Misconceptions Surrounding Penicillin Allergy: Implications for Anesthesiologists

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Administration of preoperative antimicrobial prophylaxis, often with a cephalosporin, is the mainstay of surgical site infection prevention guidelines. Unfortunately, due to prevalent misconceptions, patients labeled as having a penicillin allergy often receive alternate and less-effective antibiotics, placing them at risk of a variety of adverse effects including increased morbidity and higher risk of surgical site infection. The perioperative physician should ascertain the nature of previous reactions to aid in determining the probability of the prevalence of a true allergy. Penicillin allergy testing may be performed but may not be feasible in the perioperative setting. Current evidence on the structural determinants of penicillin and cephalosporin allergies refutes the misconception of cross-reactivity between penicillins and cefazolin, and there is no clear evidence of an increased risk of anaphylaxis in cefazolin-naive, penicillin-allergic patients. A clinical practice algorithm for the perioperative evaluation and management of patients reporting a history of penicillin allergy is presented, concluding that cephalosporins can be safely administered to a majority of such patients. (Anesth Analg 2018;127:642–9)

Postoperative surgical site infection (SSI) is of concern to surgeons and anesthesiologists alike. The development of an SSI increases hospital length of stay by approximately 7–10 days, is associated with long-term disability, has a mortality rate of 3%, and is estimated to cost over $25,000 US dollars per SSI.[1,2] There has been renewed focus on SSI prevention with the release of updated recommendations by a number of organizations, including the Centers for Disease Control and Prevention[3] and World Health Organization.[4] Administration of preoperative antimicrobial prophylaxis (AMP) is the mainstay of SSI prevention guidelines among all surgical specialties.[5–9] The choice of a prophylactic antimicrobial agent is based on the principle of effecting a minimal impact on normal microbial flora while demonstrating potency against the skin organisms of concern, namely aerobic Gram-positive cocci (streptococcal species, *Staphylococcus aureus*, and coagulase-negative staphylococci).[5] Cefazolin, a first-generation cephalosporin, is highly active against these organisms while demonstrating the least activity against Gram-negative species compared to later-generation cephalosporins[10] and is thus typically indicated as the first-line agent, with alternatives, particularly clindamycin and vancomycin, recommended for patients with β-lactam allergies.[5]

The responsibility for the initial administration of preoperative AMP is often delegated to the anesthesiologist,[11–13] as this ensures timely antimicrobial dosing and consequently, lower rates of SSI.[14] Unfortunately, due to inaccurate penicillin allergy reporting and prevalent misconceptions surrounding cephalosporin cross-reactivity, patients reporting a history of penicillin allergy do not receive the indicated antibiotic agent,[15] placing them at risk of a number of adverse effects and increased morbidity. A UK survey of the Sixth National Audit Project revealed that among perioperative antibiotics, penicillins were perceived to be the most likely agents to cause anaphylaxis, and are thus avoided most often.[16] The survey concluded that "anesthetists exhibit avoidance behaviors, and such perceptions may not correlate with actual risk."[16]

Anesthesiologists may be complacent about administering alternative AMP to patients inaccurately reporting a penicillin allergy.[2,15] In part, this is attributable to inadequate training in antibiotic selection among the majority of anesthesiologists, despite holding the belief that such education is required.[13] To bridge this gap in knowledge translation, we seek to highlight the evidence base for cephalosporin administration to patients reporting penicillin allergy to inform daily anesthesia practice.

LITERATURE SEARCH

We performed a literature search of MEDLINE (PubMed) on October 16, 2017, limited to the English language. Publication date was limited to the year 1994 onward to coincide with the publication of the first guideline on AMP in surgical procedures.[17] See Supplemental Digital Content, Appendix 1, http://links.lww.com/AA/C363, for the search strategy relating to evidence on the safety of cephalosporin administration to penicillin-allergic patients. All article types were examined. Abstracts were manually reviewed for relevance, and full-text articles of relevant manuscripts were retrieved. Additional manuscripts were identified by manually reviewing references of relevant articles.

