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Penicillin Antibiotics in Modern Therapy: Efficacy, Safety, and Resistance Trends

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Abstract

Background: Penicillin, a cornerstone of β-lactam antibiotics, remains widely used for treating bacterial infections due to its broad activity and established safety profile. However, rising antimicrobial resistance and pharmacokinetic limitations necessitate careful therapeutic selection.

Aim: This review evaluates the clinical efficacy, safety, resistance trends, pharmacology, and administration considerations of penicillin in modern practice.

Methods: A comprehensive literature synthesis was conducted, analyzing FDA-approved indications, mechanisms of action, pharmacokinetics, adverse effects, drug interactions, and patient-specific considerations.

Results: Penicillin retains effectiveness against gram-positive cocci, select gram-negative organisms, and anaerobes, with expanded-spectrum derivatives addressing resistance challenges. FDA-approved uses include anthrax, syphilis, meningitis, and streptococcal infections. Mechanistically, penicillin inhibits peptidoglycan cross-linking via irreversible binding to penicillin-binding proteins, leading to bacterial lysis. Pharmacokinetics reveal oral acid stability for penicillin V, while parenteral formulations ensure systemic exposure for penicillin G. Adverse effects range from mild gastrointestinal symptoms to severe hypersensitivity and rare neurotoxicity. Resistance, primarily mediated by β-lactamase production and altered permeability, underscores the need for β-lactamase inhibitors and stewardship strategies.

Conclusion: Despite resistance concerns, penicillin remains integral to antimicrobial therapy when guided by susceptibility testing and individualized dosing. Its favorable safety profile supports use in pregnancy, pediatrics, and lactation, provided contraindications are excluded. Interprofessional collaboration and patient education are essential to optimize outcomes and minimize complications.

Keywords: Penicillin, β-lactam antibiotics, antimicrobial resistance, pharmacokinetics, hypersensitivity, stewardship.

Introduction

Penicillin remains among the most extensively utilized antibiotics worldwide and continues to occupy a central position in antimicrobial therapy because of its broad clinical applicability. As a prototypical member of the β-lactam class, penicillin has long served as a foundational agent in the prevention and treatment of diverse infectious diseases, reflecting both its therapeutic reliability and its enduring relevance in contemporary practice. Its activity encompasses a wide spectrum of susceptible organisms, including gram-positive cocci, gram-positive bacilli, most clinically significant anaerobic bacteria, and several gram-negative cocci, thereby supporting its use across multiple infectious syndromes when microbiological susceptibility is established.[1] In this context, penicillin is frequently regarded as a cornerstone of β-lactam pharmacotherapy, providing effective and well-characterized antibacterial

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coverage that has shaped modern approaches to infectious disease management. Despite its established role, the utility of penicillin has been increasingly constrained by the progressive emergence of antimicrobial resistance among specific bacterial taxa. A notable example is the development of resistance in enterococci, which has altered traditional prescribing patterns and necessitated greater reliance on targeted therapy guided by susceptibility testing. Consequently, penicillin should be reserved for organisms proven to remain sensitive, rather than being employed empirically in settings where resistance is prevalent. Infections caused by enterococci, in particular, often require combination regimens to achieve optimal bactericidal activity; clinical practice has therefore incorporated therapeutic strategies that include penicillin in conjunction with synergistic aminoglycosides such as streptomycin or gentamicin.[2] This evolution underscores the broader imperative for judicious antibiotic selection in response to shifting resistance epidemiology.

Limitations in penicillin's spectrum are also attributable to intrinsic structural barriers present in certain gram-negative bacteria. Specific gram-negative rods demonstrate resistance not only through acquired mechanisms but also through reduced drug access to target sites, as penicillin exhibits limited capacity to traverse the porin channels of the outer membrane.[3] This restricted permeability diminishes intracellular drug concentrations and thereby compromises antibacterial efficacy, reinforcing the importance of selecting agents with enhanced penetration properties when treating infections caused by these organisms. To address these microbiological and pharmacokinetic constraints, subsequent generations of broad-spectrum penicillins were developed with expanded gram-negative activity. Second-generation agents such as ampicillin and amoxicillin possess improved ability to penetrate porin channels, enabling clinically meaningful activity against pathogens including Proteus mirabilis, Shigella, Haemophilus influenzae, Salmonella, and Escherichia coli.[4] Further structural refinement produced third-generation penicillins, exemplified by carbenicillin, which also demonstrate enhanced permeability through gram-negative porins and an associated expansion of antibacterial coverage.[4] Fourth-generation penicillins, such as piperacillin, extend this spectrum further, maintaining activity against many organisms covered by third-generation agents while additionally providing efficacy against Klebsiella species, enterococci, Pseudomonas aeruginosa, and anaerobes such as Bacteroides fragilis.[4] Collectively, these developments illustrate the progressive adaptation of the penicillin class to evolving clinical needs, enabling optimized therapeutic alignment between pathogen characteristics and antibiotic selection.

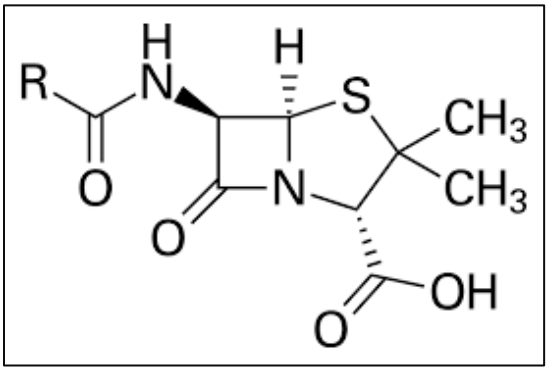

Fig. 1: Penicillin structure.

