

Anaphylactic and Anaphylactoid Causes of Angioedema

Paul A. Greenberger, MD

*Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg
School of Medicine, 676 North St Clair Street, Suite 14018, Chicago, IL 60611, USA*

Anaphylaxis was defined at a conference sponsored by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network as “a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance” [1]. It has been described as “a serious allergic reaction that is rapid in onset and may cause death” [1]. The Joint Task Force on Practice Parameters, which represents the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology, defined anaphylaxis as “a condition caused by an IgE-mediated reaction. Anaphylactoid reactions are defined as those reactions that produce the same clinical picture as anaphylaxis but are not IgE-mediated” [2]. Simons [3] has suggested that anaphylaxis be categorized as immunologic (IgE or Fc ϵ RI mediated), nonimmunologic, or idiopathic. Pseudoallergic is synonymous with anaphylactoid.

Incidence of urticaria and angioedema during anaphylaxis

Swelling (urticaria or angioedema) is the most common manifestation of anaphylaxis. It has been reported that urticaria likely occurs during anaphylaxis in about 90% of cases [2,3]. Angioedema appears to be much less frequent than acute urticaria when comparisons are made. For example, in a series of 91 patients referred for penicillin allergy skin testing, 52 (57%) patients had experienced urticaria and 36 (40%) patients reported non-urticarial maculopapular rash [4]. However, just 12 (13%) patients described angioedema of the tongue and face [4]. In that series, 16 (18%) patients

Supported by the Ernest S. Bazley Grant to Northwestern Memorial Hospital and Northwestern University.

E-mail address: p-greenberger@northwestern.edu

had at least one positive skin test reaction to the major or minor determinant penicillin skin test reagents [4]. From a series of 348 outpatients referred for skin testing, 60 (17.2%) patients similarly were positive to at least one major or minor penicillin determinant [5]. While 47 (78.3%) patients had reported having experienced urticarial lesions, 2 (3.3%) patients had developed anaphylaxis [5]. No patient had angioedema listed as the purported allergic reaction. In a series of 112 penicillin-skin-test positive patients who had experienced 143 immediate allergic reactions to penicillins, the reactions were listed as anaphylactic shock in 89 (62.2%), urticaria in 32 (22.4%), urticaria and angioedema in 21 (14.7%), and angioedema alone in 1 (0.7%) [6].

Other studies have found higher prevalence of angioedema during anaphylaxis. Angioedema was found in 40% and urticaria in 49.3% of 142 patients presenting to an ER with anaphylaxis [7]. Laryngeal edema was present in 25% of such patients [7]. In 67 patients referred to an outpatient service for evaluation of anaphylaxis, 44.8% of patients had experienced angioedema compared with 58.2% for urticaria. Dyspnea, which may have included oropharyngeal or laryngeal swelling was noted in 59.7% of patients [8]. In patients with idiopathic anaphylaxis, 335 patients, ages 5 to 83, were categorized based on whether the acute episode was generalized (urticaria or angioedema with bronchospasm, hypotension, syncope, or gastrointestinal symptoms with or without upper airway obstruction) or angioedema (urticaria or angioedema with upper airway compromise without other systemic symptoms such as shock) [9]. The patients were labeled as either IA (idiopathic anaphylaxis)-G (generalized) or IA-A (angioedema). From the 335 patients, 201 (60%) were classified as IA-G and 119 (35.5%) were designated as IA-A [9]. In this series, urticaria or angioedema occurred in all 335 patients, but anaphylaxis, implying a life-threatening emergency, involved angioedema of the upper airway in over a third of patients. Indeed, these patients had experienced laryngeal or pharyngeal edema or "massive tongue edema" [9]. Perhaps, most persuasively, in this series of 335 patients, upper airway obstruction occurred in 210 (63%) patients [9].

Angioedema in fatal cases of anaphylaxis

The importance of angioedema as a mechanism of death is highlighted from the few autopsy investigations of fatal anaphylaxis. For example, laryngeal edema was identified in 15 (37.5%) of 40 cases, but it was noted that in only 4 cases was the angioedema completely obstructing the upper airways [10]. Conversely, five of six cases reported in 1964 had pharyngeal, epiglottic, and laryngeal edema whereas the sixth patient had experienced circulatory collapse without upper airway angioedema [11]. Causes included injections of penicillin, penicillin with streptomycin, heterologous sera, bee venom, and an immunotherapy injection [11]. In

a report of a fatality in a male patient with idiopathic anaphylaxis, he developed rapid onset of respiratory distress and fecal incontinence. He self-administered epinephrine. In the emergency department his blood pressure was 155/70 and pulse was 117 [12]. However, he was cyanotic and nonresponsive. "Several attempts at endotracheal intubation were unsuccessful due to edema of the hypopharynx" [12]. This finding is similar to the presence of upper respiratory tract edema in 33 (47.8%) of 69 fatal cases of Hymenoptera anaphylaxis [13]. Upper airway angioedema was present at autopsy in four (57.1%) of seven cases of food-induced anaphylaxis [14]. In a series of 56 deaths from anaphylaxis in which the death occurred within an hour in 39 cases, pharyngeal/laryngeal edema was described in 23 (41%) cases [15]. "Cutaneous erythema/urticaria" was noted in just three cases.

