Cephalosporins Should be Avoided in Patients with Penicillin Allergy

Kirsty Challen, MBChB, PhD, FRCEM

KEYWORDS

• Penicillin • Cephalosporin • Allergy • Anaphylaxis • Cross-reactivity

KEY POINTS

- Concern has existed since cephalosporins became available that patients with penicillin allergy are at significant risk of coexisting cephalosporin allergy.
- Guidance for clinicians from regulatory bodies and specialist societies is inconsistent.
- Blanket avoidance of cephalosporins in patients with penicillin allergy is associated with other adverse consequences.
- The approach to a patient reporting a penicillin allergy requiring antibiotics should be nuanced, involving risk stratification and shared decision-making.

INTRODUCTION AND HISTORY

Concern over the possibility of allergic reactions to antibiotics has featured in the medical literature for nearly as long as the antibiotics; from Florey's first case series of penicillin use in 1943,[1] only 3 years passed before a review summarizing penicillin allergy in practice.[2] As the "new" cephalosporins came into widespread use, similar concerns emerged,[3] including caution regarding cross-reactivity between penicillin and cephalosporin allergy. By 1976, a clinical review in New England Journal of Medicine (NEJM) suggested "all cephalosporins probably should be avoided in patients with a past history of anaphylaxis (or immediate hypersensitivity) to any of the penicillins."[4]

By the early 1980s, evidence was emerging that a proportion of penicillin-related adverse reactions were likely due to degradation and transformation products rather than the drug itself; Neftel and colleagues[5] demonstrated that infusion of a freshly prepared bolus rather than stored Penicillin G greatly reduced adverse hematologic effects. Debate persisted over whether the β-lactam ring common to penicillins and cephalosporins was the culprit in allergy; by 2001, the NEJM review article classed a history of penicillin allergy as a "relative contraindication" to cephalosporin use,

Department of Emergency Medicine, Lancashire Teaching Hospitals, Sharoe Green Lane, Preston, PR2 9HT, UK
E-mail address: kirstychallen@hotmail.com

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Abbreviations	
AAAAI	American Academy of Allergy, Asthma and Immunology
IgE	immunoglobulin E
IM	intramuscular
OBGYN	obstetrics and gynecology
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis

stating that the risk of cephalosporin anaphylaxis "may be increased" in penicillin allergy, and that the risk of any allergic reaction "may be up to eight times as high." Cited to support this are publications totaling 385 patients from 1966 to 1994.[6]

Through the 2000s and 2010s, formal guidance became more nuanced. The American Academy of Allergy, Asthma and Immunology (AAAAI) stated in 2009:

> *it is reasonable to conclude that among all-comers with a history of penicillin allergy, if one excludes patients with more severe reaction histories, there is an extremely low chance of developing cephalosporin-induced allergic reactions.*

The AAAAI advised that in a patient reporting a penicillin allergy when formal allergy testing was unavailable, clinicians could weigh the risk of harm against the benefit of using a cephalosporin, with the option of an initial test dose of one-tenth of the standard dose.[7] The British Society for Allergy and Clinical Immunology advised in its 2015 guidance for allergy specialists that patients with a clinical history of penicillin allergy and a positive skin test should have a skin test of a cephalosporin with a different side chain and, if this was negative, proceed to cephalosporin provocation testing.[8] By 2020, the AAAAI guidance advised avoiding only drugs with similar R1 side chains (eg, cefadroxil, cephalexin, and cefaclor in amoxicillin or ampicillin allergy).[9]

Historic caution, however, persists in pharmaceutical advice. The US Food and Drug Administration label for cephalosporins warns of 10% cross-reactivity,[10] while the British National Formulary entry for all cephalosporins states

> *Cross-reactivity between penicillins and first and early second-generation cephalosporins has been reported to occur in up to 10%, and for third-generation cephalosporins in 2% to 3%, of penicillin-allergic patients. Patients with a history of* ***immediate hypersensitivity*** *to penicillin and other beta-lactams should not receive a cephalosporin. Cephalosporins should be used with caution in patients with sensitivity to penicillin and other beta-lactams.*

Mortality from anaphylaxis to cephalosporins clearly exists; the UK Fatal Anaphylaxis Registry recorded 12 deaths between 1992 and 1997 related to antibiotic administration. Six of these were for a first dose of a cephalosporin, 3 in patients allergic to amoxicillin, and 1 in a patient with penicillin allergy.[11] The clinical question for the practicing emergency physician is whether this historical concern for cross-reactivity should preclude the use of cephalosporins, often the preferred first-line antibiotic, in patients who report penicillin allergy.

