MANAGEMENT OF THE PATIENT REPORTING AN ALLERGY TO PENICILLIN

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Abstract

Recent emphasis on the prevention of surgical wound infection has highlighted the role of the anesthesiologist as the physician responsible for administering appropriate antibiotic prophylaxis. Patients often report a distant or unclear history of penicillin allergy. Administering an antibiotic to which the patient has a true allergy can provoke a life threatening reaction. The anesthesiologist should be aware of the prevalence, severity, and manifestations of allergies to antibiotics, as well as the available alternatives. Unnecessary administration of more powerful broad-spectrum antibiotics leads to the development of antimicrobial resistance and should be avoided. It is the anesthesiologists' duty to balance these issues when selecting appropriate antibiosis.

Introduction

Penicillin and other related antibiotics are often withheld or more potent agents given, when patients report an allergy or past adverse reaction. In a recent study, 12.7% of patients admitted to the hospital reported an allergy to penicillin[1]. Antibiotic prophylaxis has been recommended to reduce surgery related infections. Most commonly, an

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agent related to penicillin is used. Many hospitals have developed protocols but which agent to use when it is unclear as to the nature or indeed existence of a true allergy remains controversial. Usually the department of anesthesiology is held responsible for implementation of antibiosis prior to surgical intervention. The department may also be required to draft the protocol for administration of appropriate drugs.

Penicillin Allergy

From 0.7% to 10% of the population suffers some kind of adverse reaction to penicillin, most commonly a minor rash or itching, though the severity depends on exposure history, route of administration, duration of treatment, time elapsed from reaction to repeat exposure, and type of initial reaction[2].

Types of Reactions

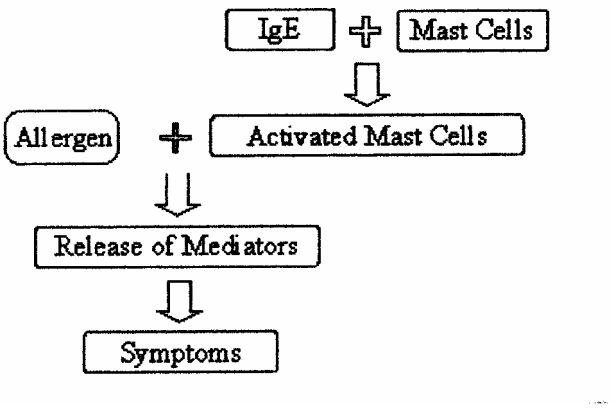
There are four types of hypersensitivity reactions involving the immune system and a foreign antigen:

1. Type I (immediate hypersensitivity): the immune system responds by immediately releasing vasoactive mediators that act on vessels and smooth muscle and pro-inflammatory cytokines, recruiting inflammatory cells, and resulting in the clinical appearance of anaphylaxis.
2. Type II (antibody-mediated disorders): secreted antibodies directly injure cells by promoting phagocytosis by macrophages or lysis by inflammatory mediators.
3. Type III (immune complex-mediated disorders): antibodies bind to antigens, inducing inflammation directly or through the activation of complement. Neutrophils and monocytes are attracted by the activation of damage tissue through the release of lysosomal enzymes and the generation of toxic free radicals.
4. Type IV (cell-mediated immune disorders): T lymphocytes are

sensitized to cause cellular and tissue injury.

A type I reaction occurs when penicillin or its reactive metabolite binds to serum proteins and cross-links mast cells or basophils expressing preformed penicillin-specific immunoglobulin E antibodies, as shown in Fig. 1. This cross-linking results in the release of mast cell mediators responsible for the clinical manifestations of anaphylaxis.

Fig. 1
Type I hypersensitivity reaction, mechanism of action



Reaction occurring after 72 hours of drug administration are considered late reactions and are either of the type II, III, or IV variety. These reactions are less severe and not life threatening, and a history positive for a non-type I reaction is unlikely to result in cross-reactivity with related drugs.

