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Evaluation of Antibiotic Allergies in Surgical Patients

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Antibiotic administration in the perioperative period is the foundation of preventing surgical site infections. β-Lactam antibiotics, notably the first-generation cephalosporin cefazolin, are the drugs of choice for this indication. However, reported antibiotic allergies often result in the use of suboptimal alternative agents that can lead to an increased risk of infection and adverse effects. A comprehensive allergy history and risk stratification should be completed preoperatively to determine whether or not a patient can be rechallenged with a β-lactam antibiotic and what testing may be necessary prior to administration. Nursing staff can play a critical role in understanding the implications and management of reported antibiotic allergies in surgical patients in order to optimize patient care.

Introduction

Perioperative antibiotic administration to prevent surgical site infection (SSI) is key to improving patient outcomes in the postoperative period and preventing the morbidity, mortality, and costs associated with SSIs. β-Lactam antibiotics, most commonly the first-generation cephalosporin cefazolin, are the guideline-recommended first-line agents for SSI prophylaxis. This is because they provide adequate coverage for typical SSI pathogens including *Staphylococcus aureus*, coagulase-negative staphylococci, streptococci, and some gram-negative bacilli while also maintaining favorable side effect profiles (Bratzler et al., 2013).

However, patients with reported allergies to β-lactam antibiotics consequently receive alternative and less effective prophylactic agents with more toxicities, including nephrotoxicity and *Clostridioides difficile* infection (CDI). Use of recommended second-line agents such as vancomycin, clindamycin, and aminoglycosides in the perioperative period has consistently been associated with an increased risk of SSIs and adverse effects (Macy & Contreras, 2013; Shenoy et al., 2019). In a retrospective cohort study of 8,285 surgical patients with and without a reported penicillin allergy, the allergy label resulted in a 50% increased risk of SSI and a higher likelihood of receiving clindamycin, vancomycin, or gentamicin than first-line cefazolin (Blumenthal et al., 2018). In addition, postoperative SSIs are one of the most costly complications due to increased length of hospital stays, readmission rates, need for additional procedures, nursing care, and direct hospital costs. Studies have estimated that SSIs following hip and knee arthroplasty result in excess hospital costs of $100,000 and $60,000, respectively (Bratzler et al., 2013).

Antibiotic allergies are reported in approximately 10% of the U.S. population, with penicillin being the most frequently documented and the leading cause of drug-induced hypersensitivity and anaphylaxis (Savic et al., 2019; Shenoy et al., 2019). However, more than 90% of those with reported allergies are not truly allergic when evaluated with either skin testing or direct oral challenges. Furthermore, true Type I or IgE-mediated allergies to penicillin actually wane over time, with about 80% of patients becoming tolerant after 10 years (Shenoy et al., 2019). Therefore, it is important to distinguish which small subsets of patients with a documented β-lactam allergy are truly allergic from those who are not.

Perioperative allergy histories and testing, including skin testing and/or direct graded challenges, are crucial in determining the validity of the allergy label and are now recommended routinely for all patients (Savic et al., 2019). Because of the significant impact a documented β-lactam allergy has in determining antibiotic selection and SSI outcomes in the perioperative period, it is important for nurses to understand the different types of allergic reactions, commonly implicated and alternative antibiotics, as well as appropriate strategies to thoroughly assess allergies to ensure optimal care for surgical patients.