PATHOPHYSIOLOGY

The typology of hypersensitivity reactions is summarized in **Table 1**.

Cross-sensitivity to cephalosporins in patients with penicillin allergy was originally thought to be due to the β-lactam ring common to penicillins, cephalosporins, carbapenems, and monobactams (**Fig. 1**).

Table 1
Pathophysiology of hypersensitivity reactions

Type	Mechanism and Timing	Typical Features/Examples
Type I (immediate)	Immediate, IgE-mediated; up to 6 h from dosing	Rapid onset, potentially life-threatening reactions such as anaphylaxis
Type I (accelerated)	IgE-mediated; up to 4–7 d into course; 1–6 h from last dose	Similar to immediate, but may occur later in the course of treatment
Type II (cytotoxic)	IgG-mediated lysis of leukocytes/platelets/red blood cells in the presence of complement	Usually with extended antibiotic use
Type III (immune complex)	IgG/IgM/immune complex; 3–4 wk after starting treatment	Can be non–immune-dependent (especially with cefaclor)
Type IV (T-cell)	T-cell mediated; >3–4 d after first dose or >1–2 h after last dose	Usually cutaneous, highly variable presentation
Type IVa (contact)	Classic contact hypersensitivity, T-cell stimulated macrophage/monocyte	Rarer due to reduced use of topical penicillin
Type IVb (T-helper 2)	Th2 cells stimulate IL4/IL5 causing eosinophil recruitment; hours to days after dosing	Classic with epstein-barr virus (EBV) plus aminopenicillins; morbilliform/maculopapular rash
Type IVc (cytotoxic)	CD4/CD8 cytotoxic T-cell activation	Severe skin reactions such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)
Type IVd	Neutrophil activation via interleukin-8	Associated with aminopenicillins

From Mirakian R, Leech S, Krishna M, et al. Management of allergy to penicillins and other beta-lactams. Clin Exp Allergy. 2015;45:300–27.[8]

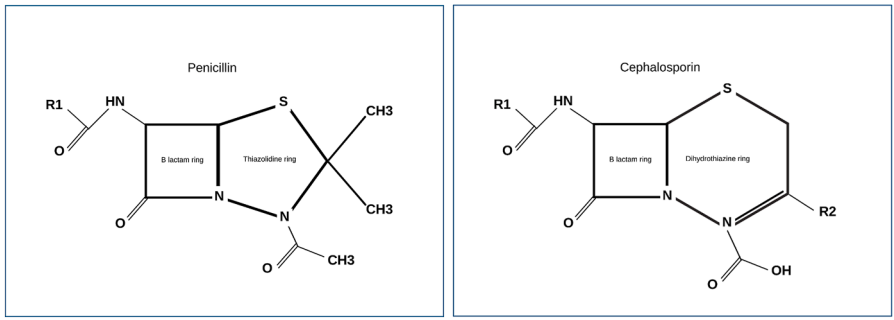

Fig. 1. Structural diagram of penicillin and cephalosporin. (*From* Chaudhry SB, Veve MP, Wagner JL. Cephalosporins: a focus on side chains and β-lactam cross-reactivity. Pharmacy. 2019;7:103.[12])

More recent evidence notes that the degradation process for penicillins and cephalosporins differs[8] and that similarities in the R1 side chain (particularly for cefadroxil, cephradrine, cefaclor, and cefalexin with ampicillin and amoxicillin) are more likely to be clinically relevant.[12]

DIRECT EVIDENCE OF CROSS-REACTIVITY IN VIVO

Picard and colleagues[13] meta-analyzed the incidence of cross-reactivity to cephalosporins and carbapenems in 21 studies including 1269 patients with penicillin allergy. To be included, studies had to describe at least 10 patients with confirmed allergies, as determined by skin prick or direct provocation testing. They calculated the absolute risk of cross-reactivity to be 0% to 14% for first-generation cephalosporins, 1% to 13% for second-generation, 0% to 1.4% for third-generation, and 0.31% for cefepime, the only fourth-generation cephalosporin studied.

Similarly, Caruso and colleagues[14] reviewed evidence of response to a graded cephalosporin challenge in patients with immunoglobulin E (IgE)-mediated penicillin sensitivity and negative cephalosporin skin testing. Reactions were observed in 11 of 1825 patients overall, with rates ranging from 0% to 7% (the highest rate was 2 of 28 patients receiving intramuscular cefuroxime).