FDA-Approved Indications

Penicillin preparations continue to hold a well-established place in clinical therapeutics, and several formulations have specific indications that are recognized within regulatory labeling. Penicillin G, in particular, is approved for the management of a wide range of infections caused by susceptible organisms, including both common and historically significant pathogens. Its approved uses include treatment of anthrax due to Bacillus anthracis and actinomycosis caused by Actinomyces israelii. In severe toxin-mediated conditions, Penicillin G is also indicated as part of combination management, such as clostridial infections administered in conjunction with the appropriate antitoxin, as well as diphtheria caused by Corynebacterium diphtheriae when paired with diphtheria antitoxin. It additionally retains approval for fusospirochetosis caused by Fusobacterium species and spirochetes, and for endocarditis attributable to sensitive Streptococcus pyogenes. Further FDA-recognized indications include rat-bite fever caused by either Spirillum minus or Streptobacillus moniliformis [5]. In the setting of tetanus, Penicillin G is indicated when used alongside immune globulin and vaccine administration, reflecting the necessity of comprehensive therapy for toxin neutralization and immune protection. It is also approved for meningitis due to Listeria monocytogenes, meningococcus, and Streptococcus species [6], and remains an essential agent for neurosyphilis caused by Treponema pallidum [7], a condition in which adequate central nervous system penetration and sustained bactericidal

exposure are critical. Penicillin V is distinguished by its oral administration and is FDA-approved for mild-to-moderate infections of the upper respiratory tract caused by susceptible Streptococcus and Pneumococcus organisms. Its indicated uses further include mild cases of scarlet fever and erysipelas due to group A Streptococcus, as well as gingivitis caused by Bacillus fusiformis and Borrelia vincentii when accompanied by appropriate dental care [8]. Benzathine penicillin, formulated for prolonged activity, is approved for prevention of rheumatic fever [9] and for the treatment of syphilis in its primary, secondary, and latent stages [10], supporting sustained therapeutic concentrations required for eradication and relapse prevention.

Mechanism of Action

Most pathogenic and commensal bacteria possess a rigid cell wall composed primarily of peptidoglycan, a macromolecular lattice that surrounds the plasma membrane and provides both structural stability and protection against osmotic rupture. This architecture is particularly essential because bacterial cells often exist in environments where osmotic gradients would otherwise drive water influx and precipitate lysis. Importantly, the peptidoglycan layer is not a static scaffold; rather, it is continuously synthesized, reorganized, and repaired as part of normal cellular growth and division. During replication, bacteria must expand their wall and create septal structures, processes that require tightly regulated enzymatic activity to ensure that newly produced peptidoglycan strands are properly integrated into the pre-existing matrix. Penicillin exerts its antibacterial activity by disrupting this critical step in cell wall biogenesis, specifically by inhibiting the cross-linking reactions that confer mechanical strength to peptidoglycan.[11] The cross-linking of adjacent peptidoglycan chains is catalyzed by a group of membrane-associated enzymes collectively termed penicillin-binding proteins, among which DD-transpeptidase is a principal functional example. Penicillin's pharmacologic effectiveness derives from its characteristic four-membered β-lactam ring, which structurally resembles the natural substrate involved in transpeptidation. Through this molecular mimicry, the β-lactam ring binds to DD-transpeptidase and forms a stable covalent complex that results in irreversible enzymatic inactivation. Once these penicillin-binding proteins are inhibited, the bacterium can no longer perform the terminal cross-linking steps needed to reinforce the peptidoglycan network. Consequently, while cell wall degradation and turnover processes continue, the compensatory synthesis required to maintain integrity is impaired, producing a progressive weakening of the wall.[12]

As structural compromise advances, the cell becomes increasingly susceptible to internal turgor pressure. Water influx driven by osmotic forces causes the already-fragile cell wall to fail, culminating in cell swelling and lysis. In addition to the direct loss of cross-linking capacity, the accumulation of peptidoglycan fragments further accelerates bacterial death by promoting activation of endogenous autolysins and hydrolases, enzymes that normally participate in controlled remodeling but, when dysregulated, contribute to destructive self-digestion of the cell wall. This combination of inhibited synthesis and unopposed degradation accounts for the bactericidal nature of penicillin in susceptible organisms.[12] In clinical practice, the efficacy of penicillin can be compromised by bacterial production of β-lactamase enzymes, which hydrolyze the β-lactam ring and thereby neutralize the antibiotic before it can inactivate penicillin-binding proteins. To counteract this resistance mechanism and preserve antibacterial activity, penicillin is often co-formulated or co-administered with a β-lactamase inhibitor, such as clavulanic acid. These inhibitors function by preventing enzymatic degradation of the β-lactam ring, thereby maintaining effective drug concentrations and enhancing bactericidal action against β-lactamase–producing strains.[13]

