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Quality corner: Safely using cephalosporins in almost all patients with penicillin allergies: Mini-review and suggested protocol to improve efficacy and surgical outcomes

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ABSTRACT

Surgical site infections (SSI) are one of the most common gynecologic oncology postoperative complications and they have a significant deleterious impact on the healthcare system and in patients' outcomes. Cefazolin is the recommended antibiotic in women undergoing gynecologic surgical procedures that require that require prophylaxis. However, 10–20% of patients may report a penicillin allergy which can result in administration of a less effective antibiotic. This quality review evaluated the literature around this common perioperative issue and demonstrated that healthcare teams should consider the implementation of a protocol to safely use cefazolin in most patients with a penicillin allergy. Overall, literature shows this is a safe adjustment and would improve antimicrobial stewardship, decrease SSI rates, avoid acute kidney injury, and increase cost savings.

Surgical site infections (SSIs) are one of the most common complications in gynecologic oncology surgery and can increase readmission rates, lengthen hospital stay, delay adjuvant therapy, and increase the risk for reoperation (Mahdi et al., 2014). It is estimated that SSIs can cost up to $20,000 per readmission and is the most expensive healthcare-associated infection per the Center for Disease Control (CDC) with a nationwide cost of 3.3 billion per year (Zimlichman et al., 2013; Network, 2024). In the field of gynecologic oncology, one of the most frequently used and effective antibiotics used for surgical prophylaxis is cefazolin in procedures that require antibiotic usage. However, if a patient has a penicillin or beta-lactam allergy, cefazolin is frequently substituted with a non-beta-lactam antibiotic to avoid the theoretical risk of cross-reaction. However, this risk is extremely low (generally quoted around 1 % or less (Campagna et al., 2012)and must be balanced against the disadvantages of using a non-beta-lactam antibiotic, including increased infection rates, acute kidney injury (AKI), antibiotic resistance, and costs (Blumenthal et al., 2018; Ahmed et al., 2022; Bhathal et al., 2022). In addition, vancomycin is regularly substituted for cefazolin in penicillin allergic patients, which can result in operating delays due to the need for prolonged infusion and side effects such as AKI or vancomycin infusion reactions. Another common alternative is clindamycin which is losing its efficacy due to an increase in resistance to it among the common SSI pathogens such as staphylococci (Clindamycin, 2023).

Cefazolin is a first-generation cephalosporin that effectively provides protection in gynecologic surgery against the most common pathogens in SSIs, with an excellent safety profile at a low cost. In addition, its short infusion time improves pre-operative logistics to allow completion within the critical 60 min prior to incision (Ahmed et al., 2022). Cefazolin has been shown to be just as effective as other later generations of cephalosporins while promoting antibiotic stewardship (Geroulanos et al., 2001). The use of generalized broad-spectrum antibiotics increases the risk of *Clostridium difficile* and antibiotic resistance (Shenoy et al., 2019). When cefazolin is not utilized, there is up to a 50 % higher risk of SSIs when non-beta-lactam antibiotics such as clindamycin, vancomycin, or gentamicin are used for prophylaxis (Blumenthal et al., 2018).

Approximately 10–20 % of patients report a penicillin allergy to their healthcare provider; however, <5% of these patients have a true allergy confirmed by official testing (Baxter et al., 2020; Vorobeichik et al., 2018; Khan et al., 2022). Unverified penicillin allergies are a growing public health concern given that the administered alternative antibiotics given may lead to poorer clinical outcomes, increased antimicrobial resistance, and healthcare costs (Krishna et al., 2021). Most patients

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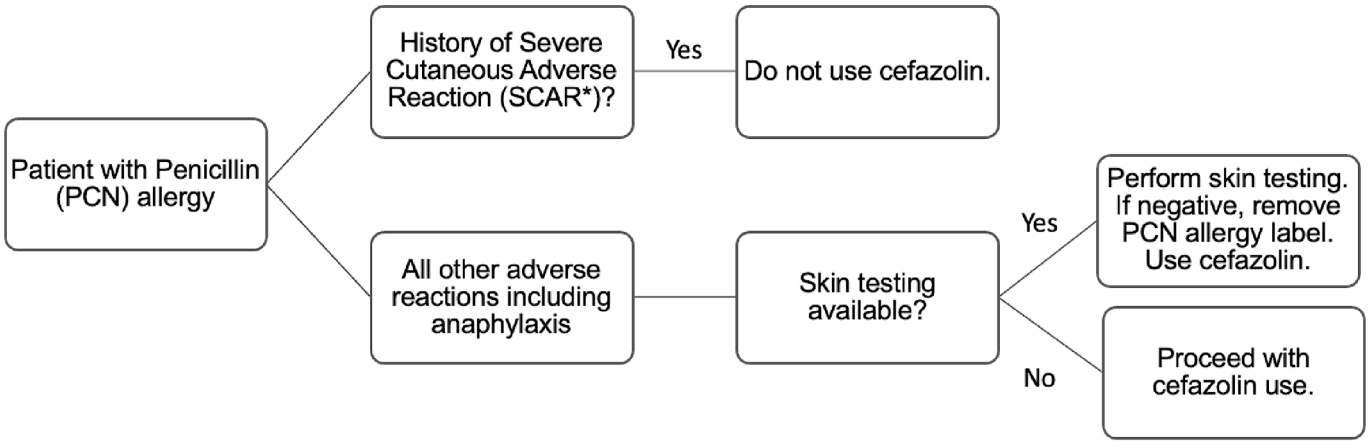