Further smaller cohorts are summarized in **Table 2**.

EVIDENCE OF CROSS-REACTIVITY IN CLINICAL PRACTICE

Many patients presenting with an emergent or urgent need for antibiotics will never have undergone a formal allergy workup, and even among those who have, the emergency clinician may not be able to access the details. Several studies have examined the pragmatic use of cephalosporins in the context of penicillin allergy.

Terico and Gallagher's[19] 2014 review reports cross-reactivity rates ranging from 40% in the 1960s to 8.1% in 1978, with approximately 1% in the 2000s. Sousa-Pinto and colleagues[10] reviewed 6001 patients in 77 studies of patients with penicillin allergy, of whom 44 had cefazolin allergy, generating a meta-analytical frequency of 0.7% (credible interval 0.1%–1.7%). This varied between self-reported penicillin allergy (0.6%) and confirmed allergy (3%).

Further studies are detailed in **Table 3**.

IMPACT OF BLANKET AVOIDANCE OF CEPHALOSPORINS

It could be argued that although severe reactions to cephalosporins are low in patients with penicillin allergy, clinicians should adopt a "better safe than sorry" approach of cephalosporin avoidance. However, cephalosporins are first-line treatment of many conditions, and clinicians should be mindful of the potential adverse consequences to the individual patient and in terms of antimicrobial stewardship of reflexively using alternatives. As detailed in **Table 4**, second-line antibiotic regimes have been associated with multiple morbidities and mortality. Notably, the National Audit Project 6 (NAP6) nationwide study of perioperative anaphylaxis from the United Kingdom demonstrated a relative rate of teicoplanin anaphylaxis 17 times that of cefuroxime; over half the patients suffering teicoplanin anaphylaxis had a stated penicillin allergy preoperatively.[28]

REAL-WORLD IMPLEMENTATION

Evidence to inform a change in practice patterns at the institutional level is accumulating (**Table 5**), mostly in case series or before and after studies involving a formal

Table 2
Immunologic investigations of cross-reactivity

Study	Date and Location	Population	Results
Abraham et al,[15] 1968	1967 San Francisco General	174 adult patients receiving penicillin treatment	10 out of 46, 13 out of 35, 2 out of 21 (dependent on treatment duration) had positive hemagglutination of cephalothin-sensitized erythrocytes
Al-Ahmad et al,[16] 2018	2009–16 Kuwait	214 patients referred for potential penicillin allergy	78 out of 214 had positive skin test to penicillin; 50 out of 78 challenged with alternatives; 5 out of 50 reacted (2 meropenem and 3 cefuroxime) 13 out of 214 had positive skin test to cephalosporin; 10 out of 13 challenged with alternatives; none reacted
Assem et al,[17] 1974	1973 United Kingdom	24 patients with penicillin allergy; 3 had previously received cephaloridine, all had reacted	11 out of 24 had positive skin test to cephaloridine
Romano et al,[18] 2016	2000–14 Italy	214 patients aged over 14 years with history of nonimmediate reaction to penicillin and positive patch/delayed reading skin test	214 out of 214 had negative skin test to cefuroxime, ceftriaxone, and aztreonam; 213 out of 214 underwent intramuscular (IM) challenge with cefuroxime, ceftriaxone, and aztreonam, all tolerated it 40 out of 214 had positive skin test to at least 1 aminocephalosporin. 170 out of 174 with negative skin test to aminocephalosporin underwent IM cefaclor challenge, 1 out of 170 developed rash at 24 h

risk stratification tool and/or clinician education. Macy and colleagues[36] and Otani and colleagues[38] describe natural experiments where policy changes or education were applied to 1 network or department and not another; both report an increased use of β-lactams without associated increases in adverse reactions. Pending at the time of writing is a stepped wedge randomized trial of a decision tree to promote the use of first-generation and second-generation cephalosporins for perioperative prophylaxis (NCT06067919).[40]

DELABELING

Delabeling patients who report penicillin allergy may represent a significant opportunity given that rates of skin test reaction in patients reporting such allergy can be as