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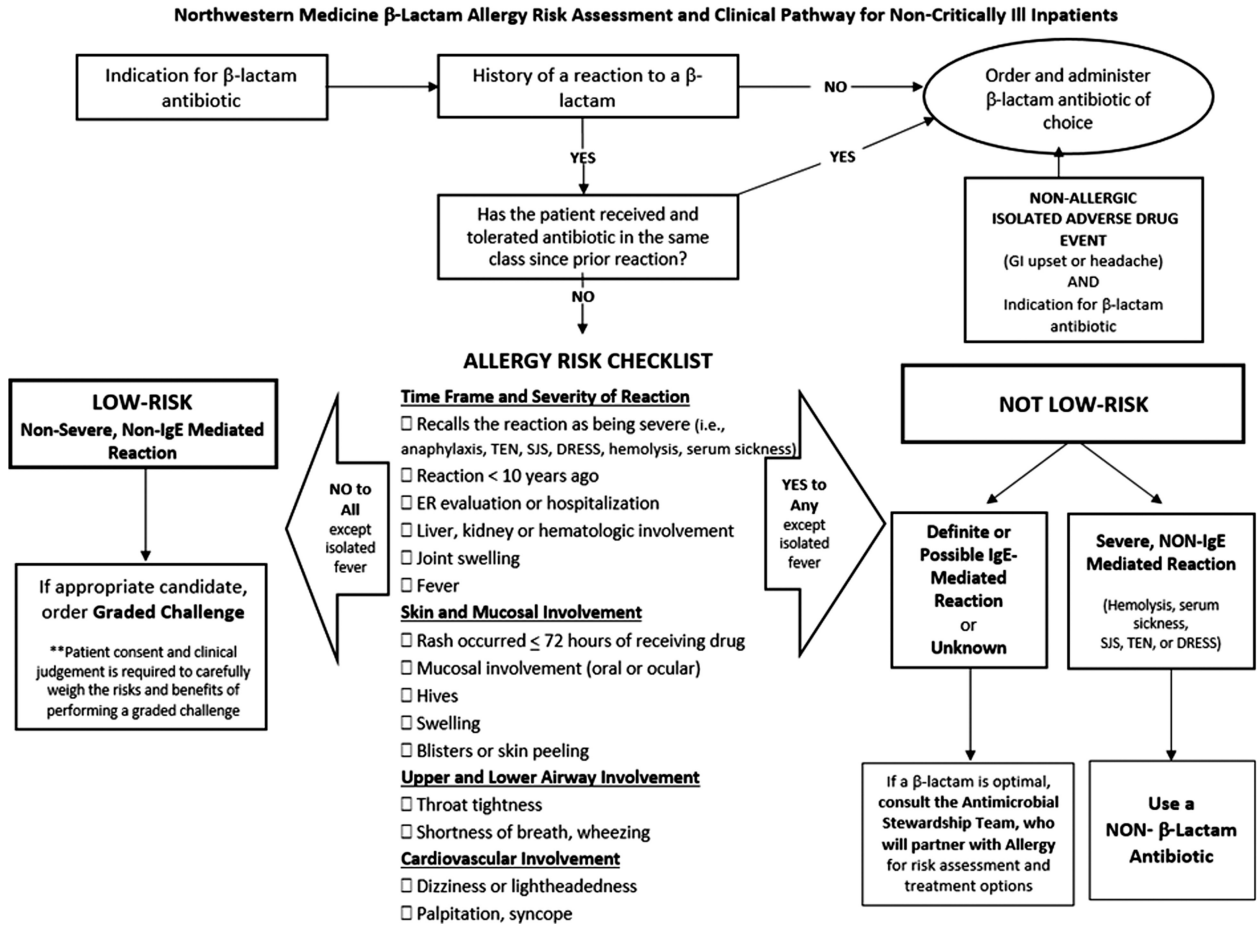

FIGURE 1. Example of an allergy risk stratification algorithm. DRESS = drug reaction with eosinophilia and systemic symptoms; ER = emergency room; GI = gastrointestinal; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis. Adapted with permission from the Northwestern Memorial Hospital Antimicrobial Stewardship Team.

Types of Allergies

Drug hypersensitivity reactions are classified into four types based on the Gell and Coombs classification. Although it was developed in the 1960s, this classification system is still widely used today. The four categories of hypersensitivities are associated with distinct mechanisms and reactions (see Figure 1).

Type I

Type I hypersensitivity reactions are also known as immediate or IgE-mediated reactions. They occur within minutes to hours after repeat exposure to the inciting drug. Upon first exposure to the drug, a process called sensitization occurs in which IgE antibodies bind to the surface of mast cells. With subsequent exposure to that drug, the drug antigen binds to and cross-links the IgE on mast cells, triggering the degranulation and release of histamine and other inflammatory mediators. These mediators are responsible for causing the clinical symptoms of Type I reactions, which include anaphylaxis, angioedema, urticaria or hives, and bronchospasm (Descotes & Choquet-Kastylevsky, 2001). Anaphylactic reactions can manifest on the skin, in the respiratory tract, in the gastrointestinal tract, and in the circulatory system. They are severe, potentially life-threatening, and require immediate medical attention and the administration of epinephrine (Kemp & Lockey, 2002).

