

Anaphylaxis for Internists

Definition, Evaluation, and Management, with a Focus on Commonly Encountered Problems



Derek K. Chu, MD, PhD, FRCPC^{*},
David J. McCullagh, MB BCH, BAO, DTM&H, FRCPC,
Susan Waserman, MD, MSc, FRCPC^{*}

KEYWORDS

- Anaphylaxis • Type I hypersensitivity (immediate hypersensitivity)
- Urticaria and pseudoallergy • Meta-analysis
- Antibiotic allergy (including penicillin and cephalosporin β -lactams)
- Graded challenge (test dose) • Desensitization • Epinephrine

KEY POINTS

- Anaphylaxis in adults is most commonly caused by medications, of which antibiotic allergy is the most commonly reported, but other causes of anaphylaxis in adults include immunoglobulin E-mediated allergy to food and insect stings.
- Mimickers of anaphylaxis include infectious, autoimmune, malignant, autoinflammatory, and pseudoallergic causes.
- The treatment of anaphylaxis involves the prompt administration of intramuscular epinephrine to the vastus lateralis (midouter thigh), with adjuncts of intravenous fluids, conservative supplemental oxygen, and H1 antihistamines. There may be a limited role for adjunctive corticosteroids for the low absolute risk for biphasic reactions ($\sim 4\%$).
- Penicillin allergy is often mislabeled out of fear of anaphylaxis, resulting in significant morbidity, increased hospital stays, medical costs, risk of hospital-acquired infections, and antibiotic-resistant infections.
- Internists can easily risk stratify patients labeled as antibiotic allergic. In urgent situations in which allergists are not available, internists should consider diagnostic graded challenge (test doses).

ANAPHYLAXIS: OVERVIEW FOR INTERNISTS

Defined by the National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network symposium 2005 to 2006 expert consensus criteria, anaphylaxis is a serious (systemic) allergic reaction that is rapid in onset and may

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Department of Medicine, McMaster University, 1200 Main Street West, HSC-3V49, Hamilton, Ontario L8N 3Z5, Canada

^{*} Corresponding author.

E-mail addresses: chudk@mcmaster.ca (D.K.C.); waserman@mcmaster.ca (S.W.)

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cause death.^{1,2} This article reviews the diagnosis and management of anaphylaxis, focusing on what may be most relevant for internists.

Classification

Diagnostic criteria for anaphylaxis are shown in [Table 1](#). Although the NIAID and World Allergy Organization use the same definition for anaphylaxis, it is important to recognize that UK and Australian professional societies also consider isolated bronchospasm without typical skin features (urticaria, angioedema) as anaphylaxis.³ Although it has been reported that up to 20% of anaphylaxis may present without cutaneous signs/symptoms,^{1,2} our unpublished (Chu DK, et al. 2019) meta-analysis shows that 92% (95% confidence interval [CI], 89%–95%) of anaphylaxis presents with cutaneous signs ([Fig. 1](#)). Severity classification is complex, with more than 20 different scoring systems and no clear consensus on which has the best test characteristics.⁴ Causes of anaphylaxis include immunoglobulin (Ig) E-mediated reactions to foods, drugs, insect stings, and latex. There are also non-IgE-mediated causes, such as to certain biologics, iron dextran, radiocontrast media, and exercise. Previously these reactions were termed anaphylactoid reactions, but the term non-IgE-mediated anaphylaxis is instead now preferred.² As discussed later, non-IgE-mediated causes are amenable to pretreatment. Some food-related causes of exercise-induced anaphylaxis are managed as IgE-mediated anaphylaxis, with avoidance of the food before exercise. Spontaneous anaphylaxis can be idiopathic or can be caused by an underlying mast cell disorder such as systemic mastocytosis. About 80% of the latter cases involve multiple small yellow-tan to red-brown macules or slightly raised papules called urticaria pigmentosa (also known as maculopapular cutaneous mastocytosis) that urticate on being scratched, eponymously called Darier sign.

Table 1 Anaphylaxis is highly likely when any of these criteria are fulfilled		
(1) Sudden onset of	(2) Two or More, After a Likely Allergen	(3) Hypotension After Exposure to a Known Allergen
Mucocutaneous manifestations (generalized hives, itching, flushing, angioedema)	Mucocutaneous manifestations (generalized hives, itching, flushing, angioedema)	SBP<90 mm Hg or >30% less than baseline
And either of:	Sudden (persistent) gastrointestinal symptoms (crampy abdominal pain, vomiting)	—
Sudden respiratory manifestations (dyspnea, wheeze, cough, stridor, hypoxemia)	Sudden respiratory manifestations (dyspnea, wheeze, cough, stridor, hypoxemia)	—
Hypotension or its consequences (hypotonia, incontinence)	Hypotension or its consequences (hypotonia, incontinence)	—

Abbreviation: SBP, systolic blood pressure.
Modified from Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117(2):393; with permission.

