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POSITION STATEMENTS OF THE PHILIPPINE SOCIETY OF ALLERGY, ASTHMA, AND IMMUNOLOGY ON ROUTINE SKIN TESTING TO PARENTERAL ANTIBIOTICS AND EVALUATION OF ANTIBIOTIC ALLERGY: 2018 UPDATE

These statements were developed by the Drug Allergy Council of the Philippine Society of Allergy, Asthma, and Immunology (PSAAI).

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ABSTRACT

Intradermal skin testing prior to administration of parenteral antibiotics is routinely done by nurses in most hospitals in the Philippines. This ongoing practice is contrary to the earlier position statements of the Philippine Society of Allergy, Asthma and Immunology (PSAAI) and Philippine Society for Microbiology and Infectious Diseases (PSMID) panel of experts, and guidelines or practice parameters from international academies. Routine skin testing to antibiotics on patients without a history of antibiotic allergy is not supported by evidence-based studies and should not be done to screen for allergy to antibiotics in the general population. At present, only penicillin has a standardized skin testing procedure. In patients with IgE-mediated penicillin allergy, immediate type skin testing using the standardized protocol is the most reliable test. It should be performed using the major determinant reagent (penicilloylpolylysine) and minor determinant reagents (penicillin G and penicilloate, and/or penilloate). For other beta-lactam and non-beta-lactam antibiotics, several studies recommend the use of non-irritating concentrations of the parent drugs in performing immediate type skin testing. However, these protocols are not standardized, and the predictive value is unknown. A negative test result therefore cannot rule out drug allergy and should be followed by a graded challenge. Clinicians should always attempt to elicit a reasonable description of a possible allergy to the same or cross-reacting antibiotic. Patients with a history of allergy to the antibiotic or cross-reacting antibiotic are best referred to an allergist for proper diagnostic testing and management. Substitution with a suitable alternative non-cross-reacting antibiotic is preferred over desensitization if allergy to the antibiotic or cross-reacting antibiotic is established. If the patient has no history of allergy to the antibiotic, careful monitoring for any reactions during the course of treatment should be done at all times. The clinician should be able to recognize the early signs and symptoms of allergic reactions, especially anaphylaxis, and promptly administer the correct treatment.

KEYWORDS: *Adverse drug reaction, drug allergy, skin testing, antibiotic hypersensitivity, drug hypersensitivity, antibiotic stewardship program*

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INTRODUCTION

Intradermal skin testing prior to administration of parenteral antibiotics is routinely done by nurses in most hospitals in the Philippines. This ongoing practice is contrary to the earlier position statements of the Philippine Society of Allergy, Asthma and Immunology (PSAAI) and Philippine Society for Microbiology and Infectious Diseases (PSMID) panel of experts[1,2,3,] and guidelines or practice parameters from international academies. The discrepancy between this common practice and the experts' recommendation may have stemmed from a notion that there is negligence with non-performance of this procedure. In fact, there is no specific law in the Philippines that requires medical practitioners to perform routine skin testing prior to parenteral antibiotic administration. A

comprehensive search of Supreme Court archives has not yielded a case of negligence for non-performance of routine skin testing to antibiotics.

In an effort to promote the proper use of skin testing and other diagnostic tests for antibiotic allergy, PSAAI, in collaboration with PSMID, released position statements on February 5, 1991.[1] PSAAI updated the statements in 1994[2] and in 2008.[3] This 2018 update is based on internationally recognized guidelines bolstered by the most current studies on the topic.

A comprehensive literature search was done by the PSAAI Drug Allergy Council using PubMed, allergy and immunology websites and journals to review the latest international guidelines and practice parameters relevant to the topics. A draft of the statements was presented to the members of PSAAI via e-mail for comments and suggestions, and legal counsel was sought for advice. The revised draft was presented to the Board members of PSAAI for final approval.

