomes, particularly in severe infections, while simultaneously managing the risk of toxicity, provided that institutions are equipped to overcome the logistical barriers to its implementation.

6. PHARMACOKINETICS AND DRUG MONITORING

6.1. ADME Profile of Vancomycin Hydrochloride: A Research-Based Overview

Vancomycin hydrochloride is a glycopeptide antibiotic widely used for treating serious Gram-positive infections, particularly those caused by methicillin-resistant Staphylococcus aureus (MRSA). Its pharmacokinetics exhibit considerable variability depending on patient demo graphics, comorbid conditions, and organ function. Recent studies have deepened our understanding of vancomycin's Absorption, Distribution, Metabolism, and Excretion (ADME) profiles across various patient populations.

a) Absorption

Vancomycin is characterised by negligible gastrointestinal absorption when administered orally, which restricts its systemic use to intravenous (IV) administration for most indications. The oral formulation is reserved for local effects in the gastrointestinal tract, such as in Clostridioides difficile infections. Studies focused on its systemic kinetics, such as in post-liver transplant children or critically ill adults, confirm that therapeutic concentrations can only be reliably achieve d through IV routes.,(93, 94)

b) Distribution

Once administered, vancomycin distributes widely throughout the body, though it demonstrates limited tissue penetration in some compartments. The volume of distribution (Vd) varies significantly with patient physiology. For example, pediatric liver transplant recipients showed altered distribution parameters due to changes in fluid balance and organ perfusion, which necessit ate careful therapeutic monitoring.(93) Similarly, obese adults and those on hemodialysis demons trated larger Vd values, indicating the need for dose individualisation based on body weight and f at composition.(95, 96)

In elderly populations, distribution kinetics become more unpredictable, as demonstrated by machine learning-based models that incorporate multiple physiological predictors to enhance dosing accuracy.(97) Moreover, a comprehensive population analysis spanning the human lifespan

reported that vancomycin's Vd is lowest in neonates and increases with age, peaking in late adultho od before slightly declining in elderly patients.(98)

c) Metabolism

Vancomycin undergoes minimal metabolism, making hepatic processing clinically insignificant. The drug is primarily excreted unchanged by the kidneys, which simplifies pharmacokinetic modelling but also amplifies the risk of accumulation in cases of renal impairment. This c haracteristic has been validated in studies involving febrile neutropenic patients and the critically ill, where altered renal clearance, not metabolism, played a pivotal role in determining vancomycin exposure and toxicity.(94, 99, 100)

d) Excretion

Excretion Renal clearance is the predominant route for vancomycin elimination. It is excreted mainly by glomerular filtration, and any impairment in renal function can dramatically affect serum drug levels. For instance, studies in obese patients on hemodialysis emphasised the need to tailor vancomycin loading and maintenance doses to account for fluctuating clearance rates.(96) In patients with augmented renal clearance, such as those with hematologic malignancies, higher doses may be necessary to reach therapeutic targets without underdosing.(99)

Clearance variability has also been tied to clinical outcomes. In bacteremia caused by *Enterococcus faecium*, suboptimal pharmacokinetic/pharmacodynamic (PK/PD) indices, such as reduced AUC/MIC ratios, were associated with increased mortality.(101) This underlines the clinical importance of achieving appropriate drug exposure via optimised excretion rates. Emerging Insights Recent nano-spectroscopy studies have added a novel layer to our understanding of vancomycin distribution, revealing how the drug interacts with bacterial membranes at the subcellular level. Although not traditionally part of systemic ADME profiling, such findings provide insight into vancomycin's mechanism of action and tissue targeting at microscopic resolution**.**

6.2. Trough-based vs. AUC-guided Dosing

Comparative Evaluation of Trough-Based versus AUC-Guided Dosing of Vancomycin Hydrochloride. Vancomycin remains the cornerstone treatment for serious methicillin-resistant Staphylococcus aureus (MRSA) infections; however, its narrow therapeutic index demands caref ul therapeutic drug monitoring (TDM). Historically, trough serum concentrations were used as a surrogate to ensure adequate exposure. Recent clinical evidence increasingly favours area-under-the-curve (AUC)–guided dosing due to improved clinical outcomes and lower nephrotoxicity risk.