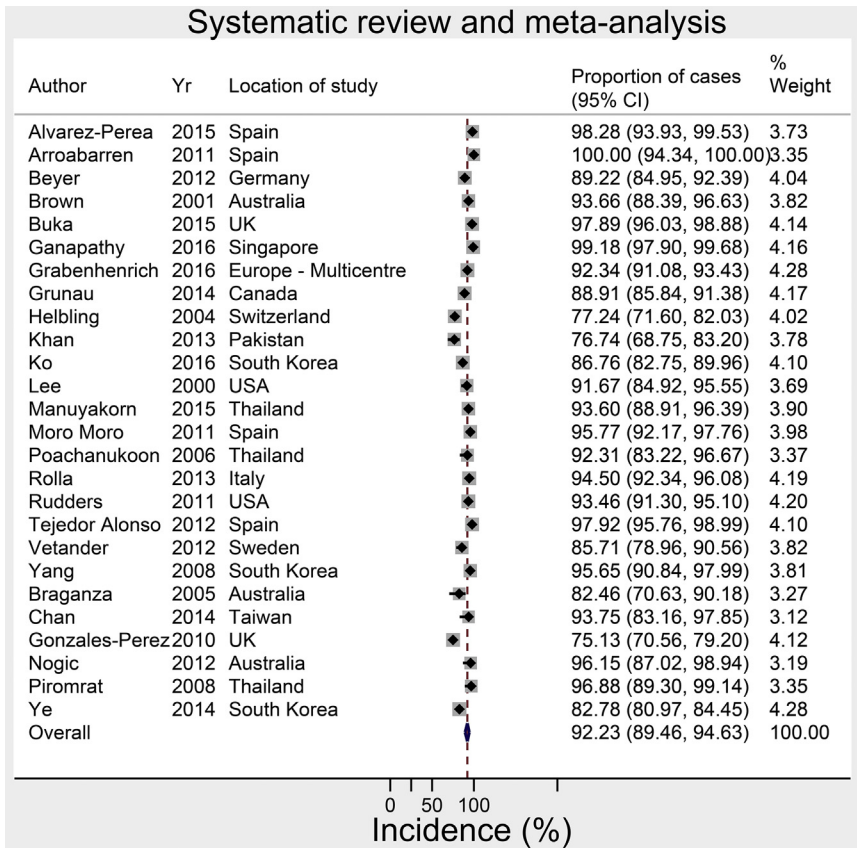


Fig. 1. Proportion of anaphylaxis with cutaneous signs (Chu DK et al, unpublished).

Investigations and Differential Diagnosis

Anaphylaxis is a clinical diagnosis, although its pathophysiology is thought to be caused by systemic mast cell and basophil activation and resultant platelet-activating factor and histamine release.^{5,6} Laboratory tests supportive of the diagnosis are time sensitive to obtain, of which the most widely available is measurement of serum or plasma tryptase level.² The latter must be drawn within 3 hours of a reaction and peaks after 30 to 90 minutes. Because the turnaround time of this test is in the order of days, it is most useful to retrospectively confirm whether or not a significant immediate hypersensitivity event mediated by mast cell activation occurred (significant increase defined as $1.2 \times$ baseline serum tryptase level [ng/mL or $\mu\text{g/L}$] + 2).⁷ This test is particularly useful when disorders mimicking anaphylaxis are present, such as asthma, vocal cord dysfunction, syncope, or flushing syndromes. Patients presenting with isolated angioedema (ie, without urticaria) should also be evaluated for bradykinin-mediated angioedema causes, such as angiotensin-converting enzyme (ACE) inhibitor or Dipeptidyl peptidase-4 (DPP4) inhibitor-induced angioedema, hereditary angioedema,⁸ or acquired angioedema (most commonly associated with lymphoproliferative disease or monoclonal gammopathy of unknown significance).⁹ A C4 level is the first-line screening test for investigation of suspected bradykinin-mediated

angioedema. If it is low, C1-esterase inhibitor level and function should then be ordered to classify the type of bradykinin-mediated angioedema. Management is distinct from anaphylaxis in that bradykinin-mediated angioedema has little to no response to antihistamines and epinephrine.

Specific Mimickers of Anaphylaxis Relevant to Internists

Although the most common causes of anaphylaxis globally are foods, medications, and insect stings (Fig. 2), and it occurs primarily in a home setting (Fig. 3), internists are most likely to encounter drug-induced anaphylaxis in hospital. However, many drugs can be nonspecific mast cell activators, often causing acute-onset urticaria with or without associated angioedema and not mediated by any underlying allergy¹⁰ (eg, specific IgE leading to anaphylactic mast cell degranulation). The 3 most common nonspecific mast cell activators that internists are likely to face are opioids, vancomycin-induced red man syndrome, and nonsteroidal antiinflammatory drugs (NSAIDs).

Opioid-induced reactions are typically mild and only involve the skin (even if generalized; Fig. 4) and can be treated with nonsedating second-generation H1 antihistamines. Similarly, *Mycoplasma* and many viral infections can cause isolated mucocutaneous urticaria with or without angioedema.

Intravenous (IV) vancomycin’s classic side effect, red man syndrome (upper body-erythema and pruritus), is a predictable pharmacologic side effect of nonspecific mast cell activation and histamine release that can be managed by slowing the infusion rate (eg, 10 mg/min or 1 g over 100 minutes) and treatment with second-generation non-sedating H1 antihistamines¹⁰ (eg, cetirizine 10–20 mg, loratadine 5–10 mg, desloratidine 5–10 mg). It is not a true allergic response. If rapid vancomycin infusion is required (eg, 1 g in <60 minutes), premedication with oral or IV antihistamines 30 to 60 minutes before infusion has been shown in at least 3 randomized trials^{11–13} to be effective in reducing the incidence of red man syndrome (random effects meta-analyzed risk ratio (RR) 0.57 [95% CI, 0.35–92]; Fig. 5). Vancomycin is a rare cause of immediate hypersensitivity; there are no large-scale epidemiologic analyses, but there are case reports.

NSAIDs are a common cause of both allergic and pseudoallergic reactions (Table 2), including urticaria and angioedema.¹⁴ Although pseudoallergic reactions

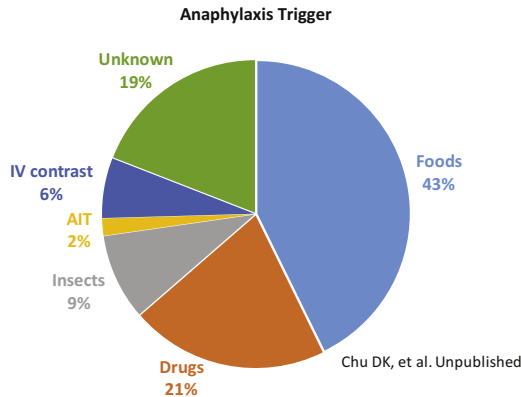


Fig. 2. Anaphylaxis triggers: systematic review and meta-analysis. AIT, allergen immunotherapy; IV, intravenous.

