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Review

How much of this is more than just talk? Does penicillin allergy really preclude beta-lactam use?

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ABSTRACT

Beta-lactam antibiotics, particularly penicillins and cephalosporins, are among the most frequently prescribed antimicrobial agents worldwide and represent the most common cause of immunologically mediated drug hypersensitivity reactions. Approximately 8%–15% of the population carries a penicillin allergy label, yet over 95% of these patients tolerate penicillins upon appropriate evaluation. The historical concern that penicillin-allergic patients have a 10% risk of cross-reactivity with cephalosporins originated from studies in the 1960s and 1970s involving first-generation cephalosporins contaminated with trace penicillin and has been substantially overestimated. Contemporary evidence demonstrates that cross-reactivity between penicillins and cephalosporins is primarily determined by structural similarity of R1 side chains rather than the shared beta-lactam ring. Cefazolin possesses a unique R1 side chain not shared with any other beta-lactam, while second-, third-, and fourth-generation cephalosporins have progressively more complex R1 structures lacking homology with penicillins, resulting in negligible cross-reactivity. Large-scale studies demonstrate that later-generation cephalosporins, particularly cefazolin with a dissimilar R1 side chain, are associated with very low reaction rates in patients with a penicillin allergy label, including carefully selected individuals with a history suggestive of anaphylaxis, when used within structured risk-stratification protocols and in accordance with institutional guidelines. However, in patients with documented severe immediate hypersensitivity reactions, decisions regarding cephalosporin use should remain individualized, taking into account the suspected culprit drug, side-chain similarity, the availability of allergy specialist consultation, and local protocols. Avoidance of cephalosporins in penicillin-allergic patients leads to increased use of alternative antibiotics such as clindamycin and vancomycin, which are associated with 50% higher odds of surgical site infections, increased adverse events, and higher healthcare costs. Risk stratification tools based on index reaction characteristics enable safe cephalosporin use in the majority of patients without routine skin testing. Knowledge gaps persist among healthcare professionals, highlighting the need for ongoing education to translate current evidence into clinical practice.

KEYWORDS

beta-lactam allergy, penicillin allergy, cephalosporin cross-reactivity, side chain, antimicrobial stewardship, surgical site infection

Introduction

Beta-lactam antibiotics represent one of the most widely used and clinically important classes of antimicrobial agents worldwide. They constitute the most common antibiotic classes reported to

cause allergic reactions; however, they remain essential in treating bacterial infections due to their excellent efficacy and favorable safety profiles [1]. The beta-lactam family includes two major classes—penicillins and cephalosporins—and four minor classes: carbapenems, monobactams, oxacephems, and beta-lactamase inhibitors [2]. The clinical significance of beta-lactams extends beyond their therapeutic utility. Approximately 5%–15% of patients in developed countries carry a penicillin allergy label, though studies demonstrate that over 95% of these patients can tolerate penicillins when appropriately evaluated [1,3]. This discrepancy between reported and true allergy has substantial implications for patient care, antimicrobial stewardship, and public health [3].

Methods

To inform this narrative review, a targeted literature search was conducted using the PubMed, MEDLINE, and Scopus databases to identify relevant English-language publications published between January 2000 and October 2025. The search strategy combined controlled vocabulary (MeSH terms) and keywords related to “penicillin allergy,” “cephalosporin allergy,” “beta-lactam cross-reactivity,” “R1 side chain,” “cefazolin,” “skin testing,” “drug provocation test,” and “antimicrobial stewardship.” In addition, reference lists of included articles and relevant clinical practice guidelines were manually screened to identify further studies. Grey literature was not included.

Priority was given to original research, systematic reviews, meta-analyses, and clinical guidelines addressing the immunogenicity of beta-lactams, cross-reactivity between penicillins and cephalosporins, diagnostic testing, or clinical outcomes in patients with a beta-lactam allergy label. Particular emphasis was placed on studies with well-characterized patient populations (e.g., those with confirmed immediate or delayed hypersensitivity) and those evaluating cephalosporins with structurally defined R1 side chains. While the search aimed for comprehensiveness, this review is narrative in nature; therefore, formal systematic review methodologies—including a PRISMA flow diagram, risk of bias assessment, or quantitative study selection numbers—were not employed. Case series with fewer than ten patients, single case reports, and non-peer-reviewed sources were generally excluded to maintain a focus on higher-quality evidence, though this review does not claim to be exhaustive.

Information from the selected literature was synthesized narratively, with emphasis on high-quality evidence from prospective studies, meta-analyses, and contemporary practice guidelines. Data extraction was performed by two reviewers to enhance accuracy and consistency, and findings were organized into thematic categories: chemical structure and classification of beta-lactams, immunopathogenesis and T-cell activation pathways, genetic susceptibility,

historical origins of the 10% cross-reactivity estimate, structural basis for differential cross-reactivity, clinical evidence for safety of later-generation cephalosporins, risk stratification algorithms, geographic and population variations, and awareness among healthcare professionals. The final structure of the review was developed through iterative discussion among the authors to ensure comprehensive coverage while maintaining clinical relevance.

