

DRUG AND VACCINE ALLERGY

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In this review, we focus on five main areas of current concern in the management of drug and vaccine allergy in pediatrics: active and passive immunization products, β -lactam antimicrobial drugs, antimicrobials in patients infected with HIV, and patients who have multiple drug allergies.

VACCINES

Active immunization against infectious disease has provided more benefit and prevented more illness than any other aspect of medicine therapeutics. At the close of the twentieth century, immunization efforts have eradicated smallpox; controlled paralytic polio, diphtheria, and tetanus; reduced the incidence of *Haemophilus influenzae* type B sepsis and meningitis; and provided partial protection from influenza, hepatitis B, and varicella infection.

Children are the most vaccinated age group in the US population. According to the Recommended Childhood Immunization Schedules, the fully immunized child should be protected by active immunization against no fewer than 10 infectious diseases, by the administration of between 8 and 14 inoculations over the first 2 years of life. In a recent survey, 79% of American children received four doses of diphtheria, pertussis, and tetanus (DPT), three doses of poliovirus, and one dose of measles, mumps, and rubella (MMR).¹⁴

As a group, these active vaccine immunogens are remarkably safe. Side effects, when they occur, are mostly mild, predictable, and consistent with the benefits associated with immunity. Expectations for an immunization to be totally safe are greatest when the likelihood of succumbing to the threatened illness is perceived to be remote. For example, a patient (or parent of a patient) receiving postexposure rabies protection is more likely to accept the likelihood of side effects, because rabies encephalitis is uniformly fatal. On the other hand,

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most parents who have no experience with pertussis are less likely to accept other than very mild adverse reactions to pertussis immunization.

The National Childhood Vaccine Injury Act of 1986 established the National Vaccine Injury Compensation Program (VCIP) as a federal no-fault compensation system for individuals who may have been injured by specific, covered vaccines.¹ The Act, which was intended to ensure childhood vaccine supplies by lowering the vaccine manufacturer's and provider's liabilities, lists specific injuries or conditions and time frames after vaccination that may be compensated under the VCIP.⁴³

The Act requires the administrator of the vaccine to record the vaccine producer's name and the vaccine lot number, and to report major reactions within the time frames indicated.² In addition, an approved information sheet on each of the covered vaccines has been prepared by the Department of Health and Human Services and must be given to the parent or the patient at the time of immunization.

Allergic Reactions

Rarely, a vaccine recipient experiences a serious adverse event or an allergic reaction to a vaccine.²⁹ In this section, we focus on hypersensitivity reactions to the current childhood immunizations, and provide guidance for dealing with patients who experience such reactions.

The current guidelines for the immunization of children specify vaccines for ten infectious diseases. Of these, live virus vaccines for MMR, varicella, and poliovirus routinely result in clinical or subclinical infections. In contrast, life-threatening infections from the vaccine virus are extremely rare in the immunocompetent population. The proper use of these vaccines in patients who have primary or secondary immunodeficiencies and the occurrence of vaccine-associated paralytic polio in the immunocompetent population have been reviewed elsewhere.²

The milder, more common subclinical vaccine-induced infections may result in exanthems that mimic hypersensitivity reactions. Clinically, the distinction between an allergic and an infectious rash may be difficult. A viral exanthem, however, should appear later than a hypersensitivity rash.

Vaccines contain several antigens that may induce hypersensitivity reactions, including egg protein, gelatin, albumin, viral or bacterial components, and cell culture additives; antibiotics, such as neomycin and streptomycin; and preservatives, such as thimerosal or surfactants, such as Tween.

Rarely, allergic reactions to vaccines have been demonstrated to be because of the recognition of an antigen by mast-cell-bound IgE.^{9, 29} Other mechanisms for adverse reactions have been reported. Delayed type hypersensitivity to mercury has been reported in Armed Forces members who developed vesicular rashes at the site of tetanus immunizations. Immediate skin-test reactivity was exceedingly rare in their series and the authors postulated that a mechanism other than IgE was responsible for the side effects noted after tetanus immunization.²⁶

Postvaccination Guillain-Barré syndrome may be an IgG-mediated disorder. In these studies, IgG antibody directed against ganglioside GM1b also reacts with the I antigen on erythrocytes. Ganglioside GM1b shares the same terminal glycosyl moiety as the I antigen on erythrocytes.^{31, 33}