Table 3
Cross-reactivity in clinical practice

Study	Date and Location	Population	Results
Apter et al,[20] 2006	1987–2001 United Kingdom	General practitioner (GP) database of patients receiving prescription for penicillin and prescription for cephalosporin at least 60 d later	43 out of 3920 patients with a penicillin allergy-like event experienced cephalosporin allergy-like event 581 out of 530,890 without a penicillin allergy-like event experienced cephalosporin allergy-like-event; unadjusted risk ratio (RR) 10 (7.4–13.6); 25 incidents of penicillin anaphylaxis; 1 patient also had cephalosporin anaphylaxis; 12 patients had cephalosporin anaphylaxis without penicillin anaphylaxis
Bukowski et al,[21] 2024	2016–22 United States	49,842 adults undergoing primary total hip or knee arthroplasty, excluding those with documented cephalosporin allergy	11% reported penicillin allergy; 90% of those received cefazolin; and 0.03% suffered perioperative anaphylaxis (16 cefazolin and 1 clindamycin) No patients with recorded penicillin anaphylaxis/severe IgE-mediated had reaction to cefazolin
Crotty et al,[22] 2017	2011–2 United States	175 hospitalized adults with self-reported penicillin allergy who received cephalosporin or meropenem	10 (6%) manifested a reaction: 6 out of 96 cefepime, 3 out of 56 meropenem, 1 out of 13 cefoxitin, 0 out of 69 ceftriaxone, and 0 out of 8 cefalexin 1 angioedema, 9 rash ± pruritis/fever
Kurcz et al,[23] 2023	2013–7 United States	2284 patients undergoing lower limb arthroplasty	1809 out of 1894 reporting no allergy and 143 out of 310 reporting penicillin allergy received cefazolin 6 out of 1887 and 4 out of 310 had an allergic reaction to perioperative antibiotic (0.3% vs 1.3%); of the 4 patients with penicillin allergy having an allergic reaction, 1 received cefazolin
Michaud et al,[24] 2023	2015 Canada	Patients undergoing elective or emergency surgery	486 out of 5433 reported non-IgE penicillin reaction; 215 out of 486 received cefazolin; 2 out of 215 had a reaction (1 rash and 1 transient perioperative hypotension) 217 out of 5433 reported pen IgE reactions; 50 out of 217 received cefazolin; 2 out of 217 reacted (1 facial swelling and itching, 1 rash)

Norvell et al,[25] 2023	2020–21 United States	1047 patients reporting penicillin or cephalosporin allergy undergoing primary total hip or knee replacement	809 received cefazolin; 2 had intraoperative reaction 319 received clindamycin or vancomycin; 4 had intraoperative reaction
Sundermann et al,[26] 2025	2017–24 New Zealand	8374 patients with a first hospital admission with cellulitis who received antibiotics and had no change to their recorded allergies during the admission	484 out of 729 patients with a previously recorded penicillin reaction received cephalosporin first line. None of these suffered anaphylaxis

Table 4
Nonhypersensitivity impacts of cephalosporin avoidance

Reference	Location	Study	Results
Desai et al,[27] 2017	2009–14 United States	42,524 Group B streptococcus-positive women delivering live infant	38% of patients with penicillin allergy received cefazolin (American College of Obstetricians and Gynecologists [ACOG] recommended antibiotic); 58% received clindamycin 30.3% rate of caesarean delivery in patients with allergy vs 27.5%
Harper et al,[28] 2018	2016 United Kingdom	NAP6 snapshot study of perioperative anaphylaxis	Relative rate of perioperative anaphylaxis 17.4 for teicoplanin, 9.2 for co-amoxiclav (reference cefuroxime). 20 out of 36 patients with reaction to teicoplanin had penicillin allergy stated preoperatively
Kaminsky et al,[29] 2022	2014–21 United States	68,748 patients hospitalized for bacterial pneumonia, and recorded penicillin allergy; 1:1 propensity matched to those without allergy	Risk ratios for recorded penicillin allergy: hospitalization 1.23; acute respiratory failure 1.14; intubation 1.18; intensive care admission 1.11; and mortality 1.08
Marinho et al,[30] 2018	2016 United Kingdom	NAP6 snapshot study of perioperative anaphylaxis	In 8.6% cases of perioperative anaphylaxis, drug choice had been influenced by previous allergy history; 64% of those were antibiotic allergy
McGuinness et al,[31] 2021	2014–19 United States	603 adults attending ED with potential sexually transmitted infection (STI)	21 out of 31 (68%) patients reporting penicillin allergy received cephalosporin vs 486 out of 569 (85%) not reporting allergy. Likelihood of cephalosporin administration was lower with attending only care (53%) vs resident (71%) vs physician assistant (PA) (88%)
Norvell et al,[25] 2023	2020–21 United States	1047 patients reporting penicillin or cephalosporin allergy undergoing primary total hip or knee replacement	7 out of 809 receiving cefazolin developed surgical site infection 12 out of 319 receiving clindamycin or vancomycin developed surgical site infection

