

Allergy to penicillin with good tolerance to other penicillins; study of the incidence in subjects allergic to betalactams

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Summary

Two hundred and eighty-eight subjects with a history of allergy to penicillin were studied for objective proof of their allergy. On the basis of skin tests, specific IgE antibody measurements and direct challenge tests, 64 patients (22%) were shown objectively to be allergic to one or more penicillins. The following tests were carried out: skin tests to benzyl-penicilloyl poly-L-lysine (BPO-PLL), minor determinant mixture (MDM), amoxycillin (AX) and ampicillin (AMP), in-vitro IgE antibody measurement to benzyl-penicilloyl (BPO) and AX and challenge with benzylpenicillin (BP), phenoxymethyl-penicillin (PV) and amoxycillin. Forty-four cases were found to respond to benzyl or phenoxymethyl-penicillin, however, 20 were shown to be sensitive to amoxycillin and unresponsive to tests with other penicillins. The contribution that any individual test gave for establishing the diagnosis was 21.8% for skin testing with BPO-PLL, 9.3% with MDM and 12.5% with AX. Nine point three per cent were RAST positive to BPO and 1.5% to AX; 7.8% developed a positive response after challenge to BP, 7.8% to PV and 14% to AX. In 16% of the 64 positive cases more than one test was found to be positive. The challenge tests suggested that not all the penicillin-sensitive subjects had IgE-mediated reactions implying other immunological mechanisms. These results clearly demonstrate the importance of side chain-specific diagnostic reagents and challenge tests. Thirty-one per cent of the positive group or 6.9% of the total group would have been missed in this study using benzyl or phenoxymethyl-penicillin diagnostic reagents alone.

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Introduction

The penicillins are a widely used group of betalactam-containing antibiotics. In use they are relatively non-toxic but nevertheless they are the commonest cause of adverse reactions with an immunological basis. These reactions are caused by a variety of immunological mechanisms but the commonest and most studied is the type I anaphylactic reaction classically mediated by IgE antibody of benzyl-penicilloyl (BPO) specificity [1,2]. However, in a number of cases, whilst symptoms suggest an anaphylactic reaction, *in-vivo* and *in-vitro* studies fail to show the

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presence of specific IgE antibody. The reason for this could, in part, be the reliance on benzylpenicillin related diagnostics, e.g. BPO-based skin tests and radio-allergo-sorbent (RAST) reagents and the minor determinant mixture (MDM) skin-test material which is also derived from benzylpenicillin. Penicillins developed after benzylpenicillin differ in their side-chain structure and several studies, both clinical and experimental, have shown the importance of the acyl side chain as a determinant of allergic/immunological responses [3,4], and for crossreactivities [5-8]. We considered that subjects could be allergic to a new penicillin and not react to benzylpenicillin-related diagnostics. A previous study confirmed this with the discovery of patients who were allergic to amoxycillin

(confirmed by challenge, skin test and RAST using amoxycillin) but negative to benzylpenicillin [9]. The current study extends that finding and investigates the frequency of this type of specificity amongst a large number of penicillin-allergic subjects and also reports some of their clinical characteristics.

Subjects and methods

Subjects

Over a period of 2 years, 288 patients who presented at the clinic with a history of an allergic reaction to a penicillin consented to take part in further investigations. Most of the patients were referred by general practitioners, a small proportion came from emergency units. The studies consisted of skin tests, specific-antibody IgE measurement (RAST) and direct challenge test with various penicillins. The testing protocol was as follows: subjects were skin tested with BPO poly-L-lysine and MDM (Stallergens, Fresnes, France) and the RAST test was carried out on their serum. If any of the tests were positive the subject was considered to be allergic to penicillin and included in the investigation. If a subject was negative in all the tests they were challenged with benzylpenicillin parenterally and if still unresponsive they were challenged orally with phenoxymethyl-penicillin. If a subject was negative to the challenge tests then they were further investigated for allergy to amoxycillin. This was carried out using skin tests, an amoxycillin-based RAST system and in most cases by direct challenge with amoxycillin to confirm the clinical diagnosis. Subjects who gave a positive challenge from these tests were included in the final subject total from which the frequency of amoxycillin allergics unresponsive to benzyl and phenoxymethyl-penicillin was to be calculated. The clinical characteristics of each case were classified as follows: urticaria for erythematous areas of different sizes elevated over the skin, exanthema or exanthematic rash for maculae of small size elements not elevated over the skin, erythema for diffuse and extensive areas of homogeneous red skin and anaphylactic shock for hypotension, generalized pruritus, malaise, nausea, vomiting and dyspnea.