Despite convincing evidence that pertussis vaccine provides substantial protection against infection, controversy persists about its safety. In Britain

between 1974 and 1978 the controversy over pertussis vaccine and brain injury was so great that vaccination levels fell to 31%. The predicted consequence of low pertussis vaccination levels was an epidemic in 1977 to 1979 with over 102,000 cases of pertussis and 27 deaths.¹⁹ As a result of the epidemic, pertussis studies were initiated. In a large prospective study, local and general reactions were reported significantly more frequently with whole cell DPT than with DT vaccine.¹⁹ Local reactions were 47.8% and 33.7% for DPT and DT, respectively; general reactions were 38.4% and 10.1% for DPT and DT. The most frequent general reactions were irritability and fever. Persistent screaming was reported in 7.4% of DPT and 1.5% of DT vaccine recipients. Serum sickness reactions after DPT appear to be infrequent, with only one case of this type reported.³⁸ High fever and seizures are much more frequent with the whole cell vaccine than with the acellular vaccines.⁴⁶

Management

The frequency of anaphylactic events to vaccine components is extremely low (Table 1).² Nonetheless, patients who have experienced convincing urticarial or anaphylactic reactions associated with vaccine administration should be evaluated with care before reexposure. The predictive value of skin testing in the diagnosis of vaccine-associated allergic reactions is uncertain. Therefore, it is essential for the patient to be examined during the course of the reaction and for a careful history to be taken, with special attention to other far more likely causes of allergic reactions. These alternative hypotheses should be examined and systematically excluded. When absolutely necessary, the patient may be skin tested with several dilutions of the putative causative vaccine, but the physician should not rely on such testing—either with positive or negative results—to make the conclusive diagnosis.

When a vaccine has been implicated in an allergic reaction, the subsequent course of action should be the product of an open exchange of information between the clinician and the patient or the parents of the patient. Considerations include the severity of the initial reaction, the likelihood of infection in a nonimmunized individual, and the severity of the disease in question. Possibilities include withholding immunization temporarily or indefinitely, immunizing

Table 1. MAJOR SIDE EFFECTS ASSOCIATED WITH COMMON VACCINES

Vaccine	Rate	Serious Side Effect
DPT	2:100,000	Anaphylaxis
Hepatitis B	1:600,000	Anaphylaxis
OPV	First dose overall 1:760,000 Recipient 1:1,500,000 Contact 1:2,200,000	Paralysis
Measles	1:1,000,000	Central nervous system abnormality
MMR	1:30,000–1,000,000	Thrombocytopenia
MMR	1:2,100,000	Anaphylaxis
HDCV Rabies	1:150,000	Neurologic abnormality
Varicella	18:100,000 person years	Mild to moderate zoster

OPV = oral polio vaccine; HDCV = human diploid cell vaccine.

with premedication, or immunizing with close observation in a hospital-based facility. In spite of isolated case reports in which graded dosing of vaccines is reported,^{9, 15, 32, 59} desensitization to vaccines is of no proven value.

Acetaminophen is often given just before or concurrent with DPT to prevent fever. In a recent Scandinavian randomized double-blind controlled trial, a single 75-mg dose of acetaminophen given 4 hours after immunization to 5-month-old infants vaccinated with either DPT or DPT-inactivated polio had no effect on temperature.⁶¹ In a US study, however, reaction scores were lower in the acetaminophen-treated group than in the placebo group. The authors concluded that prophylactic acetaminophen had a moderating effect on fever, pain, and fussiness after DPT immunization.³⁶ A recent Canadian study reported fewer local and systemic reactions in the acetaminophen group for infants aged 2, 4, and 6 months; however, no difference was noted for the booster dose at age 18 months.²⁵ Acetaminophen and diazepam were shown to be ineffective at preventing recurrent febrile seizures.⁶⁰

IMMUNE GLOBULINS

Immune globulins are administered to provide passive immunity to infection and for the immunomodulation of putative autoimmune disorders. Although the original immune globulin preparations were almost always derived from animals, few animal antisera are currently in clinical use. The classical serum sickness syndrome, originally described with these xenobiological products, can still be observed when these animal-derived proteins are injected.³⁴

When earlier human immune globulin preparations were injected intravenously, anaphylactoid reactions caused by IgG aggregates were a common experience. Modern human immune globulin preparations are treated with sugars or acid pH to prevent reaggregation, and these products have allowed the attainment of significantly higher blood levels of passively acquired antibody with fewer side effects.^{51, 56} The adverse reactions associated with human immune globulin preparations are, in general, dose related, milder, and easier to manage. Rault et al⁵¹ reported a series of three patients who had pulmonary and renal toxicity after intravenous immunoglobulin administration and postulated that contaminating IgG aggregates may have been responsible.