Type II

Unlike Type I reactions, Type II hypersensitivity reactions typically occur within days to weeks after the drug exposure. They are mediated by antibodies, primarily IgM or IgG, that are specific to the drug antigen and are cytotoxic. Agranulocytosis, thrombocytopenia, and hemolytic anemia are the most common clinical manifestations of Type II reactions (Descotes & Choquet-Kastylevsky, 2001). Treatment involves discontinuation of the inciting drug and commonly the administration of steroids.

Type III

The mechanism behind Type III hypersensitivity reactions is an immune complex-mediated pathway. The drug antigen reacts with IgM and IgG antibodies in the tissue and forms soluble immune complexes, which are deposited into blood vessel walls, causing local inflammation and injury. This occurs within days to weeks after exposure to the drug. Serum sickness and drug fever are the two most common presentations (Descotes & Choquet-Kastylevsky, 2001). Symptoms of serum sickness can include fever, itching, rash, joint pain, and

generally feeling unwell. In addition to discontinuation of the offending drug, treatment is targeted at symptom relief and may include the administration of antihistamines and steroids.

Type IV

Type IV hypersensitivity reactions are also known as delayed reactions because the onset is usually days to weeks after drug exposure. Unlike the other three types, there are no antibodies involved in Type IV reactions. The drug antigen is presented to and activates T lymphocytes, which results in a cascade of inflammatory mediators. Maculopapular rashes and severe cutaneous presentations such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are examples of Type IV reactions (Descotes & Choquet-Kastylevsky, 2001). A diffuse erythematous and blistering rash that evolves into sloughing of the skin and mucosa is characteristic of SJS and TEN. Besides discontinuation of the offending drug, treatment oftentimes involves admission to an inpatient burn unit and supportive care (Schneider & Cohen, 2017).

Evaluation of Specific Antibiotics and Antibiotic Classes

β-Lactam Antibiotics

In patients with true Type I IgE-mediated penicillin allergies, other β-lactam antibiotics such as cephalosporins, carbapenems, and the monobactam antibiotic aztreonam can often be utilized instead (see Table 1). Allergic cross-reactivity between penicillins and cephalosporins was originally thought to be approximately 10% of cases; however, more recent evidence supports the incidence to be closer to 2% (Shenoy et al., 2019). All β-lactam antibiotics share the same core β-lactam ring structure but have varying side chains attached. The similarity or dissimilarity of the side chains is believed to be the determinant for cross-reactivity between antibiotics within the β-lactam class (Haslam et al., 2012). Because there is no cross-reactivity between penicillins and aztreonam, and carbapenem cross-reactivity with penicillins appears to be very low, it is standard clinical practice to consider these agents as safe alternatives in patients with a penicillin allergy.

Cefazolin

Cefazolin is a first-generation cephalosporin that shares the same mechanism of bactericidal activity as other β-lactams by inhibiting bacterial cell wall synthesis. It is considered the antibiotic of choice for the prevention of SSIs in many surgical procedures due to its spectrum of coverage with reliable activity against common SSI pathogens, adequate penetration into tissues, and mild side effect profile. Overall, the reported incidence of allergies to first-generation cephalosporins is rare and ranges from 0.0001% to 0.1%. In addition, most reactions to cephalosporins are limited to benign rashes (Haslam et al., 2012; Macy & Blumenthal, 2018). Cefazolin is unique in that it has a distinct side chain compared with penicillins and other cephalosporins, resulting in a lower cross-reactivity risk of less than 3% in penicillin allergic patients. Thus, prescribers are becoming increasingly comfortable with its use in patients with labeled penicillin allergies (Blumenthal et al, 2018; Shenoy et al., 2019). In one retrospective study of 278 cases of total hip and knee arthroplasty and revision, 27% of patients reporting a penicillin allergy were given cefazolin, and of these, there were no adverse reactions in patients with a history of reported non-IgE-mediated penicillin allergies (Haslam et al., 2012). Therefore, cefazolin should still be considered for SSI prophylaxis in patients with reported non-life-threatening penicillin and/or cephalosporin allergies.