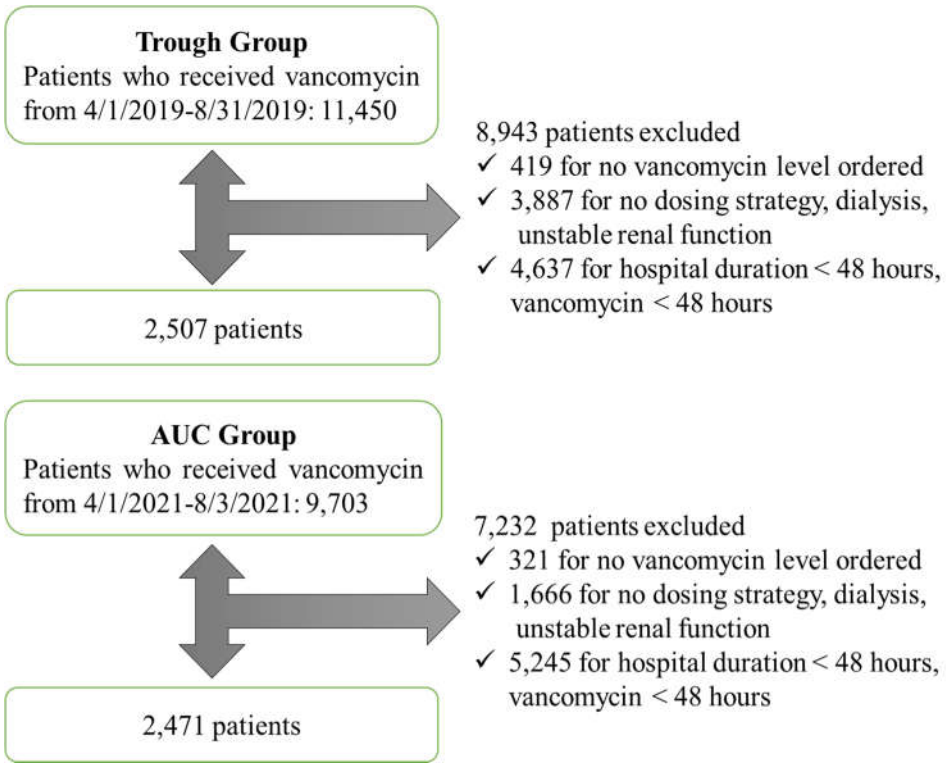


Figure-3: The exclusion criteria of this study were as follows: vancomycin duration of <48 h, hospital length of stay of <48 h, no available dosing strategy, patients on any type of dialysis, unstable renal function (as clinically determined and documented by the clinical pharmacist or a baseline serum creatinine of >1.9 mg/dL), and no vancomycin level ordered. There were 2,507 patients in the trough group and 2,471 patients in the AUC group.(102)

a) Limitations of Trough-Based Monitoring

Trough levels often correlate poorly with true drug exposure, leading to potential under- or over-dosing.(103) This imprecision is associated with higher rates of vancomycin-induced acute kidney injury (AKI) because trough targets frequently exceed the exposure needed for optimal efficacy.(104, 105) Moreover, the timing of sampling in trough-based protocols is highly error-prone, contributing to inconsistent therapeutic attainment .(106)

b) Advantages of AUC-Guided Dosing

AUC-guided dosing directly quantifies drug exposure, targeting an AUC24/MIC ratio of 400–600, which better reflects pharmacodynamic requirements for bactericidal activity.(107) Multiple studies demonstrate that transitioning to AUC-based monitoring in real-world healthcare systems reduces nephrotoxicity without compromising efficacy .(104, 108) This advantage holds across diverse patient populations and clinical environments .(109, 110) Additionally, retrospective data show significantly lower AKI incidence when AUC estimation is used instead of trough-only approaches .(111)

c) Implementation and Real-World Practice

Despite strong recommendations from updated clinical guidelines, a survey of hospital systems reveals substantial gaps in national adoption of AUC-based TDM, with barriers including staffing limitations, lack of Bayesian software, and training deficits.(112) Nevertheless, hospitals that implemented AUC-guided programs reported marked improvements in safety outcomes and target attainment.(107),(110) Continued evaluation highlights the necessity for standardised timing and workflow optimisation in all TDM approaches.(106, 113)

d) Clinical Implications

Collectively, these findings indicate that AUC-guided dosing provides superior precision in b alancing efficacy and toxicity, supporting a global shift away from trough-based strategies. H ealthcare institutions adopting AUC-based Bayesian tools demonstrate better patient outcomes and alignment with pharmacokinetic-pharmacodynamic (PK-PD) principles central to modern antimicrobial stewardship.(103, 108)

Table-5: AUC based Bayesian tools clinical implementation summary

Evidence Category	Count	Summary
Randomised / Prospective	2	AUC monitoring reduces nephrotoxicity and drug exposure burden
Large Database / Multi-centre	3	AUC improves safety + more precise PK-PD goal attainment
Implementation Studies	3	Safe adoption is feasible, improves target alignment
Systemic Review / Meta-Analysis	1	Strong confirmation of reduced nephrotoxicity
Survey Data	1	Adoption gap persists globally

6.3. Population-Specific PK Considerations (Paediatrics, Elderly, CKD)

6.3.1. Population-Specific Pharmacokinetic Considerations of Vancomycin Hydrochloride

Vancomycin hydrochloride remains a fundamental therapeutic agent for severe gram-positive infections, yet its narrow therapeutic index and substantial pharmacokinetic (PK) variability necessitate individualized dosing approaches. Different patient populations including paediatrics, elderly individuals, and those with chronic kidney dysfunction exhibit significant alterations in va ncomycin absorption, distribution, metabolism, and excretion, resulting in variable drug exposure and therapeutic uncertainty.

6.3.2. Vancomycin PK in Elderly Patients

Ageing is associated with physiological decline in renal function, changes in body composition, and comorbidity-related organ impairment, all of which directly influence vancomycin PK. A 2025 population PK model demonstrated that standard creatinine-clearance-based dosing may overestimate vancomycin elimination in advanced-age patients, increasing the potential for toxic overexposure.(114) A companion study using multi-algorithm predictive analytics confirmed that conventional monitoring strategies fail to accurately reflect exposure in elderly patients, suppo rting the need for model-informed dosing to prevent nephrotoxicity while maintaining therapeutic efficacy.(115)