Table 5
Evidence for strategies to support cephalosporin prescribing

Reference	Setting	Population	Intervention	Outcomes
Anderson et al,[32] 2024	Single-center US ED 2021–22	184 adults with moderate, severe or unknown severity β-lactam allergy	Full-dose β-lactam challenge in ED	5 reactions: 2 ceftriaxone, 2 piperacillin-tazobactam, 1 nafcillin; 4 rashes, and 1 itch No reactions in 24 patients with "severe allergy"
Backus et al,[33] 2024	Single-center US hospital 2022 (pre), 2023–24 (post)	340 adult surgical patients with penicillin allergy (not severe)	Education to increase optimal preoperative antibiotic administration (first-line cefazolin)	Cefazolin use increased from 52% to 67% No change in allergic reactions; 1 *Clostridium difficile* case preintervention and 1 blistering from vancomycin extravasation postintervention
Isserman et al,[34] 2022	Single-network US 2019–21	400 children with documented "nonsevere" penicillin allergy requiring perioperative antibiotic prophylaxis	Education, updated reference guide, and feedback emails	Cefazolin use increased from 41% to 90% No change in surgical site infection rate (0.2%) No severe allergic reactions
Jacobs et al,[35] 2023	2 center US 2017–21	119 adults with β-lactam allergy	Risk stratification algorithm Low risk: cephalosporin; high-risk type I: alternative agent or test dose of third/fourth-generation cephalosporin; high-risk type II–IV: avoid β-lactam	11 patients with reaction to test dose; 4 in first 24 h, 7 delayed

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Table 5
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Reference	Setting	Population	Intervention	Outcomes
Macy et al,[36] 2021	2 California health networks 2017–18	~4 million patients; ~400,000 with penicillin allergy	1 network removed the warning in the electronic health record to avoid cephalosporins in penicillin allergy	Cephalosporin use increased at site with change from 17.9% to 27% with no change in anaphylaxis, newly documented antibiotic allergies, antibiotic failure, mortality, length of stay, or new infections
Maguire et al,[37] 2020	Single-center US ED 2016–18	310 patients with penicillin or cephalosporin allergy receiving test doses	Hospital guideline: mild reaction: full-dose cephalosporin or test dose penicillin; type I reaction: test dose third/fourth/fifth-generation cephalosporin	10 reactions (3.2%), 5 of these not compliant with guideline pathway
Otani et al,[38] 2023	US health system 2017–20	58,906 admitted receiving intravenous antibiotics; 8643 with penicillin or cephalosporin allergy	New order set; education provided for medical specialties (order set but no education for surgery/ obstetrics and gynecology [OBGYN])	Use of full-dose penicillin or cephalosporin increased from 58% to 68% in medical patients; no change in surgical or OBGYN IM epinephrine administered 4 times, none related to guideline
Stonerock et al,[39] 2023	US single system 2021–22	914 preoperative patients with penicillin allergy label	Pharmacy-led risk stratification with cefazolin first line	Cefazolin use increased from 13% to 38% Surgical site infections increased from 2.8% to 4.9% 2 potential adverse events postintervention; 1 generalized intraoperative facial swelling; and 1 unexplained fluid-resistant hypotension

low as 10%.[7] The American Academy and College of Asthma Allergy and Immunology issued an extensive joint practice parameter in 2022 advocating for the delabeling of patients where possible with a tiered strategy for approaching this.[41] The PEN-FAST clinical decision tool was developed in Australia to support the identification of patients reporting penicillin allergy who did not require formal allergy testing before delabeling. A patient scores points for

- Five years or less since reaction (2 points)
- Anaphylaxis or angioedema *or*
- Severe cutaneous adverse reaction (2 points)
- Treatment required for reaction (1 point)

Likelihood of having a positive penicillin allergy test is indicated by the points: 0 points indicates very low risk (<1%), 1 to 2 points indicate low risk (5%), 3 points indicate moderate risk (20%), 4 to 5 points indicate high risk (50%).[42] The tool has been validated in a number of settings including US allergy clinics[43] and emergency departments (EDs),[44] Turkish pediatric outpatients,[45] and Singapore.[46]