Chemical structure and classification of beta-lactams

All beta-lactam antibiotics share a fundamental structural element: a four-membered beta-lactam ring. This cyclic amide structure is essential for their antibacterial activity [2,4]. However, the molecules differ substantially in the additional rings and side chains attached to this core. In penicillins, the beta-lactam ring is fused to a five-membered thiazolidine ring containing sulfur. This bicyclic system is known as the penam nucleus. Penicillins possess a single side chain (designated as the R group) attached to the beta-lactam ring, which differentiates the various compounds from one another, such as amoxicillin, ampicillin, and benzylpenicillin [1,2,4].

Cephalosporins share the beta-lactam ring but have a different bicyclic structure, fused to a six-membered dihydrothiazine ring, forming the cephem nucleus. A key distinction is that cephalosporins possess two side chains (designated R1 and R2) attached to the beta-lactam and dihydrothiazine rings, respectively, which distinguish different cephalosporins [1,2,5]. Cephalosporins are commonly categorized by generations based on their spectrum of activity. First-generation cephalosporins (e.g., cefazolin, cephalexin) are highly active against gram-positive bacteria. Second-generation agents (e.g., cefuroxime) have expanded gram-negative coverage, while third-generation agents (e.g., ceftriaxone, ceftazidime) offer extended-spectrum activity against enteric gram-negative bacilli. Fourth-generation agents (e.g., cefepime) offer broader coverage, and fifth-generation (anti-MRSA) cephalosporins provide activity against methicillin-resistant Staphylococcus aureus [5].

Carbapenems have a bicyclic structure similar to penicillins, but instead of a sulfur atom in the five-membered ring, they contain a carbon atom with a double bond. Like penicillins, they have a single side chain (R group) that distinguishes different carbapenems, such as imipenem and meropenem [1,2]. Monobactams are structurally distinct as they contain only the beta-lactam ring without an additional fused ring system. Aztreonam is the only monobactam commercially available [1,2]. Beta-lactamase inhibitors (e.g., clavulanic acid, sulbactam) are related compounds with weak antibacterial activity but potent inhibition of bacterial beta-lactamases, frequently combined with beta-lactam antibiotics to overcome resistance [1,6].

Clinical relevance of structural differences

While all beta-lactams share the core beta-lactam ring, the side chains attached to this ring are critically important for clinical practice. The common belief that allergy to one beta-lactam necessitates avoidance of all others is based on outdated studies from the 1960s and 1970s, when early cephalosporins were contaminated with trace amounts of penicillin [4,7]. Contemporary evidence indicates that cross-reactivity is primarily related to side chain similarity rather than the shared beta-lactam ring [2]. For example, aminopenicillins (amoxicillin, ampicillin) share an amino group in their side chain, and this sructural feature is also present in certain cephalosporins (aminocephalosporins such as cefaclor, cephalexin, cefadroxil), explaining observed cross-reactivity between these agents [1,2]. Conversely, cephalosporins with side chains different from those of penicillins, such as cefazolin and ceftriaxone, demonstrate minimal cross-reactivity [7,8].

The antibacterial activity of beta-lactams is also driven by their structure. They exert their bactericidal effect by inhibiting bacterial cell wall synthesis. The beta-lactam ring structurally resembles the D-alanyl-D-alanine terminus of the peptidoglycan precursor, allowing it to bind to and inhibit penicillin-binding proteins (PBPs), which are enzymes responsible for cross-linking the peptidoglycan strands. This inhibition disrupts cell wall synthesis, leading to bacterial lysis [4,5]. The structural differences among beta-lactam classes affect their affinity for various PBPs, contributing to differences in antibacterial spectra [5]. In clinical practice, understanding these structural relationships allows clinicians to preserve valuable therapeutic options. Patients with confirmed allergy to a specific penicillin may safely receive cephalosporins with dissimilar side chains, particularly second- and third-generation agents, provided appropriate evaluation is performed [1,7]. This knowledge helps avoid unnecessary use of broad-spectrum alternatives [3].

Immunopathogenesis and T-cell activation pathways

Beta-lactam antibiotics, as small molecular weight compounds, are not inherently immunogenic but become capable of eliciting immune responses after acting as haptens. They become fully allergenic only after in vivo or in vitro conjugation to suitable carrier molecules, primarily human serum albumin [6,9]. This conjugation occurs through opening of the beta-lactam ring and formation of covalent bonds with lysine residues on the carrier protein [6]. For penicillins, this process results in the formation of the stable penicilloyl group, which constitutes the major antigenic determinant accounting for approximately 95% of tissue-bound penicillin. For cephalosporins, degradation follows a more complex pathway—the R2 side chain frequently acts as a "leaving group," and immunological recognition becomes primarily directed toward the R1 side chain and the fragment of the beta-lactam ring that binds to the carrier protein [6].

