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Presumed β-Lactam Allergy and Cross-reactivity in the Operating Theater

A Practical Approach

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A β-LACTAM allergy is the most common suspected in-hospital drug allergy, with an incidence of 5 to 17% in hospitalized patients and up to 35% in the surgical population at the preoperative assessment clinic.[1–5] Thus, the team in the operating theater will be confronted with these patients when perioperative antibiotic prophylaxis is needed. Frequently, the consequence of a presumed β-lactam allergy is that all β-lactam antibiotics are avoided, because of the possibility of cross-reactivity, and an alternative antibiotic, *e.g.*, clindamycin, vancomycin, or ciprofloxacin, is prescribed.[1] This may be a short-term risk-avoiding strategy during surgery, but the long-term consequences are overuse of these agents and an increase in serious hospital infections by pathogens such as *Clostridium difficile* and vancomycin-resistant *Enterococcus*, with an accompanied rise in healthcare use and costs.[4] In fact, the overuse of non–β-lactam antibiotics because of reported penicillin allergy has been labeled a public health problem.[6–8] In this review, we provide an evidence-based and practical approach to patients with presumed β-lactam allergy admitted to the operating theater and give guidance on the selection of alternative antibiotics based on cross-reactivity patterns.

Literature

We performed a literature search using PubMed.gov using the initial search term ("beta-Lactams"[Mesh]) AND "Cross Reactions"[Mesh] and snowballing for relevant articles based on the relevant selected articles. First search was performed in May 2015, and the search was repeated in October 2017.

Perioperative Antibiotic Prophylaxis

Assuming that there is a solid indication for antibiotic prophylaxis, the choice for a certain antibiotic is usually based on international guidelines for perioperative antibiotic prophylaxis and the pathogens that need to be considered when choosing the antibiotic.[9–13] Furthermore, local resistance patterns need be taken into account, as well as bioavailability, including the timing of the dose(s), local costs, availability of the drug, and type of surgery.[9] Last but not least, host factors need to be considered. These include physical characteristics such as age, body mass index, colonization with multiresistant pathogens, immune status, and a reported drug allergy.

The Value of a History of β-Lactam Allergy

The main β-lactam groups are the penicillins, cephalosporins, carbapenems, and monobactams. The most frequently reported β-lactam allergy is penicillin allergy, which comprises more than 50% of all antibiotic allergies reported before surgery.[3] The reported β-lactam allergy by the patient is often not clarified in medical documentation, and taking a history can prove to be difficult. Borch *et al.*[14] illustrated in 96 patients with a history of penicillin allergy that 82% did not remember which kind of penicillin they were allergic to and the mean time between the allergic reaction and

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the study interview was 20 yr. Only 43% remembered why they were treated with penicillin at that time. However, most patients did remember the type of reaction, which was cutaneous rash in the vast majority. Patient records often also lack information on allergy, as Salden *et al.*[15] reported in a recent study. Less than 50% of patients with a documented warning against β-lactams had a description of the symptoms included in their general practitioner file. In addition, after evaluation of the symptoms alone, in 11.7% allergy to lactams could be ruled out. In a recent Dutch study in a university hospital, the prevalence of penicillin allergy was 5.6%. Histories were taken by a trained nurse or pharmacy assistant for all included patients. Surprisingly, 66 (14.5%) of these allergic patients received β-lactams, apparently without adverse effects.[8]

This is in line with other studies where 34 to 50% of patients with suspected penicillin allergy had received penicillin again, with only 2% actually experiencing an adverse reaction.[14,16] Macy[17] and Macy and Ngor[18] tested 799 patients with suspected penicillin allergy, and only 4.2% had a positive skin test or reacted on oral challenge. Of note, patients with suspected immediate type I reactions (*e.g.*, anaphylaxis), Stevens–Johnson syndrome, or toxic epidermal necrolysis were not subjected to testing.