Some human immune globulin products (in particular, certain hyperimmune preparations) continue to be administered by the intramuscular route.

Adverse Reactions

Reactions to xenobiotics such as equine antibody preparations include serum sickness and anaphylaxis; intradermal pretesting and premedication are suggested before administration of these products. A murine monoclonal antibody (muromonab-CD3) for intravenous injection can also lead to anaphylaxis. A so-called cytokine release syndrome consisting of fever, shaking chills, rash, edema, and pulmonary edema may appear 30 to 60 minutes after administration of the drug and may last for up to as long as 4 hours. Unlike anaphylaxis, which is likely to worsen with subsequent dosing, the cytokine release syndrome appears to decrease in severity with successive treatments.^{45, 54, 63}

Reactions to intramuscular human immune globulin injections are uncommon. Anaphylaxis and urticaria have been reported, but are rare.

Allergic reactions to intravenous human immune globulins are relatively

rare, although anaphylaxis has been reported.⁸ In a prospective randomized trial in 24 children with idiopathic thrombocytopenic purpura (ITP), the most common side effects were headache, fever, nausea, and vomiting; these were generally mild and lasted less than 3 hours. One child experienced an anaphylactoid reaction, and one child experienced aseptic meningitis.⁵⁵ Other reports indicate that the common side effects occur at a frequency of less than 5%.^{18, 50}

Other reported side effects include myalgia, arthralgia, back pain, chest pain, chills, fever, pruritus, vomiting, rash, light-headedness, and malaise. These usually appear in the first hour of the infusion and may be related to the rate of infusion.⁵⁶ Comenzo et al¹⁷ described a child being treated with intravenous immune globulin (IVIG) for Kawasaki disease. The child experienced immune hemolysis and disseminated intravascular coagulation with serum sickness.¹⁷ Yockey and Ahmed⁶⁷ reported a case of lichenoid dermatitis in a patient who had Sjögren's syndrome and Raynaud's phenomenon who received IVIG therapy. Biopsy revealed an overwhelming predominance of CD3⁺ lymphocytes infiltrating the lesion.⁶⁷

Potential Mechanisms

Anaphylaxis has been reported after IVIG infusions in IgA-deficient patients, with IgG and IgE anti-IgA antibodies detected in the recipients' sera. Approximately 1 in 700 persons has IgA deficiency, the most common inherited immune deficiency. Many of the IVIG preparations contain small amounts of IgA sufficient to induce anaphylaxis.⁸ The range of IgA in US commercial preparations ranges from less than 2 µg/mL to less than 970 µg/mL. The mechanisms of the other reactions are uncertain.

Management

Preparations of IVIG that have been depleted of IgA should be used in patients who have experienced anaphylactic symptoms with previous IVIG infusions. Since all IVIG preparations contain some IgA, the administration of IVIG to such patients should be handled with extreme caution. Premedication with H₁ and H₂ histamine antagonists and glucocorticoids may be advisable, but in all cases, the patient should be closely monitored. Epinephrine should be available at the bedside for immediate administration.

Other adverse reactions to IVIG are usually rate-dependent and respond to slowing the infusion rate, as well as premedication with acetaminophen or nonsteroidal anti-inflammatory agents. Occasionally, low-dose oral glucocorticoids may be required for adequate control of symptoms.