Pharmacokinetics

The pharmacokinetic behavior of penicillins is determined by formulation-dependent stability, patterns of protein binding, limited biotransformation, and predominantly renal clearance, all of which collectively guide dosing strategies and clinical selection. With respect to absorption, important distinctions exist between oral and parenteral preparations. The potassium salt of penicillin V is formulated for oral administration and demonstrates relative resistance to degradation by gastric acid, thereby permitting clinically useful systemic exposure following ingestion. In contrast, penicillin G is acid labile and is therefore largely inactivated in the stomach when administered orally, which necessitates parenteral delivery to achieve therapeutic concentrations. Long-acting depot formulations further modify absorption kinetics;

benzathine penicillin G is characterized by slow hydrolysis at the injection site and gradual systemic uptake. This delayed absorption profile produces sustained serum concentrations over an extended period and effectively prolongs the apparent half-life, supporting its use in indications where continuous low-level exposure is advantageous, such as prophylactic regimens or infections requiring prolonged exposure without frequent dosing. Following entry into the systemic circulation, distribution is influenced substantially by plasma protein binding and tissue perfusion. Penicillin V is reported to exhibit approximately 80% binding to plasma proteins, whereas penicillin G binds at a lower rate of roughly 60%, differences that affect the free, pharmacologically active fraction available for antimicrobial activity. Both agents distribute into many body tissues and fluids, with comparatively high concentrations achieved in the kidneys, reflecting both renal perfusion and the role of the organ as a primary route of elimination. Penicillin penetration into certain compartments is notably enhanced under inflammatory conditions; concentrations within abscesses, synovial fluid, and peritoneal fluid tend to increase when inflammation disrupts local barriers and augments vascular permeability. Nevertheless, distribution is not uniform across all cellular and tissue spaces. Penicillin G, for example, demonstrates relatively poor distribution into polymorphonuclear leukocytes, indicating limited intracellular accumulation and underscoring why penicillins are most effective against extracellular pathogens rather than organisms that primarily reside within host cells.

Penicillin derivatives undergo minimal hepatic metabolism, a property that contributes to their generally predictable kinetics and reduces the extent to which liver function alone alters systemic exposure. Instead, elimination is dominated by active renal processes. Organic anion transporter-3 has been identified as an important contributor to renal excretion, facilitating the movement of these β-lactams into the tubular lumen and thereby supporting efficient clearance.[14] This transporter-mediated pathway complements filtration and is especially relevant to the rapid decline in serum concentrations that is typical of many penicillin formulations. Elimination occurs primarily through the kidneys because penicillins are water soluble and therefore readily excreted in urine, although a fraction of some agents may also be eliminated via biliary routes. Overall, penicillin exhibits a relatively short elimination half-life of approximately two hours, necessitating appropriately frequent administration for many therapeutic uses. A key mechanism responsible for rapid clearance is active tubular secretion, which can be pharmacologically inhibited by probenecid. By reducing tubular excretion, probenecid increases and prolongs penicillin plasma concentrations, a strategy that has historically been used to augment exposure when sustained therapeutic levels are desired.[15][16][17]

Administration

Penicillin therapy encompasses multiple formulations designed to accommodate differences in clinical indication, required duration of exposure, and practical considerations related to route of administration. Penicillin G, which is not reliably effective when given orally because of acid instability, is typically administered via intravenous (IV) or intramuscular (IM) routes to ensure adequate systemic concentrations. Penicillin G potassium for injection, supplied in vials labeled by international units, is commonly available in strengths of 1 million units, 5 million units, and 20 million units per vial. Owing to its relatively short elimination half-life, penicillin G potassium is generally delivered in divided doses at intervals of approximately four to six hours when administered by either the IV or IM route, a schedule intended to maintain serum concentrations above the minimum inhibitory concentration for susceptible pathogens across the dosing period. Alternative parenteral preparations are used when prolonged exposure is clinically beneficial. Benzathine penicillin G, a depot formulation, is designed for slow release after IM administration, thereby sustaining a continuous low level of penicillin G for an extended period, typically ranging from two to four weeks, which can improve adherence and support indications that require long-duration antimicrobial pressure without frequent dosing. In addition, regulatory approval includes a procaine penicillin G formulation, which combines the antibiotic with a local anesthetic component to improve injection tolerability while maintaining therapeutic effectiveness.[7] For outpatient therapy and less severe infections where oral delivery is appropriate, penicillin V and its potassium salt derivative, penicillin VK, provide practical oral options. These formulations are available as solutions for reconstitution at concentrations of 125 mg/5 mL and 250 mg/5 mL, and as tablets containing 250 mg or 500 mg, enabling flexible dosing across pediatric and adult populations.[18] Although penicillin V is

more acid-stable than penicillin G, administration practices often favor dosing in a fasting state to optimize absorption and minimize any potential reduction in bioavailability. Dosing regimens are selected according to the infection being treated, the susceptibility of the causative organism, and patient-specific factors such as body weight; typical adult dose ranges commonly fall between 125 mg and 500 mg administered every six to eight hours, with adjustments made as clinically indicated.