EFFICACY OF ALTERNATIVES TO CEFAZOLIN

In response to the perceived risk of cephalosporin administration in penicillin-allergic patients, alternative antibiotics,

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often clindamycin and/or vancomycin, are used.[2,18–21] Indeed, in a survey of anesthesiologists, all respondents indicated that they would choose an alternative antibiotic when presented with a history of penicillin allergy.[15]

Unverified penicillin allergy is said to be a significant and growing public health burden.[22–24] The labeling of inpatients as penicillin allergic has been associated with longer hospital admissions, higher rates of readmission, treatment failure, and intensive care unit admission, and increased risk of exposure to significantly more antibiotics associated with *Clostridium difficile*, vancomycin-resistant *Enterococcus*, and methicillin-resistant *S aureus* (MRSA).[24–27] Accordingly, inpatient penicillin allergy testing to delabel patients was demonstrated as a successful antimicrobial stewardship measure.[28,29]

In the perioperative setting, a retrospective cohort analysis of 8385 patients found that those reporting a penicillin allergy had 50% increased odds of SSI, attributed directly to the receipt of alternative antibiotics.[2] Higher rates of SSI have been observed with vancomycin[18,30–34] and clindamycin[35–39] in orthopedic, gynecologic, otolaryngological, and neurosurgical procedures. Vancomycin is less effective than cefazolin against methicillin-susceptible *S aureus*.[40,41] Mechanisms for these observations include vancomycin's poor tissue penetration, reduced bactericidal rates, and the gradual reduction in susceptibility of *S aureus* to the drug.[42,43] Vancomycin is thus best reserved either as primary or adjuvant AMP for patients colonized with MRSA or institutions with high prevalence of MRSA, although the evidence in this setting is conflicting.[44] Furthermore, compared to cefazolin, vancomycin has a narrow spectrum of antibacterial coverage that does not include Gram-negative pathogens.[44] Clindamycin similarly has poor coverage of aerobic Gram-negative bacteria.[39,45] Because a variety of surgical procedures are associated with polymicrobial SSI, substitution of cefazolin with vancomycin alone may render the antimicrobial coverage incomplete[5]; familiarity with recommended AMP regimens for specific procedures is encouraged.

In addition, cefazolin has a favorable safety profile, while adverse effects of vancomycin include nephrotoxicity[43,46,47] and of clindamycin are associated with *C difficile* colitis.[24,48] Furthermore, slow infusion of vancomycin, necessary to prevent red man syndrome,[43] may impact timely preoperative administration.[49] Cefazolin is also the most cost-effective drug when compared to either clindamycin or vancomycin on a per-dose basis,[20,50] while continued vancomycin treatment also requires further resources for monitoring drug levels.[47]

PENICILLIN ALLERGY REPORTING AND PREVALENCE

Penicillin allergy is the most commonly reported allergy in medical records, with a prevalence of 8%–12% among the patient population.[51] However, most reported penicillin reactions are not associated with immunoglobulin-E (IgE)-mediated reactions after penicillin testing and rechallenge, with 95% of these patients having a negative penicillin skin test.[28] This discrepancy can be attributed to highly variable and inadequate beta-lactam allergy documentation in the majority of cases,[25,52,53] or due to the decrease of penicillin-specific antibodies over time.[54] Unfortunately, due to various constraints, reported drug allergies are generally not challenged by anesthesiologists.[21] One survey found that 89.5% of anesthesiologists have never referred patients for evaluation of drug allergy, although an equal number felt a referral would be helpful.[15] However, 47.3% said that they have verbally communicated to their patients that they should speak to their family doctor for further evaluation.

It is advised that the perioperative physician ascertain the nature of previous allergic reactions on preoperative assessment to differentiate true IgE-mediated allergies from other hypersensitivity and nonspecific reactions. Clinical history strongly suggestive of a non-IgE–mediated adverse reaction (ie, maculopapular or morbilliform rash, gastrointestinal side effects, isolated pruritis or dizziness, headache)[55–57] can exclude true penicillin allergy and obviate the need for further testing,[55,56] although a vague history has less discriminatory value.[58,59] Immediate hypersensitivities, classified as type I reactions, are IgE mediated, occur within 1 hour of exposure, and are characterized by urticaria, laryngeal edema, bronchospasm, angioedema, and anaphylaxis.[55,60,61] Such reactions can be supported by elevated serum tryptase levels.[61,62] The time elapsed since the penicillin reaction should also be ascertained, as approximately 50% of patients with IgE-mediated penicillin allergy lose their sensitivity after 5 years, further increasing to approximately 80% by 10 years.[61] Subsequently, in patients with a high index of suspicion of true allergy and lacking a formal diagnosis, preoperative allergy testing can be considered. Preoperative allergy consultation and penicillin skin testing have been shown to reduce vancomycin use.[63–66]