Most patients who experience anaphylaxis survive the episode. While acute urticaria and urticaria with angioedema occur in some 90% of cases [3], the angioedema may be of the lip or on the face or extremities instead of the pharynx, larynx, or tongue. However, the findings in fatal cases of anaphylaxis appear to be quite entirely different. Angioedema of the upper airway can be the mechanism of death, and urticaria may be infrequent. It remains unclear why when there is mast cell activation during anaphylaxis, the shock organ is the upper airway as opposed to the lower airway or vasculature. In episodes of nonfatal idiopathic anaphylaxis, urinary histamine has been found to be elevated acutely in both patients who had experienced episodes of IA-G or IA-A [16].

IgE-mediated angioedema

Penicillin

Penicillin is degraded (transformed) into the major determinate, penicilloyl-polylysine, and three minor determinants from the selections of penicillin G, sodium benzylpenicilloate, benzylpenicilloyl-n-propylamine, penicilloate, or penilloate, which can react with albumin or IgG and form immunogenic haptens. Angioedema can occur alone or as part of penicillin-induced anaphylaxis. Skin testing with the major and three minor determinants can help identify anti-penicillin IgE antibodies or, more often, exclude their presence. The positive predictive value of a history of penicillin allergy for being associated with current immunologic sensitization is approximately 11% to 18% [7,17–19] although the literature ranges from 1% to 76% [20,21]. Thus, on average, for every seven patients with a history of penicillin allergy, just one patient would be found to be skin test positive to penicillin determinants. The skin tests assist the allergist-immunologist in determining the current immunologic status in terms of administration of penicillin or other beta-lactam antibiotics. The negative predictive value of skin testing with the major and three minor determinants is from 98%

to 99% [16,18]. Seventeen percent of patients with a history of penicillin-induced urticaria or angioedema have been reported to be positive on skin testing with the major determinant, penicilloyl-polylysine and penicillin G [22]. This finding is from a study where, if a patient had experienced anaphylaxis, some 46% of patients were skin test positive compared with 7% for a history of a maculopapular rash [22].

As of October 2004, the penicilloyl-polylysine commercial product (Pre-Pen: Holister Stier, Spokane, WA) has not been made available [23]. Because from 34% to 82% of patients who are skin test positive during penicillin testing will react to penicilloyl-polylysine alone, the absence of this test reagent greatly reduces the negative predictive value of skin testing [23]. If the figure of 60% of penicillin skin test positive patients being reactive exclusively to the penicilloyl-polylysine is used, then the predictive value from negative skin tests is reduced from 99% to about 40%. Thus, the results of negative skin testing for penicillin has much less value in terms of excluding current penicillin sensitization. What if one has no penicilloyl-polylysine or minor determinants? Then, the physician is even less able to determine the immunologic sensitization at the time of the consultation. Fortunately, from 78% to 89% of patients with a history of penicillin allergy will be skin test negative to major and minor determinants, and these patients should tolerate administration of a beta lactam antibiotic without anaphylaxis. However, one would not be able to identify and presumably prevent the serious and potentially fatal anaphylactic reaction. Indeed, the previous history of anaphylaxis has been associated with as high as 46% skin test reactivity to penicilloyl-polylysine and penicillin G [22]. Cautious test-dosing can help avoid or minimize the anaphylactic reaction as compared with bolus administration [19,23,24]. Challenges should be performed when the indication is truly essential or very strongly indicated. An example of a test-dosing procedure is as follows:

1. Amoxicillin is essential or strongly indicated
2. Emergency therapy available
3. Patient exam is stable: vital signs, respiratory status, skin, (spirometry at baseline and FEV1 is at least 70%)
4. Amoxicillin (125 mg/5 mL) administered every 30 minutes if no signs/symptoms occur with final observation for 60 to 90 minutes
 - a. 0.1 mL (2.5 mg)
 - b. 0.5 mL (12.5 mg)
 - c. 1.0 mL (25 mg)
 - d. 3.4 mL (85 mg)
 - e. 5.0 mL (125 mg)

A template to use during a challenge is shown in Fig. 1. For some patients, the starting dose would be lower such as with 0.1 mg followed by 1 mg, doses that would be unlikely to activate mast cells.

Medication_____

Target dose_____

<u>Time</u>	<u>Dose</u>	<u>BP</u>	<u>Pulse</u>	<u>Skin</u>	<u>Chest</u>	<u>FEV₁</u> *	<u>Symptoms</u>

* Respiratory status should be stable with FEV₁ of 70%; in occasional patients, a somewhat lower FEV₁ could be acceptable depending on the indication for the challenge. A physician should be present.

Fig. 1. Example of a template for a medication challenge.

