Allergic and hypersensitivity reactions in the intensive care unit

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Hypersensitivity reactions are defined as immunologically based adverse reactions to chemicals or medicinal agents. These reactions are common in the intensive care unit and can present as a simple, mildly symptomatic rash or as life-threatening anaphylactic reactions. Hypersensitivity reactions have traditionally been classified as types I to IV reactions based on the underlying immune mechanisms, although the clinical relevance of the classification is unclear, and new subtypes to this system have been recently proposed. Given the immunologic and often unpredictable nature of these reactions, avoidance or prevention is not a feasible option. Therefore, management has primarily consisted of withdrawal of potential offending agents, supportive therapy, symptomatic management, and, in some specific examples, targeted pharmacotherapy. This article outlines the background and types of hypersensitivity reactions and provides descriptions and management strategies when applicable to common types of hypersensitivity reactions encountered in the intensive care unit. (Crit Care Med 2010; 38[Suppl.]:S162–S168)

KEY WORDS: hypersensitivity; allergic reactions; drugs; anaphylaxis

An allergic or hypersensitivity reaction is an adverse effect attributed to an antigen that involves immunologic mechanisms. The causative antigen could be a drug, a biological, an environmental toxin, a chemical, or any other substance to which an exposed individual has a local or systemic reaction that is immunologically mediated. The most extreme form of a hypersensitivity reaction is anaphylaxis, in which an immunologic reaction to an allergen in a sensitized individual results in a life-threatening event typically involving the cutaneous, respiratory, cardiovascular, and gastrointestinal systems. Less severe forms of hypersensitivity and anaphylaxis are more common, with variable end-organ involvement. Epidemiologic studies that describe the prevalence or incidence of hypersensitivity reactions or anaphylaxis are lacking largely because of the lack of standardized definitions and subsequent lack of reporting or appropriate documentation (1, 2). In the general population, the incidence of anaphylaxis ranges from 10 to 20 per 100,000 people per year (1). Similarly, self-reported adverse drug reactions affect as many as 25% of all hospitalized patients, but immunologically mediated true allergic reactions account for <15% of all adverse drug reactions (3, 4). In the intensive care unit (ICU), hypersensitivity reactions are often difficult to diagnose because sedated and intubated patients may not be able to verbalize subjective symptoms. Furthermore, the nonspecific nature of objective findings may make it difficult to distinguish anaphylaxis or hypersensitivity reactions from other diagnoses. For example, in the sedated and intubated patient, anaphylaxis may be difficult to differentiate from septic shock if the primary clinical manifestation is hypotension. Even if the diagnosis of drug-induced hypersensitivity reaction is made in the ICU patient, identifying the causative agent can be a challenge given the number of potentially new medications that ICU patients receive. The purpose of this article is to review the pathophysiology, epidemiology, and management of hypersensitivity reactions from the perspective of the critically ill patient.

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The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e3181de0c99

Pathophysiology of hypersensitivity reactions

Hypersensitivity reactions can involve all major components of the immune system, including cellular elements, immunoglobulins (Ig), complement, and cytokines. Antigens interact with cellular elements or immunoglobulins to elicit the release of chemical mediators, which include vasoactive amines (i.e., histamine, proteases), inflammatory leukotrienes, prostaglandins, platelet-activating factor, and the complement system. These mediators then interact with end organs to induce the clinical symptoms of hypersensitivity or anaphylaxis.

Mediators of hypersensitivity reactions

Histamine is a low-molecular-weight amine compound stored in the granules of mast cells and basophils and is released in response to specific antigen exposure. When released, histamine can increase capillary permeability, induce bronchospasm and vasospasm, and induce hypersecretion of mucous glands. When released systemically, histamine acts within 1 to 2 mins but is rapidly metabolized within 15 mins. Leukotrienes are metabolites of arachidonic acid and also can induce bronchospasm and vasospasm. Leukotriene C4, D4, and E4 are commonly produced by mast cells and basophils. These leukotrienes are more potent than histamine and have a more delayed and sustained effect on smooth muscle. Prostaglandins and thromboxane, also metabolites of arachidonic acid, are produced by mast cells. Prostaglandin D2 is the primary prostaglandin produced by mast cells and is a potent bronchoconstrictor and inhibitor of platelet aggregation. Thromboxanes promote platelet aggregation and play an important role in hemostatic regulation. Platelet-activating factor is a potent bronchoconstrictor and promotes platelet aggregation and lysis. It is released by mast cells, alveolar mac-