As with all antimicrobial agents, appropriate counseling is integral to effective administration. Patients should be instructed to complete the full prescribed course even if symptomatic improvement occurs early, as premature discontinuation may permit bacterial persistence and contribute to the selection of resistant subpopulations. Selection of penicillin formulations also requires awareness of physiologic distribution limits. Penicillin generally exhibits restricted penetration across the blood–brain barrier under noninflamed conditions, which is clinically relevant when central nervous system infections are being considered. Nevertheless, authoritative guidance recognizes circumstances in which penicillin G is appropriate for meningitis when the pathogen is known to be susceptible; the Infectious Diseases Society of America (IDSA), for example, recommends penicillin G in cases of bacterial meningitis caused by susceptible organisms, including Propionibacterium acnes.[19] Conversely, stewardship-oriented recommendations emphasize restraint in settings where resistance or uncertainty is common. The Centers for Disease Control and Prevention (CDC) advises that penicillin should not be used as first-line therapy for either treatment or postexposure prophylaxis of anthrax until susceptibility results are available, reflecting the necessity of aligning therapy with microbiological confirmation in high-consequence infections.[20]

Specific Patient Populations

The clinical use of penicillin across diverse patient populations requires careful attention to physiologic changes and comorbid conditions that may alter drug handling, circulating free concentrations, and overall tolerability. Although penicillins are generally regarded as well-established and relatively safe agents, individualized therapeutic planning remains essential, particularly in settings where organ dysfunction or age-related pharmacokinetic variability can meaningfully influence exposure and adverse-effect risk. In patients with hepatic impairment, penicillin use is not categorically contraindicated; however, prudence is warranted, especially among individuals with advanced liver disease such as cirrhosis. One clinically relevant concern is hypoalbuminemia, which is common in hepatic insufficiency and can modify plasma protein binding. Because a reduction in albumin may increase the proportion of unbound, pharmacologically active drug, the effective systemic exposure may be higher than anticipated even when standard doses are administered. Consequently, clinicians should approach dosing and monitoring conservatively in cirrhotic patients and remain attentive to signs of intolerance or unexpected drug effects, particularly when hepatic impairment coexists with renal dysfunction or other factors that reduce clearance.[21] Renal impairment has more direct implications for penicillin dosing because many penicillin agents are primarily eliminated through renal pathways. While impaired renal function does not necessarily preclude penicillin therapy, dosage modification becomes important in advanced disease to prevent accumulation and maintain safe yet effective concentrations. In end-stage renal disease, adjustments are typically guided by the estimated glomerular filtration rate, and protocols often employ a strategy of administering a full loading dose to rapidly achieve therapeutic levels, followed by reduced maintenance dosing. Depending on the degree of renal impairment, maintenance regimens may involve approximately half of the loading dose delivered at extended intervals, such as every eight to ten hours in some patients, or at shorter intervals such as every four to five hours when clinically justified and consistent with renal function estimates.[22] This approach seeks to preserve early treatment efficacy while mitigating the risks associated with diminished drug elimination.

Pregnancy represents a distinct physiologic state in which both safety considerations and altered pharmacokinetics must be integrated into prescribing decisions. Penicillin G has historically been classified as an FDA pregnancy category B medication, and available evidence has not demonstrated severe adverse fetal outcomes attributable to its use, supporting its continued role when clinically indicated. At the same time, pregnancy-associated changes in renal blood flow and glomerular filtration can enhance clearance of some penicillin formulations. For penicillin V, increased elimination

during pregnancy may reduce drug exposure, potentially necessitating dose optimization through higher doses at standard intervals or by shortening dosing intervals while maintaining the standard dose.[23][24] Beyond general treatment considerations, penicillin G has a prominent and specific obstetric role. According to guidance from the American College of Obstetricians and Gynecologists (ACOG), penicillin G is recommended for intrapartum prophylaxis against group B Streptococcus (GBS) to reduce the risk of neonatal infection. The recommended regimen includes a loading dose of 5 million units followed by 2.5 to 3 million units every four hours until delivery.[23][24] This schedule reflects the need for sustained maternal serum levels during labor to optimize prevention of vertical transmission. During lactation, penicillin G and penicillin V are present in breast milk at low concentrations that are generally considered unlikely to cause clinically significant adverse reactions in the nursing infant. Nevertheless, published reports have raised the possibility that exposure may alter the infant's gastrointestinal flora, with outcomes such as diarrhea or oral candidiasis (thrush) described in some instances. Importantly, these observations have not been comprehensively evaluated across large, controlled studies, and the overall evidence base supports compatibility with breastfeeding. As a result, penicillin G and penicillin V are widely regarded as acceptable options for nursing mothers when treatment is indicated.[25][26]

In pediatric populations, dosing requires weight- and size-based calculation to ensure both efficacy and safety. Pediatric regimens are commonly determined using body weight and, in some settings, body surface area, reflecting developmental differences in distribution volume and clearance. For specific infectious indications with standardized therapy, authoritative recommendations provide clear dosing guidance. The Centers for Disease Control and Prevention (CDC), for example, recommends benzathine penicillin G at 50,000 units/kg administered intramuscularly, up to a maximum of 2.4 million units given as a single dose, for the treatment of primary and secondary syphilis in children.[10] Such recommendations highlight the importance of precise dosing, particularly when long-acting depot formulations are employed. In older adults, penicillin therapy similarly warrants individualized consideration, primarily because age-related physiologic decline can reduce renal clearance even in the absence of overt kidney disease. The potential for a decreased glomerular filtration rate may increase systemic exposure and heighten susceptibility to adverse effects, particularly with repeated dosing or higher-intensity regimens. Accordingly, clinicians are advised to exercise caution, assess renal function when feasible, and adjust dosing as needed to align with the patient's elimination capacity.[27]