Vancomycin

Vancomycin is a glycopeptide antibiotic that has reliable coverage against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). Because of the difference in its structure, it can safely be used in patients with β-lactam allergies. For this reason,

Table 1. Commonly Used Antibiotics in the Perioperative Setting

Agent	Usual Dosing	Possible Side Effects	Clinical Pearls
Cefazolin	1–2 g every 8 hours[a]	Localized phlebitis, abdominal discomfort, diarrhea, nausea	• Drug of choice for SSI prophylaxis in most surgical procedures
Vancomycin	15 mg/kg every 12 hours[a]	Localized phlebitis, nephrotoxicity	• Red man syndrome not true allergic reaction • Therapeutic monitoring required for extended courses
Clindamycin	300–600 mg every 6–8 hours Preoperative doses up to 900 mg may be used[a]	Abdominal pain, diarrhea, *C. difficile*-associated diarrhea	• Not preferred because of strongest association with *C. difficile* diarrhea
Aztreonam	2 g every 6–8 hours[a]	Abdominal cramping, diarrhea, rash	• Alternative agent for patients with true Type I IgE-mediated β-lactam allergy
Aminoglycosides (gentamicin, amikacin, tobramycin)	5–20 mg/kg but varies widely depending on use	Nephrotoxicity, ototoxicity	• Therapeutic monitoring required for extended courses

Note. SSI = surgical site infection.
[a]Doses administered intraoperatively may have varying redosing intervals.

vancomycin is recommended as a second-line alternative agent for SSI prophylaxis in patients with reported β-lactam allergies. It may also be used adjunctively with cefazolin in centers with high rates of MRSA or in patients with known MRSA colonization (Bratzler et al., 2013). However, one study of 18,830 patients undergoing arthroplasty found that patients receiving vancomycin monotherapy were more likely to develop SSI than those receiving cefazolin or clindamycin (Ponce et al., 2014). Vancomycin has also consistently proven inferior to β-lactam agents such as cefazolin, nafcillin, and oxacillin for treating infections caused by methicillin-susceptible *Staphylococcus aureus* (MSSA), which is more frequently isolated than MRSA, especially in patients at low risk for harboring drug-resistant bacteria (Shenoy et al., 2019).

Hypersensitivity to vancomycin is possible and can range from mild reactions with primarily skin manifestations to severe reactions leading to hemodynamic compromise. Healthcare providers overseeing patients receiving vancomycin should be aware of the infusion-related reaction called Red man syndrome (RMS) because its presentation mimics that of an allergic reaction. Red man syndrome reportedly occurs in less than 5% of patients receiving vancomycin and is characterized by flushing, erythema, pruritus, and less commonly hypotension. Also referred to as "red neck syndrome," it most commonly presents as a rash on the upper half of the body. The exact mechanism of reaction is unknown, but it is thought to be caused by mast cell activation resulting in histamine release. Those providing care can advise patients to report any redness that occurs during or after the first or subsequent vancomycin infusions and provide education that this is not an allergic reaction. Red man syndrome is usually related to the infusion rate; therefore, vancomycin should not be infused faster than 1,000 mg per hour. Management of acute RMS typically consists of slowing the infusion rate and administering antihistamines such as diphenhydramine. If RMS occurs, vancomycin can still be safely administered in the future by preemptively slowing the rate of infusion and pretreating with antihistamines (Wallace et al., 1991).

Ultimately, vancomycin does provide effective gram-positive bacterial coverage but comes with the risk of increased adverse effects, including nephrotoxicity, and decreased efficacy compared with β-lactam antibiotics. Its use should therefore be reserved for patients with true Type I IgE-mediated penicillin allergies or when MRSA coverage is warranted.

Clindamycin

Clindamycin is another antibiotic commonly used as an alternative in patients with reported β-lactam allergies to prevent SSIs. It is a lincosamide antibiotic that works by binding bacterial ribosomes to inhibit protein synthesis. Clindamycin provides coverage of common gram-positive SSI pathogens including MRSA. The major disadvantage of clindamycin is the FDA Black Box Warning for *C. difficile*-associated diarrhea with severe and potentially fatal colitis. In addition, clindamycin has been associated with an increased risk of SSIs. In a series of 266 patients undergoing free tissue transfer involving the oral cavity and pharynx, clindamycin was associated with an approximately fourfold increased risk for SSI after controlling for potential confounders (Pool et al., 2016). Similarly, in a group of 152 patients undergoing head and neck osteomyocutaneous free flap, 50% of patients receiving clindamycin developed an SSI compared with 25% of patients receiving cefazolin (Murphy et al., 2017). This may be explained, in part, due to increasing clindamycin resistance among *S. aureus* bacteria (Prabhu et al., 2011).