HIV

Adverse reactions to cotrimoxazole (trimethoprim-sulfamethoxazole) in patients infected with HIV are common. Studies suggest an adverse reaction rate of as much as 65%¹³; in one recent pediatric study, the reaction rate was 40%.⁵³ Most reactions are dermatologic, including erythema, maculopapular eruptions, and erythema multiforme. Fever, liver toxicity, nephrotoxicity, and bone marrow toxicity are also reported.^{22, 62} Anaphylaxis and anaphylactoid reactions have also been reported.⁸ In a prospective study of HIV in sexually active homosexual

men in Amsterdam, adverse reactions to cotrimoxazole were associated with a more rapid progression of disease, independent of infection with *Pneumocystis carinii* and *Toxoplasma gondii*.⁶⁴

Mechanisms

Sulfonamides are metabolized by the cytochrome P450 oxidase system. The drugs may be acetylated or oxidized. After oxidation, the drug metabolite may be conjugated to glutathione or other carrier proteins. Glutathionylated drug, as well as acetylated drug, is excreted harmlessly in the urine. Slow acetylators and patients who have depleted levels of glutathione may be more likely to generate immunoreactive drug-protein conjugates. Such conjugates may be pathogenic in a full range of immunologic reactions.^{23, 37}

Several studies have suggested that patients infected with HIV have an increased likelihood of expressing the slow-acetylation phenotype.¹³ Others have implicated depleted glutathione stores as risk factors for adverse reactions to cotrimoxazole.⁶ Although in vitro studies have been encouraging, clinical use of N-acetylcysteine to avert cotrimoxazole-induced reactions has been disappointing.^{6, 12}

The propensity of patients infected with HIV to experience adverse drug reactions is not limited to cotrimoxazole. Carr and Garsia¹¹ reported the frequency of reactions in patients with HIV to sulfadiazine (10% to 40%), dapsone (17% to 53% in patients undergoing active therapy for *P. carinii* pneumonia, and 5% to 10% in patients receiving prophylactic doses), clindamycin (20% to 30%), atovaquone (2% to 5%), aminopenicillins (9%), penicillins (5%), cephalosporins (3%), and others.

Management

When an patient infected with HIV develops a documented hypersensitivity reaction to cotrimoxazole, several management alternatives may be pursued. The need for prophylaxis at this stage in the patient's disease may be reexamined. Alternative prophylactic drugs, for example, nebulized pentamidine or dapsone, may be considered. Occasionally, if the adverse reaction is particularly mild or if the reaction is of questionable origin, cautious reintroduction of cotrimoxazole might be attempted.¹⁰

For patients who have experienced clear-cut nonvesicular reactions and for whom alternative treatments are either not feasible or ineffective, cotrimoxazole desensitization should be considered. Several protocols of oral desensitization have been proposed. The mechanism of efficacy is uncertain. Representative regimens are listed for comparison in Table 2.^{7, 40, 42, 44, 47, 52} Note that patients who have a history of Stevens-Johnson reactions to sulfonamides should not be desensitized. Desensitization may be accomplished by protocols ranging from 4 hours to 11 days in length, with initial failure rates of 14% to 50%. In general, the protocols of more than one day in duration were associated with the fewest desensitization failures.

CEPHALOSPORINS AND PENICILLINS

There are four classes of β -lactam antibiotics used today: penicillins, cephalosporins, monobactams, and carbapenems. All have the four membered β -

Table 2. COMPARISON OF REPRESENTATIVE REPORTS OF DESENSITIZATION REGIMENS FOR TRIMETHOPRIM-SULFAMETHOXAZOLE

Author	Inclusion Criteria	No. Pts	Age Range (Yrs)	Starting Dose Sulfamethoxazole (μ g)	Interval (h)	Dose Increase	Time	Total Doses	Initial Failure Rate (%)	Treat Through Reaction
Belchi-Hernandez and Espinosa-Parrá ⁷	Previous non-life-threatening cutaneous reactions in HIV patients	33	18-34	200	12	Twofold q 24 hr	11 days	22	19	Yes
Nguyen et al ⁴⁴	Previous non-life-threatening cutaneous reactions or fever in HIV patients	45	not given	0.01	0.25-4	Varied	36 h	40	18	No
Rich et al ⁵²	Previous non-life-threatening cutaneous reactions or fever in HIV patients	22	28-49	0.02	6-8	Tenfold q 24 hr	8 d	24	14	Yes
Moreno et al ⁴⁰	Previous non-life-threatening cutaneous reactions or fever in HIV patients	2	32-33	0.01	0.25	Twofold q dose	8 h	25	50	Yes
Palusci et al ⁴⁷	Previous presumptive IgE-mediated rash in HIV children. Severe or cytotoxic reactions were excluded	5	0.6-11.8	Approximately 40	0.25	Tenfold then twofold q dose	4 h	12	40	Yes
Nagarajan et al ⁴²	Previous non-life-threatening cutaneous reactions in HIV children	5	7-17	Similar to Moreno	—	—	7 h	30	20	—

pts = patients.