Cephalosporins

Cephalosporins share the beta lactam nucleus with penicillins, yet are less likely to induce anaphylaxis [25]. There is either cross-reactivity with penicillin or independent sensitization such that penicillin-allergic patients react to cephalosporins with greater frequency than do patients who are not allergic to penicillin. Specifically, the risk of an immediate reaction with first generation cephalosporins in penicillin allergic patients has been reported to be from 5% to 16.5%, whereas for second generation cephalosporins, it is 4% (cefazolin) [23,24]. For the third and fourth generation cephalosporins, the reaction rate is 1% to 3% [23–25]. If the skin tests to the major and minor penicillin determinants are negative, cephalosporins can be administered with a great deal of safety [24,26]. However, in the absence of any skin tests for penicillin determinants, cephalosporin administration may result in anaphylaxis. Thus, the indication for the cephalosporin should be clarified, and the administration should be performed with care such as in the example in the previous section and Fig. 1. In a study of 19 penicillin allergic patients, 2 (10.5%) of 19 developed anaphylaxis from cephmandole [27]. Both patients were skin test positive to penicillin G and first received 20 mg cephmandole subcutaneously. One patient experienced “transitory hypotension, dysphonia, generalized pruritus, and upper airway breathing difficulties” [25].

The other patient tolerated the 20 mg cephmandole but next received 500 mg intramuscularly. Circulatory collapse occurred. Therefore, although most penicillin allergic patients will tolerate a cephalosporin uneventfully, and would tolerate a beta lactam antibiotic uneventfully as well, the patients who are skin test positive are at much higher risk of a severe or very severe anaphylactic reaction. Thus, caution is advised. In the absence of skin-testing reagents, the necessity of the cephalosporin should be verified. If a challenge is required, then a step-wise approach should be undertaken. The place of cephalosporin skin tests remains to be established, but experience from 101 patients is of note [28]. No patient experienced anaphylaxis if the parent cephalosporin skin test (2 mg/mL) was negative using a challenge beginning with 0.01, 0.1, and full doses. More data are needed to verify the results of negative skin testing with the parent cephalosporin.

Non-IgE-mediated angioedema

Sulfonamides

Nearly all reported allergic type reactions to sulfonamides do not mention angioedema as a primary reaction. Some evidence has been provided for the presence of antisulfamethoxazole IgE antibodies from patients who had experienced acute urticarial reactions from either sulfamethoxazole or sulfamethoxazole-trimethoprim [29]. However, because of the complexities of these investigations and the observation that most hypersensitivity to sulfonamides does not include urticaria, anaphylaxis, or angioedema, sulfonamides are presented under non-IgE mediated angioedema. Anaphylaxis has been reported in patients who have received sulfamethoxazole-trimethoprim [30,31] or trimethoprim [32]. Sulfonamide antibiotics are structurally different from nonantibiotics (furosemide, acetazolamide, celecoxib, and sulfonylureas), and the presence of a history of sulfonamide allergy does not appear to increase the risk of an allergic-type reaction from a non-antibiotic sulfonamide [23,30,31,33].

Sulfonamide therapy in patients with HIV/AIDS is associated with a greatly increased incidence of allergic-type reactions such as morbilliform rashes [23,34,35]. The administration of sulfamethoxazole-trimethoprim for *Pneumocystis carinii* pneumonia prophylaxis and treatment is used despite highly effective antiretroviral therapy. The incidence of morbilliform rash, cytopenias, or renal or hepatic impairment ranges from 44% to 100% and typically has its onset after a week of treatment [34]. A number of potential mechanisms for allergic and idiosyncratic reactions to sulfonamides have been suggested including (1) haptenation of cell surface proteins by hydroxylamine and nitroso (oxidative) metabolites of sulfamethoxazole, (2) generation of Th1 cytokines, (3) necrotic as opposed to apoptotic cell death pathways in which necrosis causes T-cell activation and apoptosis does not, (4) reduced levels of the antioxidant, glutathione, leading to

insufficient detoxification of the nitroso metabolites, and (5) slow acetylation of caffeine phenotype, which results in increased presence of the oxidative metabolites [23,34]. Alternatively, the prophylactic administration of N-acetylcysteine, which increases glutathione intracellularly, has not been shown to reduce the incidence of adverse reactions in patients [36,37]. Despite prophylactic administration of N-acetylcysteine, in the hopes of detoxifying the reactive metabolites, 20 of 96 patients receiving trimethoprim/sulfamethoxazole (80 mg/400 mg twice daily) with N-acetylcysteine (3 g twice daily) had to discontinue the antibiotics within 2 months compared with 25 of 102 patients just receiving sulfamethoxazole/trimethoprim [36]. The median time to discontinuation of the antibiotics was 13 and 14 days, and the rashes lasted about 5 days [36].

Test-dosing protocols have been suggested [24]. A history of Stevens-Johnson syndrome or toxic epidermal necrolysis is considered a contraindication to test dosing. In some cases, a report of cytopenia (or Stevens-Johnson syndrome) from a sulfonamide may have been erroneous, and a test-challenge may be indicated. Frequent evaluation and laboratory testing would be indicated to monitor the patient if there are no alternative treatments available. If a patient requires sulfamethoxazole/trimethoprim and has a history of anaphylaxis or massive angioedema attributable to sulfamethoxazole/trimethoprim, any challenge would have to be attempted after verification of the essential indication for the antibiotics. Verbal consent would be needed. The challenge would be conducted in a supervised setting with emergency therapy available as shown in Fig. 1. If there is a medical urgency, one approach would be to administer trimethoprim/sulfamethoxazole at 0.8, 7.2, 40, 80, 400, 680 mg (sulfamethoxazole) every 20 to 30 minutes [24]. Alternatively, a 4-day test-challenge would begin with 0.01 of the dose on day 1, 0.10 of the dose on day 2, 0.33 of the dose on day 3, and a full dose on day 4 [24]. Slower challenges may be indicated for some patients.