In short, we may conclude that both the information provided by the patients as well as documented history in the patient file may lack reliability and may partly explain why patients with a reported suspected but unconfirmed β-lactam allergy may be able to take β-lactams again without problems. Additionally, it has been suggested that patients with a previously proven sensitization to penicillin can lose their reactivity over the years and may also be able to take the drug again.[19]

How to Differentiate between Side Effects, Benign Rashes, and Life-threatening Allergies

The first step would be to clarify whether the patient experienced an actual unexpected drug-related reaction (type B) rather than the more prevalent and predictable side effects (type A reaction).[20,21] Many patients confuse dose-related side effects, such as isolated vomiting, diarrhea, or nausea, with allergy. A thorough clinical history is therefore warranted but often not feasible in the preoperative setting.

Table 1. Drug Reactions Classification and Symptoms

Type of Reaction	Pathophysiology	Examples of Clinical Manifestations	Time of Onset	Reexposure Possible?
Type A	Side effect, predictable based on properties of the drug	Vomiting, diarrhea (antibiotics), gastric bleeding/ulcer (NSAID), nausea (morphine)	Varies	Depends on severity of reaction
Type B				
Type I allergic reaction	IgE-mediated activation of mast cells and basophils	Mild: rash, maculopapular exanthema urticaria < 10% of the body surface Moderate/severe: generalized urticarial, angioedema, severe vomiting and/or diarrhea (in combination with skin, pulmonary, or cardiovascular symptoms), cardiovascular or pulmonary involvement	Minutes to 2 h after exposure	Mild: preferably with a different β-lactam based on the side chain structure. Moderate/severe: Temporary reexposure possible after desensitization (the state of tolerance will disappear within a few days after desensitization)
Type II allergic reaction	Antibody-dependent cytotoxicity	Hemolytic anemia, trombocytopenia, neutropenia	Days (5–8) to weeks after exposure	No
Type III allergic reaction	Immune complex disease	Serum sickness (fever, joint pain, lymphadenopathy), vasculitis	> 1 week after exposure	No
Type IV allergic reaction	T-cell–mediated	Mild: rash, maculopapular exanthema Moderate/severe: - Stevens–Johnson syndrome or toxic epidermal necrolysis: blistering of skin and mucosa - Acute, generalized erythematous pustulosis - Fixed drug eruption: well defined red round or oval patch with possible blistering - Drug reaction with eosinophilia and systemic symptoms (*e.g.*, hepatitis, nefritis) - Drug fever	48 h to weeks after exposure < 24 h after re-exposure	Mild: preferably with a different β-lactam based on the side chain structure. Moderate/severe: no, desensitization is not possible.

IgE = immunoglobulin E; NSAID = nonsteroidal antiinflammatory drug.

Follow up by an allergy specialist after the event is then recommended to ensure a safe choice in the future.

In general, drug hypersensitivity reactions are divided in four main groups (table 1), the acute type I reactions where immunoglobulin E is involved, type II cytotoxic reactions, type III complex mediated reactions, and type IV reactions, which are T-cell–mediated. Type II and III reactions are very rare and will not be discussed here.

Symptoms of type I or immunoglobulin E-mediated reactions can range from simple urticaria and angioedema to full-blown anaphylaxis with circulatory shock requiring resuscitation.[20,21] In addition, the airway can be involved with asthmatic symptoms, as well as the gastrointestinal tract.[22] Although much feared, this type reaction does offer, in case of serious need of the drug, the option of desensitization or inducing a temporary state of tolerance. This option can be useful when there is a less-urgent need for surgery in a stable patient. The most common reaction to medication is the type IV or delayed reaction, which occurs from 2 h to several days after intake. Mostly these reactions are benign rashes such as maculopapular exanthema or skin rash, which pose no risk for the development of anaphylaxis.[23] In these cases, one can give the drug without risks, other than reappearance of the rash. Very infrequent, but potentially life threatening, are toxic epidermal necrolysis or Stevens–Johnson syndrome, as well as drug reaction with eosinophilia and systemic symptoms, acute, generalized erythemateous pustulosis, and fixed drug reaction. These are T-cell–mediated reactions in which the drug is absolutely contraindicated, and desensitization is not an option (table 1).