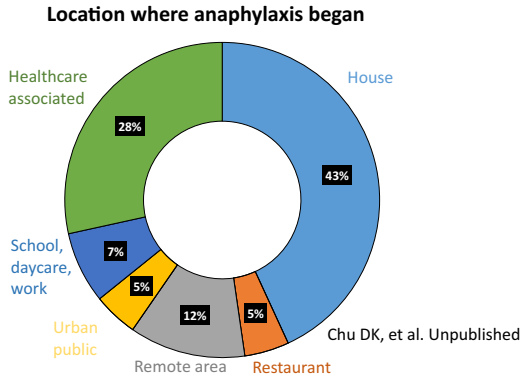


Fig. 3. Anaphylaxis starting location: systematic review and meta-analysis.

are thought to be mediated by cyclooxygenase (COX) inhibition and the balance between prostaglandins and leukotrienes, allergic reactions are mediated by specific IgE. It follows that pseudoallergic reactions occur to any NSAID, often in a dose-dependent manner, whereas allergic reactions occur specifically to only 1 type of NSAID and are elicited even at small doses. Hence, NSAID-induced reactions can range from benign to life threatening and are best referred for evaluation by an allergist. It should be noted that acetylsalicylic acid (eg, aspirin) has been reported to cause only pseudoallergic reactions, not anaphylaxis. In many cases, selective COX-2 inhibitors (eg, celecoxib) can be used in place of nonselective NSAIDs.

Rare Syndromes with Urticaria that Might Lead to Hospital Admission

Urticaria with constitutional symptoms, fever, arthritis, or bruising (purpura or ecchymoses) might suggest an underlying autoinflammatory disease (including Schnitzler syndrome), urticarial vasculitis, or cryoglobulinemia, rather than recurrent anaphylaxis. A full discussion of these conditions is beyond the scope of this article.

Classic histamine-mediated urticaria is evanescent and migratory, with each lesion being pruritic and lasting less than 24 hours in any 1 location before the skin returns to



Fig. 4. Opioid-induced urticaria.

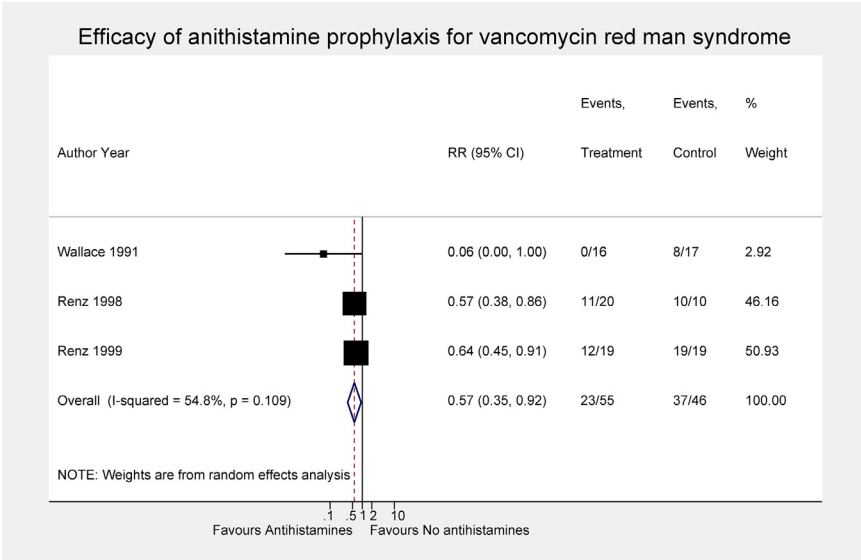


Fig. 5. Efficacy of antihistamine prophylaxis for red man syndrome, meta-analysis.

normal morphology. Urticaria that is atypical should prompt consideration of urticarial vasculitis, which may be classified as normocomplementemic or hypocomplementemic, with the latter having a more severe course. In contrast with histamine-mediated urticaria, urticarial vasculitis lesions are typically painful or burning in sensation, with each lesion lasting greater than 48 hours and healing with a bruise (Table 3).

Prognosis and Complications of Anaphylaxis

Prognostic factors for outcomes after anaphylaxis (Table 4) most consistently identify comorbid cardiac or pulmonary disease, especially asthma, as a risk factor for life-threatening or fatal reactions. Ensuring asthma control is therefore critical to

Table 2 Nonsteroidal antiinflammatory drug–induced allergic and pseudoallergic reactions classification	
Pseudoallergic: Reactions to any NSAID	Allergic: Reactions to Only 1 Specific NSAID
Type 1: AERD/Sampter triad (NSAID-induced naso-ocular and lower-respiratory responses)	Type 5: urticaria ± angioedema
Type 2: urticaria ± angioedema with a history of chronic urticaria	Type 6: anaphylaxis
Type 3: exacerbation of underlying urticaria ± angioedema without a history of chronic urticaria	—
Type 4: mixed respiratory and urticaria ± angioedema	—

Abbreviation: AERD, aspirin exacerbated respiratory disease.

Table 3
Features of classic urticaria versus urticarial vasculitis

	Classic (Histamine-mediated) Urticaria	Urticarial Vasculitis
Symptom/Sensation	Itch	Pain or burning
Duration of Each Lesion	<24 h (evanescent)	>48 h
Location of Each Lesion	Migratory	Fixed
Morphology at Resolution	Normal skin	Purpura/ecchymosis
Associations	Angioedema	Possible underlying CTD Arthritis/arthralgia, abdominal pain, and/or glomerulonephritis On skin biopsy: leukocytoclastic vasculitis

Abbreviation: CTD, connective tissue disease.

(Modified from Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117(2):393.)

the management of food allergy. Peanut and tree nuts are the most common cause of life-threatening and fatal reactions.^{15,16} In contrast, it is commonly thought that the severity of previous reactions predicts the severity of future reactions, but in actuality the severity of one reaction compared with the next is unpredictable.² Several series

Table 4
Potential modifiable risk factors to reduce risk fatal anaphylaxis

Risk Factor	Possible Intervention
Before a Reaction	
Uncontrolled asthma	Optimize asthma control, frequent follow-up
Supported self-management in allergen avoidance	Discuss avoidance strategies. Referral to registered dietician and/or patient support groups
Not always carrying epinephrine on person	Stress importance of always carrying autoinjector
During a Reaction	
Delayed recognition of anaphylaxis	Reinforce anaphylaxis criteria, which might be facilitated by video and simulation sessions
Delayed or lack of epinephrine	Prompt epinephrine injection
Sitting or standing positioning	Keep supine ± legs raised
After a Reaction	
No referral to an allergist	Refer all patients with anaphylaxis
No prescription of autoinjector	Always prescribe an epinephrine autoinjector and educate on how and when to use it
Lack of education	Discuss strategies for allergen avoidance, cofactors, and asthma control