Immediate reactions showing systemic manifestations of anaphylaxis occur in only 0.004% to 0.15% of penicillin courses administered, but fear of these type I hypersensitivity reactions often results in the administration of an alternate, broad spectrum antibiotic such as vancomycin. This fear appears to be justified as two studies found that fully one-quarter to one-third of patients who died secondary to the administration of penicillin gave a history of penicillin allergy prior to the administration of the antibiotic[3,4].

So the question, then, is how does the anesthesiologist determine when it is safe to administer a drug that has the potential to result in death in susceptible individuals?

Most individuals presenting for surgery who report an allergy to penicillin do so based on a previous reaction, although some report that they were told of an allergy but do not remember what happened or of taking the antibiotic. The patient may say only that he/she received the antibiotic as a child, had a "bad reaction" and was warned never to take the antibiotic again. Occasionally specifics of a rash, swelling, itchiness, or respiratory difficulty are recalled. Studies involving the use of skin testing to assess individuals reportedly allergic to penicillin have shown that slightly less than 10% of persons with a history of penicillin allergy are at risk for developing a type I reaction[5], and suggest that individuals who have both a history of penicillin allergy and positive skin tests could safely be given penicillin[6].

Salkind et al believe that history alone is an adequate method of determining penicillin allergy[2], concluding that, "taking a detailed history of a patient's reaction to penicillin may allow clinicians to exclude true penicillin allergy, allowing these patients to receive penicillin without testing". This recommendation is based on data suggesting that only 10% to 20% of patients who report a history of penicillin allergy are truly allergic when assessed by skin testing. While supported by data, the conclusion that a history of type 1 reaction is the only compelling need to avoid related antibiotics has not been validated in any prospective, random, double-blinded studies[7]. That cephalosporins and other related antibiotics may safely be administered to such patients is likely true but unproven.

Cross-reactivity between antibiotics

Whether or not it is safe to administer a cephalosporin to a patient who reports a penicillin allergy remains controversial. Two studies performed in 1973 and 1978 suggest the cross-reactivity rate between

cephalosporins and penicillins is as high as 50%[8,9] but subsequent studies involving the second, third and fourth generation cephalosporins report a much lower cross-reactivity rate of 8% to 12%[7]. More recently, in 2004, Daulat et al reported a cross-reactivity rate in patients with a reported penicillin allergy who were given a cephalosporin of 0.17%[10]. In this retrospective investigation, 606 patients with a reported penicillin allergy who had received at least one course of treatment with a cephalosporin were identified. There was 1 adverse reaction, reported as a mild worsening of an underlying eczema several days after cephazolin was commenced. In a letter to the editor replying to this study, Fine reported a series of 400 patients with a history of penicillin allergy that required penicillin administration[11]. Each patient underwent skin testing with a positive result in only 2% of cases. All patients with a negative skin test received penicillin without incident. Fine suggested the possibility that patients who reported a previous allergy to penicillin were simply no longer allergic to the antibiotic.

White it is not known if the allergic reactions observed in penicillin allergic patients who receive a cephalosporin are true cross reactions or merely independent reactions in susceptible individuals, it is clear that the patient with a penicillin allergy will experience more cephalosporin-induced allergic reactions than the patient who is not penicillin allergic[12]. Cephalosporins are quite similar to penicillins immunochemically. Though individual immune responses do vary widely, with third-generation cephalosporins less likely to result in cross-allergic responses than first-generation cephalosporins, the potential for cross-reactivity still exists. The penicillins and cephalosporins both share a bicyclic nucleus which is likely responsible for the appreciable but variable immunologic cross-reactivity in immune responses to these drugs[13].