lactam ring and share immunologic cross reactivity to the ring and to its breakdown products. Penicillins, cephalosporins, monobactams, and carbapenems are all low-molecular-weight compounds that covalently bind to protein. In prototypic studies, the β -lactam ring of penicillin G opens when protein binding occurs, yielding the penicilloyl-protein conjugate. This pathway accounts for approximately 95% of penicillin breakdown in vivo. Isomerization to penicillenic acid and subsequent binding to protein yields the minor determinants.⁶⁶ Specific antibody absorption experiments show that IgE antibodies to penicillin, penicilloyl, pencilloate, and penilloate are distinct and non-cross-reacting. Cephalosporins undergo a similar degradation into major and minor cephaloyl determinants, and cross-reactivity has been shown to occur between the major determinants of the penicillins and the cephalosporins.^{3, 24, 35}

Semisynthetic penicillins differ in their side chain at the 6-aminocarboxy position of the β -lactam nucleus. Cephalosporins may be substituted at the 6-aminocarboxy position of the β -lactam nucleus, and also may be substituted at the 3 position of the dihydrothiazine ring.

Side chains can elicit reactions as well. Miranda et al³⁹ demonstrated that, among 21 patients who have selective amoxicillin allergy, 8 (38%) experienced adverse responses to cefadroxil, which shares a side chain with amoxicillin. In contrast, none of the patients experienced adverse reactions after challenge with the cefamandole, which does not share side-chain specificity.³⁹

Testing

In a recent review, skin testing with penicilloyl polylysine (Prepen) and a minor determinant mixture was positive in between 7% and 63% of patients who had a history consistent with penicillin allergy. When these patients are challenged prospectively, the true sensitivity of this testing is nearly 100%.⁶⁶ Antibodies to penicillin show a time-dependent decrease beginning approximately 2 months after the adverse reaction. Sullivan et al⁵⁸ reported that skin testing performed within 1 to 2 months after an acute allergic reaction is positive as much as 90%. Levels of antibody decline to less than 20% after 10 years.^{20, 66}

Penicilloyl polylysine is available as a diagnostic reagent for penicillin allergy. The minor determinants of penicillin degradation, however, are not currently available for general use. Using fresh penicillin G and penicilloyl polylysine detects approximately 90% to 95% of hypersensitive individuals. The small population that is missed, however, may be those most at risk for serious anaphylactic reactions.²⁷

In contrast, cephalosporin skin testing is extremely imprecise.³ Many assumptions have been made, without adequate study, based on penicillin skin testing. The proper allergens and the proper dose of the allergens to be used for cephalosporin skin testing are not known. The predictive value of positive and negative skin tests has not been defined.

Management

The mainstay of clinical treatment in patients who have a history of allergy to penicillin or cephalosporin antibiotics remains judicious avoidance of the offending drug and potentially cross-reactive agents. Withholding the antibiotics is the most effective way to prevent future reactions but may increase the cost and decrease the efficacy of treatment.

A common practice is to administer cephalosporins to patients who have penicillin allergy. Although clear-cut cross-reactivity has been demonstrated, the risk of reactions to cephalosporins is probably less than the risk of reacting to penicillins. In 1976, the Boston Collaborative Drug Surveillance program found 507 cutaneous reactions among 22,227 adult inpatients. Penicillins accounted for 10.4%, but cephalosporins accounted for only 1.3% of these reactions.⁴

Recently, Pichichero and Pichichero⁴⁹ examined the specificity of pediatrician-diagnosed allergy reactions to penicillin, amoxicillin, and oral cephalosporins based on contemporaneous examination of the patient by elective skin testing. They studied 247 children and adolescents who had experienced an adverse reaction serious enough to warrant avoidance of further use of the drug. The authors found that physician-diagnosed allergic reactions to β -lactam antibiotics based on physical examination at the time of the reaction was more accurate than patient history alone but that it still overestimated the rate of possible true allergy in 66% of the patients.⁴⁹ Thus, judicious skin testing can improve the accuracy of diagnosis.