Table 1 lists the differences in clinical symptoms, time of onset, and clinical course. An important difference is the time of onset: type I reactions occur within minutes up to 2 h, whereas type IV reactions can start several days up to weeks after initiation start of the medication. To make a definite diagnosis, skin tests and provocation tests are necessary. However, in a perioperative setting, the clinical situation of the patient and the urgency of the surgery will often prohibit this, and the anesthesiologist will have to make his decision based on the clinical history provided by the patient. We suggest differentiating between mild symptoms and moderate to severe symptoms when making this choice (table 1 and fig. 1). Mild symptoms could be defined as delayed (more than 2 h after allergen) skin rash. When in doubt, consult an allergy expert or, in case of time issues, avoid the culprit medication

Cross-reactivity and the Choice for an Alternative in the Acute Situation

As stated before, the β-lactam antibiotics consist of penicillins, cephalosporins, carbapenems (meropenem, imipenem, and ertapenem), and monobactams (aztreonam). Their common feature is the central β-lactam ring, which suggests the possibility of cross-reactive hypersensitivity reactions. However, they differ with regard to side chain, thiazolidine ring, and pharmacodynamics. These differences and similarities in their structure and pharmacodynamics seem to determine the degree of cross-reactivity. We will discuss the importance of cross-reactivity between the different β-lactam groups with regard to the surgical environment.

Penicillins

Penicillin G or benzylpenicillin and penicillin V or phenoxymethylpenicillin are produced by *Penicillum chrysogenum* and are the only two naturally occurring penicillins. All

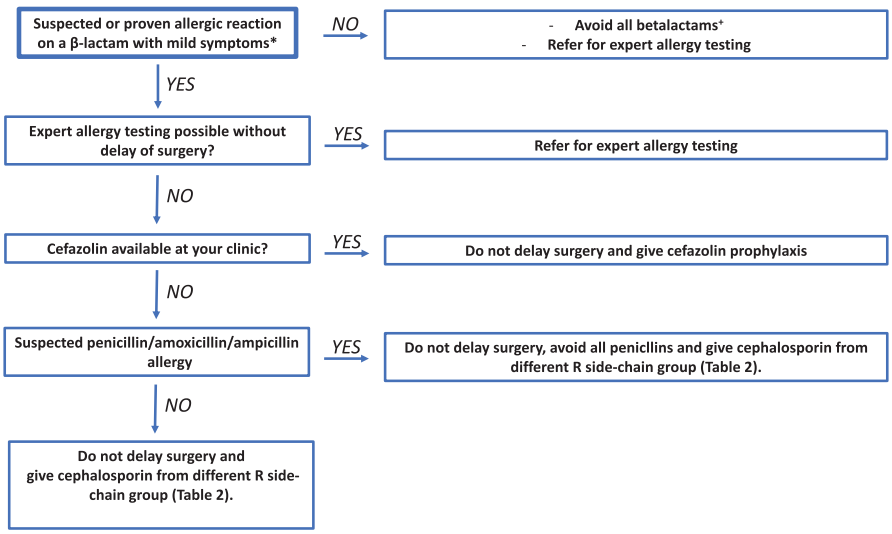

Fig. 1. Suggested management approach for patient with suspected β-lactam allergy to guide selection of appropriate antibiotic. *Mild symptoms: skin rash > 2 h after exposure to suspected allergen. +Alternative antibiotics depend on local guidelines, but include vancomycin and clindamycin for Gram-positive cover, an aminoglycoside or fluoroquinolone for Gram-negative cover, and metronidazole for anaerobic cover.