Hypersensitivity reactions to beta-lactams are classified according to the modified Gell and Coombs classification, which distinguishes four main types of immune responses [9,10]. Type I (IgE-mediated) reactions occur within 1 to 6 hours after drug administration and are mediated by specific IgE antibodies that cross-link on mast cell surfaces, triggering the release of histamine, leukotrienes, and other vasoactive mediators [4,9]. These reactions manifest clinically as urticaria, angioedema, bronchospasm, and anaphylaxis, with anaphylaxis representing the most severe and feared form of immediate hypersensitivity [1,4]. In contrast to vancomycin and fluoroquinolones, which can activate mast cells through the MRGPRX2 receptor independent of IgE, immediate reactions to beta-lactams are exclusively IgE-mediated [11]. Type II (cytotoxic) reactions are uncommon and involve IgG or IgM antibodies directed against drug-coated blood cells, leading to hemolytic anemia, thrombocytopenia, or neutropenia [10]. Type III (immune complex) reactions occur when circulating antigen-antibody complexes deposit in small blood vessels or alveolar walls, triggering complement activation and manifesting as serum sickness, vasculitis, or tissue injury typically 7 to 21 days after drug exposure [9]. Type IV (T-cell-mediated) reactions are delayed, occurring more than 6 hours after drug administration, commonly after many days of treatment, and are further subdivided based on the dominant cytokine profile and effector cells. Type IVa involves Th1 cells and interferon-gamma activation of monocytes, manifesting as eczema; Type IVb involves Th2 cells with interleukin-4, interleukin-5, and interleukin-13, leading to eosinophilic inflammation and presenting as maculopapular exanthema or drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome; Type IVc involves cytotoxic T lymphocytes releasing perforin and granzyme B, causing keratinocyte death and manifesting as bullous exanthema, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); and Type IVd involves T cells producing interleukin-8/CXCL8, leading to neutrophil recruitment and activation, manifesting as acute generalized exanthematous pustulosis (AGEP) [6,10].

The immunopathogenesis of delayed hypersensitivity reactions involves three proposed models of T-cell activation. The hapten or prohapten model proposes that the drug covalently binds to a protein, which then undergoes antigen processing to generate modified peptides recognized as neo-antigens by T cells, with beta-lactams such as piperacillin, penicillin G, and flucloxacillin forming drug-modified human serum albumin conjugates that have been isolated from patients and shown to be potent stimulators of T-cell clones [12]. The pharmacological interaction or p-i model suggests that small molecule drugs may bind non-covalently directly to the human leukocyte antigen (HLA) molecule or T-cell receptor, stimulating T cells without requiring antigen processing, as demonstrated by flucloxacillin-reactive T-cell clones that react immediately to the drug in the presence of antigen-presenting cells [12]. The altered peptide repertoire model

describes how small molecule drugs can bind non-covalently within the HLA antigen-binding cleft, altering its conformation and leading to presentation of novel peptide ligands that are recognized as foreign by T cells, though evidence for this mechanism in beta-lactam hypersensitivity remains to be established [3,12].

Genetic susceptibility and evolving sensitization patterns

Genetic susceptibility plays a role in beta-lactam hypersensitivity, but current evidence has limited applicability to routine clinical practice. Candidate gene meta-analyses have identified polymorphisms in interleukin-4 receptor alpha and interleukin-13 genes with modest effects on immediate reaction risk, though findings are inconsistent across populations [13,14]. Genome-wide association studies have reported HLA associations (e.g., HLA-DRB110:01 for immediate reactions and HLA-B57:01 for flucloxacillin-induced liver injury), but effect sizes are substantially lower than those seen for other drug hypersensitivity syndromes [3,14,15]. The low positive predictive value precludes genetic screening in routine clinical practice [10].

More clinically relevant are the evolving patterns of sensitization driven by changes in antibiotic prescribing over the past 25 years. Among patients with confirmed immediate hypersensitivity, benzylpenicillin as a culprit has declined markedly, while amoxicillin (with or without clavulanate) now represents 70% of reactions and cephalosporin involvement has risen from 7.7% to 23.9% [16]. Consequently, positive skin tests to classic penicillin determinants have decreased, whereas positive tests to amoxicillin have increased. This shift reflects the emergence of side-chain-specific selective reactions and carries a direct clinical implication: diagnostic protocols must now include an expanded battery of reagents (amoxicillin, clavulanic acid, and relevant cephalosporins) [16].

Severe cutaneous adverse reactions like DRESS, AGEP, SJS, or TEN involve drug-specific T-cell and HLA interactions, often with viral reactivation (e.g., human herpesvirus 6 in DRESS). However, routine genetic testing is not indicated for beta-lactam allergy management [1,12].

