

Penicillin allergy in children: The role of immunological tests in its diagnosis

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Of 160 hospitalized children who were thought to be allergic to penicillin, only 17 had positive immunologic tests. Of these, 16 had positive skin tests and only 10 had significant titers of hemagglutinating antibodies. Three children had acute, explosive reactions, 4 had accelerated reactions, and 11 had late-onset reactions. In the 143 children with negative immunological tests, the diagnosis of penicillin allergy was often questionable on clinical grounds alone. Whatever the clinical features, negative tests have helped to establish the safety of subsequent penicillin treatment for many of these children.

Urticaria or other skin rashes frequently accompany infectious diseases in children. If a child is receiving penicillin therapy, the physician is faced with a dilemma as to whether these manifestations are related to the disease or represent penicillin allergy.

This study was designed to evaluate the usefulness of current immunological methods in ruling out penicillin allergy in children and in identifying those few children who have become sensitized.

MATERIALS AND METHODS

Between 1960 and 1968, 160 children admitted to the University of Washington Affiliated Hospitals (Children's Orthopedic Hospital and Medical Center, King County Hospital, University Hospital, and United States Public Health Service Hospital), whose admitting physicians' diagnoses included "penicillin allergy," were studied. All patients were examined by one of the authors.

Direct skin tests were performed with the use of an old solution of

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Table I. *Summary of immunological studies*

<i>Clinical features</i>	<i>Number of patients</i>
Penicillin antibodies identified	17
No penicillin antibodies (143 patients)	
Infectious disease	121
Inappropriate clinical reaction	15
Inadvertent penicillin, no reaction	7
Total	160

benzylpenicillin* (O.P.), containing 0.6 mg. per milliliter (1,000 units per milliliter),^{1, 2} and benzylpenicilloyl polylysine (P.P.L.), 5×10^{-6} M. If preliminary scratch tests were negative, approximately 0.02 ml. of antigen was injected intradermally. The site was inspected in 15 minutes. A reaction was recorded as positive if a sharply demarcated wheal appeared, which was greater than 4 mm. in diameter, surrounded by erythema and frequently associated with itching.

Passive transfer studies for the presence of skin-sensitizing antibody were carried out by the intradermal injection of 0.1 ml. of patient's serum at two or more sites in a nonallergic recipient. Each site was challenged 24 or 48 hours later by the intradermal injection of either O.P., 6 mg. per milliliter (10,000 units per milliliter), or P.P.L. (5×10^{-6} M).

Sera were tested for passive hemagglutinating antibodies as previously described from this laboratory.^{4, 5}

Penicillin was carefully readministered to those patients with negative immunological tests whose illness necessitated penicillin therapy.

RESULTS

The ages of the 160 children studied ranged from 9 months to 14 years. Of these, 143 had negative tests as shown in Table I, suggesting the possibility of alternative explanations for their symptoms. A majority of those with negative tests (121 patients) had such diseases as roseola, herpangina, infectious mononucleosis, erythema multiforme, adenoviral infections, and mycoplasma pneumoniae. Fifteen patients had clinical features not consistent with drug allergy, such as an inappropriate fever pattern,⁶ a worsening of pre-existent bronchospasm after penicillin administration for bronchitis, rectal bleeding following parenteral penicillin administration, and vasovagal syncope. Seven patients again received penicillin or a homologue inadvertently without a recurrence of symptoms, definitely ruling out hypersensitivity.

Immunological tests were positive in 17 children. The data on these children are summarized in Table II. Eleven children were under 5 years of age, 4 were between 5 and 10 years, and 2 were 10 years or older. Ten were boys and 7 were girls. There was no apparent relationship between patient age and type of reaction.

*A sterile solution of benzylpenicillin diluted with alkaline buffered saline was permitted to stand at room temperature for at least 2 weeks and not more than 4 weeks.