The practice of administering a cephalosporin antibiotic to a patient with a known penicillin allergy is common. Solensky et al, in a survey of 600 physicians, found that antibiotic choice is influenced by the type of penicillin allergic history and suggest that skin testing should be used to identify those patients not at risk for type I hypersensitivity reactions so as to decrease the use of broad-spectrum antibiotics in patients labeled

"penicillin-allergic"[14]. While there exists some risk for cross-reactivity in patients with a history of penicillin allergy, the type of allergic reaction is not life threatening in those not at risk for a type I hypersensitivity reaction.

Assessment of Risk

Like penicillins, cephalosporins have a β-lactam ring, a six-membered dihydrothiazine ring similar enough to the five-membered thiazolidine ring found in penicillin to result in cross reactivity (Fig. 2, 3).

Fig. 2
Penicillin β-lactam ring structure

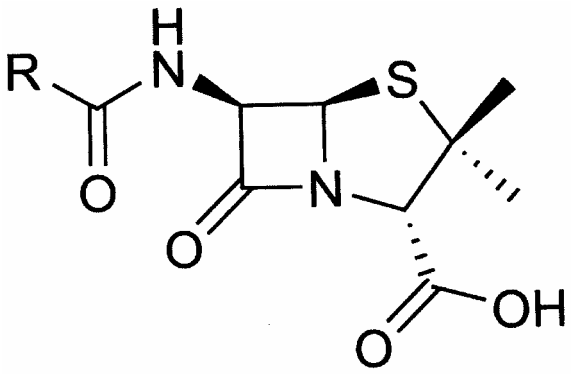
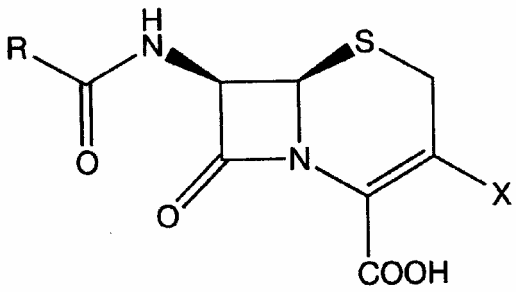


Fig. 3
Cephalosporin nucleus structure, note the β-lactam ring



The risk of a cephalosporin reaction should be taken into consideration when considering substituting this agent in a patient with reported penicillin allergy. That risk is higher with the first generation (5% to 16.5%) cephalosporins, and considerably lower with the second

generation (cefazolin 4%) and the third or fourth generation agents (cefotaxime, cefepime 1% to 3%)[15].

Situations can be stratified into high, moderate or low risk classification based on the history of the clinical presentation of the drug allergy as indicated by the patient. High risk situations, with the risk for a severe reaction estimated to be from 50% to 95%, include the following:

- The administration of a cephalosporin to a patient within 1 year of a known or suspected allergic reaction to penicillin[16].
- The administration of a bolus infusion of a cephalosporin to a patient with positive penicillin skin test reactions[9].
- The administration of imipenem (also a β-lactam antibiotic) to a patient with a known cross-reactivity between penicillin and imipenem[17].

Moderate risk situations, where the risk for a severe reaction is estimated to be from 30% to 50% include:

- The administration of a cephalosporin to a patient within 5 years of a known or suspected allergic reaction to penicillin[18].

Low risk situations, where the risk for a severe reaction is estimated to be from 0% to 5% include:

- The administration of a cephalosporin to a patient with a reported penicillin allergy but negative skin test reactions to major and minor penicillin determinants[14].
- The administration of a cephalosporin to a patient with a known or suspected history of a penicillin allergy 25 years previously (though skin testing and test dosing may still be indicated)[13].

The Test Dose

Since the cascade of mast cell activation which results in the symptoms of anaphylaxis can be triggered by a small amount of the antibiotic introduced into the patient, it is unlikely that the practice of administering a small amount of the antibiotic, commonly referred to as a

"test dose", prior to beginning an infusion, will do anything but trigger an anaphylactic reaction in truly sensitive individuals. In cases where a specific antibiotic is indicated and there is no acceptable alternative, rapid intravenous desensitization may be performed over a number of hours[19]. The process involves administering the antibiotic in small bolus doses over an extended period of time, usually between 2.5 to 8 hours depending on the agent and the protocol. The initial bolus doses are equivalent to the dose adsorbed during a skin test and doubled every 30 minutes. Once larger doses are reached, the time between doses is adjusted according to the tolerance of the patient.