The myth of 10% cross-reactivity and its origins

The long-held belief that patients with penicillin allergy have a 10% risk of cross-reactivity with cephalosporins has been a persistent clinical dogma that significantly influences antibiotic prescribing practices [17,18,19]. This figure originated from studies conducted in the 1960s and 1970s that evaluated first-generation cephalosporins such as cephalothin and cephaloridine, which possessed side chains structurally similar to those of penicillins [18,19]. However, several critical flaws in these early studies have since been identified. First, cephalosporins introduced prior to 1980 were manufactured from the Cephalosporium mold and contained trace amounts of

penicillin as contaminants, which likely contributed to the observed allergic reactions [17,18,19]. Second, the definition of penicillin allergy in these early studies was often imprecise, relying on patient self-report rather than confirmed immunological testing [18]. Third, patients with penicillin allergy have a threefold increased baseline risk of adverse reactions to any drug, including structurally unrelated antibiotics, a factor not adequately accounted for in these early analyses [17,19].

Contemporary evidence has substantially revised this understanding. A landmark meta-analysis by Pichichero and Casey encompassing nine studies with over 47,000 patients demonstrated that while first-generation cephalosporins (cephalothin, cephaloridine, cephalexin) and cefamandole showed significantly increased odds of allergic reactions in penicillin-allergic patients (OR 4.79, 95% CI 3.71–6.17), second-generation cephalosporins showed no increased risk (OR 1.13, 95% CI 0.61–2.12), and third-generation cephalosporins actually demonstrated a trend toward decreased risk (OR 0.45, 95% CI 0.18–1.13) [18,19]. More recent studies have confirmed these findings, with a systematic review and meta-analysis demonstrating that the frequency of cross-reactivity between penicillins and cefazolin is only 0.7% [17,20,21]. A large retrospective study of 5,433 surgical patients found that among 265 patients with reported penicillin allergy who received cefazolin, only 1.5% experienced any adverse reaction, with the majority of these being non-IgE-mediated and mild [18].

Structural basis for differential cross-reactivity

The structural differences between penicillins and various cephalosporin generations provide the mechanistic basis for their distinct cross-reactivity profiles. All beta-lactam antibiotics share a core four-membered beta-lactam ring, but the immunogenic determinants differ substantially between classes [17,19,21]. Penicillins possess a five-membered thiazolidine ring attached to the beta-lactam nucleus and a single side chain (R1) that determines their antigenic specificity [17]. Upon degradation, penicillins retain their thiazolidine ring, forming stable penicilloyl determinants that serve as major antigenic structures [19]. In contrast, cephalosporins have a six-membered dihydrothiazine ring and two side chains (R1 and R2), and their degradation leads to fragmentation of both the beta-lactam and dihydrothiazine rings, with the R1 side chain remaining attached to the carrier protein as the primary immunogenic component [17,19,21]. Cephalosporin degradation does not predictably produce stable haptens capable of cross-reacting with penicillin determinants, explaining the low cross-reactivity rates observed with newer agents [18,19].

The critical insight for clinical practice is that cross-reactivity between penicillins and cephalosporins is not determined by the shared beta-lactam ring but rather by the structural

similarity of the R1 side chains [19,20,21]. First-generation cephalosporins such as cephalexin, cefadroxil, and cefaclor share an amino group in their R1 side chain with aminopenicillins (amoxicillin and ampicillin), explaining the higher cross-reactivity rates observed with these agents [17,19,21]. In contrast, cefazolin—a first-generation cephalosporin widely used for surgical prophylaxis—possesses a unique R1 side chain containing a heterocyclic ring that is not shared with any other beta-lactam antibiotic, making its cross-reactivity with penicillins negligible [17,20,21]. Studies have confirmed that patients allergic to cefazolin typically demonstrate selective hypersensitivity to its unique side chains and tolerate other beta-lactams [20,22]. Second-, third-, and fourth-generation cephalosporins have progressively more complex and distinct R1 side chains that lack structural homology with penicillins, accounting for their excellent safety profiles in penicillin-allergic patients [18,19,20]. The 2022 Drug Allergy Practice Parameters issued by the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology explicitly state that cefazolin and other cephalosporins with dissimilar R1 side chains can be administered to patients with penicillin allergy, including those with a history of anaphylaxis, without routine testing [20,21]. In patients with documented severe immediate reactions, clinical decision-making should integrate precise identification of the culprit beta-lactam, assessment of R1 side-chain similarity, consultation with an allergy specialist when available, and adherence to local institutional pathways to minimize residual risk [23].

Clinical evidence for safety of later-generation cephalosporins

Multiple large-scale studies have shown that second-, third-, and fourth-generation cephalosporins, particularly agents with non–cross-reactive R1 side chains such as cefazolin, are associated with very low rates of allergic reactions in patients with a penicillin allergy label, including those with prior immediate-type reactions, when selected using risk-stratified algorithms . In a prospective study of 41 patients with confirmed penicillin allergy who received cefazolin, cefuroxime, and ceftriaxone—all with side chains dissimilar to penicillin—no allergic reactions were observed [18,19]. A retrospective review of 606 patients with penicillin allergy who received cephalosporins found only one possible allergic reaction (0.16%), and that patient's symptoms were equivocal [18]. A study of 1,741 patients with penicillin allergy labels undergoing surgical procedures at the University of Washington Medical Center found that 549 (31.5%) received perioperative cefazolin, and among these, 544 (99.1%) had no documented allergic reaction; the five patients who experienced symptoms had reactions attributed to other medications such as opioids or neuromuscular blocking agents [24]. Among patients undergoing total joint arthroplasty, 46% of those with documented penicillin allergies received cefazolin, with only one mild reaction reported, and the rate of prosthetic joint infection was nearly double in those receiving alternative