Intradermal skin testing

The following reagents were used: BPO-poly-L-lysine (BPO-PLL) 5×10 and MDM 2×10 (Stallergens), ampicillin and amoxycillin (Beecham Pharmaceuticals, Epsom, U.K.) at concentrations up to 20 mg/ml. These tests were carried out as described previously [9,10] using 0.02 ml of penicillin solution with results expressed as a percentage of the control histamine weal area. These concentrations proved to be non-irritant in a negative

control group tested [10]. The schedule for skin testing was as follows. Subjects were tested with PBO-PLL and provided no systemic reactions occurred they were tested with MDM 1 hr later. On a different day subjects were tested with ampicillin and then with amoxycillin 1 hr later unless there was a severe systemic reaction. Subjects were reassessed 24–48 hr after skin testing for evidence of delayed reactions to any of the reagents used.

Specific IgE antibody measurement (RAST)

Reagents for the measurement of specific IgE antibody against ampicillin and amoxycillin were prepared as described previously [11]. Previous studies with sera from known amoxycillin and ampicillin allergics and negative control sera had shown that this method gives RAST reagents with optimum sensitivity and discrimination. Measurements of BPO IgE antibody were carried out in a similar way using BPO-coated paper discs from Pharmacia (Uppsala, Sweden). Results were expressed as percentage uptake of label compared with the total counts added. Sera from a negative control group were also assayed using the three RAST systems. Results for the test sera greater than the mean of the control group plus 2 standard deviations were considered positive.

Provocation tests

The provocation tests with the various penicillins were carried out as follows. Subjects who were negative when skin tested with BPO-PLL and MDM and whose sera were negative in the BPO RAST were given 10^6 units of benzylpenicillin parenterally. If there was no immediate or delayed reactions during 1 week of observation, the subjects were given 600 units of phenoxymethyl-penicillin every 8 hr during 3 days. If there was no reaction to this challenge and subsequent skin tests with amoxycillin did not give a systemic reaction, then oral challenge with 5 mg of amoxycillin was carried out. If there was no reaction to this, a 500 mg capsule of amoxycillin was given every 8 hr during 3 days, followed by a further week of observation.

This protocol was approved by the ethical committee of the hospital.

Results

Subjects

The testing protocol described in the Subjects and methods section resulted in 64 subjects objectively diagnosed as allergic to penicillin out of a total number of 288 subjects evaluated. This gives a prevalence of 22% in the population studied. The mean age for the subjects was 40 yr. (range 13–70) with 35 males and 29 females. The

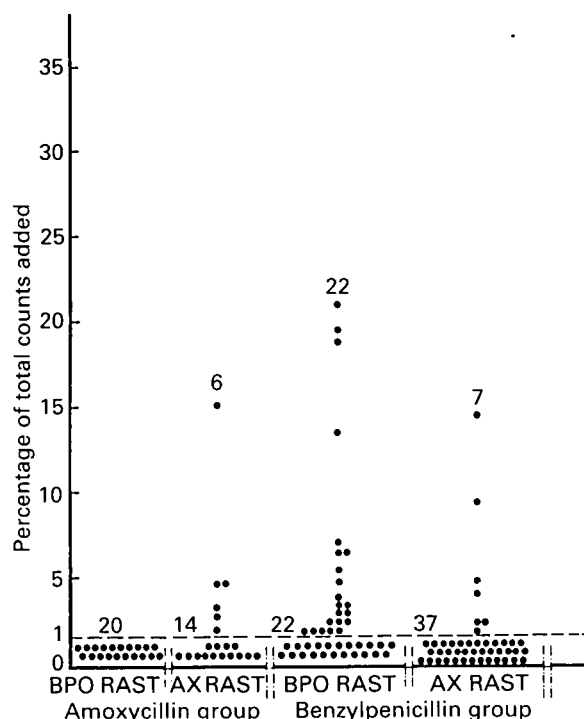


Fig. 1. Specific IgE to BPO and AX. In the right half of the figure the data from the 44 subjects that were allergic to benzylpenicillin are shown. Twenty-two cases had IgE to BPO and seven out of this 22 also had IgE to AX. In the left half of the figure the group of 20 subjects allergic to AX is shown. All of them were BPO-negative and six out of the 20 had IgE antibodies to AX.