Adverse Effects

Penicillin V and penicillin G are widely used β-lactam antibiotics with a long history of clinical effectiveness; however, their administration is associated with a spectrum of adverse effects that range from mild, self-limited symptoms to rare but potentially life-threatening reactions. At routine therapeutic doses, commonly reported effects include gastrointestinal disturbances such as nausea, vomiting, and diarrhea, as well as dermatologic manifestations including rash and urticaria. Patients may also experience nonspecific complaints such as abdominal discomfort. Penicillin G, particularly when administered parenterally, has additionally been associated with systemic reactions that may include muscle spasms, febrile episodes with chills, myalgias, headache, tachycardia, flushing, tachypnea, and hypotension, reflecting either drug-related effects or host inflammatory responses in susceptible individuals. Among all adverse outcomes, hypersensitivity reactions represent the most frequently encountered clinically significant complication of penicillin therapy. These reactions may occur with immediate onset or may present in a delayed fashion, and they are mediated by distinct immunologic mechanisms. Immediate-onset hypersensitivity typically develops rapidly, often within approximately 20 minutes of drug exposure, and may begin with pruritus and urticaria before progressing to angioedema and respiratory compromise. In severe presentations, laryngospasm or bronchospasm can occur, accompanied by hypotension and cardiovascular collapse, potentially culminating in fatal anaphylaxis if not promptly recognized and managed. By contrast, delayed-onset hypersensitivity reactions are less common, tend to emerge after prolonged exposure—often within one to two weeks of initiating therapy—and may manifest with constitutional symptoms such as fever and malaise, along with urticaria, myalgias, arthralgias, abdominal pain, and a variety of cutaneous eruptions.[28] Although uncommon, these delayed reactions require clinical vigilance because they may

be misattributed to the underlying infection or to unrelated causes.

Gastrointestinal adverse effects are particularly prominent with oral therapy and have been reported in more than 1% of patients. Symptoms such as nausea, vomiting, and stomatitis are among the most frequently described and may contribute to poor adherence, especially when dosing schedules are frequent. In addition to routine intolerance, antibiotic-associated colitis, including pseudomembranous colitis, may develop during treatment or even after the medication has been discontinued. This complication reflects disruption of normal intestinal microbiota and can result in significant morbidity, requiring prompt evaluation and appropriate management when suspected. Hematologic toxicity is an uncommon but clinically important adverse category, particularly at high penicillin exposures. When doses exceed approximately 10 million units per day—especially in patients who have previously received substantial penicillin exposure—immune-mediated and marrow-related abnormalities may occur. Reported manifestations include Coombs-positive hemolytic anemia and neutropenia, conditions that generally resolve following cessation of therapy. These potential effects emphasize the importance of monitoring when prolonged high-dose regimens are employed. Certain formulations of penicillin G may precipitate metabolic disturbances. Because penicillin G can be administered as a salt, large intravenous doses may impose a considerable electrolyte load, with hyperkalemia being a clinically relevant risk when potassium-containing preparations are infused at high amounts. This consideration is particularly important in patients with baseline renal impairment or other predispositions to electrolyte imbalance.

Neurological toxicity has been described primarily in association with high intravenous dosing and is more likely when drug clearance is reduced. Manifestations can include hyperreflexia, myoclonic cramps, seizures, and, in severe cases, coma. The risk is heightened in patients with impaired renal function, in whom accumulation can lead to excessive central nervous system exposure and lower seizure thresholds.[29] Consequently, careful dose adjustment and close monitoring are warranted in patients with renal dysfunction receiving intensive therapy. Renal and urogenital adverse effects may also occur, especially with large intravenous doses. Direct renal tubular damage has been reported in high-exposure settings, and penicillins have been implicated as a cause of acute interstitial nephritis, an inflammatory disorder affecting the renal interstitium and tubules.[30] Clinically, acute interstitial nephritis may present with hematuria, fever, rash, and declining renal function. Because progression can lead to renal failure, the primary recommendation is prompt withdrawal of the offending drug once the diagnosis is suspected or established. Additional notable reactions include the Jarisch–Herxheimer reaction, which may be precipitated when penicillin is administered for syphilis. This reaction is attributed to rapid lysis of spirochetes and the consequent inflammatory response to released bacterial components, and it can present with acute systemic symptoms shortly after therapy initiation.[31] Moreover, preparations containing procaine can provoke procaine-related reactions, reported in approximately 1 in 500 patients, which are thought to represent immediate toxic effects following administration of a large single dose and may mimic anaphylaxis in presentation, producing a pseudoanaphylactic syndrome.[32] Procaine exposure has also been associated with methemoglobinemia, a condition in which hemoglobin is oxidized to a form less capable of oxygen transport, potentially leading to cyanosis and hypoxic symptoms depending on severity.[33]

Drug-Drug Interactions

Clinically relevant drug–drug interactions with penicillin are primarily attributable to pharmacodynamic antagonism with certain antimicrobial classes and to pharmacokinetic modulation of renal elimination through competition for tubular secretion. From a pharmacodynamic perspective, concomitant administration of penicillin with bacteriostatic antibiotics may reduce therapeutic efficacy in infections where optimal bacterial killing depends on active cell-wall synthesis and rapid organism replication. In particular, the combined use of sulfonamides, erythromycin, or chloramphenicol with penicillin is generally discouraged because these agents can suppress bacterial growth and thereby diminish the bactericidal activity of β-lactam antibiotics, creating an antagonistic interaction that may compromise clinical response.[34] This consideration is especially important in severe infections in which timely bacterial eradication is critical and where combination therapy is intended to be synergistic rather than counterproductive. Pharmacokinetic interactions are most prominently