Penicillin Allergy Testing

A clinically significant IgE-mediated penicillin allergy can be safely refuted or confirmed using skin testing and, if the skin test is negative, an oral penicillin VK or amoxicillin challenge (drug provocation test [DPT]).[61] Tolerance of an oral penicillin-class antibiotic is the gold standard test for an absence of IgE-mediated penicillin allergy.[61,67,68] However, per the 2010 Joint Task Force (American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology) practice guidelines, a negative skin test is sufficient for cephalosporin administration without further testing if the underlying concern was the presence of a penicillin allergy.[61] There are few contraindications to performing a DPT after a negative skin test, namely history of severe, life-threatening cutaneous non-IgE–mediated type IV hypersensitivity reactions such as erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms syndrome that have been rarely associated with β-lactams.[67,69]

In practice, routine allergy consultation referral by anesthesiologists is fraught with challenges, including time constraints, the feeling that this is the responsibility of another physician, and the availability of alternative antimicrobials.[15] Additionally, operational constraints may hinder preoperative outpatient allergy testing, including cost, estimated to be $220–$540 US dollars per patient[70] (although, with 1 case of SSI prevented for every 112–124 patients who undergo

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testing for reported penicillin allergy,[2] the financial burden of allergy testing can potentially be mitigated by the prevention of costly SSIs). Alternatively, an emerging testing method is point-of-care β-lactam allergy skin testing, which can be conducted with minimal resources in a timely fashion by a pharmacist trained in allergy testing and anaphylaxis treatment.[29,51] A prospective multicenter trial performed skin prick and intradermal testing, which were read at 15 and 30 minutes, respectively.[29] All negative skin tests were followed by an oral challenge followed by a 4-hour observation period by the patient's nurse. The study reported 4.5-fold greater odds of patients receiving preferred β-lactam therapy. However, such trials were conducted in an inpatient setting, and adapting this process on an ambulatory basis would be logistically challenging. The potential for systemic reaction requires supervision for 1 hour after skin testing while DPT requires up to 6 hours,[71] thereby requiring a specialized setting to administer allergy tests.

There are further limitations to performing skin testing. Given the high prevalence of penicillin allergy reporting, it is not feasible to test all patients preoperatively, particularly in a timely manner. Allergy testing may thus be best reserved for patients with vague or strong history suggestive of penicillin allergy undergoing elective surgery and who have risk factors for developing SSI (those at extremes of age and with poor nutritional status, obesity, diabetes mellitus, tobacco use, corticosteroid therapy, and an immunocompromised state), as these patients would benefit most from cephalosporin AMP.[5]

There is also a lack of consensus on how to proceed when patients test positive for a penicillin allergy,[72] as it is unclear as to what information can be gleaned regarding potential cephalosporin allergy. Logically, the next step would involve cephalosporin allergy testing.[54] However, while European allergy guidelines describe skin testing methodology for specific cephalosporin agents, US guidelines recommend against cephalosporin testing due to the unknown negative predictive value of such testing and lack of validation.[71–73] An alternative strategy is a graded cephalosporin challenge. A sample protocol describes the administration of one-tenth of the dose followed by a half-hour observation, then followed by administration of the remainder of the dose with another observation period; this is similarly not strongly evidence based, requires monitoring, and is unlikely to be feasible on the day of surgery.[72]

PENICILLIN AND CEPHALOSPORIN CROSS-REACTIVITY

The often-quoted cross-reactivity between penicillins and cephalosporins of 10%–15% is not supported by current literature. The misunderstanding of such cross-reactivity is primarily historical in nature. Early studies in the 1960s and 1970s reported an 8%–18% cross-reactivity between penicillin and cephalothin, the first marketed cephalosporin,[74] in a small group of patients.[75–77] These findings have since been propagated and have broadly shaped the paradigm of cephalosporin administration in penicillin-allergic patients,[74] despite alternative early evidence of minimal cross-reactivity between penicillin and cefazolin.[78] Older studies may have, in part, overestimated the degree of cross-reactivity between penicillins and cephalosporins because, before the development of purification techniques in the 1980s, early cephalosporin antibiotics were derived from *Acremonium* (formerly *Cephalosporium*) mold and thus contaminated with penicillins.[74,79–81]