Although skin tests can be helpful in the management of patients who have reacted to β -lactam antibiotics, in the absence of optimal diagnostic tests, reasonable avoidance recommendations may be made based on side-chain similarities between substituted β -lactam drugs. Thus, a patient who has a compelling history of an allergic reaction to a β -lactam drug but who has negative skin tests to the relevant major and minor determinants should be presumed to have reacted to one or both of the side chains of the offending agent. The structures of therapeutically appropriate alternative drugs should be examined for the presence of these side chains; only drugs that lack these side chains should be used. Such structures may be found in the product insert or in references such as the Merck Index (Table 3).

Finally, desensitization regimens have been reported for several β -lactam antibiotics.^{16, 21, 48, 57, 58} These regimens appear to be safe and highly effective and can be performed as in-office procedures under most circumstances.

MULTIPLE DRUG ALLERGY AND ITS MANAGEMENT

Multiple drug allergy syndrome (MDAS) is a clinical condition characterized by reactions to several immunochemically distinct antimicrobial drugs.⁵ Smith et al⁵⁵ first reported an increased incidence of allergic reactions to drugs other than penicillin in patients who had a positive penicillin skin test. Kamada et al²⁸ reported that 35% of children who had a positive skin test to penicillin had experienced immunopathologic reaction to non- β -lactam antibiotics. Comparing 37 patients who had established drug allergy to matched controls, Moseley and Sullivan⁴¹ reported a prospective relative risk of 9.4 ($P = 0.018$) of developing an allergic reaction to an unrelated drug.

In contrast, Khoury and Warrington³⁰ found no evidence of MDAS in a matched-control retrospective study of 44 patients who had documented hypersensitivity to penicillin. The frequency of reactions to non- β -lactam drugs was not different among the index group, a control group with clinical reactions but negative skin tests, and another control group of nonatopic patients who had vasomotor rhinitis.³⁰

There is no treatment for MDAS. The prevention of infection and the avoidance of unnecessary antimicrobial exposure are essential elements of management. In urgent situations, careful desensitization may be necessary.

Asero⁵ reported a large prospective series of 120 patients who had unequivocal

Table 3. ANTIBIOTICS WITH IDENTICAL SIDE CHAINS

	amoxicillin	ampicillin	benzylpenicillin	aztreonam	cefadroxil	cefamandole	cefazolin	cefepime	cefexime	cefmenoxime	cefonicid	cefotaxime	cefotetan	cefoxitin	cefipodoxime	cefazidime	ceftriaxone	cefuroxime	cephaloridine	cephalothin	cephradine	imipenem	loracarbef	meropenem
amoxicillin	XX	1					1																	
ampicillin	1	XX					1															1	1	
benzylpenicillin			XX																					
cefadroxil				XX																				
cefamandole	1				XX																			
cefazolin						XX																		
cefepime																								
cefexime									XX															
cefmenoxime											XX													
cefonicid										XX														
cefotaxime							1				XX													
cefotetan												XX												
cefoxitin													XX											
cefipodoxime														XX										
cefazidime			1												XX									
ceftriaxone																XX								
cefuroxime																	XX							
cephaloridine																		XX						
cephalothin																			XX	1				
cephradine			1																	1	XX			
imipenem																					XX			
loracarbef																						XX		
meropenem																							XX	

(1 or 2 = identical side chains; XX = same drug)

cal documented allergic reactions induced by multiple drugs. These patients underwent 253 elective oral challenges with alternative antimicrobial products. The goal in the study was to determine at least two alternative well-tolerated antimicrobial classes in all patients. Twenty-three (19%) of the patients experienced reactions during the course of challenge, although all reactions were mild and easily controlled. The author concluded that elective oral challenges with alternative antibiotics are a sensitive and safe means to detect patients who have MDAS.⁵

The avoidance of infection is another important consideration for the treatment of patients who have MDAS. Minimizing unnecessary exposure to other sick children, optimization of treatment for upper airway allergic disease, and even elective surgery (e.g., myringotomy or adenoidectomy) should be considered.

CONCLUSIONS

Allergic reactions to vaccines and drug products have become an important and common feature of modern pediatric practice. Although few precise diagnostic tests are currently available, patients can usually be diagnosed with accuracy after careful attention to the history and the physical findings. Prevention, avoidance, the use of alternative agents, desensitization, and premedication remain the mainstays of therapy.

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