# PENICILLIN ALLERGY IN CHILDREN

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## ABSTRACT

It is not uncommon to see skin rashes during a course of treatment with penicillin and penicillin-based antibiotics. This is often assumed to be due to penicillin allergy although in most cases no testing is performed to verify the diagnosis. Many children are simply labelled 'penicillin allergic', a label which they carry into adulthood which may deny them the benefit of treatment with the most appropriate group of antibiotics. Penicillins are the most widely used antibiotics for common infections as well as being the antibiotics which most often cause allergic reactions. The incidence of self-reported penicillin allergy is 1-10% but most of these patients will test negative. Misdiagnosis of penicillin allergy may result in the unnecessary use of more expensive and less effective antibiotics as well as the emergence of multidrug-resistant organisms. History alone is unreliable in the diagnosis of penicillin allergy. Skin testing (skin-prick and intradermal testing) remains standard practice for the evaluation of patients with immediate hypersensitivity reactions (IgE-mediated) to penicillin. Skin testing combined with a thorough history, determination of specific IgE antibody level and, if indicated, a drug provocation test (DPT) should diagnose the majority of children with penicillin allergy. Patients with proven penicillin allergy can undergo desensitisation if they require penicillin therapy and no alternative is available. Accurate diagnosis of penicillin allergy is essential to avoid the morbidity, mortality and economic cost associated with unnecessary withholding of this drug in non-allergic patients.

## BACKGROUND

In the paediatric population it is not uncommon to see a skin rash during a course of treatment with a penicillin antibiotic. This is often assumed to be due to penicillin allergy. In most of these cases no testing is performed to verify the diagnosis and most children are simply labelled as 'penicillin allergic'. They end up carrying this label into adulthood and may therefore be denied the benefit of treatment with the most appropriate group of antibiotics.

Penicillin and penicillin-based antibiotics are the most widely used antibiotics for common infections.[1] They are also the antibiotics which most often cause allergic reactions[2] with the frequency of life-threatening anaphylaxis estimated to be 0.01%-0.05%.[3] The incidence of self-reported penicillin allergy varies between 1% and 10%[4] but more than 80-90% of these have no evidence of IgE antibodies to penicillin on skin-testing.[5,6] Penicillin-based antibiotics are usually less expensive and have fewer side-effects than alternative broad-spectrum antibiotics. They are also more effective for certain infections. This is especially important for patients on long-term penicillin prophylaxis (e.g. rheumatic heart disease) or treatment (e.g. bacterial endocarditis).

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## CLASSIFICATION

There are a number of ways to classify drug allergies. From a clinical perspective a practical method is to divide adverse drug reactions according to the time interval between exposure and onset of reaction – immediate, accelerated and delayed reactions. *Immediate hypersensitivity reactions* (IgE-mediated) occur up to 1 hour after exposure to the offending agent. Non-immediate reactions include *accelerated reactions* (1-72 hours) and *delayed reactions* (*>72 hours*). Immediate reactions may present with anaphylaxis, urticaria, angio-oedema and bronchospasm; accelerated/delayed reactions may manifest as serum sickness, interstitial nephritis, haemolytic anaemia, morbilliform eruptions and Stevens-Johnson syndrome.

## DIAGNOSIS (Fig. 1)

### *History*

The diagnosis of penicillin allergy begins with a detailed history. A personal or family history of drug allergies may be relevant as this may predispose to penicillin allergy[7] whereas a history of atopy does not. The signs, symptoms and severity of the reaction and any previous reactions should be documented. For example, urticaria and bronchospasm would suggest an IgE-mediated immediate drug reaction. The dose and route of administration are also important. Prolonged parenteral administration is more likely to cause a hypersensitivity reaction than the oral or topical route. A concomitant viral illness is important as this may cause a rash that is mistaken for penicillin allergy. The maculopapular rash induced by ampicillin or amoxicillin given to a child with Epstein-Barr virus infection may also be mistaken for a drug allergy.