A similar risk-stratified approach was tested in the medical intensive care unit of Vanderbilt School of Medicine. 114 patients were able to describe their index reaction, which was categorized per **Table 6** including 68 with a low-risk history. Fifty-four of those 68 agreed to an oral penicillin challenge and all were delabeled after having no immediate or delayed reaction to the challenge.[42]

Table 6
Vanderbilt risk stratification tool

Low risk	• Urticaria only, >5 y have passed • Self-limited cutaneous rash at any point • Gastrointestinal symptoms only • Remote childhood reaction with limited details • Family history of penicillin allergy only • Avoidant from fear of allergy only • Known tolerance of a penicillin since the original reaction occurred • Other symptoms, nonallergy
Moderate to high risk: anaphylaxis, especially in last 5 y	After administration of the first dose of a new treatment course with a penicillin, patient developed any of the following severe symptoms within 1 h, up to 6 h • Disseminated hives/urticaria/flushing/pruritis • Angioedema/swelling of face/throat • Shortness of breath, wheezing, and coughing • Shock • Weak pulse • Loss of consciousness/confusion • Severe gastrointestinal symptoms (diarrhea and vomiting)
Highest risk: severe delayed symptoms at any point	• Mouth or eye ulcerations • Skin or mucosal sloughing or blistering • Serum sickness • Immune-mediated kidney injury • Immune-mediated liver injury • SJS • TEN • Drug reaction with eosinophilia and systemic symptoms • Acute generalized exanthematous pustulosis • Febrile skin rash without a better explanation

LEGAL CONCERNS

Clinicians practicing in areas where medicolegal concerns more directly affect practice may feel reticent to prescribe "against" published guidelines or package inserts. Reassuringly, a 2018 US review of major legal databases identified only 27 medical malpractice cases since 1959 involving a patient with known penicillin allergy suffering an adverse reaction after β-lactam administration. In 18 of these, the patient received a penicillin, 7 received a cephalosporin, and 2 received a carbapenem. Of the 4 cephalosporin-related cases with a known outcome, the defendants prevailed in 3. In the final case of *Killeen v Reinhart*, the administration of a cephalosporin was 1 issue in a trial that proceeded primarily on the issue of placing a pregnant woman with asthma on an obstetric rather than internal medicine ward.[47]

The United Kingdom keeps a database of Prevention of Future Death reports from coroners in England and Wales. These are issued by coroners and statute requires a response from the institution (usually in this case a hospital) to which they are sent. From 2013 to 2025 only 2 relevant reports were issued, one relating to a patient with known penicillin allergy prescribed co-amoxiclav and the other to a patient receiving ceftriaxone despite a known ceftriaxone allergy.[48]

DISCUSSION AND SUMMARY

Emergency care clinicians rarely have the luxury of working with full information; patients reporting a penicillin allergy can range from those who have survived a life-threatening anaphylactic reaction to those who have never, in fact, taken a penicillin but who have acquired the label via a family history.

The history of this misconception[49] provides us with the reason it can now be laid to rest; were the hypothesis of the β-lactam ring as the primary allergen true, it would be reasonable to avoid all cephalosporins in any patient with penicillin allergy. However, as evidence evolves for the culpability of various R1 side chains, this becomes less logical. Substantial allergist-based and pragmatic literature suggests that cephalosporins, particularly later generations, are safe in many patients with genuine penicillin allergy. Equally, alternative antibiotic options are not devoid of allergic risk.

Multiple hospitals and systems are now developing risk stratification support tools that allow a nuanced approach to shared decision-making between clinician and patient. This, rather than automatic warnings in an electronic health record precluding all cephalosporin prescriptions, should be the way forward for emergency care.

CLINICS CARE POINTS

- The oft-quoted 10% prevalence of cephalosporin allergy in patients with penicillin allergy is approximately an order of magnitude higher, with the true value closer to 1% for third-generation cephalosporins and 0.31% for cefepime, based on allergist data.
- Extensive data demonstrate that cefazolin has a 1% allergy rate in patients with documented penicillin allergy.
- Alternative antibiotics may be associated with increased morbidity and are not free of allergy risk.
- Multiple tools have shown promise in supporting risk stratification of patients with penicillin allergy for receipt of cephalosporins.

DISCLOSURE

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