mediated through the kidneys, as penicillin G is largely eliminated via active tubular secretion in addition to glomerular filtration. Probenecid is a classic example of a drug that intentionally alters penicillin disposition. By inhibiting tubular secretion, probenecid reduces the renal clearance of penicillin G, resulting in higher and more sustained plasma concentrations. This effect can be clinically advantageous when prolonged exposure above the minimum inhibitory concentration is desired, such as in certain serious infections or when dosing frequency must be minimized. Beyond its effect on clearance, probenecid has also been reported to decrease the volume of distribution of penicillin, further contributing to increased circulating levels and extended systemic availability. A broader set of medications can produce similar, though often less deliberately exploited, effects by competing with penicillin for the same renal transport mechanisms. Drugs including aspirin, phenylbutazone, sulfonamides, indomethacin, and several diuretics—such as thiazides, furosemide, and ethacrynic acid—may reduce penicillin tubular secretion through competitive inhibition, thereby increasing the elimination half-life and elevating plasma exposure.[35] While this interaction may not always produce clinically significant toxicity in otherwise healthy individuals, it becomes more consequential in patients receiving high-dose penicillin regimens, those with impaired renal function, or those at increased risk of concentration-dependent adverse effects such as neurotoxicity. Accordingly, careful medication reconciliation and monitoring are warranted when penicillin is prescribed alongside agents known to influence renal tubular transport, with dose adjustment or enhanced surveillance considered when clinically appropriate [35].

Contraindications

Penicillin therapy is contraindicated in patients with a documented history of severe hypersensitivity to penicillin or related β-lactam derivatives, given the well-established risk of recurrence and the potential for life-threatening reactions. A prior episode of an immediate, severe allergic response—such as anaphylaxis or rapid-onset angioedema—represents a particularly high-risk clinical scenario in which re-exposure may precipitate catastrophic outcomes. Beyond classical IgE-mediated reactions, penicillin is also contraindicated in individuals who have previously experienced severe cutaneous adverse reactions attributable to penicillin exposure. Of particular concern is a history of Stevens–Johnson syndrome occurring after administration of penicillin or a penicillin derivative, as this entity reflects a serious immunologically mediated reaction with significant morbidity and mortality risk. In such patients, avoidance of penicillin is considered essential due to the possibility of recurrence with subsequent exposure. In addition to allergy-based contraindications, clinically meaningful pharmacodynamic considerations may limit the appropriateness of penicillin use in certain contexts. Penicillin's bactericidal activity is optimized when organisms are actively dividing and synthesizing cell wall components; therefore, agents that suppress bacterial growth can diminish penicillin's effectiveness. Tetracyclines, which are generally bacteriostatic, may antagonize the action of penicillin, and this interaction has been associated with adverse clinical consequences in specific infections. Notably, concomitant administration of tetracyclines with penicillin in the treatment of pneumococcal meningitis has been reported to increase mortality risk—estimated at 2.6 times higher—compared with treatment using penicillin alone, underscoring the importance of avoiding antagonistic combinations in severe, time-sensitive infections where rapid bacterial eradication is paramount.[36] This observation reinforces the broader principle that antibiotic selection must be guided not only by spectrum of activity but also by pharmacodynamic compatibility, particularly in invasive central nervous system infections.

Although these contraindications and interaction risks are clinically important, it is also recognized that penicillins are generally considered relatively safe for use during pregnancy and lactation when indicated, provided that the patient does not have a contraindicating allergy history.[36] This favorable safety profile has contributed to their continued use in obstetric and postpartum settings, where therapeutic options may be constrained by fetal and neonatal considerations. A separate but critical safety concern is the association between antibiotic exposure and Clostridium difficile–associated diarrhea (CDAD), a complication that has been reported with nearly all antibacterial agents, including penicillin. The pathophysiologic basis of CDAD involves disruption of the normal colonic microbiota, which ordinarily suppresses opportunistic pathogens. When antimicrobial therapy alters this protective flora, C difficile may proliferate and produce toxins A and B, leading to a spectrum of

disease that ranges from mild, self-limited diarrhea to fulminant, potentially fatal colitis.[37] Clinical severity is heightened in infections caused by hypertoxin-producing strains, which are associated with greater morbidity and mortality, and may demonstrate resistance to antimicrobial therapies and, in the most severe cases, necessitate surgical intervention such as colectomy.[37] When CDAD is suspected or confirmed, timely initiation of appropriate antibiotic therapy directed at C difficile is recommended, alongside supportive measures tailored to clinical severity. Management may include fluid and electrolyte correction, nutritional and protein supplementation when indicated, and early surgical evaluation in patients with severe or refractory disease.[37]

Monitoring

In routine clinical practice, penicillin therapy does not typically necessitate intensive monitoring, largely because these agents have a long-standing safety record, predictable pharmacokinetics in patients with normal organ function, and a wide therapeutic index. For uncomplicated infections treated with standard doses and short courses, clinical follow-up focused on symptomatic improvement and tolerability is generally sufficient, and laboratory surveillance is often unnecessary. Nevertheless, the absence of obligatory monitoring should not be interpreted as a universal rule, as specific clinical contexts and patient characteristics can increase the value of targeted assessment. In more complex infections requiring prolonged or high-intensity regimens, monitoring becomes increasingly relevant to ensure both efficacy and safety. A notable example is infective endocarditis, particularly when caused by enterococci, where achieving adequate antimicrobial exposure is essential for bactericidal activity and to reduce the likelihood of treatment failure. One study has recommended therapeutic drug monitoring in the setting of enterococcal endocarditis to better characterize penicillin exposure and support individualized dosing strategies.[38] This approach is grounded in the principle that insufficient antibiotic concentrations can contribute to suboptimal microbial eradication and potentially facilitate the emergence of resistance, whereas optimized exposure is more likely to improve therapeutic outcomes. In such high-stakes infections, therapeutic drug monitoring may therefore serve as a practical tool to balance adequate drug concentrations against the risk of concentration-related toxicity, particularly when patient-specific factors—such as renal impairment, altered volume of distribution, or interacting medications—introduce uncertainty in expected serum levels.