6.3.3. PK Variability in Renal Dysfunction and Hemodialysis

Renal impairment leads to substantial reductions in vancomycin clearance, requiring significant dose adjustment. Critically ill patients undergoing mechanical circulatory support or continuous renal replacement therapy (CRRT) experience rapidly changing renal function and extracorporeal elimination pathways. A 2024 PPK analysis incorporated dynamic CRRT status, yielding improved clearance predictions and safer dosing guidance in unstable ICU populations.(116) Similarly, individualised dosing strategies in CRRT and oliguria were shown to perform significantly better than traditional fixed regimens due to large inter-patient variability in drug handling.(117)

Patients receiving intermittent hemodialysis also demonstrate unique PK behaviour due to extracorporeal clearance fluctuations. A multinational study highlighted the need for optimised loading and post-dialysis dosing regimens to achieve appropriate AUC24 targets without excessi ve exposure.(118) Neurosurgical critical care patients, despite preserved renal function, exhibited unpredictable PK variability linked to cerebral injury-associated physiological derangements, reinforcing the necessity of population-tailored dosing models in specialised ICUs.(119)

6.3.4. Geographic and Ethnic Variability

Distinct demographic characteristics further influence PK outcomes. A study in Sudanese adults e mphasised the role of population-specific renal function baselines and physiological diversity when developing dosing guidelines.(120) In contrast, data from healthy Korean volunteers serve as a reference PK baseline to support comparative dosing in disease-affected Asian population s.(121)

Table-6: Pharmacokinetic Properties, Drug Monitoring, and Population-Specific Considerations of Vancomycin Hydrochloride

Population / Study Focus	Key Pharmacokinetic Findings	Drug Monitoring Approach	Clinical Implications	Ref. No.
Paediatric post-liver transplant patients	Increased interindividual variability in clearance due to altered hepatic function and fluctuating renal recovery post-transplant	AUC-guided TDM is superior to trough-based monitoring	Standard dosing frequently underachieves therapeutic targets; individualised PK modelling is required	(122)
Critically ill adults	Marked variability in volume of distribution and clearance; renal function alone insufficient to predict exposure	Individualized PK parameter-based monitoring	Early PK assessment improves target attainment and reduces nephrotoxicity risk	(123)
Obese adult patients	Body weight significantly impacts volume of distribution; clearance not linearly proportional to total body weight	Population PK–guided initial dosing	Weight-based dosing without modeling leads to subtherapeutic or toxic exposure	(124)
Obese patients on haemodialysis	Dialysis modality strongly affects vancomycin clearance; delayed redistribution is observed	Model-informed loading dose strategies	Individualised loading doses are essential to rapidly achieve therapeutic AUC	(125)
Elderly patients	Reduced renal clearance and prolonged half-life; high PK variability despite similar serum creatinine	Machine-learning-assisted PK prediction	Conventional dosing risks accumulation and toxicity in older adults	(115)
All age groups (lifespan analysis)	Age-dependent changes in clearance and	Population PK models across the lifespan	Uniform dosing recommendations are	(126)

	distribution from neonates to the elderly		inadequate across age extremes	
Hematologic malignancy with neutropenia and ARC	Augmented renal clearance leads to subtherapeutic exposure	AUC-based dose optimisation	Higher or more frequent dosing is needed to avoid treatment failure	(127)
Febrile neutropenia in hematologic malignancy	Altered PK parameters due to inflammation and renal hyperfiltration	Bayesian software-guided dosing	Bayesian TDM improves early target attainment	(128)
Enterococcus faecium bacteremia	Higher AUC/MIC associated with reduced mortality	PK/PD-driven exposure assessment	Achieving PK/PD targets is prognostic for survival	(129)
Real-world hospital practice (mixed populations)	Trough levels poorly correlate with AUC	Pharmacist-driven Bayesian AUC monitoring	Transitioning away from trough-based monitoring improves safety and efficacy	(103)
Mixed adult cohort (AKI outcomes)	Excessive AUC exposure is strongly linked to acute kidney injury	AUC-based TDM using propensity-weighted analysis	AUC-guided monitoring reduces AKI incidence and optimises utilisation	(104)

7. CLINICAL APPLICATIONS AND THERAPEUTIC INDICATIONS

Vancomycin hydrochloride remains a cornerstone antimicrobial agent for the management of serious Gram-positive infections, particularly those caused by methicillin-resistant Staphylococcus aureus (MRSA), coagulase-negative staphylococci, and Enterococcus species.(130) It is routinely used in clinical practice for bacteraemia, endocarditis, pneumonia, meningitis, osteomyelitis, and skin/soft-tissue infections where resistant pathogens are suspected or confirmed .(130)

Given its narrow therapeutic index, therapeutic drug monitoring (TDM) plays a critical role in ensuring optimal clinical outcomes and minimizing nephrotoxicity. Current recommendations emphasize AUC24/MIC-guided dosing over traditional trough-based monitoring, enabling improved precision in managing both underexposure and toxicity risks.(130)

In addition to therapeutic use, vancomycin has been incorporated into perioperative prophylaxis settings, particularly in orthopedic and spine surgery when MRSA colonization risk or β-lactam allergy exists .(131) However, emerging evidence suggests a need for caution: routine prophylactic use may not consistently improve postoperative infection outcomes and could contribute to antimicrobial resistance and dysbiosis if applied without proper stewardship justification.(131) T herefore, prophylactic use should be selective and risk-stratified, aligning with infection-prevention guidelines. Overall, while vancomycin continues to serve as a preferred agent against resistant Gram-positive infections, evolving stewardship perspectives and safety considerations demand patient-specific decision-making, robust TDM practices, and ongoing evaluation of clinical indication appropriateness.(130, 131)