### *Physical examination*

The clinical examination should focus on the skin, mucous membranes and the chest. On the skin one should distinguish between an urticarial and a morbilliform or maculopapular rash. Mucous membrane

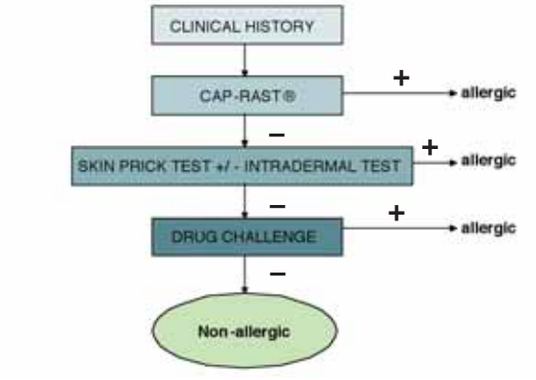


*Fig. 1. Basic algorithm for drug allergy testing.*

involvement may indicate Stevens-Johnsons syndrome or toxic epidermal necrolysis. The presence of wheezing or stridor should be noted on examination of the respiratory system.

### *Investigations*

Penicillin is metabolised into major (penicilloyl) and minor (penicilloate and penilloate) antigenic determinants. It is essential to test sensitivity to both minor and major determinants, as testing only for major determinants would miss at least 10% of penicillin-sensitive subjects.

- Blood tests

  During an acute hypersensitivity reaction a *serum tryptase* level should be performed. This is a sensitive and specific test of mast-cell activation. Ideally blood is taken at 0, 1 and 6 hours after the reaction and placed in a lithium-heparin tube. A peak at 1 hour with a fall to normal levels within 12-24 hours is diagnostic of mast-cell degranulation and an IgE-mediated reaction.

  A *CAP-RAST* for IgE antibodies to amoxicillin, ampicillin, penicillin V, penicillin G and cefaclor is available to aid in the diagnosis. The blood should be taken from 6 weeks after the acute reaction has taken place in order to get the most accurate results. The sensitivity is approximately 80-90%[8] but it does not test for the minor determinants of penicillin.[5]

  More recently the *CAST* (cellular antigen stimulation test) has become available. This test measures the *in vitro* production of sulphidoleukotrienes by leucocytes when stimulated by the specific drug. The sensitivity and specificity are approximately 46% and 85% respectively.[9]

- Skin tests (Fig. 2)

  The skin-test panel should include a positive (histamine 10 mg/ml) and a negative (0.9% saline) control as well as a major determinant mixture and minor determinant mixture. Amoxicillin (20-25 mg/ml) should be added to the skin-test panel[8,10] as its side chain is not included in the above two mixtures. If the offending drug is something other than one of these, it should be added to the panel with the understanding that the negative predictive value of such a test is unknown. A wheal 3 mm or more greater than the negative control is considered a positive test result.

  Skin-prick testing (SPT) is a reliable and relatively safe procedure for detecting IgE-mediated penicillin allergy. It has a specificity approaching 100% for IgE-mediated allergy.[10-13] The sensitivity is relatively low (50-70%)[10,12] (Table I). Anaphylaxis has never been reported in a skin-test-negative individual challenged with the medication. SPT is not indicated if the history suggests a non-IgE-mediated hypersensitivity reaction such as Stevens-Johnson syndrome or serum sickness. In these patients, penicillin should be avoided indefinitely.

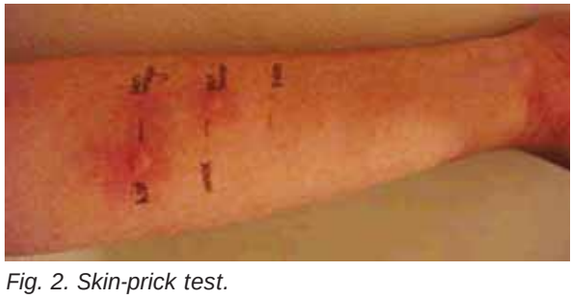

*Fig. 2. Skin-prick test.*

*Table I. The predictive value of penicillin skin tests*

| | | | | |
|---|---|---|---|---|
| History of penicillin allergy | + | + | – | – |
| Penicillin skin test status | + | – | + | – |
| Frequency of allergic reactions associated with penicillin administration | 50-70% | 1-3% | 10% | 0.5% |