Table 1. Common examples of drugs and hypersensitivity reactions

Angioedema	Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis	Acute Interstitial Nephritis
Angiotensin-converting enzyme inhibitors	Sulfonamides	Beta-lactam antibiotics
Cyclooxygenase-2 inhibitors	Nevirapine	Proton pump inhibitors
Nonsteroidal anti-inflammatory drugs	Lamotrigine	Cyclooxygenase-2 inhibitors
	Allopurinol	Nonsteroidal anti-inflammatory drugs
	Carbamazepine	Furosemide
	Phenytoin	

rophages, neutrophils, and platelets, but not basophils. Finally, the complement system comprises approximately 30 different proteins that are activated during some hypersensitivity reactions. Collectively, they promote opsonization of target cells, cell lysis, and trigger non-IgE-mediated activation of mast cells and subsequent release of inflammatory mediators.

Immunogenic potential

The immunogenic potential of an antigen often depends on its size. Low-molecular-weight antigens (i.e., <10,000 molecular weight) require binding to a carrier protein to be recognized as immunogenic. The greater the affinity for the antigen to bind to a carrier protein, the more potential it has for causing a hypersensitivity reaction (5). In the case of penicillin G (356 molecular weight), it binds to circulating serum proteins to form a hapten, which now has immunogenic potential. In the case of biological agents, the immunogenicity is dependent on the quantity and type of nonhuman material. For example, murine material is more immunogenic than chimeric material, which, in turn, is more immunogenic than human biological agents.

Classification of hypersensitivity reactions

Hypersensitivity reactions have been classified into one of four categories by Coombs and Gell based on the immunopathologic mechanism. These categories are type I, type II, type III, and type IV (6).

Type I: IgE-mediated hypersensitivity

Type I reactions are mediated by IgE. Typically, IgE specific to the antigen is produced on first exposure and is expressed on mast cells in the tissue and basophils in the blood. On repeated or secondary exposure, two or more IgE molecules on the surface of mast cells or basophils can bind to the specific antigen (referred to as *cross-linking*), causing cellular activation. Activation of the cell results in release of chemical mediators. A type I reaction manifests almost immediately (i.e., within 30 mins), may be limited to single organs, and present with laryngeal edema, bronchospasm, cutaneous reactions, or nausea and vomiting. Anaphylaxis is typically a systemic IgE-mediated type I life-threatening reaction involving multiple organs. Whereas anaphylactic reactions typically occur within minutes of exposure, delayed presentations of anaphylactic symptoms have been described (1–72 hrs).

Type II: Cytotoxic hypersensitivity

Type II reactions are mediated by IgG or IgM and result in the destruction of host cells, usually blood cells, by one of two mechanisms. In the first scenario, the antigen binds directly to the blood cell, most often an erythrocyte, leukocyte, or platelet, forming a hapten. Antibodies (usually IgG or IgM) specific for the hapten trigger a cytolytic reaction mediated by complement activation. Alternatively, target cell death can also be mediated by phagocytic cells, including neutrophils, monocytes, and macrophages that have antibody Fc (fragment, crystallizable) on their surface. Common drug causes of type II hypersensitivity reactions include methylene blue (hemolytic anemia) and heparin (thrombocytopenia).

Type III: Immune complex deposition

Type III reactions describe the creation of antigen–antibody complexes (also described as immune complexes) that can be deposited in tissues and small blood vessels causing a local inflammatory response. Clinical manifestations of a type III reaction may include serum sickness or vasculitis. Serum sickness caused by beta-lactams, quinidine-induced lupus erythematosus, and minocycline-induced vasculitis is considered a type III hypersensitivity reaction.