Aspirin and nonsteroidal anti-inflammatory drugs

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) can induce acute severe bronchoconstriction (asthma), severe oropharyngeal or laryngeal angioedema, urticaria, shock, or acute nasal congestion and rhinorrhea. In a large study of patients referred for drug hypersensitivity and in which provocation challenges were performed to confirm or refute the diagnosis, 94 (47.2%) of 199 patients had a positive aspirin challenge [38]. NSAID challenges were positive in 44 (27.3%) of 161 patients [38]. Exact details of the prior or provocation-challenge reactions were not provided, but challenges consisted of aspirin at 1, 10, 20, 50, 100, 200 and 500 mg. Aspirin and NSAIDs may cause acute urticaria/angioedema in 21% to 33% of patients with chronic idiopathic urticaria [24,39,40]. Other patients will have acute urticaria/angiodema or anaphylaxis attributable to a single NSAID for example [39,41]. Convincing proof of IgE antibodies participating in such

reactions has yet to be shown. Patients who experience acute urticaria or angioedema from aspirin or NSAIDs develop reactions within 3 (or possibly 4) hours in nearly all cases. Aspirin and nonselective NSAIDs inhibit cyclooxygenase-1 (and cyclooxygenase-2) enzymes which is the characteristic of the medications that induce these immediate reactions. Medications that are tolerated include cyclooxygenase-2 inhibitors (celecoxib, refecoxib, valdecoxib), and drugs that are very weak inhibitors of cyclooxygenase-1 such as acetaminophen (paracetamol), salsalate, and trisalicylate. Patients who have experienced acute urticaria or angioedema from cyclooxygenase-1 inhibitors can tolerate cyclooxygenase-2 inhibitors in almost all cases [23,24,41]. These patients can receive the first dose of the cyclooxygenase-2 either unsupervised or if there is significant anxiety, in the office. The full dose can be administered.

When aspirin or a cyclooxygenase-1 inhibitor is indicated and the patient has had a previous episode of acute urticaria or angioedema from either aspirin or a cyclooxygenase-1 inhibitor, alternative agents should be tried. However, often, the patient's disease (rheumatoid or osteoarthritis) has not responded to acetaminophen for example. With documentation that a cyclooxygenase-1 inhibitor is indicated, the patient can undergo a test-challenge with aspirin or ibuprofen (Table 1). These challenges can be performed in the office. If a patient has aspirin-exacerbated respiratory disease, it is important that the challenge be performed when the respiratory status is stable and the FEV1 is at least 70%. Use of Fig. 1 is advised. If the patient has experienced a single episode of ibuprofen-induced angioedema and if aspirin is indicated for coronary artery disease, a challenge could be performed with an initial target dose of 81 mg. It is possible that the patient has had a single episode of angioedema or anaphylaxis from another NSAID and could tolerate ibuprofen. Nevertheless, a challenge is advisable, in case the patient has class reactivity to cyclooxygenase-1 inhibitors. It is the author's opinion that the initial doses in Table 1 (aspirin 1 mg and ibuprofen 10 mg) serve as placebos. Thus, if within 5 minutes, there are symptoms or signs such as acute wheezing dyspnea, stridorous sounds, lightheadedness, or extreme anxiety, without associated evidence of airway obstruction or

Table 1
Examples of test-challenges with aspirin and ibuprofen^a

Aspirin (dilute 81 mg tablet in water)	Ibuprofen (100 mg/5mL)
Target dose = 81 mg	Target dose = 200 mg
1 mg	10 mg (0.5 mL)
10 mg	20 mg (1.0 mL)
30 mg	40 mg (2.0 mL)
41 mg	80 mg (4.0 mL)
	50 mg (2.5 mL)

^a The indication should be clearly documented. The patient should be observed for evidence of urticaria, angioedema, or respiratory distress. Challenges can be performed every 30 minutes in the absence of evidence of hypersensitivity.

hypotension, the patient most likely will be experiencing a panic attack and not an anaphylactoid episode. Epinephrine would not be indicated. Continued test-challenges would not be performed on that day because of the high level of anxiety. When the indication is very strong, an even faster paced challenge protocol has been described for patients with a history of aspirin or NSAID-induced urticaria or angioedema [42]. Patients were pretreated with an antihistamine (10 patients) and received a challenge as follows 0.1 mg, 0.3 mg, 1.0 mg, 3.0 mg, 10 mg, 30 mg, 40 mg, 81 mg, 162 mg, 325 mg [42]. Aspirin was administered every 10 to 30 minutes. Nine of 11 patients were able to receive aspirin without reaction [42].