- Drug provocation test (DPT)

  If the penicillin skin tests are negative and the IgE antibody levels are normal, a DPT should be performed in a setting where resuscitation equipment and trained personnel are available. A suggestive history of allergy together with a positive CAP-RAST and/or a positive skin test is sufficient for the diagnosis of penicillin allergy without the need to perform a DPT.[10,12] A DPT is not recommended if there is a history of anaphylaxis.

## MANAGEMENT

*Initial management* of acute penicillin allergy consists of discontinuing the drug and treating the clinical reactions, e.g. anaphylaxis, urticaria or wheeze. *Subsequent management* entails confirming the diagnosis, strict avoidance of the offending drug and patient education (including the use of injectable adrenaline for prevention of anaphylaxis). A Medic Alert bracelet should also be obtained.

*Desensitisation* to the drug (either by the oral or intravenous route) should be considered in children with IgE-mediated reactions if no alternative treatment to penicillin is available. Desensitisation must be conducted in an intensive care unit by experienced personnel. The aim of desensitisation is to convert a patient who is highly allergic to penicillin to a state in which they can tolerate the drug. The basic principle is to start with a minute dose, then double it every 15 minutes until a full dose is reached. Various desensitisation protocols are available (Tables II and III[14]). Penicillin therapy must be commenced immediately after completing desensitisation (tolerance is only temporary). Desensitisation must be repeated if a course of penicillin is required again.

Minor adverse reactions may occur after this procedure in a third of cases but no fatal or life-threatening

*Table II. Penicillin oral desensitisation protocol*

| Step* | Penicillin (mg/ml) | Amount (ml) | Dose given (mg) | Cumulative dose (mg) |
|---|---|---|---|---|
| 1 | 0.5 | 0.1 | 0.05 | 0.05 |
| 2 | 0.5 | 0.2 | 0.1 | 0.15 |
| 3 | 0.5 | 0.4 | 0.2 | 0.35 |
| 4 | 0.5 | 0.8 | 0.4 | 0.75 |
| 5 | 0.5 | 1.6 | 0.8 | 1.55 |
| 6 | 0.5 | 3.2 | 1.6 | 3.15 |
| 7 | 0.5 | 6.4 | 3.2 | 6.35 |
| 8 | 5 | 1.2 | 6 | 12.35 |
| 9 | 5 | 2.4 | 12 | 24.35 |
| 10 | 5 | 5 | 25 | 49.35 |
| 11 | 50 | 1 | 50 | 100 |
| 12 | 50 | 2 | 100 | 200 |
| 13 | 50 | 4 | 200 | 400 |
| 14 | 50 | 8 | 400 | 800 |

Observe patient for 30 minutes, then give full therapeutic dose by the desired route.

Modified from Sullivan TJ.[14]

*Interval between doses is 15 minutes.

*Table III.* Penicillin intravenous desensitisation protocol with drugs added by piggyback infusion

| Step* | Penicillin (mg/ml) | Amount (ml) | Dose given (mg) | Cumulative dose (mg) |
|---|---|---|---|---|
| 1 | 0.1 | 0.1 | 0.01 | 0.01 |
| 2 | 0.1 | 0.2 | 0.02 | 0.03 |
| 3 | 0.1 | 0.4 | 0.04 | 0.07 |
| 4 | 0.1 | 0.8 | 0.08 | 0.15 |
| 5 | 0.1 | 1.6 | 0.16 | 0.31 |
| 6 | 1 | 0.32 | 0.32 | 0.63 |
| 7 | 1 | 0.64 | 0.64 | 1.27 |
| 8 | 1 | 1.2 | 1.2 | 2.47 |
| 9 | 10 | 0.24 | 2.4 | 4.87 |
| 10 | 10 | 0.48 | 4.8 | 10 |
| 11 | 10 | 1 | 10 | 20 |
| 12 | 10 | 2 | 20 | 40 |
| 13 | 100 | 0.4 | 40 | 80 |
| 14 | 100 | 0.8 | 80 | 160 |
| 15 | 100 | 1.6 | 160 | 320 |
| 16 | 1000 | 0.32 | 320 | 640 |
| 17 | 1000 | 0.64 | 640 | 1280 |