Type IV: T-cell–mediated hypersensitivity

Type IV reactions refer to T-cell–mediated ($CD4^+$ or $CD8^+$) hypersensitivity reactions. These reactions are typically delayed and have dermatologic manifestations. On exposure to the antigen, memory T cells specific for the antigen become activated and elicit an inflammatory response. Type IV reactions are also utilized for diagnostic purposes, most prominently in tuberculin skin tests in which purified protein derivative antigen from *Mycobacterium tuberculosis* can elicit a local reaction when injected intradermally. Recently, type IV reactions have been further subclassified into four different groups, IVa, IVb, IVc, and IVd, based on the type of T cells and effector cells (e.g., monocytes vs. eosinophils vs. neutrophils) involved in the reaction (7). However, each clinically relevant reaction may involve more than one type of effector cell; thus, the classification may not be mutually exclusive. The clinical utility of this new subclassification remains to be established.

Clinical manifestations of hypersensitivity reactions in the ICU

Anaphylactic reactions

According to the National Institute of Allergy and Infectious Diseases, anaphylaxis is defined as a serious IgE-mediated allergic reaction that is rapid in onset, involves multiple organs systems, and may cause death (1, 2). Manifestations of anaphylaxis may include urticaria, bronchospasm, laryngospasm, hypotension, angioedema, nausea, and vomiting in any combination. Hypotension associated with anaphylaxis is generally considered a type of distributive shock and is often referred to as *anaphylactic shock*. Inflammatory mediators, including histamine, contribute directly to vasodilation and increased vascular permeability, re-

sulting in reduced tone and intravascular volume depletion. Anaphylactic reactions often occur with 30 mins of allergen exposure and rarely occur beyond 2 hrs. The risk of death is greatest within the first few hours, especially in the absence of seeking rapid medical attention. Death is usually the result of asphyxiation from airway obstruction and collapse.

The diagnostic challenge in the ICU is that many of the signs and symptoms of anaphylaxis are not uncommon among critically ill patients. Often the only diagnostic clue is a rash as part of this general constellation of symptoms. However, allergic reactions presenting without cutaneous symptoms in ventilated and sedated patients may mimic other diagnoses, like septic shock. Clinicians in the ICU should exercise vigilance when initiating first exposures of new medications in ICU patients. Common antigens that can cause anaphylaxis include medications, biologics, vaccines, anesthetics, insect bites/stings, envenomation, latex, and even exercise. Food, however, is the single most common cause of anaphylaxis in the United States. In hospitalized patients, drug-induced anaphylaxis accounts for 6% of all adverse drug reactions (3).

Anaphylactic reactions are differentiated from anaphylactoid reactions on the basis of immunologic mechanism. Anaphylactic reactions are typically IgE-mediated, whereas anaphylactoid reactions result from non-IgE-mediated release of mediators from mast cells and basophils; however, the signs, symptoms, and treatment of the two are the same, making this distinction not clinically useful and unnecessary.

Dermatologic reactions

Cutaneous reactions are the most common manifestation of hypersensitivity reactions, with most reactions being mild and self-limiting on discontinuation of antigen exposure. Some dermatologic reactions may, however, progress to more serious and potentially life-threatening reactions, such as toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS) (8). Both of these syndromes involve epidermal sloughing with mucocutaneous involvement. SJS usually involves $<$10% of body surface area, and mortality rates range from 1% to 3%. TEN often presents as a more severe syndrome than SJS, frequently involving $>$30% of the body surface area, and it almost always involves the mucosa. Mortality rates for TEN are greater than those for SJS and are in the range of 30% to 50%. Differentiation between these two syndromes is difficult, both clinically and pathologically. Most use a clinical definition based on the degree of body surface area affected. If $>$30% of the body surface area is affected, then TEN is considered the most likely diagnosis. Infectious causes of exfoliating disorders are easier to differentiate from immunologic reactions pathologically with biopsy. The exact pathogenesis of these life-threatening dermatologic reactions is unclear but is thought to be T-cell–mediated and characterized by keratinocyte apoptosis, resulting in sloughing of the epidermis from the dermis. The onset of TEN or SJS is usually delayed by days to weeks after drug exposure and may be preceded by a prodrome of fever, sore throat, and malaise. This is often followed by an acute macular rash and, finally, necrosis of skin and mucous membranes. Many patients with TEN have some ocular involvement, and half of those who survive will have long-term ocular complications. The Score for the Evaluation of Toxic Epidermal Necrolysis is a validated predictor of mortality in patients with TEN. The score consists of seven items of the patient's clinical status (demographic, laboratory, and body surface area involved), with one point assigned to each item. Score for the Evaluation of Toxic Epidermal Necrolysis should be performed on days 1 and 3 of admission, with the scores being correlated to mortality (e.g., 0–1 point = 3.2%; 2 points = 12.1%; 3 points = 35.3%; 4 points = 58.3%; $\geq$5 = 90%) (9).