TOPICS

1. The PSAAI's stand on routine skin testing to parenteral antibiotics prior to administration

2. The PSAAI's stand on the proper evaluation of patients with a history of allergy to antibiotics

POSITION STATEMENTS

Position Statement 1: **Routine skin testing to parenteral antibiotics is not recommended.**

Routine skin testing to antibiotics on patients without a history of antibiotic allergy is not supported by evidence-based studies.[4,5,6] Commonly utilized non-standardized skin testing protocols usually use the parent drug which may not always be the allergenic form appropriate for skin testing. The local skin testing protocols do not follow the recommended procedures and concentrations of the drugs. If proper history taking for drug allergy is not routinely done prior to skin testing, adequate patient selection is not undertaken. This exposes those who are truly allergic to a real risk of life-threatening reactions, which are more common with the intradermal testing.[7,8] A clinical review of antibiotic allergy has shown that systemic reactions occurred in approximately 1% of all skin test patients and 9% in positive skin test patients.[9] Routine skin testing may lead to unreliable results, mislabeling of patients and adverse events. A false-positive result, which may represent a non-specific skin irritation, may be mistakenly labeled as an allergic reaction. This may result in the administration of an alternative antibiotic which may be unnecessary, more expensive and in not a few instances, associated with more toxicity. It also carries with it the risk of developing multi-drug resistant bacterial strains and increased mortality and morbidity which translate into higher cost of medical care.[7] On the other hand, false-negative results can put a patient at risk for life-threatening reactions, such as anaphylaxis. Another potential risk is the development of sensitization after repeated skin testing to a drug.[7,8] Skin testing, therefore, is best performed by experts and should not be used to screen drug allergy in the general population. [6,10]

Drug allergy is an immunologically mediated response to pharmacologic agents or pharmaceutical excipients that results in the production of antibodies, reactive T cells, or both in a sensitized person. Since antibiotics in their native forms are mostly low molecular weight compounds which are not easily recognized by the immune cells, they must first be rendered immunogenic. This may occur via covalent bonding of the hapten with carriers (commonly proteins) to become immunogenic.[4]

The p-i concept (pharmacologic interaction with immune receptors) is another mechanism that involves a direct or non-covalent bonding of low molecular weight drugs with T-cell receptors, major histocompatibility complex receptors or both leading to a T cell immune response. In this scenario, prior sensitization to stimulate production of memory and effector T cells is not required.[7]

The Gell and Coombs classification may be used to categorize some drug allergies into IgE-mediated (type I), cytotoxic (type II), immune complex-mediated (type III), and cellular mediated (type IV) hypersensitivity reactions. Type IV hypersensitivity reactions are further categorized into type IVa (activation and recruitment of monocytes/ macrophages by TH1 cells), type IVb (eosinophil activation by TH2 cells), type IVc (CD4 or CD8 cells cytolysis) and type IVd (neutrophil activation by T cells). In Types I-III hypersensitivity reactions, drugs elicit the immune response as hapten-protein conjugate while in Type IV reactions, stimulation of T cells can result via hapten-protein conjugate or p-i mechanism. Among these hypersensitivity reactions,

types I & IV are the most common. Other drug allergic reactions cannot be easily classified because different mechanisms may be involved at the same time, resulting in a more complex mechanism or because of poorly understood immunopathogenesis.[6,7]

IgE-mediated (Type 1) hypersensitivity reaction develops as a result of activation of TH2 cells and stimulation of IgE antibody production by antigen-specific B cells during initial exposure to the allergen (sensitization phase). These IgE antibodies will bind to the high affinity FcƐRI receptors on the surface of mast cells and basophils. Upon repeated exposure to the allergen (elicitation phase), presumably a hapten protein complex cross-links the IgE antibodies on mast cells and basophils, causing the release of vasoactive mediators (e.g. histamines, tryptase, leukotrienes, prostaglandins) and cytokines, and subsequent development of signs and symptoms of IgE-mediated drug allergy.[11] Immediate-type skin testing is the most useful test for detecting IgE-mediated drug reactions.[7] It is an *in vivo* test in which the allergens are introduced into the skin by pricking and/or intradermal injection, after which the results are read in 10 to 20 minutes. In sensitized patients, these allergens will cross-link the IgE antibodies already bound to the surface of mast cells. The resulting release of vasoactive mediators, mainly histamine, causes a wheal and flare reaction on the area being tested.[11] This explains why the interpretation of the immediate-type skin test results would be most reliable only in patients presenting with a reaction compatible with an IgE-mediated mechanism to the same or a cross-reacting drug, and not in those patients exhibiting non-IgE-mediated reactions.[6] It is actually contraindicated in serious cutaneous adverse reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), exfoliative dermatitis and drug rash with eosinop hilia and systemic symptoms (DRESS), and not indicated in IgG/IgM-mediated immune reactions (e.g. vasculitic syndrome, hepatitis, hemolytic anemia, nephritis).[6,7]

Position Statement 2: A patient suspected with an allergy to an antibiotic or to a cross-reacting antibiotic is best referred to an allergist who is trained on the proper diagnostic procedures, interpretation of results, and treatment of drug allergy.