Fig. 1. Algoithm for cefazolin use in gynecologic patients with a history of penicillin allergy. *SCARs include acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens Johnson Syndroms (SJS), symmetrical drug-related intertriginous and flexural exanthema (SDRIEF), or toxic epidermal necrolysis (TEN).

with self-reported beta-lactam allergies do not have a clinically significant penicillin allergy and can safely use antibiotics such as cefazolin or other beta-lactams (Murphy et al., 2024). Even in patients with a type 1, IgE-mediated allergic reactions such as anaphylaxis to penicillin have been found to safely tolerate cefazolin (Khan et al., 2022; Murphy et al., 2024; Alexander, 2022). From 2017 through 2022, published studies show that 5,519 patients with penicillin allergy labels including 1078 patients listed to have type 1 hypersensitivity, safely tolerated cefazolin for *peri*-operative prophylaxis with improved preoperative antibiotic infusion completion timings, antibiotic selection, SSIs, and fewer AKIs (Alexander, 2022; Lessard et al., 2023; Grant et al., 2021; Sexton et al., 2022). More recent research demonstrates that the risk of cross-reactivity between penicillins and cephalosporins is more related to the R1 side chain of the antibiotic structure rather than the shared beta-lactam ring as previously believed. Uniquely, cefazolin does not share side chains with any other penicillin or cephalosporin affording it a much lower risk of cross-reactivity (Khan et al., 2022; Romano et al., 2018; Picard et al., 2019). There is a 0.7–2.0 % chance that a patient with an unverified penicillin allergy will have cross-reactivity to cefazolin, and clinically significant penicillin allergies can be evaluated with a simple skin sensitivity test (Shenoy et al., 2019; Sousa-Pinto et al., 2021; Macy, 2014).

The skin sensitivity test can provide results within 15 min and be incorporated into the pre- or *peri*-operative setting. Studies have demonstrated that integrating penicillin allergy testing into the preoperative setting allowed for almost all patients to receive first-line antibiotic prophylaxis with cefazolin as it provides a negative predictive value of over 95 % (Shenoy et al., 2019; Plager et al., 2020). Testing has been performed in a variety of ways with some clinics referring their patients to an allergist and other preoperative clinics having an in-house testing system (Plager et al., 2020; Savic et al., 2019). Some hospitals have even introduced inpatient testing to optimize antibiotic therapy (Justo et al., 2019).

The 2022 Drug Allergy Practice Parameters recommends that for patients with a history of penicillin allergy including anaphylaxis, a structurally dissimilar R1 side chain cephalosporin such as cefazolin can be administered without testing or additional precautions. (Khan et al., 2022). These guidelines are supported by both the American Academy of Allergy, Asthma, and Immunology along with the American College of Allergy, Asthma, and Immunology and the most recent surgical site infection prevention guidelines from the Society of Hospital Epidemiology, Infectious Diseases Society of America and the Association for Professionals in Infection Control and Epidemiology (Calderwood et al., 2023). To further evaluate the use of cefazolin in surgical patients with a history of a penicillin allergy, a study examined over 100,000 surgical encounters across several surgical fields and demonstrated a cefazolin-related reaction of <0.1 % in patients with a reported penicillin allergy (Murphy et al., 2024). Overall, they concluded that there was not a significant difference in cefazolin-related reactions between patients who received cefazolin with or without a reported penicillin allergy. Cefazolin should only be avoided when there is a history of penicillin or cephalosporin induced Severe Cutaneous Adverse Reactions (SCARs) (Kuruvilla et al., 2020), verified cefazolin allergy or anaphylaxis to cephalosporins. SCARs include acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens Johnson Syndrome (SJS), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), or toxic epidermal necrolysis (TEN).

Cefazolin is the gold-standard antibiotic in patients undergoing gynecologic procedures, and therefore, healthcare teams should consider the implementation of a protocol for using cefazolin in most patients with penicillin allergies including anaphylaxis (Fig. 1). It is still imperative to perform penicillin skin testing when possible so that the penicillin allergy label can be removed or penicillins are not incorrectly excluded in the event of infection. While preoperative skin testing is not required, and the use of cefazolin should be encouraged even in the setting of a penicillin allergy. Multiple studies have demonstrated that cefazolin can be safely used in patients despite their penicillin allergy and is supported by the 2022 Drug Allergy Practice Parameters. The goal of enhancing the efficacy and safety of proper surgical prophylaxis with cefazolin is to improve antimicrobial stewardship, decrease SSI rates, avoid acute kidney injury, and increase cost savings.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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