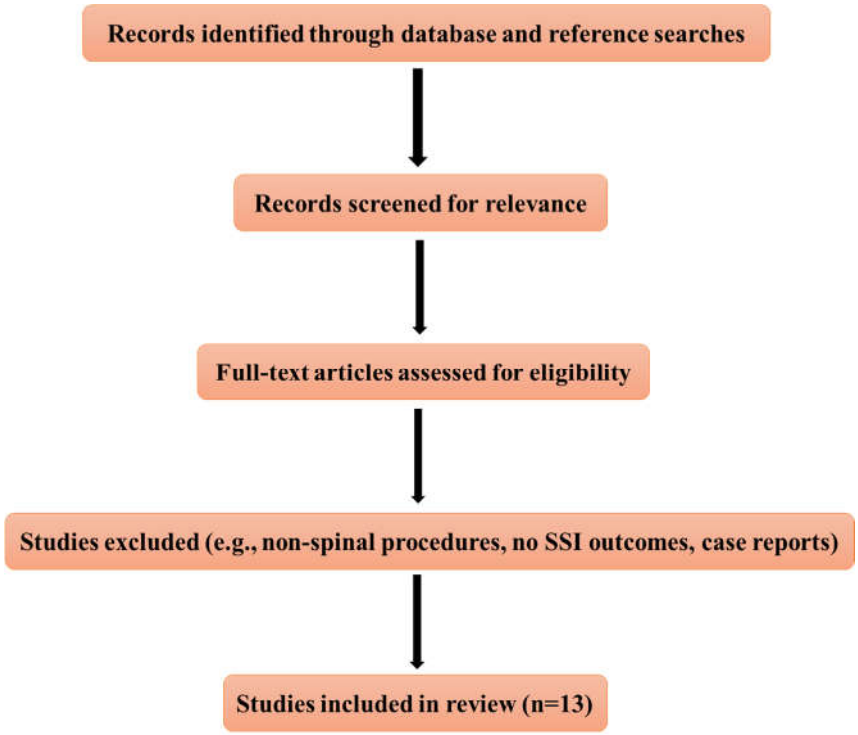


Figure-4: Simplified flow diagram of study selection for the narrative review. A total of 13 studies met the inclusion criteria and were included in the synthesis.(131)

7.1. Treatment of MRSA and Gram-Positive Infections

Vancomycin Hydrochloride in the Treatment of MRSA and Other Gram-Positive Infections

Vancomycin hydrochloride remains one of the primary therapeutic agents for managing serious methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive infections due to its ability to inhibit cell-wall synthesis in resistant organisms.(132) Although alternative antibiotics have emerged, vancomycin continues to be widely used in bloodstream infections, pneumonia, endocarditis, and complicated skin/soft-tissue infections where MRSA is suspected or confirmed.(133)

However, evolving antimicrobial resistance and concerns regarding toxicity have prompted co mparative evaluations of vancomycin versus newer or combination therapies. A recent network meta-analysis found that while vancomycin remains clinically effective, certain regimens such as linezolid or minocycline combined with rifampin, demonstrated superior clinical cure rates in some MRSA cases.(132) These results indicate that although vancomycin is effective, alternative therapies may provide improved outcomes depending on patient-specific and infection-specific characteristics. In S. aureus bacteremia, vancomycin remains an important option when β-lactam antibiotics are ineffective or contraindicated.(133) A systematic review showed it continues to achi eve satisfactory microbiological eradication; however, its use was associated with a higher incidence of adverse reactions compared to some alternative agents.(133) This highlights the importance of precision dosing and therapeutic drug monitoring to balance effectiveness with nephrotoxicity risk. Emerging evidence also supports the use of vancomycin in combination with β-lactam antibiotics to enhance bactericidal activity against MRSA. Recent clinical and in-vitro findings demonstrate that adjunctive β-lactam therapy may improve bacterial clearance rates and reduce treatment failures compared to vancomycin monotherapy.(134) This synergistic strategy may be particularly beneficial in severe or persistent MRSA bacteraemia. Vancomycin remains a cornerstone therapeutic option for Gram-positive infections; however, clinical decisio n-making must consider evolving comparative effectiveness data, risk-benefit profiles, and opportunities to optimize outcomes through combination therapy or alternative antimicrobials when appropriate.