other penicillins are semisynthetic derivates of these two penicillins. Most of these semisynthetics can be grouped into certain subgroups such as aminopenicillins (*e.g.*, amoxicillin, ampicillin, and bacampicillin), carboxypenicillins (*e.g.*, carbenicillin and ticarcillin), ureidopenicillins (*e.g.*, azlocillin, piperacillin, and mezlocillin), and isoxazolylpenicillins (*e.g.*, cloxacillin, dicloxacillin, flucloxacillin, and oxacillin). Between the various penicillins there is cross-reactivity, so it was always common practice to avoid all penicillins after a penicillin allergy was established. However, recently it was shown that there are so-called selective responders, with immediate hypersensitivity reactions to amoxicillin or clavulanic acid that could tolerate penicillins. In a recent study by Blanca-Lopez *et al.*,[24] 40 patients with proven immediate reactions to amoxicillin and 11 with proven allergy to clavulanic acid tolerated penicillin G and V. Only 7 were also sensitized to benzylpenicilloyl poly-L-lisine and/or minor determinant mix (penicillin determinants). Because usually in the perioperative setting it is unknown which penicillin the patient is allergic to, we recommend choosing a cephalosporin such as cefazolin in case of a previous reaction with mild symptoms (table 2) and avoid all β-lactams in case of a history of a reaction with moderate or severe symptoms. Patients should be referred for expert allergy testing for the definite diagnosis.

Cephalosporins

The incidence of cross-reactivity with penicillins was reported to be as high as 10% in early studies,[25,26] a much quoted figure in the literature. However, these studies were performed with first-generation cephalosporins, probably containing trace amounts of penicillin.[25,26] Nowadays, the prevalence of cephalosporin allergy in the general population is estimated around 1%[17] but reported to be up to 5.5% in the surgical population.[3] Although cephalosporins share the β-lactam ring with penicillins, they have a dihydrothiazine ring attached instead of the thiazolidine ring in penicillin[25] (fig. 2). In addition, the degradation of the β-lactam ring results in unstable products, with different pharmacokinetics as compared to penicillins.[27] The cross-reactivity with penicillins may be primarily determined by the R1 side chain attached to the β-lactam ring (fig. 2). These studies were performed with first-generation cephalosporins, probably containing trace amounts of penicillin.[25,26] Classification of cephalosporins (first through fourth generation) is according to their antimicrobial action and resistance pattern and not according to the side-chain structure.[27] Most first-generation cephalosporins do share the R1 side chain with penicillin, whereas this is far less common in second-generation cephalosporins and absent in third-generation. In 2007, Pichichero *et al.*[28] performed a meta-analysis, showing possible cross-reactivity between penicillin and first-generation cephalosporins, but this risk was not increased for second- and third-generation cephalosporins. Recently, Macy and Contreras[31] demonstrated in a large database study including more than 1.5 million patients that when cephalosporins were administered to patients with reported penicillin allergies, the incidence of new allergic reactions was only 1%, and the incidence of anaphylaxis was 0% per cephalosporin course. Although the retrospective nature of this study, relying on healthcare providers documentation, may suffer from underreporting of adverse reactions, it is unlikely that severe reactions would not have been registered. Studies looking at specific side-chain structures are few but suggest that R1 side-chain similarity is associated with most but not all clinical cross-reactivity between penicillins and cephalosporins.[29,30] Cephalosporins having side-chain similarity with penicillins and thus possible cross-reactivity are cephalotin, cephalodrine, cefadroxil, cefatrizine, cephalexin, cephradine, and cephaloglycine (first generation) and cefaclor, cefprozil, cefoxitin, and loracarbef (second generation).[25,30] Certain first-generation cephalosporins, such as cefazolin, have not been reported to cross-react with penicillin, putatively due to a different R1 side chain. For *surgical* prophylaxis, however, first-generation cephalosporins are preferred, because of their Gram-positive action and less Gram-negative cover, depending on the type of surgery. The second and third generation are best avoided if possible, because of an increased risk for *Clostridium difficile* infections due to their increasing Gram-negative cover.[31] Cefazolin could therefore be an alternative in case of suspected penicillin allergy.