Observe patient for 30 minutes, then give full therapeutic dose by the desired route.

Modified from Sullivan TJ.[14]

*Interval between doses is 15 minutes.

reactions have been reported to date. It is important to note that desensitisation will not prevent non-IgE reactions such as serum sickness, haemolytic anaemia or interstitial nephritis from occurring.

## CROSS-REACTIVITY WITH OTHER ANTIBIOTICS

Up to 20% of patients with penicillin allergy may develop an adverse reaction to *cephalosporins*[15] (particularly with 1st and 2nd generation agents). The rate of cross reactivity with the 3rd and 4th generation cephalosporins is much lower. Cross-reactivity between these drugs is believed to be due to the drugs having similar R-group side chains and not due to the β-lactam ring itself (Fig. 3). For example, amoxicillin shares a side-chain with cefadroxil, cefotaxime with ceftriaxone, and ampicillin with both cefalexin and cefaclor. It is recommended that penicillin-allergic patients who require a cephalosporin should undergo SPT. If this is negative, a cephalosporin can be safely administered[5] with a less than 1% risk of a mild systemic reaction.

In a patient with a known allergy to a *cephalosporin*, substitution with a cephalosporin with a different side chain is usually safe.

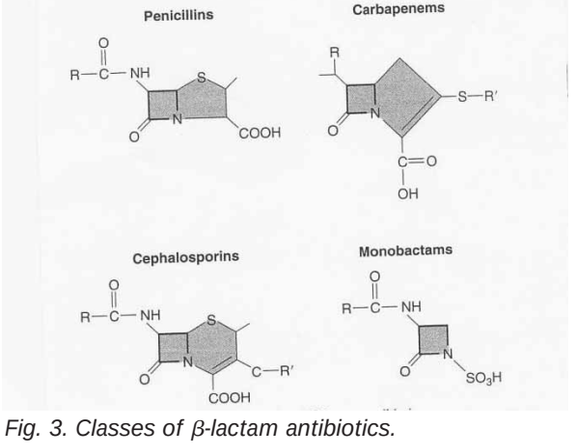


*Fig. 3. Classes of β-lactam antibiotics.*

Cross-reactivity between penicillin and c*arbapenems* is also reported: 50% with imipenem[16] and 10% with meropenem,[17] based on history and SPT. In studies where DPTs were also done, cross-reactivity was reportedly <1%.[18]

## CONCLUSIONS

Allergic reactions to penicillin (anaphylaxis in particular) are relatively infrequent in the paediatric population. The majority of children with the label of penicillin allergy can safely take this drug without fear of an allergic reaction. Misdiagnosis of penicillin allergy may result in the unnecessary use of more expensive and less effective antibiotics as well as the emergence of multidrug-resistant organisms. History alone (usually poorly documented and often vague) is unreliable in the diagnosis of penicillin allergy. SPT remains the standard practice for the evaluation of patients with immediate hypersensitivity reactions (IgE-mediated) to penicillin. SPT combined with a thorough history, determination of specific IgE antibody level and, if indicated, a DPT should diagnose the majority of children with penicillin allergy. Patients with proven penicillin allergy can undergo desensitisation if they require penicillin therapy and no alternative is available. Accurate diagnosis of penicillin allergy is essential to avoid the morbidity, mortality and economic cost associated with unnecessary withholding of this drug in non-allergic patients.

### Declaration of conflict of interest

The authors declare no conflict of interest.

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