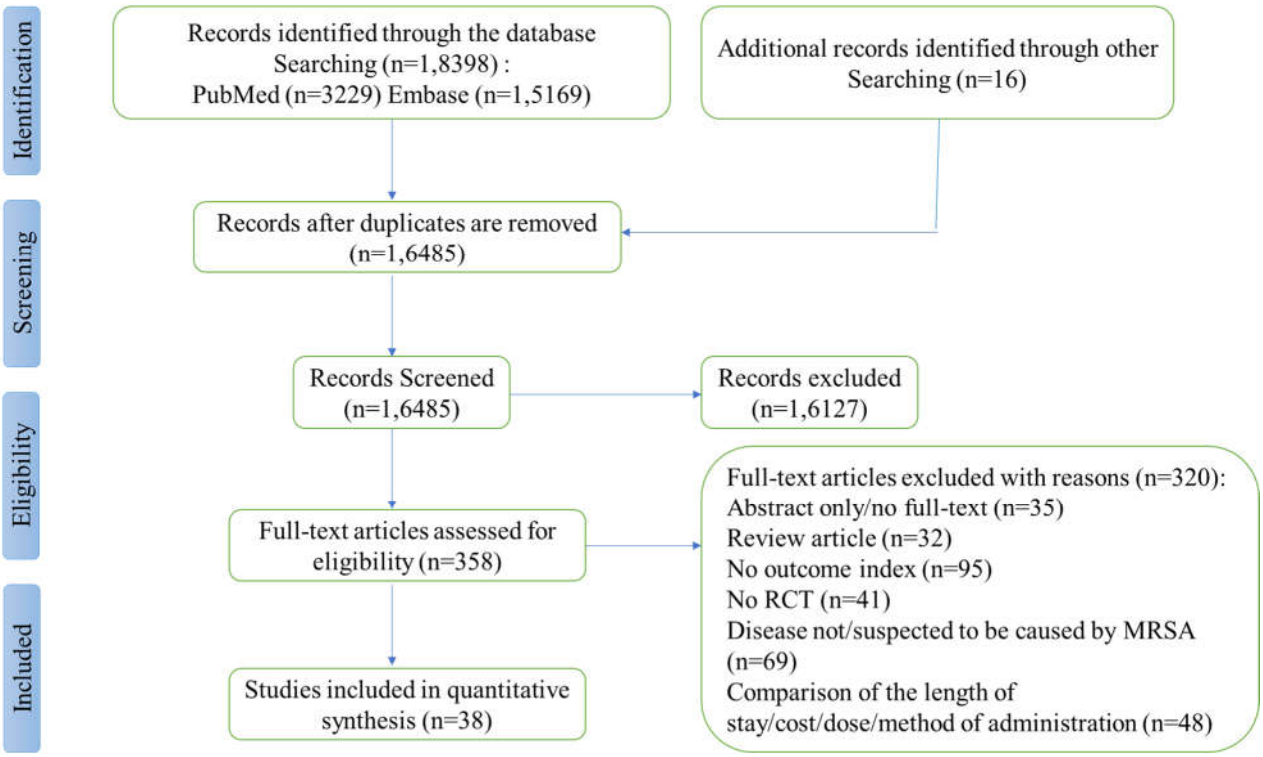


Figure-5: The flowchart of literature filtering(134)

7.2. Use in Surgical Prophylaxis and Implant Infections

Vancomycin hydrochloride has become a strategic adjunct in surgical prophylaxis, particularly in procedures where the risk of Gram-positive or implant-associated infections is pronounced. Evide nce from recent randomised trials and meta-analyses demonstrates that targeted perioperative or intrawound vancomycin use can meaningfully reduce postoperative infection rates without introducing significant safety concerns.

Intrawound administration of vancomycin powder is supported by emerging high-quality evidence. The VANCO randomised, controlled multicentre trial protocol outlines a rigorous appr oach to evaluating the prophylactic effect of vancomycin powder in instrumented posterior spinal fusion, addressing a major source of postoperative morbidity in spine surgery.(135) This trial reflects the increasing need for locally applied agents that can reach therapeutic concentrations at the surgical site while minimising systemic exposure. In joint arthroplasty, the addition of in travenous vancomycin to standard cefazolin has been reassessed. Findings show that routine co-administration provides limited incremental benefit and is often unnecessary, suggesting that cl inicians should reserve dual prophylaxis for patients with documented MRSA colonisation or beta-lactam allergy.(136) This aligns with a more individualised antimicrobial stewardship approach.

Local vancomycin delivery continues to demonstrate substantial preventive benefit in orthopaedic sports procedures. A systematic review and meta-analysis on anterior cruciate ligament (ACL) reconstruction reports that graft pre-soaking in vancomycin significantly reduces postoperative infection risk, a critical factor in preventing graft failure and repeat surgery.(137) Such techniques broaden vancomycin’s utility beyond traditional sy stemic prophylaxis.

Similarly, in total joint arthroplasty, multiple analyses confirm that intraoperative vancomycin powder application markedly reduces infection rates, particularly periprosthetic joint infection (PJI), which remains one of the most challenging postoperative complications.(138) The localized application minimizes systemic toxicity concerns while addressing biofilm-forming organisms. A comprehensive meta-analysis evaluating vancomycin powder across hip and knee arthroplasty further supports its prophylactic value. The review affirms that local vancomycin is both effective and safe, with no significant increase in wound complications or nephrotoxicity, reinforcing its role as a cost-effective adjunct in high-risk procedures.(139)

Collectively, these findings establish vancomycin hydrochloride as a critical tool in preventing surgical site and implant-associated infections, particularly when employed in a targeted, procedure-specific manner informed by emerging evidence and antimicrobial stewardship principles.

8. VISA, VRSA, AND VRE: DEFINITIONS AND TRENDS

VRE, most commonly *Enterococcus faecium*, has emerged as a major global public health concern. Nationall surveillance data from Italy demonstrate a sustained increase in VRE bloodstream infections between 2015 and 2023, with infection risk influenced by patient ch aracteristics, hospital complexity, and intensive-care exposure.(140) These findings highlight the entrenched nature of VRE in healthcare environments and its capacity for clonal dissemination.

High-risk populations are particularly affected by VRE. A systematic review focusing on hematopoietic stem-cell transplant recipients revealed substantial VRE colonisation and infection .(141) This emphasises the vulnerability of immunocompromised patients and the limited therapeutic options once resistance develops.