Likewise, a review of anaphylaxis during anesthesia concluded that first-generation cephalosporins should be avoided in patients with a history of penicillin allergy.[82] This recommendation was based on a meta-analysis whereby cefazolin was represented by only 1 trial from 1978.[83] This conclusion may be erroneous, in part, because of the manufacturing process during that time. Additionally, there is a common misconception that the classification scheme of cephalosporins by generation is based on structural characteristics of the respective molecules. In fact, cephalosporins are grouped into generations according to the spectrum of activity against Gram-negative bacteria.[10] Cefazolin, while classified as first generation, is structurally different from all other cephalosporins, accounting for its different immunogenicity profile.[81]

Penicillins and cephalosporins both have a backbone structure consisting of a β-lactam ring joined to a second ring structure, a thiazolidine ring for penicillins and a dihydrothiazine ring for cephalosporins.[84] Contrary to popular belief, cephalosporin allergy is not mediated by reaction to the β-lactam ring. Under physiological conditions, the dihydrothiazine and β-lactam rings of cephalosporins undergo rapid degradation into products that do not function as haptens.[54,74] Rather, the potential cross-reactivity of penicillins and cephalosporins is derived from structural similarities of their R1 side chains that are attached to the β-lactam ring at the 7-position on cephalosporins, corresponding to the 6-position on penicillins.[54,60,74,85] Cephalothin shares a similar side chain with penicillin G (along with cefoxitin), thereby accounting for the cross-reactivity seen in the aforementioned early studies, along with modern ones.[86] Likewise, amoxicillin, ampicillin, and cephalexin, to name a few, share similar side chains and thus may cross-react. Cefazolin has a unique R1 side chain (structure similar only to ceftezole,[74] a cephalosporin derivative not currently in clinical use) and does not cross-react with penicillins. An additional source of immunogenicity unique to cephalosporins is the R2 side chain at the 3-position of their dihydrothiazine ring; cefazolin once again has a unique structure. A matrix table of penicillin and cephalosporin drugs is available to physicians looking to assess for allergic cross-reactivity based side chain structures.[87]

Of note, in contrast to IgE-mediated reactions, severe T cell–mediated delayed hypersensitivity reactions such as Stevens–Johnson syndrome, toxic epidermal necrolysis, and drug-induced vasculitis are excluded from this discussion. In these exceedingly rare[88] reactions, T cells can recognize the whole β-lactam molecule or the core structure and possibly part of the side chain, and thus, cross-reactivity between penicillins and cephalosporins is hard to predict.[69] Expert consultation is advised regarding appropriate antibiotics in patients with a history of such reactions.

Safety of Cefazolin Administration

There is no contemporary evidence of an increased risk of anaphylaxis to cefazolin in penicillin-allergic patients.[87] Specific to the perioperative setting, 5 studies examining the