antibiotics [20]. A study of 452 patients with penicillin allergy labels who underwent allergy testing found zero positive skin tests to cefazolin or ceftriaxone, further supporting the safety of these agents [17]. Despite these reassuring data, cefazolin has emerged as a leading identifiable cause of perioperative anaphylaxis in absolute terms, underscoring that rare but severe reactions still occur. Consequently, perioperative cephalosporin use in patients with a history of anaphylaxis should be guided by a detailed allergy history, consideration of alternative explanations for prior events, and, where feasible, preoperative evaluation by an allergy specialist.

In the perioperative setting, where timely administration of appropriate prophylaxis is critical, the consequences of avoiding cefazolin in penicillin-allergic patients are substantial. Patients with a penicillin allergy label who receive alternative antibiotics such as clindamycin or vancomycin have a 50% increased odds of developing surgical site infections compared to those receiving cefazolin [17,20,21]. This increased risk is directly attributable to the inferior coverage spectrum and suboptimal pharmacokinetics of alternative agents [20]. Vancomycin requires infusion over at least one hour, making appropriate timing relative to surgical incision difficult to achieve; in one study, 97.5% of patients receiving vancomycin did not receive it within the recommended 60- to 120-minute window pre-procedure [20]. Clindamycin resistance among common skin flora has increased substantially, with 32% of Streptococcus viridans isolates and 23% of Staphylococcus species demonstrating resistance, compromising its efficacy as surgical prophylaxis [20]. Furthermore, alternative antibiotics are associated with higher rates of adverse events, including acute kidney injury with vancomycin and *Clostridioides difficile* (*C. difficile*) infection with clindamycin [20,21]. A study of patients with pneumonia and beta-lactam allergies found that implementation of a side chain-based cross-reactivity chart increased beta-lactam use from 70.4% to 89.3% without increasing allergic reactions, while healthcare facility-onset *C. difficile* infections decreased significantly [25].

Risk stratification and clinical algorithms

Given the accumulating evidence supporting the safety of cephalosporin use in penicillin-allergic patients, several clinical risk stratification tools have been developed to guide antibiotic selection. The majority of patients with a penicillin allergy label—approximately 60%—fall into a low-risk category characterized by index reactions that are either side effects (gastrointestinal symptoms, headache), limited hypersensitivity responses (self-limited cutaneous rash, urticaria occurring more than five years ago), or nonspecific reactions (unknown or remote childhood reactions) [17,24]. These patients can safely receive cefazolin or other cephalosporins with dissimilar R1 side chains without prior allergy testing [17,20,24]. Moderate-risk patients—those with prior disseminated hypersensitivity reactions or anaphylaxis (swelling of face or throat, angioedema,

difficulty breathing, urticaria within five years)—should be considered for allergy testing in elective settings or may receive clindamycin or vancomycin if testing is not feasible [17]. Severe-risk patients, representing less than 0.5% of those with penicillin allergy labels, are those with histories concerning for SJS, TEN, or multiorgan involvement; these patients should receive alternative non-beta-lactam antibiotics [17]. The classification of patients based on index reactions has been validated in intensive care unit settings, where low-risk patients receiving cefazolin without skin testing experienced no adverse reactions [17,24].

Implementation of such risk stratification algorithms has been shown to substantially improve antibiotic prescribing. A study implementing a streamlined algorithm that encouraged cefazolin use in almost all patients with penicillin allergy—including those with anaphylaxis—increased first-line cephalosporin use from 22% to over 80% without any hypersensitivity reactions attributable to cefazolin [20]. Another institution that implemented a similar algorithm and modified electronic medical record ordering to default to cefazolin for surgical prophylaxis in patients with penicillin allergy found no association between a penicillin allergy label and adverse reactions to cefazolin [20]. A pharmacist-led intervention to evaluate and address penicillin allergy labels prior to elective surgery increased cefazolin use from 28% to 65% and eliminated surgical site infections in the intervention group [21]. In pediatric populations, selective immediate responders to aminopenicillins and cephalosporins constitute an important group; a study of Turkish children found that 71.4% of patients with reactions to aminopenicillins and 93.7% of those with reactions to cephalosporins tolerated penicillin V and cephalosporins with dissimilar side chains after negative allergy workup [26]. A systematic review of carbapenem allergy found that cross-reactivity between penicillins and carbapenems is less than 1% in patients with positive penicillin skin tests, and cross-sensitivity among individual carbapenems is not well described but appears low, suggesting alternative carbapenems may be cautiously used when necessary [27].