involvement of the different penicillins according to the data of the clinical reports was: in 41.5% amoxycillin was the inducing agent, in 28.1 benzylpenicillin, in 9.8% ampicillin, in 8.5% clavulanic acid-amoxycillin, in 2.4% bacampicillin, in 1.2% metampicillin and in 8.5% the subjects could not identify the name of the penicillin derivative involved. Of the 64 cases, 34 reported an allergic episode on one occasion, 24 on two occasions and six subjects on three occasions. Objective diagnostic tests showed that 44 of the 64 subjects were allergic to benzylpenicillin or phenoxymethyl-penicillin. Thirty-four of the 44 subjects were diagnosed by skin test and/or RAST: 28 of these were skin-test positive to BPO and/or MDM (eight to BPO and MDM, 14 to BPO and six to MDM) and 22 cases had IgE antibodies to BPO. Of these 22, six subjects were skin-test negative. In addition seven sera with BPO-specific IgE antibody were also RAST-positive to AX (Fig. 1). In contrast, only three subjects who were skin-test positive were also positive to AX and AMP. The remaining 10 subjects negative by skin test and/or RAST are presented in Table 1. In five cases the reaction occurred immediately after the intake of the drug and in the other five a delayed response appeared that varied from 24 hr (case 10) to 1 week (case 1) after treatment. These 10 subjects were challenged according to the procedure described earlier. Details of the challenge are given in Table 2. Cases 2, 7, 8, and 9 gave an immediate response after challenge. Case 4 was not challenged, because although skin-test negative she developed a systemic response consisting of generalized facial erythema and conjunctivitis with itching nose and rhinorrhea. Subjects 1, 3, 5, 6 and 10 developed delayed

Table 1. Clinical characteristics of 10 subjects allergic to penicillin who were skin-test negative to BPO and MDM and RAST-negative to BPO, but responded to challenge (see Table 2)

Subject no.	Age (yr)	Sex	Clinical manifestations	Interval*
1	40	F	Pruritus and exanthema 1 week after oral intake of PV	3 months
2	50	M	Generalized pruritus, erythema, hypotension after injection of BAC	4 yr
3	38	M	Pruritus and exanthema 3 days after oral intake of AX	5 yr
4	60	F	Generalized urticaria and facial angioedema after injection of BP	8 months
5	43	F	Generalized urticaria and pruritus several days after oral intake of AX	16 months
6	58	F	Exanthema 3 days after completing a treatment of BP injections	12 months
7	62	F	Urticaria and angioedema immediately after BP injection	10 months
8	62	F	Hypotension and loss of consciousness after BP injection	4 yr
9	49	F	Generalized pruritus and facial angioedema after BP injection	2 yr
10	58	M	Erythema and pruritus 24 hr after oral intake of AMP	10 yr

*Interval is the time elapsed between the appearance of the last reaction reported and the initiation of the study.

PV: phenoxymethyl-penicillin; BAC: bacampicillin; AX: amoxycillin; BP: benzylpenicillin; AMP: ampicillin.

Table 2. Results of challenge with benzylpenicillin (BP) and phenoxymethyl-penicillin (PV) in a group of subjects with negative skin tests to BPO and MDM and RAST-negative to BPO (see Table 1)

Subject no.	Reaction induced after challenge
1	Macular rash with pruritus in chest, abdomen and legs two days after taking 600 mg PV
2	Immediate pruritus and generalized erythema after 1×10^6 units of BP injection
3	Generalized macular rash after 3 days of taking 600 mg PV
4	n.d.
5	Pruritus and macular rash in legs and abdomen after the second day of taking 600 mg of PV
6	Generalized erythema in trunk, face and abdomen after 1 day of taking 600 mg PV
7	Facial and lip angioedema 1 hr after giving 1×10^6 units of PG parenterally
8	Hypotension and nausea after injection of 1×10^6 units of PG parenterally
9	Generalized pruritus and lip angioedema after 1×10^6 units of BP parenterally
10	Macular erythema 2 days after taking 600 mg PV

Subjects 1, 3, 5, 6 and 10 experienced delayed reactions; subjects 2, 7, 8 and 9 developed immediate reactions. Subject 4 was not challenged because of systemic symptoms during skin testing: she was considered as challenge positive.