Respiratory reactions

Whereas immune-mediated respiratory symptoms are often considered in the setting of systemic hypersensitivity reactions such as anaphylaxis, they also can occur alone. Acute asthmatic reactions and rhinitis have been described with various drugs (aspirin, nonsteroidal anti-inflammatory drugs), food additives (i.e., sulfites), and environmental allergens. Less common manifestations of lung toxicity include bleomycin-induced chronic fibrotic pulmonary reactions.

Serum sickness

Serum sickness is a clinical syndrome often described as a result of circulating antigen–antibody (immune) complexes that form in the setting of antigen excess. Historically, serum sickness was first described as an illness that occurred in patients after administration of horse serum for the treatment of diphtheria and scarlet fever. Serum sickness is the prototypical type III hypersensitivity reaction with excessive immune complex formation and deposition into tissues resulting in activation of the complement cascade. The syndrome is characterized by rash, fever, and arthralgias and is associated with a good prognosis on withdrawal of the offending agent. A variety of drugs, including beta-lactam and sulfonamide antibiotics, have been implicated in causing serum sickness-like reactions. The onset usually occurs 1 to 2 wks after initial antigen exposure, and the onset may be more rapid on repeat exposure.

Hypersensitivity vasculitis

Hypersensitivity vasculitis, like serum sickness, is thought to be attributable to deposition of immune complexes in the microvasculature of skin and, less frequently, in other end organs. Clinical findings include skin lesions, palpable purpura, fever, arthralgia, urticaria, lymphadenopathy, and an elevated erythrocyte sedimentation rate. This systemic reaction is often delayed (i.e., 1–2 wks) as immune complexes accumulate. Vasculitis may also involve other visceral organs, such as the kidneys, lungs, and liver, as well as joints and the central nervous system. Although rare, the clinical manifestations can be severe, because glomerulonephritis, interstitial nephritis, and various degrees of hepatocellular injury have been reported. Drugs that have been associated with vasculitis include allopurinol, beta-lactam antibiotics, sulfonamides, thiazide diuretics, and phenytoin.

Angioedema

Angioedema, defined as swelling of the mucosa or submucosa involving the larynx or the pharynx, may also involve swelling of other mucosal tissues in the face, gastrointestinal tract, lower extremities, and genitals. Angioedema may be a result of allergic or nonallergic reactions, with the latter induced by bradykinin. This life-threatening reaction can be hereditary (i.e., C1 esterase inhibitor deficiency) or antigen-induced. Common drugs that increase bradykinin activity include angiotensin-converting enzyme

(ACE) inhibitors. Drug-induced angioedema is an IgE-mediated type I hypersensitivity reaction that begins soon after administration of the offending agent. The incidence of angioedema attributed to ACE inhibitors in the general population is approximately 0.1% to 0.7% and is more common in blacks. Most episodes of angioedema occur within the first week of starting an ACE inhibitor, but the onset can be delayed by months or even longer than 1 yr. Differentiating between allergic and nonallergic angioedema in the clinical setting is not always practical or necessary because the management of both are similar. Airway protection is the prime concern for angioedema and tracheostomy may be required. Epinephrine, either intravenously or aerosolized via the endotracheal tube, may alleviate the edema. Symptomatic relief with corticosteroids and/or antihistamine has been described, but they do not prevent the attack given the underlying mechanism. Withdrawal of the offending agent is obviously part of the treatment; however, this creates a new problem given that drugs such as ACE inhibitors are widely prescribed for a multitude of cardiovascular diseases treatment and/or prevention because of their demonstrated mortality benefits. In the past, substitution with an angiotensin receptor-blocking agent was considered contraindicated because of presumed high incidence of cross-reactivity. However, a recent case series (10) has questioned the validity of such assumptions. In this series, 26 of 54 patients who were available for follow-up after ACE inhibitor-induced angioedema were switched to therapy with an angiotensin receptor-blocking agent. Only two of the 26 patients had angioedema with the new agent after a median follow-up of 11 months (range, 1–80 mos). Such a strategy, therefore, if conducted under close observation with patient consent, may be an option without sacrificing the known mortality benefits of ACE inhibitors and, to a lesser degree, angiotensin receptor-blocking agents. Finally, several novel agents that inhibit bradykinin activity and recombinant C1 esterase inhibitors are being tested in clinical trials and may offer new alternatives in the future.