Current Recommendations for Antibiotic Prophylaxis

Preoperative antibiotic prophylaxis attempts to reduce the quantity of bacterial contamination that inevitably occurs during surgery. It has been shown that the most effective prophylactic measure involves administration of systemic antibiotics immediately before surgery[20]. Ideally prophylaxis is administered such that maximum antibiotic concentrations are achieved just prior to skin incision, and maintained throughout the procedure[21]. Current guidelines for antimicrobial prophylaxis depend on the type of surgery. When cefazolin or cefuroxime are recommended for patients who have a true type I β-lactam allergy (immediate urticaria, laryngeal edema, or bronchospasm), vancomycin and clindamycin are accepted alternatives, as they do not share the β-lactam structure and are unlikely to result in an allergic reaction[22]. Vancomycin (Fig. 4) is a branched tricyclic glycosolated nonribosomal peptide; clinamycin (Fig. 5) is a substituted lincosamide; gentamycin is an aminoglycoside, and metronidazole (Fig. 6) has a nitroimidizole ring, all structures that are different enough from penicillins and cephalosporins to avoid cross-reactivity in penicillin allergic individuals. Although aztreonam (Fig. 7) does have a β-lactam structure, there is limited cross-reactivity with other β-lactam antibiotics, and it is generally considered safe for administration to patients with known hypersensitivity reactions to penicillins.