Aztreonam

Aztreonam is a monobactam antibiotic that is typically reserved for gram-negative coverage in patients with true β-lactam allergies. Although similar to the implicated β-lactams, it can safely be used due to the difference in its structure. The only exception to this is in the case of ceftazidime hypersensitivity in which aztreonam should be avoided since it shares an identical side chain. Because it does not offer antibacterial coverage against normal skin flora, aztreonam is typically not used alone for SSI prevention. Instead, it may be administered in combination with a gram-positive active agent such as vancomycin in patients with β-lactam allergies in whom surveillance data show gram-negative bacteria to be a common cause of SSI (Bratzler et al., 2013). Although rare, hypersensitivities to aztreonam are possible, so nursing staff should be aware of this and monitor patients while on therapy, providing supportive care when needed.

Aminoglycosides

Aminoglycoside antibiotics, including amikacin, gentamicin, and tobramycin, kill bacteria through protein synthesis inhibition and are used primarily for gram-negative infections. These agents have generally fallen out of favor as the first-line treatment of most infections as they are associated with two main toxicities, nephrotoxicity and ototoxicity. However, aminoglycoside antibiotics may be a preoperative choice for SSI prevention based on institution-specific guidelines or in patients with labeled β-lactam allergies (Bratzler et al., 2013; Dubrovskaya et al., 2015). They may also be used topically for irrigation during the surgical procedure. Although the risk of nephrotoxicity exists with intravenous administration, it is typically associated with prolonged courses of therapy. In one study including patients who received a single 4.5 mg/kg preoperative dose of gentamicin for spine, knee, or hip surgeries, the nephrotoxicity rate was not statistically different between the control group and the gentamicin group, and gentamicin was determined not to be an independent predictor of nephrotoxicity (Dubrovskaya et al., 2015). However, another study found that a single 4 mg/kg dose of gentamicin was associated with a 94% increased risk of acute kidney injury as compared with cephalosporin prophylaxis (Bell et al., 2014). Therefore, nursing staff should be aware of this risk, particularly if aminoglycoside therapy is extended.

Strategies for Allergy Assessment

Allergy History

A comprehensive and thorough allergy history is imperative when documenting and evaluating antibiotic

allergies in order to determine the severity and whether or not it is even a true allergy. Symptoms such as gastrointestinal upset, nausea, vomiting, diarrhea, headache, and fatigue are frequently documented in the allergy section of patient medical records, even though they represent drug side effects or intolerance rather than true allergies. It is important for clinicians to distinguish between the two because side effects can typically be managed and should not preclude patients from using those antibiotics when needed as first-line agents to treat or prevent an infection. When collecting an allergy history, the following are key questions to ask and document (see Table 2): What symptoms did the patient have? Did they require medical treatment or hospitalization? What was the timing or onset of the reaction in relation to drug exposure? How long ago did the reaction occur? and Has the patient received and/or tolerated any other antibiotics since then? Although there are no validated allergy history questionnaires, a standardized list of questions can ensure that all key points are addressed (Shenoy et al., 2019).

Once an accurate allergy history is obtained, patients can then be risk stratified. This will assist in determining whether or not they can be rechallenged with the antibiotic and what testing may be necessary prior to administration. If a patient has tolerated the antibiotic since the initial documentation and did not experience a reaction, the patient is not allergic and can safely receive that antibiotic in the future. In addition, the allergy should be removed from the patient's medical record. Low-risk patients are those who have nonallergic symptoms (antibiotic side effects) or those with only a family history of antibiotic allergies, unknown reactions occurring more than 10 years ago not suggestive of Type I IgE-mediated reactions, and itching without a rash. Patients with moderate-risk histories include those who experienced a rash or a reaction consistent with a Type I IgE-mediated reaction (i.e., hives or swelling) with the exception of anaphylaxis. High-risk patients include those who experienced anaphylaxis, those who have had a positive penicillin skin test, hypersensitivities to multiple antibiotics, unstable patients, pregnant patients, and those on supplemental oxygen or with compromised cardiac function. Consultation with an allergy specialist is recommended for all high-risk patients. Any patient who experienced a Type II or III hypersensitivity reaction or SJS or TEN should never be rechallenged with the offending antibiotic (Shenoy et al., 2019).