Table II. *Summary of clinical and immunological data of 17 penicillin-allergic children*

Patient No.	Age (years)	Sex	Illness	Type of reaction	Skin-sensitizing antibody*		Hemagglutinating antibody titer
					P.P.L.	O.P.	
1	5½	M	Pyoderma	Immediate	++	+++	1:4
2	3	M	Cellulitis	Immediate	+++	+++	1:2
3	3	F	Bronchitis	Immediate	++	+++	1:1
4	3	M	Otitis	Accelerated	++	—	1:8
5	5½	F	Pyoderma	Accelerated	+++	—	Negative
6	4	F	Upper respiratory infection	Accelerated	++++	—	1:8
7	7	M	β-strep pharyngitis	Accelerated	++	+++	1:16
8	1½	F	Dental extraction Congenital heart disease	Late onset	++++	—	1:16
9	5¼	M	Pneumonia	Late onset	—	+++	1:128
10	3	F	Rheumatic fever	Late onset	++++	—	Negative
11	3	M	Pyoderma	Late onset			1:16
12	9½	M	Asthma	Late onset	+++	—	Negative
13	10	F	Pharyngitis	Late onset	++	+++ (delayed)	1:8
14	9½	M	Infected A-V shunt	Late onset	+++	+++	1:8
15	2½	M	Cellulitis	Late onset	+++	+	Negative
16	1½	M	Cellulitis	Late onset	+++	++	1:16
17	14	F	Pneumonia	Late onset	++++	+++	1:8

*All positive direct skin tests were confirmed by P-K testing.

Three children had acute, explosive reactions occurring within minutes after administration of penicillin, manifested by one or more of the following: (1) generalized flush; (2) urticaria; (3) spasmodic coughing; (4) dyspnea; and (5) hypotension.

Four children had accelerated reactions occurring 2 to 48 hours after penicillin administration manifested by: (1) urticaria-angioedema (4 patients); (2) fever, disappearing on discontinuation of penicillin (3 patients); (3) eosinophilia over 400 per cubic millimeter, disappearing on discontinuation of penicillin (2 patients); (4) swollen joints (2 patients); and (5) laryngeal edema (2 patients).

Ten children had late-onset reactions occurring more than 48 hours after initiating penicillin therapy manifested by: (1) fever, disappearing on discontinuation of penicillin (8 patients); (2) eosinophilia in association with other manifestations (7 patients); (3) urticaria-angioedema (6 patients); (4) swollen joints (5 patients); (5) macular rash, recurring on readministration of penicillin (4 patients); and (6) generalized adenopathy (2 patients).

All 3 children with immediate, explosive reactions had positive O.P. skin tests, and one had a positive skin test to P.P.L. Two children had negative tests to O.P. a few hours after their reaction, but the tests were positive 36 hours later. None of these had a significant hemagglutinating antibody titer. Of 4 children with accelerated reactions, one had a positive O.P. skin test and 2 had positive P.P.L. skin tests. Three had hemagglutinating antibodies in a titer greater than

1:4. Of 10 children with late-onset reactions, 9 were skin tested, the other being unavailable. Four of the 9 had positive O.P. skin tests; 7 of 9 had positive P.P.L. skin tests. Seven of 10 had significant hemagglutinating antibody titers. Positive direct skin tests were associated with circulating skin-sensitizing antibody as determined by P-K testing in all cases.

DISCUSSION

Many children have frequent acute infections for which antibiotics may be prescribed, and childhood infections are frequently accompanied by various skin rashes. For example, epidemic infections in this community with an adenovirus (type 9) in 1966 and, more recently, with *mycoplasma pneumoniae* have been commonly associated with urticaria. This study was initiated to evaluate the usefulness of immunological techniques to support or, more likely, to help rule out the diagnosis of allergy to penicillin. Patients admitted to the hospital with an initial diagnosis of "penicillin allergy" were evaluated either because their presenting symptoms were felt to be due to penicillin allergy or because they had a history of a reaction attributed to penicillin but had developed an infection for which penicillin was the appropriate antibiotic.

Many children were admitted with clinical syndromes which, in retrospect, were inconsistent with drug allergy. Others had symptoms which could have been due either to penicillin hypersensitivity or to the illness for which the drug was prescribed. In the latter, immunological studies have proved useful in ruling out penicillin allergy.