Acute interstitial nephritis

Acute interstitial nephritis (AIN) is a form of hypersensitivity reaction that accounts for a small fraction of all biopsy-proven acute kidney injury. Many drugs have been implicated in causing AIN; several are commonly seen in the ICU, such as penicillins, proton pump inhibitors, and nonsteroidal anti-inflammatory agents. The mechanism of drug-induced AIN is not well described but is postulated to involve the drug acting as a hapten, mimicking renal antigens that trigger immune complex formation and deposition within the interstitium. The traditional triad of low-grade fever, rash, and arthralgias, first described with methicillin-induced AIN, is only seen in approximately one-third of cases. Other nonspecific symptoms such as flank pain, hematuria, and eosinophiluria also are not specific or sensitive diagnostic markers (11). Therefore, the only way to definitively establish the diagnosis is renal biopsy, which, given the associated risks, is only performed in severe cases or in those cases in which discontinuation of the potential offending agent does not result in improvement and no other cause of kidney injury is apparent.

Drug-induced AIN is classically associated with penicillin antibiotics, specifically methicillin. However, other penicillins (e.g., piperacillin), cephalosporins (e.g., ceftriaxone, cefotetan), and vancomycin have been implicated (12). The onset of antibiotic-induced AIN can be from several days to several weeks, and most cases are reversible, albeit slowly over weeks to months.

Proton pump inhibitors, another class of drugs widely prescribed in the ICU, have been associated with AIN. A recent systematic review of proton pump inhibitor-induced AIN described 60 such cases, 59 of which were biopsy-proven (13). All five currently available proton pump inhibitors (i.e., omeprazole, esomeprazole, pantoprazole, rabeprazole, and lansoprazole) were implicated, although the majority of case reports were attributable to omeprazole because of its longer duration of commercial availability. Using the World Health Organization adverse drug reaction causality assessment definition, 12 of 60 reactions were classified as certain, nine of 60 were classified as probable, and 37 were classified as possible. The mean time to onset was 13 wks, with a range of 2 to 52 wks. Thus, it is not a likely event for patients who have been newly prescribed a proton pump inhibitor in the ICU; however, it would be a potential culprit in patients admitted to the ICU already using the medication. Given the widespread use of these drugs, this is not an unlikely scenario. In these cases, nonspecific symptoms were described, with six of 10 being completely asymptomatic and only 13 of 60 having eosinophiluria develop.

Corticosteroids have been used to treat AIN despite the lack of any prospective, randomized studies or any benefits demonstrated in a large case series (14). Doses of 1 mg/kg prednisone daily for 1 to 2 mos have been described. Given the nature of the disorder and risks with long-term therapy, corticosteroids should only be considered in patients whose kidney disease is severe and not improving with the withdrawal of the potential offending agent.

Management of hypersensitivity reactions

General management strategies for any hypersensitivity reactions include an accurate history of previous exposure and reactions, prompt removal of the potential offender, supportive therapies, and selection of alternative agent (if possible) to manage the original indication. Selected management strategies are discussed in the following sections.

Anaphylaxis

The goals of therapeutic management of the patient experiencing an anaphylactic reaction are three-fold. The first and most important measure of care is securing the airway, because the most common cause of death from anaphylaxis is asphyxiation. After securing the airway, fluid resuscitation and maintenance of vascular tone with vasopressors may be warranted. Finally, attempts at interrupting the immune process by suppressing mast cell degranulation can be attempted pharmacologically.