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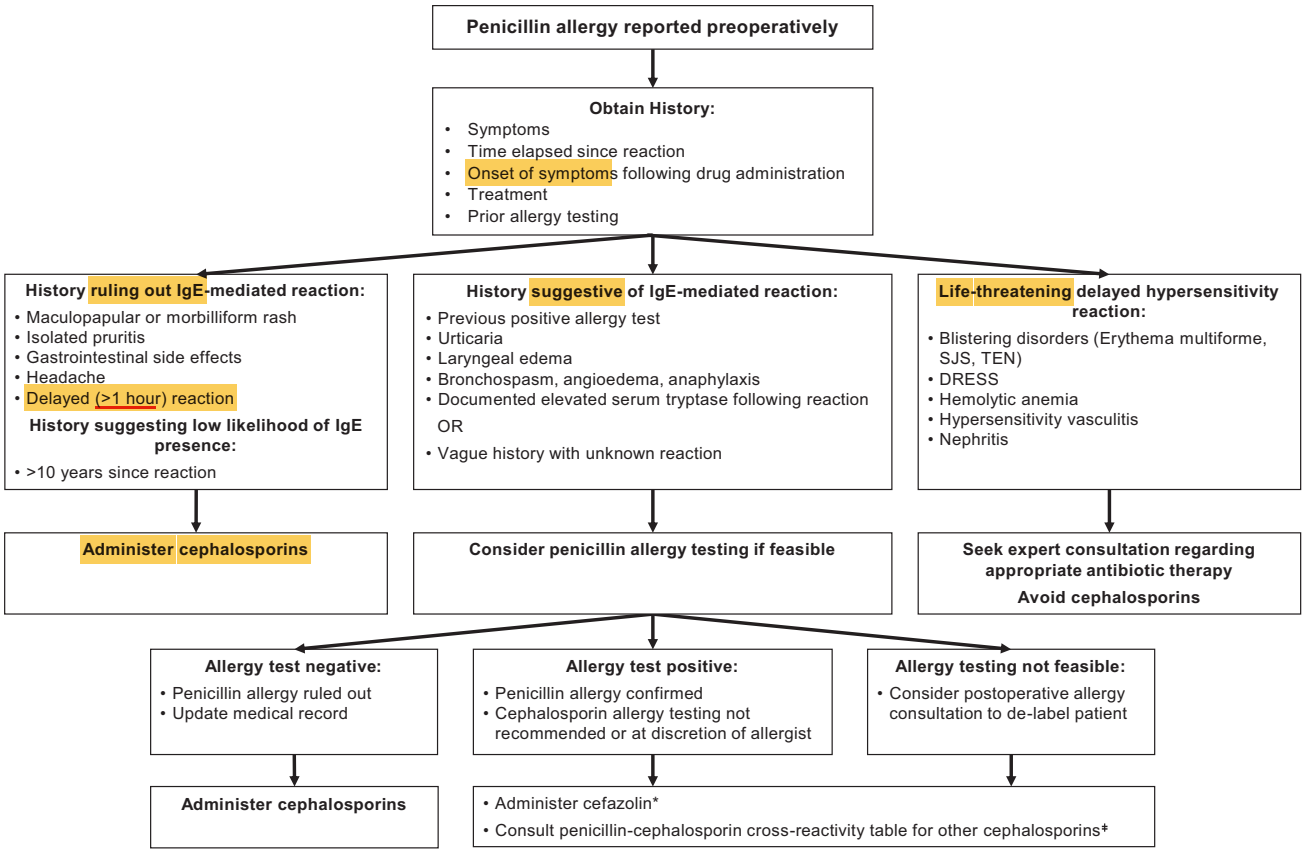

Figure. A decision algorithm for the preoperative assessment and perioperative management of the cephalosporin-naive patient reporting a penicillin allergy and requiring cephalosporin antimicrobial prophylaxis. While these recommendations are evidence based, they cannot guarantee avoidance of an allergic reaction to cephalosporins or other drugs administered during an anesthetic. *It is noted that cefazolin in particular demonstrates a lack of cross-reactivity with penicillins and other cephalosporins. ‡See the Table and Ref. 87. DRESS indicates drug reaction with eosinophilia and systemic symptoms; IgE, immunoglobulin E; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

administration of cephalosporin AMP to penicillin-allergic patients were identified;[19,20,89–91] one of these studies was limited to patients with non-IgE–mediated reactions.[20] Four of the studies reported no adverse events.[19,20,89,90] One study[91] evaluated 6 AMP strategies in patients reporting penicillin allergy, ranging from either direct cefazolin or vancomycin administration, obtaining an allergy history and administering vancomycin if suggestive of an IgE-mediated reaction, performing allergy skin testing, or combining the allergy history with testing to guide decision making. While this study reported anaphylaxis rates ranging from 0.0004% in the cefazolin-only group to 0.000134% in the most comprehensive allergy assessment group (vancomycin to patients with either positive skin tests or suggestive histories), the authors did not report sample sizes or statistical analyses on these incidence rates. Nonetheless, it is reassuring that the rates of anaphylaxis in this study were very low in patients directly receiving cefazolin.

Outside of the perioperative setting, a retrospective study of over 900,000 patients exposed to over 1.2 million courses of cephalosporins identified only 3 cephalosporin-associated cases of anaphylaxis in >65,000 patients with a history of penicillin allergy who received >127,000 courses of cephalosporin therapy.[88] While the specific cephalosporin agents implicated in those cases of anaphylaxis were not described, thereby limiting the ability to examine side chain cross-reactivity, there was no statistical difference in anaphylaxis rates when compared to cephalosporin administration to nonpenicillin-allergic patients.