Clinicians should always ask for a history of allergy to the same or a cross-reacting drug when prescribing an antibiotic. Common clinical symptoms of IgE-mediated drug allergy include urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, abdominal symptoms and anaphylaxis with typical chronology of reaction within the 1st to 6th hour after exposure to the antibiotic.[4,5,6,7,10] Asthma is a risk factor of serious allergic reactions once an IgE-mediated reaction has developed.[7] Non-IgE-mediated drug allergy that arises more than one hour to several days after drug administration, often affects the skin with variable cutaneous symptoms such as maculopapular eruptions (MPE), late occurring or delayed urticaria, fixed drug eruptions (FDE), vasculitis, acute generalized exanthematous pustulosis (AGEP), and symmetrical drug-related intertriginous and flexural exanthemas (SDRIFE). It can present as systemic reaction such as blistering diseases (e.g. TEN, SJS, and generalized bullous fixed drug eruptions), drug-induced hypersensitivity syndrome (DiHS) or DRESS. It can be an organ-specific reaction such as hepatitis, renal failure, pneumonitis, anemia, neutropenia, and thrombocytopenia, which may manifest either alone or with cutaneous symptoms.[4,6,7,10]

A patient with a history of allergy to the same or cross-reacting antibiotic is best referred to an allergist for proper diagnostic testing, in order to confirm or exclude drug allergy which will simplify the management and reduce the use of broad-spectrum antibiotics.[12] History alone cannot accurately diagnose allergy to the antibiotics.[4,5,6,7] In a clinical review of antibiotic allergy, the prevalence of patients labelled with antibiotic allergy ranges between 10-20%, but only 10-20% of them have true allergy confirmed by allergic work-up.[13] Likewise, penicillin allergy is the most commonly reported drug allergy with a prevalence rate of 5% to 10% in adults and children, but 90% of them are able to tolerate penicillin after complete evaluation. It has been observed that among patients confirmed with penicillin allergy, about 50% of them lose their sensitivity after 5 years and about 80% in 10 years. Re-sensitization may develop in these patients who have tolerated one course of parenteral penicillin with a frequency of 0.9% to 27.9%.[7]

If allergy to an antibiotic is established, giving an alternative suitable non-cross-reacting drug whenever possible is preferred over desensitization to the implicated drug. Desensitization modifies the patient's response to an antibiotic causing the

allergy, allowing them to continue with the treatment.[8] However, it is also associated with the risk of systemic reaction or anaphylaxis. This risk is considered more significant compared to the attendant risks associated with administering the second line drug. Hence, desensitization, which is best performed by an allergist, is mainly considered if there are no suitable alternative drugs.

If the patient has no history of allergy to the antibiotic, careful monitoring for any reactions during the course of treatment should be done at all times. The clinician should be able to recognize the early signs and symptoms of allergic reactions especially anaphylaxis and treat promptly and correctly. (Fig. 1)

At present, only penicillin has a standardized skin testing procedure. Penicillin is a group of beta lactam antibiotics which includes natural penicillin (sodium penicillin G, procaine penicillin G, benzathine penicillin) and semi-synthetic penicillin (e.g. phenoxymethyl penicillin, methicillin, cloxacillin, oxacillin, dicloxacillin, flucloxacillin, nafcillin, ampicillin, amoxicillin, bacampicillin, carbenicillin, ticarcillin, piperacillin, and mezlocillin). Having a low molecular weight and being immunologically inert, penicillin undergoes spontaneous conversion under physiologic conditions to reactive intermediates that haptenate proteins and form penicillin major (95%) and minor (5%) determinants. These allergenic determinants are responsible for stimulating an immune response.[7]

In patients with an IgE-mediated penicillin allergy, immediate type skin testing using the standardized protocol is the most reliable test. It should be performed using the major determinant reagent (penicilloylpolylysine) and minor determinant reagents (penicillin G and penicilloate, and/or penilloate). Using this method, the negative predictive value (NPV) for immediate reactions approaches 100%, while the positive predictive value (PPV) is between 40% and 100%.[7] Unfortunately, only penicillin G is currently available, further limiting the reliability of the test. A negative test result therefore cannot rule out drug allergy.