Guidelines and algorithms are available for the management of anaphylaxis and are based on expert and consensus opinion because of the paucity of published evidence for treatment (Fig. 1). Clinical trials in this setting would be difficult to conduct because of the low prevalence of the disease, the urgency of potentially life-saving intervention, and the ethics of patient consent and control groups. Despite these circumstances, epinephrine is recognized as the medication of choice for treating an anaphylactic episode. Epinephrine is administered as 0.3 mg to 0.5 intramuscularly for adults and 0.01 mg/kg for children, and it can be

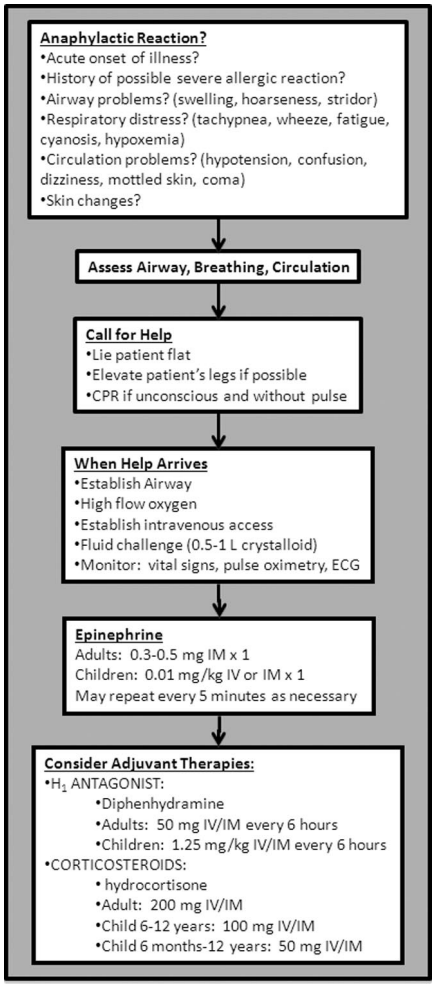

Figure 1. Anaphylaxis treatment algorithm. *CPR*, cardiopulmonary resuscitation; *ECG*, electrocardiography; *IV*, intravenous; *IM*, intramuscular.

repeated every 5 mins as necessary (15). Traditional ratio-based dosing (i.e., 3 mL of 1:1000 solution) is no longer recommended in an effort to reduce dosing errors given the narrow therapeutic window of this drug. At this dose, epinephrine will increase vascular tone, increase cardiac output, reverse bronchoconstriction, and, at a cellular level, reduce the release of bradykinin and histamine (16).

Fluid resuscitation of the patient experiencing anaphylactic shock should be aggressive and initiated early. The principles of early, aggressive resuscitation in this setting should mimic those in the setting of septic shock. Epinephrine is still considered the vasopressor of choice in anaphylaxis; however, multiple vasopressors may be required in patients with confounding shock syndromes. Unfortunately, there are no comparative trials of vasopressors for anaphylactic shock but, theoretically, vasopressin would be a reasonable choice for epinephrine refractory shock given its different mechanism of action and evidence from studies in other shock syndromes. Vasopressin has been described to be effective in many case reports involving patients with anaphylactic shock (17). Methylene blue, another novel vasoactive agent, has also been reported to be effective in case reports (18). Until more experience and controlled data are available for either of these agents, their role in the management of anaphylactic shock should only be considered as rescue therapy in patients refractory to epinephrine.

Corticosteroids and antihistamines are often used to treat anaphylaxis in the absence of convincing supportive data. Histamine blockade of both H1 (i.e., diphenhydramine) and H2 (i.e., ranitidine) receptors in combination is purported to be better than H1 alone, especially in the setting of urticaria or other cutaneous manifestations of hypersensitivity. One animal study suggests that the role of histamine in the myocardium is to increase the availability of cyclic adenosine monophosphate, which results in increased myocardial contractility and, if H_1 receptors are blocked, hypotension may be worsened. This hypothesis has not been confirmed in human studies, and the clinical relevance at this time is unclear. Systemic corticosteroids are unlikely to be of benefit in the acute management of anaphylaxis given that the clinical effects are delayed by 4 to 6 hrs. However, corticosteroids may be of benefit in patients with persistent bronchospasm, history of severe asthma, or those with serious cutaneous reactions. Neither antihistamines nor systemic corticosteroids are likely to provide benefit in non-immune-mediated angioedema.