Naturally, when side chains are important for cross-reactivity between cephalosporins and penicillin, they might also be expected to show cross-reactivity between the different cephalosporins. When a patient is allergic to a specific cephalosporin, a trial with a different cephalosporin can be considered, depending on the severity of the reaction. Pathophysiologically, this choice should be based on side-chain structure rather than on a classification by generation. In case of reactions with moderate or severe symptoms (table 1), assessing the safe alternative by means of skin tests and provocation tests may be warranted, because not every single hypersensitivity reaction can be explained by R1 and R2 side-chain cross-reactivity only.[29]

In summary, cross-reactivity between penicillin and cephalosporins can depend on the side-chain structure rather than the common β-lactam ring. When anaphylaxis or severe reactions are not reported as adverse reactions, we suggest avoiding only the cephalosporins with similar side chains (table 2). For preoperative prophylaxis, cefazolin could therefore be an alternative in case of suspected penicillin allergy with mild symptoms such as a delayed skin rash. Details on the symptoms that accompany the allergic reactions are listed in table 1.

Carbapenems

There is a structural similarity between carbapenems and penicillins regarding their bicyclic core, composed of a five-membered ring attached to the β-lactam ring.[32] Estimates for carbapenem allergy in the general population range from 0.3 to 2.3%.[33] In a study performed by Saxon *et al.*,[34]

Table 2. Similarities in R1 or R2 Side-chain Structures Attached to the β-Lactam Ring

		Penicillins			First-generation Cephalosporins (Mostly Gram-positive)								Second-generation Cephalosporins (Gram-positive and -negative)								Third-generation Cephalosporins (Mostly Gram-negative)				
		Penicillin	Amoxicillin	Ampicillin	Cefalotin	Cefazolin	Cefadroxil	Cefaloridine	Cephalexin	Cefradrine	Cefaloglycine	Cefprozil	Cefatrizine	Cefoxitin	Cefaclor	Loracarbef	Cefamandole	Cefmetazole	Cefotetan	Cefuroxime	Ceftizoxime	Cefotaxime	Cefpodoxime	Ceftriaxone	Ceftazidime
Penicillins	Penicillin				R1s			R1s																	
	Amoxicillin						R1					R1	R1												
	Ampicillin								R1	R1	R1				R1	R1									
First-generation cephalosporin	Cefalotin	R1s									R2			R1						R2					
	Cefazolin																								
	Cefadroxil		R1						R2						R1s										
	Cefalodrine	R1s												R1											
	Cephalexin			R1			R2			R2															
	Cefradrine			R1					R2																
	Cefaloglycin			R1	R2																				
Second-generation cephalosporin	Cefprozil		R1													R2									
	Cefatrizine		R1																						
	Cefoxitin	R1s			R1			R1																	
	Cefaclor			R1			R1s									R2									
	Loracarbef			R1																					
	Cefamandole																		R2						
	Cefmetazole																		R2						
	Cefotetan																R2	R2							
	Cefuroxime													R2							R1s				
Third-generation cephalosporin	Ceftizoxime																								
	Cefotaxime				R2															R1s					
	Cefpodoxime																								
	Ceftriaxone																								
	Ceftazidime																								

Antibiotics with similar side chains as an antibiotic with suspected allergy (indicated by R1[s], R2) are advised to be avoided. When an allergy to a penicillin is suspected, we advise to avoid all penicillins, indicated by a cross. Not included in this table are: cefmenoxime, cefditoren, cefonicid, aztreonam, cefepime, cephapirin, cefpiramide, ceftibuten, cefdinir, cefixime, and cefsulodin. This table is based on the results of Kim *et al.*[25]

R1 = identical R1 side chain; R1s = similar R1 side chain; R2 = identical R2 side chain; R2s = similar R2 side chain; R = main penicillin side chain.