Celecoxib and cyclooxygenase-2 inhibitors

The cyclooxygenase-2 inhibitors are remarkably well tolerated in patients who have aspirin-exacerbated respiratory disease (aspirin-induced asthma and aspirin triad) [24,39,41]. They also are an appropriate alternative for patients who have experienced aspirin or nonselective NSAID-induced urticaria or angioedema [23,41]. Very infrequent reports of anaphylaxis with urticaria and facial and tongue angioedema have been reported from cyclooxygenase-2 inhibitors [43]. The patient described initially had ingested a 200-mg celecoxib tablet; a repeat challenge resulted in anaphylactic shock again with a cumulative dose of 36 mg [43]. The patient subsequently tolerated rofecoxib. Thus, although rare, anaphylactic episodes can occur and physicians and their office staff should review their emergency preparedness periodically.

Acetaminophen

Extremely rare reports of acetaminophen hypersensitivity have been published [44,45]. However, acetaminophen is an appropriate alternative for aspirin or a nonselective NSAIDs for patients with aspirin or NSAID-induced urticaria or angioedema (or aspirin-exacerbated respiratory disease).

Physical urticaria

Exercise-induced anaphylaxis, a physical urticaria, is often accompanied by angioedema as well as urticaria. Exercise-induced anaphylaxis can be food-dependent and also may be associated with concurrent exposure to exercise and NSAIDs. Cold urticaria is another physical urticaria that is often accompanied by angioedema.

Immunomodulators

There are many immunomodulators, and their indications are growing. Cytokines, anti-cytokines, monoclonal antibodies, and immunosuppressive medications have provided new approaches to treatment. Adverse reactions may be profound such as the “cytokine storm” from an anti-CD28 antibody

that was designed to increase the numbers of T cells and activate CD4+ CD25+ T reg cells [46]. The concentrations of tumor necrosis factor alpha (TNF α), interferon gamma (IFN- γ), interleukin (IL)-2, IL-4, IL-6, and IL-10 increased by over 2000 times in association with fever, flushing, diarrhea, hypotension, bilateral pulmonary infiltrates, and respiratory failure [46]. Aternatively, omalizumab, the anti-IgE antibody that is indicated for persistent asthma, has been associated with four immediate type reactions from more than 20,000 patients who have been treated [47]. Reactions occurred from 75 to 120 minutes after subcutaneous injection, and all patients received epinephrine. Two of the 4 patients experienced anaphylactoid reactions including one patient with throat and tongue swelling [47]. Examples of selected anaphylactic/pseudoallergic, adverse, or other immunologic reactions from immunomodulators are presented in Table 2. While there may be first-dose reactions such as the toxic “cytokine storm” from the “superagonist” anti-CD28 antibody, often there is a reaction after several uneventful administrations. This pattern suggests immunologic sensitization or idiosyncrasy.

Diagnostic contrast agents

Radiographic contrast material

Anaphylactoid reactions secondary to radiographic contrast media include angioedema, which is classified as mild laryngeal edema (moderate reaction) or severe laryngeal edema (severe reaction) [53]. Radiographic

Table 2
Examples of immunologic, anaphylactic/pseudoallergic and other reactions to immunomodulators

Therapeutic agent	Reaction
Anti-CD28 antibody	Acute respiratory failure, pulmonary infiltrates, shock; nearly fatal “cytokine storm”
Omalizumab	Anaphylaxis (75–120 minutes after subcutaneous injection) in about 1 of 5000 patients
Natalizumab	Anaphylaxis; progressive multifocal leukoencephalopathy
Infliximab, adalimumab, etanercept	Reversible SLE; anti-ds DNA antibodies
Interferon α	Acute urticaria, angioedema; anti-thyroid antibodies; SLE, diabetes mellitus, vasculitis
Rituximab, alemtuzumab	Acute urticaria, hypotension, dyspnea, rigors
Sirolimus	Angioedema; bronchiolitis obliterans organizing pneumonia; lymphocytic alveolitis
Cyclosporine	Anaphylaxis/pseudoallergic reactions
Mycophenolate	Anaphylaxis/pseudoallergic reactions
Thalidomide	Stevens-Johnson syndrome, toxic epidermal necrolysis, various rashes

Abbreviation: SLE, systemic lupus erythematosus.
Data from references [23,46–52].

contrast materials are typically tri-iodinated benzene ring compounds that are clear; thus they should not be referred to as dyes. High osmolality contrast media have osmolality from approximately 500 to 1400 mOsm/kg H₂O. Lower osmolality contrast media may have osmolality as low as 290 to 322 mOsm/kg H₂O. Lower osmolality contrast media may be nonionic or ionic. Anaphylactoid (pseudoallergic) reactions occur almost immediately to 30 minutes after intravenous administration of contrast material [53–55]. Life-threatening reactions, many of which involve cardiovascular collapse, occur within the first 20 minutes after injection of contrast media [53]. There continues to be an inadequate understanding of the pathogenesis of the anaphylactoid (pseudoallergic) reactions; there is no doubt that histamine is detected as a marker of mast cell mediator release. Various discussions of the potential pathogenic mechanisms are available [53,55]. Severe life-threatening reactions to contrast media are reduced when lower osmolality contrast materials are used compared with higher osmolality agents (0.04% versus 0.22%) [56]. Nevertheless, fatalities occur with about the same frequency (0.8 to 0.9/100,000 infusions) [57,58].

