

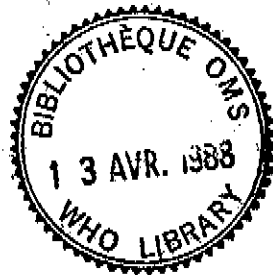


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Penicillin Reactions

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## Introduction

Penicillin and ampicillin antibiotics are recommended for the outpatient and inpatient treatment of children with pneumonia. Routine intradermal skin testing with benzyl penicillin is common in many areas of the world because of concern about severe allergic reactions, especially fatal anaphylaxis. This article reviews the three categories of penicillin allergic reactions, their frequencies, risk factors for severe reactions, the situation in which skin testing can be useful, and management of allergic reactions.

### What types of allergic reactions does penicillin produce?

Allergic penicillin reactions are classified as immediate, accelerated, or late reactions. Immediate allergic reactions occur within 30 minutes of administering penicillin. Anaphylaxis, the most severe immediate reaction, is associated with hypotension, stridor, (laryngeal edema), or wheezing (bronchospasm). Most fatal cases of anaphylaxis develop within 15 minutes of parental administration (Isdoe et al). Swelling (angioedema) and hives (urticaria) are examples of less severe and more common immediate reactions. Accelerated reactions occur from 30 minutes to 3 days after receiving penicillin. Clinical signs include wheezing, stridor, swelling, hives, and swollen joints. Late reactions occur more than 3 days after starting penicillin. Any of the clinical signs described in accelerated reactions can develop, but a rash is the most frequent sign. It is often difficult to know if the development of a rash in children treated with penicillin is caused by a viral infection or a late allergic reaction.

### How often do penicillin allergic reactions occur?

Mild allergic reactions are common, occurring in 5-10% of patients treated with penicillin (Isdoe et al). Fatal penicillin allergic reactions are very rare; 1-2 deaths occur in every 100,000 patients who receive penicillin (Isdoe et al). An additional 4 to 15 cases of non-fatal anaphylaxis occur in these 100,000 patients. Severe reactions are less likely with oral therapy; only six fatal reactions have been reported with oral administration compared to hundreds each year related to injectable penicillins. It is not clear if the form of injectable penicillin - aqueous benzyl penicillin, procaine penicillin, and benzathine penicillin - affects the frequency of fatal anaphylaxis.

### Which patients are most likely to have a severe penicillin allergic reaction?

A penicillin allergic reaction occurs in approximately 6% of individuals with a history of any type of prior reaction, as compared to 2% of individuals without an allergic history (Green G.R. et al). Individuals who have experienced an immediate type reaction are at highest risk. Ten to 30% of patients with a history of anaphylaxis or hives will have an allergic reaction on a subsequent exposure to penicillin. The age of the patient and time interval between exposures also affect the probability of a reaction (Green, G.R. et al). Reactions are more likely in young adults compared to children. Fortunately anaphylactic penicillin reactions appear to be the least frequent in children under 12 years of age (Isdoe et al). The risk of a reaction is higher when the prior reaction occurred less than 1 year prior to a subsequent exposure.

### When is penicillin skin testing useful?

The purpose of skin testing is to identify patients with skin sensitizing antibody who have a high risk of having an allergic reaction to subsequent penicillin treatment. Skin testing results cannot predict the type or severity of the reaction. Most of the penicillin given to the patient combines with a specific protein to form benzyl penicilloyl. This compound, called the major determinant, stimulates the production of skin sensitizing antibodies against benzyl penicilloyl. A special chemical, penicilloyl polylysine (PPL), must be used to skin test for reactions related to the major antigenic determinant. Penicillin also combines with proteins to form additional antigenic determinants which are present in lower concentrations and are therefore called minor determinants. The presence

of skin sensitizing antibodies related to minor determinants can be evaluated with skin tests using penicillin G. In addition, a commercial minor determinant skin testing preparation may soon become widely available. A positive skin test identifies patients at high risk for an allergic reaction; fifty to 75% of patients with positive skin tests will have an allergic reaction compared to 3-4% in patients with negative skin tests. A properly done and interpreted negative skin test to PPL and penicillin G makes the chances of an allergic reaction in a patient with a prior allergic reaction very rare. Skin testing with only penicillin G will fail to identify over half of patients who would be positive if both PPL and penicillin G were used. Unfortunately skin testing with only penicillin G will also miss approximately 1/4 of the cases who will have immediate reactions, including anaphylaxis. Therefore, a negative skin test with penicillin G does not mean that a patient with a prior allergic reaction will not have another reaction.

Also penicillin intradermal skin testing is accurate only if correctly performed and interpreted by well-trained personnel. Considerations other than the cost of skin testing reagents include the effects of delays associated with the testing, discomfort for the child, and expenses of special needles used for intradermal injections. Skin testing with appropriate reagents using correct concentrations appears to be safe.

Given the low rate of anaphylaxis (4-15 cases/100,000 patients), it is not necessary or feasible to routinely skin test with PPL and penicillin G all patients prior to giving penicillin. Skin testing with PPL and penicillin G is most useful when it is important to administer penicillin to a patient with a history compatible with a prior allergic reaction. The routine use of skin testing with penicillin G practised in developing countries has many problems. The frequencies of false positive and negative results may be high because of technical problems. False positive tests will deny patients who have no risk of a penicillin allergy the benefit of penicillin treatment. Penicillin G skin testing alone will fail to identify over half of the cases who have skin sensitizing antibody. A negative test with penicillin G in a high risk patient with a strong history of a prior reaction does not rule out the possibility of anaphylaxis.