It is suggested that biphasic reactions occur in 1% to 20% of patients experiencing an anaphylactic reaction. Biphasic reactions are secondary or rebound anaphylactic reactions that usually occur within the first 24 hrs but have been reported to occur as late as 48 hrs after the initial event. The severity of the secondary event is usually variable and can be more or less severe than the original event. Mechanisms and risk factors have not been elucidated, but it would be reasonable to treat and/or monitor patients for 24 to 48 hrs, based on patient response.

Life-threatening dermatologic hypersensitivity reactions

Patients suspected of having a life-threatening dermatologic immune-mediated reaction should have immediate discontinuation of the inciting agent. Clinical management is similar to that of burn patients, including transfer to a burn care center for patients with significant body surface area involvement. Aggressive fluid resuscitation is paramount in the acute phase, but vascular permeability is generally less that that seen in burn patients. The most common complication of SJS and TEN are skin and soft tissue infections propagating to sepsis syndromes, but empirical antibiotics are warranted only if and/or when infection is strongly suspected. Other therapies that have been described include plasmapheresis to remove cytokines and inflammatory mediators and immunosuppressants such as cyclosporine or cyclophosphamide. Adjuvant therapies such as systemic corticosteroids and intravenous immune globulins (IVIG) are often cited, along with some case reports on agents such as cyclosporine, pentoxyphylline, tumor necrosis factor-α blockers (infliximab), and thalidomide. None of these therapies has been subjected to a randomized controlled trial except thalidomide, but that trial was terminated early because of significant increase in death in the thalidomide group (19).

IVIG has been suggested as first-line therapy for SJS/TEN. The proposed mechanism of action is the blocking of keratinocyte apoptosis, a condition that occurs before epidermal detachment in SJS/TEN, by introducing death receptor Fas (CD95)-blocking antibodies in the IVIG preparations. Numerous case reports and case series have been published and were recently reviewed systematically (20). This review found 14 reports of use of IVIG for SJS/TEN that met the inclusion criteria, but only one of which was prospectively performed. A total of 200 patients was included in these 14 studies, with a mean affected body surface area of 5.7% to 48.4%. The mean daily IVIG dose was 0.8 g/kg, administered over a mean of 4 days. Most of the studies (11 of 14 studies) reported some dermatological response (e.g., less detachment progression), whereas none reported a difference in mortality. Adverse events were generally rare, including nephrotoxicity. The difference in patient population (e.g., SJS vs. TEN), treatment regimen used (e.g., dose, time to administration), reported end points and methodology (e.g., historical control), and composition of IVIG (and thus the purported beneficial fraction of antibodies) preclude any meaning-

ful aggregation of the data. In addition, this variability also does not allow for recommendations of optimal dosing and duration of therapy. In the largest cohort (n = 281) of SJS/TEN patients (EuroSCAR Study) with treatment information available, the use of IVIG was not shown to be associated with mortality in the multivariate analysis (odds ratio, 1.4; 95% confidence interval, 0.7–2.8) (21). Therefore, prospective, controlled trials for the use of IVIG in the treatment of SJS/TEN are definitely needed before it can be recommended as standard of care.

Diverging opinions on the utility of corticosteroids exist in the literature. Whereas potential benefits may seem logical if one assumes that SJS/TEN is an immune-related hypersensitivity reaction, the risk of infection must be considered. In fact, corticosteroid administered 48 hrs before admission for patients with SJS/TEN has been shown to increase infection rates, length of stay, and mortality (22). Corticosteroid also has not been shown to slow or halt the progression of the reaction. However, in the EuroSCAR treatment substudy mentioned, corticosteroid was shown to be significantly associated with lower mortality (odds ratio, 0.4; 95% confidence interval, 0.2–0.9) (21). The authors of this study commented that the association between corticosteroids and mortality benefit is conflicting and may be dependent on the dosage used. However, their unpublished subgroup analysis by dose did not yield a consistent mortality benefit. This conclusion must be taken with caution given that it was a retrospective study based on data conducted in two countries with vastly different management strategies. Therefore, the use of corticosteroid in SJS/TEN should be limited to the research setting.