Data from Refs. ^{2,15,17,20}

have shown that most case mortality in food allergy is associated with a previous history of less severe reactions and therefore the thought that there was no need to carry an epinephrine autoinjector.^{15,17,18} Consistent with this is the observation that the delay or lack of prompt epinephrine autoinjector use after a reaction is associated with more severe outcomes, including mortality and biphasic reactions.^{15,16,18} The association of β -blockers and ACE inhibitors with the severity and frequency of anaphylaxis, although potentially significant, is of very-low-quality (certainty) evidence.¹⁹ Complications of anaphylaxis include repeat reactions typically within 4 to 8 hours (up to 72 hours) without additional allergen exposure, termed biphasic reactions, occur in about 4% of cases (3.65% [95% CI, 2.12–6.19]; Fig. 6), intensive care unit (ICU) admission in about 4% (4.41% [95% CI, 2.02–9.35], Chu DK, et al. 2019), and mortality in about 1% (1.04 [95% CI, 0.14–2.49], Chu DK, et al. 2019). Death is typically secondary to respiratory obstruction and/or shock and occurs within 60 minutes. Anaphylaxis may also result in coronary vasospasm with or without myocardial infarction, termed Kounis syndrome, but this entity is limited to case reports.

Treatment of Anaphylaxis in Hospital

Acute management is prompt administration of 0.3 to 0.5 mL of 1 mg/mL (previously known as 1:1000 concentration) epinephrine intramuscularly to the mid-outer thigh (vastus lateralis) and repeated every 3 to 5 minutes as needed.² This injection can be achieved by use of commercial autoinjectors or drawing up from a

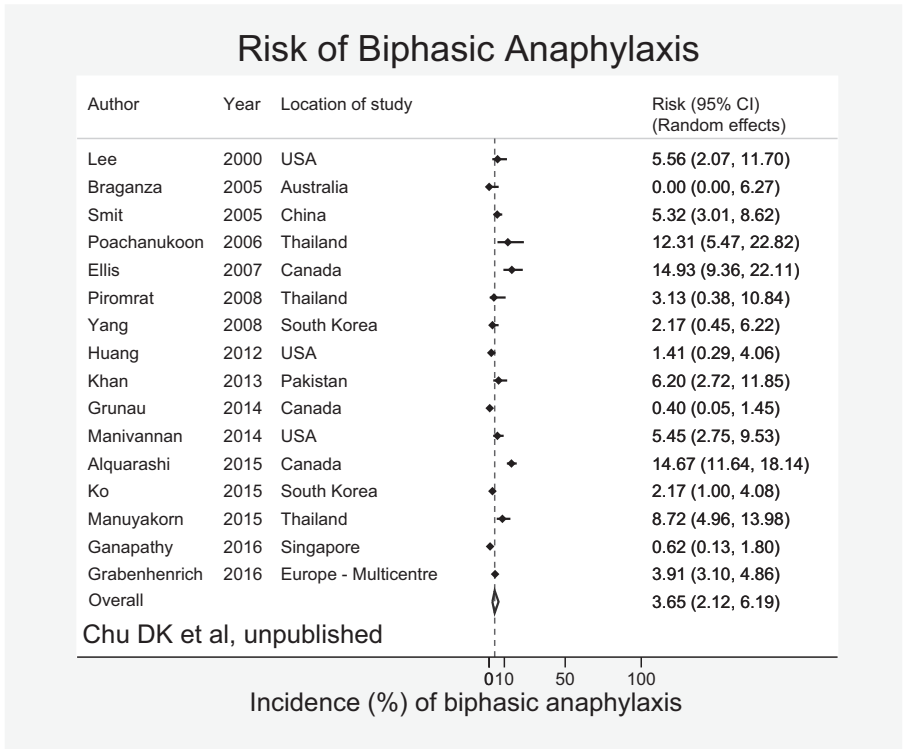


Fig. 6. Risk of biphasic anaphylaxis: systematic review and meta-analysis.

medication vial. Intramuscular epinephrine is preferred to bolus IV epinephrine as the initial treatment of anaphylaxis because the latter is associated with more complications (eg, arrhythmia) and dosing errors. There are no contraindications to epinephrine for anaphylaxis, including pregnancy, acute coronary syndrome, or comorbid cardiovascular disease. Subsequent adjunctive treatment includes² supine positioning with legs raised²¹ to encourage preload along with standard critical care management, including IV fluids with or without vasopressors for anaphylaxis-induced distributive and hypovolemic shock, conservative oxygen therapy to avoid hyperoxia-induced paradoxical tissue hypoxia,²² early intubation if laryngeal edema is suspected (eg, stridor), and appropriate acuity monitoring (eg, Step-down unit or ICU). Upright posture during reactions is associated with fatal anaphylaxis,^{15,21} thought to be caused by rapid vena cava emptying, loss of preload, and underfilled ventricles, a condition called empty heart syndrome.²¹ Inhaled short-acting beta agonists (eg, salbutamol or albuterol) with or without short-acting antimuscarinics (eg, ipratropium) should also be considered for dyspnea, wheeze, or hypoxia. Additional adjuncts include H1 antihistamines (either second-generation nonsedating antihistamines or IV diphenhydramine) and H2-blockers (typically used for gastric acid suppression but may be helpful for allergic reactions) such as ranitidine.^{1,2,23} Corticosteroids may have a modest relative effect on preventing biphasic reactions (Fig. 7), but whether this results in a clinically significant absolute risk reduction is less certain, because the risk of biphasic reactions is 3.65% without corticosteroids and 2.8% with corticosteroids, translating into a small absolute risk reduction of 0.85%. Risk factors for biphasic reactions are not clear.

Refractory anaphylaxis may require epinephrine infusion. Methylene blue may be helpful in severe refractory cases but supportive evidence is primarily from case reports and biological rationale of its effect on nitric oxide.²⁴ Glucagon (1 mg IV) may assist with inotropy and chronotropy in patients on β -blockers with refractory anaphylaxis.^{25,26}

On discharge, all patients should be given an anaphylaxis action plan (eg, <https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Libraries/Anaphylaxis-Emergency-Action-Plan.pdf> or <https://www.foodallergy.org/media/329>), prescribed epinephrine autoinjectors (several different brands available in the United States), trained in its use, suggested a medical alert bracelet, and referred to an allergist for evaluation. Patients should be encouraged to always carry an autoinjector. Cost-savings programs are available to help ensure that all patients that require an autoinjector are able to access one (<https://www.foodallergy.org/about-fare/blog/2018-patient-assistance-resources-for-epinephrine-auto-injectors>). Further, the US Food and Drug Administration provides an updated site on any drug shortages (https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Epinephrine%20Injection,%20Auto-Injector&st=c).