Beyond efficacy-oriented monitoring in select indications, extended courses of penicillin warrant periodic laboratory evaluation to detect uncommon but clinically meaningful adverse effects. Prolonged administration can be associated with hematologic abnormalities, including neutropenia or hemolytic phenomena, especially at higher cumulative doses, and thus periodic complete blood count assessment may be appropriate in long-duration therapy. Renal function monitoring is similarly important because penicillin clearance is predominantly renal; declining kidney function can lead to drug accumulation and increase the risk of dose-dependent adverse events, including neurotoxicity. Hepatic function evaluation, while penicillin is minimally metabolized by the liver, may still be prudent during prolonged therapy, particularly in patients with underlying hepatic disease or those receiving concurrent hepatotoxic medications, as systemic illness and polypharmacy can complicate interpretation of adverse events and laboratory changes. Accordingly, while penicillin often requires minimal routine surveillance, monitoring should be tailored to the clinical scenario. Therapeutic drug monitoring may be considered in select severe infections to optimize exposure and mitigate resistance risk,[38] and extended therapy should prompt periodic assessment of hematologic, renal, and hepatic parameters to support safe continuation and timely recognition of rare but important complications.

Toxicity

Penicillin is generally characterized by a relatively low propensity for systemic toxicity, a feature that has contributed to its long-standing clinical utility and its frequent use across a broad range of infectious indications. In comparison with many other pharmacologic agents, penicillin possesses a wide therapeutic index, permitting administration of comparatively high doses in appropriate clinical settings without routine harm to patients. Available estimates suggest that extraordinarily large intravenous exposures would be required to precipitate severe neurologic effects in individuals with typical physiology; one cited approximation indicates that a dose on the order of 5 g/kg body weight administered intravenously could be necessary to induce convulsions.[39] This

observation underscores that clinically significant overdose is uncommon when penicillin is prescribed and administered within standard dosing frameworks, particularly when renal function is intact and dosing intervals are appropriate. Nevertheless, the relative systemic safety of penicillin does not eliminate the possibility of toxicity, especially under circumstances of excessive exposure, impaired clearance, or atypical routes of administration. Toxicity may arise not only from systemic accumulation but also from local tissue effects when high concentrations are introduced into anatomically sensitive compartments. Reports describe local toxicity associated with high-dose injections delivered to sites such as the anterior chamber of the eye or the subarachnoid space, where even agents with favorable systemic tolerability may produce disproportionate harm due to direct contact with delicate tissues and restricted capacity for dilution or clearance.[39] These considerations highlight the importance of adhering to approved routes and formulations, as inadvertent or inappropriate administration into specialized spaces can alter risk profiles substantially.

At the same time, historical observations have suggested that pure penicillin preparations have not demonstrated intrinsic damaging effects on certain tissues, with reports noting an absence of harm to structures such as the lungs and veins under conditions described in the literature.[39] Separate reports have also indicated that topical application of penicillin in dental cavities may interfere with coagulation processes locally.[39] While such findings are not necessarily reflective of routine clinical practice today, they illustrate that penicillin's effects can vary depending on the site of exposure and the context in which the drug is applied, reinforcing the broader pharmacologic principle that route and concentration strongly influence toxicity risk. When overdose or toxicity does occur, neurotoxicity is the most clinically significant manifestation to recognize and manage. The primary intervention in suspected penicillin-related neurotoxicity is prompt discontinuation of the causative agent, as ongoing exposure may worsen neurologic excitation and increase the likelihood of severe outcomes. The mechanistic basis of this neurotoxicity has been hypothesized to involve inhibition of gamma-aminobutyric acid (GABA)–mediated neurotransmission, which can reduce inhibitory signaling within the central nervous system and thereby lower seizure threshold.[40] In clinically severe or refractory cases, management may require intravenous benzodiazepines to restore inhibitory tone and terminate seizures, alongside close neurologic observation. Because persistent or recurrent seizure activity may be difficult to identify clinically in critically ill or sedated patients, electroencephalogram (EEG) monitoring may be necessary when symptoms do not resolve promptly or when ongoing subclinical seizure activity is suspected.[40] Collectively, these measures reflect a symptom-directed approach in which discontinuation of the offending drug is paired with supportive and anticonvulsant therapy as needed to stabilize the patient and prevent secondary neurologic injury.