The few children who appeared to have true penicillin allergy had clinical reactions similar to those of adults. The 3 patients who developed acute symptoms minutes after penicillin administration presented little difficulty in diagnosis. All 3 had positive O.P. skin tests, and one had a positive P.P.L. skin test. None had significant hemagglutinating antibodies. It was interesting that skin tests performed within hours of the reaction in 2 patients were negative but became positive 36 hours to 5 days later, possibly reflecting a temporary anergic state following the reaction.

Accelerated reactions occurred 2 to 48 hours after penicillin administration in 4 children, all of whom developed urticaria. Two patients also developed acute laryngeal edema, and one required a tracheostomy. Only one of the 4 children had O.P. skin-sensitizing antibody, and this child also had significant serum hemagglutinating antibodies. The other 3 had both P.P.L. skin sensitivity and serum hemagglutinating antibodies.

The late-onset reactions encountered in 10 children, manifested by urticaria, maculopapular rashes, angioedema, swollen tender joints, or fever, were more difficult to diagnose. Four children had P.P.L., O.P., and hemagglutinating antibodies, one child had P.P.L. and hemagglutinating antibodies, 3 had P.P.L. antibodies alone, and one had both O.P. and serum hemagglutinating antibodies. All children who had O.P. antibodies also had hemagglutinating antibodies, suggesting that the latter may have protected them from explosive reactions. The child who was not skin tested is discussed later.

The antibody patterns noted in these patients are similar to those reported

by others.^{5, 7} The most important sensitivity in those children who had acute explosive reactions was the skin reaction to O.P. Old penicillin was used in this study, rather than the benzylpenicillin minor determinant mixture,¹¹ because the latter had not been developed when the study was initiated and such penicillin solutions were customarily used at that time.¹² Old penicillin was used rather than freshly prepared solutions, since skin reactions to breakdown products such as benzylpenicilloate present in old solutions¹³ are more likely to identify the patient with "minor determinant sensitivities."¹⁴

Skin sensitivity to P.P.L. has been studied extensively^{2, 5, 11} and appears to be related to accelerated or late-onset penicillin reactions, though rarely it may be responsible for immediate reactions.¹⁵

The passive penicilloyl hemagglutinating test, as performed in this laboratory, is less sensitive than that reported by others,^{3, 7, 11} and a titer of 1:8 or greater is found in less than 5 per cent of sera from adult patients with no history of allergy.⁴ It is interesting, then, that such a small number of children (10 out of 160) in this group selected for possible penicillin allergy had significant titers. All but one of these had positive skin tests in addition. The other (Patient No. 11, Table II) could not be tested directly, and the serum was inadvertently discarded before P-K testing could be done. He was included in the series to indicate that a positive hemagglutination test is interpreted as supporting the diagnosis of allergy, even though it is very unlikely that the antibody involved mediates the clinical reaction. On the other hand, it is obvious from Table II that the hemagglutination test alone does not help to rule out allergy to penicillin. A more sensitive test,⁷ which is positive even in patients who have never received penicillin, has been particularly useful in studying the nature of the antibodies involved, but in clinical specificity it has no advantage over that which was used in this study.

Negative skin tests to O.P. and P.P.L. were useful in predicting that the child could tolerate penicillin. Challenge tests, carried out with appropriate emergency equipment on hand, were administered to those 41 children with negative skin tests for whom penicillin was the indicated antibiotic. After a small dose (5 mg.), usually administered orally, was tolerated without reaction, a larger dosage (250 mg.) was administered orally prior to institution of full therapy. No adverse reactions of any sort have occurred. Challenge tests were not carried out on any of the children with positive immunological tests.

This study confirms other studies that most suspected penicillin reactions in children are not due to penicillin allergy^{9, 16} and provides further evidence that skin tests are most useful to help rule out clinical penicillin allergy.^{10, 15}

Since the patients included in this study were all hospitalized, they represent a selected population containing a disproportionate number of younger children. Accordingly, we are now engaged in a prospective study of all children with a history of suspected penicillin allergy. If skin tests and passive hemagglutinating antibody titers are negative, the patients receive a penicillin challenge. To date we have studied 41 children who have been diagnosed as "allergic to penicillin" by their referring physicians but have not been hospitalized. This study will be the subject of a further communication.

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