Antimicrobial stewardship practices play a decisive role in shaping resistance trends. Time-series analyses demonstrate a strong temporal association between oral vancomycin use and rising VRE incidence, indicating that selective antibiotic pressure contributes directly to resistance prop agation within healthcare systems.(142) These data reinforce calls for judicious vancomycin prescribing and enhanced stewardship oversight.

Recent hospital-based surveillance has also identified the emergence of vancomycin-variable enterococci, organisms capable of reversible resistance expression that complicates laboratory detection and infection control efforts.(143) The coexistence of VRE and vancomycin-variable strains further challenges current diagnostic and therapeutic strategies.

VISA, VRSA, and VRE represent distinct yet interconnected resistance phenotypes that colle ctively threaten the long-term effectiveness of vancomycin hydrochloride. Contemporary evidence indicates rising VRE prevalence, persistent but rare VISA/VRSA cases, and a growing need for integrated surveillance, molecular diagnostics, and antimicrobial stewardship to contain resistance and preserve vancomycin’s clinical value.

9. ADVERSE EFFECTS AND TOXICOLOGICAL PROFILE

Vancomycin hydrochloride remains a cornerstone therapy for severe Gram-positive infections; however, its clinical utility is tempered by a well-recognised toxicity profile that necessitates careful dosing, monitoring, and risk stratification. Contemporary evidence emphasises nephro toxicity as the predominant dose-limiting adverse effect, alongside infusion-related reactions and rarer hematologic toxicities.(144-146)

9.1. Nephrotoxicity and Ototoxicity

Vancomycin-associated acute kidney injury (VA-AKI) is the most clinically significant adverse effect and is consistently reported across diverse patient populations.(145) (144, 147) Meta-analytic evidence demonstrates that concomitant administration of vancomycin with pip eracillin/tazobactam significantly increases the risk of AKI compared with combinations involving meropenem, highlighting the impact of drug-drug interactions on renal toxicity.(144)

Exposure-dependent toxicity has been further elucidated through AUC-based analyses, where higher early or cumulative vancomycin AUC values were independently associated with nephrotoxicity in patients with enterococcal bloodstream infections.(91) Similarly, elevated trough serum concentrations correlate with both increased AKI incidence and higher short-term mortality, particularly among critically ill elderly patients.(147)

Patients with chronic liver disease represent a uniquely vulnerable population, with real-world cohort data identifying impaired baseline renal reserve and systemic inflammation as predictors of vancomycin-induced nephrotoxicity and mortality.(145) Pediatric populations are not exempt; neonatal meta-analysis data indicate that immature renal function, prolonged therapy, and con current nephrotoxic agents significantly heighten AKI risk.(148)

Although ototoxicity is now considered rare with modern dosing practices, historical data and pharmacologic plausibility continue to warrant caution, especially at supratherapeutic concentrations or with prolonged exposure, reinforcing the importance of exposure control.(91, 147)

9.2. Red Man Syndrome and Infusion Reactions

Red Man Syndrome, now more appropriately termed vancomycin infusion reaction, is a non-IgE-mediated hypersensitivity response characterised by flushing, erythema, pruritus, and, in severe cases, hypotension.(149) This reaction is primarily related to rapid infusion rates and histamine release rather than cumulative dose.(149)

Clinical reviews emphasise that adherence to recommended infusion durations and, when necessary, premedication with antihistamines effectively mitigates these reactions without nece ssitating discontinuation of therapy.(149) Beyond infusion reactions, immune-mediated hypersensitivity manifestations, including rash, fever, and rare hematologic complications, have been documented, underscoring the need for vigilant clinical observation during therapy.(150)

9.3. Risk Factors and Monitoring Recommendations

Accumulating evidence identifies several reproducible risk factors for vancomycin toxicity, including advanced age, critical illness, pre-existing renal dysfunction, prolonged therapy, and exposure to concomitant nephrotoxic medications.(144, 147, 151, 152) Elderly

patients with MRSA infections exhibit disproportionately higher nephrotoxicity rates compared with younger adults, reflecting age-related pharmacokinetic variability and reduced renal reserve.(152)

Recent studies strongly support the transition from trough-based monitoring to AUC-guided therapeutic drug monitoring as a strategy to balance efficacy with safety.(91, 147) AUC-based approaches allow early identification of excessive exposure and facilitate timely dose adjustment, thereby reducing the incidence of nephrotoxicity without compromising antimicrobial effectiveness.(91)

Additional toxicological considerations include vancomycin-induced thrombocytopenia, with real-world data demonstrating a measurable incidence over prolonged treatment courses, par ticularly in hospitalised patients with multiple comorbidities.(146) Collectively, these findings reinforce guideline recommendations advocating individualised dosing, early renal function surveillance, and continuous reassessment of benefit–risk throughout vancomycin therapy.(144-146)

10. VANCOMYCIN DERIVATIVES AND EMERGING ALTERNATIVES

The clinical utility of vancomycin hydrochloride has been challenged by the emergence of resi stant Gram-positive pathogens, suboptimal tissue penetration, and toxicity concerns. Consequently, significant research efforts have focused on developing vancomycin derivatives, synthetic and semisynthetic analogues, and synergistic combination therapies to enhance antibacterial efficacy, overcome resistance mechanisms, and improve clinical outcomes.

10.1. Telavancin, Dalbavancin, and Oritavancin

Second-generation lipoglycopeptides telavancin, dalbavancin, and oritavancin represent struc turally modified vancomycin derivatives with enhanced potency and pharmacokinetic advantages. These agents incorporate lipophilic side chains that improve membrane anchoring and bactericidal activity while retaining inhibition of cell wall synthesis.