Enhancing Healthcare Team Outcomes

Optimizing clinical outcomes with penicillin requires more than selecting an appropriate antibiotic; it depends on coordinated, interprofessional practice that aligns microbiologic evidence, patient-specific risk assessment, and effective communication across care settings. Prior to prescribing penicillin, the treating clinician, together with any consulting services, should establish that the suspected or confirmed infection is likely caused by organisms susceptible to penicillin. This step reflects a core principle of antimicrobial stewardship: therapy should be selected to achieve adequate bacterial eradication while limiting unnecessary exposure that can drive resistance, adverse events, and avoidable costs. Where feasible, clinicians should incorporate culture results, local susceptibility patterns, and clinical syndrome-specific guidance to ensure that penicillin use is purposeful rather than reflexive, particularly in contexts where resistance is common or diagnostic uncertainty is high. Patient education is a shared responsibility that directly affects safety and adherence. Clinicians, pharmacists, and nurses should provide consistent counseling regarding expected effects, administration instructions, and warning signs that warrant medical reassessment. Patients should be explicitly advised to seek care if they experience concerning symptoms such as prolonged diarrhea suggestive of antibiotic-associated colitis, or severe rash that could represent hypersensitivity or a more serious cutaneous adverse reaction. Reinforcing these messages across disciplines improves patient understanding, reduces conflicting instructions, and increases the likelihood that adverse effects are recognized early rather than progressing to more serious complications.

Infections with possible public health implications require additional coordination beyond the immediate care team. When a zoonotic disease is

suspected, clinicians should notify the CDC and pursue infectious disease consultation to support diagnostic clarification, confirm appropriate antimicrobial selection, and guide any necessary reporting, prophylaxis, or containment measures. This escalation is particularly important because zoonotic infections may involve uncommon pathogens, variable susceptibility patterns, and broader community risk considerations that extend beyond individual patient management. Effective outcomes also depend on seamless workflow between outpatient prescribers and dispensing pharmacists. Clear communication about dose, formulation, duration, and any renal or allergy considerations facilitates timely and accurate dispensing, reduces medication errors, and supports patient adherence. Pharmacists further contribute by counseling patients on administration strategies, including timing in relation to meals when relevant, storage of reconstituted preparations, and the importance of completing the full prescribed course. Such counseling reduces premature discontinuation, which can contribute to relapse and selection of resistant organisms. An interprofessional model is particularly effective when it integrates antimicrobial stewardship expertise; a retrospective study reported that team-based collaboration involving infectious disease pharmacists with advanced pharmacy practice experience strengthens stewardship interventions and improves the quality of antibiotic use.[41]

Barriers to medication access can undermine even the most clinically appropriate prescribing decisions. If patients face financial constraints, transportation challenges, or other logistical impediments to obtaining therapy, social workers and case management staff can play a pivotal role by identifying assistance programs, arranging delivery options, and coordinating follow-up resources. This support is especially important for patients requiring long-acting formulations, repeated dosing, or time-sensitive treatment, where delayed initiation or missed doses can compromise clinical response. Within inpatient settings, safe administration depends on reliable communication between prescribers and nursing staff, including clarity on dosing schedules, infusion or injection parameters, and monitoring expectations. The team should also collaborate to confirm the absence of contraindications to penicillin, such as a prior history of severe allergic reactions or severe cutaneous adverse events. Documentation of allergy history should be carefully verified, and uncertainty should prompt structured evaluation rather than assumption, as inaccurate allergy labels can lead to suboptimal antibiotic selection and broader stewardship consequences. Because severe hypersensitivity reactions such as anaphylaxis may occur rapidly, systems must ensure immediate recognition and escalation. When acute severe effects develop after administration, timely team notification and urgent treatment are critical to prevent deterioration. In parallel, consultation with a board-certified infectious disease pharmacist can provide a high-value review of antibiotic appropriateness in light of the patient's diagnosis, current antibiogram data, and concurrent medications, reducing the risk of drug–drug interactions and ensuring that penicillin remains the best therapeutic option under evolving clinical conditions. Finally, a safety-oriented culture is essential for sustained quality improvement. Implementing a flattened hierarchy encourages all team members to report errors, near misses, or clinical concerns without fear of resistance or reprisal, thereby strengthening medication safety and supporting rapid correction when problems arise. By leveraging coordinated collaboration among physicians, nurse practitioners, physician assistants, pharmacists, nurses, and supportive services, healthcare teams can maximize the therapeutic benefits of penicillin for susceptible infections while minimizing complications, improving patient experience, and reinforcing responsible antimicrobial practice [41].

Conclusion:

Penicillin continues to serve as a foundational antibiotic in clinical medicine, offering reliable efficacy against numerous bacterial pathogens when appropriately selected. Its enduring relevance reflects a balance between proven therapeutic benefits and evolving resistance challenges. While structural refinements have expanded its spectrum, judicious use remains critical to preserve effectiveness and mitigate resistance development. Clinical application should prioritize microbiological confirmation, susceptibility testing, and adherence to evidence-based guidelines, particularly in severe infections where treatment failure carries significant risk. Safety considerations reinforce penicillin's value across diverse populations, including pregnant and lactating women, children, and older adults, provided dosing adjustments account for renal or hepatic impairment. However, vigilance for hypersensitivity reactions and

rare but serious adverse effects is essential, alongside proactive monitoring during prolonged or high-dose therapy. Ultimately, optimal outcomes depend on coordinated interprofessional practice encompassing prescribers, pharmacists, nurses, and support staff. Patient education regarding adherence and recognition of adverse effects further enhances therapeutic success. By integrating stewardship principles, individualized care, and collaborative workflows, healthcare teams can sustain penicillin's role as a cornerstone of antimicrobial therapy while minimizing complications and resistance risks.

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