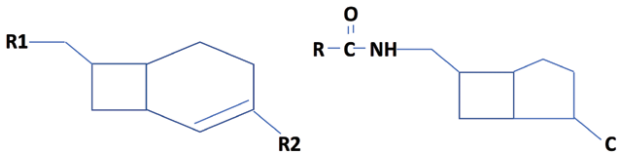

Fig. 2. Simplified structure of cephalosporin (*left*) with R1 and R2 side-chain location and penicillin (*right*). The *square* represents the β-lactam ring, and on the *right* the dihydrothiazine ring for cephalosporins and the thiazolidine ring for penicillin.

the cross-reactivity in patients with positive penicillin skin testing with positive imipenem skin testing was as high as 47.4%. However, in a recent prospective trial,[35] only 0.9% of patients with a positive skin test for penicillin responded to an oral challenge of meropenem after negative meropenem skin testing. In a meta-analysis performed by Kula *et al.*,[36] 4.7% of patients with a proven, suspected, or possible immunoglobulin E-mediated penicillin allergy had any type of reaction to a carbapenem. Interestingly, for patients with a proven immunoglobulin E-mediated penicillin allergy, the incidence of a proven immunoglobulin E-mediated carbapenem reaction was only 0.5%. A recent overview by Romano *et al.*[37] found that cross-reactivity between penicillins and carbapenems was about 1%. With regard to cephalosporins and carbapenems, data are scarce. One study by Romano *et al.*[38] among 98 patients with a demonstrated immunoglobulin E-mediated hypersensitivity to cephalosporins found a 1% (95% CI, 0.2 to 5.5%) cross-reactivity based on skin testing. Thus, overall, the incidence of cross-reactivity between carbapenems and other classes of β-lactams seems low. The low percentage of cross-reactivity in the literature suggest that in case of a suspected mild reaction to a carbapenem, an alternative β-lactam for surgical prophylaxis can be considered. This is in line with the practice of Blumenthal *et al.*,[39] who use carbapenem in case of a mild reaction on a cephalosporin or penicillin. Given the very broad treatment spectrum of carbapenems, we would not recommend using carbapenems for *surgical* prophylaxis as an alternative to penicillins or cephalosporins.

Monobactams

The relevance of possible monobactam cross-reactivity with other β-lactams is limited for several reasons. First, it has no role in current surgical prophylaxis. Second, it lacks an adjoining ring, which reduces immunogenicity and cross-reactivity.[33] It has only been implicated in cross-reacting with ceftazidime, because of their common side chain, but clinical relevance of this phenomenon is unclear. Because of the limited practical clinical relevance, we have not included monobactams in our perioperative advice.

Referral and Testing

Adequate evaluation of suspected type I and mild type IV reactions including skin testing and provocation tests could prevent any further confusion and unjustified alternative antibiotic prescriptions. Patients with a negative skin test can be subsequently exposed to an oral or intravenous challenge as the gold standard for tolerability.[40] For performing both skin tests and provocation tests, a referral to an allergy specialist is warranted. If time and the nature of the planned procedure allow, this is preferably done before surgery. However, if this is not feasible, we advocate a practical approach based on the abovementioned patterns of cross-reactivity between different β-lactam antibiotics.

Practical Approach

Guided by the fear of causing anaphylaxis, one tends to have a low threshold for avoiding β-lactam antibiotics in case of suspected allergy. By doing so, we do cause antibiotic-related morbidity and mortality by increasing the rate of hospital infections with *C. difficile* and multiresistant organisms. The actual risk of causing an anaphylaxis-related death is, however, as low as 0 to 7.3/100,000,[31] as shown in the study performed by Macy and Contreras[31] among almost 4 million patients receiving care (both out- and inpatient) in Kaiser Permanente hospitals (USA). Based on this risk–benefit ratio, we propose that in case of a possible, mild reaction to either a penicillin or cephalosporin, when allergy testing is not available in a timely manner, perioperative prophylaxis can be chosen based on R1 cross-reactivity in case of penicillin allergy and R1 and R2 cross-reactivity in case of cephalosporin allergy. A mild reaction is characterized by skin rash or exanthema more than 2 h after the event. Table 2 provides an overview of penicillins and cephalosporins with similar side-chain structures. Of note, using β-lactams with different side-chain structures does not completely exclude a possible allergic reaction but may reduce the chance. For instance, in case of a reported penicillin allergy with only skin symptoms, *e.g.*, rash, cefazolin can be administered for perioperative prophylaxis with low risk.