Clinical evidence demonstrates that dalbavancin, with its exceptionally long half-life, enables in frequent dosing and facilitates early hospital discharge in complex musculoskeletal and deep-s eated Gram-positive infections, improving patient convenience and healthcare resource ut ilisation.(153) Systematic reviews further support dalbavancin as an effective sequential therapy in infective endocarditis, particularly when prolonged intravenous treatment is required.(154)

Similarly, oritavancin has shown promise as step-down therapy for Gram-positive bloodstream infections, offering sustained antimicrobial exposure with simplified dosing regimens.(155) Comparative analyses indicate that these lipoglycopeptides achieve non-inferior or superior

clinical efficacy compared with vancomycin, with favourable safety profiles across multiple infection types.(31, 156) Collectively, these agents expand therapeutic options for methicillin-re sistant Staphylococcus aureus (MRSA) and other resistant Gram-positive pathogens.

10.2. Synthetic and Semisynthetic Analogues

Beyond approved lipoglycopeptides, innovative synthetic and semisynthetic vancomycin analogues are being designed to address resistance at a molecular level. Recent medicinal chemistry studies have reported novel vancomycin derivatives capable of simultaneously targeting cell wall biosynthesis and metallo-β-lactamases, thereby restoring activity against highly resistant bacteria.(157) These dual-mechanism compounds represent a strategic advancement over tradi tional glycopeptides, which act primarily on peptidoglycan synthesis.

Exploratory research into structurally distinct analogues, such as vanoxerine-based antibacterial agents, further illustrates how modification of existing pharmacophores can yield compounds with broad-spectrum antibacterial activity and novel mechanisms of action.(158) These developments highlight the growing role of rational drug design in extending the clinical lifespan of glycopeptide antibiotics.

10.3. Combination Therapies and Synergistic Regimens

Combination Therapies and Synergistic Regimens Combination therapy has emerged as a powerful strategy to enhance vancomycin efficacy and mitigate resistance development. Synergistic regimens combining vancomycin with other antimicrobial classes can produce rapid bacterial clearance while reducing required doses. Notably, rifampicin derivatives administered concomitantly with vancomycin have demonstrated remarkable synergy, achieving clearance of MRSA infections at single, low-dose regimens in preclinical and translational studies.(159) Such combinations exploit complementary mechanisms of cell wall inhibition and transcriptional blockade to maximise bactericidal effects.

Systematic reviews assessing recently approved antibiotics further emphasise that vancomycin derivatives and combination regimens frequently outperform vancomycin monotherapy against resistant MRSA strains, particularly in severe or refractory infections.(31) These findings support the integration of synergistic combinations into antimicrobial stewardship strategies, especially in high-risk clinical scenarios.

11. REGULATORY, MANUFACTURING, AND QUALITY ASPECTS OF VANCOMYCIN HYDROCHLORIDE

11.1. FDA/EMA Approval Status

Vancomycin hydrochloride remains a cornerstone antibiotic with long-standing regulatory approval across major jurisdictions, including the United States and Europe. Regulatory oversight has increasingly emphasised chemistry, manufacturing, and controls (CMC) to ensure batch-to-batch consistency and therapeutic equivalence between innovator and generic products. FDA bio pharmaceutics reviews for injectable vancomycin have highlighted the importance of robust analytical characterization, impurity profiling, and stability data in supporting regulatory approvals and post-approval changes

Recent FDA supplemental approval actions, such as the 2025 approval of updated vancomycin hydrochloride formulations, demonstrate ongoing lifecycle management and regulatory surveillance to ensure product quality in response to evolving manufacturing standards. In parallel, manufacturer announcements of newly approved vancomycin injection products reflect regulatory confidence in compliance with current GMP and quality requirements

Beyond product-specific approvals, regulatory authorities continue to strengthen inspection frameworks. A 2025 scoping review emphasised that risk-based GMP inspections and harmonised regulatory practices are critical for maintaining consistent quality of sterile injectable antibiotics, including vancomycin hydrochloride.(160)

11.2. GMP Manufacturing and Stability Guidelines

Good Manufacturing Practice compliance is central to the production of vancomycin hydrochloride, particularly given its parenteral administration and narrow therapeutic index. Analytical methods validated under Quality by Design (QbD) principles have been developed to ensure precise quantification and impurity control in injectable formulations, aligning with ICH and FDA expectations for method robustness and lifecycle management.(12)

Stability-indicating HPLC methods have played a pivotal role in defining acceptable storage conditions and shelf life for vancomycin dosage forms, enabling manufacturers to detect degr adation products and ensure product integrity throughout distribution.(161) Long-term stab ility studies comparing branded and generic vancomycin formulations in infusion solutions have further supported therapeutic equivalence and informed hospital compounding practices.(162)

More recent investigations have extended stability data to compounded oral vancomycin solutions, demonstrating that formulation source and preparation method significantly influence chemical stability, with direct implications for GMP-aligned compounding and beyond-use dating.(39) Similarly, stability assessments of vancomycin used in antimicrobial catheter lock solutions have provided evidence to support safe clinical application while maintaining physicochemical integr ity under prolonged contact conditions(163)

Although published earlier, FDA-supported quality assessments of parenteral vancomycin pr oducts remain highly influential, establishing benchmarks for sterility, potency, and impurity l imits that continue to guide contemporary manufacturing and regulatory decision-making.(164)