Pretreatment regimens have been published with associated low rates of repeated pseudoallergic reactions in patients who have experienced prior pseudoallergic reactions [54]. The recommended pretreatment regimen is as follows:

1. Document the essential or very strong indication for the procedure
2. Use a lower osmolality contrast medium
3. Have emergency therapy available
4. Pretreat with Prednisone 50 mg at –13 hours, –7 hours and –1 hour before the procedure
 - Diphenhydramine 50 mg at –1 hour (can be oral or intravenous)
 - Albuterol 4 mg at –1 hour orally is optional

With such pretreatment, only 0.5% of patients had repeated reactions. [54] There has been concern as to whether pretreatment should be recommended for patients who have had previous pseudoallergic reactions [59]. The argument appears to be based on the absence of controlled, randomized, placebo-controlled trials. Nevertheless, based on historical rates of reactions, pretreatment should be administered. Indeed, using high osmolality contrast media in patients who previously had experienced pseudoallergic reactions, the reaction rate was reduced from 17% to 60% to less than 10% with pretreatment [60]. The administration of lower osmolality contrast media to such patients reduced the repeated reaction rate to 4.0% to 5.5% and with pretreatment and use of lower osmolality contrast media, the repeat reaction rate was reduced to 0.5% [54,60].

Fatalities may occur albeit very rarely [61,62]. Thus, physicians performing such studies do need to review their emergency preparedness periodically. Pseudoallergic reactions can occur from orally administered contrast

media and induce life-threatening upper airway edema [63]. Fortunately, such reactions are extremely rare.

Gadolinium

Magnetic resonance contrast media uses gadolinium-based chelates. Infrequent severe pseudoallergic reactions occur [64]. In a series of 9528 magnetic resonance imaging infusions, 45 (0.48%) patients experienced some adverse reaction. There was 1 case of anaphylactic shock (1:9528) and 15 cases of rash or urticaria. Patients who report a previous pseudoallergic reaction to gadolinium chelates appear to be at greater risk of repeated reactions [64,65]. Pretreatment of such patients and use of different gadolinium chelates are advised for essential procedures. Nevertheless, additional data are needed to confirm the efficacy of this approach.

Fluorescein

Fluorescein sodium dye is injected intravenously and can cause hypotensive shock with elevation of serum tryptase [66]. Because patients may have diabetes mellitus and coronary artery disease, an episode of shock may create a life-threatening emergency. It is not clear that any pretreatment will be successful for such patients, but this author recommends the radiographic contrast material pretreatment for such patients. The procedures should be performed only if necessary with emergency therapy available.

Summary

Anaphylactic and anaphylactoid (pseudoallergic) reactions can be expected to occur with greater frequency as the number of immunomodulators are employed. The immune system will become sensitized to these new therapeutic agents or there may be first-dose reactions depending on the pathogenetic mechanism involved. Physicians should review their office or procedure room emergency preparedness protocols and medications. The lack of penicillin major and minor determinants for penicillin testing has made management of penicillin and cephalosporin allergic patients more complicated. In the absence of skin-testing materials, test-challenges will be necessary and performed with less comfort because of not knowing the current level of immunologic sensitization to penicillin. The indication for readministration of any incriminated medication/therapeutic agent should be reviewed. Often, there are not suitable alternatives. Various approaches have been presented to permit safer readministration of essential medications or diagnostic agents to prevent episodes of anaphylaxis or upper airway angioedema.