These final steps at discharge are critical because many outpatient cases of fatal anaphylaxis occur in patients with a known history of food allergy, and are consistently associated with lack of or delayed use of epinephrine.^{15,16,18,27,28} This problem is compounded by the fact that not all emergency medical technicians in the United States carry and/or are trained in the use of epinephrine for anaphylaxis.²⁹ Hence, patients should be informed that there can be a significant delay between onset of anaphylaxis as an outpatient and time to epinephrine administration. Prompt referral to an allergist helps to reinforce these points, and complete allergy testing can generate strategies for risk reduction (eg, allergen avoidance, venom immunotherapy, drug desensitization).

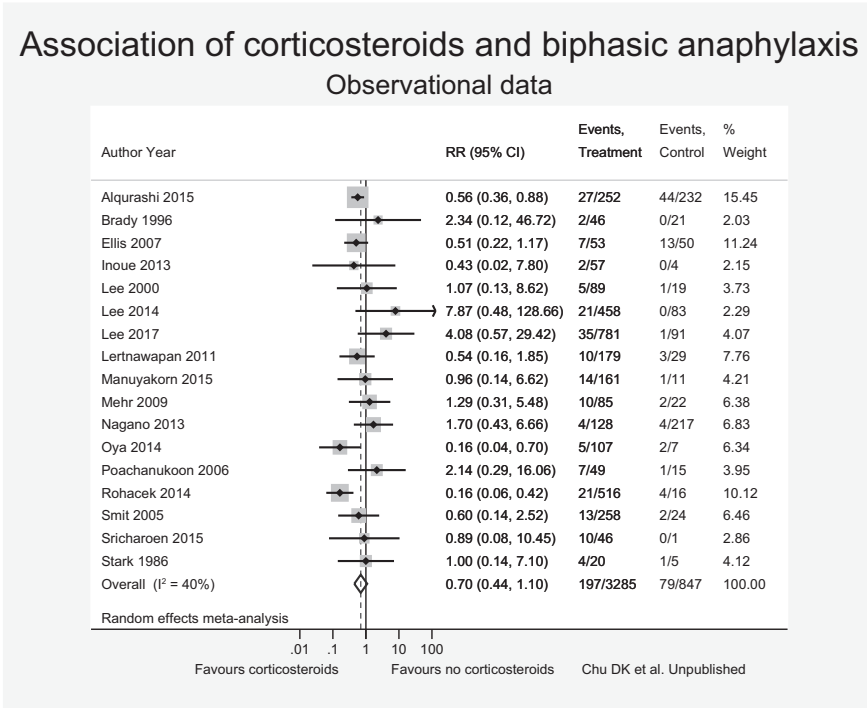


Fig. 7. Corticosteroids for biphasic anaphylaxis: systematic review and meta-analysis (no available randomized controlled trials). M-H, Mantel-Haenszel.

WHY ANAPHYLAXIS TO ANTIBIOTICS IS PARAMOUNT TO INTERNISTS

Although there are many potential causes of anaphylaxis (Table 5), the most common cause in adults is drugs. Antibiotic allergies are the most common allergies reported by patients,³⁰ critically influencing everyday clinical decisions. The complications related to erroneous labeling of antibiotic allergy are mentioned earlier. Therefore, it is paramount for internists to have a core competency in antibiotic allergy, so that patients have access to appropriate first-line therapy. Next, this article provides a practical user’s guide for internal medicine specialists (internists) to optimally evaluate and manage patients with presumed antibiotic allergy. This article builds on the recent summary of 5 critical points to know about penicillin allergy for patients and all health care providers.³¹ There are also recent more general reviews on this topic,^{14,32–35} regarding controversies and research priority setting.³⁶

The largest and most commonly used antibiotic class used for inpatients are the β -lactams. This part of the article is therefore focused on the approach to patients with anaphylactic β -lactam allergy.

DEFINITIONS: IMMEDIATE VERSUS DELAYED HYPERSENSITIVITY; ALLERGY VERSUS SIDE EFFECT

Adverse reactions to drugs are classified into those that are known pharmacologic side effects and/or predictable/anticipated (eg, hypotension after taking an antihypertensive such as a dihydropyridine calcium channel blocker), that are unpredictable

Table 5
Causes of anaphylaxis most relevant to internists

Category of Cause	Specific Causes	Notes
Infectious	Hydatid	Risk with cyst aspiration or biopsy
Malignancy/ infiltrative ⁷	Mast cell disorders	Comanagement with malignant hematology
Iatrogenic/ medications	Antibiotics NSAID (not ASA) Transfusion/blood product Radiocontrast Chlorhexidine NMBA NMBA reversal (Sugammadex) Total parental nutrition Latex Allergen immunotherapy	All cases of anaphylaxis: Trigger avoidance, prescribe epinephrine, refer to allergist Transfusion: Risk with complete selective IgA deficiency Radiocontrast: No diagnostic test. Shellfish allergy ≠ radiocontrast allergy
Idiopathic	Exercise induced	Premedication protocols vary widely ³⁷
Food ³⁸	Seafood (fish, crustaceans, mollusks), peanut, tree nut most common and often lifelong in adults	Insects: Patient with systemic reactions are at high risk (50%) for repeat reactions and venom immunotherapy is effective (RR ~0.2)
Insect stings ³⁹	Wasps (including yellow jacket), honeybees, fire ants	

Abbreviations: ASA, acetylsalicylic acid; NMBA, neuromuscular blocking agent.

and idiosyncratic (eg, drug-induced lupus, DPP4 inhibitor-induced angioedema), and those that are predictably immune-mediated hypersensitivity responses (eg, penicillin-induced anaphylaxis). The focus here is on immediate hypersensitivity responses (eg, anaphylaxis, urticaria, bronchospasm). Severe delayed reactions are discussed in greater detail in other reviews.^{32–34,40,41}

The term penicillin allergy can have different meanings among health care providers, patients, and researchers. Many use it to refer to immediate hypersensitivity to penicillins and cephalosporins, rather than solely either one, or the β -lactam class as a whole. This lack of specificity promotes misunderstanding and misnomers. For clarity, this article refers to penicillin allergy as solely to involving the subclass of β -lactams.