It is important to note that independent cephalosporin allergies, distinct from penicillin allergies, do exist.[74,85,86,92] In fact, IgE antibodies against cephalosporins may be more common than those against penicillin due the widespread use of cephalosporins.[93] Cefazolin has been implicated as a causative agent in postoperative allergy testing after intraoperative allergic reactions.[94–96] Of note, studies examining patients with proven IgE-mediated reactions to cefazolin demonstrated a lack of cross-reactivity with penicillins and other cephalosporins, further supporting the notion that cefazolin hypersensitivity is selective.[96,97] It is reassuring that anaphylaxis from cephalosporins is rare overall, with a prevalence of 0.1%–0.0001%.[74,88] Anaphylactic reactions are inherent to the practice of anesthesia, and familiarity with anaphylaxis management guidelines is recommended.[98,99]

ROLE OF THE PERIOPERATIVE PHYSICIAN

Physicians as a whole have knowledge deficits regarding the management of patients with a history of penicillin allergy.[100–103] However, antimicrobial stewardship, education programs, and concerted efforts to delabel patients have been successfully implemented in various medical disciplines to address inappropriate antibiotic therapy.[100,104–106]

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Table. Common Penicillin and Cephalosporin Drugs Grouped by Side Chain Structure

Similar R1 Side Chains: Cross-Reactions Between Drugs Within 1 Group Is Possible			Unrelated R1	Similar R2 Side Chains: Cross-Reactions Between Drugs Within 1 Group Is Possible								Unrelated R2
Group 1	Group 2	Group 3	Side Chains[a]	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Side Chains[b]
Penicillin G	Amoxicillin	Cefdinir	Cefazolin	Cefadroxil	Cefmetazole	Cefotaxime	Ceftibuten	Cefoxitin	Cefdinir	Cefsulodin	Cefamandole	Cefaclor
Cefoxitin	Ampicillin	Cefepime	Cefixime	Cephalexin	Cefoperazone	Cephalothin	Ceftizoxime	Cefuroxime	Cefixime	Ceftazidime	Cefoperazone	Cefazolin
Cephalothin	Piperacillin	Cefotaxime	Cefmetazole		Cefotetan	Cephapirin					Cefotetan	Cefepime
Cephaloridine	Cefaclor	Cefpirome	Cefotetan									Cefpodoxime
	Cefadroxil	Cefpodoxime	Cefuroxime									Ceftriaxone
	Cefamandole	Ceftazidime	Cephapirin									Cefuroxime
	Cefatrizine	Ceftriaxone										
	Cefoperazone											
	Cephalexin											

Adapted from Lagacé-Wiens and Rubinstein,[60] Pichichero and Zagursky,[74] and Pichichero.[81]

[a]No cross-reaction with any other penicillin or cephalosporin R1 side chain.

[b]No cross-reaction with any other cephalosporin R2 side chain.

AMP guidelines recommend alternative antimicrobial therapy in the presence of type I hypersensitivity to β-lactams.[5] However, a limitation of such guidelines is that recommendations are applied to cephalosporins as a whole or to specific cephalosporin generations without an examination of individual cephalosporin agents. Emerging understanding of immunogenic mechanisms underlying antimicrobial allergies enables wider administration of certain cephalosporins and facilitates the administration of first-line AMP for the prevention of SSI while avoiding the morbidity associated with second-line antimicrobials. This evidence base should be reflected in future iterations of SSI guidelines.

The perioperative setting presents a unique opportunity for anesthesiologists to play a role in improving the accuracy of allergy reporting by performing an allergy history assessment[55] and, where necessary, considering allergy consultation and penicillin testing during the preoperative period, whether for the purpose of AMP administration or for the broader public health benefit. A proposed algorithm for the preoperative assessment of the penicillin-allergic patient and intraoperative decision making is presented in the Figure. In summary, cephalosporin cross-reactivity in penicillin-allergic patients is not necessarily a class effect, provided that cephalosporins with a side chain different from the penicillin responsible for the allergic reaction are used (Table).[87] Anesthesiologists may be hesitant to administer cephalosporins to penicillin-allergic patients due to medicolegal concerns.[107] While clinical judgment should be exercised and can be guided by a documented preoperative discussion with the patient regarding the rationale for cephalosporin administration,[108] a review of legal outcomes in such cases found limited professional liability and identified precedence for clinicians prescribing cephalosporins to patients with a known penicillin allergy, with judges citing a lack of scientific evidence demonstrating that cephalosporins were contraindicated in patients with a penicillin allergy.[107]

DISCLOSURES

Name: Leon Vorobeichik, MD.
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