References

- [1] Sampson HA, Munoz-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):391–7.
- [2] Lieberman P, Kemp SF, Oppenheimer J, et al. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;115(3):S483–523.
- [3] Simons FER. Anaphylaxis, killer allergy: long-term management in the community. *J Allergy Clin Immunol* 2006;117(2):367–77.
- [4] Wong BBL, Keith PK, Waserman S. Clinical history as a predictor of penicillin skin test outcome. *Ann Allergy Asthma Immunol* 2006;97(2):169–74.
- [5] Macy E, Richter PK, Falkoff R, et al. Skin testing with penicilloate and penilloate prepared by an improved method: amoxicillin oral challenge in patients with negative skin test responses to penicillin reagents. *J Allergy Clin Immunol* 1997;100(5):586–91.
- [6] Romano A, Viola M, Gueant-Rodriquez R-M, et al. Imipenem in patients with immediate hypersensitivity to penicillins. *N Engl J Med* 2006;354(26):2835–7.
- [7] Brown AFT, McKinnon D, Chu K. Emergency department anaphylaxis: a review of 142 patients in a single year. *J Allergy Clin Immunol* 2001;108(5):861–6.
- [8] Thong BY, Cheng YK, Leong KP, et al. Anaphylaxis in adults referred to a clinical immunology/allergy center in Singapore. *Singapore Med J* 2005;46(10):529–34.
- [9] Ditto AM, Harris KE, Krasnick J, et al. Idiopathic anaphylaxis: a series of 335 cases. *Ann Allergy Asthma Immunol* 1996;77(4):285–91.
- [10] Delage C, Irey NS. Anaphylactic deaths: a clinicopathologic study of 43 cases. *J Forensic Sci* 1972;17:525–40.
- [11] James LP, Austen KF. Fatal systemic anaphylaxis in man. *N Engl J Med* 1964;270(12):597–603.
- [12] Krasnick J, Patterson R, Meyers GL. A fatality from idiopathic anaphylaxis. *Ann Allergy Asthma Immunol* 1996;76(4):376–8.
- [13] Barnard JH. Studies of 400 Hymenoptera sting deaths in the United States. *J Allergy Clin Immunol* 1973;52(5):259–64.
- [14] Yunginger JW, Sweeney KG, Sturmer WQ, et al. Fatal food-induced anaphylaxis. *JAMA* 1988;260(10):1450–2.
- [15] Pumphrey RSH, Roberts ISD. Postmortem findings after fatal anaphylactic reactions. *J Clin Pathol* 2000;53:273–6.
- [16] Greenberger PA, Miller MM. Urine histamine during episodes of anaphylaxis [abstract]. *J Allergy Clin Immunol* 1994;93:302.
- [17] Salkind AR, Cuddy PC, Foxworth JW. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA* 2001;285(19):2498–505.
- [18] Warrington RJ, Simons FER, Ho WH, et al. Diagnosis of penicillin allergy by skin testing: the Manitoba experience. *CMAJ* 1978;118:787–91.
- [19] Sogn DD, Evans R III, Shepherd GM, et al. Results of the National Institute of Allergy and Infectious Diseases collaborative clinical trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. *Arch Intern Med* 1992;152:1025–32.
- [20] Solensky R, Earl HS, Gruchalla RS. Penicillin allergy: prevalence of vague history in skin test-positive patients. *Ann Allergy Asthma Immunol* 2000;85(3):195–9.
- [21] Arroliga ME, Radojicic C, Gordon SM, et al. A prospective observational study of the effect of penicillin skin testing on antibiotic use in the intensive care unit. *Infect Control Hosp Epidemiol* 2003;24(5):347–50.
- [22] Green GR, Rosenblum AH, Sweet LC. Evaluation of penicillin hypersensitivity: value of clinical history and skin testing with penicilloyl-polylysine and penicillin G: a cooperative study of the penicillin study group of the American Academy of Allergy. *J Allergy Clin Immunol* 1977;60(6):339–45.

- [23] Greenberger PA. Drug allergy. *J Allergy Clin Immunol* 2006;117(2):S464–70.
- [24] Grammer LC, Greenberger PA. Drug allergy and protocols for management of drug allergies. 3rd edition. Providence (RI): Oceanside Pubs; 2003. p. 1–42.
- [25] Kelkar PS, Li JT-C. Cephalosporin allergy. *N Engl J Med* 2001;345(11):804–9.
- [26] Greenberger PA. Utility of penicillin major and minor determinants for identification of allergic reactions to cephalosporins. *J Allergy Clin Immunol* 2005;115(2):S182.
- [27] Blanca M, Fernandez J, Miranda A, et al. Cross-reactivity between penicillins and cephalosporins: clinical and immunologic studies. *J Allergy Clin Immunol* 1989;83(2):381–5.
- [28] Romano A, Guenant-Rodriguez R-M, Viola M, et al. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med* 2004;141:16–22.
- [29] Carrington DM, Earl HS, Sullivan TJ. Studies of human IgE to a sulfonamide determinant. *J Allergy Clin Immunol* 1987;79(3):442–7.
- [30] Strom BL, Schinnar R, Apter AJ, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med* 2003;349:1628–35.
- [31] Hemstreet BA, Page RL. Sulfonamide allergies and outcomes related to use of potentially cross-reactive drugs in hospitalized patients. *Pharmacotherapy* 2006;26(4):551–7.
- [32] Cabanas R, Caballero MT, Vega A, et al. Anaphylaxis to trimethoprim. *J Allergy Clin Immunol* 1996;97(1):137–8.
- [33] Lee AG, Anderson R, Kardon RH, et al. Presumed “sulfa allergy” in patients with intracranial hypertension treated with acetazolamide or furosemide: cross-reactivity, myth or reality? *Am J Ophthalmol* 2004;138(1):114–8.
- [34] Lin D, Tucker J, Rieder MJ. Increased adverse drug reactions to antimicrobials and anti-convulsants in patients with HIV infection. *Ann Pharmacother* 2006;40:1594–601.
- [35] Kalanadhabhatta V, Muppidi D, Sahni H, et al. Successful oral desensitization to trimethoprim-sulfamethoxazole in acquired immune deficiency syndrome. *Ann Allergy Asthma Immunol* 1996;77(5):394–400.
- [36] Walmsley SL, Khorasheh S, Singer J, et al. A randomized trial of N-acetylcysteine for prevention of trimethoprim-sulfamethoxazole hypersensitivity reactions in *Pneumocystis carinii* pneumonia prophylaxis. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;19(5):498–505.
- [37] Akerlund B, Tynell E, Bratt G, et al. N-acetylcysteine treatment and the risk of toxic reactions to trimethoprim-sulphamethoxazole in primary *Pneumocystis carinii* prophylaxis in HIV-infected patients. *J Infect* 1997;35(2):143–7.
- [38] Messaad D, Sahla H, Benahmed S, et al. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 2004;140(12):1001–4.
- [39] Gollapudi RR, Teirstein PS, Stevenson DD, et al. Aspirin sensitivity: implications for patients with coronary artery disease. *JAMA* 2004;292(29):3017–23.
- [40] Mathison DA, Lumry WR, Stevenson DD, et al. Aspirin in chronic urticaria and/or angioedema: studies of sensitivity and desensitization [abstract]. *J Allergy Clin Immunol* 1982;69:135.
- [41] Berges-Gimeno MP, Stevenson DD. Nonsteroidal anti-inflammatory drug-induced reactions and desensitization. *J Asthma* 2004;41(4):375–84.
- [42] Wong JT, Nagy CS, Krinzman SJ, et al. Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. *J Allergy Clin Immunol* 2000;105(5):997–1001.
- [43] Fontaine C, Bousquet PJ, Demoly P, et al. Anaphylactic shock caused by a selective allergy to celecoxib, with no allergy to rofecoxib or sulfamethoxazole. *J Allergy Clin Immunol* 2005;115(3):633–4.
- [44] Doan R, Greenberger PA. Nearly fatal episodes of hypotension, flushing, and dyspnea in a 47-year-old woman. *Ann Allergy Asthma Immunol* 1993;70(6):439–44.
- [45] Vidal C, Perez-Carral C, Gonzalez-Quintela A. Paracetamol (acetaminophen) hypersensitivity. *Ann Allergy Asthma Immunol* 1997;79(4):320–1.