Several studies recommend the use of non-irritating concentrations of the parent drugs in performing immediate type skin testing to other beta lactam (cephalosporins, carbapenems, monobactams) and non-beta lactam antibiotics (e.g. flouroquinolones, sulfonamides, macrolides, aminoglycosides, rifamycins, glycopeptides, clindamycin). However, these protocols are not standardized, and the predictive value is unknown.[7,14,15,16,17] A negative test result therefore cannot rule out drug allergy.

In vitro assays that detect specific IgE (e.g. radioallergosorbent test, fluorescence enzyme immunoassay, enzyme-linked immunoassay) are available but most of these assays are not standardized. They may be used in certain instances when skin testing cannot be done (e.g. dermographism, generalized rashes). Few studies on assays for penicillin specific IgE demonstrated a relatively high specificity (97% to 100%) but low sensitivity (29% to 68%).[7] A negative test result therefore cannot rule out drug allergy.

In non-IgE-mediated drug allergy, patch testing and/or intradermal skin testing with delayed reading may be helpful in documenting delayed-type hypersensitivity reactions (e.g. maculopapular eruptions, fixed drug eruptions) to the implicated drug.[7] However, the clinical relevance of these late cutaneous responses is not yet fully established, and often have insufficient sensitivity.[7,8,18] A negative test result therefore cannot rule-out drug allergy.

If the test is deemed inappropriate, impractical or inconclusive, a graded challenge, also known as test dosing, is often done or added as a next step to confirm or exclude drug allergy. It is done by exposing the patient to a small amount of drug, followed by a period of close observation. It is considered the gold standard test in establishing the diagnosis but since it carries a certain amount of risk, early recognition and prompt treatment of reactions are crucial to this procedure.[7] Graded challenge and desensitization are generally contraindicated in severe non-IgE-mediated reactions with rare exceptions when the benefit of treatment outweighs the risk of a potential life-threatening reaction.[4,7]

At present, there are no reliable tests that will identify the culprit drug causing types II and III drug allergies.

SUMMARY

Routine skin testing to parenteral antibiotics should not be done to screen for allergy to antibiotics in the general population.

Clinicians should always attempt to elicit a reasonable description of a possible allergy to the same or cross reacting antibiotic.

Patients with a history of allergy to the antibiotic or cross reacting antibiotic are best referred to an allergist for proper diagnostic testing and management. Substitution with a suitable alternative non-cross reacting antibiotic is preferred over desensitization if allergy to the antibiotic or cross reacting antibiotic is established.

If the patient has no history of allergy to the antibiotic, careful monitoring for any reactions during the course of treatment should be done at all times. The clinician should be able to recognize the early signs and symptoms of allergic reactions, especially anaphylaxis, and promptly administer the correct treatment.