Fig. 4
Vancomycin

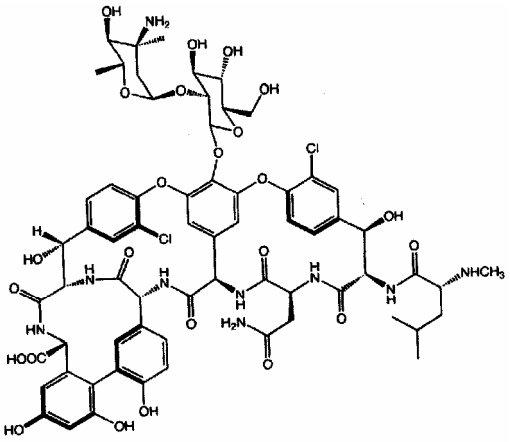


Fig. 5
Clindamycin

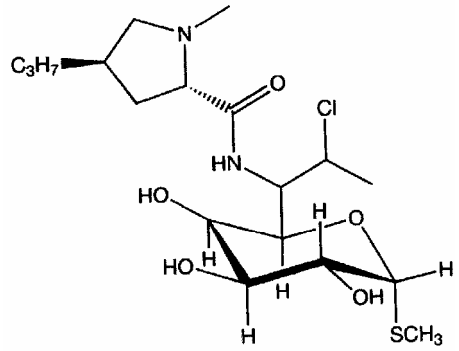


Fig. 6
Metronidazole

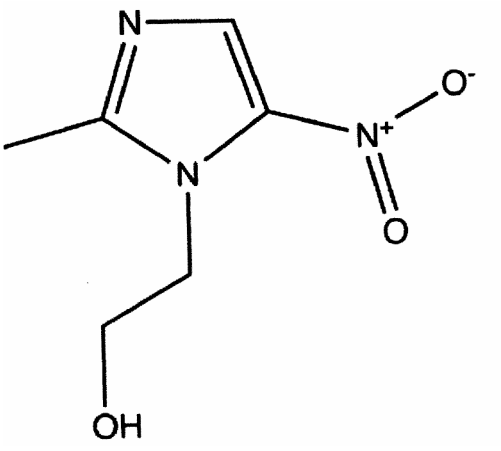
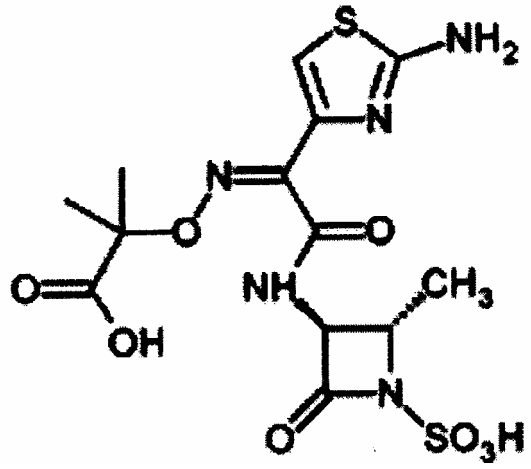


Fig. 7
Aztreonam



Specific recommendations for antibiotic prophylaxis for selected types of surgery in the United States are as follows:

- Cardiac surgery and thoracic aortic surgery:
  1. Cefazolin 1 gram intravenously (IV) every four hours and vancomycin 1000 milligrams IV prior to surgery with 500 milligrams administered after coronary pulmonary bypass (CPB), or
  2. Vancomycin 1000 milligrams IV prior to surgery with 500 milligrams after CPB only for immediate-type penicillin allergy.
- Thoracic surgery, and pacemaker or defibrillator placement:
  1. Cefazolin 1 gram IV every four hours intraoperatively, or
  2. Vancomycin 1000 milligrams IV every twelve hours for immediate-type penicillin allergy.
- Esophageal surgery:
  1. Cefazolin 1 gram IV every four hours intraoperatively and metronidazole 500 milligrams IV every six hours, or
  2. Clindamycin 600 milligrams IV every six hours and gentamicin 1.5 milligrams per kilogram of ideal body weight IV every eight hours for immediate-type penicillin allergy.

- Arterial surgery involving the abdominal aorta:
  1. Cefazolin 1 gram IV every four hours intraoperatively and metronidazole 500 milligrams IV every six hours, or
  2. Clindamycin 600 milligrams IV every six hours and gentamicin 1.5 milligrams per kilogram of ideal body weight IV every eight hours for immediate-type penicillin allergy.
- Endovascular procedures:
  1. Cefazolin 1 gram IV every four hours intraoperatively, or
  2. Clindamycin 600 milligrams IV every six hours for immediate-type penicillin allergy.
- Vascular procedures such as lower extremity bypass for ischemia, lower extremity amputation for ischemia, arteriovenous grafts for hemodialysis, and any vascular case involving a patient with methacillin resistant S aureus:
  1. Vancomycin 1000 milligrams IV every twelve hours.
- Craniotomy, cerebrospinal shunting procedures, spinal surgery and transphenoidal hypophysectomy:
  1. Cefuroxime 1.5 grams IV every six hours intraoperatively, or
  2. Vancomycin 1000 milligrams IV every twelve hours and gentamicin 1.5 milligrams per kilogram of ideal body weight IV every eight hours for immediate-type penicillin allergy.
- Neurosurgery with entry into nasal sinuses:
  1. Cefuroxime 1.5 grams IV every six hours and ampicillin 1 gram IV every six hours intraoperatively, or
  2. Vancomycin 1000 milligrams IV every twelve hours for immediate-type penicillin allergy.
- Orthopedic procedures with no implantable devices:
  1. Cefazolin 1 gram IV every four hours intraoperatively, or
  2. Vancomycin 1000 milligrams IV x 1 dose for immediate-type penicillin allergy.