#### Guidelines for the administration of penicillin

1. Primary health care workers, nurses and physicians should inquire if the patient had a reaction to a prior dose of a penicillin antibiotic. If so, the clinical signs should be documented with special reference to signs compatible with immediate, accelerated, and delayed reactions. Questioning about prior reactions to penicillin can be facilitated by the use of a standard questionnaire including the popular terms for the signs and symptoms (difficulty breathing, difficulty talking, hoarseness, swelling of the face, skin rash) which may occur after the oral or parental administration of the drug. The questionnaire should be field tested to be sure that the numbering, wording and order of questions are appropriate to reliably detect most cases of penicillin allergy.
2. Treat patients without a history of penicillin allergy without doing skin tests.
3. Ask all patients treated with injectable penicillin to remain for 30 minutes in case an immediate reaction develops.
4. Always have an emergency kit with epinephrine and diphenhydramine available for treatment of allergic reactions.
5. Treat patients with a good history of penicillin allergy with an effective alternative antibiotic.

If an alternative antibiotic is not available, consider the following options for inpatient and outpatient situations. If skin testing is not done or is negative, give an oral penicillin or ampicillin test dose of 25,000 units; observe the child for 15 minutes and increase dose to the standard dosage. If skin testing is positive, and no alternative

effective antibiotic is available, carry out an oral desensitization procedure (Sullivan, et al). Closely observe the child for the appearance of allergic reactions. Have epinephrine available to treat any immediate reactions. Give each oral dose with 30 cc of water. Administer doubled doses at 15 minute intervals as shown below:

Dose	Desensitization protocol*	
	Units	Route
1	100	oral
2	200	oral
3	400	oral
4	800	oral
5	1,600	oral
6	3,200	oral
7	6,400	oral
8	12,800	oral
9	25,000	oral
10	50,000	oral
11	100,000	oral
12	200,000	oral
13	400,000	oral
14	200,000	subcutaneous
15	400,000	subcutaneous
16	800,000	subcutaneous
17	1,000,000	intramuscular

\*Interval between doses, 15 min. The total regimen requires 4 hours.

Intravenous therapy if indicated may be started 15 minutes after completing this schedule.

#### What to do when a penicillin reaction occurs

Medical staff who administer penicillin and other antibiotics need training in the treatment of antibiotic allergic reactions. The treatment is based on the severity of the reaction as follows:

#### Severe reactions

Symptoms: Anaphylaxis with hypotension, stridor, or wheezing within 30 minutes of giving penicillin.

#### Initial treatment therapy

Epinephrine 1:1000 (aqueous)

infants less than 1 year:	0.1 ml. per dose
children 1-2 years:	0.2 ml. per dose
children older than 2 years	0.3 ml. per dose

Administer by intramuscular injection in the arm that did not receive the antibiotics. The dose can be repeated every 15 to 30 minutes.

#### Additional Therapy

When shock has developed, provide, if possible, intravenous therapy with 20 cc per kilogram per hour of normal saline solution. Give the patient oxygen. Secondary drugs which can be used in addition to epinephrine are:

- diphenhydramine, 25-50 mg. per dose (maximum 50 mg.) intramuscular or intravenous every six hours;

- methylprednisolone, 20-40 mg. per dose  
intramuscular  
or intravenous every 4 to 6 hours; or
- hydrocortisone, 100-200 mg. per dose intramuscular  
or  
intravenous every 4 to 6 hours

#### Less Severe Reactions

Symptoms: Swelling, hives, rashes, and swollen joints

#### Initial Therapy

Administer epinephrine 1:1000 (aqueous)

infants less than 1 year: 0.2 ml. per dose  
children 1-2 year: 0.2 ml. per dose  
children older than 2 years: 0.3 ml. per dose

Administer by subcutaneous or intramuscular injection. The dose may be repeated within 15 to 30 minutes. If the patient improves, treat with one of the following oral drugs for the next 24 hours:

diphenhydramine oral 25-30 mg. per dose, 3 times daily, or hydroxyzine oral 10-25 mg., 3 times daily.

When significant allergic reactions do not respond to this treatment after 24-48 hours, try oral prednisone, 1 mg/kg per dose (maximum 30 mg. per dose) twice daily for 3-5 days.

#### Non-allergic reaction to penicillin

Acute confusion, dizziness, hallucinations, or seizures can occur immediately following intramuscular injection of procaine penicillin G. These signs are usually associated with tachycardia and an elevated blood pressure. This acute non-allergic reaction called Hoigne's Syndrome is said to be caused by a sudden elevation of free procaine in the central nervous system. This reaction occurs at a low rate in adults receiving 4.8 million units of procaine penicillin for the treatment of gonorrhoea (Green R.L. *et al*). Very few reports have been published in children receiving procaine penicillin for bacterial infections (Telesy). The condition is self limiting and resolves without specific treatment (Sieber and D'Angelo).

The inadvertent intra-arterial injection of long-acting benzathine penicillin can produce persistent arterial vasospasm and arterial thrombus. Complications that result include vascular insufficiency, limb gangrene, or myelitis.

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