β -LACTAM ALLERGY

Penicillin Allergy

How common is penicillin allergy? What is the cost?

Penicillin allergy is the most common antibiotic allergy reported and its prevalence among inpatients can reach 15%.^{30,41} However, studies evaluating penicillin allergy have shown that patients can tolerate a β -lactam more than 90% of the time.⁴² The label of penicillin allergy has been shown to lead to increased health care costs. These costs occur for several reasons, including increased antibiotic costs from second-line therapies, increased length of stay, increased use of IV therapy, and higher readmission rates. Eight out of 10 patients with a penicillin allergy label that requires antibiotics receive inferior non- β -lactam antibiotics.⁴³ β -Lactam alternatives are broader spectrum and this leads to increases in antibiotic-resistant and hospital-acquired infections. Retrospective cohorts in the inpatient⁴⁴ and outpatient setting⁴⁵ have shown an increased risk of *Clostridioides difficile*, methicillin-resistant *Staphylococcus*

aureus, and vancomycin-resistant enterococcus in patients with the label of penicillin allergy. Meta-analyses show increased costs in the range of US\$1125 to US\$4254 per patient.⁴⁶ These estimates might underestimate the true cost of a penicillin allergy label, when the costs associated with resistant organisms are considered. Hence, the desire to avoid harm by commission may lead to harm by omission.

Is penicillin allergy a lifelong diagnosis?

IgE-mediated penicillin allergy wanes over time, likely because of weak IgE memory and short-lived IgE plasma cells.^{47,48} Studies including prospective cohorts have shown that there is a significant reduction in the number of patients who are skin test positive for penicillin allergy over time. As an example, a study following patients who were skin test positive to benzylpenicillin, amoxicillin, or ampicillin were followed over the course of 5 years with repeated skin testing. After 5 years, 38 of 55 (69%) were no longer allergic by skin testing.⁴⁹ Approximately 80% of patients with true penicillin allergy are not allergic after 10 years.⁴¹ Hence, there is a need to frequently reevaluate the diagnosis of penicillin allergy.

How to risk stratify, test for, and diagnose penicillin allergy

Like almost any other condition in medicine, diagnostic evaluation requires initial risk stratification by history. For β -lactam allergy, that means stratification into 1 of 3 categories:

1. Those who clearly are not allergic because the reaction was a known pharmacologic side effect (eg, antibiotic-induced isolated dyspepsia), or isolated family history of drug allergy without a personal history of penicillin allergy
2. Those in whom testing is contraindicated because of severe delayed drug reactions (eg, Steven-Johnson syndrome [SJS]/toxic epidermal necrolysis [TEN], drug reaction eosinophilia and systemic symptoms [DRESS])
3. Those appropriate for testing because of a possible history of immediate hypersensitivity (urticaria, angioedema, anaphylaxis) or delayed-onset nonspecific benign eruption

Although history alone does not always predict the outcome of skin testing,⁵⁰ pertinent information concerns the nature and course of the reported allergic reaction, when it occurred, its severity (eg, hospitalization, organ failure, skin desquamation, anaphylaxis), and whether or not the drug has been tolerated since.^{33,41,51,52} Isolated family history is unimportant and nondiagnostic for immediate penicillin allergy, because it is not a strongly heritable trait.⁴¹ The physical examination is, in general, not relevant to the diagnostic evaluation of a history of possible penicillin allergy.

Classically, skin testing is performed on all patients before challenge testing, but there is debate over whether and which patients can be challenged without skin testing, and what the optimal procedural technique is.^{36,41} The classic rationale for sequential skin tests, including epicutaneous, intradermal, followed by challenge testing, is to minimize the risk of eliciting an iatrogenic anaphylactic response.

Interfering substances that lead to indeterminate allergy skin test results Skin testing relies on the patient to mount an urticarial (wheal and flare) response to a specific allergen, which is blocked by drugs with antihistaminic action. Common in-hospital drugs that can do this include H1-blocking antihistamines, diphenhydramine (Benadryl), dimenhydrinate (Gravol), tricyclic antidepressants, sleep aids/hypnotics (eg, zopiclone, benzodiazepines), and quetiapine. High-dose glucocorticoids might

lead to false-negative skin responses, potentially through mast cell depletion over time.

What would allergists do? Challenge Negative skin tests are followed by administering a full, therapeutic dose of penicillin (eg, single-dose oral amoxicillin 250 or 500 mg, or the drug that caused the initial reaction if known) to prove tolerance.

Inpatient allergist evaluation with combined skin and challenge testing (including test dosing) of patients labeled as penicillin allergic has been shown to be rapid, safe, and cost-effective.^{41–43,46}

Cross reactivity between and among (within) β -lactam antibiotics

The pathophysiologic basis of immediate penicillin hypersensitivity is thought to involve IgE antibodies specific to haptens formed from the breakdown of either the β -lactam core ring or chemical R-group side chains of β -lactams. The shared β -lactam core defining this family of antibiotics and shared or similar R side chains between specific β -lactams (eg, amino group, methoxyamino group) raises the possibility that allergy to 1 family member may imply allergy to other members, termed cross reactivity.⁵³

Many internists face the situation in which the antibiotic of choice is a cephalosporin, but the patient reports a possible penicillin allergy, complicating therapeutic decision making. The authors and others^{14,31,33,34,41,52} stress the importance of first clarifying whether the label of penicillin allergy is true or not. Internists can identify patients at very low risk of being truly allergic (such as nonsuggestive history; eg, isolated nausea with amoxicillin), and can easily offer a direct amoxicillin challenge (eg, 1 dose of 250 or 500 mg by mouth then observing for 30–60 minutes) to clarify the diagnosis.

There exists no published rigorous systematic review or guideline to inform evidence-based management of potential cross reactivity between β -lactams. However, for patients truly allergic to penicillin, our meta-analysis shows that rates of cross reactivity are $\sim 1\%$ with cephalosporins (0.72% [95% CI, 0%–2.24%]; **Fig. 8**). Rates of $\sim 1\%$ with carbapenems and 0% with monobactams (aztreonam) have been reported.^{33,34,41,52,53} Historical reports quoting cross reactivity of 8% to 10%, which antibiotic package inserts reference, were erroneous owing to contamination of the cephalosporin test reagents with penicillin,^{33,34,41,52,53} and this is supported by our meta-analysis. For penicillin-allergic patients, cross reactivity between other penicillins is thought to be high, but there are no rigorous analyses to support this.