- [46] Suntharalingam G, Perry MR, Ward S, et al. Cytokine storm in a phase 1 trial of the anti-CD2828 monoclonal antibody TGN1412. *N Engl J Med* 2006;355:1018–28.
- [47] Chipps B. Systemic reaction to omalizumab. *Ann Allergy Asthma Immunol* 2006;97(2):267.
- [48] Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354(9):899–910.
- [49] Champion L, Stern M, Israel-Biet D, et al. Brief communication: Sirolimus-associated pneumonitis: 24 cases in renal transplant patients. *Ann Intern Med* 2006;144(7):505–9.
- [50] Nikas SN, Voulgari PV, Drosos AA. Urticaria and angioedema-like skin reactions in a patient treated with adalimumab. *Clin Rheumatol* 2006;1–2 [epub ahead of print].
- [51] Krause K, Valesini G, Scrivo R, et al. Autoimmune aspects of cytokine and anticytokine therapies. *Am J Med* 2003;115:390–7.
- [52] Stallmach A, Giese T, Schmidt C, et al. Severe anaphylactic reaction to infliximab: successful treatment with adalimumab-report of a case. *Eur J Gastroenterol Hepatol* 2004;16(6):627–30.
- [53] American College of Radiology Committee on Drugs and Contrast Media. Manual on contrast media, version 5.0. Reston (VA): American College of Radiology; 2004. p. 5–77.
- [54] Greenberger PA, Patterson R. The prevention of immediate generalized reactions to radio-contrast media in high-risk patients. *J Allergy Clin Immunol* 1991;87(4):867–72.
- [55] Canter LM. Anaphylactoid reactions to radiocontrast media. *Allergy Asthma Proc* 2005;26(3):199–203.
- [56] Katayama H, Tamagucchi K, Kozuka T, et al. Adverse reactions to ionic and nonionic contrast media. *Radiology* 1990;175:621–8.
- [57] Caro JJ, Trindale E, McGregor M. The risk of death and of severe nonfatal reactions with high-versus-low-osmolality contrast media: a meta-analysis. *AJR Am J Roentgenol* 1991;156:825–32.
- [58] Cashman JD, McCredie J, Henry DA. Intravenous contrast media: Use and associated mortality. *Med J Aust* 1991;155:618–23.
- [59] Tramer MR, von Elm E, Loubeyre P, et al. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. *BMJ* 2006;31 [epub ahead of print].
- [60] Greenberger PA. Part B: Allergic reactions to individual drugs: low molecular weight. In: Grammer LC, Greenberger PA, editors. *Patterson's allergic diseases*. 6th edition. Philadelphia: Lippincott, Williams & Wilkins; 2002. p. 335–59.
- [61] Low I, Stables S. Anaphylactic deaths in Auckland, New Zealand: a review of coronial autopsies from 1985–2005. *Pathology* 2006;38(4):328–32.
- [62] Wysowski DK, Nourjah P. Deaths attributed to X-ray contrast media on US death certificates. *AJR Am J Roentgenol* 2006;186:613–5.
- [63] Seymour C, Pryor JP, Gupta R, et al. Anaphylactoid reaction to oral contrast for computed tomography. *J Trauma* 2004;57(5):1105–7.
- [64] Li A, Wong CS, Wong MK, et al. Acute adverse reactions to magnetic resonance contrast media-gadolinium chelates. *Br J Rad* 2006;79(5):368–71.
- [65] Nelson KL, Gifford LM, Lauber-Huber C, et al. Clinical safety of gadopentetate dimeglumine. *Radiology* 1995;2:439–43.
- [66] Tanahasi S, Iida H, Dohi S. An anaphylactoid reaction after administration of fluorescein sodium during neurosurgery. *Anesth Analg* 2006;102(2):503.