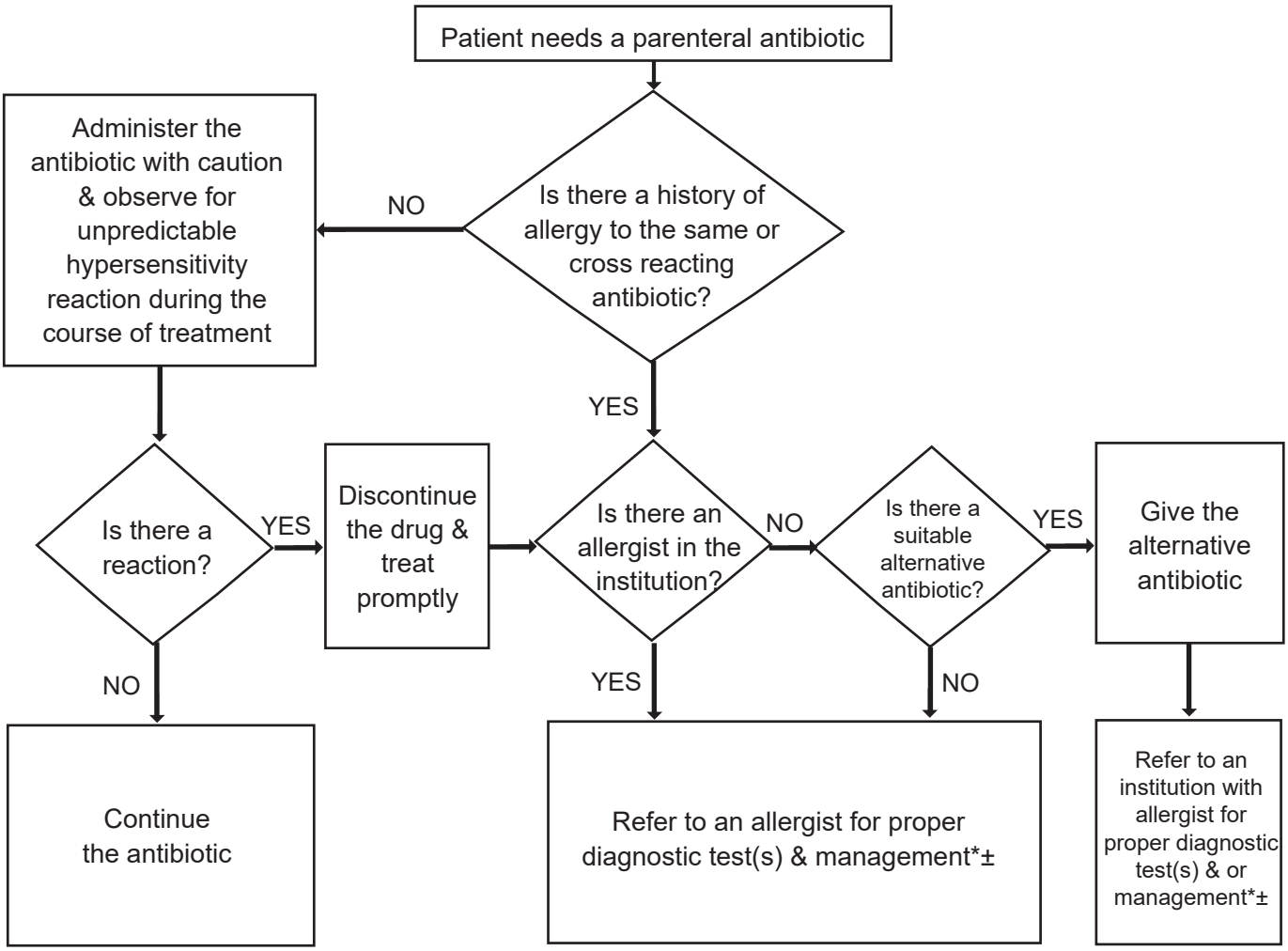
Figure 1. Flow chart when prescribing a parenteral antibiotic. *Referral mandatory; ±Referral recommended.

*Mandatory referral to an allergist for evaluation of drug hypersensitivity reaction (DHR) to antibiotics:[12]

1. Patients with history of severe DHR (e.g. anaphylaxis, SJS, TEN, DRESS) in order to identify and confirm the antibiotic that caused the reaction, and to protect patients from future reactions.
2. Patients with suspected DHR to beta lactam antibiotics who are likely to need these antibiotics in the future (e.g. primary and secondary immunodeficiencies, post-splenectomy, recurrent bacterial infections).
3. Patients with suspected or confirmed DHR to non-beta lactam antibiotics (e.g. quinolones, macrolides)

±Recommended referral to an allergist for evaluation of drug hypersensitivity reaction (DHR) to antibiotics:[12]

1. Patients with suspected non-severe DHR to beta lactam antibiotics who at the moment do not require beta lactam antibiotics. These patients are likely to be given beta lactam antibiotics in the future since beta lactams are one of the most commonly prescribed antibiotics.



DISCLAIMER

This document is based on internationally recognized guidelines bolstered by the most current studies on drug allergy diagnosis and management. Since the field of medicine is very dynamic and cases may differ, not all interventions mentioned above will be applicable to all patients. Cases that are beyond the scope of this document warrant individualized investigation and management.

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