The heterogeneous cross-reactivity patterns described above are summarized in **Table I**, which provides a practical, side-chain-based overview of estimated cross-reactivity risks and corresponding clinical recommendations for each beta-lactam class in patients with confirmed penicillin allergy. The table highlights that the risk varies from negligible (≈0.7% for cefazolin) to up to 2%–5% only when a shared R1 side chain exists (e.g., certain first-generation cephalosporins), and that most second-, third-, and fourth-generation cephalosporins, as well as carbapenems and aztreonam, can be used safely in the vast majority of penicillin-allergic patients when appropriate risk stratification is applied.

Table I. Cross-reactivity risk between beta-lactam classes in patients with confirmed penicillin allergy

Beta-lactam class	Structural similarity to penicillin	Estimated cross-reactivity rate	Clinical recommendation: unconfirmed / low-risk label	Clinical recommendation: confirmed immediate (IgE) allergy / anaphylaxis
First-generation cephalosporins (shared R1)	Similar R1 side chain	Up to 2%–5% (if shared side chain)	Consider allergy testing in elective settings; avoid if shared with culprit	Avoid if shared R1 side chain with culprit penicillin
Cefazolin	Unique R1 side chain	~0.7%	Safe to administer without routine prior testing	Safe without preemptive testing for most; individualize decision and consider specialist consult for severe anaphylaxis
Second/Thrid-generation cephalosporins	Dissimilar R1 side chain	<1%	Safe to administer without routine prior	Safe to administer without preemptive testing
Carbapenems	Distinct core structure and side chains	<1%	Safe to administer	May be cautiously used when necessary, even with a positive penicillin skin test
Monobactams (aztreonam)	Structurally distinct (except ceftazidime shared R1)	<1% (except ceftazidime cross-reactivity)	Safe to administer	Safe unless there is a documented allergy to ceftazidime

Geographic and population variations

Notable geographic differences exist in the patterns of beta-lactam cross-reactivity, reflecting variations in antibiotic prescribing practices and potentially genetic factors. A comparative study of cohorts from Australia and the United States found that positive skin testing to ampicillin—indicating aminopenicillin sensitivity—occurred in 7.6% of patients tested in Melbourne compared to only 2.2% in Nashville [22]. Among patients with cephalosporin allergy labels who tested positive to ampicillin, 93% were from the Australian cohort, and 69% of these had primary allergy labels to cephalexin, an aminocephalosporin [22]. This pattern reflects the widespread use of parenteral aminopenicillins such as amoxicillin and amoxicillin-clavulanate in Europe and Australia, whereas these agents are less commonly used in the United States [22]. These findings underscore the importance of considering regional prescribing patterns when assessing cross-reactivity risk and suggest that the aminopenicillin-aminocephalosporin cross-reactivity pattern may be less clinically relevant in the United States [22]. In a study of 328 patients with cephalosporin allergy labels, 29 (8.8%) had positive skin tests, with cefazolin and ceftriaxone accounting for 86% of positive cases; notably, 11 of 11 patients with isolated cefazolin skin test positivity were selective

to cefazolin and tolerated other cephalosporins and penicillins. This selectivity is attributed to cefazolin's unique R1 side chain [22].

The time elapsed since the index reaction is a critical predictor of skin test positivity and clinical reactivity. In patients with immediate reactions to penicillins, each year since the reaction reduces the odds of positive skin testing by 7% (OR 0.93 per year, 95% CI 0.90–0.96), while for cephalosporins, the reduction is even more pronounced at 29% per year (OR 0.71 per year, 95% CI 0.56–0.90) [22]. This finding has important practical implications, as many patients with remote histories of penicillin reactions can be safely treated with cephalosporins without extensive testing.

Awareness among healthcare professionals

Despite the growing body of evidence supporting cephalosporin use in penicillin-allergic patients, knowledge gaps persist among healthcare professionals. A survey of clinical pharmacists in Ukraine revealed that while 88%–94% correctly identified allergic reactions as a major adverse effect of beta-lactams, significant misconceptions about cross-reactivity remained [28]. Only 53% of respondents correctly identified that the R1 side chain is the primary determinant of allergic reactions to cephalosporins, and 47% erroneously believed that the beta-lactam ring itself is the main allergenic structure [28]. Regarding specific cross-reactivity rates, 85% of respondents mistakenly believed that cross-reactivity between penicillins and carbapenems exceeds 30%, and 73% believed that the risk of cross-reactivity between penicillins and monobactams is high—both views contradicting current evidence [28]. Only 50% of clinical pharmacists correctly identified ceftazidime as the cephalosporin that shares an R1 side chain with aztreonam and thus may cross-react [28]. These findings highlight the need for ongoing education to ensure that current evidence translates into clinical practice.