Finally, we do not recommend a so-called "test-dose" (*e.g.*, administering 1/10 of the dose as a test dose before giving the full dose), because for patients with a true anaphylaxis, even a small amount can provoke a reaction. In addition, after administering a test dose without symptoms, one can still develop symptoms when the full dose is administered. Thus, the added value of this test dose is nihil and may provide false reassurance. In case of doubt, one could administer the antibiotic more diluted and slowly, for example over the course of 20 to 30 min, and closely monitor the patient. The administration can be ceased immediately when symptoms develop.

Figure 1 displays an algorithm how to approach the patient with a suspected β-lactam reaction in the acute situation. In case of a reaction with moderate or severe symptoms, we advise avoiding all β-lactam antibiotics, including cephalosporins, penicillins, carbapenems, and monobactams. However, when the reaction was only a mild skin rash more than 2 h after the exposure, we advise either giving cefazolin or choosing a different cephalosporin based on the side chain, avoiding similar R1 or R2 side-chain structures. For example,

amoxicillin has R1 side-chain similarities with cefadroxil, cefprozil, and cefatrizine (table 2). These should thus be avoided after a suspected amoxicillin reaction. An overview of known similarities in side chains are displayed in table 2. If possible, expert allergy testing is advised; however, we appreciate that this is not always feasible in daily clinical practice.

We realize that the ultimate responsibility of selecting the appropriate antibiotic lies with both the anesthesiologist and the surgeon, in cooperation with infectious disease specialists and microbiologists, depending on country, local guidelines, and customs. This algorithm is intended to reinforce the anesthesiologist in this process. Both the algorithm and table 2 can be adapted according to local guidelines and downloaded in the Supplemental Digital Content (http://links.lww.com/ALN/B731) for modification.

Alternative Antibiotics

In the very few cases where all β-lactams should be avoided, such as proven β-lactam reactions with cardiologic or pulmonal involvement or patients with type IV reactions with severe symptoms, local and international consensus guidelines should guide the choice for an alternative prophylactic antibiotic. In case of avoiding all β-lactam antibiotics, most guidelines recommend clindamycine or vancomycine for Gram-positive cover, an aminoglycoside or fluoroquinolone when Gram-negative cover is needed, and metronidazole in case surgery is performed in an area with anaerobic flora.[9]

Conclusions

Although expert allergy testing would be the preferred action in case of a suspected β-lactam allergy, knowledge of one of the possible mechanisms behind cross-reactivity between the different β-lactams may guide antibiotic choices, always taking into account the antimicrobial spectrum of the antibiotic, type of surgery, and local resistance patterns. After reviewing the literature, we suggest that when urgent surgery is needed and there is a history of a previous mild skin reaction on a β-lactam suggestive for allergy, an alternative β-lactam antibiotic can be selected based on cross-reactivity patterns. We recommend avoiding all β-lactams in case of a suspected previous allergic reaction exceeding mild symptoms and opt for an alternative, as well as referring the patient to an allergy specialist after the patient is dismissed from the hospital. This approach may reduce the likelihood of a perioperative anaphylaxis without fully excluding it. Considering the incidence of reported β-lactam allergies and the frequency of perioperative antibiotic use, careful selection of perioperative antibiotics plays a major role in adequate antibiotic stewardship.

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Competing Interests

The authors declare no competing interests.

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