Table 2. Key Questions to Ask During an Allergy History

Do you have a history of an allergy or reaction to a penicillin antibiotic?
Do you have a history of an allergy or reaction to a cephalosporin antibiotic?
What is the name of the antibiotic that caused the reaction?
What happened when you took the antibiotic?
If you experienced a rash, what did it look like? Was it itchy? Was it raised on the skin?
How long ago did you experience the reaction?
How soon did the reaction occur after starting the antibiotic?
Did you have to go to the emergency department for treatment of the reaction?
Were you hospitalized because of the reaction?
Did your symptoms resolve after stopping the antibiotic?
Have you taken any antibiotics since the reaction occurred? If so, which ones?
Have you ever seen an allergy specialist?
Have you ever had a penicillin skin test or oral antibiotic challenge? If so, what were the results?

Note. Questions adapted from Northwestern Medicine Pre-Operative Clinic Penicillin Allergy Questionnaire; Covington et al. (2019); and Shenoy et al. (2019). Used with permission from the Northwestern Memorial Hospital Antimicrobial Stewardship Team.

Direct Oral Drug Challenge

In patients who fall into the low-risk category, a direct oral challenge can be considered under medical observation. This involves administering a single dose of the antibiotic in question and observing the patient for any signs of a reaction for at least 1 hour afterwards. When performing a direct oral challenge, it is always important to obtain informed consent from the patient, ensure that the patient is properly monitored, and medications such as intramuscular epinephrine, antihistamines, and bronchodilators such as albuterol are readily available (Shenoy et al., 2019).

Graded Challenge

A graded two- or three-step drug challenge is recommended for low- or moderate-risk patients if skin testing is unavailable for the antibiotic in question (Tucker et al., 2017). In a graded challenge, a full antibiotic dose is divided into two or three separate administrations, with increasing doses and medical observation for any signs of a reaction in between each administration. This can be performed using oral or intravenous antibiotics. Graded challenges have been shown to be safe and effective for patients with a non-life-threatening history for a Type I IgE-mediated reaction. Tolerance after a graded challenge confirms that the patient will not experience an immediate adverse reaction from the challenged agent (Shenoy et al., 2019). However, patients will still need to be monitored for the development of a delayed hypersensitivity reaction.

Penicillin Skin Test

Penicillin skin testing (PST) is recommended for moderate-risk patients with a documented allergy to a penicillin antibiotic (i.e., penicillin, amoxicillin ± clavulanate, ampicillin ± sulbactam, nafcillin, oxacillin, dicloxacillin, piperacillin/tazobactam). It is performed with percutaneous or intradermal injection of the major antigenic determinant, benzylpenicilloyl polylysine (PPL), and a positive (histamine) control and a negative (saline) control. Development of a wheal of at least 5 mm within 15 minutes is indicative of a positive skin test. The test can be performed by registered nurses, advanced practice providers, and physicians from any discipline who have been adequately trained, and it takes

less than 45 minutes in total. Penicillin skin testing has a very high negative predictive value of 95% on its own and approaches 100% when followed by an oral amoxicillin challenge (Shenoy et al., 2019).

Preoperative Assessment

An ideal time to perform comprehensive allergy histories and allergy testing for surgical patients is during preoperative visits. This is especially important if the patient has a documented β-lactam allergy because cefazolin is the recommended first-line antibiotic for the majority of surgical procedures. Successful preoperative antibiotic allergy evaluation has been reported in general, cardiac, and orthopedic surgery patients (Shenoy et al., 2019). One study evaluated the impact of a structured allergy history alone for preoperative patients with a self-reported β-lactam allergy and found that it dramatically increased utilization of cefazolin prophylaxis from 18% to 44% without any serious adverse events (Vaisman et al., 2017). Another study found that patients who underwent preoperative allergy evaluation with PST, followed by amoxicillin challenge, were approximately 27 times more likely to receive first-line cefazolin prophylaxis (Plager et al., 2020). By partnering with antimicrobial stewardship teams and allergy specialists, preoperative clinics can determine a safe and feasible protocol to evaluate and test patients with documented β-lactam allergies prior to their surgical procedure.

Conclusion

Antibiotic selection for surgical prophylaxis in patients with reported β-lactam allergies should be handled collaboratively with treatment teams involved in surgical care, allergy, infectious diseases, and pharmacy. All patients with questionable antibiotic allergies should undergo testing to confirm or deny the validity of the reaction to improve patient safety, infectious outcomes, and antibiotic stewardship in the preoperative period. Ultimately, the antibiotics selected for SSI prophylaxis should be based on all available patient information and a comprehensive allergy history. Registered nurses can play an important role in patient interviewing, preoperative allergy testing, as well as patient education on the ramifications of reported antibiotic allergies and the importance of assessing their significance.

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