The accumulating evidence has led to substantial revisions in clinical practice guidelines. The 2022 Drug Allergy Practice Parameters, jointly issued by the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology, recommend that cefazolin and other cephalosporins with structurally dissimilar R1 side chains can be administered to patients with penicillin allergy, including those with a history of IgE-mediated reactions such as anaphylaxis, without preemptive testing [20,21]. This recommendation is explicitly supported by the Society for Healthcare Epidemiology of America, the Infectious Diseases Society of America, and the Association for Professionals in Infection Control and Epidemiology in their 2023 surgical site infection prevention guidelines [21]. The only absolute contraindications to cephalosporin use in patients with penicillin allergy are histories of severe cutaneous adverse reactions (SJS, TEN, DRESS syndrome, AGEP) or verified allergy to the specific cephalosporin being considered [20,21].

The British National Formulary and other international guidelines have similarly revised their recommendations to reflect the low cross-reactivity rates with later-generation cephalosporins [19].

Discussion

The findings presented in this review demonstrate that the historical paradigm of universal cross-reactivity between penicillins and cephalosporins is no longer supported by contemporary evidence. The widely cited 10% cross-reactivity rate originated from methodologically flawed studies conducted before the 1980s, when cephalosporins were manufactured from Cephalosporium mold and contaminated with trace amounts of penicillin, patient allergy histories were often unverified, and the increased baseline risk of adverse reactions to any drug in penicillin-allergic patients was not adequately considered [17,18,19]. The recognition that these early estimates were substantially inflated has profound clinical implications, as the unnecessary avoidance of cephalosporins in penicillin-allergic patients leads to measurable harm.

The structural understanding of beta-lactam immunogenicity provides the mechanistic foundation for the observed low cross-reactivity rates with later-generation cephalosporins. While all beta-lactams share a core four-membered beta-lactam ring, the immunogenic determinants differ substantially between classes [17,21]. Penicillins form stable penicilloyl conjugates upon degradation, whereas cephalosporins undergo rapid fragmentation of both the beta-lactam and dihydrothiazine rings, with the R1 side chain remaining attached to the carrier protein as the primary immunogenic component [19]. This fundamental difference explains why cross-reactivity is not determined by the shared beta-lactam ring but rather by the structural similarity of the R1 side chains. The critical clinical insight is that cefazolin—a first-generation cephalosporin widely used for surgical prophylaxis—possesses a unique R1 side chain not shared with any other beta-lactam, while second-, third-, and fourth-generation cephalosporins have progressively more complex and distinct R1 structures that lack homology with penicillins [19,20,21]. This structural divergence accounts for the negligible cross-reactivity observed with these agents in clinical studies.

The clinical evidence supporting cephalosporin use in penicillin-allergic patients is robust and consistent across multiple study designs and populations. Prospective studies of patients with confirmed penicillin allergy receiving cefazolin, cefuroxime, and ceftriaxone have demonstrated no allergic reactions [18,19]. Large retrospective series have found that among thousands of penicillin-allergic patients receiving cefazolin, reaction rates are consistently below 1% [17,18,24]. Notably, the reaction rates observed in these studies are comparable to those in patients without

penicillin allergy, suggesting that the baseline risk of adverse reactions to cephalosporins is not meaningfully increased in most patients with penicillin allergy labels [24]. The finding that 452 patients with penicillin allergy labels had zero positive skin tests to cefazolin or ceftriaxone further supports the safety of these agents [17].

The clinical and economic consequences of avoiding cephalosporins in penicillin-allergic patients are substantial. Alternative antibiotics such as clindamycin and vancomycin are associated with a 50% increased odds of surgical site infections [17,20,21]. This increased risk is multifactorial: vancomycin requires prolonged infusion time, leading to suboptimal timing relative to surgical incision in 97.5% of cases, while clindamycin resistance among common skin flora has risen to 23%–32% [20]. Alternative agents also carry higher risks of adverse events, including acute kidney injury with vancomycin and *C. difficile* infection with clindamycin [20,21]. Implementation of side chain-based cross-reactivity algorithms has been shown to increase beta-lactam use from 70% to nearly 90% without increasing allergic reactions while significantly reducing healthcare facility-onset *C. difficile* infections [25]. These findings underscore that the risk of harm from cephalosporin avoidance often exceeds the risk of cross-reactivity itself.

Skin testing and drug provocation testing are valuable tools for evaluating beta-lactam allergies, their routine application is hindered by several significant clinical limitations. A primary barrier is the access limitations in many healthcare systems, where a lack of allergy specialist consultations makes testing unfeasible in time-sensitive scenarios like perioperative prophylaxis. Additionally, diagnostic approaches suffer from variability between institutions, driven by differing local clinical pathways and regional antibiotic prescribing patterns. There is also a recognized lack of standardized reagents and testing protocols; for example, cephalosporin intradermal testing has not been standardized regarding optimal test concentrations, injection volumes, the use of negative controls, or the interpretation of positive responses [29]. Crucially, these tests have limited predictive value for some cephalosporins. Large-scale prospective studies have demonstrated that routine screening intradermal tests for cephalosporins can yield 0% sensitivity and a 0% positive predictive value. Furthermore, the negative predictive value is clinically limited, as studies report that patients have still developed immediate hypersensitivity reactions—such as generalized urticaria and itching—despite having negative cephalosporin skin test results [30]. Because a negative test does not definitively rule out an allergic reaction, routine cephalosporin skin testing is often considered inefficient for predicting immediate hypersensitivity.