Cephalosporin allergy

Cephalosporin allergy affects 2% of the population,⁵⁴ and is prevalent in the perioperative setting as a cause of anaphylaxis.⁵⁵ Although there are sparse data to robustly inform evidence-based decision making, increasingly frequent reports state that cephalosporin allergy is primarily specific to the R side group, which is variable between cephalosporins. Thus, the cross reactivity between most cephalosporins is thought to be low. Those with the highest potential to cross react are thought to be predictable by similarity in R side chains (**Table 6**). Consequently, guidance varies, with some clinicians recommending to use a cephalosporin with different side chains or alternative antibiotic (including penicillins), whereas others suggest test dosing for similar side chains and strictly avoiding identical side chains.^{32–35,41,52,53}

β -Lactamase inhibitor allergy

Although a less frequent cause of allergic reactions, patients with a possible allergy to combination β -lactam/ β -lactamase inhibitors (piperacillin-tazobactam, amoxicillin–

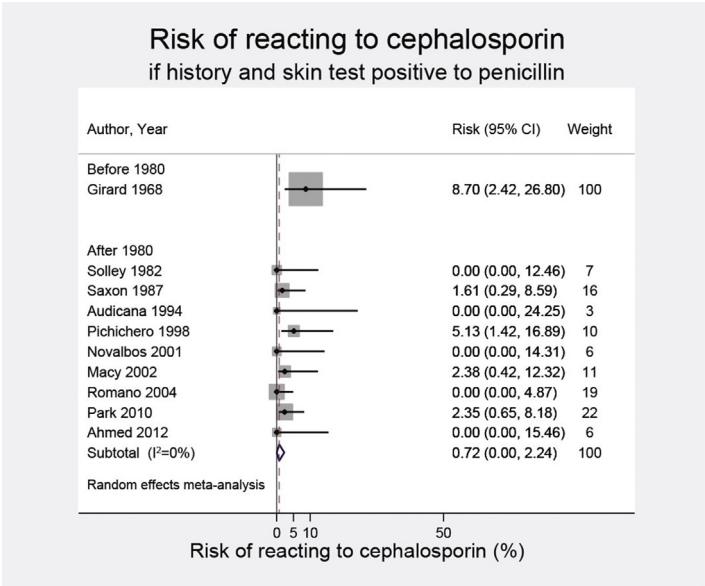


Fig. 8. Risk of cross reaction to cephalosporin in patients allergic to penicillin.

clavulanic acid, ticarcillin–clavulanic acid, ampicillin-sulbactam) could also be evaluated for allergy to the β -lactamase inhibitor component.

What should internists do in a pinch?

All patients identified carrying a label of penicillin allergy should be referred for outpatient allergy specialist evaluation to obtain diagnostic clarity. However, there are inevitably situations in which the internist has no immediate access to an allergy specialist. Here, the only rapid diagnostic tool is the history. As described earlier, the most informative pieces of information, even if collateral, for risk stratification are (1) whether the reaction was a known and predictable pharmacologic side effect; (2) whether the reaction was severe enough to cause hospitalization or had convincing features of anaphylaxis or severe delayed hypersensitivity reactions (SJS/TEN, DRESS, AIN); (3) when the reaction occurred, because more than 5 years ago, and especially more than 10 years ago, greatly decreases the risk of still having an immediate hypersensitivity; (4) whether the patient subsequently tolerated penicillins, because, if so, this strongly suggests the patient is not allergic.^{14,31,33,34,41,52}

Using this approach, a substantial proportion of patients become eligible to receive penicillin. So long as there are no features of severe delayed hypersensitivity,

Table 6 Similar or identical side chains to consider when prescribing β -lactams for patients allergic to a different cephalosporin	
Amino Group Shared	Methoxyamino Group Shared
Ampicillin: cephalexin, cefaclor	Cefuroxime, ceftriaxone, cefotaxime, cefepime
Amoxicillin: cefprozil, cefadroxil, cefratizine	—

penicillin-allergic patients have a $\sim 1\%$ chance of reacting to cephalosporins, and $\sim 1\%$ risk of reacting to carbapenems (see [Fig. 8](#)). Therefore, patients at intermediate risk of being truly penicillin allergic can undergo a graded challenge, also known as a test dose procedure.

Test dosing (graded challenge) For inpatients, in a monitored setting with anaphylaxis treatment medications and equipment at the bedside, the patient is administered either 1 in 100 (ie, 1%) or 1 in 10 (ie, 10%) of the intended full therapeutic dose ([Table 7](#)). After this, the infusion is paused and the patient monitored for 30 to 60 minutes for any allergic response. If there are no signs or symptoms of immediate hypersensitivity, the rest of the therapeutic dose is then infused and the patient monitored again for any signs of an allergic reaction. The same procedure can be done with oral antibiotics instead of IV. Although there are no rigorous analyses or evidence-based guidelines to determine contraindications to graded challenges, classic teaching is that uncontrolled cardiac or respiratory disease (primarily, asthma), or use of β -blockers may increase the risk of poor outcome if an allergic reaction did occur because of poor response to rescue epinephrine. A history of severe cutaneous adverse reaction (SCAR; eg, SJS/TEN, DRESS, acute generalized exanthematous pustulosis) is a contraindication to test dose.