11.3. Formulation Patents and Market Trends

While much of the open literature on vancomycin hydrochloride focuses on analytical quality and stability rather than patents per se, these studies directly underpin formulation innovation and market competitiveness. Enhanced stability profiles, validated analytical controls, and extended shelf-life data contribute to intellectual property strategies by supporting differentiated formulations and improved usability in clinical settings.(161, 163)

Market trends indicate sustained demand for high-quality generic vancomycin products, driven by antimicrobial stewardship programs and cost-containment strategies. Regulatory approvals of new formulations and manufacturing sites, such as recent FDA-approved injectable products, signal continued market expansion while reinforcing the importance of compliance with evolving GMP expectations. Collectively, advances in quality assurance, analytical science, and regulatory harmonisation continue to shape the commercial lifecycle of vancomycin hydrochloride in global markets.(160)

12. FUTURE DIRECTIONS AND CHALLENGES IN VANCOMYCIN HYDROCHLORIDE THERAPY

12.1. Novel Biomarker-Guided Dosing Approaches

The future of vancomycin therapy is increasingly defined by precision dosing frameworks that integrate pharmacokinetic modelling with emerging biomarkers to optimise efficacy while minimising toxicity. Traditional trough-based monitoring has demonstrated limitations in accurately predicting drug exposure and nephrotoxicity risk, particularly in critically ill and pediatric populations. Recent evidence supports a paradigm shift toward AUC-guided dosing a ugmented by biomarker surveillance.

In critically ill children, the incorporation of urinary and plasma biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) has shown promise in refining AUC estimation and enabling earlier detection of vancomycin-associated acute kidney injury (AKI), even before serum creatinine elevations occur.(165) These findings highlight the role of biomarkers as complementary tools to pharmacokinetic metrics rather than standalone safety markers.

Parallel advances in Bayesian pharmacokinetic modelling have enabled real-time dose optimisat ion across diverse clinical settings. Prospective cohort data from critical care environments dem

onstrate that Bayesian software platforms can dynamically integrate sparse concentration data to achieve AUC/MIC targets more reliably than conventional approaches.(166) Importantly, these tools are increasingly being embedded into routine clinical workflows through model-informed precision dosing (MIPD) strategies, improving target attainment while reducing clinician burden.(18)

Pediatric populations represent a particularly important frontier for biomarker-guided dosing. Updated therapeutic drug monitoring studies have proposed revised AUC therapeutic windows for children, challenging long-standing exposure thresholds derived from adult data.(167) This is especially relevant in patients with augmented renal clearance (ARC), where standard dosing frequently results in subtherapeutic exposure. Validation studies of Bayesian dosing calculators in pediatric ARC populations confirm improved predictive accuracy and exposure control, reinforcing the need for individualised dosing algorithms in this group.(168)

Collectively, these developments suggest that future vancomycin dosing guidelines will inc reasingly rely on integrated frameworks combining biomarkers, Bayesian modelling, and real-time clinical data to support individualised therapy.

12.2. Resistance Mitigation Strategies

Antimicrobial resistance remains a central challenge threatening the long-term clinical utility of vancomycin. Among Gram-positive pathogens, vancomycin-resistant Enterococcus faecium (VREfm) continues to expand globally, driven by mobile resistance operons, clonal dissemination, and selective antibiotic pressure. Contemporary reviews emphasise that resistance is not solely a microbiological phenomenon but is tightly linked to suboptimal dosing, prolonged exposure, and toxicity-driven treatment interruptions.(169)

In response, significant research efforts are focused on structural innovation of vancomycin analogues. Computationally guided modifications of the glycopeptide scaffold have yielded derivatives with enhanced binding affinity and activity against resistant strains, offering a potential pathway to extend the vancomycin class beyond its traditional spectrum.(170) In addition, contemporary reviews underscore the importance of combination therapy, anti microbial stewardship, and exposure optimisation as core resistance-mitigation strategies. Ensuring that vancomycin achieves effective AUC/MIC targets without excessive toxicity is increasingly recognised as a critical determinant of both individual patient outcomes and population-level resistance trends.(171)

Finally, studies evaluating serum and urinary biomarkers of vancomycin-induced AKI reinforce the link between toxicity monitoring and resistance control. Early identification of nephrotoxicity allows clinicians to avoid prolonged ineffective therapy, which can otherwise promote persistence and adaptation of resistant organisms.(172)

13. CONCLUSION

Vancomycin hydrochloride remains an indispensable agent against severe Gram-positive infections, yet its clinical utility is constrained by rising resistance, narrow therapeutic margins, and substantialinterpatientnt pharmacokinetic variability. Evidence across diverse populations supports a transition from traditional trough-based monitoring to AUC-guided, model-informed dosing, which better balances bactericidal efficacy with the risk of nephrotoxicity and other ad verse effects. Ongoing optimisation of fermentation yield, purification processes, and stability-oriented formulation design is crucial to ensure reliable supply and high-quality products that meet stringent regulatory expectations. In parallel, the development of long-acting lipoglycopeptides, r ationally designed semisynthetic analogues, and synergistic combination regiments offers promising avenues to overcome established resistance mechanisms and expand therapeutic options. Future vancomycin therapy will increasingly rely on precision medicine principles that integrate pharmacokinetic–pharmacodynamic targets, biomarker-guided toxicity surveillance, and robust antimicrobial stewardship to preserve the effectiveness of this last-resort antibiotic class.

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15. CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding this manuscript.

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