The development and validation of risk stratification tools have enabled a more nuanced approach to antibiotic selection in penicillin-allergic patients. Approximately 60% of patients with penicillin allergy labels fall into a low-risk category based on index reaction characteristics—including side

effects, limited hypersensitivity responses, or remote childhood reactions—and can safely receive cephalosporins without prior testing [17,24]. Moderate-risk patients may benefit from allergy testing in elective settings, while severe-risk patients with histories of SJS, TEN, or DRESS syndrome should avoid cephalosporins entirely [17,21]. Implementation of such algorithms has increased first-line cephalosporin use from 22% to over 80% without any hypersensitivity reactions attributable to cefazolin [20]. In pediatric populations, selective immediate responders to aminopenicillins and cephalosporins constitute an important group, with 71%–94% tolerating penicillin V and cephalosporins with dissimilar side chains after negative allergy workup [26].

Notable geographic differences in cross-reactivity patterns reflect variations in antibiotic prescribing practices. Positive skin testing to ampicillin—indicating aminopenicillin sensitivity—occurs in 7.6% of patients in Australia compared to only 2.2% in the United States, reflecting the widespread use of parenteral aminopenicillins in Europe and Australia [22]. The aminopenicillin-aminocephalosporin cross-reactivity pattern, while clinically relevant in these regions, appears less significant in the United States [22]. The time elapsed since the index reaction is a critical predictor of skin test positivity, with each year reducing the odds of positive testing by 7% for penicillins and 29% for cephalosporins [22]. This finding has important practical implications, as many patients with remote histories of penicillin reactions can be safely treated with cephalosporins without extensive testing.

Despite the growing body of evidence, significant knowledge gaps persist among healthcare professionals. A survey of clinical pharmacists revealed that only 53% correctly identified that the R1 side chain is the primary determinant of allergic reactions to cephalosporins, while 47% erroneously believed the beta-lactam ring itself is the main allergenic structure [28]. Furthermore, 85% mistakenly believed that cross-reactivity between penicillins and carbapenems exceeds 30%, and 73% believed the risk of cross-reactivity between penicillins and monobactams is high—both views contradicting current evidence [28]. These findings highlight the urgent need for ongoing education to ensure that current evidence translates into clinical practice and that patients are not exposed to unnecessary risks from alternative antibiotics.

The accumulating evidence has led to substantial revisions in clinical practice guidelines. The 2022 Drug Allergy Practice Parameters explicitly state that cefazolin and other cephalosporins with structurally dissimilar R1 side chains can be administered to patients with penicillin allergy, including those with a history of anaphylaxis, without preemptive testing [20,21]. This recommendation is supported by the Society for Healthcare Epidemiology of America, the Infectious Diseases Society of America, and the Association for Professionals in Infection Control

and Epidemiology [21]. The only absolute contraindications are histories of severe cutaneous adverse reactions or verified allergy to the specific cephalosporin [20,21]. Future research should focus on developing standardized testing protocols for aminocephalosporins, elucidating the mechanisms of selective cefazolin hypersensitivity, and implementing effective educational interventions to address persistent misconceptions among healthcare professionals.

Conclusions

The historical concern that penicillin-allergic patients face a 10% risk of cross-reactivity with cephalosporins has been substantially overestimated based on flawed early studies. Contemporary evidence demonstrates that cross-reactivity is primarily determined by structural similarity of R1 side chains rather than the shared beta-lactam ring. Cefazolin possesses a unique R1 side chain not shared with any other beta-lactam, while second-, third-, and fourth-generation cephalosporins have progressively more complex R1 structures lacking homology with penicillins, resulting in negligible cross-reactivity. Large-scale clinical studies confirm that later-generation cephalosporins can be safely administered to the vast majority of patients with penicillin allergy, including those with a history of anaphylaxis, with reaction rates below 1%. Avoidance of cephalosporins in these patients leads to increased use of alternative antibiotics associated with 50% higher odds of surgical site infections, increased adverse events, and higher healthcare costs. Risk stratification tools based on index reaction characteristics enable safe cephalosporin use in approximately 60% of patients without routine testing, while implementation of side chain-based cross-reactivity algorithms has been shown to increase beta-lactam use to nearly 90% without increasing allergic reactions. Persistent knowledge gaps among healthcare professionals highlight the need for ongoing education to translate current evidence into clinical practice. The updated 2022 Drug Allergy Practice Parameters recommend that cephalosporins with structurally dissimilar R1 side chains can be administered to patients with penicillin allergy, including those with a history of anaphylaxis, without preemptive testing, with the only absolute contraindications being histories of severe cutaneous adverse reactions or verified allergy to the specific cephalosporin. Adherence to these evidence-based recommendations is essential to optimize patient outcomes, reduce healthcare-associated infections, and preserve first-line antibiotic options.

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