Managing antibiotic allergies

Antibiotics for the treatment or prophylaxis of infection are one of the most commonly prescribed classes of medications, especially in the ICU. It has been estimated that up to 20% (23) of patients admitted to a hospital will report an allergy to a penicillin class of antibiotic. Unfortunately, many of these reported reactions are not true allergies, have occurred many years before the current admission, and the exact nature of the reaction is often forgotten or inaccurate. Clinicians are often forced to select an alternative antibiotic that does not cross-react with penicillin. This may result in suboptimal therapy and the development of resistant organisms that may cause further infections, potentially leading to increased patient morbidity and mortality. In this era of widespread antimicrobial resistance, efforts to clarify the nature and severity of drug "allergies" are warranted to justify selection of alternative antibiotics. Furthermore, skin testing for drug allergies may be useful tools at the bedside and desensitization to the offending drug may be appropriate. One group of investigators reported their experience in using penicillin skin testing in 100 ICU patients with a documented penicillin allergy. Skin testing was eventually performed and interpreted for 96 of these patients (two refused consent and two described serum sickness reactions) using benzylpenicilloyl polylysine (Pre-Pen; Schwarz Pharma, Milwaukee, WI) and penicillin G along with positive (histamine) and negative (saline) control using both skin prick and intradermal methods. The skin test was positive for one patient, nondiagnostic for 10, and negative in the majority (n = 85) of the patients. The test was successful in prompting the change back to a beta-lactam antibiotic in 38 of the patients, with no clinical sequelae (24). This study (and two others) highlighted the safety of penicillin skin testing and its potential utility in minimizing unnecessary exposure to alternative antibiotic (25, 26).

It should be noted that penicillin skin testing can effectively determine allergy to the major determinant, not the minor determinant, and thus reactions can still occur in patients who have "passed" skin testing. In addition, the commercial availability of manufactured penicillin major determinant (e.g., Pre-Pen) is variable across the globe and thus may limit the utility of this strategy.

Another strategy to manage hypersensitivity reactions associated with antibiotics is desensitization. Desensitization is not a new concept and is thought to be effective by gradually introducing incremental doses (from micrograms to the therapeutic dose) to the patient to induce a state of tolerance. It is unclear how the tolerance develops, but it may be attributable to mast cell desensitization. Two caveats apply to desensitization. First, the process will only help in IgE-mediated hypersensitivity reactions and not other types of hypersensitivity reactions (e.g., serum sickness). Second, the state of tolerance induced by desensitization is maintained only when the patient is continuously exposed to the offending agent; thus, interruption in dosage administration or future courses of therapy will necessitate repeating the entire desensitization process, which usually takes several hours. Most desensitization protocols involve administering a diluted amount (usually in microgram ranges) of the offending agent, and then doubling the dose every 15 to 30 mins until one reaches the desired therapeutic dose. If the patient has a mild reaction (e.g., urticaria) during the process, antihistamines may be used and then the process is resumed using the previously tolerated dose. If the reaction is severe, then the process is immediately aborted. Experienced personnel in a closely monitored setting, formalized written protocols, and readily available resuscitative equipment are prerequisites for safe desensitization. In a small series of hospitalized patients, 43 of 57 patients were successfully desensitized. In a larger series of adult cystic fibrosis patients who often require multiple antibiotics and have less pulmonary reserve, it has been demonstrated that, in 63 attempts of desensitization, only one failed, whereas six resulted in mild reactions that did not preclude completion of the procedure. In all 62 attempts, the patients went on to receive the desired antibiotic without experiencing any adverse events. Therefore, the available limited evidence suggests that there is a potential role for desensitization in ICU patients when choices of antibiotics are limited given the multitude of drug-resistant organisms that are encountered in daily practice.

Conclusion

Hypersensitivity reactions encompass a diverse range of immunologically derived reactions that can be common in ICU patients. Many of these reactions arise from drugs frequently prescribed to manage a variety of conditions commonly encountered in daily ICU practice. Unfortunately, the recognition of these reactions is difficult, and therapies are limited and are based mostly on anecdotal evidence rather than controlled clinical trials. Better elucidation of the underlying immune mechanisms, more rapid diagnostic tests, and alternative consent models for the necessary clinical trials are needed to improve the management of these situations.

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