Table 3. Subjects selected as allergic to amoxycillin (AX) with good tolerance to benzylpenicillin (BP) and phenoxymethyl-penicillin (PV)

Subject no.	Age (yr)	Sex	Clinical manifestations	Interval
11	40	F	Generalized pruritus, erythema and angioedema after oral AX	14 days
12	30	M	Generalized pruritus, erythema and hypotension after oral AX	16 days
13	40	M	Generalized erythema, facial angioedema by an unidentified betalactam	24 months
14	35	F	Hypotension and loss of consciousness after oral AX	12 months
15	60	F	Generalized urticaria and pruritus after oral AX	12 months
16	40	F	Generalized erythema and pruritus after taking oral AX	12 months
17	38	F	Generalized erythema and pruritus 8 days after a capsule of AX q.i.d.	8 months
18	30	M	Facial angioedema, pruritus, hypotension, loss of consciousness (oral (AX)	3 months
19	70	F	Generalized erythema, pruritus 48 hr after injection of unknown betalactam	23 months
20	40	M	Generalized urticaria, pruritus 72 hr after taking oral AX	4 months
21	38	M	Generalized erythema, pruritus, loss of consciousness after oral AX	10 days
22	41	F	Generalized urticaria, angioedema 2 days after taking oral AX	14 months
23	38	F	Generalized erythema, pruritus after taking oral AX	14 months
24	19	F	Nausea, vomiting, loss of consciousness, facial angioedema after oral AX	16 months
25	28	F	Generalized erythema, pruritus after taking oral AX-CLAV	3 months
26	13	F	Urticaria after oral AX	24 months
27	39	M	Hypotension, generalized erythema, angioedema after oral AX	2 months
28	70	M	Hypotension, loss of consciousness after oral AX	2 months
29	60	M	Hypotension, difficult for breathing after oral AX	10 days
30	50	M	Hypotension, generalized erythema after oral AX	24 months

AX-CLAV: amoxycillin-clavulanic acid.

Abbreviations as in Table 1.

Table 4. Results of skin tests and specific IgE measurements for the 20 subjects in Table 3

Subject no.	Immediate skin tests				RAST		
	BPO	MDM	AX	AMP	BPO	AX	AMP
11	—	—	—	—	0	0.9	0
12	—	—	100	—	0	4.1	0.7
13	—	—	—	—	0.2	0.1	0.1
14	—	—	—	—	0.4	0.2	0.2
15	—	—	—	—	0.6	0.1	0.2
16	—	—	—	—	0.4	0.2	0.3
17	—	—	—	—	0.4	0.2	0.3
18	—	—	100	90	0.4	0.3	0.4
19	—	—	—	—	0.2	0.3	0.2
20	—	—	—	—	0.2	0.3	0.4
21	—	—	500	100	0.3	4.1	0.8
22	—	—	400	—	0.3	0.2	0.4
23	—	—	—	—	0.4	0.4	0.2
24	—	—	—	—	0.4	0.3	0.2
25	—	—	100	—	0.4	1.9	0.4
26	—	—	—	—	0.3	0.2	0.3
27	—	—	200	—	0.2	0.5	0.4
28	—	—	—	—	0.1	0.2	0.4
29	—	—	100	—	0.2	15.6	0.3
30	—	—	200	—	0.6	2	0.2

— Skin test was negative. When positive it is represented as percentage of histamine weal area. RAST values are presented as percentage of maximum counts added.