- Primary orthopedic procedures without implants:
  1. Cefazolin 1 gram IV every four hours intraoperatively and every eight hours postoperatively for 24 hours, or
  2. Vancomycin 1000 milligrams IV x 2 doses for immediate-type penicillin allergy.
- Revision orthopedic procedures with implants (antibiotics should be withheld until cultures are obtained):
  1. Cefazolin 1 gram IV every four hours intraoperatively and every eight hours postoperatively for 48 hours, or
  2. Vancomycin 1000 milligram IV x 4 doses for immediate-type penicillin allergy.
- Ophthalmic procedures: topical therapy as ordered by the ophthalmologist.
- Head and neck procedures entering the oral cavity or pharynx:
  1. Cefazolin 1 gram IV every four hours intraoperatively and metronidazole 500 milligrams IV every six hours, or
  2. Clindamycin 600 milligrams IV every six hours and gentamicin 1.5 milligrams per kilogram of ideal body weight IV every eight hours for immediate-type penicillin allergy.
- Gastroduodenal procedures:
  1. Cefazolin 1 gram IV every four hours intraoperatively, or
  2. Clindamycin 600 milligrams IV every six hours and gentamicin 1.5 milligrams per kilogram of ideal body weight IV every eight hours for immediate-type penicillin allergy.
- Open procedures involving the biliary tract (nor prophylactic antibiotics indicated for elective laparoscopic cholecystectomy):
  1. Cefazolin 1 gram IV every four hours intraoperatively and metronidazole 500 milligrams IV every six hours, or
  2. Clindamycin 600 milligrams IV every six hours and gentamicin 1.5 milligrams per kilogram of ideal body weight IV every eight

hours for immediate-type penicillin allergy.

- Colorectal surgery:
  1. Cefazolin 1 gram IV every four hours intraoperatively and metronidazole 500 milligrams IV every six hours, or
  2. Clindamycin 600 milligrams IV every six hours and gentamicin 1.5 milligrams per kilogram of ideal body weight IV every eight hours for immediate-type penicillin allergy.
- Appendectomy:
  1. Cefazolin 1 gram IV every four hours intraoperatively and metronidazole 500 milligrams IV every six hours, or
  2. Clindamycin 600 milligrams IV every six hours and gentamicin 1.5 milligrams per kilogram of ideal body weight IV every eight hours for immediate-type penicillin allergy.
- Hepatic transplant:
  1. Cefotaxime 1 gram IV every eight hours intraoperatively for adults and Unasyn® (ampicillin/sulbactam) 75 milligrams per kilogram ideal body weight IV every six hours and fluconazole 5 milligrams per kilogram ideal body weight IV every twenty-four hours for children, or
  2. Vancomycin 1000 milligrams IV every twelve hours and aztreonam 1 gram IV every eight hours for immediate-type penicillin allergy.
- Open gynecological procedures including hysterectomy:
  1. Cefazolin 1 gram IV every four hours intraoperatively and metronidazole 500 milligrams IV every six hours, or
  2. Clindamycin 600 milligrams IV every six hours and gentamicin 1.5 milligrams per kilogram of ideal body weight IV every eight hours for immediate-type penicillin allergy.
- Cesarean section:
  1. Cefazolin 1 gram IV every four hours intraoperatively, or

2. Clindamycin 600 milligrams IV every six hours and gentamicin 1.5 milligrams per kilogram of ideal body weight IV every eight hours for immediate-type penicillin allergy.

- High risk genitourinary procedures:
  1. Ciprofloxacin 500 milligrams PO 2 hours prior to surgery, or
  2. Ciprofloxacin 400 milligrams IV 1 hour prior to surgery.

For procedures such as, among others, cataract extraction, electroconvulsive therapy, simple dermatologic procedures, no prophylaxis is given.

Notes Regarding Antibiotic Administration

Several precautions must be observed when administering antibiotics as severe reactions may occur, especially regarding interactions with anesthetic agents (Table 1).