Desensitization Desensitization is reserved for patients that definitely or likely have an immediate hypersensitivity to penicillin but must receive the penicillin to which they are allergic, and it is not possible to first test the patient by skin testing. Indications for this are typically those with an established long-term need for penicillins, such as syphilis (including in pregnancy), or possibly methicillin-sensitive staphylococcal bacteremia and/or its complications. Desensitization allows the patient to not react to the drug while they have routine (eg, daily) exposure to it. Without continual exposure, the allergy may regenerate in as little as 2 days if stopped. Allergist consultation is paramount to prepare for and guide management when allergic reactions during desensitization occur, which has been reported to occur in up to 20% of patients.^{41,52,56}

NON- β -LACTAM ANTIBIOTICS

Skin testing to non- β -lactam antibiotics is not standardized and has uncertain diagnostic utility. Some non- β -lactams are notorious nonspecific mast cell activators that complicate evaluation because they result in presentations that appear like immediate hypersensitivity (eg, isolated urticaria), but are not truly allergy (ie, no underlying

Table 7
Graded challenge (test dose) and desensitization

	Graded Challenge (Test Dose)	Desensitization
Purpose	Diagnostic	Therapeutic
Result	Prove tolerance to a drug, if not remove allergy label	Allergy label must remain until it can be fully evaluated
β -Lactam Tolerance	Lifelong unless further event	Lasts only duration of desensitization procedure
Starting Dose	1 in 100 (ie, 1%) or 1 in 10 (ie, 10%) of therapeutic dose	1 in 1000 (ie, 0.1%) to 1 in 100 (ie, 1%) of therapeutic dose
Number of doses or steps	2–3	7–16

specific IgE response). Examples include vancomycin and fluoroquinolones. However, the principles for evaluation, graded challenge (test dose), and desensitization are similar for β -lactams and non- β -lactams.

Examples of Specific Scenarios Internists Might Encounter

No allergist and skin tests available

History of penicillin/amoxicillin allergy is low risk and needs a β -lactam: what do you do? A previously healthy 30-year-old woman is admitted to your rural community hospital at 10 PM with fevers, chills, and paronychia, with growth of methicillin-sensitive *S aureus* (MSSA) after 8 hours of blood culture. The overnight physician started empiric vancomycin because the patient reported a penicillin allergy. Her allergic reaction was not serious in that she was not hospitalized, and there was no organ failure (including jaundice suggestive of liver failure or hemolysis), mucocutaneous desquamation, or features of anaphylaxis. She was told that as a child she had a fever with possible middle ear infection for which she was given penicillin or amoxicillin; she is not sure which. Five days into the antibiotic course, she developed isolated macular erythema with urticaria over her torso. As a result, she was evaluated by a physician who told her mother that she was allergic to penicillin and to avoid all β -lactams forever. She has not been exposed to penicillin or related antibiotics since.

Knowing this is a low-risk history of true allergy because of its benign delayed features that could have been a manifestation of a viral infection, and lack of features of SCAR or anaphylaxis, and the history more than 10 years ago, you wish to remove the label of penicillin allergy, because penicillin and β -lactams are preferred for MSSA bacteremia and its complications.^{57,58} If ordering a penicillin class antibiotic, you could choose to perform a supervised direct oral challenge to amoxicillin 250 mg and then monitor the patient for 30 to 60 minutes with medications to treat anaphylaxis at the bedside, because there is no available allergist in your community. If ordering a cephalosporin such as cefazolin, a direct oral challenge to amoxicillin 250 mg would still be a critical diagnostic procedure, because, if the label of penicillin allergy is removed, there is no specific concern for cross reactivity with cephalosporins. Should the patient be revealed to be allergic to amoxicillin after oral challenge, she would likely be able to tolerate a cephalosporin such as cefazolin because you know that cross reactivity with cephalosporins is $\sim 1\%$ (see Fig. 8), carbapenems $\sim 1\%$, and aztreonam 0%.

History of penicillin/amoxicillin allergy is higher risk and needs a β -lactam: what do you do? If the scenario presented earlier was slightly different, with the patient reporting the allergic reaction as 1 year ago and immediate-onset urticaria and lip angioedema after the first dose, this would be an intermediate to high risk of true underlying allergy. Because of this, you consider alternative β -lactams, because this is preferable to vancomycin.^{57,58} You recognize that the cross reactivity to cephalosporins in those allergic to penicillin is $\sim 1\%$ (see Fig. 8), with cross reactivity primarily being determined by shared R-group side chains (see Table 6). Therefore, you bring the patient to a monitored setting and do a test dose by administering 10% of a full therapeutic dose of cefazolin 2 g (ie, 200 mg) before pausing the infusion and monitoring the patient for 30 minutes with medications to treat anaphylaxis at the bedside. Because the patient did not react to this test dose, you then administer the remaining 90% of the cefazolin 2 g dose and again monitor for 30 minutes. If the patient reacts to this regimen, this would indicate allergy to cefazolin and you would then consider desensitization with expert allergist

consultation (see [Table 7](#)), even if by remote telephone or electronic communication, or possibly patient transfer.

Allergist and skin tests available

History of immediate penicillin/amoxicillin allergy is any risk and needs a β -lactam: what do you do? If you had access to an allergist in either scenario discussed earlier, you would perform the initial risk stratification at the bedside in the same manner. With low-risk histories, you challenge the patient directly to oral amoxicillin 250 mg. With intermediate-risk or high-risk histories, you would refer for allergist evaluation and skin testing. Severe delayed hypersensitivity reactions (already defined) are contraindications to skin testing, challenge, or desensitization.

If the allergy skin testing to penicillin is positive, this would suggest the patient is likely allergic to penicillin and the allergist would help select an alternative antibiotic. Similarly, if the initial reaction was to a cephalosporin and the patient needs a different one, the allergist could help facilitate safe cephalosporin selection. In addition, all patients with a history of possible allergy should be referred to an allergist for evaluation because antibiotic allergy diagnoses are best clarified electively before urgent situations arise.

SUMMARY

This article reviews anaphylaxis, focusing on providing internists with a practical user's guide to its diagnosis, evaluation, and management, particularly to β -lactams. Internists also face patients who present with anaphylaxis to foods, insect stings, and non-antibiotic-related causes, such as NSAIDs. Less common causes are latex, radiocontrast, and exercise. Common scenarios that internists encounter are described earlier, along with considerations for their management. Being central to hospital and outpatient medicine, one of the most common problems encountered complicating therapeutic decision making is possible anaphylactic antibiotic allergies. The antibiotic allergy label is common and most patients thought to have antibiotic allergy are labeled as penicillin allergic. However, more than 9 out of 10 cases are mislabeled and can tolerate penicillin. New proactive efforts to reduce the label are needed, because they have been shown to be successful. Internists can routinely manage patients with the penicillin allergy label by risk stratifying and performing a graded challenge or referring for definitive testing and/or desensitization, depending on the acuity of the situation. Acute management of anaphylaxis entails prompt intramuscular epinephrine to the thigh, before moving on to several potential adjuncts.

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