Results for BPO over 0.64, for AX (amoxycillin) over 0.81 and for AMP (ampicillin) over 0.58 are considered as positive. Subjects 22 and 30 were skin-test positive with 20 mg/ml AX and 2, 8, 11, 15, 17 and 19 were positive to 2 mg/ml. Subjects 11, 15, 16, 18 and 19 developed systemic responses after skin testing. Subjects 19 and 20 had a positive delayed skin-test response.

responses after the challenge (see Table 2). Table 3 shows the clinical histories of 20 subjects (numbered 11–30) who were negative to all tests and challenges with BP and PV and were subsequently shown to be allergic to AX. All but two subjects had had reactions to AX in the past, in two cases the penicillin causing the problem was not known. The results of the skin tests for this group are shown in Table 4. Eight of the 20 subjects (40%) gave positive responses to AX, subjects 12, 18, 21, 22, 25, 27, 29 and 30, with subjects 18 and 21 also responding to ampicillin. All these subjects, except 22 and 30, responded to 2 mg/ml amoxycillin (22 and 30 responded to 20 mg/ml). Three of the skin-test positive subjects (21, 25 and 29) also experienced immediate systemic reactions after skin testing. Subjects 21 and 25 developed generalized erythema and pruritus and subject 29 developed anaphylactic

Table 5. Results of challenge with amoxycillin for the 20 subjects in Tables 3 and 4

Subject no.	Reaction induced
11	Immediate generalized pruritus after 5 mg AX
12	Immediate generalized erythema and pruritus after 5 mg AX
13	Immediate dizziness, generalized pruritus and erythema after 500 mg AX
14	Generalized erythema, pruritus after 5 mg AX
15	Generalized erythema, pruritus after 24 hr of taking AX
16	Immediate erythema and pruritus after 5 mg AX
17	Generalized urticaria and pruritus after 5 mg AX
18	Generalized erythema and pruritus after 5 mg AX
19	Urticaria and pruritus with peak response 48 hr after taking 500 mg AX every 8 hr
20	Macular erythema and pruritus maximum peak 48–2 hr after starting taking 500 mg AX
21	n.d.
22	n.d.
23	Immediate urticaria and pruritus after 500 mg AX
24	Hypotension, loss of consciousness after 5 mg AX
25	n.d.
26	n.d.
27	n.d.
28	n.d.
29	n.d.
30	n.d.

Subjects 21, 22, 25, 27, 29 and 30 were skin-test positive. Subject 26 experienced hypotension and 28 immediate systemic pruritus after skin testing.

shock. Of the skin-test negative subjects, number 26 developed mild hypotension after testing with 20 mg/ml amoxycillin and number 28 generalized pruritus and erythema. Subjects 19 and 20 gave delayed positive skin tests with an area of 20 × 30 mm for 19 and 12 × 9 mm for 20.

Results of the specific IgE antibody measurement for the group of 20 patients are shown in Table 4 and Fig. 1. Values above the mean plus 2 s.d. of a group of negative control sera assayed in all three RAST systems were taken to be positive (see Table 4 for details). All these subjects sera were negative in the BPO RAST. In the amoxycillin RAST six of the 20 sera (30%) were positive and two of these were also positive in the ampicillin system. All of these RAST-positive sera, except from subject 1, were from subjects who were also skin-test positive. Results of the challenge tests in the amoxycillin allergic group are shown in Table 5. Three subjects refused to be challenged

(22, 27 and 30) but have been included because of their positive skin test responses to amoxycillin, and five others (21, 25, 26, 28 and 29) were not challenged because of systemic reactions after skin testing (see Skin test section). Seven subjects (11, 12, 14, 16, 17, 18, 24 in Table 5) gave immediate responses after the 5 mg amoxycillin challenge with subject 14 suffering anaphylactic shock. The five remaining subjects experienced reactions during the 500 mg amoxycillin treatment schedule; two (13, 23) gave immediate responses and three experienced delayed reactions (15, 19, 20). Subject 15 responded 5 hr after the initial amoxycillin challenge and was finally treated with corticoids and antihistamines. Subject 19 responded 6 hr after the initial amoxycillin challenge with a maximum clinical response at 48–72 hr that required treatment with corticoids and antihistamines. Number 20 responded 10 hr after challenge with mild generalized pruritus. This response was maximal at 24–48 hr and at this time the initial amoxycillin skin-test area also became positive.

A further 19 subjects from the 64 diagnosed as allergic were negative by skin tests and/or RAST to the reagents used (10 to benzylpenicillin or phenoxymethyl-penicillin shown in Table 2 and eight to amoxycillin shown in Table 5). This represented a total of 243 subjects who were skin test and RAST negative. After the challenge tests, 7.8% (19/243) gave positive responses in spite of the negative diagnostic tests.