Table 1
Precautions to be taken when antibiotics are given

● Antibiotic infusions should be completed 30-60 minutes prior to skin incision.
● Penicillins should not be given as rapid IV boluses as they may cause seizures.
● Gentamicin should be infused over 30 minutes to avoid ototoxicity.
● Vancomycin should be infused over 30-60 minutes in a monitored setting, one hour prior to the induction of anesthesia as adverse reactions have been reported when it is administered concurrent with anesthetic agents.
● Vancomycin tissue levels rise slowly, and rapid infusion has been associated with an anaphylactoid reaction, therefore the infusion should be completed 1 hour prior to skin incision.
● Standard adult doses may need to be increased in morbidly obese patients.

Also, antibiotic administration is required for children. Dosages and precautions are listed in Table 2.

Table 2
Pediatric Dosages of Antibiotics for IV Administration (Note, for pediatric patients < 1 month of age, appropriate experts should be consulted. In no case should the pediatric dose exceed the standard adult dose).

● Cefazolin	25 mg/kg IV q4h
● Vancomycin	10 mg/kg IV q12h
● Cefurozime	50 mg/kg IV q6h
● Gentamicin	1.5 mg/kg IV q8h (> 5 years old; ideal body weight)
● Gentamicin	2.5 mg/kg IV q8h (< 5 years old)
● Clindamycin	10 mg/kg IV q6h
● Ampicillin	100 mg/kg IV q8h
● Metronidazole	7.5 mg/kg IV q6h
● Aztreonam	30 mg/kg q6h

Treatment for Type I Hypersensitivity Reactions

It is not always possible to prevent a type I hypersensitivity reaction, even if care is taken not to expose an allergic individual to a triggering agent. When such a reaction occurs, the key is to recognize the complication and aggressively treat the patient. Management of an acute allergic drug reaction involves identifying the causative agent and discontinuing its administration (if possible) while providing supportive therapy as indicated.

Physical findings may include any of the following: urticaria, pruritus, skin flushing, angioedema, weakness, dizziness, dyspnea, cough, malaise, difficulty swallowing wheezing, tachycardia, hypotension, and vascular collapse.

If anaphylaxis is suspected, the airway must be secured. If the patients' trachea is not already intubated, consideration should be given to placing an endotracheal tube early as the success rate is improved when intubation is attempted before soft tissue swelling progresses[23]. Intravenous access is imperative and two large bore lines should be placed at the earliest possible moment, allowing for aggressive fluid management as needed to maintain blood pressure. Pharmacologic

therapy should be begun as early as possible, with aqueous epinephrine 1:1000 (0.01 milliliter per kilogram, maximum adult dose 0.3 to 0.5 milliliter) administered via intramuscular or subcutaneous route. This dose may be repeated approximately every 5-10 min if symptoms persist[24]. Administration of H_1 – and H_2 – receptor antagonists is also indicated. Diphenhydramine (50 to 75 milligrams) may be administered either by the intravenous or intramuscular route and cimetidine (300 milligrams) or ranitidine (50 milligrams) may be given intravenously[25]. Corticosteroids are not useful in the treatment of acute anaphylaxis due to the slow onset of action, but they should be administered to prevent prolonged or recurrent anaphylaxis.

Hydrocortisone sodium succinate (250 to 500 milligrams for adults, 4 to 8 milligrams per kilogram for children) may be given every 4 to 6 hours intravenously. Alternatively, a single dose of methylprednisolone (60 to 125 milligrams for adults, 1 to 2 milligrams per kilogram for children) may be administered intravenously. Aerosolized β-agonists such as albuterol control bronchospasm. For patients maintained on β-blocking agents, glucagon may be helpful for those who do not respond to epinephrine and antihistamines[26].

Summary

Though cross-reactivity between cephalosporins and penicillins does exist, most patients with a penicillin allergy tolerate cephalosporins without significant reaction. For the patient requiring a cephalosporin who reports a history of penicillin allergy, the anesthesiologist should determine the likelihood that the allergy represents a true type I hypersensitivity reaction. If it becomes clear from the history that the patent does not have this reaction, a cephalosporin can then safely be administered.

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