Discussion

Of the 64 subjects evaluated as positive, 44 were shown to be responsive to either benzyl or phenoxymethyl-penicillin by skin test, RAST or provocation test. The percentage of skin-test positivity to both BPO and MDM in this group was 43.8% (28/64) or 63.6% (28/44) if only the cases shown to be allergic to benzyl or phenoxymethyl-penicillin are considered. The percentage RAST-positive to BPO was 50%. The percentage RAST-positives to amoxycillin was 15% in this group. All these cases were also RAST-positive to BPO. This is presumably because the antibody in these subjects recognizes a structural feature common to AX and BPO, perhaps the thiazolidine ring. In 9.3% of cases the RAST was positive to BPO and skin tests were negative to both BPO and MDM. Kraft *et al.* [12] have found a similar proportion (8.3%) in a group of patients allergic to betalactams. Ten cases allergic to benzylpenicillin needed to be challenged for confirmation (9% of the total group).

Twenty (31%) subjects were considered to be allergic to determinants generated by amoxycillin but not benzyl or phenoxymethyl-penicillin. This result differs from those in previous reports [13,14], but this may be because of differences in prescribing habits. In Spain 45% of anti-

biotic prescriptions are for amoxycillin whereas in the study of Warrington *et al.* [13] benzylpenicillin was the most common followed by ampicillin. Amongst the 20 cases allergic to amoxycillin only 13 were challenged with amoxycillin (see Results) but all gave positive responses. In one case this was confirmed by skin tests, in another by a positive RAST and in a third case by a positive skin test and RAST. Three of the 13 subjects experienced delayed reactions to challenge suggesting a non-IgE-mediated response. A further four subjects gave positive skin tests and RAST with three suffering systemic reactions following the skin test. Two other subjects gave positive skin tests to amoxycillin and the remaining subjects, numbers 16 and 18, gave a systemic reaction following skin test, although the skin test itself was negative. These results support the view that the acyl side chain contributes an important specificity to the immune response against penicillins. This topic has been reviewed by Dewdney [3], but recently de Haan [4] showed, using monoclonal antibodies, that the side chain of penicillin can induce antibodies that fail to react with the penicillin nucleus. Clinically, Moss *et al.* [15] and Solley *et al.* [16] have reported that amongst groups of penicillin-allergic patients the use of semi-synthetic penicillins as skin-test reagents resulted in more responders than when traditional benzylpenicillin-related reagents were used. The importance of the side-chain structure has also been highlighted in studies examining the crossreactivity between betalactam antibiotics of different classes, e.g. penicillins and cephalosporins [5,8], monobactams and cephalosporins [17]. The differences in the side chain structure between benzylpenicillin and amoxycillin are small. Amoxycillin has an α -amino group and a *p*-hydroxy group in the benzene ring, but minor changes can greatly influence the specificity of human immune responses. Voorhorst and Sparreboom [18] described a penicillin-allergic patient who only reacted, on patch tests, to penicillins containing an α -amino group with the correct stereochemistry. The percentage of positive skin tests to amoxycillin in the groups of 20 subjects represents 40% and it is lower than the percentage of skin tests positive to BPO and MDM in the other group of 44 subjects (63.6%). These differences can be related to the fact that in the first group only amoxycillin was used instead of using a conjugate of amoxycillin–poly-L-lysine and a minor determinant mixture equivalent of this (amoxycillin itself and the alkaline hydrolysate).

Considering our group of 64 diagnosed allergics, 45 gave positive skin tests and/or RAST, leaving 19 (30%) who were negative by these tests and required challenges to confirm the diagnosis. A study of 60 patients by Kraft *et al.* [12] showed a similar percentage of RAST and skin-test negative patients (32%). As 45 of our total subjects

were positive to skin tests and/or RAST 243 (288-45) were negative by these tests. Of these, 19 were positive to challenge, i.e. 7.8%. This figure is slightly higher than that reported by Solley *et al.* [16] of 4.1%.

Overall, in this study, although tests using benzyl or phenoxymethyl-penicillin were adequate diagnostic tests for 44 of 64 subjects, additional tests using amoxycillin were required for the other 20 subjects who had responded to amoxycillin. These results emphasize the importance of using a relevant material to aid diagnosis as well as the usual benzylpenicillin reagents.

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